Doctoral Thesis

Data-driven approaches to screening and prescreening of cardiovascular diseases: advancing early detection and risk identification

Zastosowanie modeli opartych o dane do rozwoju narzędzi pozwalających na lepsze przesiewowe wykrywanie i szacowanie ryzyka wystąpienia chorób sercowo-naczyniowych

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DECLARATION OF AUTHORSHIP

I, Urszula Białończyk-Cyba, declare that this thesis titled, "Data-driven approaches to screening and prescreening of cardiovascular diseases: advancing early detection and risk identification" and the work presented in it is my own. I confirm that:

- This work was done wholly or mainly while in candidature for a research degree at the Doctoral School of Information and Biomedical Technologies at the Polish Academy of Sciences.
- Where I have consulted the published work of others, this is always clearly attributed.
- Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work.
- I have acknowledged all main sources of help.
- Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself.

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CONTENTS

LIST OF ABBREVIATIONS

ABI	Ankle-Brachial Index
ACR	Albumin-to-Creatinine Ratio
AGEs	Advanced Glycation End Products
AU	Agatston Units
BAC	Breast Arterial Calcification
baPWV	brachial-ankle Pulse Wave Velocity
CAC	Coronary Artery Calcification
CAD	Coronary Artery Disease
cfPWV	carotid-femoral Pulse Wave Velocity
CKD	Chronic Kidney Disease
CLTI	Chronic Limb-Threatening Ischemia
crPWV	carotid-radial Pulse Wave Velocity
CT	Computed Tomography
CVD	Cardiovascular Disease
eGFR	estimated Glomerular Filtration Rate
ESRD	End-Stage Renal Disease
FFT	Fast Fourier Transform
FPR	False Positive Rate
GFR	Glomerular Filtration Rate
GTF	Generalized Transfer Function
HU	Hounsfield Units
ICER	Incremental Cost-Effectiveness Ratio
IVUS	Intravascular Ultrasound
iVC	intimal Vascular Calcification
JCR	Journal Citation Reports
KDIGO	Kidney Disease: Improving Global Outcomes
LOOCV	Leave-One-Out Cross-Validation
MAP	Mean Arterial Pressure
ML	Machine Learning
mVC	medial Vascular Calcification
OCT	Optical Coherence Tomography
OFDI	Optical Frequency Domain Imaging
PAD	Peripheral Artery Disease
PET	Positron Emission Tomography
PP	Pulse Pressure
PW	Pulse Wave
PW-FDFs	Pulse Wave–Frequency Domain Features
PWV	Pulse Wave Velocity
QALYs	Quality-Adjusted Life Years
ROC	Receiver Operating Characteristic
SCORE	Systematic Coronary Risk Evaluation
SVM	Support Vector Machines
TPR	True Positive Rate
VC	Vascular Calcification
VSMCs	Vascular Smooth Muscle Cells

LIST OF PUBLICATIONS

Publications included in the thesis

(P1) **U. Bialonczyk**, L. Dai, A. R. Qureshi, L. Bobrowski, M. Soderberg, B. Lindholm, P. Stenvinkel, T. Lukaszuk, M. Debowska, J. Poleszczuk „Balancing accuracy and cost in machine learning models for detecting medial vascular calcification in chronic kidney disease: a pilot study", *Scientific Reports* 15 (2025), p. 17453. ISSN: 2045-2322. DOI: 10.1038/s41598-025-02457-2;

(P2) **U. Bialonczyk**, M. Debowska, L. Dai, A. R. Qureshi, M. Soderberg, B. Lindholm, P. Stenvinkel, J. Poleszczuk „Detection of medial vascular calcification in chronic kidney disease based on pulse wave analysis in the frequency domain", *Biomedical Signal Processing and Control* 94 (2024), p. 106250, ISSN: 1746-8094. DOI: 10.1016/j.bspc/2024.106250;

(P3) **U. Bialonczyk**, L. Pstras, M. Debowska, L. Dai, A. R. Qureshi, M. Soderberg, T. B. Brismar, J. Ripsweden, B. Lindholm, P. Stenvinkel, J. Poleszczuk „Leveraging pulse wave signal properties for coronary artery calcification screening in CKD patients", *Computers in Biology and Medicine* 194 (2025), p. 110519, ISSN: 0010-482. DOI: 10.1016/j.compbiomed.2025.110519.

Publications not included in the thesis

1. M. Wieliczko, M. Twardowska-Kawalec, M. Debowska, M. Pietribiasi, **U.Bialonczyk**, J. Waniewski, K. Leypoldt, J. Matuszkiewicz-Rowinska, J. Malyszko „Effect of time-dependent dialysate bicarbonate concentrations on acid-base and uremic solute kinetics during hemodialysis treatments", *Scientific Reports* 14 (2024). DOI: 10.1038/s41598-024-52757-2;

2. H. Kamecki, A. Tokarczyk, M. Dębowska, **U. Białończyk**, W. Malewski, P. Szostek, O. Tayara, S. Gonczar, S. Poletajew, Ł. Nyk, P. Kryst, S. Szempliński „A Simple Nomogram to Predict Clinically Significant Prostate Cancer at MRI-Guided Biopsy in Patients with Mild PSA Elevation and Normal DRE", *Cancers*, 2025; 17(5), 753. DOI: 10.3390/cancers17050753;

3. M. Debowska, M. Wieliczko, M. Pietribiasi, **U. Białończyk**, J. Malyszko, J. Leypoldt, J. Waniewski „Change in plasma electrolyte concentrations during hemodialysis following a controlled step-up in dialysate bicarbonate concentration", *The International Journal of Artificial Organs*, 2025; 48(5):293-301. DOI: 10.1177/03913988251337323;

4. K. Wolos, L. Pstras, **U. Bialonczyk**, M. Debowska, W. Dabrowski, D. Siwicka-Gieroba, J. Poleszczuk „Personalized Pulse Wave Propagation Modeling to Improve Vasopressor Dosing Management in Patients with Severe Traumatic Brain Injury", *PLoS Computational Biology*, 2025; 21(9). DOI: 10.1371/journal.pcbi.1013501.

SUMMARY

English summary

Cardiovascular diseases (CVDs) remain the leading cause of death worldwide, with vascular calcification (VC) recognized as an independent risk factor for adverse cardiovascular events. Although the exact prevalence of VC in the general population is not well established, certain groups are particularly susceptible to this condition. Among them, patients with chronic kidney disease (CKD) often experience an accelerated and widespread calcification process, which makes them particularly well-suited for VC research. Data collected from this population offer, therefore, a valuable source for developing, validating, and refining novel screening strategies designed to improve cardiovascular risk stratification. By focusing on this high-risk group, it becomes possible to design data-driven frameworks that not only address the clinical need for early VC detection in CKD but also generate insights with direct relevance for the broader challenge of CVDs screening and prescreening.

Vascular calcification can occur in two distinct layers of the vessel wall: the intima (intimal vascular calcification, iVC) and the media (medial vascular calcification, mVC). Although these two types differ in their underlying pathophysiology and clinical implications, both are highly prevalent in CKD patients.

Despite their clinical importance, VC status assessment remains a major challenge. Current diagnostic methods, such as arterial biopsies, are highly invasive, while advanced imaging techniques, e.g., computed tomography (CT), are relatively expensive, not always accessible, and involve exposure to radiation. These methods are not well-suited for routine monitoring, particularly in CKD patients who already endure a high treatment burden and are often reluctant to undergo additional procedures that are uncomfortable or time-consuming. As a result, vascular calcification, particularly in the medial layer, often goes unassessed in routine clinical practice, limiting opportunities for early detection and intervention. Therefore, there is an urgent need for safe, cost-effective, and minimally burdensome tools specifically designed for the screening of VC in CKD patients.

The aim of my work was to address the need for clinically feasible and cost-effective methods for medial and intimal vascular calcification screening by proposing novel, data-driven frameworks tailored for individuals with chronic kidney disease. The thesis evaluates models for early detection of vascular calcification in CKD patients, thereby providing a basis for the future development of scalable, broadly accessible tools for cardiovascular disease risk stratification.

My work consists of three thematically related scientific papers that were published between 2024 and 2025 in recognized journals listed in the JCR database with a total impact factor of 15.70.

The first part of my research, described in [P1], focused on the detection of medial vascular calcification using a panel of biomarkers known or suspected to be associated

with this pathology. While previous studies have explored the potential of various biomarker sets as input features for machine learning models aimed at mVC screening, none have evaluated the economic implications of such approaches. Moreover, the proposed biomarker sets vary widely between studies, often achieving similar statistical performance despite significant differences in availability, acquisition cost, and clinical feasibility. To develop a framework that is both practical and clinically applicable, I restricted the candidate features to circulating biomarkers, other non-invasively acquired parameters, and anthropometric measurements, with the latter being readily accessible in routine clinical practice. Using a range of advanced statistical methods, I trained classification models to detect mVC and evaluated their performance not only in terms of predictive accuracy but also cost-effectiveness, assessed via the incremental cost-effectiveness ratio (ICER). For this purpose, I proposed and applied an ICER calculation formula specifically tailored to this application. The findings of this comprehensive analysis support earlier observations: no single biomarker set was identified that consistently achieved superior predictive performance across the frameworks. However, the inclusion of ICER as a comparative metric revealed clinically relevant distinctions, demonstrating that broader sets of inexpensive, easily obtainable features may yield improved cost-effectiveness and, consequently, greater potential for clinical implementation. These results underscore the value of incorporating economic evaluation into the development of screening tools for vascular calcification. This investigation directly addresses my first main research hypothesis:

(H1) Integrating cost-effectiveness assessment into the selection of machine learning models trained for medial vascular calcification detection in patients with end-stage chronic kidney disease facilitates the identification of the most clinically relevant approaches.

Nevertheless, the obtained results also indicated that, in most cases, a smaller number of required inputs while maintaining predictive power enhances the feasibility and scalability of a screening tool. This observation motivated me to explore approaches based on a single, fully non-invasive biomarker, rather than panels requiring multiple assays and blood sampling. The pressure pulse wave signal represents an ideal candidate: it can be captured quickly, painlessly, and at low cost, yet carries rich physiological information about arterial wall properties. Building on this insight, the second part of my research focused on leveraging pressure pulse wave morphology as input to machine learning models for detecting medial vascular calcification in CKD patients. For this purpose, I developed a novel framework in which pressure pulse wave signals, acquired from a single peripheral arterial location, were transformed from the time domain to the frequency domain, and features extracted from this spectral analysis were used as inputs to statistical classification models. I demonstrated that this method outperforms models based solely on conventional risk factors, indicating its potential as a cost-effective and patient-friendly screening tool for medial vascular calcification. Those results, published in [P2], directly address the second main research thesis formulated in this dissertation:

(H2) A data-driven framework that integrates conventional vascular calcification risk factors with pressure pulse wave frequency-domain features (PW-FDFs) derived from non-invasive peripheral pressure pulse wave measurements can be used to detect medial vascular calcification in patients with end-stage chronic kidney disease.

Building on the promising results of the proposed pressure pulse wave-based framework for medial vascular calcification detection, in the third part of my work, my focus shifted to identifying coronary artery calcification (CAC), most commonly located in the intimal layer of the arterial wall. It is evaluated through CT imaging, followed by expert analysis to derive a coronary artery calcification score, which informs about the extent of CAC. Utilizing data on pressure pulse wave signals and CAC scores from CKD patients, I demonstrated that frequency-domain features derived from these signals can serve as effective input for statistical models aimed at identifying patients with elevated CAC scores. Importantly, the model exhibited superior ability to distinguish between individuals with and without elevated CAC scores in both younger and older patient subgroups, compared to the model based solely on conventional clinical predictors. These findings suggest that single-site, non-invasive pressure pulse wave analysis in the frequency domain may offer a viable, low-burden alternative for the early detection of intimal vascular calcification. Those results have been published in [P3] and support the third research thesis formulated for this dissertation:

(H3) Statistical models based on pressure pulse wave frequency-domain features (PWFDFs) can effectively identify end-stage chronic kidney disease patients with elevated coronary artery calcification scores.

In summary, my work presents a multi-faceted approach to the detection of vascular calcification in chronic kidney disease patients, addressing both medial and intimal types of this pathology. By integrating statistical performance with economic evaluation, the first part provides novel insights into the cost-effectiveness of biomarker-based screening models. The second part introduces an entirely non-invasive framework leveraging frequency-domain features of single-site pressure pulse wave signals, offering a promising alternative to traditional risk-based models for medial calcification screening. Finally, this approach is extended to the detection of intimal calcification in the coronary artery, demonstrating the potential of pressure pulse wave spectral analysis as a low-burden, accessible method for identifying patients with elevated coronary artery calcification scores. Collectively, these contributions provide a foundation for further development of clinically feasible and economically viable vascular calcification screening tools with strong potential for clinical implementation.

STRESZCZENIE

Streszczenie w języku polskim

Choroby sercowo-naczyniowe (CVDs, *ang. cardiovascular diseases*) stanowią główną przyczynę zgonów na świecie, a zwapnienia naczyń krwionośnych (VC, *ang. vascular calcification*) uznaje się za istotny czynnik ryzyka wystąpienia niepożądanych zdarzeń sercowo-naczyniowych. Dokładna częstość występowania VC w populacji ogólnej nie została jednoznacznie określona. Wiadomo jednak, że wyjątkowo narażone na ich rozwój są wybrane grupy osób. Wśród nich na szczególną uwagę zasługują osoby z przewlekłą chorobą nerek (CKD, *ang. chronic kidney disease*), u których proces powstawania zwapnień przebiega szybko i ma nasilony charakter, co powoduje, że populacja ta stanowi odpowiedni model do badań VC. Gromadzenie danych dotyczących zwapnień u chorych z CKD umożliwia opracowanie, walidację oraz doskonalenie nowatorskich strategii badań przesiewowych w kierunku VC, które mogą znacząco poprawić dokładność oceny ryzyka sercowo-naczyniowego. Przykładem takich rozwiązań są techniki uczenia maszynowego wykorzystujące zgromadzone dane do tworzenia modeli predykcyjnych. Skupienie się na pacjentach z CKD jest podejściem praktycznym - umożliwia zebranie niezbędnych danych w stosunkowo niedługim czasie, a także odpowiada na realne potrzeby kliniczne tej grupy, która może szczególnie skorzystać z wdrożenia wczesnych metod oceny VC. Warto również zaznaczyć, że wnioski wynikające z analiz mogą mieć bezpośrednie przełożenie na udoskonalenie badań przesiewowych w kierunku chorób sercowo-naczyniowych w szerszej populacji.

Zwapnienia naczyń krwionośnych mogą być zlokalizowane w dwóch odrębnych warstwach ściany naczyń: w błonie wewnętrznej (iVC, *ang. intimal vascular calcification*) oraz w błonie środkowej (mVC, *ang. medial vascular calcification*). Procesy te różnią się zarówno pod względem patofizjologii, jak i konsekwencji klinicznych. Oba występują powszechnie u pacjentów z przewlekłą chorobą nerek.

Pomimo istotnego znaczenia klinicznego, ocena występowania VC pozostaje poważnym wyzwaniem. Dostępne metody diagnostyczne, takie jak biopsja tętnic, są wysoce inwazyjne, natomiast zaawansowane techniki obrazowania, np. tomografia komputerowa, wiążą się ze znacznymi kosztami, ograniczoną dostępnością i ekspozycją na promieniowanie jonizujące. Z tego względu nie nadają się one do rutynowych badań, szczególnie pacjentów z CKD, którzy z uwagi na przebieg choroby poddawani są intensywnemu leczeniu i niechętnie akceptują dodatkowe, uciążliwe lub czasochłonne procedury diagnostyczne. W efekcie, występowanie zwapnień, zwłaszcza w obrębie błony środkowej, rzadko jest oceniane w codziennej praktyce klinicznej. Ogranicza to możliwości ich wczesnego wykrywania oraz podejmowania działań prewencyjnych i terapeutycznych. Niezbędne jest zatem opracowanie narzędzi przeznaczonych do badań przesiewowych w kierunku VC u pacjentów z CKD, które będą bezpieczne, koszt-efektywne i jak najmniej obciążające dla chorego.

Celem mojej pracy było opracowanie metod badań przesiewowych w kierunku zwapnień błony środkowej i błony wewnętrznej ścian naczyń, które będą koszt-efektywne oraz możliwe do wdrożenia w praktyce klinicznej. Zaproponowałam nowe narzędzia oparte na analizie danych, dostosowane do specyfiki populacji pacjentów z przewlekłą

chorobą nerek. W ramach pracy przeprowadziłam ocenę modeli umożliwiających wczesne wykrywanie zwapnień ścian naczyń krwionośnych w tej grupie chorych, tworząc podstawę do przyszłego opracowania rozwiązań wspomagających precyzyjną ocenę ryzyka sercowo-naczyniowego, a jednocześnie łatwych do wdrożenia na szeroką skalę.

Moja praca składa się z trzech powiązanych tematycznie artykułów naukowych, opublikowanych w latach 2024–2025 w renomowanych czasopismach wymienionych w bazie danych JCR, o całkowitym współczynniku wpływu IF = 15.70 oraz liczbie punktów MNiSW N = 380.

Pierwsza część pracy, opisana w [P1], poświęcona jest wykrywaniu zwapnień błony środkowej naczyń za pomocą technik uczenia maszynowego z wykorzystaniem paneli biomarkerów potencjalnie powiązanych z tą patologią. Chociaż powstały już prace podejmujące tę tematykę, żadna z nich nie uwzględniała w analizie jakości rozwiązania kosztów poszczególnych pomiarów. Można było natomiast zauważyć, że proponowane przez poszczególne algorytmy zestawy biomarkerów różniły się znacznie w zależności od zastosowanej metody. Pomimo istotnych różnic w dostępności i kosztach pozyskania poszczególnych danych, jakość predykcyjna modeli była jednak porównywalna.

Aby opracować metody możliwe do zastosowania w praktyce klinicznej, ograniczyłam analizowane cechy do biomarkerów oznaczanych z krwi, innych parametrów uzyskiwanych nieinwazyjnie oraz pomiarów antropometrycznych. Wykorzystując zaawansowane algorytmy statystyczne, wytrenowałam modele klasyfikacyjne służące do wykrywania mVC i oceniłam ich skuteczność nie tylko pod kątem trafności prognoz, lecz także kosztów ich wykonania. W tym celu zaproponowałam wzór do wyznaczenia wskaźnika koszt-efektywności (ICER, *ang. incremental cost-effectiveness ratio*) dostosowany do specyfiki badanego zagadnienia. Wyniki przeprowadzonych testów potwierdziły wcześniejsze obserwacje: nie znaleziono jednego zestawu biomarkerów, który konsekwentnie osiągałby najlepsze rezultaty w każdej z analizowanych miar jakości klasyfikatorów. Uwzględnienie wskaźnika ICER jako metryki porównawczej ujawniło jednak istotne klinicznie różnice, wykazując, że szerszy zestaw niedrogich i łatwo dostępnych cech może zapewnić lepszą koszt-efektywność, a tym samym większy potencjał do zastosowania w praktyce klinicznej. Wyniki te pokazują znaczenie włączenia oceny ekonomicznej do procesu opracowywania narzędzi do badań przesiewowych w kierunku zwapnienia naczyń krwionośnych. Praca ta bezpośrednio odnosi się do mojej pierwszej hipotezy badawczej:

(H1) Włączenie oceny koszt-efektywności do procesu wyboru modeli uczenia maszynowego, szkolonych w celu wykrywania zwapnień błony środkowej naczyń krwionośnych u pacjentów ze schyłkową chorobą nerek, umożliwia bardziej precyzyjną identyfikację metod o największym potencjale klinicznym.

Uzyskane wyniki wskazały jednak, że w większości przypadków mniejsza liczba wykorzystywanych biomarkerów przy zachowaniu zdolności prognostycznej zwiększa użyteczność oraz możliwość szerokiego zastosowania narzędzia przesiewowego. Obserwacja ta zmotywowała mnie do zbadania podejść opartych na pojedynczym, całkowicie nieinwazyjnym markerze, zamiast na panelach wymagających wielu testów i pobierania próbek krwi. Do dalszych analiz postanowiłam wykorzystać sygnał fali pulsu, który można szybko, bezboleśnie i niskim kosztem zarejestrować, a jednocześnie zawiera informacje fizjologiczne o właściwościach ścian naczyń krwionośnych.

W drugiej części moich badań skupiłam się zatem na wykorzystaniu informacji pozyskanych z fali pulsu jako danych wejściowych do modeli uczenia maszynowego w celu wykrywania zwapnień błony środkowej tętnic u pacjentów z CKD. Opracowałam metodę, w której sygnał fali pulsu, rejestrowany z tętnicy obwodowej, został przekształcony z dziedziny czasu do dziedziny częstotliwości. Cechy wyodrębnione w wyniku przeprowadzonej analizy spektralnej posłużyły jako dane wejściowe do statystycznych modeli klasyfikacyjnych. Wykazałam, że uwzględnienie informacji pochodzących z fali pulsu w klasyfikatorze przewyższa modele oparte wyłącznie na konwencjonalnych czynnikach ryzyka powstawania zwapnień naczyń, co wskazuje na potencjał tego podejścia jako koszt-efektywnego i przyjaznego dla pacjenta narzędzia do badań przesiewowych w kierunku mVC. Wyniki te, opublikowane w [P2], odnoszą się bezpośrednio do drugiej hipotezy badawczej sformułowanej w niniejszej rozprawie:

(H2) Metoda oparta na analizie danych, która łączy tradycyjne czynniki ryzyka powstawania zwapnień naczyń z cechami częstotliwościowymi fali pulsu (PWFDFs) uzyskanymi z nieinwazyjnych pomiarów tętna obwodowego, może być użyta do wykrywania zwapnień błony środkowej tętnic u pacjentów ze schyłkową chorobą nerek.

Opierając się na obiecujących wynikach uzyskanych w badaniach wykorzystania sygnału fali pulsu do wykrywania zwapnień błony środkowej tętnic, w trzeciej części niniejszej pracy skoncentrowałam się na identyfikacji zwapnień tętnic wieńcowych (CAC, *ang. coronary artery calcification*), najczęściej zlokalizowanych w warstwie błony wewnętrznej ściany naczynia. Stopień ich zaawansowania standardowo ocenia się za pomocą tomografii komputerowej, a jego podstawową miarą jest wskaźnik uwapnienia tętnic wieńcowych (*ang. CAC score*). Wykorzystując dane obejmujące sygnał fali pulsu oraz wyniki oceny CAC u pacjentów z CKD, wykazałam, że cechy uzyskane z analizy spektralnej tych sygnałów mogą stanowić efektywne dane wejściowe dla modeli klasyfikacyjnych, umożliwiających identyfikację pacjentów z podwyższonymi wartościami CAC. Co istotne, zaproponowany model charakteryzuje się wyższą precyzją w rozróżnianiu osób z istotnymi zwapnieniami i osób bez zwapnień, zarówno w podgrupach pacjentów młodszych, jak i starszych, w porównaniu z modelem opartym wyłącznie na konwencjonalnych czynnikach ryzyka CAC. Uzyskane rezultaty sugerują, że nieinwazyjnie mierzona fala pulsu, analizowana w dziedzinie częstotliwości, może stanowić mało uciążliwą, potencjalnie szeroko dostępną alternatywę dla tradycyjnych metod wczesnego wykrywania CAC. Wyniki te zostały opublikowane w [P3] i odnoszą się do trzeciej hipotezy badawczej sformułowanej w niniejszej rozprawie:

(H3) Modele statystyczne oparte na cechach częstotliwościowych fali pulsu (PWFDFs) mogą skutecznie identyfikować pacjentów ze schyłkową chorobą nerek, u których występuje podwyższony poziom zwapnienia tętnic wieńcowych.

Podsumowując, moja praca przedstawia wielowymiarowe podejście do wykrywania zwapnień ścian naczyń krwionośnych u pacjentów z przewlekłą chorobą nerek, uwzględniające zarówno zwapnienia błony środkowej, jak i wewnętrznej. Pierwsza część, łącząca analizę statystyczną z oceną ekonomiczną, dostarcza nowych informacji na temat koszt-efektywności modeli uczenia maszynowego opartych na biomarkerach służących do badań przesiewowych w kierunku mVC. Druga część prezentuje całkowicie nieinwazyjną metodę wykorzystującą cechy sygnału fali pulsu w dziedzinie częstotliwości, stanowiącą obiecującą alternatywę dla modeli bazujących jedynie

na tradycyjnych czynnikach ryzyka w ocenie zwapnień błony środkowej. Podejście to zostało następnie rozszerzone na wykrywanie zwapnień błony wewnętrznej w tętnicach wieńcowych, gdzie wykazano potencjał analizy spektralnej fali pulsu jako łatwo dostępnej, mało obciążającej pacjenta metody wspomagającej identyfikację osób z podwyższonym poziomem zwapnień.

Uzyskane wyniki stanowią podstawę do dalszego rozwoju praktycznych i ekonomicznie uzasadnionych narzędzi przesiewowych w kierunku zwapnień naczyń krwionośnych, posiadających istotny potencjał wdrożeniowy w praktyce klinicznej.

1

INTRODUCTION

This thesis aims to address the broad challenge of cardiovascular diseases (CVD) screening by proposing and investigating various data-driven methodologies in the specific context: detecting vascular calcification (VC) in patients with advanced chronic kidney disease. CKD patients are particularly well-suited for research on VC identification because the pathology is highly prevalent in this group, enabling the assembly of a sufficiently large study cohort within a reasonable timeframe and with fewer resources compared to populations where VC is much less common. The specific focus on VC is equally intentional as it is one of the most powerful independent predictors of adverse cardiovascular events. By developing data-driven techniques to assess this important marker in a high-risk population, my research supports the broader goal of advancing early detection and risk assessment of cardiovascular diseases.

1.1 Chronic kidney disease

1.1.1 Definition and diagnosis

According to the definition provided by Kidney Disease: Improving Global Outcomes (KDIGO), one of the most widely recognized organizations in the field, chronic kidney disease (CKD) is described as "*abnormalities of kidney structure or function, present for a minimum of 3 months, with implications for health*" [1]. Alarmingly, such abnormalities are becoming increasingly common worldwide [2]. In 2017, it was estimated that nearly one in ten people globally were affected by CKD, making it the 12^{th} leading cause of death [3]. By 2021, it had already reached the 9^{th} position [4]. This upward trend is closely linked to demographic and epidemiological shifts. With rising life expectancy, and the global increase in the prevalence of diabetes mellitus [5] and hypertension [6], which are both major risk factors for CKD [7], the disease burden is projected to escalate [8, 9, 10]. Forecasts suggest that by 2040, CKD could become the fifth leading cause of years of life lost globally [8]. Collectively, these trends underscore the urgent need for monitoring and management strategies for CKD.

Despite its broad definition, CKD diagnosis in clinical practice relies on two primary criteria:

- Assessment of kidney function usually done by evaluating glomerular filtration rate (GFR), which reflects how effectively the kidneys filter the blood [11]. Although GFR is considered the gold standard for evaluating kidney filtration, its direct measurement is complex and costly [12]. Therefore, in routine clinical

practice, the estimated GFR (eGFR) is commonly used and treated as a GFR proxy. Various formulas exist for its calculation, but the most widely adopted and recommended approach is based on serum creatinine levels [1]. In addition to creatinine, patient age and sex are incorporated into the calculation to improve estimation accuracy [13].

- Assessment of kidney damage which can be determined through several methods, including persistent hematuria, imaging abnormalities, or biopsy findings. However, the albumin-to-creatinine ratio (ACR) in urine is the most commonly used marker due to its simplicity and diagnostic utility [1]. The presence of albuminuria indicates abnormal protein leakage into the urine, reflecting structural kidney damage.

CKD is diagnosed when either reduced kidney function (GFR (eGFR) $<$ 60 mL/min/1.73 m^2) or evidence of kidney damage (e.g., albuminuria) persists for more than three months. Next, the disease is classified into stages based on the degree of kidney function decline, as indicated by GFR (eGFR) levels [1]. This classification, summarized in Table 1.1, is essential for risk stratification and treatment planning [1].

CKD Stage	**GFR (eGFR)** (mL/min/1.73 m^2)	**Severity**
Stage 1	$\geq$ 90	Mild kidney damage*
Stage 2	60–89	Mild kidney damage*
Stage 3a	45–59	Mild to moderate kidney damage
Stage 3b	30–44	Moderate to severe kidney damage
Stage 4	15–29	Severe kidney damage
Stage 5	<15	Severe kidney damage or kidney failure

Abbreviations: CKD, chronic kidney disease; (e)GFR, (estimated) glomerular filtration rate.
* Kidney damage must be confirmed to classify patients with GFR $\geq$ 60 mL/min/1.73 m^2.

Table 1.1: CKD Stages

From a clinical perspective, staging provides crucial information on the likelihood of progression to kidney failure and the risk of cardiovascular and other systemic complications [1]. It therefore guides the intensity and type of intervention required at each stage. The most advanced form of CKD is stage 5, also known as end-stage renal disease (ESRD). Patients at this stage exhibit profound kidney dysfunction and are at the highest risk of comorbidities, including CVD [1]. Given its clinical complexity and the heavy burden it imposes on both patients and healthcare systems, ESRD demands targeted attention.

My research, described in this thesis, focuses specifically on stage 5 CKD patients, who are both the most likely to exhibit vascular calcification [14] and are at the greatest risk of cardiovascular complications among all CKD stages [15].

1.1.2 Relation to cardiovascular diseases

Chronic kidney disease is now widely recognized as a systemic disorder [16]. Beyond the progressive renal impairment, CKD contributes to a wide range of complications, including mineral and bone disorders [17], anemia [18], immune dysfunction [19], metabolic disturbances [20], or neurological problems [21]. Among these, cardiovascular disease is the most prevalent and deadly comorbidity - particularly in patients with ESRD, where it remains the leading cause of mortality [22, 23, 24]. The clinical significance of cardiovascular complications in CKD is strongly emphasized in the recent KDIGO 2024 guidelines, which highlight both the relative and absolute cardiovascular risks across CKD stages, as demonstrated by data from the CKD Prognosis Consortium [25]. Among the ten major CKD-related complications discussed in their work, more than half were cardiovascular in nature, including cardiovascular mortality, myocardial infarction, stroke, heart failure, atrial fibrillation, and peripheral artery disease. In patients with CKD stage 5, the risk of these conditions is estimated to be 2.6 to 14 times higher than in individuals with proper kidney function, depending on the analyzed outcome and the degree of albuminuria [25].

The relationship between CKD and CVD is complex and bidirectional. While both conditions share common major risk factors such as hypertension and diabetes mellitus [26], which can partially explain this link, CKD also causes a number of metabolic and structural changes that directly contribute to cardiovascular pathology. These include an altered lipid profile specific to CKD patients [27], chronic inflammation (CKD is recognized as a state of persistent systemic inflammation) [28], myocardial remodeling and fibrosis [29], and, notably, vascular calcification, which is one of the most prevalent and clinically significant vascular complications in this population [30, 31]. As a pathological process influenced by mineral metabolism disturbances, chronic inflammation, and uremic toxins, VC exemplifies the systemic consequences of advanced kidney disease. It is strongly associated with arterial stiffness, left ventricular hypertrophy, and increased risk of sudden cardiac death [30, 32]. Despite its clinical significance, VC still remains underdiagnosed [33].

Given the cardiovascular burden faced by CKD patients and the role of vascular calcification in this context, a deeper understanding and improved screening of VC may lead to better patient outcomes, particularly among those with ESRD. The following chapters will explore vascular calcification in greater detail, highlighting its pathophysiological mechanisms, clinical implications, and the rationale for targeted screening strategies in this high-risk population.

1.2 Vascular calcification in chronic kidney disease

Although my work concerns the methods of VC screening, it would be difficult to create such tools without a deep understanding of the underlying mechanisms of this pathology and the consequences it carries. Therefore, in this section, I will give an overview of the process of VC formation as well as the current assessment methods with a particular focus on their clinical utility.

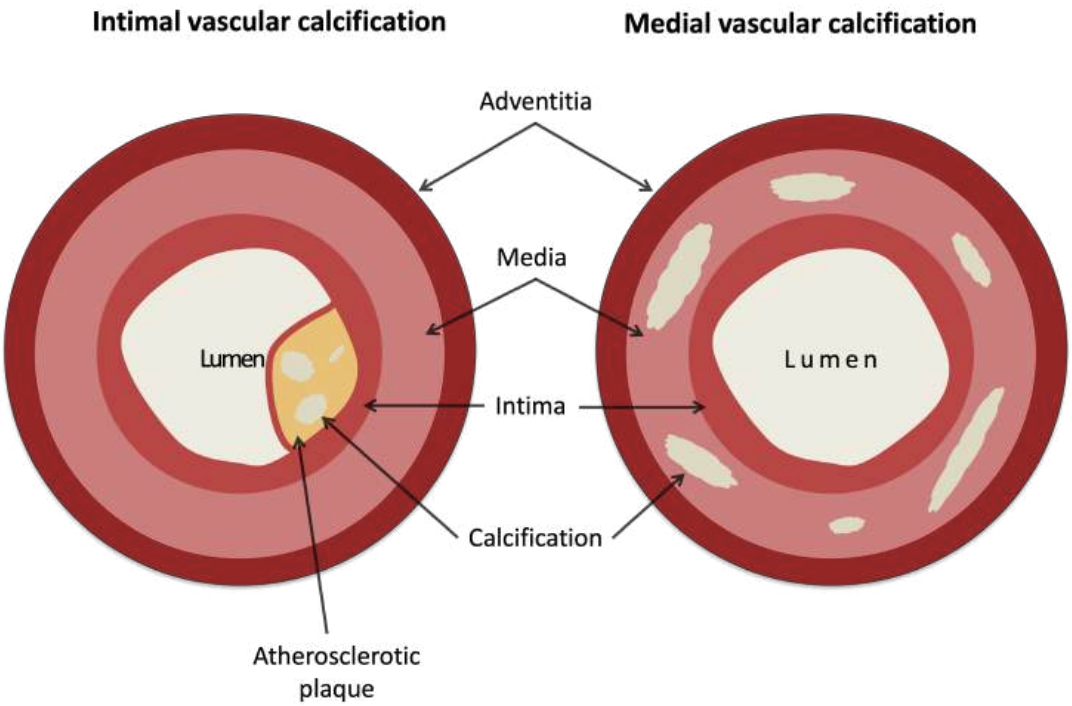

FIGURE 1.1: Schematic of a vessel cross-section depicting the distinct forms of vascular calcification. The left panel illustrates intimal vascular calcification, characterized by the deposition of calcium within an atherosclerotic plaque in the vessel intima, narrowing the lumen. The right panel depicts medial vascular calcification, where calcium accumulates directly within the smooth muscle layer (media) of the vessel wall.

1.2.1 Definition and clinical significance

Vascular calcification is a pathological process characterized by the abnormal deposition of calcium phosphate crystals in the form of hydroxyapatite (a mineral naturally found in bones and teeth) within the arterial wall [34]. Although originally considered a passive and degenerative consequence of aging, VC is now recognized as an active, highly regulated cellular mechanism that closely resembles physiological bone formation [35, 36, 37]. This revised understanding not only highlights the biological complexity of VC [38], but also indicates its potential reversibility, making it a compelling target for clinical research.

VC can affect both medial (middle) and intimal (innermost) layers of the arterial wall, as depicted in Figure 1.1, and may occur in various vascular sites [39, 30, 32]. Furthermore, it may present as microcalcification or macrocalcification, each with distinct clinical implications for vascular function [39]. This heterogeneity of VC complicates its evaluation and prognostic interpretation in clinical settings, emphasizing the need for more nuanced diagnostic and risk stratification strategies.

1.2.2 Pathophysiological mechanisms

VC is mainly driven by the vascular smooth muscle cells (VSMCs). Under physiological conditions, VSMCs maintain a contractile phenotype, while when exposed to a pathological stimulus, they undergo phenotypic switching resulting in the adoption of an osteogenic (i.e., bone-like) phenotype [35]. This transformation resembles the

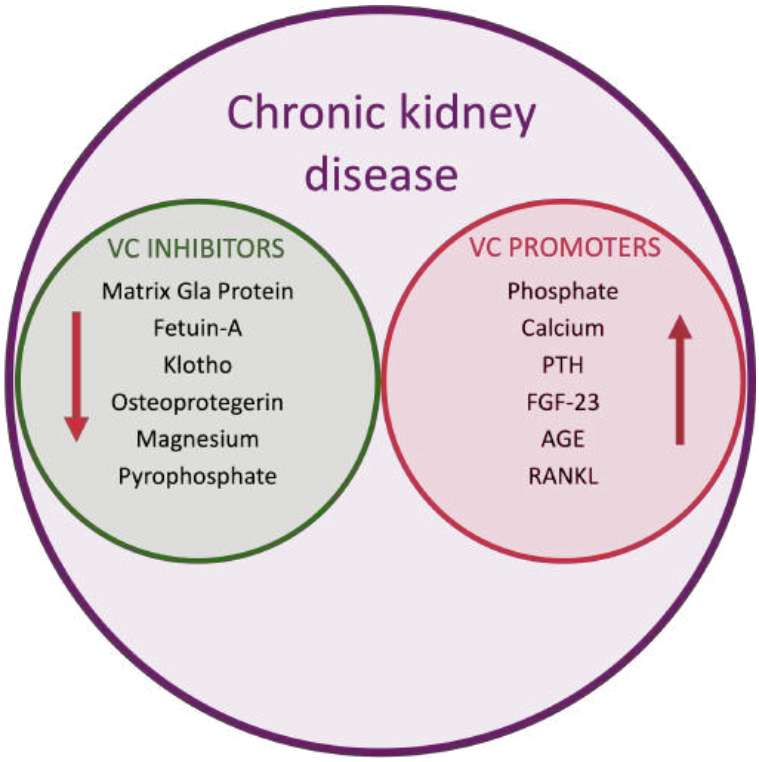

FIGURE 1.2: Selected vascular calcification inhibitors and promoters whose levels are commonly disturbed in chronic kidney disease.
VC, vascular calcification; PTH, parathyroid hormone; FGF-23, fibroblast growth factor 23; AGE, advanced glycation end product; RANKL, receptor activator of nuclear factor kappa-B ligand.

process of bone formation and involves the expression of bone-related proteins [40]. In the intima, in addition to VSMCs, macrophages also contribute to the process, particularly through inflammatory signaling and vesicle release [41]. In CKD, in addition to mineral disturbances, various factors such as chronic inflammation, oxidative stress, and uremic toxins (e.g., advanced glycation end products - AGEs) act as promoters of this osteogenic differentiation by inducing vessel wall injuries [42, 43].

The development of vascular calcification in chronic kidney disease is closely linked to disturbances in mineral metabolism - particularly elevated levels of phosphate (P) and calcium (Ca) [44]. Hyperphosphatemia, highly prevalent in CKD, is considered a key driver of VC [45, 46, 47]. Increased calcium levels and an elevated calcium–phosphate ($Ca \times P$) product also contribute significantly to the calcification process [48, 49, 30]. Notably, VC can develop even before serum phosphate levels rise above the normal range, suggesting that local phosphate concentrations within tissues and cumulative exposure over time may play a more critical role than what is reflected in serum measurements [50]. It is also worth noting that the calcification process slows down to rates seen in patients with normal renal function but does not regress after a kidney transplant, which makes prevention extremely important [51].

Under physiological conditions, vascular tissues are protected from mineral deposition by several active inhibitors of calcification, including matrix Gla protein (MGP), fetuin-A, and osteoprotegerin. In CKD, their levels are often reduced, impairing the vasculature's protective mechanisms against calcification [52]. This, combined with the usual simultaneous accumulation of calcification promoters, creates a pro-calcific

environment in the vasculature. The selected VC inhibitors and promoters related to CKD [52] are presented in Figure 1.2.

While medial vascular calcification (mVC) and intimal vascular calcification (iVC) share core cellular mechanisms, they differ in their initiating stimuli, vascular location, and clinical implications. mVC is typically associated with arterial stiffness and is prevalent in CKD [32], whereas iVC, although present in CKD patients as well, is more closely related to atherosclerotic plaque formation [34]. Understanding these distinctions is crucial for accurate risk assessment, as well as for the development of targeted diagnostic and therapeutic strategies. Thus, mVC is described in detail in Chapter 3.1 while iVC is discussed in Chapter 5.1.

1.3 Clinical management of vascular calcification

1.3.1 Treatment

To this date, there does not exist causal treatment for VC, but strategies to slow down its progression have been proposed. Multiple trials targeting VC have been conducted, and their detailed reviews can be found in [53, 54, 34]. It is evident that there is still much to be discovered regarding VC's pathophysiological mechanisms, and each component of this complex process is a potential direction in the search for therapeutic strategies. In the context of my work, two aspects need to be highlighted. First, many of the proposed therapies to slow down VC's progression are focused on targeting disrupted biomarkers associated with this pathology, including inhibitors such as sodium thiosulfate, magnesium, and SNF472. Researchers acknowledge that due to the heterogeneity of the mechanism, multiple simultaneous interventions may be required [54]. From this perspective, trying to uncover combinations of features that may indicate calcification using various machine learning techniques [P1] is my contribution to this aspect of research. Second, given the current lack of methods to reverse calcification, early detection is essential. This target was pursued not only through the proposal and evaluation of screening strategies aimed at improving VC's detection, but also through the careful formulation of the objectives in each study. Mild and extensive calcification were marked as positive in [P1]. In [P2], the PW-FDFs method I proposed allowed for the detection of mVC at an earlier stage, with even minimal calcification being labelled as positive. Finally, in my third work [P3], I have targeted CAC $>$ 100 AU, a threshold indicating mild coronary artery disease risk. The results demonstrated that the proposed method shows potential for identifying even lower CAC levels, since the probability of being classified as positive increased with the true CAC score. This screening approach for CAC may therefore support earlier referral for scanning in patients who are most likely to benefit from it.

1.3.2 Screening

Although there are multiple ways to describe the screening process, for the purpose of this work, I will employ the following definition: screening refers to testing individuals to evaluate their likelihood of having a particular disease or disorder. Those identified as high-risk can then be referred for definitive diagnostic evaluation. The principal aim of screening is to reduce morbidity or mortality at the population level by detecting disease early enough that interventions can meaningfully change the course of illness.

It is important to distinguish screening from diagnostic testing. A diagnostic test should reliably distinguish between individuals with and without the disease; such tests are often called *gold standards* and, in principle, should not make classification errors. In the context of VC, arterial biopsy would meet this definition. In practice, since invasive methods are unsuitable for routine use, highly accurate non-invasive techniques (e.g., PET–CT scans capable of differentiating iVC and mVC patterns) can serve as surrogate gold standards.

The distinction between screening and pre-screening, on the other hand, can be defined by what follows the initial assessment rather than by the method itself. If a non-definitive assessment is followed by a definitive diagnostic test, the initial step functions as a screening test. Conversely, if it is followed by a more informative but still non-definitive method, the first step can be considered pre-screening. Consequently, the same non-definitive method may serve as either a screening or pre-screening tool, depending on the subsequent diagnostic pathway. To maintain clarity and consistency, in the remainder of this thesis, the term *screening* will be used to refer to any non-definitive diagnostic process, regardless of what diagnostic steps follow.

A useful screening test does not need to provide perfect accuracy. Its value depends on the balance of benefits (earlier detection, prevention of events) against harms and costs (false positives, unnecessary investigations, patient burden, expense). Screening performance is typically assessed using *sensitivity* (the proportion of true positives correctly identified) and *specificity* (the proportion of true negatives correctly identified). The optimal trade-off between sensitivity and specificity depends on the screened population and the consequences of false results. For example, in older adults, where disease prevalence is higher, maximizing specificity may reduce unnecessary testing, whereas in younger populations, a higher sensitivity may be prioritized to avoid missing rare early cases.

Because perfect accuracy (the proportion of observations correctly classified) is not required for screening, many useful tools rely on indirect measurements. In VC, an example can be pulse wave velocity (PWV), which measures arterial stiffness rather than calcification directly [55]. Since VC contributes to vessel stiffening, it makes PWV a reasonable initial indicator - its elevated values can then prompt confirmatory imaging, improving cost-effectiveness and limiting unnecessary radiation exposure.

The qualities of an effective screening method have been described most famously by Wilson and Jungner, whose principles, introduced in the 1960s, remain influential to this date [56]. Above all, a good screening tool should be simple, safe, inexpensive, and easy to integrate into routine care so as to encourage clinician uptake and patient compliance [57]. Taken together, VC satisfies many Wilson–Jungner criteria. It is a significant medical problem linked to increased mortality. It can be detected at initial stages with advanced imaging techniques such as PET–CT, and early identification is clinically important because only treatments that slow down its progression are currently available.

Nonetheless, mVC detection remains a subject of debate, in contrast to iVC assessment in coronary arteries, which is strongly recommended in current cardiovascular risk evaluation. While many clinicians and researchers highlight the added value of mVC assessment for refined risk stratification, especially in CKD patients [53], others argue that it offers limited benefit in the absence of a proven causal therapy capable of reversing the calcification process [58]. This position is partially reflected in the KDIGO guidelines, which only weakly recommend VC testing even in CKD populations, despite their markedly elevated calcification risk.

The evidence reviewed in the present work challenges this view. First, although reversal is not yet possible, several interventions can slow calcification progression (as outlined in 1.3.1), and these are likely to be most effective when initiated early, making timely detection clinically valuable. Second, research into mVC detection itself can yield valuable insights into the underlying mechanisms and potential therapeutic targets, informing future treatment strategies [59]. Third, improved risk stratification has immediate clinical relevance, particularly for ESRD patients being evaluated for kidney transplantation, where vascular health can influence both perioperative safety and long-term outcomes.

For these reasons, advancing not only iVC but also mVC detection remains both a scientific challenge and a clinically meaningful goal. In Table 1.2, the major VC detection methods are briefly discussed with a particular focus on their utility for screening purposes. As shown there, no single, widely accessible diagnostic tool combines early-detection sensitivity with a favorable safety-cost profile. This motivates a pragmatic two-stage strategy in which an inexpensive, safe, and reproducible screening method is used to triage individuals to a reliable diagnostic test for confirmation.

My work addresses this gap by developing and evaluating screening approaches that are both practical for routine measurement and compatible with machine learning integration. Specifically, I conducted the first systematic economic evaluation of laboratory biomarkers for mVC, providing novel evidence on their cost-effectiveness as part of a screening pathway. Such evaluation is crucial before integrating a screening tool into clinical practice [57]. In parallel, I explored pressure pulse wave information beyond single summary indices (such as PWV or ankle-brachial index) by implementing a Pulse Wave - Frequency Domain Features (PW-FDFs) extraction pipeline that captures multiple frequency domain descriptors of the waveform that are sensitive to calcification-induced hemodynamic alterations.

Both the laboratory-based panels and the PW-FDFs approach are intentionally simple, reproducible, and potentially inexpensive. These characteristics make them suitable as pre-screening/screening tools in routine clinical settings. Crucially, these multivariate, multimodal data sources align naturally with machine learning (ML) methods that can combine weak but complementary signals into robust predictors; the next section outlines the ML concepts and rationale behind the frameworks used in this thesis.

Table 1.2: Summary of major VC detection methods: ability to distinguish intimal vs medial calcifications, pros and cons with respect to screening-fit.

Method	**Distinguishes iVC vs mVC?**	**Advantages**	**Disadvantages**
Histopathology (arterial biopsy)	Yes	Gold standard - definitive identification of layer and microstructure.	Highly invasive; unsuitable for routine diagnosis and screening.
IVUS / OCT / OFDI	Yes (in most cases)	Very high resolution; good concordance with histology; distinguishes iVC and mVC when no overlapping is present.	Invasive, resource-intensive, and costly; unsuitable for routine diagnosis and screening.
Non-contrast CT (Agatston)	No	Quantitative, non-invasive, reproducible; good for total coronary artery calcification assessment.	Ionizing radiation, limited availability; no layer discrimination; low microcalcification sensitivity; suitable for CAC screening when needed.
PET-CT (e.g. ^{18}F-NaF)	Partial	Detects early microcalcification activity; high-resolution enables capturing patterns of iVC and mVC; useful for research/targeted cases.	High cost; tracer and radiation; invasiveness; limited availability for routine screening.
Plain X-ray / Mammography	Partial	Cheap, widely available; mammography detects breast arterial calcification (BAC).	Low sensitivity for early disease; poor quantification and specificity; radiation; BAC limited only to women; not suitable for routine screening - can detect only advanced calcification.
Ultrasound	No	Radiation-free, portable; good for superficial or peripheral vessels.	Operator-dependent; limited penetration and standardization; modest sensitivity; not suitable for routine screening - can detect only advanced calcification.
Laboratory tests	No (potential for ML-based inference)	Minimally invasive, widely available, can be measured repeatedly for monitoring, may detect early biological changes preceding macroscopic calcification.	Investigational; most candidate biomarkers lack specificity and clinical validation for VC detection; no standardized biomarker panel yet; unknown cost-effectiveness; may be suitable for screening in the future after further investigation.
PW-based (e.g. PWV, PP, ABI)	No (potential for ML-based inference)	Non-invasive, inexpensive, reproducible; functional surrogate - reflects consequences of VC such as hemodynamic changes, most notably arterial stiffness.	Indirect measure; single markers have low specificity for calcification detection; thresholds vary by population; suitable for routine screening when inference is improved.

Abbreviations: VC, vascular calcification; iVC, intimal vascular calcification; mVC, medial vascular calcification; IVUS, intravascular ultrasound; OCT, optical coherence tomography; OFDI, optical frequency-domain imaging; CT, computed tomography; PET, positron emission tomography; CAC, coronary artery calcification; ML, machine learning; PW, pulse waves; PWV, pulse wave velocity; PP, pulse pressure; ABI, ankle-brachial index.

1.4 Data-driven machine learning models in clinical practice

Machine learning has attracted considerable interest because it can uncover complex, multivariable relationships that are not immediately apparent from conventional analyses. Although its main goal is to automate processes, its application is far from automatic and requires a deep understanding of this domain. A responsible use of ML methods requires much more than simply selecting an algorithm (conventionally referred to as a model) and providing it with data - every algorithm encodes particular mathematical assumptions (such as linearity, independence, smoothness, or stationarity) that must be met or at least considered [60]. Neglecting these principles or failing to address the issues of data quality and model validation risks in its misspecification, overfitting (i.e., the algorithm learns patterns specific to the training data and cannot generalize well), and misleading conclusions.

1.4.1 Principles of machine learning in classification tasks

Building a robust ML classification pipeline can be broadly divided into three stages: data preparation, model development (algorithm selection, training and evaluation), and model validation. Each of these stages presents unique challenges in medical applications, where datasets are often small, heterogeneous, and prone to bias [61, 62].

Data preparation

The foundation of any machine learning pipeline is careful data preparation. In clinical studies, acquiring the data itself can pose significant challenges, such as obtaining ethical approval and recruiting enough patients. Once acquired, the dataset must be examined for quality, consistency, and completeness [63]. A key early step is defining the target variable, which denotes what the model is expected to predict, along with a set of candidate predictors, i.e., features which may potentially influence the target's value.

Once the dataset is gathered, an initial exploratory analysis should be conducted, which can examine univariate associations between predictors and the target to gain initial insights and data understanding. Ultimately, predictive modeling requires handling noise, outliers, and missing values [64]. The latter poses a major challenge: depending on the extent and pattern of missingness, entries may be imputed using statistical or model-based methods, or observations may be excluded. This choice requires a balance between maximizing sample size and minimizing bias.

Clinical expertise can be incorporated at this stage through domain-informed feature engineering, such as transforming variables or explicitly modeling biologically plausible interactions. Variable selection is another critical task. It may be expert-driven, algorithmic (e.g., filter methods, wrapper methods), or embedded within the predictive model itself, as is the case with LASSO or decision trees [65]. The analyst must balance parsimony (simpler, interpretable models) with the possibility that complex, multivariate interactions carry predictive value that cannot be captured by intuition alone [64].

Algorithm selection and model training

The choice of an algorithm depends on several factors, including dataset size, predictor characteristics, class balance, interpretability, and computational feasibility [64]. The issue of an imbalanced target variable (when one of its values is significantly under-represented compared to the other), which is a frequent scenario in clinical data, must be addressed using re-sampling techniques, class-weight adjustments, or algorithmic modifications to prevent biased predictions [64].

Equally important is aligning the choice of algorithm with the study's goals. Broadly, algorithms can be employed for exploratory purposes (to uncover associations and interactions) or for predictive performance [66, 64]. In medical applications, these goals often coexist: clinicians not only want to know how well a model performs, but also why it produces a given result. Black-box predictions may face resistance if they cannot be explained to clinicians and patients.

A wide range of supervised learning classification methods (relying on the true labels while training) is available, each with advantages and limitations:

- Generalized linear models (e.g., logistic regression, LASSO) remain widely used for their transparency and ability to quantify the contribution of predictors [65].
- Tree-based methods (e.g., decision trees, random forests) can capture complex, non-linear interactions, though interpretation is less direct and often requires post-hoc tools [64].
- Kernel-based methods such as support vector machines (SVM), and other regularized linear schemes (e.g., relaxed linear separability, RLS [67]) offer strong predictive performance in certain settings, particularly with high-dimensional data [65].
- Neural networks, the most complex algorithms in the list, can model highly non-linear patterns and are particularly effective for rich data types (imaging, signals), but are typically considered "black-boxes" and require dedicated interpretability techniques [64].

The above methods represent only a small subset of available approaches; many other frameworks are in active use and development. Thus, algorithm selection should be guided by the tackled problem, data structure, study aims, and the balance between predictive performance and interpretability [65]. Deployment simplicity should also be considered.

While this thesis primarily utilizes supervised classification, unsupervised methods (ignoring labels while training), such as clustering or dimensionality reduction, can provide valuable insights by uncovering hidden structures, identifying patient subgroups, or generating new features to enrich supervised models [65]. They can also be used as a missing data imputation tool, which was applied in my first research [P1].

Performance evaluation

An integral component of any ML pipeline specification is the selection of a metric used to assess the quality of the results produced by the trained algorithm. This process is often referred to as a performance evaluation. The choice is not trivial,

as different metrics capture different aspects of model behavior, and they should be tailored both to the specific task and to the characteristics of the dataset used in the study. In most clinical classification tasks, including those presented in this thesis, true labels are known and can therefore serve as a reference for evaluating the model's predictions.

Simple scalar measures are often used to quantify specific aspects of a classifier's performance. Examples include the already discussed sensitivity and specificity, or accuracy, which reflects the overall proportion of correctly classified observations [65]. More informative composite measures are also common, such as the F-score, which integrates both sensitivity and specificity into a single value. Evaluation can also take a visual form, for instance, through inspection of predicted probability distributions or the receiver operating characteristic (ROC) curve, which illustrates the trade-off between sensitivity and specificity across different thresholds [64].

It needs to be highlighted that the chosen evaluation metric must adapt to the underlying data distribution. In highly imbalanced datasets, for example, accuracy may misleadingly suggest good performance even when all observations are assigned to the majority class. In such contexts, metrics that explicitly assess the discriminatory power of the model, such as sensitivity and specificity (or their derivatives) are more appropriate [64].

However, the quality of results is not always reducible to the ability to separate classes alone. Depending on the application, alternative metrics may be more appropriate. For example, in my first study [P1], I used the incremental cost-effectiveness ratio (ICER), which incorporates not only the predictive power of the classifier but also the cost of the predictors used to produce the results, thus aligning the statistical evaluation with the practical goal of cost assessment. It is a common situation to encounter multiple algorithms with comparable conventional performance metrics. In such cases, additional criteria, such as cost-effectiveness, ease of implementation, or clinical interpretability, become crucial for guiding the choice of which model should be prioritized for further development.

It is also important to note that metric selection plays a critical role not only in the evaluation phase but also in model development. Many algorithms, such as LASSO or random forests, require hyperparameter tuning [65]. The primary metric chosen to guide this process directly determines which parameter set is considered optimal, and thus shapes the final model [65]. Therefore, selecting the right evaluation criteria is a fundamental and scenario-specific decision, with implications throughout the entire modeling process.

Model validation

Validation is critical to determine whether a model generalizes beyond the data it was trained on. Validation can be *internal* (on data from the same source, but not seen by the model) or *external* (on independent data, ideally from a different cohort or institution) [62]. In clinical applications, external validation is the gold standard for demonstrating robustness, though proof-of-concept studies may initially rely on internal validation only. Conventional practice involves splitting data into training and testing sets [65]. On the training set, the model learns associations, and performance is then evaluated on the test set. If results are consistent across both, confidence increases that the model will perform similarly on new patients. However, a limited sample size often precludes this approach. In such cases, resampling strategies such

as k-fold cross-validation provide more efficient use of available data [65]. Here, the dataset is partitioned into k subsets, and the model is trained repeatedly, each time leaving one subset for testing. Performance is then averaged across folds. A special case is leave-one-out cross-validation (LOOCV), in which each observation is left out once, producing the most data-efficient but computationally intensive approach [65]. In this method, the model's performance is evaluated on a vector of the predictions made up from the left-out observations.

An important subtlety arises when feature selection or preprocessing is performed: to avoid data leakage, all such steps must occur within each fold using only training data. This means that across folds, different features may be selected and model coefficients may vary. In such cases, cross-validation evaluates the *framework* (i.e., the overall procedure of preprocessing, selection, and modeling) rather than a single fixed model. In practice, once a framework has demonstrated stable performance, a final model is retrained on the entire dataset for potential deployment. This is the standard approach implemented in widely used software frameworks (e.g. *glmnet*, *caret*) and the inferences about the selected features, their importance, and the model's parameters are made from the model retrained on the whole dataset [68, 69]. Consequently, the reported coefficients and selected variables represent this final, retrained model, which may differ slightly from the features selected in individual folds due to sampling variability. In my work, I have followed this approach as well. First, I evaluated the performance of the tested frameworks using LOOCV, and in the case of robust predictions, I employed the frameworks on the entire dataset to make inferences about the selected features, their importance, and fitted parameters.

In addition to discrimination, calibration is an important property of predictive classification models: a well-performing classifier should not only separate cases from controls but also assign probabilities that reflect true clinical risk [64]. This step, however, was not applied in the present work. With the limited dataset available, adding a separate calibration model could have introduced instability and overfitting, and my analyses focused on establishing the existence of a predictive signal. The successful demonstration of the model's discriminatory power achieves this primary goal. Calibration, alongside other engineering refinements required for a deployable clinical tool, remains an important avenue for future work.

Clinical translation

While the technical aspects of data preparation, algorithm choice, and validation are essential, the ultimate test of an ML framework in medicine is whether it integrates well into clinical decision-making. This requires not only accuracy and robustness, but also interpretability, cost-effectiveness, and reproducibility across populations. The methods explored in this thesis were therefore evaluated with these considerations in mind, aiming to identify approaches that balance predictive performance with practical feasibility for real-world vascular calcification screening.

1.4.2 Machine learning in vascular calcification detection

To date, several studies have explored the use of machine learning models for vascular calcification detection [59]. Most of these approaches have been image-based, relying on imaging techniques such as CT scans or X-rays, where ML was primarily employed to automate the interpretation of established diagnostic tests rather than

to enable novel screening strategies [70, 71]. CAC scoring remains the main focus, while investigations specifically addressing medial calcification are relatively scarce [72, 73]. Beyond imaging, ML has been applied to conventional cardiovascular risk factors to improve the prediction of elevated CAC levels [74], creating nomograms for total VC prediction [75], and more recently to the discovery of candidate calcification biomarkers using genetic data [76]. Collectively, these efforts underscore both the promise of ML in vascular research and its present limitations, with most applications still centered on image interpretation rather than on developing simple, scalable, and cost-effective screening tools. To the best of current knowledge, no prior study has examined pressure pulse wave signal properties as direct input for ML models for VC detection, apart from the occasional use of PWV in addition to other risk factors in CAC prediction frameworks [77]. This gap highlights the originality of approaches that leverage detailed pressure pulse wave features for ML-based detection of VC.

2

RESEARCH AIMS AND HYPOTHESES

The aim of my work was to address the need for clinically feasible and cost-effective methods for medial and intimal vascular calcification screening by proposing novel, data-driven frameworks tailored for individuals with chronic kidney disease. The thesis evaluates the potential of biomarker- and pressure pulse wave signal-based models for early detection of vascular calcification in CKD patients, thereby providing a basis for the future development of scalable, broadly accessible tools for cardiovascular disease risk stratification.

I have formulated three research hypotheses to accomplish the research objective:

(H1) Integrating cost-effectiveness assessment into the selection of machine learning models trained for medial vascular calcification detection in patients with advanced chronic kidney disease facilitates the identification of the most clinically relevant approaches.

(H2) A data-driven framework that integrates conventional vascular calcification risk factors with pressure pulse wave frequency-domain features (PW-FDFs) derived from non-invasive peripheral pulse wave measurements can be used to detect medial vascular calcification.

(H3) Statistical models based on pressure pulse wave frequency-domain features (PW-FDFs) can effectively identify end-stage renal disease patients with elevated coronary artery calcification scores.

In addition, I have established a set of detailed research questions corresponding to each of the hypotheses. Addressing these questions provides a structured approach to testing the hypotheses and strengthens the evidence supporting them.

(H1Q1) Do different machine learning methods applied to the same dataset yield substantially different sets of selected features while achieving comparable predictive accuracy?

(H1Q2) Can cost-effectiveness metrics help to discriminate between models with comparable predictive performance?

(H1Q3) How does the incremental cost-effectiveness ratio vary depending on the assumptions made?

(H1Q4) Is there a subset of features consistently selected across models, highlighting which predictors are most promising for future studies?

(H2Q1) How can the information from pressure pulse wave signal be incorporated as input to machine learning models?

(H2Q2) Can predictions from a model working with pulse wave - frequency domain features (PW-FDFs) yield clinically relevant accuracy?

(H2Q3) Does the model incorporating both PW-FDFs and traditional mVC risk factors achieve superior performance in medial vascular calcification detection among patients with end-stage renal disease, compared to model using conventional risk factors alone?

(H3Q1) Can pressure pulse wave measurements obtained at different arterial sites, once transformed to the central waveform, be used to extract PW-FDFs that reliably predict elevated CAC scores?

(H3Q2) To what extent do time-domain features of the central pressure pulse wave contribute to the prediction of elevated CAC scores?

(H3Q3) Does the model trained with PW-FDFs achieve superior performance compared to conventional vascular calcification risk factor–based approaches in specific age groups?

(H3Q4) Does the model trained with PW-FDFs have the potential to differentiate between the patients with various extents of CAC?

Verification of the formulated research hypotheses has resulted in the publication of three journal articles, which together form the foundation of my thesis [P1, P2, P3]. Each article corresponds to one of the research hypotheses. Accordingly, the following three chapters are structured around these publications: each chapter provides a detailed introduction to the scientific background of the study, explains how my work aligns with the research aims, and discusses how the obtained results support the corresponding research hypothesis.

3

COST-EFFECTIVENESS OF BIOMARKER PANELS IN MEDIAL VASCULAR CALCIFICATION SCREENING

3.1 Medial vascular calcification

3.1.1 Clinical implications

Medial vascular calcification, also known as Monckeberg's arteriosclerosis, is primarily associated with aging and diabetes, and is particularly common in ESRD due to the altered mineral metabolism in this group of patients [30, 78]. In CKD it is also positively associated with the duration of hemodialysis [30] and the severity of kidney function's loss [79].

mVC is most frequently detected in the peripheral arteries of the lower extremities [80] but can be present in nearly all arterial territories, including upper limb [81], aorta [82], mammary [83], temporal [84], and, in rare cases, coronary arteries [85]. Moreover, it can develop simultaneously in several vascular regions [86, 87]. The assessment is usually performed in a selected arterial site, and the extent of mVC can be classified into stages depending on its severity. The categories are typically marked from 0, denoting being free from calcification, up to 4, denoting massive calcification [88, 89].

mVC affects the middle layer of the arterial wall and does not block the arterial lumen; therefore, at first, it was not considered to be clinically significant [35, 39]. This view started to change when arterial medial calcification presence was proved to be a strong marker of future cardiovascular risk in diabetic patients [90]. Since then, multiple studies have shown that mVC is a strong independent predictor of all-cause and cardiovascular mortality, especially in the CKD population [30, 88]. This association is attributed to mVC-induced arterial stiffening, which reduces arterial compliance [80]. The severity of stiffening closely correlates with the extent of medial calcification, and higher degrees of calcification have been linked to an increased risk of all-cause mortality [30, 91, 92, 55, 88, 93].

Multiple clinical studies have found that patients with higher medial calcification scores in the lower extremities are at significantly increased risk of chronic limb-threatening ischemia (CLTI) and major limb amputation [94, 95]. For example, a recent multi-center study showed that higher mVC scores assessed in feet using X-rays were associated with higher rates of major limb amputation within six months among patients with CLTI [96].

Another condition affecting the limbs is peripheral artery disease (PAD), which involves occlusion or narrowing of the upper and lower extremity arteries, causing insufficient blood flow. As a consequence, patients suffering from PAD are highly predisposed to cardiovascular morbidity and mortality [97]. Although mVC is not necessarily indicative of PAD, the co-incidence is common [85, 98]. The exact prevalence of mVC in PAD is imprecisely reported because of the methods by which diagnosis is reached, as well as asymptomatic cases that are often unreported [99, 97]. However, it is worth noting that in the data from the CKD Prognosis Consortium, out of all studied adverse cardiovascular outcomes of CKD, PAD is associated with the highest relative risk in ESRD in comparison to patients with a proper renal function [25]. It cannot be ruled out that it is because of the prevalent co-occurrence of mVC in PAD.

3.1.2 Detection

While it has been shown that mVC incidence increases with CKD stage [79], the true prevalence of mVC in the CKD population remains unknown, as it varies across studies and arterial sites [100]. This uncertainty is mainly associated with the lack of accessible and reliable diagnostic tools. As a result, mVC is often detected incidentally or misdiagnosed as atherosclerosis, due to the difficulty in distinguishing between medial and intimal calcification. Consequently, many studies report the total burden of vascular calcification without differentiating between these two forms, despite their distinct pathophysiological and clinical implications.

Below, the most popular techniques for mVC detection are described. Other, less frequently used tools, are discussed in detail in [58].

Invasive techniques

The most reliable method for mVC assessment is histopathological examination of arterial biopsies performed by pathologists. However, this approach is highly invasive and therefore impractical for clinical use or utilization in large-scale research. For this reason, histological assessments are typically limited to studies involving patients undergoing other surgical procedures, such as kidney transplantation, or to post-mortem analyses [88, 101].

Other invasive techniques with high sensitivity include intravascular ultrasound (IVUS) or optical frequency domain imaging (OFDI), which utilize a catheter with a tiny ultrasound transducer inserted into an artery, and optical coherence tomography (OCT), requiring intracoronary injection of contrast media [102]. These methods provide high-resolution images of the arterial wall, allowing for assessment of calcification based on depth and arterial layer. Their diagnostic accuracy is highest when medial and intimal calcifications do not overlap - under such conditions, their sensitivity can exceed 80% [102]. Nevertheless, the invasiveness significantly limits their use in both clinical practice and research.

Minimally invasive imaging techniques

Due to the limitations of highly accurate but impractical, invasive procedures, non-invasive imaging techniques have been widely adopted in mVC research. Computed tomography (CT), although commonly used, is generally considered unreliable in differentiating between medial and intimal calcification [39]. However, several scoring

systems have been recently developed based on characteristic calcification patterns in specific vascular beds, such as the carotid artery [103] and lower limb arteries [104]. Typically, iVC appears as patchy, thick, irregular, and dot-like, whereas mVC tends to be more continuous, regular, thin, and tube-like. While the CT-based detection offers some utility, it demonstrates moderate accuracy when compared with histological findings. A related approach involved the use of full-body PET-CT imaging to identify the morphological patterns across multiple vascular territories simultaneously [105], which is a distinct advantage in terms of systemic assessment.

Conventional radiography is frequently used as a proxy for advanced mVC detection. Circumferential or "pipe-stem" calcification patterns indicate mVC, in contrast to the more irregular and patchy appearance of iVC [30]. While limited by sensitivity, particularly in earlier pathology stages, this approach is simple and widely accessible, typically used for assessing calcification in lower limbs [30]. A more specific radiographic technique, mammography, can detect breast arterial calcification in female patients and is considered a potential indicator of mVC, given that mammary arteries are usually free of atherosclerotic lesions [83, 106].

Among other imaging techniques, ultrasound should be noted. It showed greater effectiveness in mVC detection in comparison to radiography, especially in mild calcification stages [107]. Nevertheless, its sensitivity is still rather poor, making it rarely used in clinical research.

Functional and hemodynamic surrogates

Given the mVC's contribution to arterial stiffening, hemodynamic measurements have been widely explored as potential screening tools. Among them, the ankle-brachial index (ABI), defined as the ratio of the highest systolic blood pressure at the ankle to that at the brachial artery, has been frequently utilized as a surrogate marker for mVC detection. An ABI > 1.4 was interpreted as indicative of medial calcification. However, subsequent studies have demonstrated that elevated ABI alone is insufficient as a diagnostic marker, and conclusions about mVC based solely on ABI may significantly underestimate the true associations between mVC and cardiovascular outcomes [108]. However, it is important to acknowledge that in the cited research, mVC was assessed using CT-based scoring methods [103], which themselves are not definitive; therefore, the results should be interpreted with caution.

Pulse wave velocity offers another indirect measure reflecting arterial stiffness. Since stiffness increases with the extent of medial calcification, PWV can serve as a surrogate for mVC burden. Carotid-femoral PWV is considered the gold standard for central arterial stiffness assessment, with a threshold of 10 m/s commonly used to indicate significantly stiffened arteries. Nevertheless, it has been emphasized that a single threshold may not be appropriate for all subpopulations, particularly those differing in age or underlying pathology [109].

Laboratory biomarkers

Finally, laboratory biomarkers have been investigated as potential tools for identifying patients at risk for mVC [110]. The multifactorial nature of mVC pathogenesis suggests a broad range of potential biological indicators. Multiple single biomarkers have been tested [111], including fetuin A, pyrophosphate, fibroblast growth factor 23, osteopontin, osteoprotegerin, and matrix Gla protein, but only a few studies have

attempted to evaluate combinations of markers comprehensively [73]. Moreover, various biomarkers generate different costs of testing, and their cost-effectiveness remains to be evaluated. The development of a reliable biomarker set remains a major research priority, as early identification of at-risk individuals could open a window for preventive intervention [112]. Furthermore, laboratory testing yields structured, quantitative data that are well-suited for machine learning frameworks. Building on previous studies that evaluated a limited number of biomarker panels using only a few modeling approaches, in the first part of my research, I expanded this line of investigation by exploring a broader range of ML frameworks for mVC detection and assessing the cost-effectiveness of multiple biomarker combinations.

3.2 My work

3.2.1 Laboratory biomarkers as input to machine learning frameworks

Several studies have investigated the relationship between serum biomarkers and medial vascular calcification [110]. Individual markers such as osteoprotegerin, matrix Gla protein, copeptin, and sclerostin [110, 113, 114] have each been independently associated with mVC. While identifying such associations is an important first step, the next challenge lies in understanding how biomarkers interact with one another. This is relevant not only from a diagnostic perspective, where combining multiple biomarkers may improve pathology detection, but also from an economic standpoint. If two biomarkers convey overlapping information, as reflected by strong correlations or predictable physiological relationships, measuring both may be inefficient, especially if one is considerably more costly. In real-world data, however, these relationships are often complex: a relatively expensive biomarker may potentially be approximated by a combination of several cheaper ones, which could substantially improve cost-effectiveness. Identifying such patterns usually exceeds the capabilities of conventional statistical analyses, but can be addressed more effectively with advanced machine learning techniques.

From a health-economic perspective, the most useful screening tool is not necessarily the one with the highest predictive accuracy, particularly when performance differences between the competing models are small. In such cases, cost considerations may play an equally important, if not decisive, role. Different machine learning frameworks frequently select distinct subsets of features, as demonstrated in [73], where two algorithms produced markedly different sets in both composition and size. Yet, despite this variability, model evaluation in clinical studies has traditionally focused almost exclusively on predictive performance, with little attention given to the trade-off between accuracy and utilization cost.

These observations motivated me to evaluate machine learning models from a dual perspective: not only in terms of predictive performance, which is critical in clinical applications, but also in terms of cost-effectiveness of the produced predictions, which is equally important for assessing the feasibility of clinical implementation. To achieve this, I employed the incremental cost-effectiveness ratio (ICER) as a comparative metric to integrate predictive performance with economic considerations and to guide model selection.

3.2.2 ICER: incremental cost-effectiveness ratio

Evaluating the trade-off between accuracy and utilization cost of competing machine learning models belongs to the broader field of health economics, which addresses the efficiency, effectiveness, and cost of healthcare interventions [115]. The primary goal of health economics is to optimize the allocation of limited resources in order to maximize health gains for the population [116].

One of the main types of health economic evaluation is cost-effectiveness analysis [117]. It compares two or more healthcare strategies in terms of their relative costs and outcomes, with the latter typically measured in natural units such as life-years gained. In my research, I employed a particular cost-effectiveness metric, the incremental cost-effectiveness ratio [118]. In its standard definition, it is given by:

$$\text{ICER} = \frac{C_1 - C_0}{E_1 - E_0} \tag{3.1}$$

where C_1, C_0 are the costs and E_1, E_0 are the effects of the new intervention and comparator, respectively. Therefore, the numerator represents the incremental cost, while the denominator reflects the incremental effect. This formulation is most commonly used to compare two alternative medical strategies.

However, in the context of mVC detection, no routine screening method currently exists. It is therefore appropriate to adopt a "do-nothing" comparator [115], where both C_0 and E_0 equal 0. Under this assumption, ICER simplifies to:

$$ICER = \frac{C_1}{E_1} \tag{3.2}$$

where C_1 is the cost of performing the screening procedure and E_1 represents the expected health benefit. This adjustment is further justified by the fact that my primary goal was to compare the cost of inputs to multiple machine learning frameworks; subtracting a constant baseline cost or effect would not have altered their relative ranking.

I additionally adapted the ICER formulation to reflect its specific role within the evaluation pipeline. In particular, I assumed that any positive case identified by the method based on a machine learning framework would require confirmatory imaging, incurring additional costs. However, I did not include the cost of subsequent medical intervention after diagnosis, as this would be identical regardless of the screening approach and therefore would not influence the comparative evaluation of the frameworks. Consequently, the ICER used in my work quantifies the cost of screening relative to the quality-adjusted life years gained and was calculated as follows:

$$ICER = \frac{\text{measure\_cost} + [\text{prevalence} \cdot TPR + (1 - \text{prevalence}) \cdot FPR] \cdot \text{ct\_price}}{\text{prevalence} \cdot TPR \cdot \text{years\_gained}} \tag{3.3}$$

where:

- measure_cost - total cost of biomarker evaluation per patient,
- prevalence - true prevalence of mVC in the advanced CKD population,

- TPR - true positive rate of the screening model,
- FPR - false positive rate of the screening model,
- ct_price - cost of confirmatory PET-CT scan for mVC,
- years_gained - expected number of QALYs gained through earlier detection. The QALY is a summary measure that incorporates both improvements in life expectancy and quality of life, and is a standard metric for evaluating the benefits of healthcare interventions [115].

Several of these parameters, i.e., prevalence, years_gained, and cost estimates, are uncertain. For this reason, I calculated and reported ICER results across a range of assumed parameter values to explore different clinical scenarios. In addition, sensitivity analyses were performed to examine the influence of varying biomarker costs on the resulting ICER values.

3.2.3 Research overview

Introduction

The assessment of circulating biomarkers is a well-established approach in health evaluation, and many screening strategies across different diseases are based on their measurement [119]. For this reason, I initially considered this method for the screening of medial vascular calcification.

Given the complex physiological mechanisms underlying vascular calcification, it is highly unlikely that a single biomarker could serve as a reliable indicator of its presence. Therefore, studies investigating panels of phenotypic biomarkers as potential indicators of mVC are of particular importance [73]. However, when coupled with machine learning techniques, the choice of the algorithm strongly influences the results of such analyses, not only in terms of predictive accuracy but also in the subset of features selected. This raises the question, how to select a classifier detecting mVC that is not only accurate but also clinically feasible.

To address this issue, I concluded that the cost of biomarker acquisition should be explicitly incorporated into model evaluation, which is an aspect that, to my knowledge, had not previously been considered in this context. I proposed the use of the incremental cost-effectiveness ratio as an additional criterion for model assessment. Specifically, I developed a formula tailored for classifiers trained to detect mVC, as described in 3.2.2, which integrates the statistical performance of a classifier with the cost of the biomarkers it relies upon.

In the following publication, I present the results of a comprehensive analysis I performed in which several machine learning algorithms were trained for mVC detection and evaluated not only by conventional metrics but also through the proposed ICER-based framework.

Relation of the publication to the research aims of the thesis

A panel of phenotypic biomarkers, measured non-invasively or minimally invasively and used as input for machine learning models, has the potential to serve as a practical screening tool. This approach is clinically appealing, as many established

screening tests already rely on blood-based or similarly simple measurements, making such a concept readily translatable into clinical practice. Detecting medial vascular calcification in particular is clinically valuable, as it provides refined stratification of patients at risk of adverse cardiovascular outcomes. In my first publication, I addressed two key aspects of a screening tool development: its cost-effectiveness and clinical feasibility. I demonstrated that different machine learning frameworks for mVC detection, when applied to the same dataset, selected markedly different sets of predictive features. The largest feature set contained more than four times as many predictors as the smallest, yet predictive performance across models was broadly comparable, with no single approach consistently outperforming the others across all evaluation metrics (H1Q1). This finding underscored the challenge of feature selection and the need for additional criteria to guide model choice.

To address the limitations of purely statistical evaluation, I introduced the incremental cost-effectiveness ratio as an additional criterion for model assessment, adapting its formula to the context of mVC screening. This addition provided a more decisive basis for model selection (H1Q2). Specifically, it revealed that logistic regression, despite its simplicity and use of the smallest feature set, achieved the most favorable balance of predictive performance and cost-efficiency quantified through ICER. Sensitivity analyses further confirmed the robustness of this finding, showing that the conclusions remained valid despite changes in cost assumptions (H1Q3). Apart from the assessment of cost and availability of the analysed circulating biomarkers, I also provided a detailed example of how cost-effectiveness may change depending on the threshold used for testing purposes on the example of results obtained using the logistic regression model (H1Q3).

Finally, I also examined the clinical interpretability of the models by analyzing patterns of feature selection. While each framework selected different subsets of predictors, certain biomarkers were consistently chosen across multiple models, suggesting a core set of promising candidates for future research (H1Q4). These findings not only highlight that the choice of modeling framework can substantially influence which predictors are selected but may also provide a foundation for prioritizing features with the greatest clinical relevance.

Conclusions

Taken together, this publication supports my research aims by analysing the cost-effectiveness of a phenotypic feature-driven approach to the screening of medial vascular calcification. Specifically, this research supports my first hypothesis (H1). It demonstrates that, through ICER calculation, cost-effectiveness assessment can be successfully integrated into the selection of machine learning models trained for mVC detection in patients with advanced CKD, and this approach facilitates the identification of the most clinically relevant frameworks. My work addresses a gap in the literature regarding the economic evaluation of ML models for mVC detection, a perspective that has been largely absent not only in studies applying ML to phenotypic biomarker-based mVC detection but also in many other clinical investigations. Consequently, I believe that the exploration of this aspect will not only strengthen the feasibility of data-driven solutions in mVC identification but also promote the broader adoption of cost-effectiveness evaluation of ML models aimed to be used in clinical practice.

3.3 The publication (P1)

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Balancing accuracy and cost in machine learning models for detecting medial vascular calcification in chronic kidney disease: a pilot study

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Machine learning algorithms that integrate multiple biomarkers are increasingly used in disease detection, yet economic considerations are often overlooked. Medial vascular calcification (mVC), a pathology associated with elevated cardiovascular risk in chronic kidney disease (CKD), requires cost-effective diagnostic approaches. This pilot study evaluated the cost-effectiveness of machine learning models for mVC detection using traditional risk markers and circulating biomarkers in 152 CKD patients undergoing living donor kidney transplantation. Patients were classified as having no/minimal ($n = 93$) or moderate/extensive ($n = 59$) mVC. Five classification frameworks with automatic variable selection identified predictors of mVC. Age and copeptin were selected by all algorithms, while diabetes, male sex, choline, and osteoprotegerin were chosen by four methods. The number of features selected ranged from 5 to 21. Although accuracy differences among classifiers were limited to 3%, models using more features nearly tripled the procedure's cost. By incorporating the incremental cost-effectiveness ratio, the study highlighted significant disparities in performance versus cost among classifiers. The present findings suggest that machine learning has the potential to complement imaging techniques for mVC detection and uncover novel biomarkers. However, modest performance improvements may not justify higher costs, underscoring the importance of considering cost-effectiveness when selecting classification models.

Keywords Classification, Feature selection, Medial vascular calcification, Chronic kidney disease, Incremental cost-effectiveness ratio

Medial vascular calcification (mVC) is a pathological condition, with estimated prevalence rates ranging from 27 to 80% in the chronic kidney disease (CKD) population[1–3]. The pathology contributes to the high cardiovascular morbidity and mortality in this group of patients[4,5]. Moreover, a recent study has revealed that it is associated with the progression of CKD[6]. While the pathogenesis of mVC is not fully understood and a causal therapy is not available as of today, new therapeutic possibilities are currently being studied[7–10]. Moreover, the feasibility of slowing down mVC progression in patients with CKD has been demonstrated[11,12]. Therefore, improved methods for mVC detection, especially at early stages, is highly warranted.

At present, there is a lack of a dedicated and reliable method of mVC assessment in clinical practice[2,13,14]. Invasive techniques such as artery biopsy[15] or transcutaneous ultrasound[16] are rarely performed and cannot be considered as screening procedures. Both direct semi-quantitative methods such as computed tomography, plain X-rays, or ultrasound[13], and indirect methods such as measurement of pulse wave velocity that reflects

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increased arterial stiffness in calcified arteries[17,18], are not always available and not easy to perform; therefore, the presence of mVC is likely underestimated. Moreover, currently used tools struggle to differentiate between the two types of vascular calcification: medial and intimal[19–21]; this is clinically significant, as these types have distinct implications and require different patient care strategies. Recently, a method enabling this differentiation, involving the identification of mVC patterns on PET-CT scans, has been introduced[22]. Nonetheless, the expense and limited availability of PET-CT scans highlight the need for an approach that can indicate the presence of mVC and readily determine which patients truly require this imaging technique.

Machine learning algorithms, which are designed to detect patterns in data, are thought to have the potential to radically improve our ability to diagnose and treat diseases. The large number of potential mVC markers complicates mVC diagnosis and statistical feature selection procedures may therefore play a crucial role in establishing future diagnostics. In previous studies, numerous biomarkers have been linked with vascular calcification including serum biomarkers[23], vitamin-K dependent proteins[24], various phenotypic features[25,26] and risk factors such as high age, male sex, and diabetes mellitus[20]. While models for mVC detection have demonstrated promising performance quality[25], the variability in their cost-effectiveness across different frameworks remains unexplored.

In a clinical setting, besides evaluating the statistical performance of the newly introduced methods, their overall applicability is a crucial consideration. This covers factors such as the procedure's availability, safety, and the overall expense of the diagnostic procedure. One of the indicators that can characterize the latter is the incremental cost-effectiveness ratio (ICER) which provides insights into the method's cost in relation to the potential benefits for patients[27].

The objective of this pilot study was to investigate the cost-effectiveness of various machine learning frameworks for mVC detection in the chronic kidney disease population. For each of the tested models, in addition to conventional classification correctness metrics, ICER was calculated to incorporate both performance and cost considerations into evaluation. The most favorable model in terms of ICER was further investigated to showcase its possible clinical utility. Finally, we discussed possible pathophysiological associations between mVC and the variables selected by the applied algorithms.

Methods

Data investigation, model building process, and performance evaluation were implemented in R version 4.0.5 and Python version 3.7.

Patients and study design

In this retrospective study, a cohort of patients with advanced CKD undergoing living donor kidney transplantation at Karolinska University Hospital was included. The study's eligibility criteria aligned with those established for patients eligible for kidney transplantation. Exclusion criteria were age under 18 years and unwillingness to participate in the study. The clinical procedures and protocol of measurements were described previously[28]. The patients gave their informed consent for all performed procedures. The study was approved by the regional ethical review board in Stockholm and adhered to the Declaration of Helsinki.

The participants were classified into two groups according to the extent of medial calcification in inferior epigastric artery biopsies assessed by an experienced pathologist. '*Group 0*' included patients with *no* and *minimal* signs of VC ($n = 93$), whereas patients having *moderate* and *extensive* signs of VC were classified into '*Group 1*' (n = 59). The procedure of histological mVC examination was presented in detail in[25,28].

The dataset consisted of 60 features in 152 patients. All 60 features were available in 71% of the patients; in total, 8.3% of the data were missing. The full data flow is described in[25]. The dataset included demographic and clinical data, circulating biomarkers, body composition and anthropometric measurements, and skin content of advanced glycation end products measured by autofluorescence. The investigated features are presented in Table 1.

Data preprocessing

First, we standardized the predictors proportionally within the range from 0 to 1. Missing values imputation was performed using the k-nearest neighbors algorithm with k = 3 and Euclidean distance measure between the patients. mVC, as an outcome variable, was not involved in the imputation process. The distributions of the imputed and non-imputed variables did not exhibit statistical differences (Kolmogorov-Smirnov and Chi-square test for continuous and discrete distributions, respectively). Feature selection and patient classification were performed on the complete, standardized set of variables, while the univariable analysis was performed on the raw data.

Data investigation

To choose the appropriate feature selection and classification algorithms, a preliminary data investigation was conducted. Firstly, the Spearman rank correlation coefficient was used to reveal interdependencies between the analyzed features. Categorical variables (sex, smoking, and diabetes mellitus) were excluded from the analysis. Secondly, logistic regression was carried out to assess the interrelationship between a single feature and mVC. To account for multiple comparisons, p-values were adjusted using Benjamini-Hochberg correction[29].

Methods of feature selection and patient classification

In the process of feature selection and patient classification, the following methods were applied: logistic regression with forward Akaike feature elimination process (LR)[30], support vector machine with recursive feature elimination (SVM)[31], random forest with permutation importance (RF)[32], logistic regression with elastic net penalty (EN)[33,34], and, less explored, relaxed linear separability method (RLS)[35].

Feature	Median [IQR] ornumber (%)	Univariable logistic regression OR (95% CI), *p*-value[a]	*P*-value adjusted[b]
Clinical and demographic			
Age, years	46 [32–56]	**4.14 (2.08–8.48), < 0.001**	**< 0.001**
Diabetes mellitus	14 (9%)	NA[c)]	
Mean arterial blood pressure (meanBP), mmHg	103 [93–111]	1.10 (0.57–2.12), 0.77	0.94
Sex, male	100 (66%)	**3.44 (1.63–7.73), 0.002**	**0.03**
Smoker	63 (41%)	1.59 (0.80–3.18), 0.19	0.54
Biomarkers			
Albumin, g/L	35 [33–38]	0.79 (0.41–1.52), 0.48	0.78
Alkaline phosphatase (ALP), U/L	66.2 [51.7–85.1]	1.48 (0.77–2.86), 0.25	0.57
Angiopoietin 2, pg/mL	4368 [3353–5987]	**2.17 (1.08–4.44), 0.03**	0.17
Apolipoprotein A1 (ApoA1), mmol/L	1.38 [1.19–1.56]	0.68 (0.35–1.31), 0.25	0.57
Apolipoprotein B1 (ApoB1), mmol/L	0.87 [0.72–1.04]	0.91 (0.47–1.76), 0.79	0.94
Betaine, µmol/L	43.0 [29.0–63.0]	1.36 (0.68–2.72), 0.39	0.70
Bone alkaline phosphatase (BALP), µg/L	16.40 [11.3–25.5]	1.06 (0.55–2.03), 0.87	0.99
Calciprotein particles (CPPs), nm	57,170 [23221–134954]	1.00 (0.46–2.16),1.00	1.00
Calcium, mmol/L	2.28 [2.18–2.41]	0.86 (0.45–1.66), 0.66	0.90
Carboxylated osteocalcin (GlaOC), ng/mL	35.9 [19.8–67.3]	0.69 (0.35–1.33), 0.27	0.57
Carboxy-terminal collagen crosslinks (CTX), pg/mL	1.88 [1.00–3.38]	0.79 (0.39–1.60), 0.52	0.78
Cholesterol, mmol/L	4.4 [3.8–5.1]	0.69 (0.36–1.33), 0.27	0.57
Choline, µmol/L	94 [77–115]	**2.03 (1.01–4.13), 0.047**	0.22
Copeptin, pg/mL	386 [312–490]	**2.96 (1.47–6.12), 0.003**	**0.04**
Desphospho-uncarboxylated MGP (duMGP), pmol/L	1323 [948–1687]	**2.20 (1.07–4.62), 0.03**	0.17
Fibroblast growth factor 19 (FGF19), pg/mL	126 [67–194]	0.56 (0.28–1.09), 0.09	0.32
Fibroblast growth factor 23 (FGF23), pg/mL	4055 [1634–14998]	1.18 (0.62–2.28), 0.62	0.88
Folate, ng/mL	11.0 [8.8–16.0]	0.59 (0.29–1.20), 0.15	0.48
Free thyroxine (fT4), pg/mL	14.4 [13.3–16.7]	1.13 (0.59–2.19), 0.71	0.92
Free triiodothyronine (fT3), pg/mL	3.29 [2.57–3.94]	0.72 (0.37–1.39), 0.33	0.66
Hemoglobin, g/L	114 [105–121]	1.04 (0.50–2.14), 0.92	0.99
High-density lipoprotein (HDL), mmol/L	1.35 [1.10–1.60]	0.68 (0.35–1.30), 0.25	0.57
High sensitivity C-reactive protein (hsCRP), mg/L	0.72 [0.31–2.10]	**2.07 (1.07–4.07), 0.03**	0.17
Homocysteine, µmol/L	36 [27–47]	1.91 (0.95–3.89), 0.07	0.27
Humanin, pg/mL	385 [358–421]	0.90 (0.43–1.85), 0.77	0.94
8-hydroxydeoxyguanosine (8-OHdG), ng/mL	0.21 [0.15–0.30]	1.36 (0.70–2.66), 0.36	0.68
IgM anti-MDA, U/mL	102 [67–139]	0.67 (0.33–1.37), 0.28	0.57
IgM anti-PC, U/mL	102 [69–130]	**0.45 (0.21–0.92), 0.03**	0.17
Insulin-like growth factor 1 (IGF1), ng/mL	236 [158–293]	**0.35 (0.17–0.72), 0.005**	**0.05**
Interleukin 6 (IL6), pg/mL	1.20 [0.52–2.01]	0.96 (0.48–1.94), 0.91	0.99
Interleukin 8 (IL8), pg/mL	5.41 [3.77–8.73]	1.28(0.64–2.54), 0.49	0.78
Klotho, pg/mL	399 [296–537]	1.06 (0.55–2.04), 0.87	0.99
Lipoprotein (a), (LPA), mg/L	122 [50–319]	1.29 (0.60–2.76), 0.52	0.78
Mmitochondrial open reading frame of the 12 S rRNA-c (MOTSc), ng/mL	178 [140–226]	0.71 (0.34–1.47), 0.35	0.68
Osteoprotegerin, pg/mL	6.26 [5.00–8.14]	**4.32 (2.01–9.66), < 0.001**	**< 0.001**
Parathyroid hormone, intact (PTH), ng/L	253 [153–377]	1.91 (0.97–3.81), 0.06	0.25
Pentraxin-related protein (PTX3), ng/mL	3.83 [2.00–6.39]	1.20 (0.62–2.32), 0.60	0.87
Phosphate, mmol/L	1.7 [1.4–2.0]	0.90 (0.46–1.75), 0.76	0.94
Sclerostin, pg/mL	436 [343–651]	**2.22 (1.14–4.41), 0.02**	0.16
Soluble receptor activator of nuclear factor-κB ligand (RANKL), pmol/L	0.07 [0.03–0.12]	1.02 (0.47–2.22), 0.96	1.00
Tartrate resistant acid phosphatase 5a (TRAP5a), U/L	4.01 [2.93–5.38]	0.64 (0.30–1.31), 0.22	0.57
Thyroid-stimulating hormone (TSH), mIU/L	0.85 [0.52–1.36]	0.97 (0.50–1.86), 0.92	0.99
Triglycerides (fPTG), mmol/L	1.3 [1.0–1.8]	1.57 (0.82–3.04) 0.18	0.53
Trimethylamine N-oxide (TMAO), µmol/L	62.0 [42.0–96.0]	1.01 (0.51–2.01), 0.98	1.00
Troponin T, µg/L	23.0 [14.0–38.5]	**2.70 (1.30–5.76), 0.009**	0.08
Tumor necrosis factor (TNF), pg/mL	11.0 [8.96–14.12]	1.27 (0.63–2.58), 0.50	0.78
Undercarboxylated osteocalcin (GluOC), ng/mL	17.4 [5.3–56.15]	0.97 (0.50–1.87), 0.92	0.99
Uric acid (UricAcid), µmol/L	363 [308–442]	0.88 (0.44–1.74), 0.70	0.92
Continued			

Feature	Median [IQR] ornumber (%)	Univariable logistic regression OR (95% CI), *p*-value[a]	*P*-value adjusted[b]
Vitamin D 25 (D25Vitamin), nmol/L	34 [26–48]	1.29 (0.66–2.50), 0.46	0.78
Anthropometric measurements			
Body mass index (BMI), kg/m^2	24.3 [22.3–26.5]	**3.33 (1.70–6.73), 0.001**	**0.02**
Fat body mass index (FBMI), kg/m^2	6.29 [4.73–8.16]	2.13 (0.99–4.68), 0.06	0.24
Hand grip strength (HandGripStrength), % of control	97.7 [78.1–108.1]	0.80 (0.41–1.57), 0.52	0.78
Lean body mass index (LBMI), kg/m^2	18.1 [16.4–19.7]	1.57 (0.73–3.39), 0.25	0.57
Other measurements			
Advanced glycation end products (skin autofluorescence), (AGEAF)	3.0 [2.6–3.4]	1.81 (0.86–3.87), 0.12	0.41
Aortic augmentation index (AorticAI), %	20 [11–26]	1.17 (0.59–2.31), 0.66	0.90

Table 1. The association of individual features, median with interquartile (IQR) range or frequency, with medial vascular calcification (VC) as an outcome of univariable logistic regression measured by odds ratio (OR) with a 95% confidence interval (95% CI). [a]The analysis was performed per median value of each quantitative feature (e.g., odds ratio of 4.14 for age means that the odds ratio of mVC in patients above the age of 46 years was 4.14 times higher than in a group younger than the median age) or per each dichotomized categorical variable (e.g., males were 3.44 times more likely to have mVC than females). [b]After adjusting for multiple comparisons, age, male sex, copeptin, IGF1, osteoprotegerin, and BMI remained statistically significant (marked with bold font). [c]NA, not applicable, because all patients with diabetes belong to one group, i.e., mVC.

Each of the methods was applied in its standard configuration, with algorithm-specific hyperparameter optimization conducted where appropriate. For feature selection, we opted for well-established algorithms commonly used within the applied classification frameworks. A brief description of the chosen methods can be found in the supplementary material. LR, EN, RF and SVM models were built using R *caret* package, for training RLS we used our own MATLAB implementation.

Performance evaluation

All methods were validated in the leave-one-out cross-validation (LOOCV) process. In the algorithms where hyperparameter tuning was required, a nested 5-fold cross-validation was incorporated aiming to maximize accuracy as the primary optimization criterion. The metrics used to evaluate the predictions were accuracy, area under the receiver operating characteristic curve (AUC), precision, recall, and F-score, which are discussed in the supplementary material. Additionally, confidence intervals for the LOOCV AUC values were estimated using the bootstrap method with 1,000 resamples.

Incremental cost-effectiveness ratio

The incremental cost-effectiveness ratio (ICER)[27,36] represents the additional cost incurred for achieving an additional unit of health outcome, usually measured in quality-adjusted life years (QALYs). It allows decision-makers to ensure that limited healthcare resources are directed towards treatments that provide the most substantial health benefits relative to their associated costs. Thus, the evaluation of ICER facilitates informed decisions about the adoption and funding of medical interventions. In our study, ICER was calculated as:

$$ICER = \frac{measure\_cost + (prevalence*TPR + (1 - prevalence)*FPR)*ct\_price}{prevalence*TPR*years\_gained}$$

Where:

- *measure_cost* – expense associated with evaluating the biomarkers. For certain biomarkers, their costs are considered hyperparameters (parameters with unknown true value) since they are not routinely measured - see Supplementary Table S2 for a list. For the biomarkers with unknown costs, where only the kit price is available, we introduce an additional factor called the *unavailability weight* which used to scale the kit prices accordingly.
- *prevalence* – a hyperparameter indicating true prevalence of mVC among the advanced CKD population.
- *TPR* – the rate of correctly identified true positive cases by the evaluated method.
- *FPR* – the rate at which the evaluated method incorrectly identifies cases as positive when they are actually negative.
- *ct_price* – the price of a PET-CT scan to confirm mVC presence; sourced from a polish laboratory in June 2023 and converted from PLN to USD at a rate of 0.23, was assumed to be 1127 USD.
- *years_gained* – quality of life years gained due to mVC detection. A hyperparameter.

The pricing details for the biomarkers, sourced from Polish laboratories in June 2023 are presented in Table 2. The prices were converted from PLN to USD for clarity using an exchange rate of 0.23. Biomarkers denoted with an asterisk (*) represent hyperparameters. In addition, we performed a sensitivity analysis to assess how the assumed prices influence the results; see supplementary material. We decided to incorporate the cost of a PET-

Feature	LR	SVM	RF	EN	RLS	Cost (USD)	Sum
Age	X	X	X	X	X	0	5
Copeptin	X	X	X	X	X	58	5
Diabetes mellitus	X	X		X	X	2	4
Choline		X	X	X	X	9	4
Osteoprotegerin		X	X	X	X	5*	4
Sex, male	X	X		X	X	0**	4
BMI		X	X	X		0**	3
FBMI	X	X			X	0**	3
Sclerostin		X	X	X		5*	3
CTX		X			X	29	2
duMGP		X		X		5*	2
Homocysteine		X		X		23	2
IgMantiPC		X		X		7*	2
AGEAF		X				0**	1
Angiopoietin 2		X				5*	1
ApoB1					X	21	1
fT3					X	8	1
fPTG					X	5	1
GlaOC					X	23	1
GluOC		X				5*	1
hsCRP		X				7	1
IGF1		X				21	1
IgMantiMDA		X				23	1
LBMI		X				0**	1
PTX3					X	5*	1
TMAO					X	44	1
TroponinT		X				14	1
TSH					X	9	1
Uric Acid					X	9	1
Total number of features	5	21	6	11	16		

Table 2. Features selected using (1) logistic regression (LR), (2) support vector machine (SVM), (3) random forest (RF), (4) elastic net (EN), and (5) relaxed linear separability method (RLS). For full feature names, see Table 1. *Not measured in clinical practice. The cost is calculated based on the price of the kit per measurement. **Cost disregarded because of the relatively low machine expenses; the price per measurement is negligible when assuming testing of numerous individuals.

CT scan in the equation as we presume that, irrespective of how well the classifiers perform, cases with a certain likelihood of being positive would be additionally verified using a more direct method.

Results

Data investigation

Spearman correlation analysis revealed the presence of collinearity among certain feature pairs. Associations are presented as a heat map in Fig. S1.

Using a univariable logistic regression model, we identified age, male sex, angiopoietin 2, choline, copeptin, duMGP, hsCRP, IgM anti-PC, insulin-like growth factor 1, osteoprotegerin, sclerostin, troponin T, and body mass index as factors associated with mVC (Table 1). However, after adjusting for multiple comparisons, only age, male sex, copeptin, IGF1, osteoprotegerin, and BMI remained statistically significant (Table 1).

Classification frameworks

In a multivariable analysis, we applied five classification frameworks with appropriate variable selection methods. To fine-tune SVM, RF, and EN, we conducted hyperparameter optimization. Table S1 in the supplementary material presents the calculated optimal values and short parameter descriptions.

The algorithms applied to the data differed regarding features identified as being potentially associated with mVC (Table 2). Only age and copeptin were chosen by all five methods (Table 2). The number of selected features varied between the methods with 21 features being selected by SVM, 16 by RLS, 11 by EN, 6 by RF, and 5 features chosen by LR.

The classification ability of the applied methods was measured, among others, by the area under the receiver operating characteristic curve (AUC). In the cross-validation evaluation process, the highest AUC was achieved

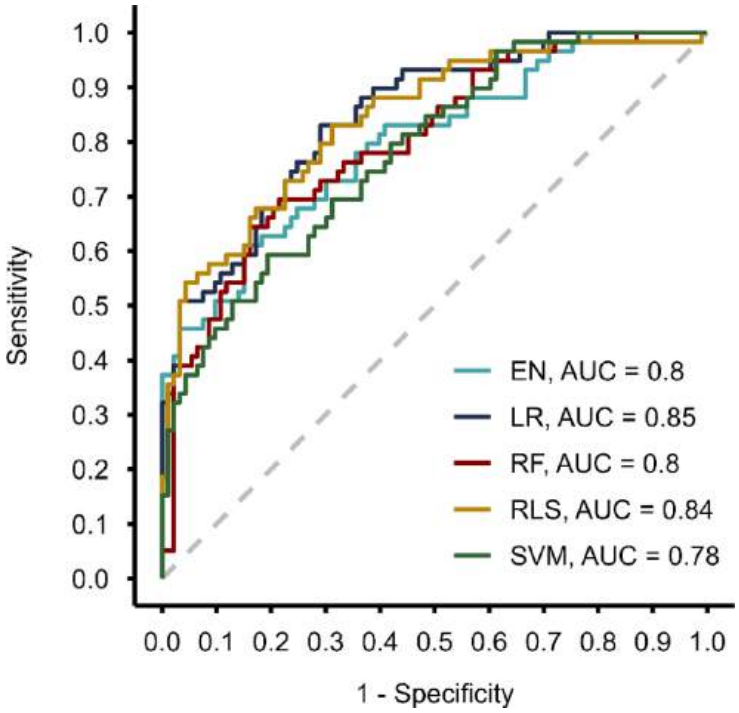

Fig. 1. Receiver operating characteristic (ROC) curves with area under the curve (AUC) for elastic net (EN), logistic regression (LR), random forest (RF), relaxed linear separability method (RLS) and support vector machine (SVM).

Method	Accuracy	AUC	Precision	Recall	F-score
LR	0.74	0.85	0.71	0.58	0.64
SVM	0.71	0.78	0.65	0.54	0.59
RF	0.74	0.80	0.74	0.49	0.59
EN	0.76	0.80	0.87	0.46	0.60
RLS	0.77	0.84	0.71	0.68	0.69

Table 3. Performance evaluation metrics, including area under the curve (AUC), calculated for the applied classification frameworks using leave-one-out cross-validation: (1) logistic regression (LR), (2) support vector machine (SVM), (3) random forest (RF), (4) elastic net (EN) and (5) relaxed linear separability method (RLS).

by LR (0.85 [0.78–0.90]), followed by RLS (0.84 [0.77–0.90]), EN (0.80 [0.72–0.87]), RF (0.80 [0.73–0.86]), and SVM (0.78 [0.70–0.85]) (Fig. 1). The values in square brackets represent bootstrapped 95% confidence intervals.

All computed performance evaluation metrics are summarized in Table 3. None of the applied methods outperformed the others across all the assessed measures.

Incremental cost-effectiveness ratio

Figure 2 illustrates the Incremental Cost-Effectiveness ratio for the built models across three unknown parameters: unavailability weights (1, 10, 20, 30), reflecting the possible increase in procedure costs caused by the biomarkers with the unknown prices; true mVC prevalence in CKD population (0.4, 0.6, 0.8); and Quality Adjusted Life Years gained. In general, ICER decreases as QUALYs gained increase, indicating better cost-effectiveness with more QUALYs. Higher unavailability weights lead to higher ICER values for models relying on features with unknown costs (all except LR). Additionally, higher disease prevalence tends to result in lower ICER values suggesting better cost-effectiveness of the models. Moreover, the examination of the ICER indicate that irrespective of the model employed, the procedural costs remain notably low[37] when compared with the potential gain in quality-adjusted life years (Fig. 2). Logistic Regression (LR), a model requiring only five input features, of which only one incurs a substantial cost, remains the cheapest procedure, while SVM, which takes 21 features as an input, remains the most expensive (Fig. 2). When sticking to the current state of knowledge about the prices, i.e., taking into account kit price for the features unavailable to examine in a laboratory, the order of ICER follows the order of the number of features. However, when considering the scenario where features not currently routinely measured are presumed to be significantly more expensive than the kit price, which is much more plausible, there is a shift in ICER outcomes among the methods evaluated. Averaged over

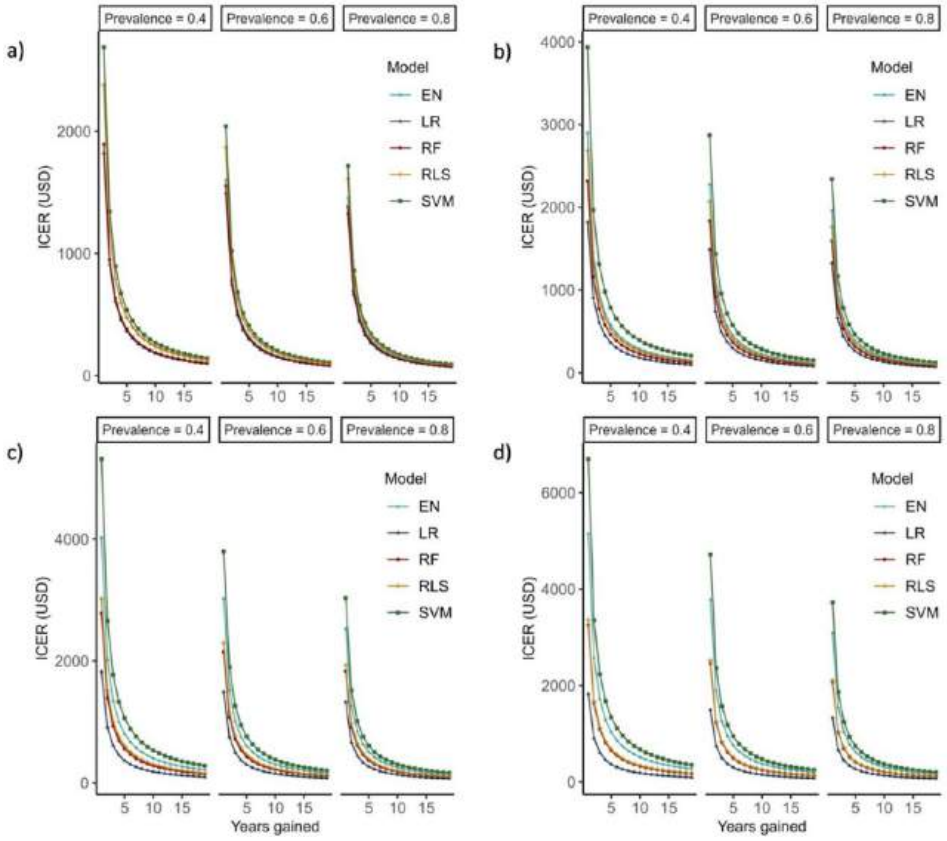

Fig. 2. ICER plots with respect to mVC prevalence, quality of life years gained, and unavailability weight. (**a**) unavailability weight = 1, (**b**) unavailability weight = 10, (**c**) unavailability weight = 20, (**d**) unavailability weight = 30. The prices were converted from PLN to USD for clarity.

prevalence, QUALYs, and unavailability weights, LR emerges as the most cost-effective option with mean ICER equal to $278, followed by RF ($412), RLS ($445), EN ($608), and SVM ($769). Sensitivity analysis revealed that the presented results are consistent regardless of the established feature prices. The only exception is sclerostin; assuming a 50% increase in its cost, RLS is favored over RF.

In the supplementary material we explored the LR model's coefficients and showcase its possible clinical utility by calculating ICER for various probability thresholds.

Discussion

In our research, based on the data from 152 participants, we demonstrated the cost-effectiveness of five machine learning frameworks for detecting medial vascular calcification in CKD patients, a group susceptible to mVC. The algorithms were assessed in terms of statistical performance (Table 3) and cost-effectiveness assessed by the incremental cost-effectiveness ratio, ICER (Fig. 2).

Whereas the tested methods had similar predictive power with AUC values between 0.80 and 0.84 and most of them identified traditional risk factors including age, diabetes, male sex, and body mass index (BMI) as important predictors of mVC in patients with CKD, they yielded different results regarding mVC-related features (Table 2). However, the cost differs significantly between the frameworks with LR working on 5 features appearing as the most efficient option.

The accuracies of the models were not perfect, underscoring that there is still much to uncover regarding the biomarkers associated with mVC and that machine-learning-based algorithms cannot serve as a standalone method for assessing mVC presence in CKD patients. However, they can help reduce the frequency of performing unnecessary CT scans for individuals who are found to be less likely to have the pathology, based on the initial assessment of the biomarkers. This reduction can lead to significant savings in healthcare costs, limit radiation exposure, and decrease the time required for diagnostic procedures. In the supplementary material, we provide a detailed example using logistic regression to illustrate how model outputs can be translated into clinical decision-making. Lowering the cut-off threshold for recommending scans increases diagnostic accuracy but reduces potential savings from avoiding unnecessary imaging. The final choice of threshold should be guided by clinical context and resource availability, allowing practitioners to balance diagnostic performance with operational constraints.

In this pilot study, logistic regression emerged as the most effective method. Besides favorable cost-effectiveness, as well as simplicity, and interpretability of the coefficients, it offered another advantage over

the other built classifiers: it required only 5 easily obtainable features (Table 2). This minimizes the likelihood of encountering missing values, a situation more common in complex models. However, this interpretation is possible only after looking at the models' cost-effectiveness and the sets of their required features. Solely examining performance evaluation metrics (Table 3) makes determining the best of the built models much more complex.

Furthermore, examining a panel of different outcomes of the applied feature selection frameworks may provide valuable insights into biomarkers potentially related to mVC. A predictor that emerged as particularly important in our analysis is copeptin that was chosen by all utilized algorithms (Table 2). This confirms findings from a previous study on this topic[38]. Osteoprotegerin and sclerostin, chosen by 4 and 3 models, respectively, have also been demonstrated to be associated with mVC presence[15,39]. Hence, it would be worthwhile to perform a longitudinal study to assess whether it is justified to incorporate one or more of these three biomarkers into regular clinical practice.

Finally, we highlight some of the well-established or plausible underlying pathophysiological links between the selected variables and mVC (Table S4). This may reinforce the rationale for including some of the identified predictors when designing studies aiming at detecting mVC in future investigations.

In the context of applied biomedicine, it is increasingly recognized that the criteria for assessing a successful statistical model should extend beyond the predictive power of the classifiers; they ought to also be tailored to align with the medical facilities' condition and capabilities. Thus, the cost of the procedure, the availability, and interpretability of the utilized features, should be also considered. Our findings demonstrated that, given certain conditions, a framework employing less expensive variables can outperform another that relies on fewer but costly ones. This was exemplified by RLS, which produced better results in terms of ICER when compared to EN despite utilizing 5 additional features (Fig. 2b–d) and obtaining far worse precision. Moreover, it produced equivalent results when compared to RF which employed 10 additional features (Fig. 2c, d). Although effective therapies specifically targeting mVC are currently lacking, there are interventions available that can slow its progression[11,12]. This supports the inclusion of *years_gained* in the ICER calculation, as early detection of mVC followed by appropriate clinical management may lead to gains in quality-adjusted life years. In the future, the development of therapies capable of reversing mVC would likely increase the expected *years_gained*, thereby reducing the relative cost of using biomarkers as a pre-screening tool, as illustrated in Fig. 2.

A major strength of our study is the comprehensiveness of the performed analysis and that it is based on a unique clinical material with histological identification of mVC in artery specimens. To the best of our knowledge, this represents one of the most extensive clinical datasets of arterial biopsies gathered from chronic kidney disease patients. The collected database includes, inter alia, an evaluation of several factors with documented involvement in the disturbed mineral metabolism in CKD and plausible involvement in the etiology of mVC such as sclerostin[38] osteoprotegerin[39], calciprotein particles[40], FGF23[41], klotho[41], and parathyroid hormone[42]. We showed the interdependencies between features (Spearman rho, Fig. S1), univariable associations between mVC and each one of the 60 investigated features (Table 1) and performed a multivariable analysis that allowed us to select subsets of features associated with mVC, which entered classification models (Table 2). To the best of our knowledge, no previous studies on mVC detection analyzed ICER or any other price-related metrics of the evaluated procedures.

Our study has several limitations which should be considered when interpreting the results. First, the database includes missing values. Whereas their imputation can change the original dataset, including only complete cases may result in a considerable reduction of the number of included patients and features and therefore, a loss of statistical power. Additionally, many statistical tools and algorithms require a complete dataset; for this reason, and considering the relatively small sample size, we decided to fill in the missing data and ensured that the variable distribution did not alter significantly post-imputation. It should also be noted that imputation may interfere with the stability of feature selection. Furthermore, the lack of external validation is a key limitation, as it prevents us from fully assessing the generalizability and robustness of the developed models.

Moreover, due to the retrospective nature of this long-lasting study, some potentially relevant features were not analysed which may limit the comprehensiveness of our findings. Missing features include, for example, N-terminal pro b-type natriuretic peptide (NT-proBNP) and Gla-rich protein, a vitamin K dependent calcification inhibitor[43,44].

Another issue is that the costs related to the measurements needed for ICER analysis can vary significantly between countries, laboratories, and over time. While the sensitivity analysis revealed the consistency of the presented results, it is important to emphasize that the conducted investigation is only a rough estimation of the potential costs associated with each procedure. Before implementation of such a detection method, medical facilities should estimate the costs based on their resources and capabilities.

Lastly, it is important to note that mVC distribution varies across different vascular beds[45,46]. In the past, mVC presence assessed in the inferior epigastric artery was linked with higher values of coronary artery calcification (CAC) score[15], which altogether demonstrates the complexity and variability of the condition. However, further studies are needed to assess the impact of the selected features on calcification in different vascular beds, as the current findings may not be universally applicable.

Conclusion

Our findings showcase the importance of employing analysis that considers not only statistical accuracy but also economic implications of proposed machine learning frameworks. In the present study, the incremental cost-effectiveness ratio (ICER), was found to provide a suitable criterion for model selection, as analysis using ICER is where the difference between the models becomes evident. This highlights the importance of considering cost-effectiveness when selecting the final classifier, as a minor increase in model performance might not balance the costs related to measuring model-required inputs. While the findings from this pilot study warrant validation

on a larger dataset, we believe that it may encourage other researchers using machine learning algorithms for detection of medial vascular calcification to seek optimal solutions that consider not only predictive capabilities but also the applicability of the implemented methods.

Data availability

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at Karolinska Institutet.

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Author contributions

UB – conceptualization, methodology, software, visualization, writing – original draft; MD – conceptualization, writing – review & editing; LD – data curation, writing – review & editing; AQ – data curation; LB – software; MS – supervision; BL – supervision, writing – review & editing; PS – supervision; TL – software; JP – conceptualization, supervision, writing – review & editing.

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Declarations

Competing interests

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Additional information

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Supplementary material

S1. Univariate analysis

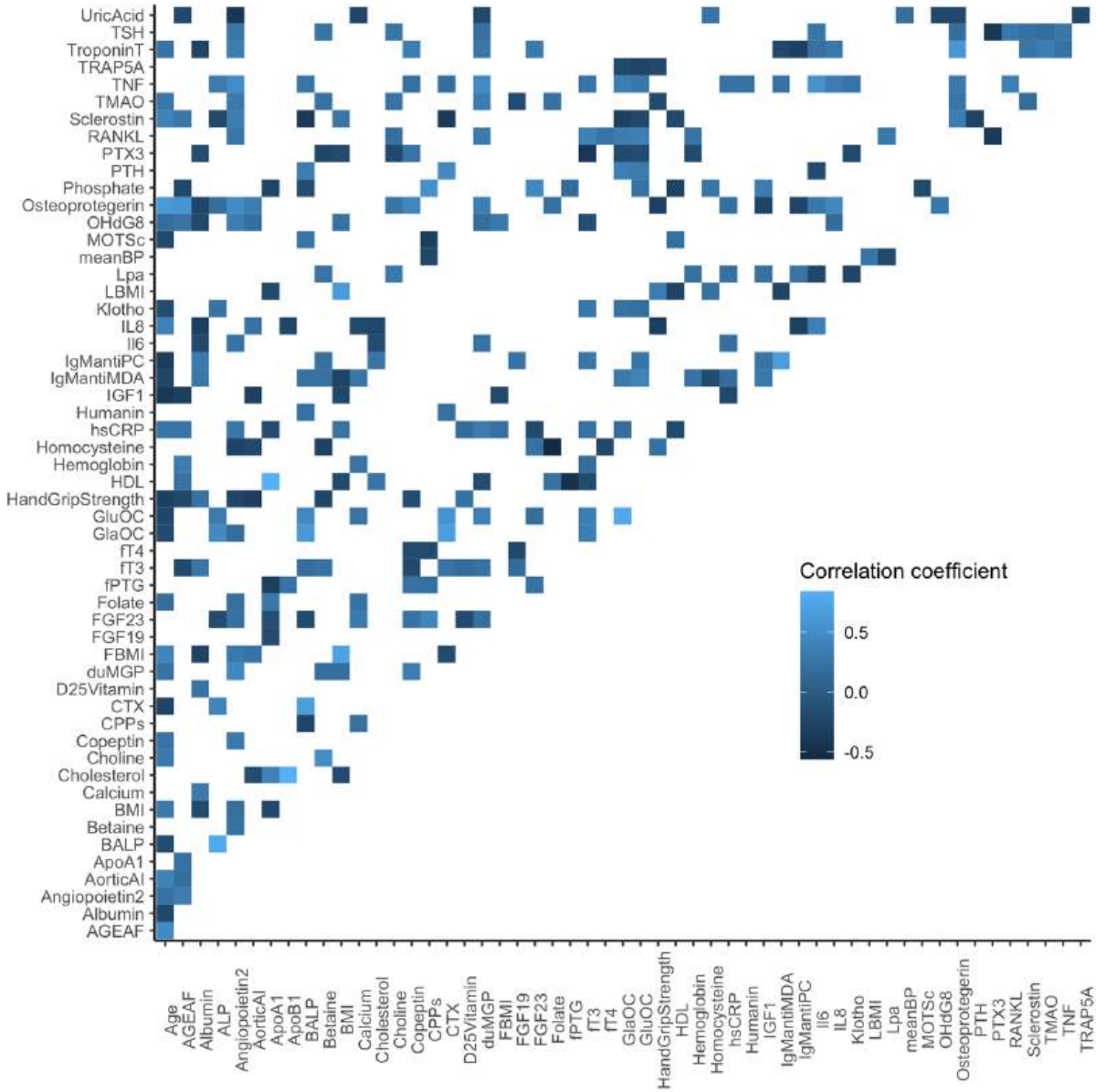

Fig. S1. Spearman correlation plot of the analyzed features. Only statistically significant ($p < 0.5$) correlations are marked. For full feature names, see Table 1 in the main text.

S2. Multivariate analysis

S2.1. Logistic regression with the forward feature elimination process

Logistic regression is one of the most popular supervised learning algorithms utilized for binary target prediction. It estimates the probability of an event occurrence by having the logarithm of odds for the event be a linear combination of one or more independent features [1]. The modeled probability is then mapped into class labels.

Logistic regression combined with forward stepwise feature selection using *Bayesian Information Criterion* (BIC) is a powerful tool that can choose relevant features almost surely and make use of them to perform the classification [2]. The procedure starts with an empty set of variables and adds one variable at a time. In each step, the criterion is evaluated and the decision on whether to add any more features is made. Although BIC can be used in the setting of backward feature elimination, which is sometimes considered to be preferable [3], such a method cannot be applied to our dataset. This is due to the presence of multicollinearity (**Fig. S1**) in our data – fitting a full logistic model correctly would be impossible.

S2.2. Support vector machine with recursive feature elimination

SVM is a machine learning algorithm introduced by Vapnik [1,4]. The algorithm follows the principle of *'structural risk minimization'* to find the best hyperplane that separates two classes of the input space [4]. The optimal decision rule is the one whose distance to the nearest element of each label is the largest [4]. The data vectors closest to the constructed hyperplane are called the support vectors because they directly influence the shape and position of the hyperplane. Originally, SVM performed only linear classification, but it was further developed to solve nonlinear problems by incorporating the kernel trick concept in high-dimensional spaces.

The method known as SVM-Recursive Feature Elimination (SVM-RFE) is considered one of the most common wrapper approaches for feature selection in linear SVM [1]. The SVM-RFE method is a backward feature elimination process. Its main purpose is to find a smaller subset of all the available features which maximizes the model's performance. The elimination procedure is conducted by fitting a model, computing the weights' ranking for all features, and sorting them accordingly to the influence they have on the weight vectors to remove the

least important ones [1]. The top-ranked variables are not necessarily the ones that are individually the most relevant, but their combination with other features makes them appropriate for a given model. In our approach the number of top-ranked features entering the model was selected using a nested cross validation process.

S2.3. Random forest with permutation importance

Tree based algorithms are a wide range of methods allowing to solve both classification and regression problems. One of its members is random forest (RF) – an ensemble learning method which is based on constructing multiple decision trees during training [1]. The individual trees are trained on different parts of the training set which allows for a better generalization of the model than using a single decision tree. The output of a random forest classifier is the class selected by most of the constructed trees.

To gain insight into how each feature influences random forest's performance the permutation importance method can be used [1]. First, the model is scored over the entire dataset. Then the feature column from the training or validation set is randomly permuted and the metric is measured again. Permutation importance is defined as the difference between the score obtained for the primary dataset and the score measured after the permutation of the variable column. This technique breaks the relationship between the variable and the target by randomly shuffling a single feature column; the change in the model's performance indicates how much it depends on the variable. We decided to include in training the features whose mean importance was more than twice as high as its standard deviation.

S2.4. Elastic net penalty on top of logistic regression

Another possibility of utilizing a logistic regression model in a feature selection process is to combine it with a regularization penalty added to the objective function of the algorithm. In our work, we decided to use the *elastic net* penalty proposed by Zou and Hastie [5], which is equal to a linear combination of a sum of absolute values of the model's coefficients and a sum of their squares. Such a method has two main purposes. The L1 term, controlled by a parameter α, causes some of the coefficients to shrink exactly to zero; therefore, it is responsible for feature selection [5]. The L2 term, controlled by $1-\alpha$, is responsible for shrinking coefficients towards zero - it is particularly useful when significant correlations

between the explanatory variables are observed since it provides numerical stability to the algorithm [5]. The overall strength of the penalty is controlled by a tuning parameter λ. With the increase of λ, more coefficients shrink to zero and, as a result, are eliminated from the model. Therefore, EN is not only a method of fitting a model but also performs feature selection. One of its special cases, when α=1, is called the *least absolute shrinkage and selection operator* (Lasso) algorithm [6].

S2.5. Relaxed linear separability

The RLS method of classification and feature selection is based on the concept of linear separability which means the possible separation of two sets by a hyperplane [7]. The term 'relaxed' denotes the deterioration of the linear separability (between two groups of patients) resulting from subsequent neglect of the selected features. In the first step, a hyperplane described by a large number of features that provides the best separation of objects from the two decision classes is determined. Then, by gradually increasing the value of the regularization parameter of the criterion function, the degree of separation is reduced, and a sequence of feature subspaces is obtained. In the last step, each subspace in the sequence is tested by determining the classification quality of the convex and piecewise-linear (CPL) classifier in a cross-validation procedure [8]. Finally, the feature subset with the best classification quality is selected [7].

S3. Performance measures

- Accuracy (ACC) - the ratio of correctly predicted observations to the total number of examples in the dataset.
- Area under the receiver operating characteristic curve (AUC ROC). ROC curve shows the trade-off between the true positive fraction and the false-positive fraction at different cutoff points. The area under the curve (AUC) serves as a summary of the curve and reflects how much the model is capable of distinguishing between classes.
- Precision - the ratio of correctly predicted positive examples to the total predicted positive observations.

- Recall (sensitivity) - the ratio of correctly predicted positive examples to the total number of positive examples in the dataset.
- F-score - the harmonic mean of precision and recall.

Table S1. Hyperparameters tuned in the selected classification frameworks. The presented optimal value was calculated for the entire dataset using 5-fold cross validation.

Method	Parameter	Description	Searched hyperparameter space	Optimal value
SVM	C	Regularization parameter associated with a squared L2 penalty.	0.001, 0.01, 0.05, 0.1, 0.5, 1, 2, 5, 10	1
	kernel	Kernel type used in the algorithm.	Linear, radial	Linear
	size	Number of features used by the algorithm for training.	Sequence from 5 to 21 by 2	21
RF	mtry	Number of features to consider by a decision tree at any point of time.	Sequence from 5 to 21 by 2	9
	ntree	Number of trees used in aggregation.	10*number of features, 600, 800, 1000	600
EN	α	Constant controlling L1 and L2 penalty terms.	0.00001, 0.0001, 0.001, Sequence from 0 to 1 by 0.1	0.4
	λ	Shrinkage parameter.	Sequence from 0.0001 to 0.2 of length 5	0.15

Table S2. Hyperparameters regarding ICER assessed in the experiments.

Parameter	Description	Searched hyperparameter space
unavailability_weight	A constant by which to multiply the cost of the kit needed to perform the examination for the currently unavailable to check biomarkers.	1, 10, 20, 30
years_gained	Quality years of life gained when detecting mVC and application of the appropriate treatment.	1-20
prevalence	True prevalence of the disease among CKD5 patients.	0.4, 0.6, 0.8

S4. Sensitivity analysis

To evaluate the variability in ICER outcomes based on different biomarker prices, we analyzed the impact of increasing or decreasing a particular biomarker's price by 25% and 50% relative to the price presented in Table 3. Each feature was assessed independently

while keeping the prices of all other biomarkers constant. The results were averaged across prevalence, potential quality-adjusted life years gained, and unavailability weight.

We then ranked the models from the lowest to the highest mean ICER for each adjusted feature cost and compared these rankings to those obtained using the original prices from Table 3. The original ranking, LR, RF, RLS, EN, and SVM, remained consistent for all variables except sclerostin. When the price of sclerostin was assumed to be 50% higher than the baseline, RLS, which did not select this feature, emerged as the second-best option. In contrast, RF, which incorporates sclerostin, moved to third place.

S5. Logistic regression model

In the current analysis, logistic regression, utilizing age, sex, diabetes mellitus, FBMI, and copeptin, emerged as the most favourable model in terms of simplicity, AUC ROC, and ICER. Therefore, it is worthwhile to explore how such classifier could be effectively employed. According to the model, the probability of mVC presence can be calculated as follows:

$$P(mVC|Age, Sex, DM, FBMI, Copeptin) = \frac{1}{1+e^{-(-9.92+0.06\times Age+19.12\times DMPresent+3.04\times MaleSex+0.33\times FBMI+0.01\times Copeptin)}}$$

The presented results were derived from a dataset that underwent reverse standardization, allowing for the coefficients to be interpreted in standard measurement units. In practical terms, if we consider a one-year increase in the patient's age, it results in the odds of mVC increasing by a factor of approximately 1.06, as calculated using the value $e^{0.06}$. In simpler terms, for each additional year of age, there is approximately a 6% increase in the likelihood of mVC occurring, provided that all other variables will remain constant.

Except for diabetes mellitus, which is characterized by high variability, each of the variables displayed statistical significance with a p-value < 0.01. The calculated probability provides clinicians with information about the likelihood of a patient having mVC. However, the specific threshold for this probability can be subject to interpretation and may be utilized differently by various medical practitioners or healthcare facilities.

Figure S2 illustrates the ICER calculated based on leave-one-out cross-validation results obtained using the same model but with the application of different probability thresholds.

For instance, setting a threshold of 0.06 implies that any observation with an mVC probability exceeding 0.06 will classified as “positive” (class 1), while a threshold of 0.17 indicates that observations with a probability of mVC greater than 0.17 will be assigned class 1, and so on. The plot demonstrates that, in terms of ICER, employing a very low threshold is generally inefficient, unless the prevalence of mVC in the population is exceptionally high. The reason is that it results in a large number of patients being tested with a significant proportion of them not having the pathology. Conversely, setting the threshold at 0.17 or higher yields more efficient results in terms of ICER.

However, the same results can also be examined from a clinical perspective. **Table S3** presents the distribution of the true negatives and true positives achieved through cross-validation with respect to various thresholds. It can be observed that for the threshold 0.06, the classifier assigns all true positives to class 1, correctly identifying 27% of truly negative patients at the same time (**Table S3**). This implies that by applying a classifier in this manner, approximately 27% of patients free from mVC might avoid unnecessary PET-CT, and none of the truly positive ones will be misclassified because they all proceed for further scanning. On the other hand, if a medical unit aims to reduce costs, a clinician may choose to direct a patient with the probability of having the pathology exceeding 0.17 for a PET-CT scan. In such a scenario, it can be anticipated that 97% of the patients will have mVC correctly identified, and 57% of unnecessary scans will be avoided (**Table S3**). This approach is favoured by ICER when compared to setting the threshold at 0.06 but is less effective in terms of sensitivity which may be more important to some practitioners.

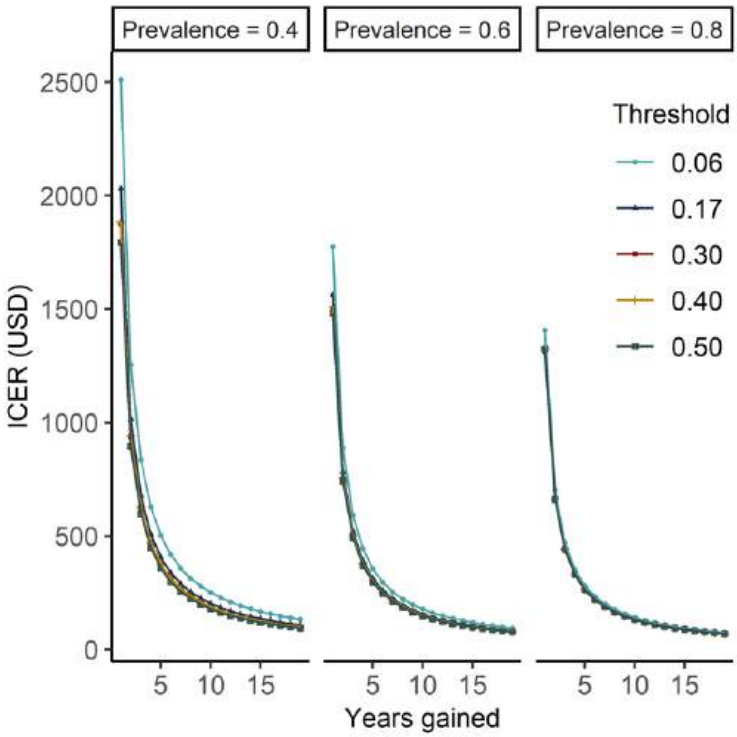

Fig. S2. ICER logistic regression plots with respect to mVC prevalence, quality of life years gained and probability threshold value.

Table S3. Detection rate of positive and negative examples with respect to the threshold value for the logistic regression model. Underlined the possible cutoff values.

Model	Logistic regression	
Threshold	Below threshold negative	Above threshold positive
0.01	5/93 (5%)	59/59 (100%)
0.02	12/93 (13%)	59/59 (100%)
0.03	15/93 (16%)	59/59 (100%)
0.04	19/93 (20%)	59/59 (100%)
0.05	22/93 (24%)	59/59 (100%)
0.06	25/93 (27%)	59/59 (100%)
0.07	27/93 (29%)	58/59 (98%)
0.08	30/93 (32%)	58/59 (98%)
0.09	32/93 (34%)	57/59 (97%)
0.10	34/93 (37%)	57/59 (97%)
0.11	36/93 (39%)	57/59 (97%)
0.12	37/93 (40%)	57/59 (97%)
0.13	42/93 (45%)	57/59 (97%)
0.14	45/93 (48%)	57/59 (97%)
0.15	47/93 (51%)	57/59 (97%)
0.16	50/93 (54%)	57/59 (97%)
0.17	53/93 (57%)	57/59 (97%)
0.18	54/93 (58%)	56/59 (95%)
0.19	57/93 (61%)	55/59 (93%)
0.20	59/93 (63%)	54/59 (92%)

S6. Discussion

From the five tested methods, each algorithm chose a different set of features as important factors in VC prediction. Multiple reasons might be accountable for such behaviour. The first, obvious explanation is the fact that the applied algorithms are very different in construction. All of them rely on the underlying classification method and since the decision rules vary, so do the selected features. The second possible reason is the presence of correlations between the features. One of the biggest challenges in most cases of clinical datasets modelling is how to handle multicollinearity between the variables. Our dataset is not an exception in this matter (**Fig. S1**). From the tested algorithms, the only classification framework that can deal with correlations between variables is the elastic net. If predictors are correlated in groups, setting the hyperparameter $\alpha = 0.5$ tends to either select or leave out the entire group of features associated with the outcome [5,9]. Fortunately, experimenting with different values of α showed that there is no sign of the groups of correlated variables having a predictive impact on the target. Therefore, it can be assumed

that the remaining methods, which tend to select only one variable from the group of correlated features, gave valid results in this area.

Table S4. The pathophysiological link between chosen features and vascular calcification (VC). For full names of features, see Table 1 in the main text.

	Feature	Pathophysiological relation with VC
1.	Age	Aging is a hallmark of VC. The incidence of VC increases with advanced age and is amplified in the uremic milieu. The underlying mechanisms include loss of stress-induced adaptive homeostasis and cellular senescence [10].
2.	Copeptin	Despite not being fully explored, copeptin has been reported to be a marker of atherosclerosis and arteriosclerosis [11] and we observed an association between circulating copeptin and mVC in epigastric arteries collected from living donor kidney recipients [12].
3.	Diabetes mellitus	Mönckeberg's medial sclerosis characterized by increased expressions of transcription factors programming osteogenesis in the medial arterial layer is a common feature in type 2 diabetes. Multiple factors contribute to the development of mVC in diabetes, including oxidative stress, inflammation, hyperphosphatemia, insulin resistance, and advanced glycation end-products [13].
4.	Choline	Dietary choline intake and the TMAO metabolism pathway plays a role in mediating cardiovascular pathogenesis [14]. Circulating choline is reported to be an emerging biomarker of coronary plaque instability with platelet thrombus formation and ischemia [15]. The relation between circulating choline and mVC needs to be further explored.
5.	Osteoprotegerin	Osteoprotegerin plays an important role in the bone-vascular axis. It acts as a soluble receptor for RANKL and inhibits the binding of RANKL to RANK, thereby preventing osteoclast activation and bone resorption [16]. Osteoprotegerin-/- mice present evident features of osteoporosis and VC [17]. Elevated circulating levels of osteoprotegerin in humans are however associated with increased VC as a compensatory mechanism against VC [18].
6.	Sex, male	Though the underlying mechanism remains to be elucidated, male sex is recognized as a potential risk mediator of VC in CKD [19].
7.	BMI	Obesity is a risk factor for increased risk of subclinical atherosclerosis (measured by CAC) in the general population [20]. The relationship between BMI and mVC warrants further investigation. Given obesity per se and obesity-related systemic inflammation in mediating adverse CV events, it is plausible that obesity, together with other concomitant metabolic disorders, plays a role in the development of mVC.
8.	FBMI	Evidence linking fat body mass index and mVC is currently lacking. Investigations on fat tissue and measurement of regional fat distribution (e.g., visceral, subcutaneous fat, epicardial adipose tissue) and their impact on VC development may provide additional information [21].
9.	Sclerostin	Sclerostin is a negative regulator of the Wnt/β-catenin signaling [22] and thus plays a role in bone formation and ectopic calcification [23] . Serum sclerostin is increased in CKD patients though its correlation with degree of VC is unequivocally reported (e.g. no association [24], positive association [25] and negative association [26]).
10.	CTX	CTX produced by osteoclasts is a marker of bone resorption. Elevated bone resorption with increased CTX secretion could be indicative of a 'calcification paradox' and linked with subsequent increased VC.
11.	duMGP	Matrix Gla protein (MGP) is a vitamin K dependent protein primarily synthesized and secreted by VSMCs[27]. MGP inhibits VC *in vivo*[28–30], possibly by directly binding the hydroxyapatite in the arterial walls[31] and by downregulating the function of bone morphogenetic proteins [32][33]. High circulating dp-ucMGP levels, indicative of functional vitamin K deficiency, is associated with mortality in various populations

		including CKD[34–36], diabetes[37], cardiovascular disease (CVD)[38–40], and in the general population[41,42].
12.	Homocysteine	Homocysteine is well recognized as an independent risk factor for atherosclerosis and is associated with increased oxidative stress, thrombogenicity, and impaired endothelial function in the pathogenesis of atherogenesis [43]. The direct link between homocysteine and mVC remains to be addressed.
13.	IgM anti-PC	High circulating IgM anti-PC is reported to be protective against atherosclerosis development, cardiovascular risk, and mortality in CKD [44].
14.	AGEAF	AGEs act through AGEs receptors (RAGE) and cause pathological alteration in vessels and induces vascular calcification [45]. AGEs measured by skin autofluorescence is associated with increased risk of cardiovascular events and all-cause mortality in both non-dialysis and dialysis patients [46,47].
15.	Angiopoietin 2	The role of angiopoietin 2 in VC has not been well explored. Angiopoietin 2 was reported to be associated with the severity of arterial stiffness in CKD stages 3-5 non-dialysis patients [48].
16.	ApoB1	It was suggested that apoB more accurately measures the atherogenic risk than does conventional markers such as low-density lipoprotein cholesterol or non–high-density lipoprotein cholesterol[49].
17.	fT3	fT3 inhibits VC [50]. In vitro, T3 suppresses VSMCs calcification via PI3K/Akt signaling pathway [50] and upregulates MGP gene expression [51].
18.	fPTG	Hypertriglyceridemia was associated with subclinical noncoronary atherosclerosis regardless of LDL-C (i.e., high or normal levels), and with arterial inflammation[52].
19.	GlaOC	The bone-specific protein osteocalcin (OC) is a well-established marker of vascular smooth muscle cell (VSMC) osteochondrogenic transdifferentiation [53]. The vitamin K-dependent posttranslational γ-carboxylation of its three glutamic residues (Gla domain), i.e., GlaOC, confers OC's hydroxyapatite binding ability as an inhibitor of vascular calcification. Recent in vitro and ex vivo data suggest OC may be directly involved in Wnt-driven VSMC calcification via the regulation of mitochondrial activity and thus induce arterial calcification [54].
20.	GluOC	In contrast to GlaOC, GluOC is a form of undercarboxylated OC. As carboxylation of the residues is regulated by vitamin K, GluOC is considered as a clinical marker of vitamin K status and reflects a deficient anti-calcification system [55]. High serum GluOC is associated with increased risk of coronary artery calcification independent of traditional risk factors [56].
21.	hsCRP	Though the predictive value of systemic inflammatory markers such as hsCRP in VC is inconclusive, its association to high-risk noncalcified plaques could partially allude the relationship between hsCRP and clinical CV events[57,58].
22.	IGF1	IGF-1 is generally considered as a vascular protective factor[59]. Moderate calcium levels increase OPG, which then induces IGF1 receptor in VSMC to enhance VSMC survival and block calcification induced by calcium[60].
23.	IgMantiMDA	Limited studies have reported the protective role of IgM anti-MDA in CVD and SLE [61,62]. Further studies are warranted to elucidate its role in cardiovascular pathology.
24.	LBMI	The association between LBMI and VC is not well documented in literature. Measurement of skeletal muscle mass index indicated an negative association with coronary calcification[63].
25.	PTX3	Recent data from MESA showed that PTX3 as a marker of vascular inflammation, was associated with cardiovascular risk factors, subclinical cardiovascular events, CAC and incident coronary heart disease events independently of CRP and CVD risk factors[64].
26.	TMAO	The role of TMAO in VC has been extensively explored. TMAO promotes VC activation of NLRP3 inflammasome and NF-κB signal as demonstrated in vitro, ex

		vivo, and in vivo models[65,66]. High circulating TMAO is a well-established risk factor of adverse CV events in CKD[67,68].
27.	TroponinT	Serum high sensitivity Troponin T has been recognized as a marker to improve risk stratification of coronary artery disease [69,70] and is associated with increased risk of subclinical atherosclerosis indicated by coronary artery calcium [71] in high CV risk population. The relation between Troponin T and medial calcification remains to be explored.
28.	TSH	Low levels of TSH have been reported to be associated with increased prevalence and degree of coronary calcification represented by CAC score as well as increased risk of atherosclerotic cardiovascular mortality both in CKD and in the general population [72–74]. The association between TSH and mVC is less explored.
29.	Uric acid	Epidemiological studies suggested hyperuricemia as an independent risk factor of CAC score in various study populations[75–77]; transporters of uric acid were expressed both in VSMCs[78,79], which could address its direct or indirect vascular effect.

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4

POTENTIAL OF PULSE WAVE SIGNAL FREQUENCY-DOMAIN ANALYSIS FOR MEDIAL VASCULAR CALCIFICATION SCREENING

4.1 Pressure pulse waves

As noted by van de Vosse and Stergiopulos, specialists in the cardiovascular system, "waves carry information about the matter in which they propagate" [120]. This concept encourages the study of arterial pressure waves, whose morphology is shaped by their propagation through the vascular system, and therefore may provide diagnostic insights into cardiovascular disorders [120]. Building on this idea, I investigated the potential of the pressure pulse wave signal (hereafter referred to simply as the pulse wave signal) as an input to machine learning models, evaluating it as a surrogate marker for the presence of vascular calcification. In the following sections, I will present the rationale for this approach and outline the methods of pulse wave feature extraction applied in my research.

4.1.1 Pulse wave propagation

The cardiac cycle begins with ventricular contraction (systolic phase), when the left ventricle pumps blood into the arterial system, and ends with ventricular relaxation (diastolic phase), when the heart is refilled. The rapid ejection of blood during systole generates a pressure disturbance, known as the pulse wave [121]. Although it is the heart that initiates the wave, its shape, propagation, and characteristics are highly influenced by two factors: the arterial wall properties and the interaction with the reflected waves [122].

The aorta and large arteries serve not only as conduits transporting oxygenated blood to peripheral tissues, but also as buffers which amortize stroke volume - the volume of blood ejected with each contraction [123]. In healthy vessels, the elastic arterial walls expand under pressure and accommodate part of the stroke volume. It is then released during diastole, maintaining arterial pressure and ensuring continuous blood flow. This buffering property is known as the Windkessel effect [124]. The expansion and recoil of successive arterial segments transmit the pulse wave throughout the vascular tree - a process termed pulse wave propagation [121].

The mechanical properties of the aorta and its branches depend largely on the viscoelastic components of the arterial wall - primarily elastin, collagen, and, most importantly in the context of my work, vascular smooth muscle cells [125]. As discussed in the

section 1.2.2, in vascular calcification, VSMCs undergo phenotypic changes from contractile to osteogenic, contributing to the stiffening of arterial walls. With the addition of calcium deposits accumulated in the medial or intimal layer, this results in the loss of elasticity, which impairs the Windkessel effect: less blood is buffered in the aorta during systole, and more is transmitted directly into the periphery. Consequently, the pulse wave is propagated at a higher velocity, which further alters its morphology [123].

Importantly, forward wave propagation is not the only determinant of the observed pressure wave signal. As the forward wave encounters sites of impedance mismatch, it generates reflected waves of substantial magnitude [123]. Major physiological reflection sites include arterial bifurcations and the peripheral resistance vessels [123]. Pathological obstacles such as atherosclerotic plaques further increase the frequency of wave reflection generation [126]. It needs to be noted that because the circulatory system is a relatively small, closed circuit where the pulse waves travel at a high speed, the reflected waves do not interfere with subsequent cardiac cycles but instead superimpose on the original forward wave [123]. The observed pulse wave at any location is therefore a composite signal: the sum of the forward wave and multiple reflected components. In stiffened arteries, both the forward and reflected waves travel faster, leading to their earlier superposition during systole and amplifying central systolic pressure while reducing diastolic pressure [123]. This alteration of wave shape is a direct consequence of arterial stiffness influenced by vascular calcification and atherosclerosis.

4.1.2 Central vs peripheral pulse wave signal

Pulse wave recordings differ substantially depending on whether they are obtained centrally (e.g., in the ascending aorta) or peripherally (e.g., brachial or radial arteries). Peripheral arteries are major sites of wave reflection, so the superposition of forward and backward waves occurs early in systole, making the peripheral systolic pressure peak strongly influenced by reflections [123]. In contrast, in healthy and compliant central arterial sites, mainly in the aorta, the forward and reflected waves meet at the end of systole. Their superposition extends through diastole, giving the central waveform a rounded diastolic contour, while leaving the systolic peak largely determined by ventricular ejection and aortic compliance [121]. This difference between central and peripheral systolic pressure is known as pulse pressure amplification [127] and is schematically shown in figure 4.1. However, when arterial stiffness develops, this pattern changes. The increased pulse wave velocity causes the reflected waves to return earlier, merging with the forward wave during systole, even at the central arterial sites. This elevates central systolic pressure and widens pulse pressure by raising systolic and lowering diastolic values [128]. In the periphery, these alterations are even more pronounced due to the stronger influence of early reflected waves [128].

4.1.3 Pulse wave velocity

An important quantity in studying pulse wave propagation, which partially reflects arterial properties, is pulse wave velocity (PWV). Its increased value is a well-established marker of vascular stiffness and therefore is associated with higher systolic and pulse pressures, increased cardiac workload, and the development of complications such as left ventricular hypertrophy, diastolic dysfunction, and congestive heart failure [129,

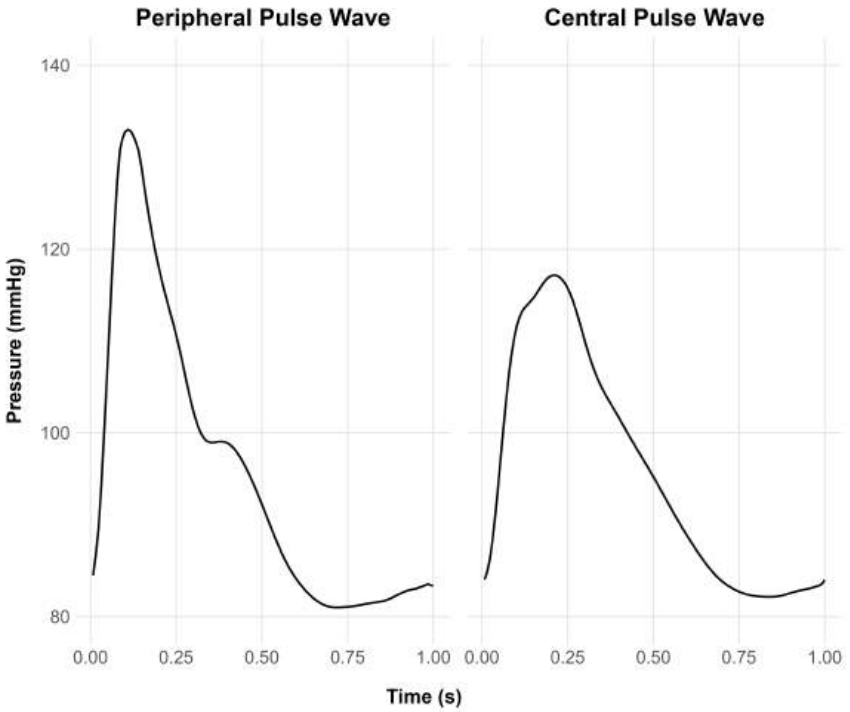

FIGURE 4.1: Peripheral (left panel) and central (right panel) arterial pressure waveforms from a single cardiac cycle recorded at the brachial artery and transformed to a central signal using SphygmoCor System.

130]. PWV can be measured at various arterial segments, providing insights into both central and peripheral arterial stiffness. The gold standard for assessing central stiffness (particularly that of the elastic aorta and thoracic arteries) is carotid-femoral PWV (cfPWV). Carotid-radial PWV (crPWV) reflects stiffness in muscular peripheral arteries, such as the brachial artery, while brachial-ankle PWV (baPWV) captures a mixed profile of both central and peripheral segments [123]. Regardless of the arterial sites chosen, the principle of measurement is the same: pulse waveforms are recorded at two distinct sites, the transit time of the wave between them is determined, and the path length is estimated. PWV is then calculated as the distance between two arterial measurement sites divided by the pulse transit time between them.

Although the PWV measurement is conceptually simple, both components required for its calculation, i.e., distance and transit time, present some methodological challenges. The most significant limitation is the estimation of arterial path length, which remains the main source of inaccuracies in PWV measurement [123, 131]. Since the arterial course cannot be measured directly, surface distances are used as surrogates. However, different studies apply different measurement techniques or correction formulas, leading to variability and complicating both clinical application and cross-study comparisons [131]. Although reference values for PWV are available, their validity relies on a clear specification of the distance estimation method, a detail that is not consistently reported [123].

The second component of the PWV formula, transit time, can be determined using two approaches [123]. The first involves simultaneous pulse wave signal acquisition with two sensors: one positioned to record it at the proximal site and the other at the distal site. The second method employs a single sensor sequentially, often synchronized with an electrocardiographic tracing. While, when properly performed,

simultaneous and sequential measurements provide comparable results [123], the accuracy of the latter is highly sensitive to beat-to-beat variability, which can compromise assessment reproducibility [131]. Furthermore, the position of the subject is an important factor, as transit times are strongly influenced by the vertical placement of sensors due to gravitation [132]. Taken together, these methodological considerations introduce significant variability in PWV determination, limiting the reproducibility and interpretation of the results.

Nevertheless, PWV research provided several interesting insights into arterial stiffness. Some studies suggest a compensatory interaction between central and peripheral arterial stiffness - a decrease in brachial stiffness has been observed as a response to increased central aortic stiffness [133]. While cross-sectional data show that brachial PWV increases with age, the rate of increase is significantly lower than that of aortic PWV [134]. Moreover, longitudinal observations report a decline in crPWV (a surrogate marker of brachial artery stiffness) over time, supporting the hypothesis that reduced brachial stiffness may serve as an adaptive mechanism to counterbalance the progressive stiffening of central elastic arteries [133].

4.1.4 Measurement techniques

A variety of techniques are available for acquiring pulse wave signals at different arterial sites, ranging from invasive gold-standard methods to non-invasive approaches employing pressure, optical, or acoustic sensors [135]. Among the most widely used non-invasive methods are applanation tonometry and volume-clamp techniques [136]. These approaches differ in their complexity of use, accuracy, and suitability for specific arterial sites. Comprehensive reviews of their methodology, advantages, and limitations can be found in [135, 137].

In the present work, I focus specifically on the data collection methods employed in my studies [P2, P3]: applanation tonometry of the radial artery and a cuff-based volumetric displacement technique at the brachial artery. Both methods are implemented within the SphygmoCor System (AtCor Medical, Sydney, Australia) [138]. The following section introduces the principles of these measurement techniques and describes how peripheral signals are mathematically transformed into central pressure waveforms.

Arterial applanation tonometry can be used to record pulse waves in several arterial sites, including the radial artery [139]. It is a non-invasive technique that employs a pen-like pressure sensor to slightly flatten the artery at the wrist against the underlying bone. This method directly captures the arterial pressure waveform by sensing the artery's mechanical pulsations with high temporal resolution. Because it requires accurate and stable sensor positioning, the radial artery's superficial and easily accessible location makes it particularly suitable for this technique [140]. Several studies have confirmed that blood pressure values and arterial pressure waves recorded non-invasively by tonometry are equivalent to invasive intra-arterial catheter recordings [141, 142].

The brachial artery pulse wave can be obtained using a cuff-based volumetric displacement technique. In this approach, after the initial measurement of systolic and diastolic brachial pressure, a standard blood pressure cuff is inflated to a sub-diastolic pressure level on the upper arm, allowing the device to register volumetric changes associated with the pulse in the underlying brachial artery [139]. These pulsations are then used to reconstruct the arterial waveform. In contrast to applanation tonometry,

the cuff-based technique does not require highly precise placement over the artery and is therefore easier to apply in routine clinical settings [139].

Central aortic waveforms can be estimated from the peripheral pulse wave signal [123]; both radial and brachial waveforms can be mathematically transformed into a central aortic waveform [143, 144]. The principle underlying this transformation is that arterial waveforms at different sites are mathematically related, even though they differ morphologically due to wave reflections, variations in arterial compliance, and vascular geometry. This transformation is performed by analyzing the waveform and then applying a validated generalized transfer function (GTF) [145, 144]. While there exist several formulas for GTF, it often employs Fourier analysis to reconstruct the central aortic pressure signal [145]. The algorithm corrects for pressure amplification and waveform alterations that occur when the pulse wave propagates from the aorta to peripheral sites. To improve accuracy, the results are typically calibrated with brachial systolic and diastolic blood pressure values. The GTF implemented in devices such as the SphygmoCor System has been validated against invasive intra-aortic measurements, demonstrating good agreement and reliability for non-invasive estimation of central pressures [141, 144].

4.2 My work

4.2.1 PW-FDFs: pulse wave - frequency domain features

Pulse waves in the frequency domain

Pulse waves are most often represented in the time domain, where their characteristic waveform depicts changes in arterial pressure over time. An alternative approach is to analyze the signal in the frequency domain. The idea builds on a mathematical concept introduced by Fourier that any complex, repeating signal, such as the arterial pulse wave, can be represented as a sum of simple sine waves. While these principles apply to all periodic signals, I will formulate them specifically in terms of the arterial pulse wave for clarity.

The pulse wave, as a periodic signal, can be described as a combination of sine waves at specific frequencies (i.e., how many times per second a wave oscillates, measured in hertz (Hz)):

- **Fundamental frequency** (f_0): the base frequency, which corresponds directly to the heart rate. For example, if the heart rate is 60 beats per minute (1 beat per second), then $f_0 = 1$ Hz.
- **Harmonics**: sine waves with frequencies that are integer multiples of the fundamental ($2f_0, 3f_0, 4f_0, \ldots$). The first few harmonics determine the broad shape of the wave, whereas higher harmonics allow for reconstructing sharper details.

The overall pulse wave is reconstructed by summing these harmonics, each defined by two parameters:

- **Modulus (Amplitude, $|H_n|$)**: represents the contribution of the n-th harmonic to the signal. A larger modulus indicates a stronger influence of that harmonic on the pulse waveform. By definition, the modulus is always non-negative.

- **Argument (Phase Angle, φ_n)**: represents when the harmonic occurs relative to the start of the cardiac cycle and is essential for reproducing the correct waveform shape. Angle is typically expressed in radians.

Importantly, the 0th harmonic (H_0) represents the constant component of the signal. Since it has a frequency of 0 Hz, it has no associated phase. Physiologically, H_0 corresponds to the mean value of the pressure signal over one cardiac cycle, i.e., the mean arterial pressure (MAP).

The original pulse wave signal $P(t)$ can thus be reconstructed using the harmonic form of the Fourier series [146]:

$$P(t) = H_0 + \sum_{n=1}^{N} |H_n| \cos\left(2\pi n f_0 t + \varphi_n\right)$$

where:

- $P(t)$ is the arterial pressure at time t,
- H_0 is the 0th harmonic modulus (mean arterial pressure),
- $|H_n|$ is the modulus of the n-th harmonic,
- nf_0 is the frequency of the n-th harmonic,
- φ_n is the phase of the n-th harmonic,
- N is the number of harmonics considered (even first six harmonics accurately define the pressure waveform [123]; typically, up to 20 harmonics are used for pulse wave reconstruction [147]).

The Fourier coefficients $|H_n|$ and φ_n may be obtained using the Fast Fourier Transform (FFT) algorithm [146], which decomposes the signal from the time domain into the frequency domain. The number of harmonics included in the analysis can be adjusted depending on the desired precision. Figure 4.2 illustrates the schematic reconstruction of a peripheral pulse wave using different numbers of constituent harmonics.

One of the properties of the arterial pulse waves is that their energy is concentrated in the lower frequencies: f_0 and the first few harmonics contain the majority of the signal's energy, reflecting the pumping action of the heart. Higher-frequency harmonics introduce minor wave fluctuations as depicted in Figure 4.2. Physiologically, this can be explained by the behavior of the arterial system, which acts as a low-pass filter where low-frequency components propagate efficiently, while higher harmonics are quickly dampened due to the viscoelastic properties of arterial walls.

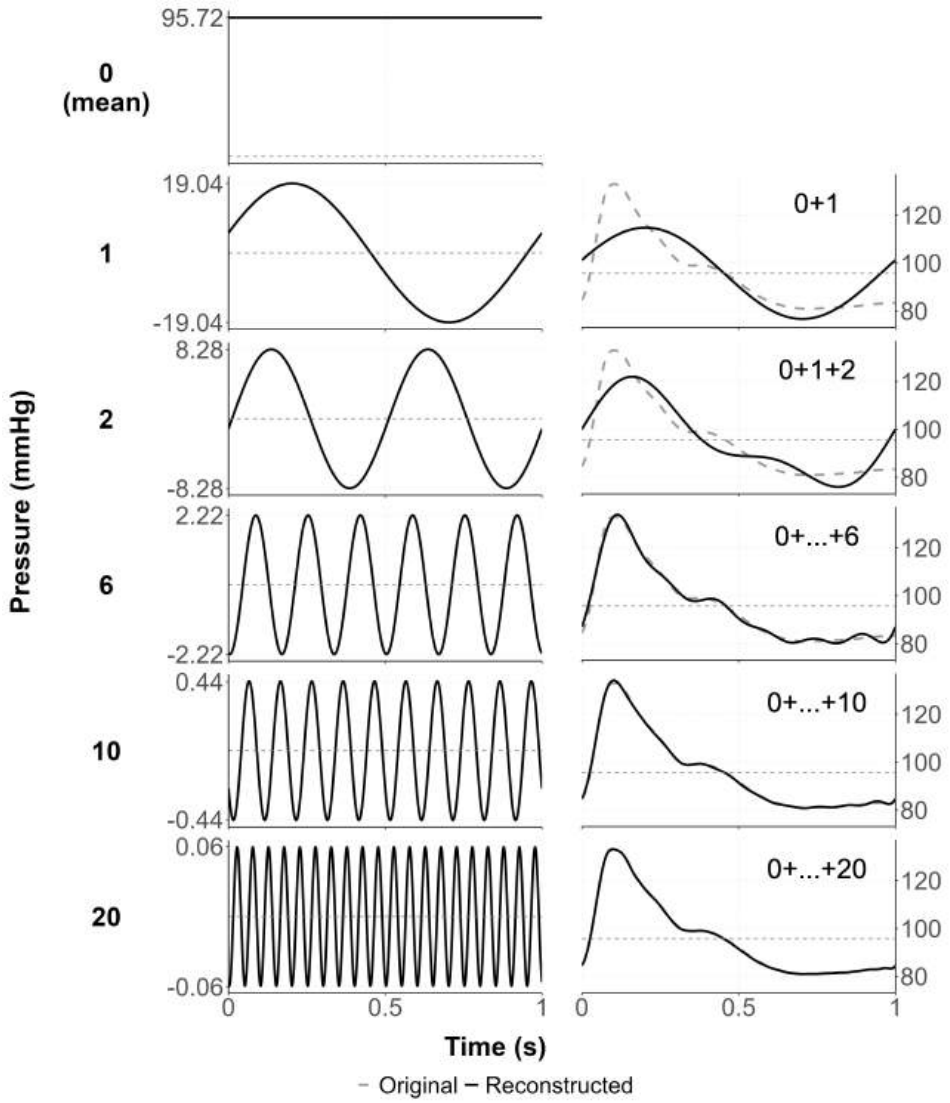

FIGURE 4.2: Fourier analysis and reconstruction of a peripheral pulse wave from a representative subject. The left panel displays the signal's mean pressure (95.72 mmHg) and a selection of its constituent harmonics. The depicted harmonics and their respective amplitudes and phase angles are: harmonic 1 (19.03 mmHg, -1.28 rad), harmonic 2 (8.28 mmHg, -1.71 rad), harmonic 6 (2.22 mmHg, 2.99 rad), harmonic 10 (0.44 mmHg, -2.72 rad), and harmonic 20 (0.06 mmHg, -1.76 rad). The right panel shows the progressive reconstruction of the waveform by cumulatively summing these harmonics, demonstrating that the addition of higher-frequency components refines the signal's morphology to closely approximate the original wave.

Rationale and description of the method

Since the pulse wave signal results from the superposition of forward and reflected waves (as discussed in Section 4.1.1), applying Fourier analysis to decompose it into its constituent harmonics provides a compelling framework for investigation. Each harmonic can be interpreted as a feature that captures a specific aspect of waveform complexity. Pathological vascular changes, such as additional reflection sites caused by calcified plaques or alterations in arterial viscoelastic properties, may thus be reflected in the harmonic structure of the signal. Moreover, analysis of the phase relationships among harmonics can provide insight into the timing of interactions between forward and reflected waves.

Based on this rationale, my further research focused on features derived from the frequency-domain representation of the pressure pulse wave. Specifically, I examined the modulus and phase angle of the signal's sinusoidal components [P2, P3], as well as the derivatives of harmonic amplitudes introduced in [P3]. For clarity, I collectively refer to these parameters as pulse wave–frequency domain features (PW-FDFs). It is also important to recognize that vascular calcification, as well as natural variability in pulse wave morphology, is also influenced by traditional risk factors such as age, sex, height, and heart rate [148]. These covariates were therefore included in my analyses [P2, P3] to ensure appropriate adjustment for potential confounders.

Finally, it needs to be highlighted that although frequency-domain analysis of the pulse wave has been described in several studies [140], to the best of my knowledge, PW-FDFs have not previously been used as direct input to any machine learning model for the detection of vascular calcification. The two papers presented in this and the following chapter are, therefore, the first to evaluate the clinical utility of PW-FDFs in VC assessment.

4.2.2 Research overview

Introduction

In the following paper, I present a framework for detecting medial vascular calcification using a machine learning framework incorporating PW-FDFs extracted from brachial artery signals. I trained easily interpretable logistic regression models, incorporating several embedded feature selection methods to identify the most relevant predictors. Although the study was limited by a relatively small sample size, I ensured a high methodological quality of my work by performing comprehensive data preparation from raw pulse wave signals, addressing class imbalance during model training, and applying cross-validation to evaluate performance. Furthermore, I implemented an ensemble learning strategy [149], which enabled inference from multiple models trained on different feature subsets. This approach allowed me to leverage a broader set of pulse wave-related features while reducing the risk of overfitting, which is a major challenge when working with small datasets.

Taken together, these methodological choices strengthen the validity of my findings and support the reliability of the conclusions derived from my work.

Relation of the publication to the research aims of the thesis

Non-invasive pulse wave measurements offer an attractive avenue for cardiovascular risk stratification [135]. Pressure pulse wave signals can currently be acquired at relatively low cost and with minimal patient burden: cuff-based devices record the wave in a manner similar to routine blood pressure measurement, while pen-like tonometers require more precision but still remain convenient. In some Asian countries, such measurements are taken routinely during patient check-ups, while in the United States and Europe, they are gaining recognition in clinical studies [150]. With the rapid development of wearable technology, it is increasingly plausible that consumer devices such as watches or bracelets will soon capture pressure pulse waves with sufficient precision to match specialized tools, further increasing accessibility. Together, these factors make pressure pulse waves a promising biomarker that can be utilized as a basis for scalable screening tools, thus aligning well with the overall objectives of my research. In this study, I investigated whether peripheral pressure pulse wave signals, acquired from the brachial artery, can provide informative input for machine learning classifiers aimed at detecting medial vascular calcification. I demonstrated that analyzing the wave in the frequency domain yields a set of features suitable for ML model development (H2Q1). The proposed framework achieved clinically relevant accuracy, effectively discriminating between patients with and without mVC (H2Q2). Furthermore, I performed a comparative analysis of models trained on traditional mVC risk factors alone, PW-FDFs alone, and a combined feature set. The results showed that incorporating PW-FDFs alongside conventional risk factors improved predictive performance, underscoring the added value of this approach for mVC detection (H2Q3).

Conclusions

In summary, this research targets the aims of my dissertation by introducing a novel, data-driven framework for early mVC detection. The framework incorporates features derived from frequency-domain analysis of pulse waves, coupled with machine learning algorithms for feature selection and classification. Importantly, this approach enabled reliable classification even when minimal mVC was labeled as a positive case, thereby supporting early detection in patients with advanced CKD without compromising predictive power. In particular, the findings address the second research hypothesis (H2), demonstrating that PW-FDFs provide clinically meaningful input for detecting medial vascular calcification.

4.3 The publication (P2)

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Detection of medial vascular calcification in chronic kidney disease based on pulse wave analysis in the frequency domain

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ABSTRACT

Medial vascular calcification (mVC), particularly prevalent in patients with chronic kidney disease (CKD), is a pathological deposition of minerals in the medial layer of the vessel wall and is associated with an increased risk of cardiovascular disease. Currently, there is no cost–effective and non-invasive procedure of mVC assessment in routine clinical practice. We explored whether in–depth analysis of non-invasively recorded peripheral pulse waves can serve as an effective mVC biomarker.

The study included 97 CKD patients with histological assessment of mVC in the epigastric artery and pulse wave measurements in the brachial artery. Pulse waves were analysed in the frequency domain to obtain features, which, together with traditional mVC risk factors (i.e., age, sex, and body mass index), were used to build generalized linear models for mVC prediction. The classifiers with the best scores in terms of balanced accuracy were combined in an ensemble establishing the final model.

The final, ensembled model, assessed using a leave-one-out cross-validation process, achieved a balanced accuracy equal to 0.87, an accuracy of 0.93, an AUC ROC of 0.91, and an F-score of 0.96. Apart from the features associated with pulse waves, the selected variables included age, sex, body mass index, heart rate and diastolic blood pressure.

Analysis of non-invasively recorded peripheral pulse waveforms combined with traditional risk factors, can help to detect mVC in CKD patients and thus, potentially introduce risk-lowering therapeutic strategies at earlier disease stages in the future.

1. Introduction

Early vascular aging with medial vascular calcification (mVC) is a pathological deposition of minerals occurring in the vascular system [1,2], which is particularly prevalent in patients with chronic kidney disease (CKD) [3,4]. It is accountable for an increased risk of cardiovascular disease (CVD) morbidity and mortality in patients with CKD [5,6]. It has been also reported that the scoring of mVC is an independent predictor of cardiovascular events [7].

While the clinical utility of predicting mVC is uncertain at present, it is possible that therapeutic tools could be developed in the future that would make it meaningful to diagnose and treat those with mVC. Several therapeutic strategies have been already proposed to slow down the progression of vascular calcification [8–10]. For this reason, a simple detection method for determining the presence of mVC, especially at its early stages, is needed. Various techniques have been suggested to accomplish this task. Currently, computed tomography (CT) is a gold-standard non-invasive method of vascular calcification assessment. However, the radiation exposure, high costs, and availability of the examination are potential concerns for utilizing this method in routine clinical practice [11]. Qualitative methods including ultrasonography or x-rays can be utilized in the assessment of macroscopic calcification within the aorta and peripheral arteries [1]. The main limitation of all the aforementioned methods is that they cannot distinguish between the two types of vascular calcification: medial and intimal calcification [12]. One of the biomarkers claimed to be able to specifically detect mVC is

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breast arterial calcification (BAC) which can be assessed using mammography. There have been several studies linking BAC with mVC in CKD patients [13–15]. However, the method is limited to women and involves radiation from x-ray imaging as well. Recently, attempts to make use of machine learning algorithms, relying on circulating biomarkers to predict mVC in CKD patients, have also been made [16].

Another group of methods exploited for the indirect detection of vascular calcification utilizes pulse wave measurements which can be performed non–invasively at various points of the arterial tree [17]. One such method is pulse wave velocity (PWV) assessment, a measure of arterial stiffness [18,19]. The stiffness is associated with vascular calcification; therefore, it is being reasoned that the arteries stiffer than a certain threshold imply a significant calcification. Gathering information regarding patients' arterial condition based on their pulse wave shapes has been extensively studied over the years [20–22] and this approach is commonly used for the initial diagnosis of CVD [23].

The aim of this study is to establish a novel, non-invasive technique of mVC detection in CKD patients based on their peripheral pulse wave measurements. The unique aspect of our method lies in the utilization of pulse wave transformation from the time domain to the frequency domain, extracting distinctive features that have not been explored in previous statistical models trained for the detection of mVC. Such characteristics are much easier to obtain than, for example, PWV measurements. The created variables, together with the traditional risk factors of mVC, serve as input to a statistical model whose task is to distinguish the patients with mVC from those who are free from this pathology. The results were compared with the models relying on pulse wave-associated features only (PW) and patients' characteristics only (PC) to assess the predictive power of pulse waves and traditional risk factors separately.

2. Methods

2.1. Data collection

The study included patients with CKD stage 5 undergoing a living donor kidney transplant. During the procedure, fragments of epigastric arteries were collected to perform histological mVC scoring. The patients were assigned to two groups based on mVC presence. Class 'No mVC' consisted of patients without mVC (n = 18) while class 'mVC' included patients with calcification presence (n = 79). For each patient, a measurement of pulse wave at brachial artery was taken by SphygmoCor System (AtCor Medical, Sydney, Australia). The basic characteristics of the analyzed groups can be found in Table 1. The clinical characteristics considered were those required for conducting pulse wave analysis. In addition to the above measurements, coronary artery calcium (CAC) score was evaluated. A detailed description of all data collection procedures can be found in the supplementary material.

Table 1
Clinical and demographic features of the analyzed patients. Data presented as median [interquartile range] or number (percentage).

Variable	No mVC (n = 18)	mVC (n = 79)	P-value	P-value adj
Age, year	29 [26,44]	47 [36,59]	0.001	0.03
Sex, male**, n (%)	9 (50 %)	61 (77.2 %)	0.04	0.19
BMI, kg/m^2	22.9 [21.2, 24.4]	25.1 [22.6, 27.9]	0.03	0.19
DM **, n (%)	0 (0 %)	7 (8.9 %)	0.42	0.75
HR*, beats/min	64 [59,74]	73 [67, 81]	0.05	0.19
P_SP*, mmHg	149 [134,160]	149 [136, 158]	0.78	0.87
P_DP*, mmHg	95 [89, 103]	90 [82,98]	0.06	0.19

BMI – Body Mass Index, DM – Diabetes Mellitus, P_SP – brachial systolic blood pressure, P_DP – brachial diastolic blood pressure, HR – heart rate, P-value adj – p-value after adjustment for multiple comparisons.

* Welch's *t*-test was performed; otherwise, Wilcoxon rank sum test was performed.

** Pearson's chi-square test was performed.

The inclusion criteria for the study were the same as inclusion for patients who are eligible for kidney transplantation, i.e., CKD5, able to cope with immunosuppressants, and other serious conditions, including chronic infections, cancer, and recent heart attack or stroke. Exclusion criteria were age below 18 years and unwillingness to participate in the study. The patient's informed consent was obtained for all the performed medical procedures. The study conformed to the Declaration of Helsinki and was approved by the regional ethical review board in Stockholm. The selection criteria, clinical procedures, and measurement protocol were described in [16,24].

The only missing value occurring in the analyzed data was one indicator of diabetes mellitus presence. The empty field was imputed with the variable's mode, which was the absence of diabetes; however, we also tested imputing the empty field with a value indicating diabetes presence; the results, significance of the selected variables and overall conclusions did not change.

2.2. Data analysis

A detailed description of the utilized methods is included in the supplementary material.

$P < 0.05$ was considered significant. The full data flow is presented in Fig. 1.

2.2.1. Data preprocessing

Firstly, the signal obtained from brachial arteries was transformed from the time domain to the frequency domain using the Discrete Fourier Transform (DFT) algorithm [25]. Moduli and arguments of the selected harmonics forming the sequence were used as the input features associated with the pulse waves. A set of traditional risk factors such as age, sex, and body mass index were added to the analyzed dataset.

2.2.2. Statistical analysis

Univariable analysis was performed to discover the individual relationships between the explanatory variables (predictors) and the outcome. Initially, the Shapiro-Wilk test of normality [26] was conducted for all continuous predictors grouped with the respect to the value of the target feature. If the assumption of the distribution's normality was not violated, Welch's t-tests [27] were performed to assess the statistical difference in means between the two groups under consideration. Otherwise, Wilcoxon rank sum tests [28] were carried out to detect the location shifts in the variables' distributions. For the categorical features, Pearson's chi-square test [29] was conducted. P-values were adjusted for multiple comparisons using Benjamini-Hochberg correction [30]. Pairwise correlations were investigated using Spearman correlation coefficient.

To show that mVC present in the epigastric artery is an indicator of the calcification process in the general arterial tree, we linked mVC with the CAC score. This validation approach aligns with methodologies employed in previous studies [24,31]. Statistical difference assessment between CAC score levels in the two analyzed groups was performed using the Wilcoxon rank sum test on the subset of 77 patients for whom the CAC score was measured.

Multivariate relationships between mVC presence and the analyzed predictors were assessed using generalized linear models for binary responses [32] with various link functions [33]. To select a subset of independent predictors that would have the best predictive power, stepwise variable selection algorithms were applied. We utilized both forward and backward variable selection methods, each of them used Akaike Information Criterion (AIC) [34] as a stopping rule. The criterion is commonly applied with generalized linear models, and it is a suitable approach in predictive modelling [35]. We handled the problem of class imbalance within the GLM framework by specifying a vector of weights that correspond to a particular class [32]. In our implementation, we

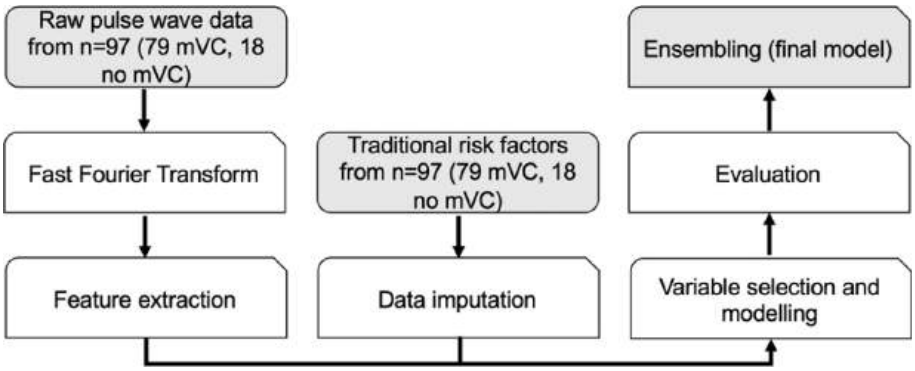

Fig. 1. Data flow. The chart depicts the process of data preparation and modeling. mVC – the presence of medial vascular calcification; no mVC – lack of medial vascular calcification.

performed a grid search to find the best set of weights that would make up for the distorted proportion of classes.

The final model was constructed as an ensemble [36] of the models with the best leave-one-out cross-validation performance in terms of balanced accuracy, which is a proper measure for highly imbalanced datasets [37]. A combination of models which gave the highest classification score with respect to balanced accuracy is presented as the final model. The predicted probabilities of the ensemble were calculated as an arithmetic mean of the cross-validated probabilities returned by the selected models. The optimal cutoff point was determined using Youden index [38].

To validate the predictive power of the proposed method, we conducted similar experiments both for dataset in which only the features related to the harmonics were available (PW features, PW) in the variable selection process and for the dataset which covered only the patients' characteristics (PC features, PC).

2.3. Performance evaluation

The classifiers' performance was assessed using precision, recall (sensitivity), specificity, accuracy, balanced accuracy, F-score, receiver operating characteristic curve (ROC) and area under ROC curve (AUC ROC), whose formulas can be found in the supplementary material. The measures were calculated using the leave-one-out cross-validation process [39] which is an alternative procedure to dividing data into train and test sets, preferred when dealing with a small sample size. We followed a convention that a positive example means the one having the pathology of interest. Therefore, the positive examples are the patients with mVC, and the negative observations are the patients free from this pathology.

3. Results

Following the approach found in the literature [40] and our visualizations, we decided to include up to 20 frequencies in the model-building process. Fig. 2 shows pulse waves of randomly selected patients with medial vascular calcification. Fig. 2a) depicts the pulse waveform in a time domain while Fig. 2b) and 2c) represent the same waveform in a time domain but transformed back from a frequency domain utilizing the first 10 and 20 harmonics, respectively. The transformations from the frequency domain back to the time domain were performed using the inverse Fast Fourier Transform.

For each of the considered harmonics, their moduli and angles were extracted and served as the explanatory variables. A few demographic and clinical features complemented the variables extracted from the pulse waveforms; their list can be found in Table 1.

3.1. Univariate analysis

Univariate analysis revealed that there are significant differences between groups in age, body mass index (BMI) and heart rate (Table 1). Among the features derived from the pulse waves and selected by the models composing the ensemble, the modulus of the mean value of the harmonics (mod0) was significantly different between the groups (Table 2). After the correction for multiple comparisons, only differences between groups in age are statistically significant (Tables 1 - 2).

Spearman correlation analysis showed that the analyzed variables are highly correlated. It is an expected result, especially for the features related to pulse waves. A correlation plot of the continuous features can be found in the supplementary material **(Figure S1)**.

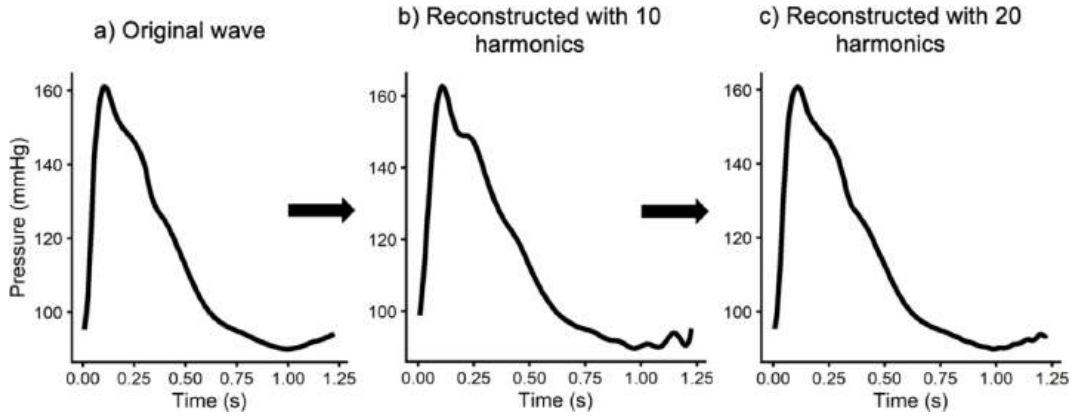

Fig. 2. Pulse wave of an exemplary patient with medial vascular calcification; a) the original waveform, b) the waveform after applying fast Fourier transform, reconstructed using 10 harmonics, c) the waveform after applying fast Fourier transform, reconstructed using 20 harmonics.

Table 2
Features extracted from pulse waveforms that were included in the five models with the best performance presented as their median and interquartile range.

Variable	No mVC (n = 18)	mVC (n = 79)	P-value	P-value adj
Mod0	13063.7 [11832.8 15592.9]	11930.1 [10368.4 13224.0]	0.01	0.18
Mod1	1236.0 [937.5 1427.7]	1203.6 [969.3 1461.8]	0.98	0.98
Mod2	519.2 [476.7 596.4]	545.6 [459.2 597.7]	0.92	0.96
Mod4	190.9 [127.82 212.0]	174.4 [134.7 232.2]	0.77	0.87
Mod5	143.7 [117.4 163.4]	129.9 [95.0 175.7]	0.55	0.86
Mod6	100.5 [57.5 140.4]	75.9 [56.3 106.4]	0.16	0.48
Mod7	62.5 [30.6 91.2]	45.6 [37.2 67.3]	0.36	0.75
Mod8	38.3 [28.1 57.2]	33.5 [23.7 52.4]	0.44	0.75
Mod9	23.9 [19.2 42.8]	25.4 [18.0 33.6]	0.58	0.86
Mod13	9.5 [5.0 14.0]	9.2 [3.4 14.5]	0.71	0.87
Mod15	5.6 [3.4 9.4]	4.9 [2.5 9.9]	0.73	0.87
Mod16	4.6 [2.1 7.3]	3.5 [2.3 7.0]	0.76	0.87
Arg1*	−1.5 [-1.7—1.3]	−1.6 [-1.7—1.4]	0.66	0.87
Arg2	−2.0 [-2.1—1.9]	−2.1 [-2.2—1.9]	0.11	0.38
Arg3	−2.5 [-2.8—2.3]	−2.7 [-2.8—2.4]	0.39	0.75
Arg4	−2.7 [-2.8—2.6]	−2.7 [-2.9—2.5]	0.40	0.75
Arg7	2.5 [2.3 2.7]	2.4 [2.1 2.7]	0.26	0.71
Arg9	2.3 [1.9 2.6]	2.1 [1.5 2.4]		0.32
Arg17	1.2 [0.6 1.7]	1.2 [0.4 2.1]	0.91	0.96
Arg19	1.3 [0.1 2.0]	0.9 [-0.5 1.7]	0.31	0.75

Mod *i* - modulus of the i-th frequency, arg *i* – the angle of the i-th frequency. P-value adj – p-value after adjustment for multiple comparisons.
* Welch's *t*-test was performed; otherwise, Wilcoxon rank sum test was performed.

3.2. mVC and CAC score

CAC scores of the patients with mVC present in the epigastric artery were significantly higher than those of the patients with mVC absent in the epigastric artery (Fig. 3). The mean CAC score of the patients without mVC was 10 ± 35 (median ± IQR: 0 ± 0) while the mean CAC score of patients with mVC was 360 ± 700 (median ± IQR: 12 ± 352). This allows us to conclude that the presence of mVC in the epigastric artery reflects calcification in the general arterial tree.

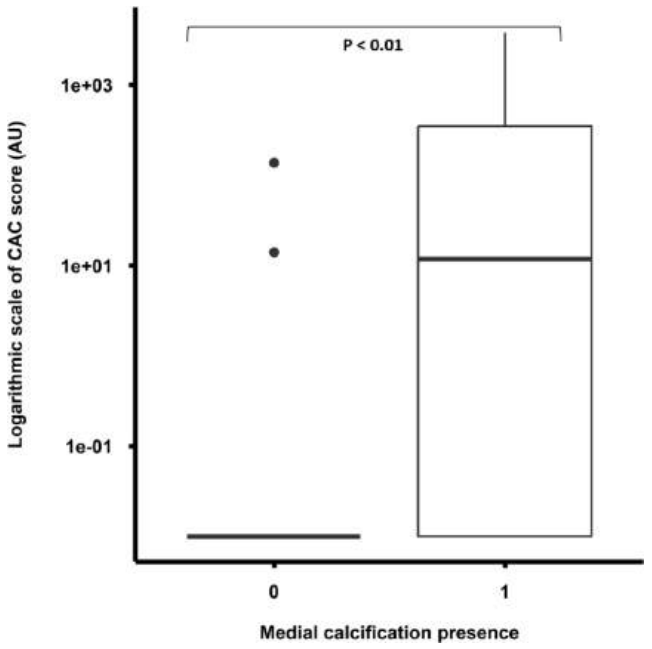

Fig. 3. Coronary artery calcium (CAC) score with respect to medial calcification presence. P – p-value.

3.3. Statistical modelling

In a classification process, combined with stepwise variable selection algorithms, eleven generalized linear models achieved balanced accuracy above the average which was 0.75. Next, all their combinations were tested and the ensemble which had the highest balanced accuracy is presented as the final model. It consists of five regression models with various link functions which are described in detail in the supplementary material.

The classification frameworks differed while training each of the above models, therefore each of them chose a different subset of variables as input features. The number of predictors varied from 6 in the weighted logistic and probit regressions (models PWPC1 and PWPC3) up to 15 in logistic regression combined with backward stepwise variable selection working with 20 harmonics (model PWPC5) (Table 3). The amplitude of the second harmonic and age were selected by each of the algorithms (Table 3). In the models with the smallest number of predictors, all of them were statistically significant (Table 3).

The balanced accuracy of the five models varied from 0.75 for model PWPC5 up to 0.82 for model PWPC3. The calculated metrics for the classifiers comprising the ensemble are presented in the supplementary material in **Table S3**. The ensemble, which was built out of these five models, outperformed all the individual classifiers in each of the analyzed metrics (**Table S3**). The threshold for the final, ensembled classifier, determined using Youden Index, was 0.54. Therefore, each of the observations with a probability higher than 0.54 of belonging to class 'mVC' was labeled accordingly.

The mean balanced accuracy of the built classifiers working both with the PW features only and with the PC features only was 0.7. A detailed description and the results of these experiments can be found in the supplementary material. We compared the performance of the built ensembles in terms of all the analyzed measures. The ROC curves of the discussed models are plotted in Fig. 4 while confusion matrices of the ensembles are presented in Fig. 5. The full list of the computed metrics and their values can be found in Table 4.

The confusion matrices of the final classifiers show that even though the group without mVC is greatly underrepresented, we can identify correctly most of its members both by the classifiers working with pulse waves and with the traditional risk factors. The model working with PW and PC features outperformed the classifiers deprived of one of the types of variables (Table 4). It is also worth noting that it is the most robust out of the built ensembles, displaying minimal differences between the results obtained using assessment with nested cross-validation and without it (data not shown). The model working with pulse waves only is

Table 3
The input features used by the models that made up the PW and PC features ensemble.

Model PWPC1	Model PWPC2	Model PWPC3	Model PWPC4	Model PWPC5
Mod0*	Mod0	Mod0*	Mod1*	Mod2
Mod2*	Mod2	Mod2*	Mod2*	Mod4
Mod16*	Mod4	Mod16*	Mod5*	Mod5
Arg3*	Mod9	Arg3*	Arg1	Mod6
Age*	Arg2	Age*	Arg3*	Mod7
Sex*	Age	Sex*	Arg4	Mod8
	BMI		Arg7	Mod13
	HR		Age*	Mod15
	P_DP		HR*	Arg1
	Sex		P_DP*	Arg9
			Sex*	Arg17
				Arg19
				Age
				BMI
				HR

HR – heart rate, BMI – body mass index, P_DP – brachial diastolic blood pressure, Mod *I* - modulus of the i-th frequency, arg *i* – the angle of the i-th frequency.
* $P < 0.05$.

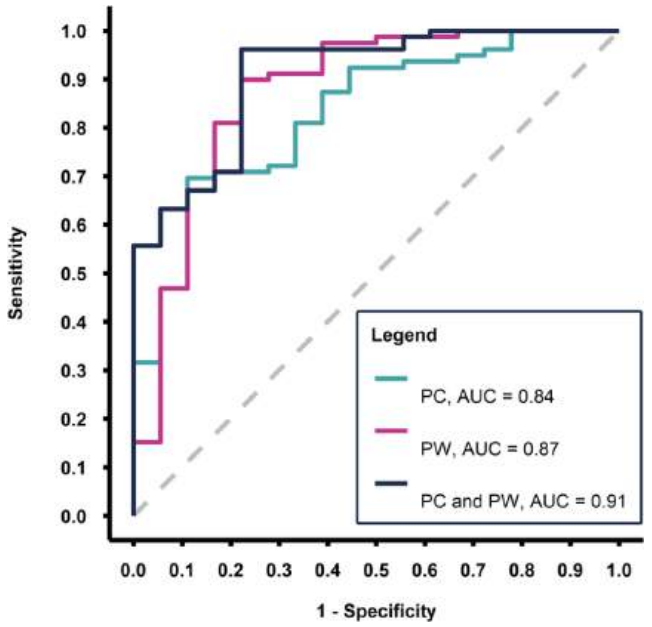

Fig. 4. Receiver operating characteristic curves of the three probit regression models and their ensemble. PC – the model with patientś characteristics only, PW – the model with pulse waves only, PC an PW – the model with both types of features, AUC – area under the curve.

capable of detecting most of the classes' true members; however, it is worse in the detection of the positive class than the PW and PC ensemble (Fig. 4). It also exhibits a little overfitting mostly in terms of specificity (0.78 vs 0.72 when comparing results without and with nested cross-validation). On the other hand, the model working with patients' characteristics only is worse in the detection of the negative observations than the PW and PC ensemble (Fig. 4). In the PW and PC features ensemble, among those patients, who were misdiagnosed as the ones not having mVC, one suffered from minimal mVC while two had moderate mVC. The three individuals were under the age of 30, making them outliers according to Table 1. All patients with extensive mVC were classified correctly.

4. Discussion

In our study, we developed a simple, non-invasive framework to detect mVC in patients with CKD. For this purpose, we utilized the features derived from the pulse waves analyzed in the frequency domain, whose signal was captured in the patients' brachial arteries. With the addition of traditional risk factors for mVC such as age and sex, we performed variable selection and patient classification. The final model, built out of an ensemble of five generalized linear models, relied on the features associated with the waveforms as well as on the patients' characteristics such as age, sex, and BMI. It achieved satisfactory predictive power with an accuracy of 0.93, an F-score of 0.96, and an AUC of 0.91. Most of the selected features were significant at the level of 0.05, which shows that the wave complements the traditional risk factors for mVC [2]. In the classifiers with the highest number of predictors, the selected variables were not significant. The reason behind it is a high degree of collinearity present in the data which was shown using Spearman correlation coefficient (**Figure S1**). Traditionally, such setting violates the assumption of the predictors' independence in linear models. However, if one is interested only in prediction, not the inference, it is not an issue [41]. Since we do not want to reason how the particular features related to pulse waves impact the probability of calcification presence, we decided not to discard these models. Moreover, the multicollinearity between the features associated with pulse waves is expected and the omission of some of them could negatively impact the performance.

The univariate analysis revealed that we cannot reject the hypothesis of no significant differences in the means of the amplitudes and phase angles between the patients with and without mVC. On the other hand, all the applied classification frameworks selected some of the features associated with the waveforms and, in most of the models, they were statistically significant. This proves that it is the combination of the variables associated with pulse waves that transmits information about the mVC presence, not the individual features. To prove the real clinical value of the pulse wave in mVC detection, we additionally assessed predictive performance of models built without the traditional risk factors and with the traditional risk factors only. Even though the sample size was small, the classifier working with both PC and PW features outperformed the aforementioned ones. However, it is worth noting that the classifier built with PC features only achieved promising results as well and, in the lack of the tools to capture pulse wave signal, could be alternatively used as a low-cost mVC assessment method.

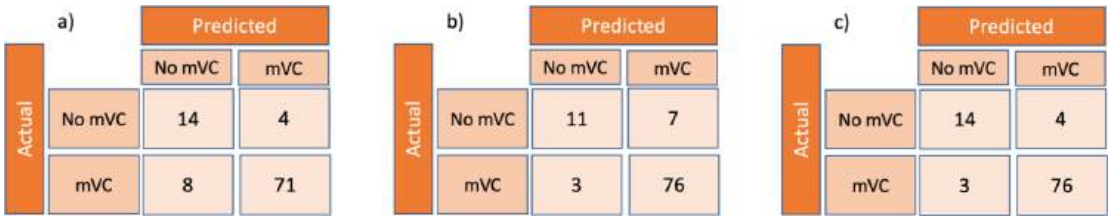

Fig. 5. Confusion matrices of a) the ensemble built with PW features only and b) the ensemble built with PC features only and c) the ensemble built with both PW and PC features. mVC – the presence of medial vascular calcification; no mVC – lack of medial vascular calcification.

Table 4
Performance metrics of the built ensembles.

Model	Precision	Recall	Specificity	Accuracy	Balanced accuracy	F-score	AUC
Ensemble PW only	0.95	0.90	0.78	0.88	0.84	0.92	0.87
Ensemble PC only	0.92	0.96	0.61	0.90	0.79	0.94	0.84
Ensemble PW and PC	**0.95**	**0.96**	**0.78**	**0.93**	**0.87**	**0.96**	**0.91**

AUC – area under the receiver operating characteristic curve, PW only – the model with pulse wave associated features only, PC only – the model with patients' characteristics only,
PW and PC – the model with all of the analyzed features. The latter outperformed the other classifiers, which is highlighted by the bold values.

Medial vascular calcification is a pathological mineral deposition in the walls of vessels associated with an increased risk of cardiovascular events [3]. To the best of our knowledge, its assessment is rarely carried out and its detection is mainly incidental. Based on the location of calcification, two main types are distinguished: intimal and medial calcification. The latter is particularly prevalent in patients with CKD [3]. This prevalence is reflected in the proportion of the patients with the pathology (81 %) in the analysed sample and is consistent with the previous studies considering mVC in end-stage renal disease patients [13] The distinction between the two types of calcifications is relevant from a clinical point of view because they lead to different clinical consequences and require separate treatment [42,43]. Currently, there does not exist a dedicated method of mVC assessment and each of the used tools has its limitations. Computed tomography and x-ray imaging, apart from exposing the patients to radiation and high operating costs, cannot distinguish between medial and intimal calcification [12]. BAC, limited only to women, also relies on x-ray imaging. Ultrasonography cannot distinguish between the two types of vascular calcification and is unable to detect the initial stages of the early vascular ageing processes [1]. The studies utilizing statistical modelling were trying to predict whether the patient has no or minimal calcification vs moderate or extensive calcification [16] whereas early detection of the pathology can be crucial for providing the treatment that can slow down the progression. One of the reasons why mVC is not examined may be the lack of an easy-to-use efficient diagnostics tool that can be used in routine clinical practice.

The commonly used methods of pulse wave analysis describe predefined characteristics of the recorded waves rather than the whole waveform [44–46]. Parameters such as pulse height, ejection duration, diastolic duration, augmented pressure, augmentation index, end-systolic pressure or subendocardial viability ratio derived from pulse wave profile are usually separately studied [47]. Considering only the parameters obtained through the pulse wave analysis, important information may be lost. Our process, contrary to popular methods of analyzing pulse signals, ensures the inclusion of the whole waveform in the analysis. The proposed approach is closely related to the physiological aspects of arteries. The primary wave travels along the arteries where it generates reflected waves from bifurcations, plaques, and from the peripheral vascular beds [48]. All these small, reflected waves return to the aorta and then propagate again. The captured signal is therefore the sum of the outgoing and reflected waves at various arterial tree locations. The speed at which the outgoing and reflected waves travel is dependent on the stiffness of the arteries along which they are traveling. So, if a person has stiffer arteries, the waves will travel out and back quicker. By using the discrete Fourier transform, we, in a sense, reverse this process. The idea is to decompose the waveform into its sinusoidal components. The properties of these individual waves, namely their amplitudes and phase angles, should reflect the patients' arterial condition. For this reason, they may differ between the patients with and without mVC.

A novelty of our study is the proposed method of detection of mVC presence. According to our knowledge, up to this date, pulse waves were not directly used to assess the presence of mVC. Although statistical modelling algorithms are becoming increasingly popular in many areas of biomedicine, only a few studies have attempted to use them for mVC detection [6,49]. The previously conducted studies relied on the features derived mostly from the patients' blood, based on which the statistical models predicting calcification presence were built [6,49]. While the results were promising, all the algorithms needed very specific, rarely measured, and costly to evaluate biomarkers [6,24,49]. Therefore, such models may be inefficient to be used in clinical practice.

The proposed method is characterized by its applicability. When capturing pulse wave signals and performing pulse wave analysis, the traditional risk factors of mVC and patients' characteristics are entered into the machine. Moreover, the discrete Fourier transform is used by the recorder to transmute the peripheral signal to the central one, so the amplitudes and phase angles are calculated. Therefore, all the measurements and transformations needed to be gathered to execute the proposed procedure are already performed while capturing pulse waves using applanation tonometry. Implementation of the model's weights would require minimal input. The applicability of the proposed method is also shown by using cross-validation procedure to assess the predictive power of the model. We proved that the selected features are not only statistically significant but that they also carry real clinical value which can help with mVC diagnostics.

In our study, we had brachial pulse wave measurements at our disposal, and they were used for the modeling; it can be assumed though, that the waves measured at different points of the arterial tree provide a similar or even greater amount of information about the patient's arterial condition. Therefore, it would be possible to build models similarly based on the waveforms captured in the other points of the patient's body. Especially interesting would be to measure the wave at fingers or toes since pulse wave propagation can be influenced by atherosclerosis [50]. The same logic applies to patients without CKD. After adjustment, our method could be used to detect the discussed pathology in patients without CKD.

One of the limitations of our study was the relatively small number of patients. This can cause a lack of the classifier's generalization, i.e., the model would overfit and have trouble assigning the correct labels to the new observations. To prevent such behavior, we created an ensemble of models built with the use of various techniques. Such a method is known to be more robust than the utilization of individual models [36]. Moreover, it allowed us to consider a relatively large number of predictors concerning pulse waves despite a small sample size. Furthermore, we introduced nested cross-validation into the ensemble learning process to evaluate its robustness, revealing no (PWPC ensemble) or minimal (PC, PW ensembles) signs of overfitting (data not shown). Nevertheless, we maintain the perspective that a longitudinal study is essential to ascertain the optimal classification threshold, beyond which patients warrant further investigation. Another possible limitation is how the mVC presence was assessed in our study. To show that we can make inferences about the calcification in the arterial tree from the information about calcification in the epigastric artery, we included CAC score analysis in the research. However, a more extensive analysis should be performed to confirm the initial findings. Additionally, it is important to note that the study's scope did not allow for a detailed investigation of the distinction between medial and intimal calcification. This limitation underscores the need for further investigation to ascertain the feasibility of differentiating between these calcification types.

In summary, we show that pulse wave signal is an independent mVC biomarker and its utilization to detect mVC presence is justified in CKD - the pathology can be identified with satisfactory result using statistical algorithms working on the features associated with pulse waves. Such an approach is non-invasive, low-cost, and safe. Moreover, the method is easy to implement in the pulse wave recorders since they already use the discrete Fourier transform in the process of translating the peripheral pulse signal into the central pulse signal. In addition, we managed to show that alternatively, in the absence of the tool required to capture pulse wave signal, a model working with basic patient characteristics can be applied. We believe that this study has potential for further research and development; a longitudinal study is needed to determine whether the proposed framework can be used as an independent tool of mVC detection. In the future, such a method may be used in a clinical routine to assess mVC presence not only in CKD but also other patient groups.

5. Sources of founding

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CRediT authorship contribution statement

U. Bialonczyk: Writing – original draft, Visualization, Methodology, Formal analysis, Data curation. **M. Debowska:** Writing – review & editing, Validation. **L. Dai:** Writing – review & editing, Validation. **A.R. Qureshi:** Data curation. **M. Söderberg:** Validation, Supervision. **B. Lindholm:** Writing – review & editing, Validation, Supervision. **P. Stenvinkel:** Writing – review & editing, Validation, Supervision. **J. Poleszczuk:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bspc.2024.106250.

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SUPPLEMENTARY MATERIAL

Suplemental software

Data preprocessing, modeling, and performance evaluation were implemented in R version 4.0.5 using the following packages:

- stats 4.0.5 – a built-in package for statistical analysis,
- dplyr 1.0.5 – a package for data manipulation,
- data.table 1.14.0 – a package for data manipulation,
- PRROC 1.3.1 – a package for performance evaluation,
- ggplot2 3.3.5 – a package for visualizations,
- corrplot 0.84 – a package for correlation plots.

Supplemental data collection

To assess mVC presence, a small segment (approximately 1-2 cm long) of the inferior epigastric artery was collected shortly after making an incision on the skin to begin the surgery. These samples were immediately placed in All Protect Tissue Reagent from Qiagen (Hilden, Germany) and frozen in isopentane before being stored at -70 °C. Alternatively, some samples were fixed in 4% phosphate-buffered formalin; the formalin-fixed materials from the

epigastric arteries were embedded in paraffin. Thin sections (approximately 1-2 µm thick) were stained with hematoxylin and eosin and von Kossa staining for further evaluation. An experienced pathologist assessed the sections. The extent of medial calcification was analyzed on the von Kossa-stained sections, using a semi-automated quantification method. In this process, the slides were captured at four times magnification with a Nikon Eclipse E1000 light microscope from Nikon, Tokyo, Japan. Using the ImageJ software (http://rsb.info.nih.gov/ij/), the tunica media and intima of each slide were identified manually, and their respective areas were measured. Subsequently, a threshold was set to select the calcified area, and the degree of calcification was calculated as the ratio of the calcified area to the area of tunica media and intima.

In order to calculate CAC score, first cardiac CT scans were conducted with a 64-channel detector scanner (LightSpeed VCT; General Electric (GE) Healthcare, Milwaukee, WI) operating in cine mode. The scans were ECG-gated, and a standard non-contrast protocol was utilized, with the following parameters: tube voltage of 100 kV, tube current of 200 mA, rotation time of 350 ms, slice thickness of 2.5 mm, and a displayed field of 25 cm. The identification of calcium deposits in the coronary arteries was carried out by a highly qualified radiologist. Data processing and analysis were conducted using an Advantage Workstation 4.4 (GE Healthcare) while to assess CAC scores, Smartscore 4.0 (GE Healthcare) was utilized considering calcified plaques as present when their values exceeded the standard threshold of 130 Hounsfield units. The total CAC score, expressed in Agatston units (AU), was calculated by summing the CAC scores in the left main artery, the left anterior descending artery, the left circumflex artery, and the right coronary artery.

Supplemental data analysis

Discrete Fourier Transform

Discrete Fourier Transform (DFT) [25] is a mathematical procedure that can be used to convert a finite sequence of equally spaced data points of a function of time into a complex-valued function of frequency under the assumption that the input signal is periodic. The sequence is represented as harmonics – each characterized by two values: the modulus (mod) of the complex value representing the amplitude of a constituent sinusoid associated with the harmonic's frequency and the argument (arg) of the complex value associated with that sinusoid's phase offset. The smoother the signal is, the fewer harmonics are needed to describe it. For this reason, discrete Fourier transform is a commonly-used tool enabling reducing data dimensions without losing any important information – the harmonics' frequencies that contain little information about the signal can be neglected. Formally, let $x_0, \dots, x_{n-1}$ be a sequence of equally spaced, complex numbers; the discrete Fourier transform is defined by the following formula [50]:

$$X_k = \sum_{j=0}^{n-1} x_j e^{-\frac{i2\pi kj}{n}} \qquad (S1)$$

Where $k = 0, \dots, n-1$ and $e^{-i2\pi/n}$ is a primitive n-th root of 1. The harmonics' amplitude and phase can be calculated using the below formulas.

Amplitude (modulus):

$$mod(X_k) = \frac{1}{n}|X_k| = \sqrt{Re(X_k)^2 + Im(X_k)^2}, \quad (S2)$$

phase (argument):

$$\arg(X_k) = -i \cdot \ln\left(\frac{X_k}{|X_k|}\right). \quad (S3)$$

One of the most popular algorithms used for computing DFT, which was utilized in our research, is the fast Fourier transform (FFT) [51].

Generalized linear models

A generalized linear model (GLM) is a modeling technique that allows the outcome variable Y to have an error distribution other than a normal one. In GLM the response is assumed to be generated from an exponential family distribution – a large class of probability distributions that includes, among others, normal, binomial, or Poisson distribution [31]. The fundamental equation of the GLMs states that the conditional expected value of the outcome is related to the independent variables through a particular link function [31]. The latter depends on the response's distribution. Due to our data characteristics, in the present work, we focused on GLMs for binary responses i.e., the models for the outcome following binomial distribution such as logistic or probit regression [31]. It is possible to model the probability using other link functions for the Bernoulli distribution, such as Cauchy or complementary log-log [32]. All the aforementioned methods were tested during the experimental part. Regardless of the chosen link function, the goal is to estimate the probability of an observation belonging to one of the two alternative classes

given a set of features. Based on this probability, and after finding the optimal threshold (a cutoff value for the calculated probability above which we can say that the observation belongs to a particular class), labels can be assigned to the observations. One of the challenges which can occur in modeling binary responses is the dataset's imbalance i.e., one class has considerably more representatives than the other. In such cases, special techniques need to be applied to compute valid coefficients' estimates and their standard errors. The problem can be handled within the GLM framework by specifying a vector of weights that correspond to a particular class [31]. In our implementation, we performed a grid search to find the best set of weights that would make up for the distorted proportion of classes.

Ensemble learning

In statistics, an ensemble of models can be used to reduce the variability of a machine-learning model [35]. Moreover, ensembles usually achieve better predictive performance than could be obtained from any of the built models alone [52]. It is particularly useful when dealing with small, imbalanced datasets, where more generalization is needed. The main idea of ensemble learning is to combine the trained models and to predict the class labels based on all of them. Making predictions out of an ensemble can be done using, for example, a (weighted) average of the probabilities returned by the classifiers or calculating a mode of the labels predicted by the individual models. In our work, during the modeling part, various models were constructed – variable selection methods differed, several link functions in GLMs were tested and weighting techniques were applied to put

more focus on the underrepresented class. Therefore, it was possible to utilize ensemble learning in our research.

Youden Index

The Youden index, sometimes called Youden's J statistic, is a measure whose aim is to summarize the performance of a classifier. It is defined as a sum of sensitivity and specificity reduced by 1 and its value ranges from 0 (worst) to 1 (best). The Youden index is often used as a complementary tool to ROC analysis. The index can be defined for all points of the curve and its maximum value may be used to select an optimum cutoff point. Therefore, instead of assigning a particular label above an arbitrarily chosen threshold (e.g., probability > 0.5 means assigning a new observation into a positive class), we may use the index to find the best threshold for the built classifier. This method was applied in our classification framework for the final, ensembled classifier.

Performance measures

The classifiers' performance was assessed using the following metrics.

- Precision – a fraction of truly positive examples among the ones classified as positive.

$$Precision = \frac{TP}{TP + FP} \quad (S4)$$

- Recall (sensitivity) – a fraction of correctly predicted positive examples out of all positives.

$$Recall = \frac{TP}{TP + FN} \quad (S5)$$

- Specificity – a proportion of correctly identified negatives over the total negative prediction.

$$Specificity = \frac{TN}{TN + FP} \quad (S6)$$

- Accuracy – a proportion of correctly identified observations over the total number of predictions made.

$$Accuracy = \frac{TN + TP}{TN + TP + FN + FP} \quad (S7)$$

- Balanced accuracy (Balanced ACC) – a mean of specificity and recall. Useful when assessing models' performance on imbalanced datasets.

$$Balanced\ ACC = \frac{Specificity + Recall}{2} \quad (S8)$$

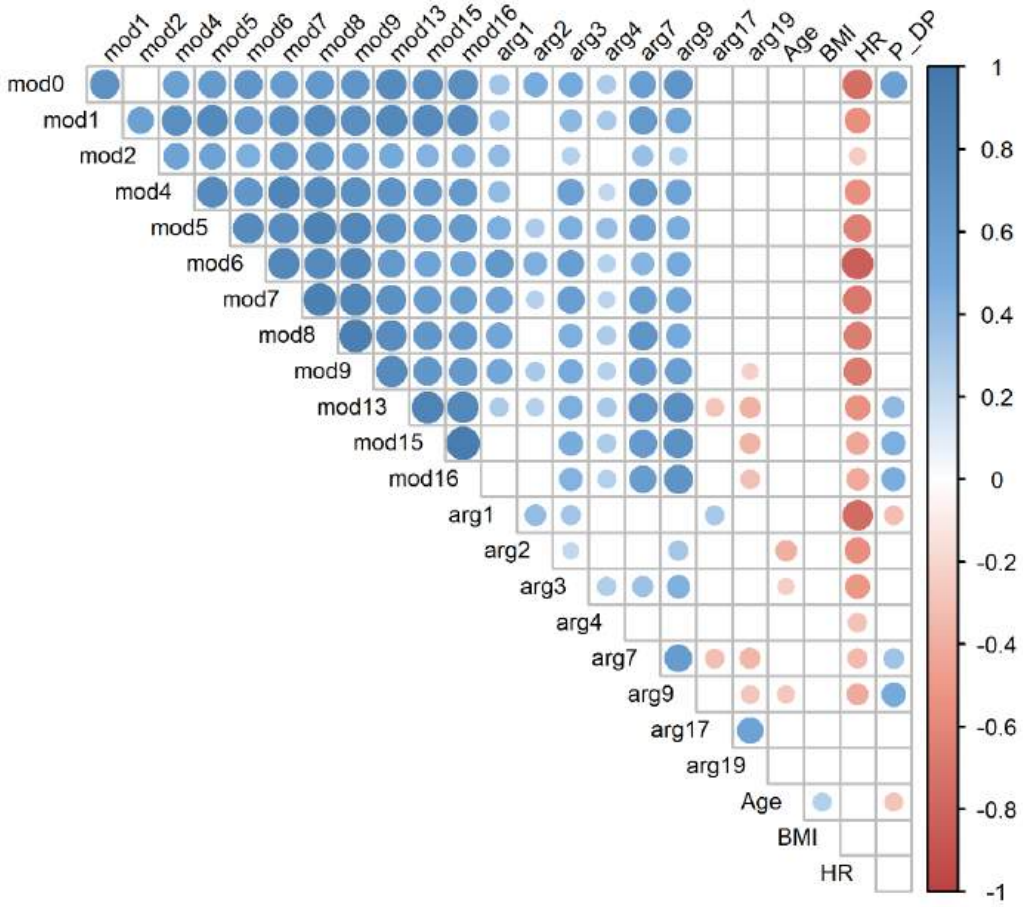
- F-score – a harmonic mean of precision and recall.

$$F - score = 2 \cdot \frac{Precision \cdot Recall}{Precision + Recall} \quad (S9)$$

- Receiver operating characteristic curve (ROC) – a chart created by plotting recall against 1-specificity.
- The area under the ROC curve (AUC) – a summary of the ROC curve. The probability that the built classifier will rank a randomly selected positive observation higher than a randomly selected negative one.

Supplemental results

Figure S1: Correlation plot of the input features used by the PW and PC ensemble. Blank spaces denote correlations statistically insignificant. The calculated p-values were adjusted for multiple comparisons using Benjamini-Hochberg method.



Models comprising the PWPC features ensemble:

- Model PWPC1: weighted logistic regression, forward stepwise variable selection. The weights' value was 1 for positive examples and 2 for negative ones.
- Model PWPC2: weighted Cauchy regression, forward stepwise variable selection. The weights' value was 1 for positive examples and 2 for negative ones.
- Model PWPC3: weighted probit regression, forward stepwise variable selection. The weights' value was 1 for positive examples and 2 for negative ones.
- Model PWPC4: logistic regression, backward stepwise variable selection with 10 harmonics and patients' characteristics seen during selection process.

- Model PWPC5: logistic regression, backward stepwise variable selection with 20 harmonics and patients' characteristics seen during selection process.

Models comprising the PW features ensemble:

- Model PW1: Cauchy regression, forward feature selection with variables related to 10 harmonics seen during fit.
- Model PW2: Cauchy regression, forward feature selection with variables related to 20 harmonics seen during fit.
- Model PW3: weighted probit regression, forward feature selection with variables related to 20 harmonics seen during fit. The weights' value was 1 for positive examples and 2 for negative ones.

Table S1: The input features used by the models that made up the PW features ensemble.

Model PW1	**Model PW2**	**Model PW3**
Mod0*	Mod0	Mod0*
Mod1*	Mod1	Mod1*
Mod5	Mod3	Mod5*
Mod6	Mod4	Mod7*
Arg1*	Mod5	Mod10
Arg4	Mod6	Mod13*

	Mod18	Mod16
	Arg1	Mod18
	Arg4	Mod19
	Arg17	Arg1*
	Arg18	Arg3*
		Arg4*
		Arg8
		Arg17
		Arg19

Mod *I* - modulus of the i-th frequency, arg *i* – the angle of the i-th frequency.

* p-value < 0.05.

Models comprising the PC features ensemble:

- Model PC1: Weighted logistic regression, forward variable selection. The weights' value was 1 for positive examples and 2 for negative ones.
- Model PC2: Cauchy regression with backward variable selection.

Table S2: The input features used by the models that made up the PC features ensemble.

Model PC1	**Model PC2**
Age*	Age*
HR*	HR*

P_DP*	P_DP*
Sex*	P_SP
	Height

HR – heart rate, P_DP – brachial diastolic blood pressure, P_SP – brachial systolic blood pressure.

* p-value < 0.05.

Table S3: Performance metrics of the classifiers comprising the PW and PC ensemble. The bolded values of the measures indicate the highest value.

Model	**Precision**	**Recall**	**Specificity**	**Accuracy**	**Balanced accuracy**	**F-score**	**AUC**
Model PWPC1	0.93	0.90	0.72	0.88	0.81	0.92	0.87
Model PWPC2	0.91	0.92	0.61	0.87	0.77	0.92	0.87
Model PWPC3	0.94	0.91	0.72	0.88	0.82	0.92	0.88
Model PWPC4	0.91	0.95	0.61	0.89	0.78	0.93	0.87

Model PWPC5	0.91	0.90	0.61	0.85	0.75	0.90	0.75
Ensemble PWPC	**0.95**	**0.96**	**0.78**	**0.93**	**0.87**	**0.96**	**0.91**

Table S4: Performance metrics of the classifiers comprising the ensemble of models working with PW features only. The bolded values of the measures indicate the highest value.

Model	**Precision**	**Recall**	**Specificity**	**Accuracy**	**Balanced accuracy**	**F-score**	**AUC**
Model PW1	0.90	0.95	0.56	0.88	0.75	0.93	0.81
Model PW2	0.92	**0.96**	0.61	**0.90**	0.79	**0.94**	0.86
Model PW3	0.93	0.86	0.72	0.84	0.79	0.89	0.77
Ensemble PW	**0.95**	0.90	**0.78**	0.88	**0.84**	0.92	**0.87**

Table S5: Performance metrics of the classifiers comprising the ensemble of models working with patients' characteristics only. The bolded values of the measures indicate the highest value.

Model	Precision	Recall	Specificity	Accuracy	Balanced accuracy	F-score	AUC
Model PC1	0.89	0.92	0.5	0.85	0.71	0.91	0.83
Model PC2	0.89	**0.97**	0.5	0.89	0.74	0.93	0.79
Ensemble PC	**0.92**	0.96	**0.61**	**0.90**	**0.79**	**0.94**	**0.84**

5

POTENTIAL OF PULSE WAVE SIGNAL FREQUENCY-DOMAIN ANALYSIS FOR ELEVATED CORONARY ARTERY CALCIFICATION SCORE SCREENING

5.1 Intimal vascular calcification

Background and clinical implications

Coronary artery calcification (CAC) score, discussed in detail in the subsequent section, serves as a proxy for intimal vascular calcification. iVC is closely linked to atherosclerosis and is typically observed in large arteries such as the aorta and coronary vessels; however, it is not confined to these sites and can also be detected in other locations such as renal arteries and peripheral arteries of the limbs [151]. Moreover, it can co-occur in multiple arterial sites [152]. It is more frequently observed in older individuals and in patients with cardiovascular risk factors such as hypertension, diabetes, dyslipidemia, and CKD, who often exhibit both accelerated atherosclerosis and an increased VC burden [153].

iVC develops within the intimal layer of the arterial wall, specifically within atherosclerotic plaques. It indicates an advanced stage of plaque progression and arises as a consequence of endothelial injury, which triggers a chronic inflammatory response - one of the key drivers of VC. Such an environment promotes not only further lipid accumulation but also the infiltration of immune cells, including macrophages and T-lymphocytes, which act as mediators and stimulate VSMCs to migrate from the media to the intima [154]. There, they proliferate and undergo osteogenic differentiation, which contributes to the formation of calcified plaque components. As the lesion evolves, apoptotic bodies, matrix vesicles, and necrotic debris from dying macrophages and VSMCs provide nucleation sites for calcium phosphate crystallization, initiating the biomineralization process [155]. iVC typically progresses from small, spotty microcalcifications to larger, consolidated macrocalcifications [155].

Microcalcifications, often appearing as punctate or spotty deposits, are associated with increased plaque instability - they create points of mechanical stress within the fibrous cap, increasing the risk of plaque rupture [154]. Ruptured plaques may, in turn, lead to thrombus formation, which can abruptly occlude the vessel and cause acute cardiovascular events such as myocardial infarction or stroke. Indeed, studies have demonstrated that microcalcifications are more frequently observed in patients with acute coronary syndromes compared to those with stable coronary artery disease [156]. However, these small calcific deposits are typically beyond the

resolution limits of conventional CT imaging used for iVC assessment [157]. PET-CT imaging with sodium fluoride has been proposed as a tool for identifying early-stage microcalcifications and high-risk plaques, but its availability in clinical settings remains limited [154]. In contrast, macrocalcifications (larger, more extensive calcium deposits) are often considered stabilizing features within atherosclerotic plaques. These dense calcific regions may serve as reinforcements of the plaque structure, thereby reducing the likelihood of rupture or erosion [157]. Patients with macrocalcifications tend to have a lower risk of acute coronary events due to rupture, but they are prone to suffer from chronic lumen narrowing (stenosis) and impaired blood flow [158]. Extensive calcification contributes to increased arterial stiffness and reduced vascular compliance [159].

In clinical practice, intimal macrocalcification is most commonly assessed in the coronary arteries. A widely adopted method for this is the CT-based coronary artery calcification scoring system. However, as mentioned previously, this method cannot differentiate between intimal and medial calcification. Consequently, the CAC score reflects the total arterial calcification burden, encompassing both calcification types. Nonetheless, several studies have shown that mVC is relatively uncommon in the coronary arteries [80]. Even in CKD patients, coronary mVC has been observed only occasionally [101]. Therefore, it is reasonable to assume that the CAC score in this context predominantly reflects intimal calcification and can be interpreted as its proxy.

5.1.1 Coronary artery calcification (CAC)

CAC is one of the most extensively studied markers of coronary artery disease, serving as a robust indicator of atherosclerotic plaque burden. The development of the coronary artery calcification score (CAC score) has enabled standardized and reproducible quantification of calcific lesions in the coronary arteries and has become a valuable tool in cardiovascular risk stratification.

The conventional method for CAC scoring relies on a non-contrast, ECG-gated CT scan of the chest. This imaging approach captures the entire epicardial coronary system and detects calcific areas based on radiodensity thresholds. Specifically, a calcific lesion is defined as a hyperdense region with a radiodensity of $\geq$130 HU (*Hounsfield Units*, a measure of tissue density in CT imaging) and must cover an area of at least three adjacent pixels, corresponding to ≥ 1 mm^2. CAC assessment is typically performed using the Agatston method [160], which assigns a score by multiplying the area of each calcified lesion by a weighting factor based on the peak density of calcium within that lesion. Summing up the scores for all calcific lesions gives the total CAC score expressed in Agatston units (AU). This approach provides a semi-quantitative estimate of both the extent and density of coronary calcification. To stratify cardiovascular risk, standardized CAC categories have been proposed [161] as shown in Figure 5.1.

In some cases, scores exceeding 1000 AU are used to indicate exceptionally high coronary calcification and correspondingly elevated cardiovascular risk [162].

The relative simplicity and cost-effectiveness of CAC scoring have enabled its widespread use in large-scale, multi-center studies such as the *Coronary Artery Calcium Consortium* [163] or the *Multi-Ethnic Study of Atherosclerosis (MESA)* [164]. These studies have consistently demonstrated that the CAC score is an independent predictor of cardiovascular risk and all-cause mortality. Its predictive value has been validated across various subgroups, including younger adults [165], men and women

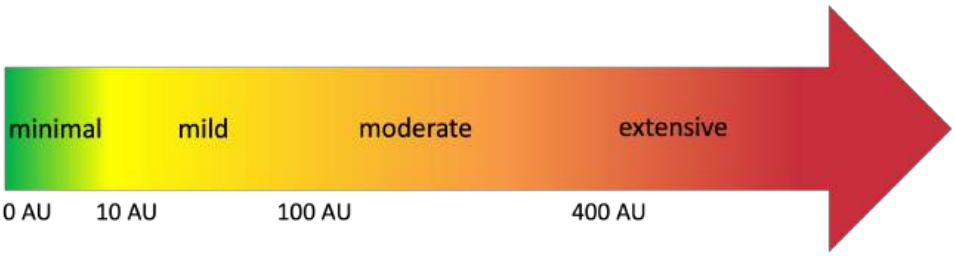


FIGURE 5.1: CAC score severity scale. The values in the picture are in Agatston Units (AU). **0 AU** - no detectable calcified plaque; **1 - 10 AU** - minimal plaque; **11 - 100 AU** - mild plaque; **101 - 400 AU** - moderate plaque; **> 400 AU** - extensive plaque.

[166], and individuals from diverse ethnic backgrounds [167, 168]. Importantly, CAC scoring provides incremental prognostic information beyond traditional risk factors for individuals at low, intermediate, and high baseline risk, including CKD patients [169, 170, 171].

There is a well-established, graded association between CAC score categories and cardiovascular risk [172]. Even mild calcification (positive scores below 100 AU) is associated with a higher probability of major coronary events compared to individuals with no detectable calcification. When the CAC score exceeds 100 AU, this likelihood increases markedly. Furthermore, patients with CAC scores above 300 or 400 AU (depending on the study) exhibit rates of major adverse cardiovascular events and mortality comparable to those seen in individuals with clinically established CAD [173]. Conversely, a CAC score of 0 has emerged as a powerful negative risk marker and is associated with a low likelihood of future coronary or cardiovascular events [174]. This so-called "warranty period" may extend up to 10–15 years, even among individuals with traditional risk factors such as hypertension, diabetes, or chronic kidney disease [174, 175].

Taken together, the addition of CAC scoring to traditional coronary heart disease risk models significantly enhances predictive accuracy and enables meaningful patient reclassification, particularly among individuals at intermediate risk, thereby allowing for more precise preventive therapies. This improvement has been shown to be both statistically and clinically significant across major risk models, including the Framingham Risk Score, SCORE, and ASCVD calculators [169, 176]. As a result, CAC scoring has been integrated into worldwide preventive cardiology guidelines to support personalized treatment decisions, especially when the need for statin therapy is uncertain [177]. It is important to note thet the progressive nature of CAC is associated with elevated future cardiovascular risk, and repeated scanning can offer prognostic value beyond a single baseline measurement [175].

Despite strong evidence supporting CAC as a marker of CAD and its inclusion in clinical guidelines for therapeutic decision-making, CAC scans remain underutilized in routine practice [173]. The reasons for this are not entirely clear, but possible concerns include limited CT scanner availability and the issue of radiation exposure, which often influences decisions regarding CT-based imaging [178, 179]. This is particularly relevant for patients with CKD, who often undergo multiple scans over the course of their disease to monitor its progression. Although each of them involves only low-dose radiation, the cumulative exposure can become significant. In this context, a reliable pre-screening tool, beyond traditional risk factors, could help clinicians identify patients unlikely to benefit from CAC scanning, while flagging those for whom CAC assessment may offer meaningful clinical insights.

As previously discussed, macrocalcifications detectable by CT scans contribute to plaque stability, altering arterial stiffness and overall hemodynamics. It is therefore plausible that pulse wave characteristics could carry clinically relevant information. Several earlier studies have examined the connection between pulse waves and CAC, particularly focusing on pulse pressure (PP), defined as the difference between systolic and diastolic blood pressure. Its elevated values have been associated with increasing CAC scores, offering some insight into calcification trends. A PP threshold of 60 mmHg has been proposed in multiple studies to identify the presence of CAC, but this cutoff appears overly simplistic and lacks the precision necessary for broad clinical application [180, 181, 182]. Other parameters derived from pulse wave analysis, particularly those obtained from central aortic waveforms, have also been explored and shown to be valuable in assessing arterial stiffness related to atherosclerosis [183].

PWV, as a surrogate marker of arterial stiffness, has also been extensively studied in the context of both CAC and CAD [179]. While cfPWV is considered the gold standard for central arterial stiffness measurement, the majority of studies, particularly those conducted in East Asian populations, have used baPWV, likely due to its clinical availability and widespread use in that region [184]. In individuals with CAC, baPWV has been shown to be independently associated with both the presence and progression of coronary calcification [185, 186, 187, 188]. Similarly, cfPWV has also demonstrated a significant association with the extent of CAC, particularly in studies focused on CKD populations [189, 190, 191]. In parallel, several studies have attempted to incorporate PWV measurements into machine learning models aimed at identifying high-risk patients. However, these models often suffer from limited sensitivity, underscoring the importance of integrating additional information to improve predictive performance [192, 193].

An emerging but still experimental concept involves combining pulse wave imaging (an ultrasound-based technique) with vector flow imaging to create an integrated framework for simultaneous assessment of vascular stiffness and hemodynamics. While this approach shows promise, it has yet to be validated in human populations [194].

Given the substantial evidence of altered hemodynamics in the presence of calcified atherosclerotic plaques, I decided to apply the PW-FDFs extraction method for their detection. While commonly used parameters such as PWV and pulse pressure are valuable indicators of arterial stiffness, they may not fully capture the subtle waveform distortions caused by calcified lesions. In contrast, the PW-FDFs approach analyzes multiple components of the pulse wave and extracts a range of features that reflect both its shape and temporal dynamics. This multidimensional analysis may offer improved sensitivity to calcified plaque-induced alterations in hemodynamic signals and thus enhance detection performance.

5.2 My work

5.2.1 Research overview

Introduction

Building on the promising results obtained using PW-FDFs within a machine learning framework, I extended this approach to the detection of elevated CAC scores ($\geq 100 AU$), which indicate at least a mild risk of adverse cardiovascular events. In this study, however, PW-FDFs were extracted from the central pulse wave signal,

i.e., the waveform transformed from peripheral measurements into a central arterial representation.

This choice was motivated by the characteristics of the retrospective dataset I acquired, which contained pulse wave recordings from both the brachial and radial arteries. To ensure consistency across samples and maximize the available dataset size, I standardized all signals by using their representation in the central waveform domain. This strategy not only enabled me to unify the input data and thereby increase the sample available for model training, but it also offers a broader methodological advantage. Specifically, the trained model can be applied independently of the arterial site of acquisition, as long as the peripheral signal can be reliably transformed into its central representation.

Therefore, in the following publication, I present the results of applying the PW-FDFs method to central pulse wave signals for the detection of elevated CAC scores. The analysis was further stratified by age groups, with particular attention to how PW-FDFs may enhance risk stratification both by identifying younger patients with elevated CAC scores (a group typically considered low-risk for calcification) and by distinguishing older patients without elevated CAC scores (a group generally regarded as a high-risk population).

Relation of the publication to the research aims of the thesis

With multiple methods available for pulse wave acquisition, the ability to transform peripheral measurements into a central waveform, from which clinically meaningful information can be extracted, offers a major advantage. This flexibility broadens the applicability of the pulse wave signal, making the biomarker easier to obtain. In this study, I investigated whether PW-FDFs derived from peripheral signals transformed into central waveforms can be used to predict elevated CAC scores, a proxy for intimal vascular calcification. The results showed that models trained on PW-FDFs alone reliably discriminated between patients with CAC $\geq$100 AU and those below this threshold (H3Q1).

Further analysis revealed that when PW-FDFs were included, time-domain features of the central pulse wave were often omitted during feature selection and, consequently, did not contribute to the final predictions (H3Q2). While the overall performance of the PW-FDFs-based model was comparable to conventional CAC risk factor-based models, subgroup analysis indicated an added value of pulse wave signal in age-stratified cohorts (H3Q3). In older patients, the PW-FDF-based model achieved higher specificity, which could result in reducing the number of unnecessary imaging scans in a group where age alone is already a dominant predictor of calcification. In younger patients, by contrast, the model demonstrated higher sensitivity, improving the detection of cases despite their lower baseline risk.

Finally, I assessed whether the PW-FDFs-based model could capture gradations in CAC severity. My analysis showed that the predicted probability of $\geq$ 100AU increased in line with actual CAC scores, suggesting that PW-FDF-based models have the potential to differentiate between varying levels of calcification burden (H3Q4).

Conclusions

This research supports my third hypothesis (H3) by demonstrating that statistical models based on PW-FDFs derived from central pressure pulse waveforms can effectively identify end-stage renal disease patients with elevated coronary artery calcification scores. Beyond confirming the hypothesis, it also advances my broader research aims by proposing a novel, data-driven framework for early iVC detection with strong potential as a widely accessible screening tool. Compared to conventional CAC risk factor models, the PW-FDFs-based approach showed particular advantages in the youngest and oldest patient groups - populations in which risk is often assessed primarily by age. Taken together, these findings suggest that incorporating frequency-based information from pulse wave signals into clinical practice could enhance conventional CAC risk assessment and enable more precise, individualized patient stratification.

5.3 The publication (P3)

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Leveraging pulse wave signal properties for coronary artery calcification screening in CKD patients

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ABSTRACT

Background and aims: Chronic kidney disease (CKD) patients are particularly susceptible to coronary atherosclerosis, which can be assessed using computed tomography (CT)-based coronary artery calcium (CAC) score. However, such a costly examination might not always be required and cost-effective. This study investigates a novel screening approach utilizing pulse wave analysis combined with machine learning models to identify CKD patients at high risk for coronary atherosclerosis.

Methods: We analyzed retrospective data from 124 CKD stage 5 patients who underwent kidney transplantation. Pulse wave signals were collected using SphygmoCor system (AtCor Medical, Sydney, Australia), and CAC scores were determined via CT scans. Machine learning models were developed using either pulse wave features or traditional risk factors (TRF) to detect high CAC scores ($\geq$100 Agatston units).

Results: The pulse wave-based model outperformed TRF-based model in identifying high CAC scores, particularly among younger patients. Specifically, the pulse wave-based classifier showed superior balanced accuracy in all analyzed age groups and superior sensitivity in patients under 60 years old, especially in those under 50 years old. The overall balanced accuracy of the pulse wave-based model exceeded 80 %, suggesting its potential as a reliable screening tool for detecting high risk of coronary atherosclerosis in CKD patients.

Conclusions: Pulse wave analysis combined with machine learning offers a promising, non-invasive method for preliminary CAC screening in CKD patients. This approach could enhance early risk identification and improve clinical management, although further research is needed to validate and refine this method in larger, more diverse populations.

1. Introduction

Chronic kidney disease (CKD) is closely linked to an elevated risk of cardiovascular disease, significantly contributing to the higher morbidity and mortality in this patient population [1,2]. Among the various biomarkers for cardiovascular health, the coronary artery calcium (CAC) score stands out as a robust indicator of the degree of coronary atherosclerosis with calcification [3–7]. This score, derived from computed tomography (CT) scans, quantifies the extent of calcified plaques in the coronary arteries, offering valuable insights into an individual's likelihood of developing coronary artery disease [8,9]. A high CAC score is strongly associated with significant coronary atherosclerosis and an increased likelihood of adverse cardiac events [10,11]. While specific thresholds for *high* CAC scores vary, clinical guidelines often consider scores above 100 Agatston units (AU) as indicative of elevated cardiovascular risk and scores above 1000 AU as a marker of extensive coronary atherosclerosis [7,12,13]. Moreover, multiple guidelines across the world suggest using the 100 AU threshold when evaluating intermediate-risk patients for statin therapy [14].

CAC assessment methods rely predominantly on CT scans, which,

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while highly accurate, are expensive, expose patients to radiation, and may not be feasible for routine practice due to resource constraints [15]. This emphasizes the need for a simple and non-invasive screening procedure that could identify individuals with likely high CAC scores who would benefit most from a CT-based CAC assessment. It is worth noticing that, despite the increased cardiovascular risk associated with CKD, not all CKD patients, even those in advanced stages (CKD stage 5), exhibit high CAC scores [16].

Current CAC screening procedures utilize traditional risk factors, such as high age, male sex, hypertension, and elevated cholesterol levels [7,14,17]. Although useful, these parameters may not be suitable for predicting CAC scores in all subpopulations, especially in patients with chronic conditions such as CKD which may disrupt cholesterol levels [18].

Pulse wave analysis has emerged as a promising avenue for enhancing CAC assessment. Various studies have linked CAC scores with pulse wave characteristics, primarily pulse wave velocity (PWV); it has been shown that PWV (assessed in large arteries) correlates with CAC extent [19] and progression [20], suggesting there is a connection between atherosclerosis of coronary and large arteries. While PWV is a well-established measure of arterial stiffness, its utility is somewhat limited by the variability in measurement techniques, such as carotid-femoral PWV (cf-PWV) and brachial-ankle PWV (ba-PWV), which complicates the establishment of straightforward guidelines [21]. Additionally, the availability of these examinations is often limited, leading to the exploration of alternative, more accessible methods, such as estimating cf-PWV based on risk factors [22] or based on the pulse waveform recorded at a specific arterial site, e.g. using applanation tonometry [23]. The latter approach, relying solely on pulse wave contour, although having its own limitations, relieves the burden of estimating the wave travel distance, a known challenge in traditional approaches to measuring PWV [24].

Recognizing the limitations of CAC screening based solely on traditional risk factors and the unique cardiovascular vulnerabilities of CKD patients, our study aimed to explore a novel approach to preliminary screening for high CAC scores ($\geq$100 AU) specifically tailored for this high-risk population. By leveraging machine learning algorithms applied to features derived from pulse waves (PW), we sought to evaluate the potential of this method as a cost-effective and relatively easily accessible screening tool for CKD patients. Such an approach could enable the early identification of individuals with CKD who are particularly likely to have high CAC scores, before resorting to invasive and resource-intensive diagnostic procedures, such as CT scans. We also wanted to compare the performance of this novel method with traditional risk factors (TRF) based model to assess its relative efficacy in the CKD population.

2. Materials and methods

2.1. Data collection

This retrospective study involved 124 patients with CKD stage 5 who underwent a living donor kidney transplant in the years 2009–2018 at Karolinska University Hospital. The study adhered to the principles of the Declaration of Helsinki and received approval from the regional ethical review board in Stockholm. Before any medical procedures, explicit informed consent was obtained from each patient. The inclusion criteria were the same as those used to determine eligibility for kidney transplantation, namely CKD stage 5, capacity to manage immunosuppressants, and absence of other serious medical conditions. Individuals below 18 years of age and those unwilling to participate in the study were excluded. A detailed description of the measurement protocol can be found in previous papers [25,26].

For each participant, pulse wave signals at the brachial or radial artery were obtained using the SphygmoCor System (AtCor Medical, Sydney, Australia). To determine the CAC score, cardiac CT scans were performed using a 64-channel detector scanner (LightSpeed VCT; General Electric (GE) Healthcare, Milwaukee, WI) operating in cine mode. The ECG-gated scans followed a standard non-contrast protocol with the tube voltage of 100 kV, tube current of 200 mA, rotation time of 350 ms, slice thickness of 2.5 mm, and a displayed field of 25 cm. An experienced radiologist identified calcium deposits in coronary arteries. Subsequent data processing and analysis was performed using the Advantage Workstation 4.4 (GE Healthcare), while Smartscore 4.0 (GE Healthcare) was employed for CAC score assessment. Each calcified lesion was first identified, and its area was measured in square millimeters. The density of each lesion was then quantified in Hounsfield units (HU). Lesions with a density greater than 130 HU were assigned a weighting factor based on their peak density: 1 for 130–199 HU, 2 for 200–299 HU, 3 for 300–399 HU, and 4 for peak densities above 400 HU. The lesion's area was then multiplied by its weighting factor to yield the lesion's score in Agatston Units (AU). The total CAC score, expressed in AU, was calculated by summing the CAC scores from the left main coronary artery, the left anterior descending artery, the left circumflex artery, and the right coronary artery.

2.2. Data analysis

Data exploration, construction of predictive models, and assessment of their performance were conducted using R version 4.0.5. Statistical significance was established at $P < 0.05$.

2.2.1. Data preprocessing

Data from 2 patients were excluded from analysis due to missing pulse-wave-related features. The remaining group of 122 patients was divided into two classes based on their CAC scores. The negative class consisted of patients with a CAC score <100 AU (n = 89), while the positive class included patients with a CAC score$\geq$100 AU (n = 33). Table 1 provides an overview of the analyzed patients' characteristics. All features listed in this table, i.e. age, sex, body mass index, systolic and diastolic pressure, and heart rate, are later considered as traditional risk factors (TRF) and used in statistical modelling.

PW signals were collected from either the radial or brachial artery, with 68 % of the measurements taken at the latter. In both cases, for our study we used the central PW signal obtained via a transfer function applied directly within the SphygmoCor System [23], and hence we did not distinguish the site of PW signal acquisition in further analysis. We employed the Discrete Fourier Transform (DFT) algorithm [27] to convert the central PW signal from the time domain to the frequency domain. Drawing on insights from the literature [28,29] and our prior study [30], we analyzed only the first 20 harmonics, which proved to be

Table 1
Characteristics of the analyzed patients. Data are presented as medians [interquartile range] or frequencies (percentages). Abbreviations: BMI – body mass index, P_SP – peripheral systolic pressure, P_DP – peripheral diastolic pressure, HR – resting heart rate, P-value adj – P-value after adjustment for multiple comparisons, CAC – coronary artery calcium, AU – Agatston units.

	CAC score < 100 AU (n = 89)	CAC score ≥ 100 AU (n = 33)	P-value	P-value adj
Age, years	38 [29–50]	61 [51–64]	<0.01	<0.01
Sex, male[b], n (%)	61 (69 %)	20 (61 %)	0.54	0.65
BMI, kg/m^2	23.8 [22.1–26.1]	26.5 [23.9–28.5]	<0.01	<0.01
P_SP[a], mmHg	147 [134–156]	149 [139–163]	0.27	0.41
P_DP[a], mmHg	91 [83–97]	85 [79–91]	0.01	0.02
HR[a], beats/min	75 [66–83]	73 [67–82]	0.86	0.86

[a] Welch's *t*-test was performed; otherwise, the Wilcoxon rank sum test was performed.
[b] Pearson's chi-square test was performed.

sufficient for accurate pulse wave reconstruction. The moduli (*mod*) and arguments (*arg*) of these harmonics were extracted, and the relative energy of each harmonic (*e_mod*) was computed as the modulus of the given harmonic divided by the sum of the moduli of all analyzed harmonics. Additional pulse wave-related features included parameters directly measured by the SphygmoCor device, such as central wavelength (*C_PERIOD*), central systolic pressure (*C_SP*), central diastolic pressure (*C_DP*), central Buckberg sub-endocardial viability ratio (*C_SVI*), central augmented pressure (*C_AP*), normalized central augmented pressure-to-pulse height ratio (*C_AGPH*), central mean pressure (*C_MEANP*), central augmentation index (*C_AI*), and central end-systolic pressure (*C_ESP*). All these features, along with the moduli, arguments, and relative energy of the 20 harmonics, were used as inputs for our statistical model and were referred to as PW features. Further details regarding the parameters computed by SphygmoCor included in our analysis are provided in Supplementary Table S1.

Finally, data standardization was performed to prepare the dataset for subsequent analysis.

2.2.2. Statistics

Continuous variables were described by median and interquartile range (IQR). Categorical features were reported as frequencies and percentages. Pearson's chi-square test [31] was used to compare the categorical features between the patients with high vs low CAC scores. For continuous features, the suitability of Welch's *t*-test [32] was first evaluated using the Shapiro-Wilk test of normality [33]. When the assumption of normality was met, Welch's *t*-test was used to assess the differences in means between the two analyzed subgroups of patients. Conversely, if normality was violated, Wilcoxon rank sum test [34] was used to detect shifts in the distributions of variables. To address the problem of multiple comparisons, P-values were adjusted using the Benjamini-Hochberg correction [35].

2.2.3. Classification frameworks

The classification of high vs low CAC score (target variable) was conducted using two separate sets of predictors (independent variables): pulse wave-related features and traditional risk factors. To account for potential relationships between the considered predictors, we employed the elastic net (EN) algorithm [36]. It is well-suited for this purpose due to its capability to automatically select the most influential predictors and manage highly correlated predictors [37]. Furthermore, to address class imbalance, we implemented an upsampling procedure. Specifically, we performed random sampling with replacement on the minority class to equalize its size with the majority class. This technique was applied exclusively to the training set within the leave-one-out cross-validation framework.

Initial experiments revealed that classification models using PW features tended to overfit the training data, irrespective of the chosen hyperparameter values (data not shown). To mitigate this issue, we incorporated a stepwise forward feature selection using the logistic regression model and Akaike Information Criterion (AIC) as a preprocessing step for selecting the most promising PW features. In the final EN model, we used the features that were selected most frequently by AIC during the leave-one-out cross-validation process (Fig. 1).

2.2.4. Performance evaluation

The performance of the proposed classification frameworks was evaluated using leave-one-out cross-validation (LOOCV), a robust method particularly suited for small datasets. LOOCV provides an alternative to conventional data partitioning into training and test sets by using a single data point as a test set, with the remaining points serving as the training set, and repeating it for every single data point. A standard threshold of 0.5 was used for classification decisions. Model performance was assessed using several metrics tailored for imbalanced datasets, including balanced accuracy, sensitivity, specificity, and the area under the receiver operating characteristic curve (AUC-ROC).

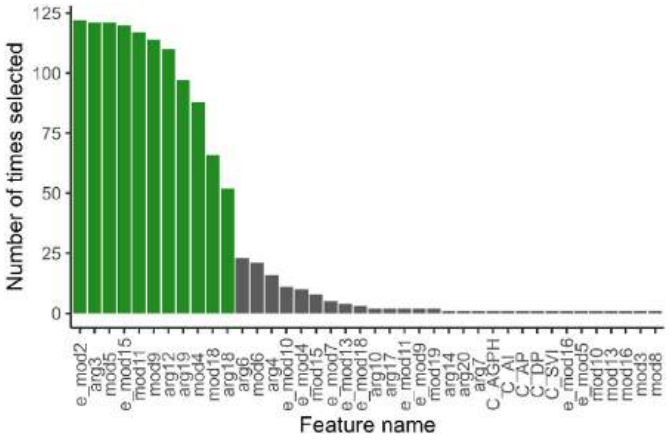

Fig. 1. Frequency of feature selection using Akaike Information Criterion in the leave-one-out cross-validation process. This figure illustrates the number of times each pulse wave-based feature was chosen as significant for the classification model during 122 leave-one-out cross-validation procedures. The features entering the final model are highlighted in green. *Mod, arg, and e*_mod *stand for moduli,* arguments, and relative energy of the analyzed harmonics of the pulse wave signal, respectively. For the names of other features, please refer to Supplementary Table S1.

These metrics provide a comprehensive evaluation of the models' ability to correctly classify cases belonging to each class with imbalanced classes.

3. Results

Among the traditional risk factors, age, body mass index (BMI), and peripheral diastolic pressure showed statistically significant differences between patients with low vs high CAC scores, both before and after adjusting for multiple comparisons (Table 1). Notably, age was particularly effective in distinguishing between the two analyzed classes of patients, suggesting it may have a substantial impact on the results of classification models that use traditional risk factors.

The selection of pulse wave-based features to be used in the classification model was conducted in 122 LOOCV procedures using AIC. Upon reviewing the features selected in each case, we established a threshold of 52 as the minimum number of times a feature should be selected to be included in the final model. This cutoff was determined due to a significant gap between the last feature deemed important, which was chosen 52 times, and the next feature, selected only 23 times (Fig. 1). Therefore, only the pulse wave-based features that were consistently identified as important were included as predictors in the elastic net model.

The final classification model utilizing traditional risk factors and that using the selected pulse wave-based features showed similar overall performance with leave-one-out cross-validation sensitivities close to 0.85 and AUC ROCs approaching 0.9 (Table 2). However, differences between the two classifiers became apparent when the LOOCV results were analyzed within subsets of data stratified by patient age, the most influential factor in the TRF-based model. The age groups were defined based on the distribution of available data. The first subset included

Table 2
Leave-one-out cross-validation results of the analyzed classifiers. Abbreviations: TRF – classifier trained with traditional risk factors only (age, sex, body mass index, heart rate, systolic and diastolic pressure); PW – pulse wave-based only classifier, AUC ROC - area under the receiver operating characteristic curve.

Classifier	Balanced accuracy	AUC ROC	Sensitivity	Specificity
TRF	0.84	0.88	0.85	0.83
PW	0.83	0.89	0.82	0.84

patients younger than 39 years, which, despite being the largest group (Table 3), contained only one patient with a high CAC score. The remaining age groups— (39–49], (49–59], and over 59 years—were of similar sizes (Table 3), but the proportion of high CAC scores increased with age (Table 3).

Fig. 2 illustrates the comparative performance of the classification model employing PW features versus that relying on TRF in predicting high CAC scores across different age groups. The PW-based model consistently outperformed the TRF-based model in terms of balanced accuracy and showed superior or comparable performance in terms of AUC ROC. Only the classifier utilizing PW features successfully identified the patient with a high CAC score among those aged 39 years and younger. As a result, it outperformed the TRF-only classifier across all analyzed metrics in this age group. The latter labelled every patient as having a low CAC score.

In the middle age groups (39–49 and 49–59 years), the PW-based classifier continues to perform better or similarly to the TRF-based classifier in terms of balanced accuracy and sensitivity, highlighting its superiority in high CAC score detection among the younger and middle-aged patients. The only subpopulation where the PW-based classifier showed lower sensitivity compared to the TRF-based classifier was the group of the oldest patients. However, this does not indicate that the TRF-based model provides better CAC discrimination in this subgroup. Rather, the TRF-based model classified nearly all older patients as likely having high CAC scores, leading to high sensitivity at the cost of specificity. In contrast, the PW-based classifier demonstrates better specificity, meaning it is more capable of identifying older CKD patients with low CAC scores. This suggests that the TRF-based model's predictive capability in this age group is largely driven by age alone.

As mentioned above, the PW-based model demonstrated higher sensitivity compared to the TRF-based model in patients under 50. However, our cohort was relatively small, with only six patients under 50 with CAC $\geq$100 AU. Therefore, to further assess the performance of the PW-based model in those younger patients, we examined how the model outputs (i.e. the probabilities of CAC $\geq$100 AU) were distributed in these patients divided into several groups according to their CAC scores. As shown in Fig. 3, the PW-based model assigned higher probabilities to patients with higher true CAC scores. Moreover, for the subgroups including patients with low CAC scores, the range of probabilities returned by the PW-based model was wider, thus more effectively distinguishing between patients with low and high CAC scores. In contrast, the TRF-based model assigned relatively similar probabilities across all CAC subgroups in this younger population, which again suggests that its predictions are primarily driven by age.

To further assess the performance of our models, we analyzed cases where the models made errors in patient classification. In the LOOCV process, the TRF-based model incorrectly classified five patients as having low CAC scores, with a mean true CAC score of 515 AU and a standard deviation of 550 AU. In comparison, the PW-based model resulted in six false negatives, but the mean CAC score for these misclassified patients was notably lower, at 394 AU with a standard deviation of 375 AU. For false positives, the results were similar for the two classifiers: the TRF-based model incorrectly classified 15 patients as having high CAC scores, while the PW-based model misclassified 14 patients. The mean CAC scores for these false positives were comparable (21 $\pm$ 27 AU and 18 $\pm$ 25 AU for TRF and PW-based model, respectively).

Table 3
Sample sizes of the analyzed age groups.

Age group	Group size	Number of patients with CAC score $\geq$ 100 AU
<39	47	1(2 %)
(39–49]	25	5 (20 %)
(49–59]	26	10 (38 %)
>59	24	17 (71 %)

An interesting observation emerged when analyzing the distribution of high CAC score probabilities returned by the two classifiers during the LOOCV process (Fig. 4). Compared with the TRF-based classifier, the outputs of the PW-based classifier were higher for true positives ($p = 0.04$) and lower for true negatives ($p < 0.01$), indicating that the PW-based classifier was more confident when correctly identifying both positive and negative cases. On the other hand, the probabilities returned by the PW-based model showed greater variability among incorrectly classified patients (Fig. 4), which may be caused by the relatively wide range of true CAC scores in these patients (cf. Fig. 3).

4. Discussion

The coronary artery calcium score is a well-established marker of arterial calcification, which is strongly associated with the development of coronary artery disease. Although the threshold defining a high CAC score remains a topic of ongoing debate, multiple clinical guidelines converge on a threshold of 100 AU as the point at which statin therapy should be initiated in asymptomatic intermediate = risk patients above 40 years old [14]. High CAC scores are particularly common among patients with chronic kidney disease, which is recognized as a significant risk factor for CAC [14,16]. As a result, some clinical guidelines suggest routine CAC assessment in all CKD patients [14]. However, even in severe cases of CKD, such as end-stage renal disease, CAC scores exceeding 100 AU are not entirely common, especially among younger patients [38]. While research consistently shows that CKD patients have a higher likelihood of elevated CAC scores compared to the general population, the actual prevalence of high CAC scores varies across studies and never approaches 100 % [16]. Therefore, it is essential to develop effective screening methods to identify CKD patients at higher risk for coronary atherosclerosis, indicated by an elevated CAC score, enabling timely referral for a confirmatory CT scan.

Given the need for such CAC screening procedures in CKD patients, we aimed to assess whether pulse wave signals coupled with classification algorithms could be utilized as an effective screening tool. In our analysis of 122 patients with stage 5 CKD, we found that while the overall performance differences between classifiers using PW features and those based on TRF were marginal, the classifier based on PW-related features consistently provided superior balanced accuracy across different age groups (Fig. 2). It is worth noting that the proposed PW-based approach achieved higher sensitivity among the younger and middle-aged patients (<60 years), which is a demographic group often overlooked in traditional CAC assessment. The superiority of PW- based model among younger patients (<50 years) is also visible when examining the probabilities of CAC $\geq$100AU assigned by the model to patients with different levels of true CAC scores (Fig. 3). The overall balanced accuracy of the PW-based classifier exceeded 80 %, suggesting that pulse wave may transmit certain information about CAC (Table 2).

These findings align with the results from our earlier study [30], where we demonstrated that pulse wave signals could effectively detect medial vascular calcification (mVC) in the inferior epigastric artery. Given the link between mVC of the epigastric artery and coronary artery calcification [25], it is not surprising that in the present study pulse wave signals were also found to be useful in identifying patients with elevated CAC scores.

In our analysis, we employed the elastic net algorithm for patient classification due to its superior performance compared to other machine learning algorithms tested during the experimental phase of the study. Alternatives such as XGBoost, support vector machines, and random forest demonstrated slightly lower performance, leading us to focus on the elastic net model for clarity and conciseness of the paper. However, future studies on different or expanded datasets should consider reevaluating these alternative algorithms to determine their relative effectiveness.

Our study compared the PW-based model with the TRF-based model. However, one may wonder about the performance of a model combining

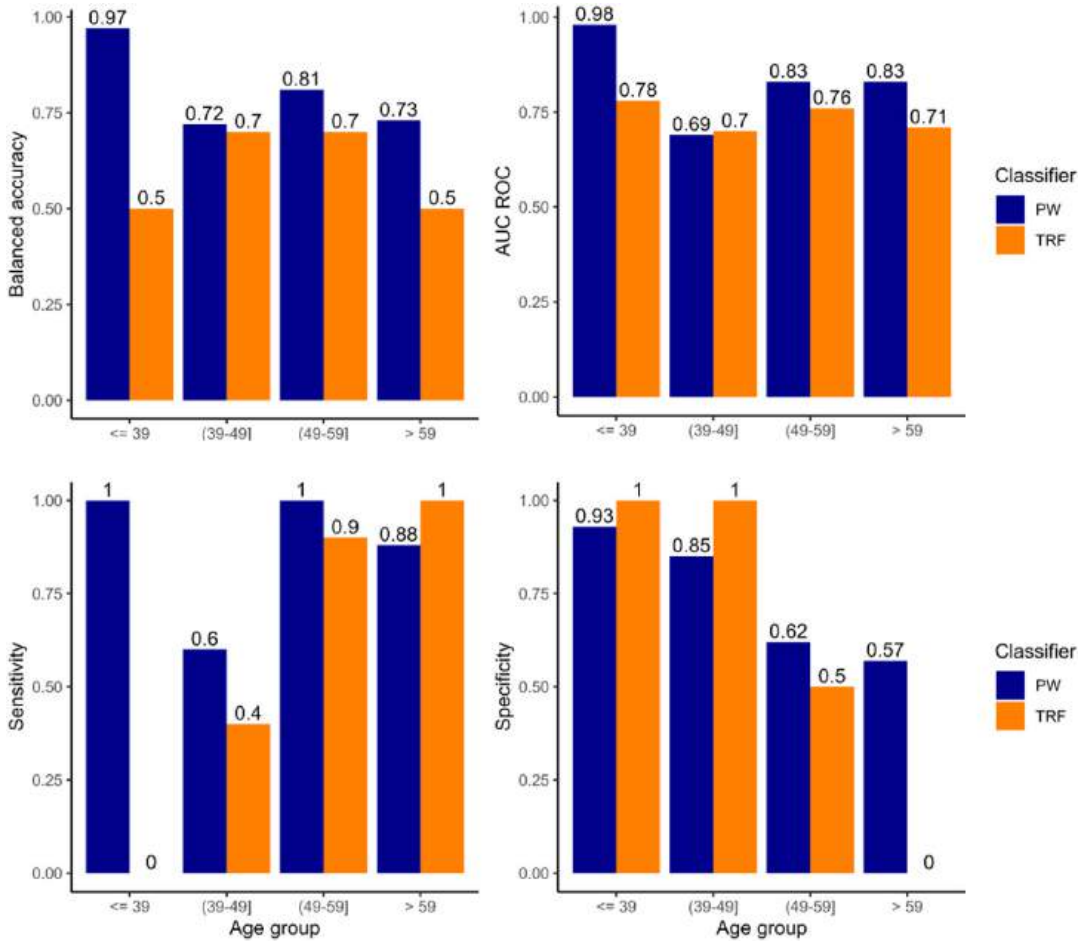

Fig. 2. Performance metrics of the two analyzed classifiers across different age groups. AUC ROC – area under the receiver operating characteristic curve; PW – pulse wave-based only classifier, TRF – classifier trained with traditional risk factors only (age, sex, body mass index, heart rate, systolic and diastolic pressure).

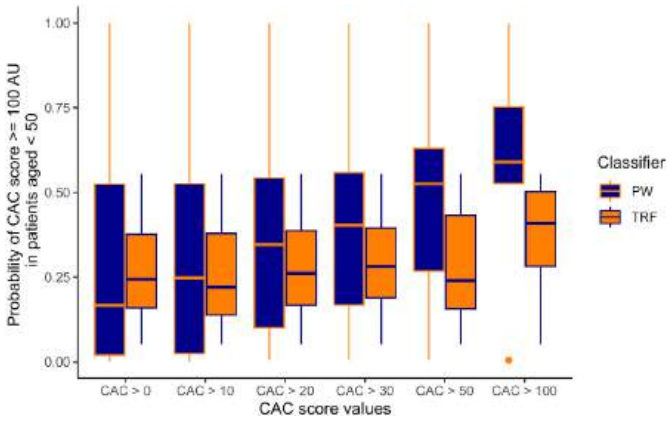

Fig. 3. Distribution of the outputs of the analyzed predictive models (i.e. the assigned probabilities of CAC score ≥100 AU) in patients below 50 years divided into subgroups according to their true CAC score. PW – pulse wave-based classifier; TRF – classifier based on traditional risk factors (age, sex, body mass index, systolic and diastolic pressure and heart rate). There are no patients with CAC scores within the range 40–50, hence boxes for CAC >40 are not shown.

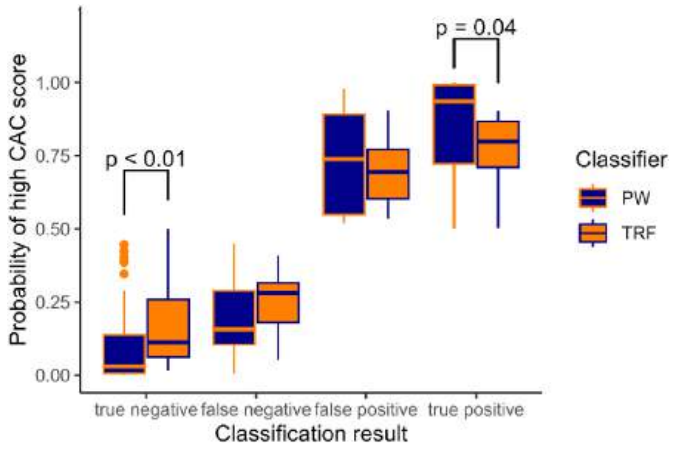

Fig. 4. Distribution of high CAC score probabilities assigned during the leave-one-out cross-validation process. To compare the probability distributions between the two classifiers, the Wilcoxon test was applied, with p-values adjusted for multiple comparisons using the Benjamini-Hochberg correction. Only significant differences are annotated in the plot; PW – pulse wave-based only classifier, TRF – classifier trained with traditional risk factors only (age, sex, body mass index, heart rate, systolic and diastolic pressure).

TRF and PW features. We performed such an additional analysis and found only a marginal difference between the model based on TRF alone and that incorporating both TRF and PW features (data not shown). This seems to be caused by the fact that both these models were strongly influenced by age, which was a dominant predictor (Table 1). This suggests that it is difficult to improve the performance of a TRF-based model, when patients of all ages are assessed together, and age is one

of the predictors. It further suggests that CAC assessment could be more accurate if performed in specific age groups where age would not be such a dominant predictor. In particular, with a larger dataset, one could train separate classification models (e.g. with both TRF and PW features) for different age groups, where age would still be taken into account, but other features would then likely become more useful (as shown for the results of our PW-based model analyzed in specific age groups).

Our study has several strengths. First, it specifically investigates a population with chronic kidney disease stage 5, a group known to be at high risk for cardiovascular diseases. This focus on a particularly vulnerable group increases the clinical relevance of our analysis, as early and accurate detection of high CAC scores in these patients could significantly impact their treatment and outcomes. Moreover, our study introduces an innovative approach by utilizing machine learning algorithms employing central pulse wave features for predicting the presence of high CAC scores. This method could provide a preliminary screening procedure to identify patients who would benefit most from the more accurate but costly CT-based CAC assessment, and could potentially even provide a cost-effective, non-invasive, and more accessible alternative to the traditional CT-based method. Our study employs advanced statistical techniques, including elastic net regression and upsampling, to handle class imbalance and avoid overfitting. These methods enhance the robustness and generalizability of our analysis, making the results more reliable. By demonstrating that the PW-based classifier may outperform the TRF-based one, especially in younger and middle-aged patients, the study shows the potential of using PW features for CAC screening in certain populations. Unlike PWV measurements, which require pulse wave assessment at two arterial sites, the proposed method relies on a single-point measurement, offering a more convenient and practical method of indirect assessment of the state of vascular system for both clinicians and patients. Furthermore, it should be noted that central pulse wave features have previously been established as significant mortality predictors in end-stage renal disease patients [39,40], which further suggests that our approach may be particularly useful in CKD patients.

A significant limitation of our study is the relatively small sample size combined with highly imbalanced classes. This poses challenges, particularly in the feature selection process for the classifier using PW-related features, where the number of potential predictors nearly matches the number of observations. Given the limitations of the elastic net algorithm in handling this issue, we introduced a method of feature preselection before feeding features into the final model. Specifically, we employed logistic regression combined with forward AIC selection in the leave-one-out cross-validation process. The set of features used in the elastic net model comprised those selected in the AIC-based procedure far more frequently than others. While we acknowledge that this preselection approach might result in overly optimistic outcomes (with potentially limited generalizability to other datasets), we believe it is sufficient for the purpose of this study. It should be noted that in such a small dataset, the variability in selected features was relatively high (Fig. 1), making it relatively difficult to assess individual classifiers built with different feature subsets. However, our approach demonstrates that there exists a subset of PW-related features that, when utilized by a machine learning model, can outperform the TRF-based model in terms of balanced accuracy of the model across the analyzed age groups. We believe that this finding provides a strong basis for further investigation into this topic.

Another limitation of our study is the absence of data on some of the established risk factors associated with elevated CAC scores such as LDL cholesterol, which is a key factor mentioned in the clinical guidelines for CAC assessment [14]. However, the applicability of this risk factor to CKD patients remains uncertain. Given that cholesterol levels in CKD patients are often disrupted, it is questionable whether a direct link between LDL cholesterol and high CAC scores is valid in this population. Further research is needed to determine the relevance of LDL cholesterol as a predictor of CAC in CKD patients. Finally, it is important to note that our study did not include external validation, which remains an important step to assess the generalizability of our findings. Although we employed leave-one-out cross-validation to evaluate the model on data excluded from the training set, this approach does not replace true external validation on a separate dataset. Future studies should aim to validate the model in a larger, independent CKD cohort to confirm its predictive performance and clinical utility.

In conclusion, this preliminary study presents a novel, non-invasive approach to identifying high coronary artery calcium scores in patients with chronic kidney disease using pulse wave analysis combined with machine learning algorithms. By comparing this method with the traditional risk factor-based model, we showed that, on the analyzed dataset, the PW-based classifier consistently achieved superior balanced accuracy, particularly in younger and middle-aged patients. The overall balanced accuracy of the proposed PW-based model exceeding 0.8 suggests that PW analysis may offer a reliable method for identifying CKD patients who are at greater risk of coronary atherosclerosis and could benefit from further diagnostic procedures. This applies particularly to those who are younger and may be overlooked by traditional methods. While these initial findings are promising, the study limitations, such as the relatively small sample size, the lack of external validation, and class imbalance, highlight the need for further research to validate and refine the proposed models. Moreover, future studies should explore whether pulse wave-based screening could not only detect high CAC scores at a single time point but also track disease progression and improve risk stratification over time.

CRediT authorship contribution statement

Urszula Bialonczyk: Writing – original draft, Visualization, Software, Methodology, Conceptualization. **Leszek Pstras:** Writing – review & editing. **Malgorzata Debowska:** Writing – review & editing. **Lu Dai:** Data curation. **Abdul Rashid Qureshi:** Data curation. **Magnus Soderberg:** Supervision. **Torkel B. Brismar:** Data curation. **Jonaz Ripsweden:** Data curation. **Bengt Lindholm:** Writing – review & editing, Supervision. **Peter Stenvinkel:** Supervision. **Jan Poleszczuk:** Writing – review & editing, Supervision, Conceptualization.

Ethical statement

The study adhered to the principles of the Declaration of Helsinki and received approval from the regional ethical review board in Stockholm. Before any medical procedures, explicit informed consent was obtained from each patient.

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Declaration of competing interest

Magnus Soderberg is a full-time employee of AstraZeneca. Bengt Lindholm has a grant to Karolinska Institutet from Baxter Healthcare Corporation and was previously employed by Baxter Healthcare Corporation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.compbiomed.2025.110519.

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Supplementary Material

Table S1. Parameters calculated (estimated) by SphygmoCor System used in the present study.

Parameter	Full name	Description
C_SP	Central systolic pressure	The maximum pressure exerted by the blood against the central arterial walls during ventricular contraction, reflecting the force generated by the heart's pumping action.
C_DP	Central diastolic pressure	The lowest pressure in the central arteries during the resting phase of the cardiac cycle, indicating the pressure when the heart is relaxed and refilling with blood.
C_SVI	Central Buckberg sub-endocardial viability ratio	Assesses myocardial oxygen delivery by comparing diastolic pressure to systolic pressure in central arteries, offering insights into the adequacy of blood flow to the heart muscle.
C_AP	Central augmented pressure	Measures the additional pressure from arterial wave reflections during systole, providing information about arterial stiffness and wave reflection.
C_AGPH	Normalized central augmented pressure-to-pulse height ratio	Central augmented pressure-to-pulse height ratio normalized to a heart rate of 75 beats per minute - quantifies arterial stiffness and wave reflection, aiding in cardiovascular risk assessment.
C_MEANP	Central mean pressure	Represents the average pressure throughout the cardiac cycle in central arteries, offering a comprehensive measure of hemodynamic load on the heart and vasculature.
C_AI	Central augmentation index	Central augmented pressure-to-pulse height ratio - a percentage representing arterial stiffness and wave reflection in central arteries, with higher values indicating increased arterial stiffness and wave reflection.
C_ESP	Central end-systolic pressure	Reflects the pressure in central arteries at the end of systole, indicating the residual pressure in the arterial system after ventricular ejection.
C_PERIOD	Pulse period	The length of a central pulse in milliseconds.

6

DISCUSSION AND FUTURE PERSPECTIVES

Achievements of research aims

The primary aim of my work, introduced in Chapter 2 and discussed in detail throughout this thesis, was to propose novel, data-driven frameworks for the screening of medial and intimal vascular calcification that are both cost-effective and clinically feasible. The biomarker- and pulse wave-based models investigated here, parametrized for individuals with chronic kidney disease, demonstrated these qualities and therefore fulfilled the stated aim. Across all three studies, the emphasis was placed on early detection, an essential step for timely intervention. Moreover, the proposed approaches not only improve VC risk stratification but also strengthen cardiovascular risk assessment itself, which aligns the thesis title with the research it presents.

The research aims stated in this thesis are complex and multi-dimensional, collectively describing the purpose of my work. Yet, in these final remarks, I would like to summarise the core principle guiding the entire research with a single word: applicability. I believe that this term captures the multifaceted approach required to develop solutions that can be seamlessly translated from research into clinical practice. It has guided every stage of my work: from identifying a clinically meaningful problem in need of an improved detection, finding a relevant study population, providing a transparent rationale for the proposed solutions, and ensuring robust model performance, to prioritizing methods that are simple to implement and impose minimal burden on patients.

The focus on applicability also justifies the choice of screening methods explored in this thesis. Phenotypic biomarkers are already part of routine clinical workflows, and integrating them into machine learning models that output individualized disease probabilities represents a natural and accessible extension. Similarly, pressure pulse wave measurement is increasingly accessible and non-invasive, which makes it an attractive candidate for use as a clinical biomarker. The extraction of the analysed PW-FDFs relies on Fourier decomposition, which is already implemented in many commercially available devices using peripheral-to-central generalized transfer functions. This means the proposed approach could be incorporated into existing technologies with minimal additional development. Furthermore, I demonstrated that PW-FDFs derived from centrally transformed waveforms can be used for CAC screening, enabling broader applicability regardless of the arterial site where the signal is captured.

Applicability is also reflected in the choice of the study population. End-stage renal

disease patients are particularly susceptible to vascular calcification and its consequences, making them a suitable group for developing and validating early screening strategies. Not only is data collection more feasible in this population, but CKD patients are most likely to benefit from implementing such screening tools in clinical practice.

It is also important to emphasize why this research falls within the scope of biomedical engineering. As an interdisciplinary field, biomedical engineering applies, among others, engineering principles, mathematical and computational methods, and biological knowledge to address challenges in medicine and healthcare. In this thesis, I applied machine learning techniques - computational methods originating from mathematical concepts - to data selected on the basis of established biological and physiological knowledge of vascular calcification, thereby integrating insights from multiple disciplines. Furthermore, by prioritizing feasibility, cost-effectiveness, and compatibility with existing clinical workflows, my work bridges the gap between methodological innovation and real-world applicability, reinforcing its position within the field of biomedical engineering.

To conclude, applicability is not only the unifying principle of this research but also the quality that situates it within the biomedical engineering field. I hope that this focus will ensure the proposed methods can be applied in future real-world cardiovascular screening strategies, ultimately helping to improve care for patients at risk of vascular calcification.

Limitations and future perspectives

Naturally, my work is not free from limitations. Although they are discussed in detail within the individual publications, here I highlight those most relevant to interpreting the results and guiding future work.

First, while the developed frameworks demonstrated robust performance within the studied cohorts, their generalisability remains to be confirmed. Large-scale, multicenter studies across diverse CKD populations are needed to validate the models and refine their parameters for broader use. Nonetheless, the results obtained here provide a strong basis and, I believe, offer a compelling motivation to collect larger datasets and pursue further validation efforts.

Second, extending the models beyond CKD populations could provide valuable insights. Directly comparing models trained in CKD and non-CKD cohorts would help clarify how CKD influences feature selection, model behavior, and ultimately the mechanisms linking vascular calcification with measurable biomarkers.

Third, a formal comparison between information captured by pulse wave velocity and pulse wave frequency-domain features remains an important next step. While PWV is currently regarded as the gold standard in arterial stiffness assessment, it requires measurements at multiple arterial sites and is technically demanding. PW-FDFs, by contrast, can be derived from a single-site recording, making them potentially more accessible. Exploring whether PW-FDFs can serve as a viable alternative or complementary biomarker is, therefore, an important future direction.

Finally, the study on CAC score prediction raises the question of whether the conventional 100 AU threshold could be lowered or refined. With larger datasets, regression-based or multinomial classification approaches could enable modeling CAC severity

more granularly, potentially identifying clinically meaningful lower CAC score values.

In conclusion, this thesis has presented novel, data-driven frameworks for vascular calcification screening that emphasize cost-effectiveness, clinical feasibility, and applicability. While limitations remain, the findings demonstrate the potential of both phenotypic biomarker-based and pressure pulse wave–based models as scalable screening approaches. At the same time, the research has raised important new questions, underscoring that the proposed methods are not an endpoint but rather a promising starting point for continued exploration into clinically applicable, patient-centered cardiovascular screening tools.

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APPENDIX I

CONFERENCES

- Artery Conference, Nancy, France, October 19-22, 2022

  Poster presentation (presenting author): "Pulse waveform-based prediction of vascular calcification in patients with end-stage renal disease" **U. Białończyk**, M. Dębowska, L. Dai, A. Qureshi, M. Soderberg, B. Lindholm, P. Stenvinkel, J. Poleszczuk;

- XXIII Polish Conference on Biocybernetics and Biomedical Engineering, Łódź, Poland, September 27-29, 2023

  Oral presentation (presenting author): "Detection of medial vascular calcification in chronic kidney disease based on the pulse wave analysis in the frequency domain" **U. Bialonczyk**, M. Debowska, L. Dai, A. Qureshi, M. Soderberg, B. Lindholm, P. Stenvinkel, J. Poleszczuk

- ASN Kidney Week, San Diego, USA, October 23-27, 2024

  Poster presentation (co-author): "Detection of Medial Vascular Calcification Using Cost-Effective Classifiers" **U. Bialonczyk**, L Dai, A. Qureshi, L. Bobrowski, M. Soderberg, B. Lindholm, P. Stenvinkel, T. Lukaszuk, M. Debowska, J. Poleszczuk

- NBC 2025 & PCBBE 2025 Warsaw, Poland, June 16–18, 2025

  Poster presentation (presenting author): „Leveraging pulse wave signal properties for coronary artery calcification screening in CKD patients" **U. Bialonczyk**, L. Pstras, M. Debowska, L. Dai, AR. Qureshi, M. Soderberg, T. Brismar, J. Ripsweden, B. Lindholm, P. Stenvinkel, J. Poleszczuk

A P P E N D I X I I

DECLARATION OF AUTHORS' CONTRIBUTIONS

In paper „**Balancing accuracy and cost in machine learning models for detecting medial vascular calcification in chronic kidney disease: a pilot study**", published in *Scientific Reports*, 15 (2025), DOI: 10.1038/s41598-025-02457-2,

Urszula Bialonczyk (first author, corresponding author):

- conceptualized the study,
- designed the methodological approach,
- performed formal data analysis,
- developed the formula for ICER tailored for mVC detection,
- performed computations,
- prepared the figures, tables and supplementary material,
- wrote the manuscript;

Małgorzata Dębowska:

- conceptualized the study,
- revised the manuscript;

Leon Bobrowski:

- developed the methodology for RLS;

Tomasz Łukaszuk:

- developed the software for RLS calculation and carried out its computation;

Jan Poleszczuk (supervisor):

- conceptualized the study,
- supervised the research,
- revised the manuscript;

Lu Dai*:

- curated the data,
- prepared the Table S4,
- revised the manuscript;

Abdul Rashid Qureshi*:

- curated the data;

Magnus Söderberg*:

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Peter Stenvinkel*:

- supervised the research;

Bengt Lindholm*:

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Signed by: Tomasz Łukaszuk

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As Head of Baxter Novum, Renal Medicine, Karolinska Institutet, I hereby confirm that the individual authors' contributions to the publication are in accordance with the authorship contribution statement, and declare that I am signing this confirmation on behalf of the authors marked with (*).

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In paper „**Detection of medial vascular calcification in chronic kidney disease based on pulse wave analysis in the frequency domain**", published in *Biomedical Signal Processing and Control*, 94 (2024), DOI: 10.1016/j.bspc/2024.106250,

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As Head of Baxter Novum, Renal Medicine, Karolinska Institutet, I hereby confirm that the individual authors' contributions to the publication are in accordance with the authorship contribution statement, and declare that I am signing this confirmation on behalf of the authors marked with (*).

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In paper „ **Leveraging pulse wave signal properties for coronary artery calcification screening in CKD patients**", published in *Computers in Biology and Medicine*, 194 (2025), DOI: 10.1016/j.compbiomed.2025.110519,

Urszula Bialonczyk (first author, corresponding author):

- conceptualized the study,
- designed the methodological approach,
- performed formal data analysis,
- performed computations,
- prepared the figures, tables and supplementary material,
- wrote the manuscript;

Leszek Pstraś:

- revised the manuscript;

Malgorzata Dębowska:

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Jan Poleszczuk (supervisor):

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Polish Academy of Sciences

Doctoral Thesis

Data-driven approaches to screening and prescreening of cardiovascular diseases: advancing early detection and risk identification

Author:
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Advisor:
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A thesis submitted in fulfillment of the requirements for the degree of Doctor of Philosophy

in the

Nalecz Institute of Biocybernetics and Biomedical Engineering
Polish Academy of Sciences

September 29, 2025

DECLARATION OF AUTHORSHIP

I, Urszula Białończyk-Cyba, declare that this thesis titled, "Data-driven approaches to screening and prescreening of cardiovascular diseases: advancing early detection and risk identification" and the work presented in it is my own. I confirm that:

- This work was done wholly or mainly while in candidature for a research degree at the Doctoral School of Information and Biomedical Technologies at the Polish Academy of Sciences.
- Where I have consulted the published work of others, this is always clearly attributed.
- Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work.
- I have acknowledged all main sources of help.
- Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself.

Signed: Signed by: Urszula Białończyk-Cyba 3D050AE7DCA442D...

Date: 9/24/2025

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CONTENTS

LIST OF ABBREVIATIONS

ABI	Ankle-Brachial Index
ACR	Albumin-to-Creatinine Ratio
AGEs	Advanced Glycation End Products
AU	Agatston Units
BAC	Breast Arterial Calcification
baPWV	brachial-ankle Pulse Wave Velocity
CAC	Coronary Artery Calcification
CAD	Coronary Artery Disease
cfPWV	carotid-femoral Pulse Wave Velocity
CKD	Chronic Kidney Disease
CLTI	Chronic Limb-Threatening Ischemia
crPWV	carotid-radial Pulse Wave Velocity
CT	Computed Tomography
CVD	Cardiovascular Disease
eGFR	estimated Glomerular Filtration Rate
ESRD	End-Stage Renal Disease
FFT	Fast Fourier Transform
FPR	False Positive Rate
GFR	Glomerular Filtration Rate
GTF	Generalized Transfer Function
HU	Hounsfield Units
ICER	Incremental Cost-Effectiveness Ratio
IVUS	Intravascular Ultrasound
iVC	intimal Vascular Calcification
JCR	Journal Citation Reports
KDIGO	Kidney Disease: Improving Global Outcomes
LOOCV	Leave-One-Out Cross-Validation
MAP	Mean Arterial Pressure
ML	Machine Learning
mVC	medial Vascular Calcification
OCT	Optical Coherence Tomography
OFDI	Optical Frequency Domain Imaging
PAD	Peripheral Artery Disease
PET	Positron Emission Tomography
PP	Pulse Pressure
PW	Pulse Wave
PW-FDFs	Pulse Wave–Frequency Domain Features
PWV	Pulse Wave Velocity
QALYs	Quality-Adjusted Life Years
ROC	Receiver Operating Characteristic
SCORE	Systematic Coronary Risk Evaluation
SVM	Support Vector Machines
TPR	True Positive Rate
VC	Vascular Calcification
VSMCs	Vascular Smooth Muscle Cells

LIST OF PUBLICATIONS

Publications included in the thesis

(P1) **U. Bialonczyk**, L. Dai, A. R. Qureshi, L. Bobrowski, M. Soderberg, B. Lindholm, P. Stenvinkel, T. Lukaszuk, M. Debowska, J. Poleszczuk „Balancing accuracy and cost in machine learning models for detecting medial vascular calcification in chronic kidney disease: a pilot study", *Scientific Reports* 15 (2025), p. 17453. ISSN: 2045-2322. DOI: 10.1038/s41598-025-02457-2;

(P2) **U. Bialonczyk**, M. Debowska, L. Dai, A. R. Qureshi, M. Soderberg, B. Lindholm, P. Stenvinkel, J. Poleszczuk „Detection of medial vascular calcification in chronic kidney disease based on pulse wave analysis in the frequency domain", *Biomedical Signal Processing and Control* 94 (2024), p. 106250, ISSN: 1746-8094. DOI: 10.1016/j.bspc/2024.106250;

(P3) **U. Bialonczyk**, L. Pstras, M. Debowska, L. Dai, A. R. Qureshi, M. Soderberg, T. B. Brismar, J. Ripsweden, B. Lindholm, P. Stenvinkel, J. Poleszczuk „Leveraging pulse wave signal properties for coronary artery calcification screening in CKD patients", *Computers in Biology and Medicine* 194 (2025), p. 110519, ISSN: 0010-482. DOI: 10.1016/j.compbiomed.2025.110519.

Publications not included in the thesis

1. M. Wieliczko, M. Twardowska-Kawalec, M. Debowska, M. Pietribiasi, **U.Bialonczyk**, J. Waniewski, K. Leypoldt, J. Matuszkiewicz-Rowinska, J. Malyszko „Effect of time-dependent dialysate bicarbonate concentrations on acid-base and uremic solute kinetics during hemodialysis treatments", *Scientific Reports* 14 (2024). DOI: 10.1038/s41598-024-52757-2;

2. H. Kamecki, A. Tokarczyk, M. Dębowska, **U. Białończyk**, W. Malewski, P. Szostek, O. Tayara, S. Gonczar, S. Poletajew, Ł. Nyk, P. Kryst, S. Szempliński „A Simple Nomogram to Predict Clinically Significant Prostate Cancer at MRI-Guided Biopsy in Patients with Mild PSA Elevation and Normal DRE", *Cancers*, 2025; 17(5), 753. DOI: 10.3390/cancers17050753;

3. M. Debowska, M. Wieliczko, M. Pietribiasi, **U. Białończyk**, J. Malyszko, J. Leypoldt, J. Waniewski „Change in plasma electrolyte concentrations during hemodialysis following a controlled step-up in dialysate bicarbonate concentration", *The International Journal of Artificial Organs*, 2025; 48(5):293-301. DOI: 10.1177/03913988251337323;

4. K. Wolos, L. Pstras, **U. Bialonczyk**, M. Debowska, W. Dabrowski, D. Siwicka-Gieroba, J. Poleszczuk „Personalized Pulse Wave Propagation Modeling to Improve Vasopressor Dosing Management in Patients with Severe Traumatic Brain Injury", *PLoS Computational Biology*, 2025; 21(9). DOI: 10.1371/journal.pcbi.1013501.

SUMMARY

English summary

Cardiovascular diseases (CVDs) remain the leading cause of death worldwide, with vascular calcification (VC) recognized as an independent risk factor for adverse cardiovascular events. Although the exact prevalence of VC in the general population is not well established, certain groups are particularly susceptible to this condition. Among them, patients with chronic kidney disease (CKD) often experience an accelerated and widespread calcification process, which makes them particularly well-suited for VC research. Data collected from this population offer, therefore, a valuable source for developing, validating, and refining novel screening strategies designed to improve cardiovascular risk stratification. By focusing on this high-risk group, it becomes possible to design data-driven frameworks that not only address the clinical need for early VC detection in CKD but also generate insights with direct relevance for the broader challenge of CVDs screening and prescreening.

Vascular calcification can occur in two distinct layers of the vessel wall: the intima (intimal vascular calcification, iVC) and the media (medial vascular calcification, mVC). Although these two types differ in their underlying pathophysiology and clinical implications, both are highly prevalent in CKD patients.

Despite their clinical importance, VC status assessment remains a major challenge. Current diagnostic methods, such as arterial biopsies, are highly invasive, while advanced imaging techniques, e.g., computed tomography (CT), are relatively expensive, not always accessible, and involve exposure to radiation. These methods are not well-suited for routine monitoring, particularly in CKD patients who already endure a high treatment burden and are often reluctant to undergo additional procedures that are uncomfortable or time-consuming. As a result, vascular calcification, particularly in the medial layer, often goes unassessed in routine clinical practice, limiting opportunities for early detection and intervention. Therefore, there is an urgent need for safe, cost-effective, and minimally burdensome tools specifically designed for the screening of VC in CKD patients.

The aim of my work was to address the need for clinically feasible and cost-effective methods for medial and intimal vascular calcification screening by proposing novel, data-driven frameworks tailored for individuals with chronic kidney disease. The thesis evaluates models for early detection of vascular calcification in CKD patients, thereby providing a basis for the future development of scalable, broadly accessible tools for cardiovascular disease risk stratification.

My work consists of three thematically related scientific papers that were published between 2024 and 2025 in recognized journals listed in the JCR database with a total impact factor of 15.70.

The first part of my research, described in [P1], focused on the detection of medial vascular calcification using a panel of biomarkers known or suspected to be associated

with this pathology. While previous studies have explored the potential of various biomarker sets as input features for machine learning models aimed at mVC screening, none have evaluated the economic implications of such approaches. Moreover, the proposed biomarker sets vary widely between studies, often achieving similar statistical performance despite significant differences in availability, acquisition cost, and clinical feasibility. To develop a framework that is both practical and clinically applicable, I restricted the candidate features to circulating biomarkers, other non-invasively acquired parameters, and anthropometric measurements, with the latter being readily accessible in routine clinical practice. Using a range of advanced statistical methods, I trained classification models to detect mVC and evaluated their performance not only in terms of predictive accuracy but also cost-effectiveness, assessed via the incremental cost-effectiveness ratio (ICER). For this purpose, I proposed and applied an ICER calculation formula specifically tailored to this application. The findings of this comprehensive analysis support earlier observations: no single biomarker set was identified that consistently achieved superior predictive performance across the frameworks. However, the inclusion of ICER as a comparative metric revealed clinically relevant distinctions, demonstrating that broader sets of inexpensive, easily obtainable features may yield improved cost-effectiveness and, consequently, greater potential for clinical implementation. These results underscore the value of incorporating economic evaluation into the development of screening tools for vascular calcification. This investigation directly addresses my first main research hypothesis:

(H1) Integrating cost-effectiveness assessment into the selection of machine learning models trained for medial vascular calcification detection in patients with end-stage chronic kidney disease facilitates the identification of the most clinically relevant approaches.

Nevertheless, the obtained results also indicated that, in most cases, a smaller number of required inputs while maintaining predictive power enhances the feasibility and scalability of a screening tool. This observation motivated me to explore approaches based on a single, fully non-invasive biomarker, rather than panels requiring multiple assays and blood sampling. The pressure pulse wave signal represents an ideal candidate: it can be captured quickly, painlessly, and at low cost, yet carries rich physiological information about arterial wall properties. Building on this insight, the second part of my research focused on leveraging pressure pulse wave morphology as input to machine learning models for detecting medial vascular calcification in CKD patients. For this purpose, I developed a novel framework in which pressure pulse wave signals, acquired from a single peripheral arterial location, were transformed from the time domain to the frequency domain, and features extracted from this spectral analysis were used as inputs to statistical classification models. I demonstrated that this method outperforms models based solely on conventional risk factors, indicating its potential as a cost-effective and patient-friendly screening tool for medial vascular calcification. Those results, published in [P2], directly address the second main research thesis formulated in this dissertation:

(H2) A data-driven framework that integrates conventional vascular calcification risk factors with pressure pulse wave frequency-domain features (PW-FDFs) derived from non-invasive peripheral pressure pulse wave measurements can be used to detect medial vascular calcification in patients with end-stage chronic kidney disease.

Building on the promising results of the proposed pressure pulse wave-based framework for medial vascular calcification detection, in the third part of my work, my focus shifted to identifying coronary artery calcification (CAC), most commonly located in the intimal layer of the arterial wall. It is evaluated through CT imaging, followed by expert analysis to derive a coronary artery calcification score, which informs about the extent of CAC. Utilizing data on pressure pulse wave signals and CAC scores from CKD patients, I demonstrated that frequency-domain features derived from these signals can serve as effective input for statistical models aimed at identifying patients with elevated CAC scores. Importantly, the model exhibited superior ability to distinguish between individuals with and without elevated CAC scores in both younger and older patient subgroups, compared to the model based solely on conventional clinical predictors. These findings suggest that single-site, non-invasive pressure pulse wave analysis in the frequency domain may offer a viable, low-burden alternative for the early detection of intimal vascular calcification. Those results have been published in [P3] and support the third research thesis formulated for this dissertation:

(H3) Statistical models based on pressure pulse wave frequency-domain features (PWFDFs) can effectively identify end-stage chronic kidney disease patients with elevated coronary artery calcification scores.

In summary, my work presents a multi-faceted approach to the detection of vascular calcification in chronic kidney disease patients, addressing both medial and intimal types of this pathology. By integrating statistical performance with economic evaluation, the first part provides novel insights into the cost-effectiveness of biomarker-based screening models. The second part introduces an entirely non-invasive framework leveraging frequency-domain features of single-site pressure pulse wave signals, offering a promising alternative to traditional risk-based models for medial calcification screening. Finally, this approach is extended to the detection of intimal calcification in the coronary artery, demonstrating the potential of pressure pulse wave spectral analysis as a low-burden, accessible method for identifying patients with elevated coronary artery calcification scores. Collectively, these contributions provide a foundation for further development of clinically feasible and economically viable vascular calcification screening tools with strong potential for clinical implementation.

STRESZCZENIE

Streszczenie w języku polskim

Choroby sercowo-naczyniowe (CVDs, *ang. cardiovascular diseases*) stanowią główną przyczynę zgonów na świecie, a zwapnienia naczyń krwionośnych (VC, *ang. vascular calcification*) uznaje się za istotny czynnik ryzyka wystąpienia niepożądanych zdarzeń sercowo-naczyniowych. Dokładna częstość występowania VC w populacji ogólnej nie została jednoznacznie określona. Wiadomo jednak, że wyjątkowo narażone na ich rozwój są wybrane grupy osób. Wśród nich na szczególną uwagę zasługują osoby z przewlekłą chorobą nerek (CKD, *ang. chronic kidney disease*), u których proces powstawania zwapnień przebiega szybko i ma nasilony charakter, co powoduje, że populacja ta stanowi odpowiedni model do badań VC. Gromadzenie danych dotyczących zwapnień u chorych z CKD umożliwia opracowanie, walidację oraz doskonalenie nowatorskich strategii badań przesiewowych w kierunku VC, które mogą znacząco poprawić dokładność oceny ryzyka sercowo-naczyniowego. Przykładem takich rozwiązań są techniki uczenia maszynowego wykorzystujące zgromadzone dane do tworzenia modeli predykcyjnych. Skupienie się na pacjentach z CKD jest podejściem praktycznym - umożliwia zebranie niezbędnych danych w stosunkowo niedługim czasie, a także odpowiada na realne potrzeby kliniczne tej grupy, która może szczególnie skorzystać z wdrożenia wczesnych metod oceny VC. Warto również zaznaczyć, że wnioski wynikające z analiz mogą mieć bezpośrednie przełożenie na udoskonalenie badań przesiewowych w kierunku chorób sercowo-naczyniowych w szerszej populacji.

Zwapnienia naczyń krwionośnych mogą być zlokalizowane w dwóch odrębnych warstwach ściany naczyń: w błonie wewnętrznej (iVC, *ang. intimal vascular calcification*) oraz w błonie środkowej (mVC, *ang. medial vascular calcification*). Procesy te różnią się zarówno pod względem patofizjologii, jak i konsekwencji klinicznych. Oba występują powszechnie u pacjentów z przewlekłą chorobą nerek.

Pomimo istotnego znaczenia klinicznego, ocena występowania VC pozostaje poważnym wyzwaniem. Dostępne metody diagnostyczne, takie jak biopsja tętnic, są wysoce inwazyjne, natomiast zaawansowane techniki obrazowania, np. tomografia komputerowa, wiążą się ze znacznymi kosztami, ograniczoną dostępnością i ekspozycją na promieniowanie jonizujące. Z tego względu nie nadają się one do rutynowych badań, szczególnie pacjentów z CKD, którzy z uwagi na przebieg choroby poddawani są intensywnemu leczeniu i niechętnie akceptują dodatkowe, uciążliwe lub czasochłonne procedury diagnostyczne. W efekcie, występowanie zwapnień, zwłaszcza w obrębie błony środkowej, rzadko jest oceniane w codziennej praktyce klinicznej. Ogranicza to możliwości ich wczesnego wykrywania oraz podejmowania działań prewencyjnych i terapeutycznych. Niezbędne jest zatem opracowanie narzędzi przeznaczonych do badań przesiewowych w kierunku VC u pacjentów z CKD, które będą bezpieczne, koszt-efektywne i jak najmniej obciążające dla chorego.

Celem mojej pracy było opracowanie metod badań przesiewowych w kierunku zwapnień błony środkowej i błony wewnętrznej ścian naczyń, które będą koszt-efektywne oraz możliwe do wdrożenia w praktyce klinicznej. Zaproponowałam nowe narzędzia oparte na analizie danych, dostosowane do specyfiki populacji pacjentów z przewlekłą

chorobą nerek. W ramach pracy przeprowadziłam ocenę modeli umożliwiających wczesne wykrywanie zwapnień ścian naczyń krwionośnych w tej grupie chorych, tworząc podstawę do przyszłego opracowania rozwiązań wspomagających precyzyjną ocenę ryzyka sercowo-naczyniowego, a jednocześnie łatwych do wdrożenia na szeroką skalę.

Moja praca składa się z trzech powiązanych tematycznie artykułów naukowych, opublikowanych w latach 2024–2025 w renomowanych czasopismach wymienionych w bazie danych JCR, o całkowitym współczynniku wpływu IF = 15.70 oraz liczbie punktów MNiSW N = 380.

Pierwsza część pracy, opisana w [P1], poświęcona jest wykrywaniu zwapnień błony środkowej naczyń za pomocą technik uczenia maszynowego z wykorzystaniem paneli biomarkerów potencjalnie powiązanych z tą patologią. Chociaż powstały już prace podejmujące tę tematykę, żadna z nich nie uwzględniała w analizie jakości rozwiązania kosztów poszczególnych pomiarów. Można było natomiast zauważyć, że proponowane przez poszczególne algorytmy zestawy biomarkerów różniły się znacznie w zależności od zastosowanej metody. Pomimo istotnych różnic w dostępności i kosztach pozyskania poszczególnych danych, jakość predykcyjna modeli była jednak porównywalna.

Aby opracować metody możliwe do zastosowania w praktyce klinicznej, ograniczyłam analizowane cechy do biomarkerów oznaczanych z krwi, innych parametrów uzyskiwanych nieinwazyjnie oraz pomiarów antropometrycznych. Wykorzystując zaawansowane algorytmy statystyczne, wytrenowałam modele klasyfikacyjne służące do wykrywania mVC i oceniłam ich skuteczność nie tylko pod kątem trafności prognoz, lecz także kosztów ich wykonania. W tym celu zaproponowałam wzór do wyznaczenia wskaźnika koszt-efektywności (ICER, *ang. incremental cost-effectiveness ratio*) dostosowany do specyfiki badanego zagadnienia. Wyniki przeprowadzonych testów potwierdziły wcześniejsze obserwacje: nie znaleziono jednego zestawu biomarkerów, który konsekwentnie osiągałby najlepsze rezultaty w każdej z analizowanych miar jakości klasyfikatorów. Uwzględnienie wskaźnika ICER jako metryki porównawczej ujawniło jednak istotne klinicznie różnice, wykazując, że szerszy zestaw niedrogich i łatwo dostępnych cech może zapewnić lepszą koszt-efektywność, a tym samym większy potencjał do zastosowania w praktyce klinicznej. Wyniki te pokazują znaczenie włączenia oceny ekonomicznej do procesu opracowywania narzędzi do badań przesiewowych w kierunku zwapnienia naczyń krwionośnych. Praca ta bezpośrednio odnosi się do mojej pierwszej hipotezy badawczej:

(H1) Włączenie oceny koszt-efektywności do procesu wyboru modeli uczenia maszynowego, szkolonych w celu wykrywania zwapnień błony środkowej naczyń krwionośnych u pacjentów ze schyłkową chorobą nerek, umożliwia bardziej precyzyjną identyfikację metod o największym potencjale klinicznym.

Uzyskane wyniki wskazały jednak, że w większości przypadków mniejsza liczba wykorzystywanych biomarkerów przy zachowaniu zdolności prognostycznej zwiększa użyteczność oraz możliwość szerokiego zastosowania narzędzia przesiewowego. Obserwacja ta zmotywowała mnie do zbadania podejść opartych na pojedynczym, całkowicie nieinwazyjnym markerze, zamiast na panelach wymagających wielu testów i pobierania próbek krwi. Do dalszych analiz postanowiłam wykorzystać sygnał fali pulsu, który można szybko, bezboleśnie i niskim kosztem zarejestrować, a jednocześnie zawiera informacje fizjologiczne o właściwościach ścian naczyń krwionośnych.

W drugiej części moich badań skupiłam się zatem na wykorzystaniu informacji pozyskanych z fali pulsu jako danych wejściowych do modeli uczenia maszynowego w celu wykrywania zwapnień błony środkowej tętnic u pacjentów z CKD. Opracowałam metodę, w której sygnał fali pulsu, rejestrowany z tętnicy obwodowej, został przekształcony z dziedziny czasu do dziedziny częstotliwości. Cechy wyodrębnione w wyniku przeprowadzonej analizy spektralnej posłużyły jako dane wejściowe do statystycznych modeli klasyfikacyjnych. Wykazałam, że uwzględnienie informacji pochodzących z fali pulsu w klasyfikatorze przewyższa modele oparte wyłącznie na konwencjonalnych czynnikach ryzyka powstawania zwapnień naczyń, co wskazuje na potencjał tego podejścia jako koszt-efektywnego i przyjaznego dla pacjenta narzędzia do badań przesiewowych w kierunku mVC. Wyniki te, opublikowane w [P2], odnoszą się bezpośrednio do drugiej hipotezy badawczej sformułowanej w niniejszej rozprawie:

(H2) Metoda oparta na analizie danych, która łączy tradycyjne czynniki ryzyka powstawania zwapnień naczyń z cechami częstotliwościowymi fali pulsu (PWFDFs) uzyskanymi z nieinwazyjnych pomiarów tętna obwodowego, może być użyta do wykrywania zwapnień błony środkowej tętnic u pacjentów ze schyłkową chorobą nerek.

Opierając się na obiecujących wynikach uzyskanych w badaniach wykorzystania sygnału fali pulsu do wykrywania zwapnień błony środkowej tętnic, w trzeciej części niniejszej pracy skoncentrowałam się na identyfikacji zwapnień tętnic wieńcowych (CAC, *ang. coronary artery calcification*), najczęściej zlokalizowanych w warstwie błony wewnętrznej ściany naczynia. Stopień ich zaawansowania standardowo ocenia się za pomocą tomografii komputerowej, a jego podstawową miarą jest wskaźnik uwapnienia tętnic wieńcowych (*ang. CAC score*). Wykorzystując dane obejmujące sygnał fali pulsu oraz wyniki oceny CAC u pacjentów z CKD, wykazałam, że cechy uzyskane z analizy spektralnej tych sygnałów mogą stanowić efektywne dane wejściowe dla modeli klasyfikacyjnych, umożliwiających identyfikację pacjentów z podwyższonymi wartościami CAC. Co istotne, zaproponowany model charakteryzuje się wyższą precyzją w rozróżnianiu osób z istotnymi zwapnieniami i osób bez zwapnień, zarówno w podgrupach pacjentów młodszych, jak i starszych, w porównaniu z modelem opartym wyłącznie na konwencjonalnych czynnikach ryzyka CAC. Uzyskane rezultaty sugerują, że nieinwazyjnie mierzona fala pulsu, analizowana w dziedzinie częstotliwości, może stanowić mało uciążliwą, potencjalnie szeroko dostępną alternatywę dla tradycyjnych metod wczesnego wykrywania CAC. Wyniki te zostały opublikowane w [P3] i odnoszą się do trzeciej hipotezy badawczej sformułowanej w niniejszej rozprawie:

(H3) Modele statystyczne oparte na cechach częstotliwościowych fali pulsu (PWFDFs) mogą skutecznie identyfikować pacjentów ze schyłkową chorobą nerek, u których występuje podwyższony poziom zwapnienia tętnic wieńcowych.

Podsumowując, moja praca przedstawia wielowymiarowe podejście do wykrywania zwapnień ścian naczyń krwionośnych u pacjentów z przewlekłą chorobą nerek, uwzględniające zarówno zwapnienia błony środkowej, jak i wewnętrznej. Pierwsza część, łącząca analizę statystyczną z oceną ekonomiczną, dostarcza nowych informacji na temat koszt-efektywności modeli uczenia maszynowego opartych na biomarkerach służących do badań przesiewowych w kierunku mVC. Druga część prezentuje całkowicie nieinwazyjną metodę wykorzystującą cechy sygnału fali pulsu w dziedzinie częstotliwości, stanowiącą obiecującą alternatywę dla modeli bazujących jedynie

na tradycyjnych czynnikach ryzyka w ocenie zwapnień błony środkowej. Podejście to zostało następnie rozszerzone na wykrywanie zwapnień błony wewnętrznej w tętnicach wieńcowych, gdzie wykazano potencjał analizy spektralnej fali pulsu jako łatwo dostępnej, mało obciążającej pacjenta metody wspomagającej identyfikację osób z podwyższonym poziomem zwapnień.

Uzyskane wyniki stanowią podstawę do dalszego rozwoju praktycznych i ekonomicznie uzasadnionych narzędzi przesiewowych w kierunku zwapnień naczyń krwionośnych, posiadających istotny potencjał wdrożeniowy w praktyce klinicznej.

1

INTRODUCTION

This thesis aims to address the broad challenge of cardiovascular diseases (CVD) screening by proposing and investigating various data-driven methodologies in the specific context: detecting vascular calcification (VC) in patients with advanced chronic kidney disease. CKD patients are particularly well-suited for research on VC identification because the pathology is highly prevalent in this group, enabling the assembly of a sufficiently large study cohort within a reasonable timeframe and with fewer resources compared to populations where VC is much less common. The specific focus on VC is equally intentional as it is one of the most powerful independent predictors of adverse cardiovascular events. By developing data-driven techniques to assess this important marker in a high-risk population, my research supports the broader goal of advancing early detection and risk assessment of cardiovascular diseases.

1.1 Chronic kidney disease

1.1.1 Definition and diagnosis

According to the definition provided by Kidney Disease: Improving Global Outcomes (KDIGO), one of the most widely recognized organizations in the field, chronic kidney disease (CKD) is described as "*abnormalities of kidney structure or function, present for a minimum of 3 months, with implications for health*" [1]. Alarmingly, such abnormalities are becoming increasingly common worldwide [2]. In 2017, it was estimated that nearly one in ten people globally were affected by CKD, making it the 12^{th} leading cause of death [3]. By 2021, it had already reached the 9^{th} position [4]. This upward trend is closely linked to demographic and epidemiological shifts. With rising life expectancy, and the global increase in the prevalence of diabetes mellitus [5] and hypertension [6], which are both major risk factors for CKD [7], the disease burden is projected to escalate [8, 9, 10]. Forecasts suggest that by 2040, CKD could become the fifth leading cause of years of life lost globally [8]. Collectively, these trends underscore the urgent need for monitoring and management strategies for CKD.

Despite its broad definition, CKD diagnosis in clinical practice relies on two primary criteria:

- Assessment of kidney function usually done by evaluating glomerular filtration rate (GFR), which reflects how effectively the kidneys filter the blood [11]. Although GFR is considered the gold standard for evaluating kidney filtration, its direct measurement is complex and costly [12]. Therefore, in routine clinical

practice, the estimated GFR (eGFR) is commonly used and treated as a GFR proxy. Various formulas exist for its calculation, but the most widely adopted and recommended approach is based on serum creatinine levels [1]. In addition to creatinine, patient age and sex are incorporated into the calculation to improve estimation accuracy [13].

- Assessment of kidney damage which can be determined through several methods, including persistent hematuria, imaging abnormalities, or biopsy findings. However, the albumin-to-creatinine ratio (ACR) in urine is the most commonly used marker due to its simplicity and diagnostic utility [1]. The presence of albuminuria indicates abnormal protein leakage into the urine, reflecting structural kidney damage.

CKD is diagnosed when either reduced kidney function (GFR (eGFR) $<$ 60 mL/min/1.73 m^2) or evidence of kidney damage (e.g., albuminuria) persists for more than three months. Next, the disease is classified into stages based on the degree of kidney function decline, as indicated by GFR (eGFR) levels [1]. This classification, summarized in Table 1.1, is essential for risk stratification and treatment planning [1].

CKD Stage	**GFR (eGFR)** (mL/min/1.73 m^2)	**Severity**
Stage 1	$\geq$ 90	Mild kidney damage*
Stage 2	60–89	Mild kidney damage*
Stage 3a	45–59	Mild to moderate kidney damage
Stage 3b	30–44	Moderate to severe kidney damage
Stage 4	15–29	Severe kidney damage
Stage 5	<15	Severe kidney damage or kidney failure

Abbreviations: CKD, chronic kidney disease; (e)GFR, (estimated) glomerular filtration rate.
* Kidney damage must be confirmed to classify patients with GFR $\geq$ 60 mL/min/1.73 m^2.

Table 1.1: CKD Stages

From a clinical perspective, staging provides crucial information on the likelihood of progression to kidney failure and the risk of cardiovascular and other systemic complications [1]. It therefore guides the intensity and type of intervention required at each stage. The most advanced form of CKD is stage 5, also known as end-stage renal disease (ESRD). Patients at this stage exhibit profound kidney dysfunction and are at the highest risk of comorbidities, including CVD [1]. Given its clinical complexity and the heavy burden it imposes on both patients and healthcare systems, ESRD demands targeted attention.

My research, described in this thesis, focuses specifically on stage 5 CKD patients, who are both the most likely to exhibit vascular calcification [14] and are at the greatest risk of cardiovascular complications among all CKD stages [15].

1.1.2 Relation to cardiovascular diseases

Chronic kidney disease is now widely recognized as a systemic disorder [16]. Beyond the progressive renal impairment, CKD contributes to a wide range of complications, including mineral and bone disorders [17], anemia [18], immune dysfunction [19], metabolic disturbances [20], or neurological problems [21]. Among these, cardiovascular disease is the most prevalent and deadly comorbidity - particularly in patients with ESRD, where it remains the leading cause of mortality [22, 23, 24]. The clinical significance of cardiovascular complications in CKD is strongly emphasized in the recent KDIGO 2024 guidelines, which highlight both the relative and absolute cardiovascular risks across CKD stages, as demonstrated by data from the CKD Prognosis Consortium [25]. Among the ten major CKD-related complications discussed in their work, more than half were cardiovascular in nature, including cardiovascular mortality, myocardial infarction, stroke, heart failure, atrial fibrillation, and peripheral artery disease. In patients with CKD stage 5, the risk of these conditions is estimated to be 2.6 to 14 times higher than in individuals with proper kidney function, depending on the analyzed outcome and the degree of albuminuria [25].

The relationship between CKD and CVD is complex and bidirectional. While both conditions share common major risk factors such as hypertension and diabetes mellitus [26], which can partially explain this link, CKD also causes a number of metabolic and structural changes that directly contribute to cardiovascular pathology. These include an altered lipid profile specific to CKD patients [27], chronic inflammation (CKD is recognized as a state of persistent systemic inflammation) [28], myocardial remodeling and fibrosis [29], and, notably, vascular calcification, which is one of the most prevalent and clinically significant vascular complications in this population [30, 31]. As a pathological process influenced by mineral metabolism disturbances, chronic inflammation, and uremic toxins, VC exemplifies the systemic consequences of advanced kidney disease. It is strongly associated with arterial stiffness, left ventricular hypertrophy, and increased risk of sudden cardiac death [30, 32]. Despite its clinical significance, VC still remains underdiagnosed [33].

Given the cardiovascular burden faced by CKD patients and the role of vascular calcification in this context, a deeper understanding and improved screening of VC may lead to better patient outcomes, particularly among those with ESRD. The following chapters will explore vascular calcification in greater detail, highlighting its pathophysiological mechanisms, clinical implications, and the rationale for targeted screening strategies in this high-risk population.

1.2 Vascular calcification in chronic kidney disease

Although my work concerns the methods of VC screening, it would be difficult to create such tools without a deep understanding of the underlying mechanisms of this pathology and the consequences it carries. Therefore, in this section, I will give an overview of the process of VC formation as well as the current assessment methods with a particular focus on their clinical utility.

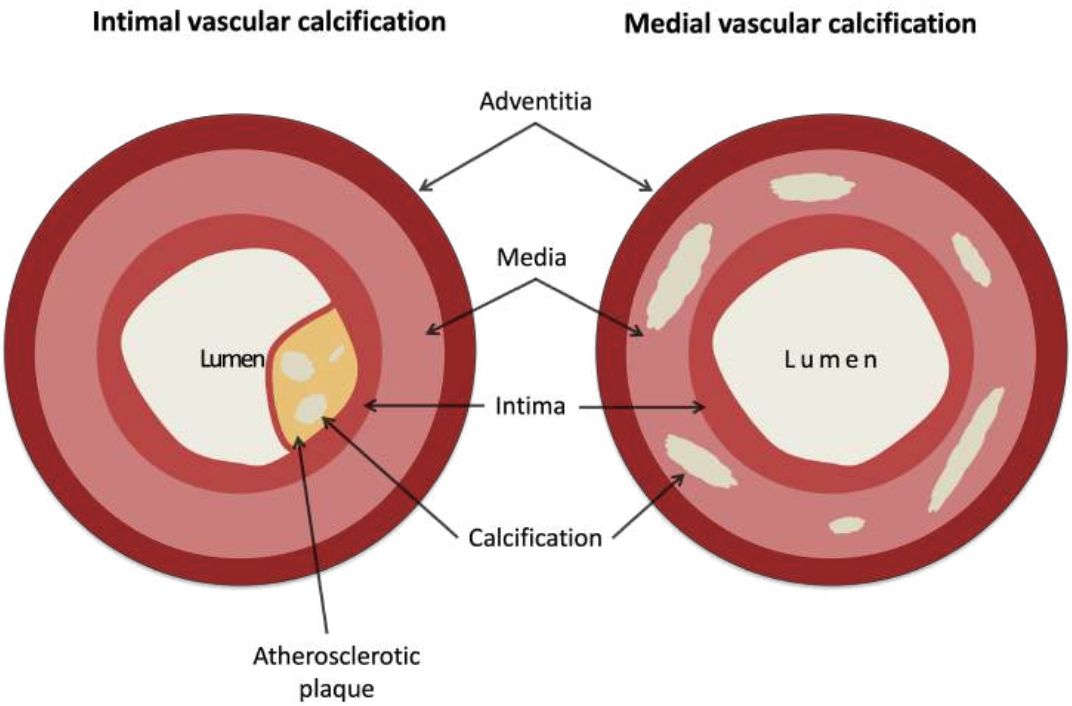

FIGURE 1.1: Schematic of a vessel cross-section depicting the distinct forms of vascular calcification. The left panel illustrates intimal vascular calcification, characterized by the deposition of calcium within an atherosclerotic plaque in the vessel intima, narrowing the lumen. The right panel depicts medial vascular calcification, where calcium accumulates directly within the smooth muscle layer (media) of the vessel wall.

1.2.1 Definition and clinical significance

Vascular calcification is a pathological process characterized by the abnormal deposition of calcium phosphate crystals in the form of hydroxyapatite (a mineral naturally found in bones and teeth) within the arterial wall [34]. Although originally considered a passive and degenerative consequence of aging, VC is now recognized as an active, highly regulated cellular mechanism that closely resembles physiological bone formation [35, 36, 37]. This revised understanding not only highlights the biological complexity of VC [38], but also indicates its potential reversibility, making it a compelling target for clinical research.

VC can affect both medial (middle) and intimal (innermost) layers of the arterial wall, as depicted in Figure 1.1, and may occur in various vascular sites [39, 30, 32]. Furthermore, it may present as microcalcification or macrocalcification, each with distinct clinical implications for vascular function [39]. This heterogeneity of VC complicates its evaluation and prognostic interpretation in clinical settings, emphasizing the need for more nuanced diagnostic and risk stratification strategies.

1.2.2 Pathophysiological mechanisms

VC is mainly driven by the vascular smooth muscle cells (VSMCs). Under physiological conditions, VSMCs maintain a contractile phenotype, while when exposed to a pathological stimulus, they undergo phenotypic switching resulting in the adoption of an osteogenic (i.e., bone-like) phenotype [35]. This transformation resembles the

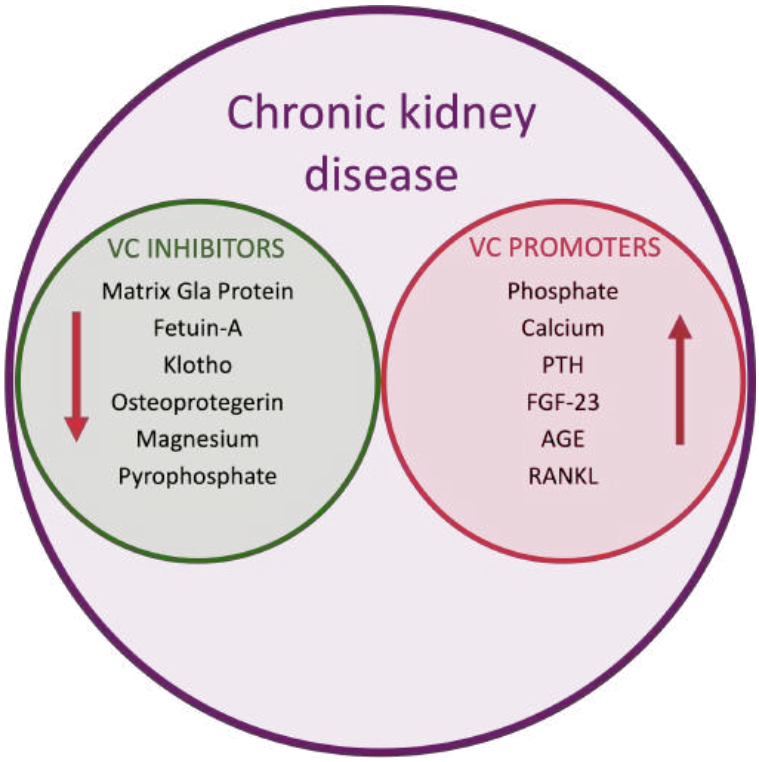

FIGURE 1.2: Selected vascular calcification inhibitors and promoters whose levels are commonly disturbed in chronic kidney disease.
VC, vascular calcification; PTH, parathyroid hormone; FGF-23, fibroblast growth factor 23; AGE, advanced glycation end product; RANKL, receptor activator of nuclear factor kappa-B ligand.

process of bone formation and involves the expression of bone-related proteins [40]. In the intima, in addition to VSMCs, macrophages also contribute to the process, particularly through inflammatory signaling and vesicle release [41]. In CKD, in addition to mineral disturbances, various factors such as chronic inflammation, oxidative stress, and uremic toxins (e.g., advanced glycation end products - AGEs) act as promoters of this osteogenic differentiation by inducing vessel wall injuries [42, 43].

The development of vascular calcification in chronic kidney disease is closely linked to disturbances in mineral metabolism - particularly elevated levels of phosphate (P) and calcium (Ca) [44]. Hyperphosphatemia, highly prevalent in CKD, is considered a key driver of VC [45, 46, 47]. Increased calcium levels and an elevated calcium–phosphate ($Ca \times P$) product also contribute significantly to the calcification process [48, 49, 30]. Notably, VC can develop even before serum phosphate levels rise above the normal range, suggesting that local phosphate concentrations within tissues and cumulative exposure over time may play a more critical role than what is reflected in serum measurements [50]. It is also worth noting that the calcification process slows down to rates seen in patients with normal renal function but does not regress after a kidney transplant, which makes prevention extremely important [51].

Under physiological conditions, vascular tissues are protected from mineral deposition by several active inhibitors of calcification, including matrix Gla protein (MGP), fetuin-A, and osteoprotegerin. In CKD, their levels are often reduced, impairing the vasculature's protective mechanisms against calcification [52]. This, combined with the usual simultaneous accumulation of calcification promoters, creates a pro-calcific

environment in the vasculature. The selected VC inhibitors and promoters related to CKD [52] are presented in Figure 1.2.

While medial vascular calcification (mVC) and intimal vascular calcification (iVC) share core cellular mechanisms, they differ in their initiating stimuli, vascular location, and clinical implications. mVC is typically associated with arterial stiffness and is prevalent in CKD [32], whereas iVC, although present in CKD patients as well, is more closely related to atherosclerotic plaque formation [34]. Understanding these distinctions is crucial for accurate risk assessment, as well as for the development of targeted diagnostic and therapeutic strategies. Thus, mVC is described in detail in Chapter 3.1 while iVC is discussed in Chapter 5.1.

1.3 Clinical management of vascular calcification

1.3.1 Treatment

To this date, there does not exist causal treatment for VC, but strategies to slow down its progression have been proposed. Multiple trials targeting VC have been conducted, and their detailed reviews can be found in [53, 54, 34]. It is evident that there is still much to be discovered regarding VC's pathophysiological mechanisms, and each component of this complex process is a potential direction in the search for therapeutic strategies. In the context of my work, two aspects need to be highlighted. First, many of the proposed therapies to slow down VC's progression are focused on targeting disrupted biomarkers associated with this pathology, including inhibitors such as sodium thiosulfate, magnesium, and SNF472. Researchers acknowledge that due to the heterogeneity of the mechanism, multiple simultaneous interventions may be required [54]. From this perspective, trying to uncover combinations of features that may indicate calcification using various machine learning techniques [P1] is my contribution to this aspect of research. Second, given the current lack of methods to reverse calcification, early detection is essential. This target was pursued not only through the proposal and evaluation of screening strategies aimed at improving VC's detection, but also through the careful formulation of the objectives in each study. Mild and extensive calcification were marked as positive in [P1]. In [P2], the PW-FDFs method I proposed allowed for the detection of mVC at an earlier stage, with even minimal calcification being labelled as positive. Finally, in my third work [P3], I have targeted CAC $>$ 100 AU, a threshold indicating mild coronary artery disease risk. The results demonstrated that the proposed method shows potential for identifying even lower CAC levels, since the probability of being classified as positive increased with the true CAC score. This screening approach for CAC may therefore support earlier referral for scanning in patients who are most likely to benefit from it.

1.3.2 Screening

Although there are multiple ways to describe the screening process, for the purpose of this work, I will employ the following definition: screening refers to testing individuals to evaluate their likelihood of having a particular disease or disorder. Those identified as high-risk can then be referred for definitive diagnostic evaluation. The principal aim of screening is to reduce morbidity or mortality at the population level by detecting disease early enough that interventions can meaningfully change the course of illness.

It is important to distinguish screening from diagnostic testing. A diagnostic test should reliably distinguish between individuals with and without the disease; such tests are often called *gold standards* and, in principle, should not make classification errors. In the context of VC, arterial biopsy would meet this definition. In practice, since invasive methods are unsuitable for routine use, highly accurate non-invasive techniques (e.g., PET–CT scans capable of differentiating iVC and mVC patterns) can serve as surrogate gold standards.

The distinction between screening and pre-screening, on the other hand, can be defined by what follows the initial assessment rather than by the method itself. If a non-definitive assessment is followed by a definitive diagnostic test, the initial step functions as a screening test. Conversely, if it is followed by a more informative but still non-definitive method, the first step can be considered pre-screening. Consequently, the same non-definitive method may serve as either a screening or pre-screening tool, depending on the subsequent diagnostic pathway. To maintain clarity and consistency, in the remainder of this thesis, the term *screening* will be used to refer to any non-definitive diagnostic process, regardless of what diagnostic steps follow.

A useful screening test does not need to provide perfect accuracy. Its value depends on the balance of benefits (earlier detection, prevention of events) against harms and costs (false positives, unnecessary investigations, patient burden, expense). Screening performance is typically assessed using *sensitivity* (the proportion of true positives correctly identified) and *specificity* (the proportion of true negatives correctly identified). The optimal trade-off between sensitivity and specificity depends on the screened population and the consequences of false results. For example, in older adults, where disease prevalence is higher, maximizing specificity may reduce unnecessary testing, whereas in younger populations, a higher sensitivity may be prioritized to avoid missing rare early cases.

Because perfect accuracy (the proportion of observations correctly classified) is not required for screening, many useful tools rely on indirect measurements. In VC, an example can be pulse wave velocity (PWV), which measures arterial stiffness rather than calcification directly [55]. Since VC contributes to vessel stiffening, it makes PWV a reasonable initial indicator - its elevated values can then prompt confirmatory imaging, improving cost-effectiveness and limiting unnecessary radiation exposure.

The qualities of an effective screening method have been described most famously by Wilson and Jungner, whose principles, introduced in the 1960s, remain influential to this date [56]. Above all, a good screening tool should be simple, safe, inexpensive, and easy to integrate into routine care so as to encourage clinician uptake and patient compliance [57]. Taken together, VC satisfies many Wilson–Jungner criteria. It is a significant medical problem linked to increased mortality. It can be detected at initial stages with advanced imaging techniques such as PET–CT, and early identification is clinically important because only treatments that slow down its progression are currently available.

Nonetheless, mVC detection remains a subject of debate, in contrast to iVC assessment in coronary arteries, which is strongly recommended in current cardiovascular risk evaluation. While many clinicians and researchers highlight the added value of mVC assessment for refined risk stratification, especially in CKD patients [53], others argue that it offers limited benefit in the absence of a proven causal therapy capable of reversing the calcification process [58]. This position is partially reflected in the KDIGO guidelines, which only weakly recommend VC testing even in CKD populations, despite their markedly elevated calcification risk.

The evidence reviewed in the present work challenges this view. First, although reversal is not yet possible, several interventions can slow calcification progression (as outlined in 1.3.1), and these are likely to be most effective when initiated early, making timely detection clinically valuable. Second, research into mVC detection itself can yield valuable insights into the underlying mechanisms and potential therapeutic targets, informing future treatment strategies [59]. Third, improved risk stratification has immediate clinical relevance, particularly for ESRD patients being evaluated for kidney transplantation, where vascular health can influence both perioperative safety and long-term outcomes.

For these reasons, advancing not only iVC but also mVC detection remains both a scientific challenge and a clinically meaningful goal. In Table 1.2, the major VC detection methods are briefly discussed with a particular focus on their utility for screening purposes. As shown there, no single, widely accessible diagnostic tool combines early-detection sensitivity with a favorable safety-cost profile. This motivates a pragmatic two-stage strategy in which an inexpensive, safe, and reproducible screening method is used to triage individuals to a reliable diagnostic test for confirmation.

My work addresses this gap by developing and evaluating screening approaches that are both practical for routine measurement and compatible with machine learning integration. Specifically, I conducted the first systematic economic evaluation of laboratory biomarkers for mVC, providing novel evidence on their cost-effectiveness as part of a screening pathway. Such evaluation is crucial before integrating a screening tool into clinical practice [57]. In parallel, I explored pressure pulse wave information beyond single summary indices (such as PWV or ankle-brachial index) by implementing a Pulse Wave - Frequency Domain Features (PW-FDFs) extraction pipeline that captures multiple frequency domain descriptors of the waveform that are sensitive to calcification-induced hemodynamic alterations.

Both the laboratory-based panels and the PW-FDFs approach are intentionally simple, reproducible, and potentially inexpensive. These characteristics make them suitable as pre-screening/screening tools in routine clinical settings. Crucially, these multivariate, multimodal data sources align naturally with machine learning (ML) methods that can combine weak but complementary signals into robust predictors; the next section outlines the ML concepts and rationale behind the frameworks used in this thesis.

Table 1.2: Summary of major VC detection methods: ability to distinguish intimal vs medial calcifications, pros and cons with respect to screening-fit.

Method	**Distinguishes iVC vs mVC?**	**Advantages**	**Disadvantages**
Histopathology (arterial biopsy)	Yes	Gold standard - definitive identification of layer and microstructure.	Highly invasive; unsuitable for routine diagnosis and screening.
IVUS / OCT / OFDI	Yes (in most cases)	Very high resolution; good concordance with histology; distinguishes iVC and mVC when no overlapping is present.	Invasive, resource-intensive, and costly; unsuitable for routine diagnosis and screening.
Non-contrast CT (Agatston)	No	Quantitative, non-invasive, reproducible; good for total coronary artery calcification assessment.	Ionizing radiation, limited availability; no layer discrimination; low microcalcification sensitivity; suitable for CAC screening when needed.
PET-CT (e.g. ^{18}F-NaF)	Partial	Detects early microcalcification activity; high-resolution enables capturing patterns of iVC and mVC; useful for research/targeted cases.	High cost; tracer and radiation; invasiveness; limited availability for routine screening.
Plain X-ray / Mammography	Partial	Cheap, widely available; mammography detects breast arterial calcification (BAC).	Low sensitivity for early disease; poor quantification and specificity; radiation; BAC limited only to women; not suitable for routine screening - can detect only advanced calcification.
Ultrasound	No	Radiation-free, portable; good for superficial or peripheral vessels.	Operator-dependent; limited penetration and standardization; modest sensitivity; not suitable for routine screening - can detect only advanced calcification.
Laboratory tests	No (potential for ML-based inference)	Minimally invasive, widely available, can be measured repeatedly for monitoring, may detect early biological changes preceding macroscopic calcification.	Investigational; most candidate biomarkers lack specificity and clinical validation for VC detection; no standardized biomarker panel yet; unknown cost-effectiveness; may be suitable for screening in the future after further investigation.
PW-based (e.g. PWV, PP, ABI)	No (potential for ML-based inference)	Non-invasive, inexpensive, reproducible; functional surrogate - reflects consequences of VC such as hemodynamic changes, most notably arterial stiffness.	Indirect measure; single markers have low specificity for calcification detection; thresholds vary by population; suitable for routine screening when inference is improved.

Abbreviations: VC, vascular calcification; iVC, intimal vascular calcification; mVC, medial vascular calcification; IVUS, intravascular ultrasound; OCT, optical coherence tomography; OFDI, optical frequency-domain imaging; CT, computed tomography; PET, positron emission tomography; CAC, coronary artery calcification; ML, machine learning; PW, pulse waves; PWV, pulse wave velocity; PP, pulse pressure; ABI, ankle-brachial index.

1.4 Data-driven machine learning models in clinical practice

Machine learning has attracted considerable interest because it can uncover complex, multivariable relationships that are not immediately apparent from conventional analyses. Although its main goal is to automate processes, its application is far from automatic and requires a deep understanding of this domain. A responsible use of ML methods requires much more than simply selecting an algorithm (conventionally referred to as a model) and providing it with data - every algorithm encodes particular mathematical assumptions (such as linearity, independence, smoothness, or stationarity) that must be met or at least considered [60]. Neglecting these principles or failing to address the issues of data quality and model validation risks in its misspecification, overfitting (i.e., the algorithm learns patterns specific to the training data and cannot generalize well), and misleading conclusions.

1.4.1 Principles of machine learning in classification tasks

Building a robust ML classification pipeline can be broadly divided into three stages: data preparation, model development (algorithm selection, training and evaluation), and model validation. Each of these stages presents unique challenges in medical applications, where datasets are often small, heterogeneous, and prone to bias [61, 62].

Data preparation

The foundation of any machine learning pipeline is careful data preparation. In clinical studies, acquiring the data itself can pose significant challenges, such as obtaining ethical approval and recruiting enough patients. Once acquired, the dataset must be examined for quality, consistency, and completeness [63]. A key early step is defining the target variable, which denotes what the model is expected to predict, along with a set of candidate predictors, i.e., features which may potentially influence the target's value.

Once the dataset is gathered, an initial exploratory analysis should be conducted, which can examine univariate associations between predictors and the target to gain initial insights and data understanding. Ultimately, predictive modeling requires handling noise, outliers, and missing values [64]. The latter poses a major challenge: depending on the extent and pattern of missingness, entries may be imputed using statistical or model-based methods, or observations may be excluded. This choice requires a balance between maximizing sample size and minimizing bias.

Clinical expertise can be incorporated at this stage through domain-informed feature engineering, such as transforming variables or explicitly modeling biologically plausible interactions. Variable selection is another critical task. It may be expert-driven, algorithmic (e.g., filter methods, wrapper methods), or embedded within the predictive model itself, as is the case with LASSO or decision trees [65]. The analyst must balance parsimony (simpler, interpretable models) with the possibility that complex, multivariate interactions carry predictive value that cannot be captured by intuition alone [64].

Algorithm selection and model training

The choice of an algorithm depends on several factors, including dataset size, predictor characteristics, class balance, interpretability, and computational feasibility [64]. The issue of an imbalanced target variable (when one of its values is significantly under-represented compared to the other), which is a frequent scenario in clinical data, must be addressed using re-sampling techniques, class-weight adjustments, or algorithmic modifications to prevent biased predictions [64].

Equally important is aligning the choice of algorithm with the study's goals. Broadly, algorithms can be employed for exploratory purposes (to uncover associations and interactions) or for predictive performance [66, 64]. In medical applications, these goals often coexist: clinicians not only want to know how well a model performs, but also why it produces a given result. Black-box predictions may face resistance if they cannot be explained to clinicians and patients.

A wide range of supervised learning classification methods (relying on the true labels while training) is available, each with advantages and limitations:

- Generalized linear models (e.g., logistic regression, LASSO) remain widely used for their transparency and ability to quantify the contribution of predictors [65].
- Tree-based methods (e.g., decision trees, random forests) can capture complex, non-linear interactions, though interpretation is less direct and often requires post-hoc tools [64].
- Kernel-based methods such as support vector machines (SVM), and other regularized linear schemes (e.g., relaxed linear separability, RLS [67]) offer strong predictive performance in certain settings, particularly with high-dimensional data [65].
- Neural networks, the most complex algorithms in the list, can model highly non-linear patterns and are particularly effective for rich data types (imaging, signals), but are typically considered "black-boxes" and require dedicated interpretability techniques [64].

The above methods represent only a small subset of available approaches; many other frameworks are in active use and development. Thus, algorithm selection should be guided by the tackled problem, data structure, study aims, and the balance between predictive performance and interpretability [65]. Deployment simplicity should also be considered.

While this thesis primarily utilizes supervised classification, unsupervised methods (ignoring labels while training), such as clustering or dimensionality reduction, can provide valuable insights by uncovering hidden structures, identifying patient subgroups, or generating new features to enrich supervised models [65]. They can also be used as a missing data imputation tool, which was applied in my first research [P1].

Performance evaluation

An integral component of any ML pipeline specification is the selection of a metric used to assess the quality of the results produced by the trained algorithm. This process is often referred to as a performance evaluation. The choice is not trivial,

as different metrics capture different aspects of model behavior, and they should be tailored both to the specific task and to the characteristics of the dataset used in the study. In most clinical classification tasks, including those presented in this thesis, true labels are known and can therefore serve as a reference for evaluating the model's predictions.

Simple scalar measures are often used to quantify specific aspects of a classifier's performance. Examples include the already discussed sensitivity and specificity, or accuracy, which reflects the overall proportion of correctly classified observations [65]. More informative composite measures are also common, such as the F-score, which integrates both sensitivity and specificity into a single value. Evaluation can also take a visual form, for instance, through inspection of predicted probability distributions or the receiver operating characteristic (ROC) curve, which illustrates the trade-off between sensitivity and specificity across different thresholds [64].

It needs to be highlighted that the chosen evaluation metric must adapt to the underlying data distribution. In highly imbalanced datasets, for example, accuracy may misleadingly suggest good performance even when all observations are assigned to the majority class. In such contexts, metrics that explicitly assess the discriminatory power of the model, such as sensitivity and specificity (or their derivatives) are more appropriate [64].

However, the quality of results is not always reducible to the ability to separate classes alone. Depending on the application, alternative metrics may be more appropriate. For example, in my first study [P1], I used the incremental cost-effectiveness ratio (ICER), which incorporates not only the predictive power of the classifier but also the cost of the predictors used to produce the results, thus aligning the statistical evaluation with the practical goal of cost assessment. It is a common situation to encounter multiple algorithms with comparable conventional performance metrics. In such cases, additional criteria, such as cost-effectiveness, ease of implementation, or clinical interpretability, become crucial for guiding the choice of which model should be prioritized for further development.

It is also important to note that metric selection plays a critical role not only in the evaluation phase but also in model development. Many algorithms, such as LASSO or random forests, require hyperparameter tuning [65]. The primary metric chosen to guide this process directly determines which parameter set is considered optimal, and thus shapes the final model [65]. Therefore, selecting the right evaluation criteria is a fundamental and scenario-specific decision, with implications throughout the entire modeling process.

Model validation

Validation is critical to determine whether a model generalizes beyond the data it was trained on. Validation can be *internal* (on data from the same source, but not seen by the model) or *external* (on independent data, ideally from a different cohort or institution) [62]. In clinical applications, external validation is the gold standard for demonstrating robustness, though proof-of-concept studies may initially rely on internal validation only. Conventional practice involves splitting data into training and testing sets [65]. On the training set, the model learns associations, and performance is then evaluated on the test set. If results are consistent across both, confidence increases that the model will perform similarly on new patients. However, a limited sample size often precludes this approach. In such cases, resampling strategies such

as k-fold cross-validation provide more efficient use of available data [65]. Here, the dataset is partitioned into k subsets, and the model is trained repeatedly, each time leaving one subset for testing. Performance is then averaged across folds. A special case is leave-one-out cross-validation (LOOCV), in which each observation is left out once, producing the most data-efficient but computationally intensive approach [65]. In this method, the model's performance is evaluated on a vector of the predictions made up from the left-out observations.

An important subtlety arises when feature selection or preprocessing is performed: to avoid data leakage, all such steps must occur within each fold using only training data. This means that across folds, different features may be selected and model coefficients may vary. In such cases, cross-validation evaluates the *framework* (i.e., the overall procedure of preprocessing, selection, and modeling) rather than a single fixed model. In practice, once a framework has demonstrated stable performance, a final model is retrained on the entire dataset for potential deployment. This is the standard approach implemented in widely used software frameworks (e.g. *glmnet*, *caret*) and the inferences about the selected features, their importance, and the model's parameters are made from the model retrained on the whole dataset [68, 69]. Consequently, the reported coefficients and selected variables represent this final, retrained model, which may differ slightly from the features selected in individual folds due to sampling variability. In my work, I have followed this approach as well. First, I evaluated the performance of the tested frameworks using LOOCV, and in the case of robust predictions, I employed the frameworks on the entire dataset to make inferences about the selected features, their importance, and fitted parameters.

In addition to discrimination, calibration is an important property of predictive classification models: a well-performing classifier should not only separate cases from controls but also assign probabilities that reflect true clinical risk [64]. This step, however, was not applied in the present work. With the limited dataset available, adding a separate calibration model could have introduced instability and overfitting, and my analyses focused on establishing the existence of a predictive signal. The successful demonstration of the model's discriminatory power achieves this primary goal. Calibration, alongside other engineering refinements required for a deployable clinical tool, remains an important avenue for future work.

Clinical translation

While the technical aspects of data preparation, algorithm choice, and validation are essential, the ultimate test of an ML framework in medicine is whether it integrates well into clinical decision-making. This requires not only accuracy and robustness, but also interpretability, cost-effectiveness, and reproducibility across populations. The methods explored in this thesis were therefore evaluated with these considerations in mind, aiming to identify approaches that balance predictive performance with practical feasibility for real-world vascular calcification screening.

1.4.2 Machine learning in vascular calcification detection

To date, several studies have explored the use of machine learning models for vascular calcification detection [59]. Most of these approaches have been image-based, relying on imaging techniques such as CT scans or X-rays, where ML was primarily employed to automate the interpretation of established diagnostic tests rather than

to enable novel screening strategies [70, 71]. CAC scoring remains the main focus, while investigations specifically addressing medial calcification are relatively scarce [72, 73]. Beyond imaging, ML has been applied to conventional cardiovascular risk factors to improve the prediction of elevated CAC levels [74], creating nomograms for total VC prediction [75], and more recently to the discovery of candidate calcification biomarkers using genetic data [76]. Collectively, these efforts underscore both the promise of ML in vascular research and its present limitations, with most applications still centered on image interpretation rather than on developing simple, scalable, and cost-effective screening tools. To the best of current knowledge, no prior study has examined pressure pulse wave signal properties as direct input for ML models for VC detection, apart from the occasional use of PWV in addition to other risk factors in CAC prediction frameworks [77]. This gap highlights the originality of approaches that leverage detailed pressure pulse wave features for ML-based detection of VC.

2

RESEARCH AIMS AND HYPOTHESES

The aim of my work was to address the need for clinically feasible and cost-effective methods for medial and intimal vascular calcification screening by proposing novel, data-driven frameworks tailored for individuals with chronic kidney disease. The thesis evaluates the potential of biomarker- and pressure pulse wave signal-based models for early detection of vascular calcification in CKD patients, thereby providing a basis for the future development of scalable, broadly accessible tools for cardiovascular disease risk stratification.

I have formulated three research hypotheses to accomplish the research objective:

(H1) Integrating cost-effectiveness assessment into the selection of machine learning models trained for medial vascular calcification detection in patients with advanced chronic kidney disease facilitates the identification of the most clinically relevant approaches.

(H2) A data-driven framework that integrates conventional vascular calcification risk factors with pressure pulse wave frequency-domain features (PW-FDFs) derived from non-invasive peripheral pulse wave measurements can be used to detect medial vascular calcification.

(H3) Statistical models based on pressure pulse wave frequency-domain features (PW-FDFs) can effectively identify end-stage renal disease patients with elevated coronary artery calcification scores.

In addition, I have established a set of detailed research questions corresponding to each of the hypotheses. Addressing these questions provides a structured approach to testing the hypotheses and strengthens the evidence supporting them.

(H1Q1) Do different machine learning methods applied to the same dataset yield substantially different sets of selected features while achieving comparable predictive accuracy?

(H1Q2) Can cost-effectiveness metrics help to discriminate between models with comparable predictive performance?

(H1Q3) How does the incremental cost-effectiveness ratio vary depending on the assumptions made?

(H1Q4) Is there a subset of features consistently selected across models, highlighting which predictors are most promising for future studies?

(H2Q1) How can the information from pressure pulse wave signal be incorporated as input to machine learning models?

(H2Q2) Can predictions from a model working with pulse wave - frequency domain features (PW-FDFs) yield clinically relevant accuracy?

(H2Q3) Does the model incorporating both PW-FDFs and traditional mVC risk factors achieve superior performance in medial vascular calcification detection among patients with end-stage renal disease, compared to model using conventional risk factors alone?

(H3Q1) Can pressure pulse wave measurements obtained at different arterial sites, once transformed to the central waveform, be used to extract PW-FDFs that reliably predict elevated CAC scores?

(H3Q2) To what extent do time-domain features of the central pressure pulse wave contribute to the prediction of elevated CAC scores?

(H3Q3) Does the model trained with PW-FDFs achieve superior performance compared to conventional vascular calcification risk factor–based approaches in specific age groups?

(H3Q4) Does the model trained with PW-FDFs have the potential to differentiate between the patients with various extents of CAC?

Verification of the formulated research hypotheses has resulted in the publication of three journal articles, which together form the foundation of my thesis [P1, P2, P3]. Each article corresponds to one of the research hypotheses. Accordingly, the following three chapters are structured around these publications: each chapter provides a detailed introduction to the scientific background of the study, explains how my work aligns with the research aims, and discusses how the obtained results support the corresponding research hypothesis.

3

COST-EFFECTIVENESS OF BIOMARKER PANELS IN MEDIAL VASCULAR CALCIFICATION SCREENING

3.1 Medial vascular calcification

3.1.1 Clinical implications

Medial vascular calcification, also known as Monckeberg's arteriosclerosis, is primarily associated with aging and diabetes, and is particularly common in ESRD due to the altered mineral metabolism in this group of patients [30, 78]. In CKD it is also positively associated with the duration of hemodialysis [30] and the severity of kidney function's loss [79].

mVC is most frequently detected in the peripheral arteries of the lower extremities [80] but can be present in nearly all arterial territories, including upper limb [81], aorta [82], mammary [83], temporal [84], and, in rare cases, coronary arteries [85]. Moreover, it can develop simultaneously in several vascular regions [86, 87]. The assessment is usually performed in a selected arterial site, and the extent of mVC can be classified into stages depending on its severity. The categories are typically marked from 0, denoting being free from calcification, up to 4, denoting massive calcification [88, 89].

mVC affects the middle layer of the arterial wall and does not block the arterial lumen; therefore, at first, it was not considered to be clinically significant [35, 39]. This view started to change when arterial medial calcification presence was proved to be a strong marker of future cardiovascular risk in diabetic patients [90]. Since then, multiple studies have shown that mVC is a strong independent predictor of all-cause and cardiovascular mortality, especially in the CKD population [30, 88]. This association is attributed to mVC-induced arterial stiffening, which reduces arterial compliance [80]. The severity of stiffening closely correlates with the extent of medial calcification, and higher degrees of calcification have been linked to an increased risk of all-cause mortality [30, 91, 92, 55, 88, 93].

Multiple clinical studies have found that patients with higher medial calcification scores in the lower extremities are at significantly increased risk of chronic limb-threatening ischemia (CLTI) and major limb amputation [94, 95]. For example, a recent multi-center study showed that higher mVC scores assessed in feet using X-rays were associated with higher rates of major limb amputation within six months among patients with CLTI [96].

Another condition affecting the limbs is peripheral artery disease (PAD), which involves occlusion or narrowing of the upper and lower extremity arteries, causing insufficient blood flow. As a consequence, patients suffering from PAD are highly predisposed to cardiovascular morbidity and mortality [97]. Although mVC is not necessarily indicative of PAD, the co-incidence is common [85, 98]. The exact prevalence of mVC in PAD is imprecisely reported because of the methods by which diagnosis is reached, as well as asymptomatic cases that are often unreported [99, 97]. However, it is worth noting that in the data from the CKD Prognosis Consortium, out of all studied adverse cardiovascular outcomes of CKD, PAD is associated with the highest relative risk in ESRD in comparison to patients with a proper renal function [25]. It cannot be ruled out that it is because of the prevalent co-occurrence of mVC in PAD.

3.1.2 Detection

While it has been shown that mVC incidence increases with CKD stage [79], the true prevalence of mVC in the CKD population remains unknown, as it varies across studies and arterial sites [100]. This uncertainty is mainly associated with the lack of accessible and reliable diagnostic tools. As a result, mVC is often detected incidentally or misdiagnosed as atherosclerosis, due to the difficulty in distinguishing between medial and intimal calcification. Consequently, many studies report the total burden of vascular calcification without differentiating between these two forms, despite their distinct pathophysiological and clinical implications.

Below, the most popular techniques for mVC detection are described. Other, less frequently used tools, are discussed in detail in [58].

Invasive techniques

The most reliable method for mVC assessment is histopathological examination of arterial biopsies performed by pathologists. However, this approach is highly invasive and therefore impractical for clinical use or utilization in large-scale research. For this reason, histological assessments are typically limited to studies involving patients undergoing other surgical procedures, such as kidney transplantation, or to post-mortem analyses [88, 101].

Other invasive techniques with high sensitivity include intravascular ultrasound (IVUS) or optical frequency domain imaging (OFDI), which utilize a catheter with a tiny ultrasound transducer inserted into an artery, and optical coherence tomography (OCT), requiring intracoronary injection of contrast media [102]. These methods provide high-resolution images of the arterial wall, allowing for assessment of calcification based on depth and arterial layer. Their diagnostic accuracy is highest when medial and intimal calcifications do not overlap - under such conditions, their sensitivity can exceed 80% [102]. Nevertheless, the invasiveness significantly limits their use in both clinical practice and research.

Minimally invasive imaging techniques

Due to the limitations of highly accurate but impractical, invasive procedures, non-invasive imaging techniques have been widely adopted in mVC research. Computed tomography (CT), although commonly used, is generally considered unreliable in differentiating between medial and intimal calcification [39]. However, several scoring

systems have been recently developed based on characteristic calcification patterns in specific vascular beds, such as the carotid artery [103] and lower limb arteries [104]. Typically, iVC appears as patchy, thick, irregular, and dot-like, whereas mVC tends to be more continuous, regular, thin, and tube-like. While the CT-based detection offers some utility, it demonstrates moderate accuracy when compared with histological findings. A related approach involved the use of full-body PET-CT imaging to identify the morphological patterns across multiple vascular territories simultaneously [105], which is a distinct advantage in terms of systemic assessment.

Conventional radiography is frequently used as a proxy for advanced mVC detection. Circumferential or "pipe-stem" calcification patterns indicate mVC, in contrast to the more irregular and patchy appearance of iVC [30]. While limited by sensitivity, particularly in earlier pathology stages, this approach is simple and widely accessible, typically used for assessing calcification in lower limbs [30]. A more specific radiographic technique, mammography, can detect breast arterial calcification in female patients and is considered a potential indicator of mVC, given that mammary arteries are usually free of atherosclerotic lesions [83, 106].

Among other imaging techniques, ultrasound should be noted. It showed greater effectiveness in mVC detection in comparison to radiography, especially in mild calcification stages [107]. Nevertheless, its sensitivity is still rather poor, making it rarely used in clinical research.

Functional and hemodynamic surrogates

Given the mVC's contribution to arterial stiffening, hemodynamic measurements have been widely explored as potential screening tools. Among them, the ankle-brachial index (ABI), defined as the ratio of the highest systolic blood pressure at the ankle to that at the brachial artery, has been frequently utilized as a surrogate marker for mVC detection. An ABI > 1.4 was interpreted as indicative of medial calcification. However, subsequent studies have demonstrated that elevated ABI alone is insufficient as a diagnostic marker, and conclusions about mVC based solely on ABI may significantly underestimate the true associations between mVC and cardiovascular outcomes [108]. However, it is important to acknowledge that in the cited research, mVC was assessed using CT-based scoring methods [103], which themselves are not definitive; therefore, the results should be interpreted with caution.

Pulse wave velocity offers another indirect measure reflecting arterial stiffness. Since stiffness increases with the extent of medial calcification, PWV can serve as a surrogate for mVC burden. Carotid-femoral PWV is considered the gold standard for central arterial stiffness assessment, with a threshold of 10 m/s commonly used to indicate significantly stiffened arteries. Nevertheless, it has been emphasized that a single threshold may not be appropriate for all subpopulations, particularly those differing in age or underlying pathology [109].

Laboratory biomarkers

Finally, laboratory biomarkers have been investigated as potential tools for identifying patients at risk for mVC [110]. The multifactorial nature of mVC pathogenesis suggests a broad range of potential biological indicators. Multiple single biomarkers have been tested [111], including fetuin A, pyrophosphate, fibroblast growth factor 23, osteopontin, osteoprotegerin, and matrix Gla protein, but only a few studies have

attempted to evaluate combinations of markers comprehensively [73]. Moreover, various biomarkers generate different costs of testing, and their cost-effectiveness remains to be evaluated. The development of a reliable biomarker set remains a major research priority, as early identification of at-risk individuals could open a window for preventive intervention [112]. Furthermore, laboratory testing yields structured, quantitative data that are well-suited for machine learning frameworks. Building on previous studies that evaluated a limited number of biomarker panels using only a few modeling approaches, in the first part of my research, I expanded this line of investigation by exploring a broader range of ML frameworks for mVC detection and assessing the cost-effectiveness of multiple biomarker combinations.

3.2 My work

3.2.1 Laboratory biomarkers as input to machine learning frameworks

Several studies have investigated the relationship between serum biomarkers and medial vascular calcification [110]. Individual markers such as osteoprotegerin, matrix Gla protein, copeptin, and sclerostin [110, 113, 114] have each been independently associated with mVC. While identifying such associations is an important first step, the next challenge lies in understanding how biomarkers interact with one another. This is relevant not only from a diagnostic perspective, where combining multiple biomarkers may improve pathology detection, but also from an economic standpoint. If two biomarkers convey overlapping information, as reflected by strong correlations or predictable physiological relationships, measuring both may be inefficient, especially if one is considerably more costly. In real-world data, however, these relationships are often complex: a relatively expensive biomarker may potentially be approximated by a combination of several cheaper ones, which could substantially improve cost-effectiveness. Identifying such patterns usually exceeds the capabilities of conventional statistical analyses, but can be addressed more effectively with advanced machine learning techniques.

From a health-economic perspective, the most useful screening tool is not necessarily the one with the highest predictive accuracy, particularly when performance differences between the competing models are small. In such cases, cost considerations may play an equally important, if not decisive, role. Different machine learning frameworks frequently select distinct subsets of features, as demonstrated in [73], where two algorithms produced markedly different sets in both composition and size. Yet, despite this variability, model evaluation in clinical studies has traditionally focused almost exclusively on predictive performance, with little attention given to the trade-off between accuracy and utilization cost.

These observations motivated me to evaluate machine learning models from a dual perspective: not only in terms of predictive performance, which is critical in clinical applications, but also in terms of cost-effectiveness of the produced predictions, which is equally important for assessing the feasibility of clinical implementation. To achieve this, I employed the incremental cost-effectiveness ratio (ICER) as a comparative metric to integrate predictive performance with economic considerations and to guide model selection.

3.2.2 ICER: incremental cost-effectiveness ratio

Evaluating the trade-off between accuracy and utilization cost of competing machine learning models belongs to the broader field of health economics, which addresses the efficiency, effectiveness, and cost of healthcare interventions [115]. The primary goal of health economics is to optimize the allocation of limited resources in order to maximize health gains for the population [116].

One of the main types of health economic evaluation is cost-effectiveness analysis [117]. It compares two or more healthcare strategies in terms of their relative costs and outcomes, with the latter typically measured in natural units such as life-years gained. In my research, I employed a particular cost-effectiveness metric, the incremental cost-effectiveness ratio [118]. In its standard definition, it is given by:

$$\text{ICER} = \frac{C_1 - C_0}{E_1 - E_0} \tag{3.1}$$

where C_1, C_0 are the costs and E_1, E_0 are the effects of the new intervention and comparator, respectively. Therefore, the numerator represents the incremental cost, while the denominator reflects the incremental effect. This formulation is most commonly used to compare two alternative medical strategies.

However, in the context of mVC detection, no routine screening method currently exists. It is therefore appropriate to adopt a "do-nothing" comparator [115], where both C_0 and E_0 equal 0. Under this assumption, ICER simplifies to:

$$ICER = \frac{C_1}{E_1} \tag{3.2}$$

where C_1 is the cost of performing the screening procedure and E_1 represents the expected health benefit. This adjustment is further justified by the fact that my primary goal was to compare the cost of inputs to multiple machine learning frameworks; subtracting a constant baseline cost or effect would not have altered their relative ranking.

I additionally adapted the ICER formulation to reflect its specific role within the evaluation pipeline. In particular, I assumed that any positive case identified by the method based on a machine learning framework would require confirmatory imaging, incurring additional costs. However, I did not include the cost of subsequent medical intervention after diagnosis, as this would be identical regardless of the screening approach and therefore would not influence the comparative evaluation of the frameworks. Consequently, the ICER used in my work quantifies the cost of screening relative to the quality-adjusted life years gained and was calculated as follows:

$$ICER = \frac{\text{measure\_cost} + [\text{prevalence} \cdot TPR + (1 - \text{prevalence}) \cdot FPR] \cdot \text{ct\_price}}{\text{prevalence} \cdot TPR \cdot \text{years\_gained}} \tag{3.3}$$

where:

- measure_cost - total cost of biomarker evaluation per patient,
- prevalence - true prevalence of mVC in the advanced CKD population,

- TPR - true positive rate of the screening model,
- FPR - false positive rate of the screening model,
- ct_price - cost of confirmatory PET-CT scan for mVC,
- years_gained - expected number of QALYs gained through earlier detection. The QALY is a summary measure that incorporates both improvements in life expectancy and quality of life, and is a standard metric for evaluating the benefits of healthcare interventions [115].

Several of these parameters, i.e., prevalence, years_gained, and cost estimates, are uncertain. For this reason, I calculated and reported ICER results across a range of assumed parameter values to explore different clinical scenarios. In addition, sensitivity analyses were performed to examine the influence of varying biomarker costs on the resulting ICER values.

3.2.3 Research overview

Introduction

The assessment of circulating biomarkers is a well-established approach in health evaluation, and many screening strategies across different diseases are based on their measurement [119]. For this reason, I initially considered this method for the screening of medial vascular calcification.

Given the complex physiological mechanisms underlying vascular calcification, it is highly unlikely that a single biomarker could serve as a reliable indicator of its presence. Therefore, studies investigating panels of phenotypic biomarkers as potential indicators of mVC are of particular importance [73]. However, when coupled with machine learning techniques, the choice of the algorithm strongly influences the results of such analyses, not only in terms of predictive accuracy but also in the subset of features selected. This raises the question, how to select a classifier detecting mVC that is not only accurate but also clinically feasible.

To address this issue, I concluded that the cost of biomarker acquisition should be explicitly incorporated into model evaluation, which is an aspect that, to my knowledge, had not previously been considered in this context. I proposed the use of the incremental cost-effectiveness ratio as an additional criterion for model assessment. Specifically, I developed a formula tailored for classifiers trained to detect mVC, as described in 3.2.2, which integrates the statistical performance of a classifier with the cost of the biomarkers it relies upon.

In the following publication, I present the results of a comprehensive analysis I performed in which several machine learning algorithms were trained for mVC detection and evaluated not only by conventional metrics but also through the proposed ICER-based framework.

Relation of the publication to the research aims of the thesis

A panel of phenotypic biomarkers, measured non-invasively or minimally invasively and used as input for machine learning models, has the potential to serve as a practical screening tool. This approach is clinically appealing, as many established

screening tests already rely on blood-based or similarly simple measurements, making such a concept readily translatable into clinical practice. Detecting medial vascular calcification in particular is clinically valuable, as it provides refined stratification of patients at risk of adverse cardiovascular outcomes. In my first publication, I addressed two key aspects of a screening tool development: its cost-effectiveness and clinical feasibility. I demonstrated that different machine learning frameworks for mVC detection, when applied to the same dataset, selected markedly different sets of predictive features. The largest feature set contained more than four times as many predictors as the smallest, yet predictive performance across models was broadly comparable, with no single approach consistently outperforming the others across all evaluation metrics (H1Q1). This finding underscored the challenge of feature selection and the need for additional criteria to guide model choice.

To address the limitations of purely statistical evaluation, I introduced the incremental cost-effectiveness ratio as an additional criterion for model assessment, adapting its formula to the context of mVC screening. This addition provided a more decisive basis for model selection (H1Q2). Specifically, it revealed that logistic regression, despite its simplicity and use of the smallest feature set, achieved the most favorable balance of predictive performance and cost-efficiency quantified through ICER. Sensitivity analyses further confirmed the robustness of this finding, showing that the conclusions remained valid despite changes in cost assumptions (H1Q3). Apart from the assessment of cost and availability of the analysed circulating biomarkers, I also provided a detailed example of how cost-effectiveness may change depending on the threshold used for testing purposes on the example of results obtained using the logistic regression model (H1Q3).

Finally, I also examined the clinical interpretability of the models by analyzing patterns of feature selection. While each framework selected different subsets of predictors, certain biomarkers were consistently chosen across multiple models, suggesting a core set of promising candidates for future research (H1Q4). These findings not only highlight that the choice of modeling framework can substantially influence which predictors are selected but may also provide a foundation for prioritizing features with the greatest clinical relevance.

Conclusions

Taken together, this publication supports my research aims by analysing the cost-effectiveness of a phenotypic feature-driven approach to the screening of medial vascular calcification. Specifically, this research supports my first hypothesis (H1). It demonstrates that, through ICER calculation, cost-effectiveness assessment can be successfully integrated into the selection of machine learning models trained for mVC detection in patients with advanced CKD, and this approach facilitates the identification of the most clinically relevant frameworks. My work addresses a gap in the literature regarding the economic evaluation of ML models for mVC detection, a perspective that has been largely absent not only in studies applying ML to phenotypic biomarker-based mVC detection but also in many other clinical investigations. Consequently, I believe that the exploration of this aspect will not only strengthen the feasibility of data-driven solutions in mVC identification but also promote the broader adoption of cost-effectiveness evaluation of ML models aimed to be used in clinical practice.

3.3 The publication (P1)

4

POTENTIAL OF PULSE WAVE SIGNAL FREQUENCY-DOMAIN ANALYSIS FOR MEDIAL VASCULAR CALCIFICATION SCREENING

4.1 Pressure pulse waves

As noted by van de Vosse and Stergiopulos, specialists in the cardiovascular system, "waves carry information about the matter in which they propagate" [120]. This concept encourages the study of arterial pressure waves, whose morphology is shaped by their propagation through the vascular system, and therefore may provide diagnostic insights into cardiovascular disorders [120]. Building on this idea, I investigated the potential of the pressure pulse wave signal (hereafter referred to simply as the pulse wave signal) as an input to machine learning models, evaluating it as a surrogate marker for the presence of vascular calcification. In the following sections, I will present the rationale for this approach and outline the methods of pulse wave feature extraction applied in my research.

4.1.1 Pulse wave propagation

The cardiac cycle begins with ventricular contraction (systolic phase), when the left ventricle pumps blood into the arterial system, and ends with ventricular relaxation (diastolic phase), when the heart is refilled. The rapid ejection of blood during systole generates a pressure disturbance, known as the pulse wave [121]. Although it is the heart that initiates the wave, its shape, propagation, and characteristics are highly influenced by two factors: the arterial wall properties and the interaction with the reflected waves [122].

The aorta and large arteries serve not only as conduits transporting oxygenated blood to peripheral tissues, but also as buffers which amortize stroke volume - the volume of blood ejected with each contraction [123]. In healthy vessels, the elastic arterial walls expand under pressure and accommodate part of the stroke volume. It is then released during diastole, maintaining arterial pressure and ensuring continuous blood flow. This buffering property is known as the Windkessel effect [124]. The expansion and recoil of successive arterial segments transmit the pulse wave throughout the vascular tree - a process termed pulse wave propagation [121].

The mechanical properties of the aorta and its branches depend largely on the viscoelastic components of the arterial wall - primarily elastin, collagen, and, most importantly in the context of my work, vascular smooth muscle cells [125]. As discussed in the

section 1.2.2, in vascular calcification, VSMCs undergo phenotypic changes from contractile to osteogenic, contributing to the stiffening of arterial walls. With the addition of calcium deposits accumulated in the medial or intimal layer, this results in the loss of elasticity, which impairs the Windkessel effect: less blood is buffered in the aorta during systole, and more is transmitted directly into the periphery. Consequently, the pulse wave is propagated at a higher velocity, which further alters its morphology [123].

Importantly, forward wave propagation is not the only determinant of the observed pressure wave signal. As the forward wave encounters sites of impedance mismatch, it generates reflected waves of substantial magnitude [123]. Major physiological reflection sites include arterial bifurcations and the peripheral resistance vessels [123]. Pathological obstacles such as atherosclerotic plaques further increase the frequency of wave reflection generation [126]. It needs to be noted that because the circulatory system is a relatively small, closed circuit where the pulse waves travel at a high speed, the reflected waves do not interfere with subsequent cardiac cycles but instead superimpose on the original forward wave [123]. The observed pulse wave at any location is therefore a composite signal: the sum of the forward wave and multiple reflected components. In stiffened arteries, both the forward and reflected waves travel faster, leading to their earlier superposition during systole and amplifying central systolic pressure while reducing diastolic pressure [123]. This alteration of wave shape is a direct consequence of arterial stiffness influenced by vascular calcification and atherosclerosis.

4.1.2 Central vs peripheral pulse wave signal

Pulse wave recordings differ substantially depending on whether they are obtained centrally (e.g., in the ascending aorta) or peripherally (e.g., brachial or radial arteries). Peripheral arteries are major sites of wave reflection, so the superposition of forward and backward waves occurs early in systole, making the peripheral systolic pressure peak strongly influenced by reflections [123]. In contrast, in healthy and compliant central arterial sites, mainly in the aorta, the forward and reflected waves meet at the end of systole. Their superposition extends through diastole, giving the central waveform a rounded diastolic contour, while leaving the systolic peak largely determined by ventricular ejection and aortic compliance [121]. This difference between central and peripheral systolic pressure is known as pulse pressure amplification [127] and is schematically shown in figure 4.1. However, when arterial stiffness develops, this pattern changes. The increased pulse wave velocity causes the reflected waves to return earlier, merging with the forward wave during systole, even at the central arterial sites. This elevates central systolic pressure and widens pulse pressure by raising systolic and lowering diastolic values [128]. In the periphery, these alterations are even more pronounced due to the stronger influence of early reflected waves [128].

4.1.3 Pulse wave velocity

An important quantity in studying pulse wave propagation, which partially reflects arterial properties, is pulse wave velocity (PWV). Its increased value is a well-established marker of vascular stiffness and therefore is associated with higher systolic and pulse pressures, increased cardiac workload, and the development of complications such as left ventricular hypertrophy, diastolic dysfunction, and congestive heart failure [129,

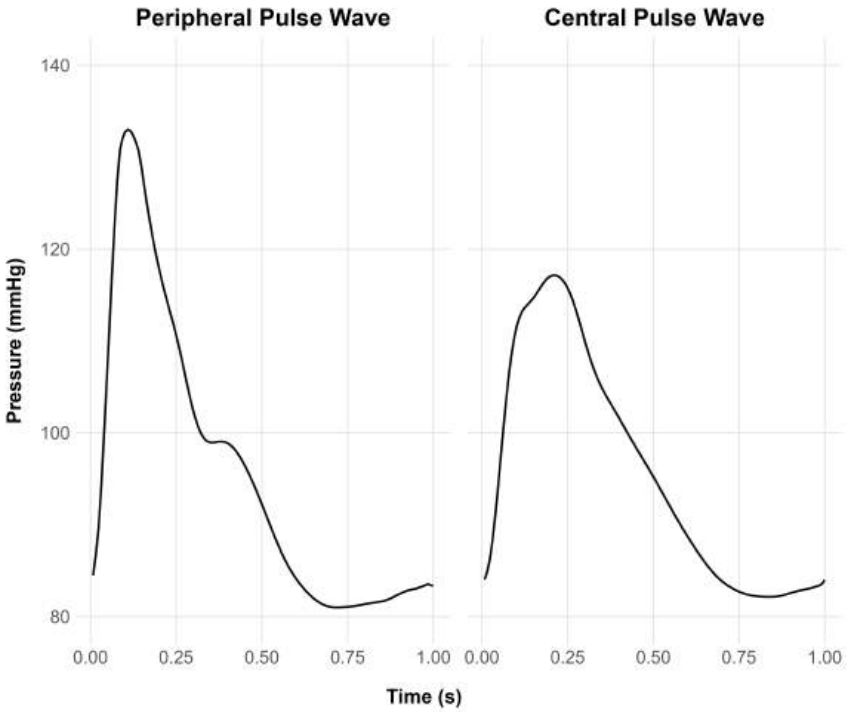

FIGURE 4.1: Peripheral (left panel) and central (right panel) arterial pressure waveforms from a single cardiac cycle recorded at the brachial artery and transformed to a central signal using SphygmoCor System.

130]. PWV can be measured at various arterial segments, providing insights into both central and peripheral arterial stiffness. The gold standard for assessing central stiffness (particularly that of the elastic aorta and thoracic arteries) is carotid-femoral PWV (cfPWV). Carotid-radial PWV (crPWV) reflects stiffness in muscular peripheral arteries, such as the brachial artery, while brachial-ankle PWV (baPWV) captures a mixed profile of both central and peripheral segments [123]. Regardless of the arterial sites chosen, the principle of measurement is the same: pulse waveforms are recorded at two distinct sites, the transit time of the wave between them is determined, and the path length is estimated. PWV is then calculated as the distance between two arterial measurement sites divided by the pulse transit time between them.

Although the PWV measurement is conceptually simple, both components required for its calculation, i.e., distance and transit time, present some methodological challenges. The most significant limitation is the estimation of arterial path length, which remains the main source of inaccuracies in PWV measurement [123, 131]. Since the arterial course cannot be measured directly, surface distances are used as surrogates. However, different studies apply different measurement techniques or correction formulas, leading to variability and complicating both clinical application and cross-study comparisons [131]. Although reference values for PWV are available, their validity relies on a clear specification of the distance estimation method, a detail that is not consistently reported [123].

The second component of the PWV formula, transit time, can be determined using two approaches [123]. The first involves simultaneous pulse wave signal acquisition with two sensors: one positioned to record it at the proximal site and the other at the distal site. The second method employs a single sensor sequentially, often synchronized with an electrocardiographic tracing. While, when properly performed,

simultaneous and sequential measurements provide comparable results [123], the accuracy of the latter is highly sensitive to beat-to-beat variability, which can compromise assessment reproducibility [131]. Furthermore, the position of the subject is an important factor, as transit times are strongly influenced by the vertical placement of sensors due to gravitation [132]. Taken together, these methodological considerations introduce significant variability in PWV determination, limiting the reproducibility and interpretation of the results.

Nevertheless, PWV research provided several interesting insights into arterial stiffness. Some studies suggest a compensatory interaction between central and peripheral arterial stiffness - a decrease in brachial stiffness has been observed as a response to increased central aortic stiffness [133]. While cross-sectional data show that brachial PWV increases with age, the rate of increase is significantly lower than that of aortic PWV [134]. Moreover, longitudinal observations report a decline in crPWV (a surrogate marker of brachial artery stiffness) over time, supporting the hypothesis that reduced brachial stiffness may serve as an adaptive mechanism to counterbalance the progressive stiffening of central elastic arteries [133].

4.1.4 Measurement techniques

A variety of techniques are available for acquiring pulse wave signals at different arterial sites, ranging from invasive gold-standard methods to non-invasive approaches employing pressure, optical, or acoustic sensors [135]. Among the most widely used non-invasive methods are applanation tonometry and volume-clamp techniques [136]. These approaches differ in their complexity of use, accuracy, and suitability for specific arterial sites. Comprehensive reviews of their methodology, advantages, and limitations can be found in [135, 137].

In the present work, I focus specifically on the data collection methods employed in my studies [P2, P3]: applanation tonometry of the radial artery and a cuff-based volumetric displacement technique at the brachial artery. Both methods are implemented within the SphygmoCor System (AtCor Medical, Sydney, Australia) [138]. The following section introduces the principles of these measurement techniques and describes how peripheral signals are mathematically transformed into central pressure waveforms.

Arterial applanation tonometry can be used to record pulse waves in several arterial sites, including the radial artery [139]. It is a non-invasive technique that employs a pen-like pressure sensor to slightly flatten the artery at the wrist against the underlying bone. This method directly captures the arterial pressure waveform by sensing the artery's mechanical pulsations with high temporal resolution. Because it requires accurate and stable sensor positioning, the radial artery's superficial and easily accessible location makes it particularly suitable for this technique [140]. Several studies have confirmed that blood pressure values and arterial pressure waves recorded non-invasively by tonometry are equivalent to invasive intra-arterial catheter recordings [141, 142].

The brachial artery pulse wave can be obtained using a cuff-based volumetric displacement technique. In this approach, after the initial measurement of systolic and diastolic brachial pressure, a standard blood pressure cuff is inflated to a sub-diastolic pressure level on the upper arm, allowing the device to register volumetric changes associated with the pulse in the underlying brachial artery [139]. These pulsations are then used to reconstruct the arterial waveform. In contrast to applanation tonometry,

the cuff-based technique does not require highly precise placement over the artery and is therefore easier to apply in routine clinical settings [139].

Central aortic waveforms can be estimated from the peripheral pulse wave signal [123]; both radial and brachial waveforms can be mathematically transformed into a central aortic waveform [143, 144]. The principle underlying this transformation is that arterial waveforms at different sites are mathematically related, even though they differ morphologically due to wave reflections, variations in arterial compliance, and vascular geometry. This transformation is performed by analyzing the waveform and then applying a validated generalized transfer function (GTF) [145, 144]. While there exist several formulas for GTF, it often employs Fourier analysis to reconstruct the central aortic pressure signal [145]. The algorithm corrects for pressure amplification and waveform alterations that occur when the pulse wave propagates from the aorta to peripheral sites. To improve accuracy, the results are typically calibrated with brachial systolic and diastolic blood pressure values. The GTF implemented in devices such as the SphygmoCor System has been validated against invasive intra-aortic measurements, demonstrating good agreement and reliability for non-invasive estimation of central pressures [141, 144].

4.2 My work

4.2.1 PW-FDFs: pulse wave - frequency domain features

Pulse waves in the frequency domain

Pulse waves are most often represented in the time domain, where their characteristic waveform depicts changes in arterial pressure over time. An alternative approach is to analyze the signal in the frequency domain. The idea builds on a mathematical concept introduced by Fourier that any complex, repeating signal, such as the arterial pulse wave, can be represented as a sum of simple sine waves. While these principles apply to all periodic signals, I will formulate them specifically in terms of the arterial pulse wave for clarity.

The pulse wave, as a periodic signal, can be described as a combination of sine waves at specific frequencies (i.e., how many times per second a wave oscillates, measured in hertz (Hz)):

- **Fundamental frequency** (f_0): the base frequency, which corresponds directly to the heart rate. For example, if the heart rate is 60 beats per minute (1 beat per second), then $f_0 = 1$ Hz.
- **Harmonics**: sine waves with frequencies that are integer multiples of the fundamental ($2f_0, 3f_0, 4f_0, \ldots$). The first few harmonics determine the broad shape of the wave, whereas higher harmonics allow for reconstructing sharper details.

The overall pulse wave is reconstructed by summing these harmonics, each defined by two parameters:

- **Modulus (Amplitude, $|H_n|$)**: represents the contribution of the n-th harmonic to the signal. A larger modulus indicates a stronger influence of that harmonic on the pulse waveform. By definition, the modulus is always non-negative.

- **Argument (Phase Angle, φ_n)**: represents when the harmonic occurs relative to the start of the cardiac cycle and is essential for reproducing the correct waveform shape. Angle is typically expressed in radians.

Importantly, the 0th harmonic (H_0) represents the constant component of the signal. Since it has a frequency of 0 Hz, it has no associated phase. Physiologically, H_0 corresponds to the mean value of the pressure signal over one cardiac cycle, i.e., the mean arterial pressure (MAP).

The original pulse wave signal $P(t)$ can thus be reconstructed using the harmonic form of the Fourier series [146]:

$$P(t) = H_0 + \sum_{n=1}^{N} |H_n| \cos\left(2\pi n f_0 t + \varphi_n\right)$$

where:

- $P(t)$ is the arterial pressure at time t,
- H_0 is the 0th harmonic modulus (mean arterial pressure),
- $|H_n|$ is the modulus of the n-th harmonic,
- nf_0 is the frequency of the n-th harmonic,
- φ_n is the phase of the n-th harmonic,
- N is the number of harmonics considered (even first six harmonics accurately define the pressure waveform [123]; typically, up to 20 harmonics are used for pulse wave reconstruction [147]).

The Fourier coefficients $|H_n|$ and φ_n may be obtained using the Fast Fourier Transform (FFT) algorithm [146], which decomposes the signal from the time domain into the frequency domain. The number of harmonics included in the analysis can be adjusted depending on the desired precision. Figure 4.2 illustrates the schematic reconstruction of a peripheral pulse wave using different numbers of constituent harmonics.

One of the properties of the arterial pulse waves is that their energy is concentrated in the lower frequencies: f_0 and the first few harmonics contain the majority of the signal's energy, reflecting the pumping action of the heart. Higher-frequency harmonics introduce minor wave fluctuations as depicted in Figure 4.2. Physiologically, this can be explained by the behavior of the arterial system, which acts as a low-pass filter where low-frequency components propagate efficiently, while higher harmonics are quickly dampened due to the viscoelastic properties of arterial walls.

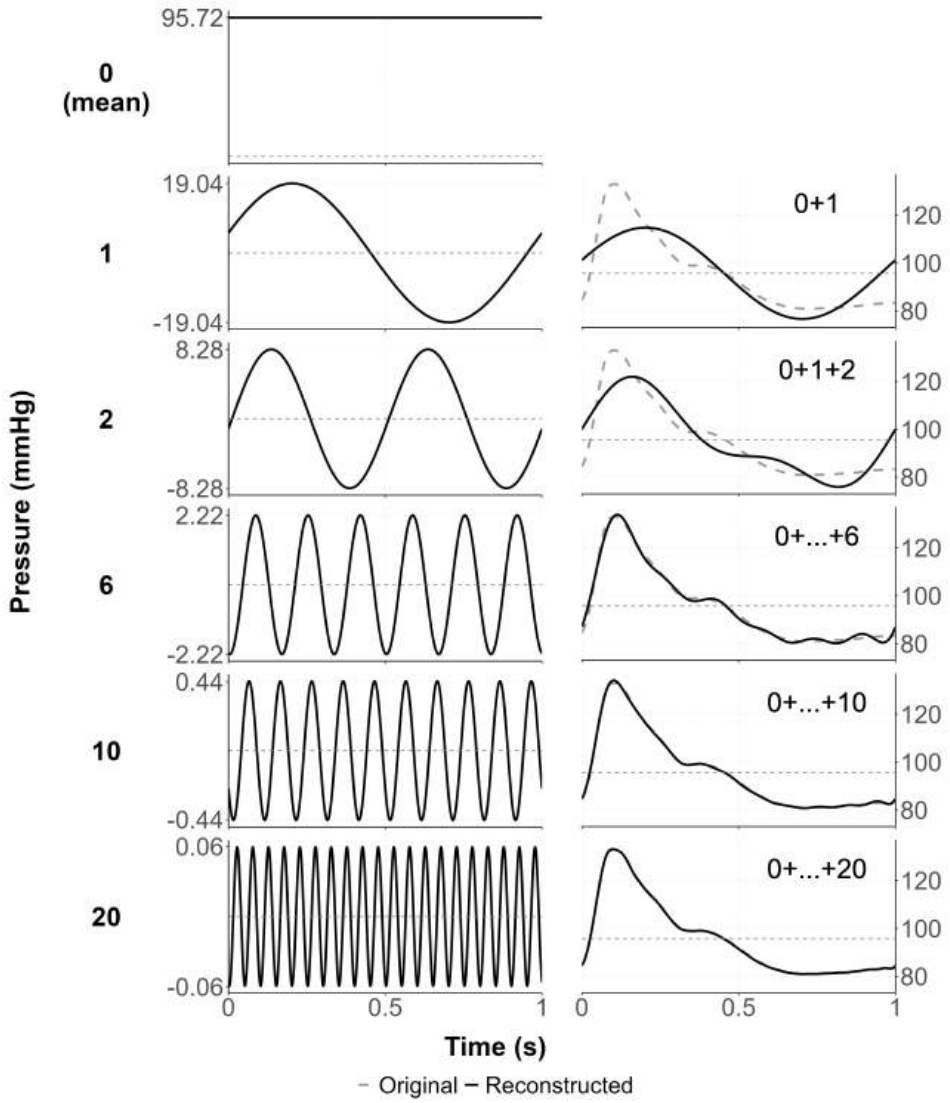

FIGURE 4.2: Fourier analysis and reconstruction of a peripheral pulse wave from a representative subject. The left panel displays the signal's mean pressure (95.72 mmHg) and a selection of its constituent harmonics. The depicted harmonics and their respective amplitudes and phase angles are: harmonic 1 (19.03 mmHg, -1.28 rad), harmonic 2 (8.28 mmHg, -1.71 rad), harmonic 6 (2.22 mmHg, 2.99 rad), harmonic 10 (0.44 mmHg, -2.72 rad), and harmonic 20 (0.06 mmHg, -1.76 rad). The right panel shows the progressive reconstruction of the waveform by cumulatively summing these harmonics, demonstrating that the addition of higher-frequency components refines the signal's morphology to closely approximate the original wave.

Rationale and description of the method

Since the pulse wave signal results from the superposition of forward and reflected waves (as discussed in Section 4.1.1), applying Fourier analysis to decompose it into its constituent harmonics provides a compelling framework for investigation. Each harmonic can be interpreted as a feature that captures a specific aspect of waveform complexity. Pathological vascular changes, such as additional reflection sites caused by calcified plaques or alterations in arterial viscoelastic properties, may thus be reflected in the harmonic structure of the signal. Moreover, analysis of the phase relationships among harmonics can provide insight into the timing of interactions between forward and reflected waves.

Based on this rationale, my further research focused on features derived from the frequency-domain representation of the pressure pulse wave. Specifically, I examined the modulus and phase angle of the signal's sinusoidal components [P2, P3], as well as the derivatives of harmonic amplitudes introduced in [P3]. For clarity, I collectively refer to these parameters as pulse wave–frequency domain features (PW-FDFs). It is also important to recognize that vascular calcification, as well as natural variability in pulse wave morphology, is also influenced by traditional risk factors such as age, sex, height, and heart rate [148]. These covariates were therefore included in my analyses [P2, P3] to ensure appropriate adjustment for potential confounders.

Finally, it needs to be highlighted that although frequency-domain analysis of the pulse wave has been described in several studies [140], to the best of my knowledge, PW-FDFs have not previously been used as direct input to any machine learning model for the detection of vascular calcification. The two papers presented in this and the following chapter are, therefore, the first to evaluate the clinical utility of PW-FDFs in VC assessment.

4.2.2 Research overview

Introduction

In the following paper, I present a framework for detecting medial vascular calcification using a machine learning framework incorporating PW-FDFs extracted from brachial artery signals. I trained easily interpretable logistic regression models, incorporating several embedded feature selection methods to identify the most relevant predictors. Although the study was limited by a relatively small sample size, I ensured a high methodological quality of my work by performing comprehensive data preparation from raw pulse wave signals, addressing class imbalance during model training, and applying cross-validation to evaluate performance. Furthermore, I implemented an ensemble learning strategy [149], which enabled inference from multiple models trained on different feature subsets. This approach allowed me to leverage a broader set of pulse wave-related features while reducing the risk of overfitting, which is a major challenge when working with small datasets.

Taken together, these methodological choices strengthen the validity of my findings and support the reliability of the conclusions derived from my work.

Relation of the publication to the research aims of the thesis

Non-invasive pulse wave measurements offer an attractive avenue for cardiovascular risk stratification [135]. Pressure pulse wave signals can currently be acquired at relatively low cost and with minimal patient burden: cuff-based devices record the wave in a manner similar to routine blood pressure measurement, while pen-like tonometers require more precision but still remain convenient. In some Asian countries, such measurements are taken routinely during patient check-ups, while in the United States and Europe, they are gaining recognition in clinical studies [150]. With the rapid development of wearable technology, it is increasingly plausible that consumer devices such as watches or bracelets will soon capture pressure pulse waves with sufficient precision to match specialized tools, further increasing accessibility. Together, these factors make pressure pulse waves a promising biomarker that can be utilized as a basis for scalable screening tools, thus aligning well with the overall objectives of my research. In this study, I investigated whether peripheral pressure pulse wave signals, acquired from the brachial artery, can provide informative input for machine learning classifiers aimed at detecting medial vascular calcification. I demonstrated that analyzing the wave in the frequency domain yields a set of features suitable for ML model development (H2Q1). The proposed framework achieved clinically relevant accuracy, effectively discriminating between patients with and without mVC (H2Q2). Furthermore, I performed a comparative analysis of models trained on traditional mVC risk factors alone, PW-FDFs alone, and a combined feature set. The results showed that incorporating PW-FDFs alongside conventional risk factors improved predictive performance, underscoring the added value of this approach for mVC detection (H2Q3).

Conclusions

In summary, this research targets the aims of my dissertation by introducing a novel, data-driven framework for early mVC detection. The framework incorporates features derived from frequency-domain analysis of pulse waves, coupled with machine learning algorithms for feature selection and classification. Importantly, this approach enabled reliable classification even when minimal mVC was labeled as a positive case, thereby supporting early detection in patients with advanced CKD without compromising predictive power. In particular, the findings address the second research hypothesis (H2), demonstrating that PW-FDFs provide clinically meaningful input for detecting medial vascular calcification.

4.3 The publication (P2)

5

POTENTIAL OF PULSE WAVE SIGNAL FREQUENCY-DOMAIN ANALYSIS FOR ELEVATED CORONARY ARTERY CALCIFICATION SCORE SCREENING

5.1 Intimal vascular calcification

Background and clinical implications

Coronary artery calcification (CAC) score, discussed in detail in the subsequent section, serves as a proxy for intimal vascular calcification. iVC is closely linked to atherosclerosis and is typically observed in large arteries such as the aorta and coronary vessels; however, it is not confined to these sites and can also be detected in other locations such as renal arteries and peripheral arteries of the limbs [151]. Moreover, it can co-occur in multiple arterial sites [152]. It is more frequently observed in older individuals and in patients with cardiovascular risk factors such as hypertension, diabetes, dyslipidemia, and CKD, who often exhibit both accelerated atherosclerosis and an increased VC burden [153].

iVC develops within the intimal layer of the arterial wall, specifically within atherosclerotic plaques. It indicates an advanced stage of plaque progression and arises as a consequence of endothelial injury, which triggers a chronic inflammatory response - one of the key drivers of VC. Such an environment promotes not only further lipid accumulation but also the infiltration of immune cells, including macrophages and T-lymphocytes, which act as mediators and stimulate VSMCs to migrate from the media to the intima [154]. There, they proliferate and undergo osteogenic differentiation, which contributes to the formation of calcified plaque components. As the lesion evolves, apoptotic bodies, matrix vesicles, and necrotic debris from dying macrophages and VSMCs provide nucleation sites for calcium phosphate crystallization, initiating the biomineralization process [155]. iVC typically progresses from small, spotty microcalcifications to larger, consolidated macrocalcifications [155].

Microcalcifications, often appearing as punctate or spotty deposits, are associated with increased plaque instability - they create points of mechanical stress within the fibrous cap, increasing the risk of plaque rupture [154]. Ruptured plaques may, in turn, lead to thrombus formation, which can abruptly occlude the vessel and cause acute cardiovascular events such as myocardial infarction or stroke. Indeed, studies have demonstrated that microcalcifications are more frequently observed in patients with acute coronary syndromes compared to those with stable coronary artery disease [156]. However, these small calcific deposits are typically beyond the

resolution limits of conventional CT imaging used for iVC assessment [157]. PET-CT imaging with sodium fluoride has been proposed as a tool for identifying early-stage microcalcifications and high-risk plaques, but its availability in clinical settings remains limited [154]. In contrast, macrocalcifications (larger, more extensive calcium deposits) are often considered stabilizing features within atherosclerotic plaques. These dense calcific regions may serve as reinforcements of the plaque structure, thereby reducing the likelihood of rupture or erosion [157]. Patients with macrocalcifications tend to have a lower risk of acute coronary events due to rupture, but they are prone to suffer from chronic lumen narrowing (stenosis) and impaired blood flow [158]. Extensive calcification contributes to increased arterial stiffness and reduced vascular compliance [159].

In clinical practice, intimal macrocalcification is most commonly assessed in the coronary arteries. A widely adopted method for this is the CT-based coronary artery calcification scoring system. However, as mentioned previously, this method cannot differentiate between intimal and medial calcification. Consequently, the CAC score reflects the total arterial calcification burden, encompassing both calcification types. Nonetheless, several studies have shown that mVC is relatively uncommon in the coronary arteries [80]. Even in CKD patients, coronary mVC has been observed only occasionally [101]. Therefore, it is reasonable to assume that the CAC score in this context predominantly reflects intimal calcification and can be interpreted as its proxy.

5.1.1 Coronary artery calcification (CAC)

CAC is one of the most extensively studied markers of coronary artery disease, serving as a robust indicator of atherosclerotic plaque burden. The development of the coronary artery calcification score (CAC score) has enabled standardized and reproducible quantification of calcific lesions in the coronary arteries and has become a valuable tool in cardiovascular risk stratification.

The conventional method for CAC scoring relies on a non-contrast, ECG-gated CT scan of the chest. This imaging approach captures the entire epicardial coronary system and detects calcific areas based on radiodensity thresholds. Specifically, a calcific lesion is defined as a hyperdense region with a radiodensity of $\geq$130 HU (*Hounsfield Units*, a measure of tissue density in CT imaging) and must cover an area of at least three adjacent pixels, corresponding to ≥ 1 mm^2. CAC assessment is typically performed using the Agatston method [160], which assigns a score by multiplying the area of each calcified lesion by a weighting factor based on the peak density of calcium within that lesion. Summing up the scores for all calcific lesions gives the total CAC score expressed in Agatston units (AU). This approach provides a semi-quantitative estimate of both the extent and density of coronary calcification. To stratify cardiovascular risk, standardized CAC categories have been proposed [161] as shown in Figure 5.1.

In some cases, scores exceeding 1000 AU are used to indicate exceptionally high coronary calcification and correspondingly elevated cardiovascular risk [162].

The relative simplicity and cost-effectiveness of CAC scoring have enabled its widespread use in large-scale, multi-center studies such as the *Coronary Artery Calcium Consortium* [163] or the *Multi-Ethnic Study of Atherosclerosis (MESA)* [164]. These studies have consistently demonstrated that the CAC score is an independent predictor of cardiovascular risk and all-cause mortality. Its predictive value has been validated across various subgroups, including younger adults [165], men and women

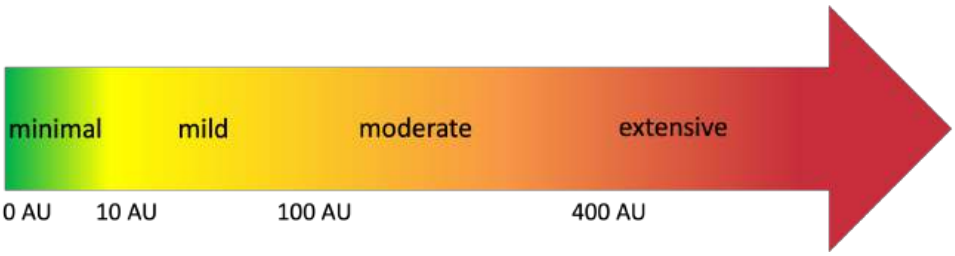

FIGURE 5.1: CAC score severity scale. The values in the picture are in Agatston Units (AU). **0 AU** - no detectable calcified plaque; **1 - 10 AU** - minimal plaque; **11 - 100 AU** - mild plaque; **101 - 400 AU** - moderate plaque; **> 400 AU** - extensive plaque.

[166], and individuals from diverse ethnic backgrounds [167, 168]. Importantly, CAC scoring provides incremental prognostic information beyond traditional risk factors for individuals at low, intermediate, and high baseline risk, including CKD patients [169, 170, 171].

There is a well-established, graded association between CAC score categories and cardiovascular risk [172]. Even mild calcification (positive scores below 100 AU) is associated with a higher probability of major coronary events compared to individuals with no detectable calcification. When the CAC score exceeds 100 AU, this likelihood increases markedly. Furthermore, patients with CAC scores above 300 or 400 AU (depending on the study) exhibit rates of major adverse cardiovascular events and mortality comparable to those seen in individuals with clinically established CAD [173]. Conversely, a CAC score of 0 has emerged as a powerful negative risk marker and is associated with a low likelihood of future coronary or cardiovascular events [174]. This so-called "warranty period" may extend up to 10–15 years, even among individuals with traditional risk factors such as hypertension, diabetes, or chronic kidney disease [174, 175].

Taken together, the addition of CAC scoring to traditional coronary heart disease risk models significantly enhances predictive accuracy and enables meaningful patient reclassification, particularly among individuals at intermediate risk, thereby allowing for more precise preventive therapies. This improvement has been shown to be both statistically and clinically significant across major risk models, including the Framingham Risk Score, SCORE, and ASCVD calculators [169, 176]. As a result, CAC scoring has been integrated into worldwide preventive cardiology guidelines to support personalized treatment decisions, especially when the need for statin therapy is uncertain [177]. It is important to note thet the progressive nature of CAC is associated with elevated future cardiovascular risk, and repeated scanning can offer prognostic value beyond a single baseline measurement [175].

Despite strong evidence supporting CAC as a marker of CAD and its inclusion in clinical guidelines for therapeutic decision-making, CAC scans remain underutilized in routine practice [173]. The reasons for this are not entirely clear, but possible concerns include limited CT scanner availability and the issue of radiation exposure, which often influences decisions regarding CT-based imaging [178, 179]. This is particularly relevant for patients with CKD, who often undergo multiple scans over the course of their disease to monitor its progression. Although each of them involves only low-dose radiation, the cumulative exposure can become significant. In this context, a reliable pre-screening tool, beyond traditional risk factors, could help clinicians identify patients unlikely to benefit from CAC scanning, while flagging those for whom CAC assessment may offer meaningful clinical insights.

As previously discussed, macrocalcifications detectable by CT scans contribute to plaque stability, altering arterial stiffness and overall hemodynamics. It is therefore plausible that pulse wave characteristics could carry clinically relevant information. Several earlier studies have examined the connection between pulse waves and CAC, particularly focusing on pulse pressure (PP), defined as the difference between systolic and diastolic blood pressure. Its elevated values have been associated with increasing CAC scores, offering some insight into calcification trends. A PP threshold of 60 mmHg has been proposed in multiple studies to identify the presence of CAC, but this cutoff appears overly simplistic and lacks the precision necessary for broad clinical application [180, 181, 182]. Other parameters derived from pulse wave analysis, particularly those obtained from central aortic waveforms, have also been explored and shown to be valuable in assessing arterial stiffness related to atherosclerosis [183].

PWV, as a surrogate marker of arterial stiffness, has also been extensively studied in the context of both CAC and CAD [179]. While cfPWV is considered the gold standard for central arterial stiffness measurement, the majority of studies, particularly those conducted in East Asian populations, have used baPWV, likely due to its clinical availability and widespread use in that region [184]. In individuals with CAC, baPWV has been shown to be independently associated with both the presence and progression of coronary calcification [185, 186, 187, 188]. Similarly, cfPWV has also demonstrated a significant association with the extent of CAC, particularly in studies focused on CKD populations [189, 190, 191]. In parallel, several studies have attempted to incorporate PWV measurements into machine learning models aimed at identifying high-risk patients. However, these models often suffer from limited sensitivity, underscoring the importance of integrating additional information to improve predictive performance [192, 193].

An emerging but still experimental concept involves combining pulse wave imaging (an ultrasound-based technique) with vector flow imaging to create an integrated framework for simultaneous assessment of vascular stiffness and hemodynamics. While this approach shows promise, it has yet to be validated in human populations [194].

Given the substantial evidence of altered hemodynamics in the presence of calcified atherosclerotic plaques, I decided to apply the PW-FDFs extraction method for their detection. While commonly used parameters such as PWV and pulse pressure are valuable indicators of arterial stiffness, they may not fully capture the subtle waveform distortions caused by calcified lesions. In contrast, the PW-FDFs approach analyzes multiple components of the pulse wave and extracts a range of features that reflect both its shape and temporal dynamics. This multidimensional analysis may offer improved sensitivity to calcified plaque-induced alterations in hemodynamic signals and thus enhance detection performance.

5.2 My work

5.2.1 Research overview

Introduction

Building on the promising results obtained using PW-FDFs within a machine learning framework, I extended this approach to the detection of elevated CAC scores ($\geq 100 AU$), which indicate at least a mild risk of adverse cardiovascular events. In this study, however, PW-FDFs were extracted from the central pulse wave signal,

i.e., the waveform transformed from peripheral measurements into a central arterial representation.

This choice was motivated by the characteristics of the retrospective dataset I acquired, which contained pulse wave recordings from both the brachial and radial arteries. To ensure consistency across samples and maximize the available dataset size, I standardized all signals by using their representation in the central waveform domain. This strategy not only enabled me to unify the input data and thereby increase the sample available for model training, but it also offers a broader methodological advantage. Specifically, the trained model can be applied independently of the arterial site of acquisition, as long as the peripheral signal can be reliably transformed into its central representation.

Therefore, in the following publication, I present the results of applying the PW-FDFs method to central pulse wave signals for the detection of elevated CAC scores. The analysis was further stratified by age groups, with particular attention to how PW-FDFs may enhance risk stratification both by identifying younger patients with elevated CAC scores (a group typically considered low-risk for calcification) and by distinguishing older patients without elevated CAC scores (a group generally regarded as a high-risk population).

Relation of the publication to the research aims of the thesis

With multiple methods available for pulse wave acquisition, the ability to transform peripheral measurements into a central waveform, from which clinically meaningful information can be extracted, offers a major advantage. This flexibility broadens the applicability of the pulse wave signal, making the biomarker easier to obtain. In this study, I investigated whether PW-FDFs derived from peripheral signals transformed into central waveforms can be used to predict elevated CAC scores, a proxy for intimal vascular calcification. The results showed that models trained on PW-FDFs alone reliably discriminated between patients with CAC $\geq$100 AU and those below this threshold (H3Q1).

Further analysis revealed that when PW-FDFs were included, time-domain features of the central pulse wave were often omitted during feature selection and, consequently, did not contribute to the final predictions (H3Q2). While the overall performance of the PW-FDFs-based model was comparable to conventional CAC risk factor-based models, subgroup analysis indicated an added value of pulse wave signal in age-stratified cohorts (H3Q3). In older patients, the PW-FDF-based model achieved higher specificity, which could result in reducing the number of unnecessary imaging scans in a group where age alone is already a dominant predictor of calcification. In younger patients, by contrast, the model demonstrated higher sensitivity, improving the detection of cases despite their lower baseline risk.

Finally, I assessed whether the PW-FDFs-based model could capture gradations in CAC severity. My analysis showed that the predicted probability of $\geq$ 100AU increased in line with actual CAC scores, suggesting that PW-FDF-based models have the potential to differentiate between varying levels of calcification burden (H3Q4).

Conclusions

This research supports my third hypothesis (H3) by demonstrating that statistical models based on PW-FDFs derived from central pressure pulse waveforms can effectively identify end-stage renal disease patients with elevated coronary artery calcification scores. Beyond confirming the hypothesis, it also advances my broader research aims by proposing a novel, data-driven framework for early iVC detection with strong potential as a widely accessible screening tool. Compared to conventional CAC risk factor models, the PW-FDFs-based approach showed particular advantages in the youngest and oldest patient groups - populations in which risk is often assessed primarily by age. Taken together, these findings suggest that incorporating frequency-based information from pulse wave signals into clinical practice could enhance conventional CAC risk assessment and enable more precise, individualized patient stratification.

5.3 The publication (P3)

6

DISCUSSION AND FUTURE PERSPECTIVES

Achievements of research aims

The primary aim of my work, introduced in Chapter 2 and discussed in detail throughout this thesis, was to propose novel, data-driven frameworks for the screening of medial and intimal vascular calcification that are both cost-effective and clinically feasible. The biomarker- and pulse wave-based models investigated here, parametrized for individuals with chronic kidney disease, demonstrated these qualities and therefore fulfilled the stated aim. Across all three studies, the emphasis was placed on early detection, an essential step for timely intervention. Moreover, the proposed approaches not only improve VC risk stratification but also strengthen cardiovascular risk assessment itself, which aligns the thesis title with the research it presents.

The research aims stated in this thesis are complex and multi-dimensional, collectively describing the purpose of my work. Yet, in these final remarks, I would like to summarise the core principle guiding the entire research with a single word: applicability. I believe that this term captures the multifaceted approach required to develop solutions that can be seamlessly translated from research into clinical practice. It has guided every stage of my work: from identifying a clinically meaningful problem in need of an improved detection, finding a relevant study population, providing a transparent rationale for the proposed solutions, and ensuring robust model performance, to prioritizing methods that are simple to implement and impose minimal burden on patients.

The focus on applicability also justifies the choice of screening methods explored in this thesis. Phenotypic biomarkers are already part of routine clinical workflows, and integrating them into machine learning models that output individualized disease probabilities represents a natural and accessible extension. Similarly, pressure pulse wave measurement is increasingly accessible and non-invasive, which makes it an attractive candidate for use as a clinical biomarker. The extraction of the analysed PW-FDFs relies on Fourier decomposition, which is already implemented in many commercially available devices using peripheral-to-central generalized transfer functions. This means the proposed approach could be incorporated into existing technologies with minimal additional development. Furthermore, I demonstrated that PW-FDFs derived from centrally transformed waveforms can be used for CAC screening, enabling broader applicability regardless of the arterial site where the signal is captured.

Applicability is also reflected in the choice of the study population. End-stage renal

disease patients are particularly susceptible to vascular calcification and its consequences, making them a suitable group for developing and validating early screening strategies. Not only is data collection more feasible in this population, but CKD patients are most likely to benefit from implementing such screening tools in clinical practice.

It is also important to emphasize why this research falls within the scope of biomedical engineering. As an interdisciplinary field, biomedical engineering applies, among others, engineering principles, mathematical and computational methods, and biological knowledge to address challenges in medicine and healthcare. In this thesis, I applied machine learning techniques - computational methods originating from mathematical concepts - to data selected on the basis of established biological and physiological knowledge of vascular calcification, thereby integrating insights from multiple disciplines. Furthermore, by prioritizing feasibility, cost-effectiveness, and compatibility with existing clinical workflows, my work bridges the gap between methodological innovation and real-world applicability, reinforcing its position within the field of biomedical engineering.

To conclude, applicability is not only the unifying principle of this research but also the quality that situates it within the biomedical engineering field. I hope that this focus will ensure the proposed methods can be applied in future real-world cardiovascular screening strategies, ultimately helping to improve care for patients at risk of vascular calcification.

Limitations and future perspectives

Naturally, my work is not free from limitations. Although they are discussed in detail within the individual publications, here I highlight those most relevant to interpreting the results and guiding future work.

First, while the developed frameworks demonstrated robust performance within the studied cohorts, their generalisability remains to be confirmed. Large-scale, multicenter studies across diverse CKD populations are needed to validate the models and refine their parameters for broader use. Nonetheless, the results obtained here provide a strong basis and, I believe, offer a compelling motivation to collect larger datasets and pursue further validation efforts.

Second, extending the models beyond CKD populations could provide valuable insights. Directly comparing models trained in CKD and non-CKD cohorts would help clarify how CKD influences feature selection, model behavior, and ultimately the mechanisms linking vascular calcification with measurable biomarkers.

Third, a formal comparison between information captured by pulse wave velocity and pulse wave frequency-domain features remains an important next step. While PWV is currently regarded as the gold standard in arterial stiffness assessment, it requires measurements at multiple arterial sites and is technically demanding. PW-FDFs, by contrast, can be derived from a single-site recording, making them potentially more accessible. Exploring whether PW-FDFs can serve as a viable alternative or complementary biomarker is, therefore, an important future direction.

Finally, the study on CAC score prediction raises the question of whether the conventional 100 AU threshold could be lowered or refined. With larger datasets, regression-based or multinomial classification approaches could enable modeling CAC severity

more granularly, potentially identifying clinically meaningful lower CAC score values.

In conclusion, this thesis has presented novel, data-driven frameworks for vascular calcification screening that emphasize cost-effectiveness, clinical feasibility, and applicability. While limitations remain, the findings demonstrate the potential of both phenotypic biomarker-based and pressure pulse wave–based models as scalable screening approaches. At the same time, the research has raised important new questions, underscoring that the proposed methods are not an endpoint but rather a promising starting point for continued exploration into clinically applicable, patient-centered cardiovascular screening tools.

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APPENDIX I

CONFERENCES

- Artery Conference, Nancy, France, October 19-22, 2022

  Poster presentation (presenting author): "Pulse waveform-based prediction of vascular calcification in patients with end-stage renal disease" **U. Białończyk**, M. Dębowska, L. Dai, A. Qureshi, M. Soderberg, B. Lindholm, P. Stenvinkel, J. Poleszczuk;

- XXIII Polish Conference on Biocybernetics and Biomedical Engineering, Łódź, Poland, September 27-29, 2023

  Oral presentation (presenting author): "Detection of medial vascular calcification in chronic kidney disease based on the pulse wave analysis in the frequency domain" **U. Bialonczyk**, M. Debowska, L. Dai, A. Qureshi, M. Soderberg, B. Lindholm, P. Stenvinkel, J. Poleszczuk

- ASN Kidney Week, San Diego, USA, October 23-27, 2024

  Poster presentation (co-author): "Detection of Medial Vascular Calcification Using Cost-Effective Classifiers" **U. Bialonczyk**, L Dai, A. Qureshi, L. Bobrowski, M. Soderberg, B. Lindholm, P. Stenvinkel, T. Lukaszuk, M. Debowska, J. Poleszczuk

- NBC 2025 & PCBBE 2025 Warsaw, Poland, June 16–18, 2025

  Poster presentation (presenting author): „Leveraging pulse wave signal properties for coronary artery calcification screening in CKD patients" **U. Bialonczyk**, L. Pstras, M. Debowska, L. Dai, AR. Qureshi, M. Soderberg, T. Brismar, J. Ripsweden, B. Lindholm, P. Stenvinkel, J. Poleszczuk

A P P E N D I X I I

DECLARATION OF AUTHORS' CONTRIBUTIONS

In paper „**Balancing accuracy and cost in machine learning models for detecting medial vascular calcification in chronic kidney disease: a pilot study**", published in *Scientific Reports*, 15 (2025), DOI: 10.1038/s41598-025-02457-2,

Urszula Bialonczyk (first author, corresponding author):

- conceptualized the study,
- designed the methodological approach,
- performed formal data analysis,
- developed the formula for ICER tailored for mVC detection,
- performed computations,
- prepared the figures, tables and supplementary material,
- wrote the manuscript;

Małgorzata Dębowska:

- conceptualized the study,
- revised the manuscript;

Leon Bobrowski:

- developed the methodology for RLS;

Tomasz Łukaszuk:

- developed the software for RLS calculation and carried out its computation;

Jan Poleszczuk (supervisor):

- conceptualized the study,
- supervised the research,
- revised the manuscript;

Lu Dai*:

- curated the data,
- prepared the Table S4,
- revised the manuscript;

Abdul Rashid Qureshi*:

- curated the data;

Magnus Söderberg*:

- supervised the research;

Peter Stenvinkel*:

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Bengt Lindholm*:

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As Head of Baxter Novum, Renal Medicine, Karolinska Institutet, I hereby confirm that the individual authors' contributions to the publication are in accordance with the authorship contribution statement, and declare that I am signing this confirmation on behalf of the authors marked with (*).

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In paper „**Detection of medial vascular calcification in chronic kidney disease based on pulse wave analysis in the frequency domain**", published in *Biomedical Signal Processing and Control*, 94 (2024), DOI: 10.1016/j.bspc/2024.106250,

Urszula Bialonczyk (first author):

- conceptualized the study,
- designed the methodological approach,
- performed formal data analysis,
- performed computations,
- prepared the figures, tables and supplementary material,
- wrote the manuscript;

Malgorzata Debowska:

- revised the manuscript;

Jan Poleszczuk (supervisor, corresponding author):

- conceptualized the study,
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- revised the manuscript;

Lu Dai*:

- revised the manuscript;

Abdul Rashid Qureshi*:

- curated the data;

Magnus Söderberg*:

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In paper *„***Detection of medial vascular calcification in chronic kidney disease based on pulse wave analysis in the frequency domain**", published in *Biomedical Signal Processing and Control*, 94 (2024), DOI: 10.1016/j.bspc/2024.106250

Urszula Bialonczyk (first author):

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Malgorzata Debowska:

- revised the manuscript;

Jan Poleszczuk (supervisor, corresponding author):

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- curated the data;

Magnus Söderberg*:

- supervised the research;

Peter Stenvinkel*:

- supervised the research,
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As Head of Baxter Novum, Renal Medicine, Karolinska Institutet, I hereby confirm that the individual authors' contributions to the publication are in accordance with the authorship contribution statement, and declare that I am signing this confirmation on behalf of the authors marked with (*).

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In paper „ **Leveraging pulse wave signal properties for coronary artery calcification screening in CKD patients**", published in *Computers in Biology and Medicine*, 194 (2025), DOI: 10.1016/j.compbiomed.2025.110519,

Urszula Bialonczyk (first author, corresponding author):

- conceptualized the study,
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In paper „ **Leveraging pulse wave signal properties for coronary artery calcification screening in CKD patients**", published in *Computers in Biology and Medicine*, 194 (2025), DOI: 10.1016/j.compbiomed.2025.110519,

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