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**Davies, EM ORCID logoORCID: https://orcid.org/0009-0004-8635-771X, Ezenwekere, M, Chetwynd, AJ ORCID logoORCID: https://orcid.org/0000-0001-6648-6881, Oni, L, McDowell, G ORCID logoORCID: https://orcid.org/0000-0002-2880-5236 and Rao, A (2025) Biomarkers**

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*kidney and dialysis*

MDPI

*Systematic Review*

# Biomarkers Predicting Major Adverse Cardiovascular Events in End-Stage Kidney Disease: A Systematic Review

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## Abstract

**Background:** Cardiovascular disease is the leading cause of death in chronic kidney disease populations. The risk of major adverse cardiovascular events (MACE) is greater than that of progression to end-stage kidney disease. An exponential increase in mortality risk is associated with declining kidney function. This study aimed to review the current landscape of traditional and novel blood biomarkers in predicting MACE in ESKD patients. **Methods:** The systematic review was registered on PROSPERO (CRD42024497403). Standard and extensive Cochrane search methods were used. The latest search date was July 2023. Participants were aged ≥18 years with end-stage kidney disease. Descriptive analysis was performed and data was presented in tabular form. The hazard ratio or odds ratio was presented for potential biomarkers discovered. **Results:** Overall, 14 studies (4965 participants) were included for analysis; 12 focused on participants requiring haemodialysis and 2 on haemodialysis and peritoneal dialysis. The biomarkers analysed were Troponin I ($n$ = 3), Troponin T ($n$ = 3), B-type natriuretic peptide ($n$ = 2), N-Terminal Pro-Brain-Natriuretic Peptide ($n$ = 7), soluble receptors for advanced glycation end products ($n$ = 2), Galectin 3 ($n$ = 4), and the serum-soluble suppression of tumorigenicity-2 ($n$ = 2). Reported study outcomes included all-cause mortality ($n$ = 11), MACE ($n$ = 5), cardiac specific mortality ($n$ = 6), sudden cardiac death ($n$ = 2), and first cardiovascular event ($n$ = 3). **Conclusions:** This review outlines the potential role of traditional and novel biomarkers in predicting MACE in end-stage kidney disease. Further larger-scale research is required to establish the validity of the study outcomes to develop new methods of cardiovascular risk prediction in this high-risk population.

**Keywords:** cardiovascular; end-stage kidney disease; biomarker

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Academic Editor: Jaime Uribarri

Received: 20 May 2025
Revised: 30 July 2025
Accepted: 14 August 2025
Published: 20 August 2025

**Citation:** Davies, E.M.; Ezenwekere, M.; Chetwynd, A.J.; Oni, L.; McDowell, G.; Rao, A. Biomarkers Predicting Major Adverse Cardiovascular Events in End-Stage Kidney Disease: A Systematic Review. *Kidney Dial.* **2025**, *5*, 39. https://doi.org/10.3390/kidneydial5030039

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## 1. Introduction

Chronic kidney disease (CKD) is increasingly acknowledged as a significant non-communicable disease worldwide, projected to become the fourth leading cause of life years lost by 2040 following ischaemic heart disease (IHD), stroke, and chronic obstructive pulmonary disease [1,2]. The global all-age CKD mortality has increased by 41.5% between 1990 and 2019 [3,4]. This impending health crisis calls for developments in identifying and managing complications associated with CKD [5–7].

CKD is an independent risk factor for cardiovascular disease (CVD) [8,9], the leading cause of death in CKD populations [10]. For individuals with CKD, the risk of major adverse cardiovascular events (MACE) is greater than the risk of progression to end-stage kidney disease (ESKD) [10,11]. The exact mechanism of premature cardiovascular ageing in CKD is likely to be multi-factorial and secondary to the chronic systemic pro-inflammatory state associated with uraemic toxins, vascular and myocardial remodelling, atherosclerosis, vascular calcification, and complex dyslipidaemia [12–14]. A meta-analysis of over 100,000 participants with varying estimated glomerular filtration rate (eGFR) demonstrated an exponential increase in mortality risk with declining kidney function with pooled cardiovascular mortality at eGFR 15–29 mL/min/1.73 $m^2$ hazard ratio (H.R.) 13.51 [4.89–37.35] [15]. In the UK National Health Service, the cost of excess strokes and MIs in the CKD population is estimated at GBP 174–GBP 178 million, translating to an estimated GBP 434,618 annual CVD morbidity expenditure, specifically in the CKD stage 5 with macroalbuminuria cohort per 1000 patient years [16,17].

In 2016, the United States Food and Drug Administration (FDA) and the National Institutes of Health (NIH) task group coined the definition of a biomarker: "A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention" [18]. Cardiac Troponin is universally accepted as the biomarker of myocardial injury [19]. However clinically utilised cardiac biomarkers such as Troponin, B-type natriuretic peptide (BNP) and its N-Terminal precursor (NTproBNP) continue to be scrutinised in their ability to represent the cardiovascular risk profile in CKD [20]. Elevated troponin is associated with cardiovascular remodelling and ventricular hypertrophy and fibrosis, a phenomenon in CKD whereas BNP [20], released during cardiomyocyte stretch, is associated with fluid overload often seen in ESKD [21].

In addition, there are several promising new cardiovascular biomarkers, but their role in risk stratification in ESKD is unknown. For example, ST-2 is a circulating form of the interleukin-33 receptor released in response to vascular congestion, inflammation, and pro-fibrotic stimuli and is a strong independent predictor of poor outcomes in heart failure [22,23]. Further, Galectin-3 has also been associated with cardiac morbidity in HD patients [24–26]. Galectin-3 is a promising marker of acute- and chronic inflammation and fibrosis prognostic of heart failure and cardiovascular morbidity [27,28]. However, as circulating plasma levels are influenced by kidney function, their role in ESKD is poorly understood [27]. It is therefore imperative to identify highly sensitive and specific biomarkers, with defined threshold concentrations that can identify sub-clinical disease leading to better risk prediction models for MACE in ESKD [29].

This study aimed to perform a systematic literature review summarising the current landscape of traditional and novel blood biomarkers in predicting all-cause mortality and MACE in ESKD patients to identify strengths and areas of unmet need.

## 2. Materials and Methods

This systematic review was registered in PROSPERO (CRD42024497403).

**Population:** Patients aged ≥ 18 years, any sex or ethnicity with end-stage kidney disease (ESKD) (defined by the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [11]) receiving haemodialysis or peritoneal dialysis

**Intervention:** Blood-based biomarker measurement.

**Outcome:** Major adverse cardiovascular events (MACE) as a composite or split into individual components such as—ischaemic heart disease, angina, acute myocardial infarction, heart failure, atrial fibrillation or flutter, ischaemic stroke, and all-cause mortality (death).

Two online databases were searched on the 1st of July 2023: Ovid MEDLINE, and PubMed databases.

The study designs included meta-analyses, cohort studies, case–control studies, cross-sectional studies and case series ($n > 5$). The filters applied to the search tool were an original publication date between 2013 and 2023 (allowing for an inclusion period of 10 years) and an abstract available in English with sufficient data for extraction. Studies that did not report outcomes as hazard ratios or odds ratios were excluded alongside secondary data and non-human studies. The reference lists of relevant literature were hand-searched to identify any additional eligible studies. The search strategy is available in the Supplementary Materials, Table S1.

**Selection process**

Four reviewers independently completed the title and subsequent abstract screening: E.D., M.E., GMc and A.R. Full-text screening was completed by E.D. with GMc and A.R. also reviewing half the full-text screen each. At every level of review, any conflicts were discussed and subsequently resolved. Duplicate results were screened electronically by Rayaan software (https://www.researchgate.net/publication/311443509_Rayyan-a_web_and_mobile_app_for_systematic_reviews, accessed on 3 June 2024), and any further remaining duplicates were manually removed after cross-checking. Critical Appraisal Skills Programme (CASP), a cohort study checklist was applied to each included study to evaluate the quality of the study and determine the risk of bias [30].

**Data collection and analysis**

Descriptive analysis was applied to the data collected from the included studies and presented in tabular form. The data outcomes extracted from each study were first named author, country of study, publication year, study design, dialysis modality: Haemodialysis (HD) or peritoneal dialysis (PD.), dialysis vintage, cohort demographics, cardiovascular risk factors, biomarker, outcome measured, hazard ratio or odds ratio. Meta-analysis was not performed due to heterogeneity in the data and variability of reported outcomes and the definitions of MACE. If a study included a composite outcome, their definition was included in the data extraction, which accounts for any inter-study variation in MACE.

Sex distribution was converted to a percentage of males. Cardiovascular risk factors were quoted as the percentage of cohort where available. Incomplete data values were recorded as N.A.

Biomarkers analysed in more than one study were included for full data extraction to facilitate comparative analysis. Biomarkers included in one study or biomarkers constituted of ratio measurements were listed separately, and their full data was not extracted or analysed.

## 3. Results

### *3.1. Data Extraction*

An online database search was completed in July 2023 and yielded 658 results. A total of 197 duplicates were identified and removed. The remaining 461 records were screened by abstract, and a subsequent 124 were included for full-text review. The final number of

papers included for full data extraction and analysis was 14. A further 13 studies reported biomarkers unique to one study or biomarker ratios. No further papers were included from screening reference lists. The process of study selection is summarised in Figure 1.

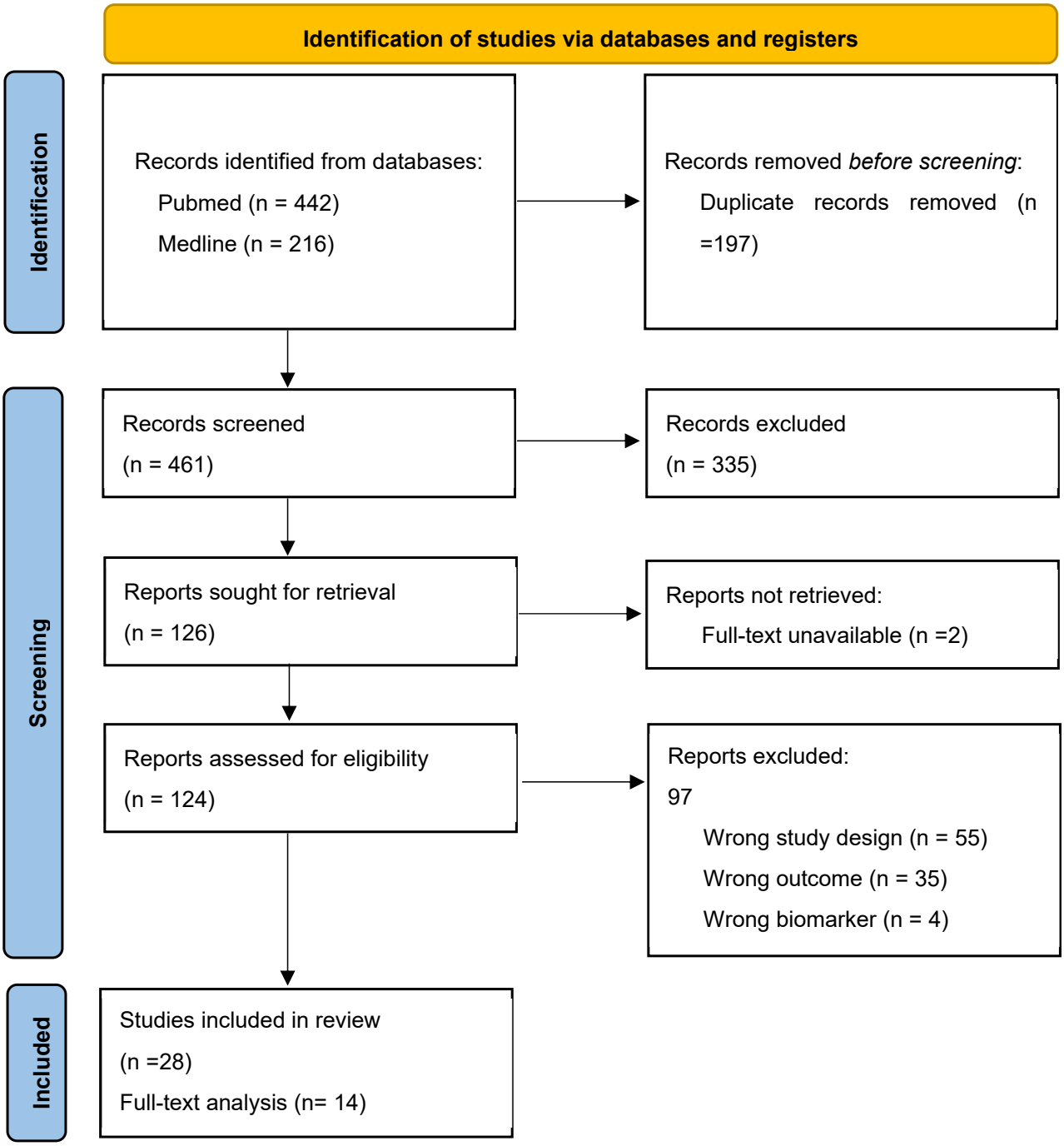


**Figure 1.** Prisma flowchart outlining process for study selection for inclusion in review.

### *3.2. Quality Assessment*

The CASP checklist was applied to all included studies. The checklist highlighted the risk of bias in those studies whereby exclusion criteria was not stipulated. Furthermore, cardiovascular risk factors were deemed important confounding factors that were not reported within some studies. See Supplementary Table S2 for CASP checklist results.

### *3.3. Demographics and Study Design*

The total number of participants included in the 14 papers for full-text extraction was 4965 (range 104–3218). The mean age was 63 years (range 57–71), and 58% of participants were male sex. The mean body mass index (B.M.I) of the participants was 24 kg/m$^2$, the number of participants who smoke was 33% and 43% of participants had a diagnosis of diabetes. There was variation in the cardiovascular co-morbidities reported between studies, with 3 studies not reporting any data in this regard. See Supplementary Table S3 for full details.

Of the included studies, 12 were based on patients who were receiving haemodialysis (HD) [31–42], and 2 studies were based on patients who were receiving HD and/or peritoneal dialysis (PD) [43,44]. The median dialysis vintage was 3.5 years (range < 3 months–9.3 years), although there was variability in the completeness of reporting, with some studies only referencing the inclusion/exclusion criteria without explicitly including dialysis vintage. The median follow-up period was 32 months (range 20–60).

Reported study outcomes included all-cause mortality ($n$ = 11), cardiac specific mortality ($n$ = 6), major adverse cardiovascular events (MACE) ($n$ = 6), sudden cardiac death ($n$ = 2), and the first cardiovascular event ($n$ = 3).

### *3.4. Included Biomarkers*

A summary of included studies, biomarkers and outcomes reported is included in Table 1. The biomarkers included for analysis were Troponin I ($n$ = 3), Troponin T ($n$ = 3), B-type natriuretic peptide (BNP) ($n$ = 2), N-Terminal Pro-Brain-Natriuretic Peptide (NTproBNP), ($n$ = 7), soluble receptor for advanced glycation end products (sRAGE) ($n$ = 2), Galectin 3 (Gal–3) ($n$ = 4) and serum-soluble suppression of tumorigenicity-2 (sST2) ($n$ = 2). Studies reporting biomarkers unique to one study or biomarkers ratios that were not included for full data analysis are found in Supplementary Table S4.

Due to heterogeneity of the data and the definitions of outcome, a formal meta-analysis was not conducted. Report HR for all-cause mortality, ranged from 1.41 to 23.7.

Cardiac Troponin: Troponin I ($n$ = 3), Troponin T ($n$ = 3)

Cardiac troponin forms part of the contractile apparatus of the cardiac myofilament. Three isoforms of troponin are present designated T, I and C. Currently immunoassays, of high analytical sensitivity are used in clinical practice to measure cardiac specific troponin T and I. Cardiac troponin is accepted as a biomarker of myocardial injury [19]. The results are summarised in Table 1. Six studies analysed Troponin as a biomarker: Troponin I ($n$ = 3), Troponin T ($n$ = 4). Apart from Otsuka et al. [38], all these studies selected a biomarker threshold for Troponin. All-cause mortality was calculated for Troponin across all the studies apart from Kruzan et al. [35] whereby the outcome was sudden cardiac death only. Hayashi et al. [43] was one of only two studies that recruited incident dialysis patients, both PD ($n$ = 220) and HD ($n$ = 28), analysing all-cause and cardiac specific mortality. PD and HD outcomes were not directly compared. In 89 participants, sample collection for Troponin T levels occurred at two time points: 3–6 months and 1–2 weeks before dialysis initiation. This additional analysis showed an increase in Troponin T level from 0.02 to 0.04 ng/mL ($p$-value < 0.001 with multi-variate logistic regression analysis showing male sex and the degree of change in diastolic blood pressure were associated with the observed Troponin T increase [43].

**Table 1.** Study design, biomarker threshold and outcome data.

| First Author Country Year | Study Design | Dialysis Modality | Participants (n) | Biomarker | Biomarker Threshold | Outcome Measure | Number with Outcome | Hazard Ratio or Odds Ratio with [95% Confidence Interval] |
|---|---|---|---|---|---|---|---|---|
| Alam et al. [31] Canada 2013 | Single Centre Prospective | HD [a] | 133 | Troponin I | 0.06 µg/L | All-cause mortality | 23 | 2.83 [1.49–5.37] |
| | | | | | | Cardiac specific mortality (AMI [b], CCF [c], fatal arrhythmia) | 15 | 4.04 [1.46–11.2] |
| Hayashi et al. [43] Japan 2017 | Single Centre Prospective | HD PD [d] | 248 220 HD 28 PD | Troponin T | 0.01 ng/mL | All-cause mortality | 51 | 1.47 [1.15–1.88] |
| | | | | | | Cardiac specific mortality (Not specified) | 10 | 1.479 [0.93–2.36] |
| Kawagoe et al. [33] Japan 2018 | Multi-centre Prospective | HD | 1310 | NTproBNP | Continuous pg/mL | All-cause mortality | 144 | 4.62 [3.48–6.14] |
| | | | | | | Cardiac specific mortality (ischemic or haemorrhagic stroke, AMI, CCF, or rupture of an aortic aneurysm) | 54 | 4.95 [3.11–7.89] |
| Schwermer et al. [39] Poland 2015 | Multi-centre Prospective | HD | 321 | NT-proBNP | Continuous pg/mL | All-cause mortality | 97 | 1.41 [1.17–1.70] |
| Dozio et al. [44] Italy 2018 | Single–centre Prospective | HD PD | 123 56 HD 67 PD | sRAGE [e] | Continuous pg/mL | All-cause mortality | 23 | 1.04 [1.01–1.08] (ODDS RATIO) |
| Jung et al. [32] Korea 2017 | Single- centre Prospective | HD | 199 | sRAGEs | Continuous ng/mL | All-cause mortality | 27 | 1.074 [0.59–1.97] |
| Kruzan et al. [35] USA 2016 | Multi-centre Prospective SECONDARY DATA | HD | 503 | NTproBNP | (ng/mL) Continuous and tertiles | Sudden cardiac death (out-of-hospital deaths) | 75 | 1.33 [1.21–1.46] |
| | | | | | 59–1710 | | | Reference |
| | | | | | 1728–7269 | | | 1.99 [1.25–3.14] |
| | | | | | 7350–273,502 | | | 4.49 [2.61–7.71] |
| | | | | Troponin I | (pg/mL) Continuous and tertiles | | | 1.19 [1.06–1.32] |
| | | | | | <0.0015 | | | Reference |
| | | | | | 0.015–0.039 | | | 1.82 [1.06–3.10] |
| | | | | | 0.040–3.09 | | | 2.14 [1.46–3.13] |

**Table 1.** *Cont.*

| First Author Country Year | Study Design | Dialysis Modality | Participants (n) | Biomarker | Biomarker Threshold | Outcome Measure | Number with Outcome | Hazard Ratio or Odds Ratio with [95% Confidence Interval] |
|---|---|---|---|---|---|---|---|---|
| Otsuka et al. [38] Japan 2019 | Single centre Prospective | HD | 104 | hs Troponin T | Continuous (ng/Ml) | MACE (all-cause death, AMI requiring coronary revascularisation, and stroke) | 51 | 3.12 [1.79–5.44] |
| | | | | BNP | Continuous (pg/mL) | | | 1.90 [1.09–3.32] |
| Shafi et al. [40] USA 2014 | Multi-centre Prospective | HD | 446 | Troponin I | ≥0.1 ng/mL | All-cause mortality | 323 | 1.75 [1.37–2.24] |
| | | | | NT-proBNP | ≥9252 pg/mL | Cardiac specific mortality | 143 | 2.29 [1.55–3.38] |
| | | | | (All outcome measured for one of the biomarkers above threshold and not demonstrated separately) | | First CVE | 271 | 1.67 [1.32–2.10] |
| Sun et al. [41] China 2021 | Single centre Prospective | HD | 180 | hs-Troponin T | 14 pg/mL | All-cause mortality | 37 | hs-Troponin T: 3.32 [1.93–5.71]; BNP: 2.24 [1.47–3.43] |
| | | | | BNP | Continuous pg/mL | First fatal or non-fatal CVE | 84 | 3.02 [2.11–4.31]; 2.36 [1.83–3.04] |
| | | | | | | MACE (non-fatal AMI; non-fatal CVA [h]; CCF; Cardiac specific mortality | 78 | 3.37 [2.32–4.89]; 2.22 [1.43–3.34] |
| Voroneanu et al. [42] Romania 2018 | Multi-centre Prospective | HD | 173 | Galectin 3 (Gal–3) | *median levels* 28.1 ng/mL | MACE (Death and CV events (AMI; SCD [i]; non-fatal CVA) | 47 | |
| | | | | NT-proBNP | 4234 pg/mL | low NT-proBNP–low Gal-3 | | reference |
| | | | | | | low NT-proBNP–high Gal-3 | | 2.1 [0.79–5.63] |
| | | | | | | high NT-proBNP–low Gal-3 | | 1.98 [0.73–5.35] |
| | | | | | | high NT-proBNP–high Gal-3 | | 3.65 [1.45–9.21] |
| Liu et al. [36] China 2022 | Single centre Prospective | HD | 506 | Gal–3 | 8.65 ng/mL | All-cause mortality | 188 | 1.92 [1.17–3.17] |
| | | | | | | Cardiac specific mortality | 125 | 2.47 [1.25–4.87] |

**Table 1.** *Cont.*

| First Author Country Year | Study Design | Dialysis Modality | Participants (n) | Biomarker | Biomarker Threshold | Outcome Measure | Number with Outcome | Hazard Ratio or Odds Ratio with [95% Confidence Interval] | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Gal–3 | sST2 |
| Kim et al. [34] Korea 2021 | Single centre Prospective | HD | 296 | Gal–3 | Continuous ng/mL | All-cause mortality | 36 | 1.35 [0.93–1.97] | 1.81 [1.24–2.65] |
| | | | | Serum-soluble suppression of tumorigenicity-2 (sST2) | | MACE (Unstable angina pectoris, AMI, TIA [j], CVA, and CCF) | 69 | 1.04 [0.82–1.33] | 1.100 [0.855–1.414] |
| Obokata et al. [37] Japan 2016 | Single centre Prospective | HD | 423 | Gal–3 | Continuous ng/mL | All-cause mortality | 48 | 23.7 [6.45–86.9] | |
| | | | | | <8.1 | | | Reference | |
| | | | | | 8.1–15.2 | | | 2.89 [1.04–8.02] | |
| | | | | | >15.2 | | | 6.51 [2.52–16.8] | |
| | | | | sST2 | Continuous ng/mL | | | 10.6 [4.98–22.5] | |
| | | | | | <0.237 | | | Reference | |
| | | | | | 0.237–0.299 | | | 1.12 [0.43–2.91] | |
| | | | | | >0.299 | | | 4.15 [1.91–9.03] | |
| | | | | NTproBNP | Continuous pg/mL | | | 3.85 [2.22–6.68] | |
| | | | | | <2440 | | | Reference | |
| | | | | | 2440–8220 | | | 1.55 [0.60–4] | |
| | | | | | >8220 | | | 4.7 [2.07–10.7] | |

**Table 1.** *Cont.*

| First Author Country Year | Study Design | Dialysis Modality | Participants (n) | Biomarker | Biomarker Threshold | Outcome Measure | Number with Outcome | Hazard Ratio or Odds Ratio with [95% Confidence Interval] |
|---|---|---|---|---|---|---|---|---|
| Obokata et al. [37] Japan 2016 | | | | Gal–3 | Continuous ng/mL | Composite-all cause death and MACE (non-fatal AMI; CCF hospitalisation; non-fatal CVA) | 78 | 50.1 [16.7–151] |
| | | | | | <8.1 | | | Reference |
| | | | | | 8.1–15.2 | | | 2.13 [0.96–4.73] |
| | | | | | >15.2 | | | 7.06 [3.47–14.4] |
| | | | | sST2 | Continuous ng/mL | | | 8.87 [4.73–16.6] |
| | | | | | <0.237 | | | Reference |
| | | | | | 0.237–0.299 | | | 0.93 [0.46–1.88] |
| | | | | | >0.299 | | | 3.21 [1.82–5.66] |
| | | | | NTproBNP | Continuous pg/mL | | | 3.31 [2.02–4.83 |
| | | | | | <2440 | | | Reference |
| | | | | | 2440–8220 | | | 0.91 [0.47–1.77] |
| | | | | | >8220 | | | 2.71 [1.57–4.71] |

*All results were displayed as hazards ratio apart from one which used odds ratio,* [a] *HD—Haemodialysis,* [b] *AMI—Acute myocardial infarction,* [c] *CCF—Congestive cardiac failure,* [d] *PD—Peritoneal dialysis,* [e] *sRAGE—Soluble receptor for advanced glycation end products,* [h] *CVA—Cerebrovascular accident,* [i] *SCD—Sudden cardiac death,* [j] *TIA—Transient ischaemic attack.*

BNP and NTpro BNP: BNP ($n$ = 2), NTproBNP ($n$ = 7)

The natriuretic peptides are polypeptide hormones produced and secreted by the cardiac atria or ventricular myocytes. For various reasons, including in vivo and in vitro stability B-type Natriuretic Peptide (BNP) and its N-terminal precursor are recommended for clinical use. BNP and NT-proBNP are released in a 1:1 molar ratio from predominately the cardiac ventricular myocytes in response to an increase in ventricular stretch. BNP and NTproBNP are recommended as screening biomarkers for heart failure, with high negative predictive value [45].

Nine studies analysed BNP ($n$ = 2) and NTproBNP ($n$ = 7) in their ability to predict all-cause mortality (Table 1).

In their study, Shafi et al. [40] chose a specific threshold for NTproBNP based on one previous HD study of MACE outcomes in diabetic HD patients [46]. In this study, all outcome measures (all-cause mortality, cardiac specific mortality, first CV event) were evaluated for one of the biomarkers (Troponin I or NTproBNP) when above the defined threshold; therefore, their predictive value cannot be fully interpreted, neither can the efficacy of a combined biomarker strategy using Troponin I and NTproBNP. Voroneanu et al. [42] used the median level of NTproBNP as the threshold, with H.R. for incident MACE based on a combination of NTproBNP and Galectin 3 (Gal–3). The risk of incident MACE was increased when both biomarkers were above threshold, H.R 3.65 (95% confidence interval (CI), 1.45–9.21).

Soluble suppression of tumorigenicity-2 (sST2): ($n$ = 2)

Serum-soluble suppression of tumorigenicity 2 (sST2) is an inflammatory mediator, part of the interleukin (IL)-1 receptor family [47]. It has been identified as a potential cardiovascular biomarker as it has been proven to be upregulated in cardiomyocytes exposed to mechanical [48,49] stretch or strain [47]. Kim et al. [34], in a study of 296 prevalent HD patients with a dialysis vintage of 4 years investigated sSt2 as a continuous variable; all-cause mortality H.R 1.811 [CI 1.240–2.645], MACE H.R 1.100 [CI 0.855–1.414]. Obokota et al. [37] with 423 HD participants, dialysis vintage 5.8 years again analysing sSt2 as a continuous variable demonstrated that it was able to predict all-cause mortality with a H.R of 10.6 [4.98–22.5] and predict MACE with a H.R of 8.87 [4.73–16.6].

Soluble receptor for advanced glycation end products (sRAGE): ($n$ = 2)

sRAGE binding results in a cascade of pro-inflammatory cytokines, including nuclear factor kappa-β activation, expression of pro-inflammatory cytokines and oxidative stress which is linked to the pathophysiology of CVD [50,51]. Dozio et al. [44] included 123 participants (56 HD and 67 PD), reported an odds ratio for all-cause mortality of 1.044 [CI 1.009–1.083]. While Jung et al. [32] reported a H.R of 1.074 [CI 0.587–1.967] for all-cause mortality in 199 HD patients. Both studies analysed sRAGE as a continuous variable.

Galectin 3 (Gal–3): ($n$ = 4)

Galectin 3 can be considered a multi-functional regulatory molecule found in multiple different human tissues and has been associated with a plethora of diseases, hence lacking in clinical specificity [52]. It promotes pro-inflammatory characteristics that can be associated with atherosclerotic plaque formation and the development of cardiac fibrosis in heart failure [53,54].

Liu et al. [36] defined a Gal-3 threshold of 8.65ng/mL using a bioinformatic software X-tile version 3.6.1 [55]. This study of 506 HD patients of dialysis vintage of >3 months and 60 months follow up, reported an all-cause mortality H.R 1.92 [1.17–3.17] and cardiac-specific mortality H.R 2.47 [1.25–4.87], although limited cardiovascular demographics were reported or included in the analysis. Kim et al. [34], a single centre study of 296 preva-

lent HD patients with 36 months follow up found no association between Gal-3 and all-cause mortality H.R 1.354 [0.931–1.971], MACE (unstable angina pectoris, acute coronary syndrome, transient ischaemic attack, stroke, and congestive cardiac failure) H.R 1.042 [0.820–1.325].

## 4. Discussion

This systematic review provides an overview of the range of currently used and emerging biomarkers in clinical practice. This review identified two routinely used clinical biomarkers, Troponin and BNP, and three other biomarkers, namely ST2, Soluble RAGE and Galectin-3. However, there remains a gap in the clinical use of biomarkers to stratify patients. This study highlighted the heterogeneity of the literature in terms of methodology and the definition of outcomes. The most frequently studied biomarkers were Troponin and NTproBNP; biomarkers already utilised in current clinical practice for cardiac disease. These circulating blood cardiac biomarkers provide insight into cardiovascular structure and function, including myocyte injury (cardiac Troponin), myocyte stress (natriuretic peptides), inflammation and fibrosis. Cardiac Troponins and natriuretic peptides have become incorporated into many national and international guidelines, providing advice on their measurement, diagnostic utility, interpretation of results and diagnostic accuracy [56–58]. acute myocardial infarction and heart failure [58]. It is worth noting, however, that circulating plasma levels of natriuretic peptides are influenced by kidney function. As such, diagnostic threshold levels proposed in guidelines for acute myocardial infarction and heart failure may not be appropriate in this specific population [59]. Similarly, for reasons that are not fully understood, patients with ESKD often have higher baseline Troponin levels, which require more cautious interpretation, leading to some suggestions that it is preferable to assess dynamic biomarker results as opposed to set thresholds [60–62].

In the absence of novel biomarkers for CV risk prediction in CKD, clinically utilised cardiac biomarkers such as Troponin T and NTproBNP have been applied to CKD cohorts [63]. Lidgard et al. [64] investigated the superiority of including Troponin T and NTproBNP to Framingham and Pooled Cohort Equation (PCE), proposing that adding Troponin T, but not NTproBNP, improved the prediction of cardiovascular events. Bundy et al. [65] aimed to develop a risk score to predict the 10-year risk of atherosclerotic cardiovascular disease inherent to CKD by adapting the American College of Cardiology/American Heart Association PCE. High-sensitivity C-reactive protein (hs-CRP), Troponin-T, and NT-proBNP were included in the PCE in a cohort of 2604 participants with CKD (average eGFR 56.0) and demonstrated a net reclassification improvement of 10.0% (95% CI, 6.8% to 13.3%) [65].

Utilising biomarkers in combination with other causal CVD risk factors should improve the risk prediction for MACE, including mortality above the currently established standard of care [66]. Presently no validated risk prediction model acknowledges or adjusts for the increased risk of CVD as a consequence of CKD, and more specifically ESKD, utilising biomarkers. There is a significant increase in mortality for incident HD patients, especially within the first six months, and an 80% higher death risk in the first 2 months [67,68]. Recently, Matsushita and colleagues [69] have evidenced that kidney specific variables such as eGFR and proteinuria enhance the PCE's predictive value which highlights the need for CKD to be acknowledged when developing risk prediction models for MACE. A systematic review by Anderson et al. [70] evidenced that multiple studies have validated prognostic risk scores in incident dialysis patients; however, these prognostic indices only use co-morbidity data or adapted current mortality scores such as the Charlson co-morbidity index (CCI) [71] rather than including cardiac biomarkers as additional discriminators. Adopting scoring indices such as CCI (including modified versions), Renal Epidemiology and Information Network (REIN) score [72], and the Kahn–Wright

Index [73] was guarded given the inclusion of multiple variables and risk cut-off values, which led to significant bias and the absence of comprehensive external validation [70]. Floege et al. [74] have developed a mortality risk score, Analysing Data, Recognising Excellence, and Optimising Outcomes cohort score [AROii score] adapted from the Framingham score that utilises routinely collected biochemical parameters such as c-reactive-protein and albumin to predict one- and two-year mortality. In our review, Obokota et al. [37] compared sST2 and Gal-3 to the AROii, where incorporating both novel biomarkers resulted in an increase in predictive accuracy of all-cause mortality compared to the AROii model alone (c-statistic 0.828 vs. 0.79). Further analysis also reported an incremental value of sST2 and Gal-3 over NTproBNP.

Risk prediction utilising cardiac biomarkers has also been demonstrated in population-based studies and non-dialysis CKD. Nowak et al. [75] investigated the role of including kidney biomarkers such as eGFR and urine albumin-to-creatinine ratio (ACR) to the Atherosclerosis Risk in Communities (ARIC) [76] calculator to predict incident heart failure in asymptomatic patients. Samples were analysed from 450,212 participants in the UK Biobank to reflect a broad patient demographic in the primary care setting. The results demonstrated that adding Cystatin C-based eGFR and urine albumin-to-creatinine ratio improved the detection of incident heart failure risk (ΔC = 0.019 [95% CI, 0.015–0.022]) [75]. None of the papers in this review compared their outcome measures with currently validated and utilised CVD prediction scores. Gregg et al. [77], a study of 3218 participants within the population-based Dallas Heart Study, included a CKD and non-CKD cohort to evaluate both BNP and NTproBNP at a threshold of > 75th sex-based percentile to predict all-cause mortality. This study showed all-cause mortality for BNP H.R 2.47 [95% CI, 1.63, 3.75] versus NTproBNP with a H.R of 3.66 [95% CI, 2.28, 5.88].

CKD mineral bone disease (CKD-MBD) is associated with vascular calcification, left ventricular hypertrophy and MACE [78]. Dimkovic et al. [79] analysed 220 prevalent HD patients and applied a Composite calcification Score (CCS) to predict the risk of cardiovascular death. The CCS required X-ray and ultrasound imaging to quantify the degree of calcification. Participants with CCS in the highest quartile cardiovascular death H.R 3.776 [CI 2.063–6.912, *p*-value 0.000] [79]. Given the cost implications of additional imaging modalities to complete the scoring system, utilisation of imaging markers is unlikely to be considered a clinically applicable tool. In this systematic review, two studies utilised imaging alongside biomarkers to form a risk prediction tool. Sun et al. [41] did not evidence an improvement in the prediction of CV outcome by combining echocardiogram measures of left ventricular mass index and flow velocities with Troponin T. Otsuka et al. [38] investigated the combination of abnormal ankle brachial index and Troponin T, concluding that a combination of imaging and blood biomarker was a better predictor of MACE, H.R, 4.42 (95% CI 2.29–8.51; *p*-value < 0.001).

### Limitations

This study presents the data for the most investigated clinically utilised cardia biomarkers (BNP, NTpro BNP and Troponin) as well as potential cardiac biomarkers (sST2, sRAGE, Gal–3). However, we also acknowledged that novel biomarkers may have an emerging role which is a limitation of this paper. Further limitations include the heterogeneity in the study protocols that were compared. While all studies did collect pre-dialysis samples, there was no standard approach to the sample collection process. Moreover, there was variation in the threshold chosen for biomarkers, which was especially noted in NTproBNP and Troponin. This study focused on a specific outcome measure, MACE; however, there was variation in the definition of MACE adopted by each study as the outcome measure. A systematic review by Bosco [80] et al. looked at 58 observational studies with MACE as an outcome measure and found only 8.6% matched the traditional three-point MACE

randomised control trial (RCT) definition of acute myocardial infarction, stroke, or cardiovascular death. The authors reported the commonest MACE component definitions were as follows: AMI, stroke, 15.5% (9/58); AMI, stroke, all-cause mortality, 13.8% (8/58). A further article by Bhatty et al. [81] has also called for standardising composite outcome measures in cardiology to allow the true comparison and interpretation of trial data. In addition, all-cause mortality has been utilised as a composite outcome in some interventional cardiology trials such as the CvLPRIT trial [82]. Further studies should aim to standardise the methodology to enable more accurate comparisons to establish meaningful conclusions from analysed results.

## 5. Conclusions

MACE, including all-cause mortality, is a significant risk in patients with ESKD. This systematic review highlights the potential role of biomarkers to stratify intervention to reduce the CV risk in this cohort. Further discovery science is required to uncover specific cardiovascular biomarkers relevant to this population due to the great unmet need.

**Supplementary Materials:** The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/kidneydial5030039/s1, Table S1: Search strategy; Table S2: Quality assessment of included papers using CASP Cohort Checklist; Table S3: Study inclusion/exclusion criteria, cohort sociodemographic and dialysis data; Table S4: Studies reporting biomarkers unique to one study or biomarkers ratios not included for full data analysis [83–95].

**Author Contributions:** E.M.D.: Writing—original draft, writing—review and editing. M.E.: Conceptualization, interpretation of data, writing—review and editing. A.J.C.: Conceptualization, methodology. L.O.: Conceptualization, methodology. G.M.: Supervision, conceptualization, writing—review and editing. A.R.: Supervision, conceptualization, writing—review and editing. All authors have read and agreed to the published version of the manuscript.

**Funding:** This work was supported by the Wellcome Trust [219574/Z/19/Z]; and the Faculty of Health and Life Sciences, University of Liverpool.

**Informed Consent Statement:** Informed consent was not required for this study as secondary data is reported and analysed.

**Data Availability Statement:** No new data were created or analysed in this study. Data sharing is not applicable to this article.

**Conflicts of Interest:** The authors declare no conflicts of interest.

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