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REVIEW ARTICLE

Biomarkers in predicting mortality in hemodialysis patients: recent advances

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Abstract

Patients undergoing maintenance hemodialysis face annual mortality rates of 15–27%, with cardiovascular causes accounting for more than half of all deaths. Despite advances in dialytic technology, conventional prognostic models derived from the general population systematically underestimate risk in end-stage renal disease, failing to capture the complexity of uremic pathophysiology that drives this excess mortality: immune dysregulation, chronic

inflammation, oxidative stress, vascular calcification, uremic cardiomyopathy, protein-energy wasting, and accelerated vascular aging.

This narrative review synthesizes current evidence on biomarkers predicting all-cause and cardiovascular mortality in haemodialysis patients, spanning established markers (albumin, CRP, ferritin, hemoglobin, high-sensitivity troponins, and NT-proBNP) to an emerging frontier encompassing IL-6, PTX3, sST2, galectin-3, FGF-23, Klotho, and multi-omics signatures. We further examine composite neutrophil-derived indices, adipokines, and mineral metabolism markers as tools for pathway-specific risk interrogation.

The evidence converges on a clear practical message: combination and dynamics outperform single, static measurements. Multi-biomarker models consistently outperform individual markers, and longitudinal trajectories carry prognostic information, with divergence between survivors and non-survivors detectable many months before death, that a single time-point value cannot replicate. Advances in artificial intelligence and multi-omics further support this shift toward dynamic, personalized risk stratification, though these approaches remain at an early, largely exploratory stage. Critically, clinical translation remains limited by the lack of dialysis-specific thresholds, poor standardization, and the absence of randomized evidence demonstrating that biomarker-guided strategies improve outcomes. Bridging this gap between prognostic insight and clinical application remains the central challenge of precision nephrology.

Key words

biomarkers, cardiovascular mortality, hemodialysis, inflammation, multi-omics.

Introduction

The high mortality rate among patients undergoing hemodialysis (HD), largely driven by cardiovascular causes, remains a major challenge in the management of end-stage renal

disease (ESRD). Despite significant progress in dialytic technology and supportive care, the mortality risk in this population is markedly higher than in the general population. This suggests the existence of complex, kidney-specific pathophysiological mechanisms that traditional clinical variables fail to fully explain. In developed counties, annual mortality rates range from 5% to 27%, with a particularly high-risk period immediately following dialysis initiation. During the first three months, mortality can reach 27.5 deaths per 100 person-years, underlining the extreme vulnerability of this early phase [1]. The 5-year survival rate for HD patients remains approximately 40% [2], with cardiovascular disease accounting for more than 50% of deaths [3].

Compared to the general population, HD patients face a dramatically elevated cardiovascular risk, estimated to be 10- to 20-fold higher overall, and potentially exceeding 100-fold in patients under 45. This translates into a drastically reduced life expectancy: patients aged 65–74 on HD have an average survival of approximately five years, roughly half that of age-matched peers in the general population [1]. In the United States, the annual mortality rate for HD patients is approximately 15%, peaking among those over 65 at 615 deaths per 1000 patient-years during the first two months of treatment [4]. Beyond cardiovascular causes, infections represent the second leading cause of mortality, with septicemia rates up to 50 times higher than in the general population.

Cardiovascular risk escalates progressively as kidney function deteriorates in the pre-dialysis chronic kidney disease (CKD) population, doubling at stage 3 and tripling at stage 4 relative to preserved renal function [5]. Importantly, the transition to dialysis introduces a qualitatively distinct risk profile rather than a simple continuation of this trajectory: progressive CKD drives volume overload and pressure stress, culminating in left ventricular hypertrophy, whereas HD sessions superimpose recurrent hemodynamic instability, promoting subendocardial ischemia, myocardial fibrosis, and electrical vulnerability. Sudden

cardiac death accounts for approximately 40% of cardiovascular deaths, far outpacing acute myocardial infarction (AMI) at 18% [4], with dialysis withdrawal contributing an additional and often underrecognized share of overall mortality [6].

Conventional prognostic models derived from the general population (e.g., Framingham Risk Score; Pooled Cohort Equations; Kidney Failure Risk Equation), systematically underestimate risk in ESRD because they fail to account for kidney-specific determinants including uremic toxins, chronic inflammation, oxidative stress, endothelial dysfunction, and mineral metabolism disturbances [7]. This limitation has been formally recognized: the 2024 KDIGO guidelines advocate for models developed specifically in CKD cohorts [8], and data from the CRIC study further confirm that CKD-specific models enriched with biomarkers achieve superior discrimination [9]. Moreover, these conventional models rely largely on static, single time-point variables, fundamentally failing to reflect the dynamic and multifactorial nature of mortality risk in dialysis patients.

In this context, the role of biomarkers has progressively shifted from diagnosis to long-term risk stratification. Multimarker approaches are emerging as essential tools to better characterize uremic mortality: by capturing biological processes not reflected by conventional clinical variables, the biomarkers could improve risk stratification, particularly when integrated into composite models. Evidence from large dialysis cohorts shows that combining inflammatory, nutritional, and cardiorenal markers with traditional risk factors enhances predictive accuracy and discrimination compared with single-marker approaches [10]. However, important challenges remain, including biological variability, dialysis-related fluctuations in biomarker concentrations, and lack of standardized thresholds for clinical use.

Literature was identified through a structured search of PubMed/MEDLINE and Web of Science, covering articles published between January 2010 and March 2026, with deliberate emphasis on evidence from the last five years to reflect the review's focus on recent advances.

Search terms combined "hemodialysis" OR "end-stage renal disease" AND "biomarker" AND "mortality" OR "survival" OR "risk stratification", further refined with pathway-specific terms (e.g., "inflammation", "troponin", "NT-proBNP", "FGF-23", "multi-omics", "machine learning"). Reference lists and recent systematic reviews/meta-analyses were screened to identify additional relevant studies (snowball search). Priority was given to meta-analyses, large multicentre prospective cohorts, and guideline statements (e.g., KDIGO); single-centre or mechanistic studies were included selectively to illustrate specific pathophysiological pathways. A small number of older landmark publications were retained for historical and conceptual relevance. As a narrative rather than systematic review, no formal PRISMA-based screening or quality scoring was performed; selection reflects the authors' clinical and methodological judgment.

The central question this review seeks to address is not merely which biomarkers associate with mortality, but whether and how this prognostic data can responsibly inform clinical decision-making in the absence, to date, of interventional evidence that biomarker-guided management improves outcomes. Figure 1 provides a schematic overview of the conceptual framework guiding this review, summarizing the clinical problem, the major biomarker pathways discussed, the key findings, and their current clinical implications.

Pathophysiology of mortality in hemodialysis patients

Mortality in HD patients arises from interconnected pathophysiological processes driving both cardiovascular and non-cardiovascular death. Uremia induces a paradoxical immune state combining activation and suppression. On one hand, monocyte and neutrophil priming drive cytokine overproduction, promoting inflammation and oxidative stress. On the other hand, immune suppression increases susceptibility to infection and malignancy through T-cell exhaustion, B-cell lymphopenia, and impaired phagocytic function, and reduced vaccine

responsiveness [11]; this duality helps explain why both mortality categories remain elevated during the first three years of dialysis.

Persistent systemic inflammation is a defining feature of the uremic milieu and a robust predictor of all-cause and cardiovascular mortality [12]. Its origins are multifactorial: uremic toxin accumulation, gut dysbiosis with bacterial translocation, leukocyte activation driven by dialysis membrane bioincompatibility, and unremitting immune stimulation [13]. The central pro-inflammatory cytokines (IL-6, TNF-α, and IL-10) converge on endothelial dysfunction, protein-energy wasting (PEW), and accelerated atherosclerosis [14], with C-reactive protein (CRP), ferritin, Pentraxin-3 (PTX3), and procalcitonin serving as principal measurable correlates alongside inversely trending albumin [15]. Closely intertwined is oxidative stress, which intensifies with renal function decline and dialysis itself: uremic toxins impair nitric oxide (NO) bioavailability and drive cardiac remodeling, processes reflected in malondialdehyde, F2-isoprostanes, and advanced oxidation protein products [16].

The gut–kidney axis constitutes a further distinct contributor, with ESRD dysbiosis expanding toxin-generating species whose products (e.g. indoxyl sulfate, p-cresyl sulfate, and TMAO) drive vascular calcification, endothelial dysfunction, and renal fibrosis [17], a causal relationship underscored by murine microbiota transplantation experiments [18].

Vascular calcification, present in up to 79% of CKD stages 3–5 patients, is an actively regulated process: hyperphosphatemia induces osteogenic trans-differentiation of vascular smooth muscle cells through BMP2 and RUNX2 signaling, while deficiency of fetuin-A, carboxylated MGP, and vitamin K removes the physiological brake on mineralization [19,20]. The overall calcification burden can be tracked through FGF-23, serum phosphate, PTH, fetuin-A, and the T50 serum calcification propensity test.

Beyond calcification, Klotho deficiency drives premature arterial stiffness, producing an accelerated vascular aging phenotype. Aortic pulse wave velocity, emerges as a powerful

independent predictor of both all-cause and cardiovascular mortality [21]. At the cardiac level, uremic cardiomyopathy, present in the larger majority of dialysis patients, encompasses left ventricular hypertrophy, myocardial fibrosis, and diastolic dysfunction [22,23]. This vulnerability is amplified in patients with coexisting diabetes, where pro-fibrotic and pro-inflammatory mediators correlate with myocardial involvement even at early stages of diabetic cardiomyopathy [24]. HD sessions superimpose dramatic hemodynamic swings that produce repetitive subendocardial ischemia and myocardial stunning [4], and the temporal clustering of sudden cardiac death on Mondays and Tuesdays following the two-day interdialytic interval implicates electrolyte and volume fluctuations as proximate triggers [25]. High-sensitivity troponins, NT-proBNP, FGF-23, sST2, and galectin-3 reflect the breadth of myocardial stress in this population.

The cumulative effect of uremic toxins, inflammation, and restrictive diets converges on PEW and sarcopenia [26], both highly prevalent in this population, while frailty substantially increases mortality and the combined risk of death and hospitalization by 60% [27]. Beyond conventional anthropometry, body composition parameters add prognostic information: a high ECW/ICW ratio combined with a low simplified creatinine index identifies a particularly high-risk sarcopenic phenotype. Notably, higher mid-arm circumference and body fat are associated with reduced mortality risk, consistent with the so-called obesity paradox and the broader phenomenon of reverse epidemiology observed in HD cohort [28]. This nutritional dimension is captured by albumin, prealbumin, body-surface-normalized creatinine, and the Prognostic Nutritional Index.

Finally, anemia, driven by reduced erythropoietin synthesis, hepcidin-mediated iron dysregulation, and uremic inhibition of erythropoiesis, independently worsens morbidity and mortality rates [29]. Importantly, erythropoiesis-stimulating agent (ESA)–driven normalization of hemoglobin confers no survival benefit and may increase cardiovascular

risk, so anemia management should be approached as careful titration rather than normalization [30,31]. Hemoglobin, ferritin, transferrin saturation, and reticulocyte count constitute the monitoring toolkit for this pathway. To integrate these interconnected mechanisms into a clinically applicable framework, Table 1 summarizes the major pathophysiological pathways and their associated prognostic biomarkers in HD patients, while Table 2 maps the biomarkers with the most mature evidence onto monitoring frequency and management guidance.

Traditional biomarkers: established associations and inherent limitations

Serum albumin, CRP, ferritin, and hemoglobin constitute the backbone of routine risk stratification in HD patients, as they are widely available, inexpensive, and embedded in monitoring protocols (Table 2). Their clinical utility, however, is fundamentally constrained by low pathophysiological specificity and susceptibility to multiple confounding influences.

Serum albumin is the most extensively studied traditional biomarker in this population. Low levels are associated with markedly increased mortality [32], and in an early landmark analysis, albumin proved to be a 21-fold stronger predictor of death than the urea reduction ratio (Table 1) [33]. Critically, as a negative acute-phase reactant, albumin decreases in response to systemic inflammation independently of nutritional status, and its association with mortality is attenuated in patients with normal CRP levels, suggesting that hypoalbuminemia primarily reflects inflammatory burden rather than nutritional depletion, and therefore inflammatory status should be taken into account when interpreting albumin [15]. A declining trajectory in the pre-ESRD period also carries adverse prognostic significance for post-ESRD survival, independent of the absolute value reached [34].

CRP independently predicts all-cause and cardiovascular mortality in general population [35], and persistently elevated levels carry an almost threefold mortality excess in HD population compared with stably low values [36]. When added to conventional risk factors, CRP

meaningfully improves mortality prediction, with performance comparable to albumin and superior to ferritin or leukocyte count [10]. Nevertheless, it exhibits substantial intra-individual variability driven by intercurrent clinical events and provides no information on which specific inflammatory pathway is activated.

Ferritin occupies a particularly ambiguous position. Elevated levels associate with increased cerebrocardiovascular disease, infection, and death, while very low levels signal iron deficiency (Table 1) [37]. The PIVOTAL trial demonstrated that a proactive iron supplementation strategy reduced major cardiovascular events versus a reactive approach, reinforcing the clinical relevance of iron status as an actionable target [38]. Yet ferritin is also a positive acute-phase reactant that rises with inflammation and iron overload irrespective of true iron stores, and transferrin saturation ≤20% combined with ferritin identifies at-risk patients more reliably than ferritin alone.

Hemoglobin shows a non-linear relationship with mortality: levels below 10 g/dL increase risk, while ESA-driven normalization above 13 g/dL confers no benefit and may increase cardiovascular risk [31]. Beyond absolute levels, hemoglobin variability over time is itself an independent adverse prognostic factor, with wide fluctuations conferring significantly higher risks of cerebrocardiovascular events, infections, and hospitalization [39].

Taken together, none of these markers possesses pathophysiological specificity, as each being shaped by multiple overlapping processes that cannot be disentangled from a single measurement. Mutual confounding is pervasive, albumin suppressed by inflammation, ferritin elevated by both inflammation and iron overload, hemoglobin modulated by ESA therapy, and even composite models incorporating all four markers only achieve an integrated AUC of 0.74 for all-cause mortality [10]. These limitations have driven the search for novel biomarkers capable of capturing specific pathophysiological pathways with greater precision.

Emerging biomarkers: towards pathophysiological precision

The limitations of traditional markers have catalyzed an active search for biomarkers capable of interrogating specific disease pathways. By targeting discrete biological processes, including myocardial stress, vascular calcification, immune dysfunction, and metabolic disturbances, these biomarkers enable more detailed and potentially actionable risk stratification in HD patients.

Inflammatory biomarkers Among inflammatory mediators, IL-6 stands out as the most powerful predictor of mortality in HD patients [40], carrying considerably greater predictive power than CRP albumin, and TNF-α in multivariable models [41]. Inflammatory burden is, moreover, cumulative: patients with multiple simultaneously elevated inflammatory markers face a 3.05-fold greater mortality risk than those without measurable inflammation [42]. Myeloperoxidase and resistin, markers of neutrophil degranulation, independently predict all-cause and cardiovascular mortality after adjustment for traditional risk factors and nutritional indices in 1,182 patients. MPO correlates significantly with CRP, IL-6, TNF-α, and leukocyte count, suggesting a mechanistic role at the intersection of leukocyte activation and oxidative stress [43].

PTX3, produced locally by neutrophils and endothelial cells, reflects tissue-level inflammation and endothelial dysfunction rather than the hepatic acute-phase response captured by CRP. It is markedly elevated in HD patients versus non-dialysis CKD and rises further during dialysis sessions, emerging as the sole independent predictor of all-cause mortality in models adjusted for classical inflammatory markers [44], while additionally predicting arteriovenous fistula patency loss, cardiovascular, infectious, and all-cause mortality [45]. PCSK9 has recently attracted attention as a cardiovascular risk marker in this population, displays a U-shaped relationship of mortality [46] and an excess risk of

cardiovascular events at the highest levels, an effect that appears particularly pronounced in women (Table 1) [47].

Beyond classical inflammatory markers, emerging neutrophil-based composite indices have demonstrated superior or complementary predictive capacity. The neutrophil percentage-to-albumin ratio, a novel composite reflecting both immune activation and nutritional-inflammatory status, shows strong associations with all-cause and cardiovascular mortality in large HD cohort [48]. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), together with the systemic immune-inflammation index (SII) are similarly derived from routine complete blood count and carry meaningful prognostic value at essentially no additional cost, while the CRP-to-albumin ratio emerging as an independent predictor explaining considerable outcome variation [49]. The soluble urokinase-type plasminogen activator receptor (suPAR), a marker of chronic immune activation, independently predicts ESRD progression at higher circulating levels [50]. Soluble TNF receptors (TNFR) represent an emerging dimension of the inflammatory pathway in HD patients: both TNFR1 and TNFR2 independently predicted all-cause mortality, while only TNFR1 retains significance for cardiovascular mortality, suggesting differential pathway specificity between the two receptors (Table 1) [51].

Cardiac biomarkers Given that cardiovascular disease accounts for the majority of deaths in HD patients, cardiac biomarkers occupy a central role in risk stratification.

High-sensitivity cardiac troponins (hs-cTn) are chronically elevated in CKD even without acute coronary syndromes, reflecting ongoing subclinical myocardial injury: a large proportion of ambulatory CKD patients without known cardiovascular disease exceed conventional hs-cTnT thresholds, requiring CKD-specific reference ranges substantially higher than those used in the general population (Table 2) [52]. Whether these specific reference ranges, derived in pre-dialysis CKD, apply unchanged to the HD population

remains incompletely defined and warrants caution in direct extrapolation Despite this baseline elevation, hs-cTn retain strong prognostic value, with both hs-cTnT[53] and hs-cTnI independently predicting long-term all-cause and cardiovascular mortality in multivariable models [54].

NT-proBNP is a powerful predictor of incident heart failure (HF) and mortality, with patients in the highest quintile (>433 pg/mL) facing a 9.57-fold greater risk in the CRIC study [55], providing greater prognostic added value over traditional risk factors than either cTnT or hs-CRP among incident HD patients[56], suggesting the marker retains prognostic relevance across the CKD-to-dialysis continuum, although the evidence bases derive from distinct populations and are not directly comparable in magnitude. Its CKD-specific 99th percentile reaches 3,592 pg/mL and increases by ~40% for every 15 mL/min/1.73m² decrease in eGFR [57]. Moreover, combining NT-proBNP and hs-cTnT with renal biomarkers provides the highest prognostic accuracy for ESRD [52,57].

Soluble ST2 acts as a decoy receptor for IL-33, blocking its cardioprotective signaling and promoting myocardial fibrosis; it provides independent and incremental prognostic value beyond NT-proBNP, identifying a particularly high-risk subgroup at elevated levels [58]. Galectin-3 promotes fibroblast proliferation and collagen deposition and independently predicts all-cause mortality, significantly improving risk reclassification when added to NT-proBNP-based models. GDF-15, a TGF-β superfamily member rising with cellular stress and tissue injury, associates strongly with mortality and shows further elevation during HD sessions, positioning it as a marker of acute dialysis-induced stress [58].

Nutritional and metabolic biomarkers Prealbumin (transthyretin), with a markedly short half-life than albumin, is theoretically more responsive to acute nutritional changes but shares albumin's inflammatory susceptibility [59]. Low levels predict increased mortality even in normoalbuminemic patients, and a decline trajectory over time independently predicts death

[60], though KDOQI guidelines caution against interpretation in isolation from inflammatory context [59]. Leptin and adiponectin, adipokines with opposing cardiovascular effects, have been reported in some studies to display a paradoxical pattern in HD patients, whereby a higher leptin-to-adiponectin ratio is associated with lower mortality, extending the obesity paradox to the adipokine level, however these findings are not consistent across all studies. In parallel, low leptin and high adiponectin levels have been associated with PEW [61]. Glycated albumin reflects glycemic control over 2–3 weeks, without the confounding effects of anemia or ESA therapy that reduce HbA1c reliability in dialysis patients, though its accuracy is limited by hypoalbuminemia [62]. Novel composite nutritional indices integrate multiple pathophysiological dimensions simultaneously and have demonstrated superior prognostic performance: the CRP-albumin-lymphocyte (CALLY) index, merging inflammatory, nutritional, and immune parameters, was independently associated with all-cause mortality (Table 1) [63]. Carbonyl proteins also bear direct nutritional relevance, remaining independent predictors of mortality in multivariate analysis, with consistently higher concentrations among non-survivors [64].

Mineral metabolism and vascular calcification biomarkers Fibroblast Growth Factor 23 (FGF-23) rises earlier in CKD than phosphorus, calcium, or PTH making it among the first detectable signals of mineral metabolism disruption, with a pooled analysis confirming higher all-cause and cardiovascular mortality at higher levels (Table 1) [65]. Trajectory analyses from the CRIC study, conducted in a non-dialysis CKD population, identified three distinct FGF-23 patterns, with rapidly rising trajectories conferring a 15.23-fold greater mortality risk versus stable trajectories [66]. However, in a separate analysis of prevalent HD patients from the DOPPS cohort, this association was attenuated with increasing dialysis vintage, suggesting that long-term dialysis survivors may be less susceptible to its deleterious effects [67]. Klotho, the renal anti-aging protein that co-receptors FGF-23, declines progressively

with renal function loss, but its prognostic role remains contested: the CRIC study found no significant associations with mortality or cardiovascular events, and FGF-23 retains its mortality association independently of Klotho levels [68,69]. Among bone-derived markers, osteopontin (OPN) associates with increased risks of kidney failure and all-cause mortality [70,71] with an estimated 31% of renal failure events over six years attributable to elevated OPN [72], while osteoprotegerin predicts cardiovascular but not all-cause mortality (HR 2.53) [65]. The T50 serum calcification propensity test provides an integrative measure of the net calcification balance: in a prospective HD cohort, patients who died had significantly lower T50 values at baseline, and cross-validated models confirmed T50 as a linear predictor of all-cause mortality, positioning it as a potentially global calcification marker compared with any single mineral metabolism parameter [73].

Multi-omics and artificial intelligence approaches The frontier of risk stratification in dialysis patients increasingly lies at the intersection of omics technologies and machine learning. Metabolomic profiling has identified distinctive signatures across CKD stages and in response to dialysis, with TMAO, kynurenine, and citrulline as leading candidates among a broad panels of circulating metabolites [74]. At the proteomics level, the CKD273 classifier, a urinary panel of 273 peptides including type-1 collagen fragments and uromodulin, represents the most clinically advanced proteomic tool for CKD progression prediction [75], while circulating microRNAs are under active investigation as both diagnostic biomarkers and therapeutic targets [76]. Machine learning models have achieved strong discriminative performance for both short- and longer-term mortality prediction [77], with SHAP (SHapley Additive exPlanations) analysis enabling interpretable attribution of variable contributions, identifying dialysis duration, creatinine, leukocyte count, phosphorus, and iron as key predictors [78]. An innovative trajectory-based approach, modeling compliance with dialysis quality indicators, achieved 92% accuracy using an ExtraTrees model, subsequently deployed

as a web-based clinical tool [79]. Federated learning frameworks enabling multi-center collaboration without individual data sharing represent a promising research direction, although these approaches remain at an early, largely exploratory stage, have not yet undergone robust external validation or prospectively tested for implementation in routine clinical practice.

Dynamic and longitudinal biomarkers: predict the decline before it becomes evident

Growing evidence challenges the conventional reliance on single biomarker measurements: intra-individual variability and longitudinal trajectories carry prognostic information that point-in-time assessments fundamentally cannot capture. Increasing variability across multiple biological parameters reflects a deterioration in the organism's regulatory capacity, a signature of physiological frailty rather than any single deranged value. In a HD cohort, principal component analysis of variability across a panel of routine blood parameters yielded a first component independently predicting frailty. Critical transition theory applied to long-term HD data provides additional mechanistic support: in a cohort of chronically hemodialyzed patients monitored with multiple biomarkers collected biweekly, synchronized variability generated powerful mortality predictions, with biomarker variability beginning increasing markedly in the months prior to death [80]. The concept of Moving Multivariate Distance, which quantifies shifts in the multivariate biomarker profile between consecutive visits, shows a marked increase prior to death (Table 1) [81].

Longitudinal trajectory analyses reveal that the divergence between survivors and non-survivors begins far earlier than any clinical event would suggest. In a multinational study of over 52 000 HD patients, albumin, interdialytic weight gain, and systolic blood pressure began declining more than a year before death in non-survivors while remaining stable in survivors, with CRP rising sharply only in the terminal period, patterns invisible to any baseline measurement. Joint models integrating longitudinal trajectories and Cox survival

models consistently outperform conventional approaches in mortality prediction. Multivariate joint models incorporating inter-biomarker relationships achieve the highest accuracy, with serum albumin as a key predictor, and robust versions accounting for outliers and competing risks show superior discriminative accuracy up to 5 years when tested separately in peritoneal dialysis and HD cohorts, two modalities with distinct uremic exposure and residual renal function profiles, such that performance in one should not be assumed to generalize automatically to the other[82]. Longitudinal monitoring can thus identify patients entering a phase of accelerating risk before overt decompensation, with joint models producing dynamic predictions that update with each new measurement and align naturally with the repeated-assessment structure of the dialysis setting.

Multi-biomarker approaches and risk scores

The pathophysiological complexity of mortality in HD patients makes it inherently unlikely that any single biomarker can adequately capture overall risk. The evidence increasingly converges on composite multi-biomarker models as the most effective prognostic strategy. In a ten-year prospective study, a composite score integrating hs-cTnT, BNP, and CRP stratified patients into low-, intermediate-, and high-risk group with markedly divergent survival, with substantially higher mortality in the high-risk. In a large multicentre cohort, the combination of albumin, CRP, leukocyte count, and ferritin with conventional risk factors achieved the highest predictive power [10], while a large-scale proteomic three-protein model (SVEP1, R-spondin 4, and tetranectin), outperformed the conventional clinical model for mortality prediction [83]. Moreover, frailty assessments integrated with molecular biomarkers demonstrate particular prognostic synergy: in a prospective study, myostatin, IGF-1, and DHEA-S individually predicted 5-year mortality; combining the Fried frailty score with any single biomarker significantly improved prediction [84]. This approach highlights the

importance of integrating physical assessment with molecular biomarkers for enhanced prognostication.

Among the more extensively studied composite tools, the AROii score was developed specifically in an incident European HD cohort and subsequently externally validated in a prevalent HD populations (DOPPS), a cross-population validation that strengthens generalizability but also means its discriminative performance may not be uniform across the incident-to-prevalent spectrum [85]. The Survival Index, validated on DOPPS data, demonstrated superior accuracy over albumin alone, with the lowest-score group facing a markedly elevated mortality risk (HR 7.97) [86]. Despite this evidence, translation to clinical practice remains severely limited. A systematic review of predictive models found that only 3 of 17 had undergone external validation and only 1 was rated at low risk of bias [87], while methodological heterogeneity (*e.g.* divergent outcome definitions, incomplete model reporting, non-comparable statistical approaches) makes replication essentially impossible [88], consistent with the population-specific caveats discussed throughout this review. The optimal biomarker combination also differs between HD and peritoneal dialysis, limiting cross-modality transferability. Most critically, no novel biomarker has demonstrated that its clinical integration actually improves patient outcomes in randomized trials, and whether these markers are modifiable through intervention remains unknown [89]. The increasing complexity and interconnection of these biomarker domains is summarized in a unified conceptual framework presented in Figure 2.

Clinical applicability: can we actually use these biomarkers?

The substantial body of prognostic evidence contrasts with the limited clinical adoption of these biomarkers, reflecting not only logistical constraints but also unresolved challenges related to interpretability, standardization, and therapeutic impact. The most consequential obstacle is the absence of dialysis-specific decision thresholds. Reference limits for cardiac

biomarkers were derived from populations without CKD, yet reduced renal clearance substantially elevates circulating concentrations independently of cardiac pathology. As noted above, hs-cTnT and NT-proBNP necessitate CKD-specific reference ranges. GFR-specific thresholds significantly improve risk reclassification but have not been incorporated into clinical guidelines. A further interpretive challenge is the 9.9% post-dialysis decline in hs-cTnT due to hemodilution, below the 20% delta conventionally used to diagnose AMI, creating diagnostic ambiguity precisely where clarity is most needed [90].

Most emerging biomarkers — IL-6, PTX3, sST2, galectin-3, FGF-23 and Klotho — remain unavailable in routine laboratories, requiring specialized immunoassay platforms at substantially higher cost. Inter-laboratory standardization is an additional critical weakness: different analytical platforms and calibrators yield non-comparable results for the same biomarker, rendering universal cutoffs and cross-centre comparisons effectively meaningless. Emerging biosensor technologies based on electrochemical, optical, impedimetric, and nanophotonic principles offer the prospect of continuous or minimally invasive monitoring of parameters such as potassium, phosphorus, PTH, β2-microglobulin, and creatinine, but biofouling, calibration drift, and workflow integration remain unsolved challenges [91].

Among currently available markers, NT-proBNP and hs-cTn are the most widely accessible and familiar to clinicians; however, “readiness” here reflects assay availability rather than demonstrated impact on clinical decision-making, and their interpretation still requires CKD-specific thresholds and careful consideration of volume status.

Beyond these practical barriers, the underlying evidence base itself warrants caution. Most studies reviewed are observational, predominantly single-centre cohorts, while randomized controlled trials remain confined almost exclusively to anemia and iron management [30,38]. This imbalance matters because observational associations between biomarkers and mortality are vulnerable to confounding and reverse causation: low albumin, elevated IL-6, and rising

ferritin may as plausibly reflect advancing comorbidity, frailty, or subclinical illness as causally contribute to death, and adjustment for inflammatory or nutritional status does not fully resolve this ambiguity [15]. Heterogeneity further complicates synthesis: cutoffs, assay platforms and populations vary considerably across studies, limiting the generalizability, and outcome definitions are similarly inconsistent. Finally, publication bias likely inflates the apparent prognostic value of novel biomarkers, as positive single-centre findings are more readily published than null results, and few markers discussed here have undergone independent external validation. These considerations do not negate the biological plausibility, but argue for caution in interpreting effect sizes and cutoffs as generalizable values rather than population- and context-specific estimates.

A related limitation is that much of the cited evidence pools, or fails to distinguish, CKD, incident HD, and prevalent HD populations, despite their differing uremic exposure, dialysis vintage, and dominant causes of death. Associations established in non-dialysis CKD cohorts should not be assumed to transfer unchanged to the HD population, and associations in incident HD patients, where early hemodynamic instability and catheter-related complications dominate mortality, may differ from prevalent patients with longer cumulative uremic and inflammatory exposure. Where possible we have specified the source population; where studies do not stratify by dialysis status, this should be regarded as an additional source of heterogeneity.

The most fundamental limitation, however, is evidential. No novel biomarker has demonstrated that its integration into clinical decision-making actually improves patient outcomes. Whether the biological signals these markers capture are modifiable through intervention, and whether targeting them translates into survival benefit, remains unanswered. Until randomized evidence establishes that biomarker-guided management reduces mortality, their role will remain confined to prognostic stratification rather than therapeutic guidance.

Future perspectives

The directions outlined below are largely derived from retrospective, single-cohort, or proof-of-concept studies; while conceptually compelling, most have not yet undergone prospective, multi-centre validation or demonstrated an effect on patient outcomes, and they should be interpreted as exploratory rather than imminently practice-changing. Risk stratification in HD is evolving towards a precision medicine framework integrating AI, multi-omics, and continuous monitoring, moving beyond from static disease snapshots toward dynamic, individualized biological portraits. Machine learning algorithms have shown superior discriminative performance compared with conventional statistical models in several retrospective predictive tasks: AI applications span hypotension prediction, mortality risk, anemia management, and vascular access monitoring [92]. Model interpretability tools, including SHAP, are essential for translating algorithmic outputs into clinically meaningful insights [78]. At the biological level, initiatives such as the Kidney Precision Medicine Project aim to define molecular disease subtypes through integrated multi-omic biopsy analysis and deep clinical phenotyping [93]. Unsupervised approaches have already identified distinct molecular CKD classes with markedly different progression risks. In parallel, genetic and transcriptomic studies are revealing regulatory variants influencing inflammatory pathways, suggesting future integration of genotype-informed biomarker panels [94,95]. Wearable technologies extend this paradigm to continuous physiological monitoring, including thoracic bioimpedance-based fluid assessment and emerging cutaneous sensors for volume status [96]. Future systems (e.g. Body Area Networks) are expected to integrate multimodal data streams into real-time predictive networks [97]. Challenges related to calibration, privacy, and data integration remain substantial, and whether continuous, personalized monitoring will translate into improved clinical outcomes remains to be demonstrated.

Conclusions

Mortality in HD patients remains high, with annual rates exceeding 15–20% and cardiovascular causes predominating, while conventional risk models systematically underestimate risk in this population. Three conclusions emerge from the evidence reviewed, alongside one overarching caveat. No single biomarker is sufficient: the concurrent pathophysiological complexity of kidney failure cannot be captured by any individual marker, whether traditional or emerging. The future lies in combination and dynamics: multi-biomarker models consistently outperform single markers, and longitudinal trajectories carry prognostic information, with divergence between survivors and non-survivors detectable many months before death, that static measurements cannot replicate. Digital integration is a plausible future direction: the convergence of AI, multi-omics, and continuous monitoring may eventually create the infrastructure for personalized, continuously updated risk stratification, though this remains contingent on prospective validation. Critically, none of the approaches reviewed here has yet been shown in a randomized or interventional study to improve outcomes when used to guide clinical management; until such evidence emerges, their role remains prognostic rather than actionable.

The central obstacle remains the absence of interventional evidence. Bridging the gap between biomarker discovery and clinical implementation will require large-scale multicenter prospective studies with standardized protocols, external validation across diverse populations, and randomized trials demonstrating that biomarker-guided management translates into measurable improvements in survival. Only then will these markers fulfil their potential not merely as prognostic tools, but as guides for therapeutic decisions that meaningfully alter the course of disease in one of medicine's most vulnerable populations.

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Conflict of interest LL is co-inventor on the International Patent (WO/2020/226993), filed in April 2020, relating to the use of antibodies which specifically bind IL-1α to reduce various sequelae of ischemia–reperfusion injury to the central nervous system. LL has received speaker fees outside of this work from Daichi-Sankyo. MF and CF have received funding from the Italian Ministry of Health. The other authors have no conflicts of interest or financial relationships to disclose.

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Table 1 Pathophysiological pathways and prognostic biomarkers in hemodialysis patients

Pathway	**Biomarker(s)**	**Prognostic cutoff**	**Prognostic value**	**Notes / source**	**Ref.**
Chronic Inflammation	IL-6	>13.9 pg/mL	RR 5.20 all-cause mortality; ~2× stronger than CRP	Most powerful inflammatory predictor	[40-42]
	CRP / hs-CRP	>12.8 mg/L	HR 1.63 all-cause; HR 1.11 CV; NRI 12.8% vs conv. factors	Rising trajectory: HR 2.79–3.13	[35-36]
	NPAR (neutrophil-to-albumin ratio)	Elevated (highest quartile)	HR 3.73 all-cause; HR 2.38 CV mortality (n = 10,067)	Novel; superior to classic CRP in composite performance	[48]
	NLR / PLR / MLR / SII	High	MLR: NPV 83.9%; SII independently linked to CV disease	Derived from routine CBC; low cost	[49]

	Albumin	<3.5 g/dL (optimal 3.4)	OR 2.34–3.13; 21× stronger predictor than URR	Negative acute-phase reactant; interpret with CRP	[32-34]
	PTX3	Elevated vs CKD non-dialysis	Sole independent predictor of all-cause mortality in adjusted models	Reflects tissue/endothelial inflammation, not hepatic	[44-45]
	PCSK9	U-shaped (highest tertile)	HR 1.97 composite death; HR 2.31 CV events	Women: doubling CV risk at highest levels	[46-47]
Oxidative Stress	Carbonyl proteins	>117.85 ng/mL	Independent predictor; lower in survivors (105 vs 130 ng/mL)	Strongest oxidative marker in head-to-head comparison	[64]
	MDA, AOPP, F2-isoprostanes	Not standardized	Associated with endothelial dysfunction & cardiac remodeling	Mechanistic markers; no standard clinical cutoffs	[16]

Gut–Kidney Axis / Uremic Toxins	TMAO	Elevated	Associated with vascular calcification and CV mortality	Causal evidence from murine transplantation studies	[17-18]
	Indoxyl sulfate / p-cresyl sulfate	Elevated	Promotes VSMC osteogenic trans-differentiation, renal fibrosis	Expanded by ESRD dysbiosis	[17-18]
	KIM-1	<82.98 pg/mL (low = worse)	50.73% mortality at 48 months in low-KIM-1 group	Correlates with CRP, IL-6, anemia markers	[98]
	suPAR	>3904 pg/mL (top tertile)	HR 1.53 for ESRD progression; glomerulonephritis HR 1.61	Marker of immune activation; predicts ESRD transition	[50]
Vascular Calcification & CKD-MBD	FGF-23	Highest vs lowest tertile	HR pooled 1.94 all-cause; 2.40 CV; rising trajectory HR 15.23	Rises before phosphate/PTH; attenuates with dialysis vintage	[65-67]

	Phosphate	>5.5 mg/dL	HR 1.2 all-cause mortality	Coupled with BMP2/RUNX2 signaling	[19]
	PTH	>600 pg/mL	HR 3.46 mortality	CKD-MBD pathway	[65]
	Klotho	Deficient	Contested: CRIC found no independent mortality link	FGF-23 retains significance independently of Klotho	[68-69]
	T50 serum calcification test	Lower = worse (269.6 vs 287.7 min)	Independent linear predictor of all-cause mortality (sHR/min: 0.9957)	Tested in 776 HD pts, 8 Spanish centers, 2-yr follow-up	[73]
	Fetuin-A / dp-ucMGP / OPN / OPG	Low fetuin-A; OPG elevated	OPG: HR 2.53 (pooled) for CV mortality OPN: estimated 31% of renal failure events over six years	Physiological brakes on mineralization	[19,70.72]
Arterial Stiffness	Pulse wave velocity	Elevated	Strong independent predictor of all-	Klotho deficiency →	[21]

			cause and CV mortality	accelerated vascular aging	
Cardiac Dysfunction	hs-cTnT	≥102 ng/L; CKD 99th%ile: 126 ng/L	HR 3.34 long-term mortality; 40–88% exceed conventional threshold	CKD-specific ranges mandatory; 9.9% post-dialysis drop	[52-54]
	NT-proBNP	>433 pg/mL; 99th %ile: 3592 pg/mL	HR 9.57 incident HF; C-stat 0.834 with hsCRP+β2-microglobulin	+40% per 15 mL/min eGFR decrement; best combined predictor	[55-57]
	sST2 (soluble)	Log(sST2) elevated; >32 ng/mL	HR 2.89 CV events; multiv. HR 2.78 (>32 ng/mL)	Decoy for IL-33; promotes myocardial fibrosis	[58]
	Galectin-3	Elevated	Independently predicts all-cause mortality; improves NRI vs NT-proBNP alone	Fibroblast activation, collagen deposition	[58]
	GDF-15	Elevated; rises during	Associated with mortality and	TGF-β superfamily;	[58]

		HD sessions	dialysis-induced stress	cellular stress marker	
	MOTS-c (mitochondrial peptide)	Elevated at composite endpoint	AUC 0.743; C-index 0.700; NRI 15.87% (n = 94)	Emerging; improves discrimination over age/LVM/diastolic dysfunction models	[99]
	LA/LV strain (echocardiographic)	LA reservoir strain HR 0.90; LVGLS HR 1.21	C-index 0.79 vs 0.70 clinical model	Superior to conventional CV risk factors for MACE	[100]
	TNFR1 / TNFR2	Elevated (top vs bottom)	TNFR1 HR 2.34 all-cause; HR 2.15 CV mortality (n = 319, 53 mo)	Soluble TNF receptors; stronger than TNF-α itself	[51]
Protein–Energy Wasting & Nutrition	Prealbumin	<20 mg/dL; decline ≥10 mg/dL/6mo	Predicts mortality even in	Half-life 2–3 d vs albumin 20 d; interpret with CRP	[59-60]

			normoalbuminemic patients		
	Leptin/adiponectin ratio	Higher ratio → lower mortality	HR 0.14 (higher ratio)	Obesity paradox at adipokine level	[61]
	Glycated albumin	Elevated in poor glycemic control	Superior to HbA1c in diabetic HD patients	No ESA/anemia confounding; 2–3 week window	[62]
	CALLY index (CRP-albumin-lymphocyte)	Composite	AUC 0.821 (95% CI 0.778–0.861) for all-cause mortality (n = 436)	Integrates inflammation + nutrition + immunity	[63]
Frailty & Sarcopenia	Myostatin / IGF-1 / DHEA-S	AUC 0.72–0.73 individually	Combined with Fried frailty score AUC 0.79 (5-yr mortality)	Physical + molecular integration; strong prognostic synergy	[84]
	Simplified creatinine index	<20.4 mg/kg/day	HR 2.25; combined ECW/ICW HR 12.22	Sarcopenia proxy	[28]

	ECW/ICW ratio	>0.57	HR 3.66 mortality; HR 12.22 if also low creatinine index	Fluid distribution marker; strong in combination	[28]
Anemia	Hemoglobin	Target 10–11.5 g/dL (no normalization)	HR 0.66 all-cause; diabetic subgroup non-significant	Non-linear; normalization increases CV risk	[39]
	Ferritin / TSAT	Ferritin >500 ng/mL; TSAT ≤20%	Proactive iron strategy reduced MACE (PIVOTAL trial)	Positive acute-phase reactant; interpret with TSAT	[37-38]
	RDW	>14.9% with declining trajectory	Higher mortality vs stable/increasing RDW (n = 326, 2.7 yr)	Simple CBC marker; progressive rise predicts CV events	[39]
Dynamic / Longitudinal	Moving Multivariate Distance (MMD)	97.5th vs 2.5th percentile	HR 21.1; rises sharply before death (n = 763)	Mahalanobis distance across multi-marker profiles	[81]

Biomarkers	Multi-marker variability PCA	1st PC of 20-parameter variability	OR 2.31/SD for frailty; C-stat 0.85 (n = 580)	Synchronized variability: HR95=9.7; AUC 0.82; begins 3 mo before death	[80]
	NT-proBNP trajectory	>232 pg/mL rise/2yr	HR 1.79 incident HF; HR 2.32 atrial fibrillation	Dynamic monitoring in CRIC study	[57]
Genetic & Molecular	IL-6 polymorphism rs1800795	CC genotype	Higher mortality risk; highest hsCRP in deceased	Modulates inflammatory response in ESRD	[94]
	PTX3 polymorphism rs2305619	Risk genotype	Associated with inflammatory response in ESRD	Candidate for personalized biomarker profiling	[94]
	lncRNA ENST00000561762	Expression in PBMCs	Correlates with LVEF; predicts HFrEF in HD patients	1,429 differentially expressed lncRNAs identified	[95]

Omics & AI	CKD273 urinary proteomics	273-peptide panel	Most clinically advanced proteomic tool for CKD progression	Collagen fragments + uromodulin; validated in CKD	[75]
	TMAO / kynurenine / citrulline metabolomics	Panels of up to 278 metabolites	Distinctive CKD-stage and dialysis-response signatures	Metabolomic candidates for precision stratification	[74]
	microRNA	Circulating levels	Under investigation as diagnostic + therapeutic targets	Multi-omic integration frontier	[76]
	ML models (XGBoost, RNN-autoencoder)	Feature importance: creatinine, age, albumin	AUC 0.979 (1-yr); AUC 0.8357 RNN-autoencoder (n = 3,284)	SHAP enables interpretability; federated learning for scale	[77]

This table provides a structured overview of the major pathophysiological pathways involved in mortality among hemodialysis patients and links each pathway to its corresponding prognostic biomarkers. For each biological axis, key circulating or functional markers are reported, along with available prognostic thresholds and their associated clinical significance for cardiovascular and all-cause mortality. The aim is to

integrate the complex and overlapping mechanisms of uremic disease into a single clinically oriented framework. Rather than representing isolated variables, the table highlights how different biomarkers converge on shared pathological processes, thereby facilitating a more unified interpretation of risk stratification in this population.

Table 2 Practice-oriented summary: what to measure, in whom, how often, and management implications

Biomarker	**In whom / when**	**Frequency**	**Key threshold(s) and action if abnormal**	**Evidence basis**	**Ref.**
Albumin	All HD patients	Monthly	<3.5 g/dL: check CRP before attributing to malnutrition; consider dietitian referral; not a standalone intervention trigger	Cohort data; KDOQI	[33,34]
CRP / hs-CRP	All HD patients, esp. if albumin low	With albumin, or if clinically suspected inflammation	Persistent elevation: investigate occult infection (access/dental/GI); reinterpret albumin/ferritin accordingly	Cohort data; pragmatic, no RCT trigger	[35,36]
Hemoglobin	All HD patients	Monthly	Target 10–11.5 g/dL; avoid >13 g/dL. ESA titration toward target,	KDIGO anemia guideline	[39]

			not normalization; investigate cause if highly variable rather than reflex up-titration		
Ferritin + TSAT	All HD patients	Every 1–3 months	Ferritin >500 ng/mL with TSAT ≤20%: proactive IV iron (PIVOTAL protocol); avoid further iron if ferritin >800 ng/mL without TSAT-confirmed need	PIVOTAL RCT; KDIGO	[37-38]
PTH	All HD patients	Every 1–3 months	>600 pg/mL: adjust CKD-MBD therapy (vitamin D analogues/calcimimetics) per local protocol	KDIGO CKD-MBD framework	[65]
hs-cTn (T/I)	Suspected ACS; selected high-risk risk-stratification	Not established for routine serial use	CKD-specific 99th percentile substantially higher than general population. Use CKD-specific thresholds; account	Cohort/consensus; no interventional trial	[52-54]

			for post-dialysis hemodilution; never rule in/out ACS on a single value alone		
NT-proBNP	Suspected heart failure; research-grade stratification	Not established for routine serial use	eGFR-adjusted thresholds; rising trajectory over time is prognostic but has no validated management trigger	Cohort/trajectory data only	[55-57]
IL-6, sST2, galectin-3, FGF-23, PCSK9, composite AI/multi-omics scores	Not currently recommended outside research settings	Not established	Strong prognostic associations (Table 1) but no validated clinical cutoff; no demonstrated change in management; investigational/risk-stratification use only	Cohort data; no outcome trial	[40-42,46-47,58,65–67,75–77]
Practice-oriented summary of biomarkers with the most mature evidence base, organized around the clinical question of what to measure, in which patients, at what frequency, and what management implication, if any, follows from an abnormal result. Markers without an established monitoring frequency or validated management pathway are listed separately to					

make explicit that, despite strong prognostic associations, no validated clinical cutoff or demonstrated change in management currently exists for these markers.

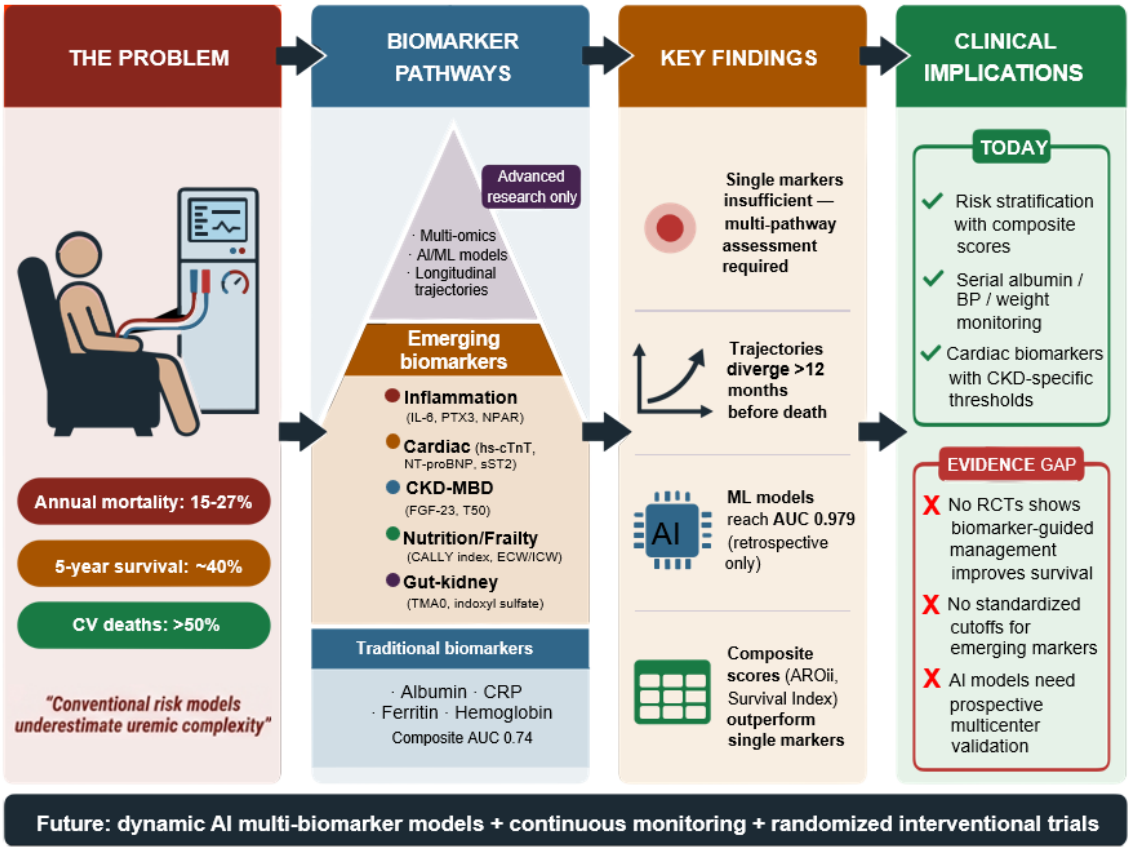

Figure 1 Graphical summary of biomarkers for mortality prediction in haemodialysis (HD) patients. HD is associated with high mortality and poor long-term survival, while conventional risk models underestimate its complexity. Biomarkers are organized from established markers to pathway-specific and research-level approaches (multi-omics and AI models). Key findings indicate that single biomarkers are insufficient, longitudinal trajectories improve risk discrimination, and composite scores outperform individual markers, while AI models show high retrospective performance but lack prospective validation. Clinically, current use is limited to composite scores and selected serial biomarkers, with major gaps including the absence of randomized controlled trials demonstrating outcome benefit, lack of

standardized cut-offs, and insufficient external validation of advanced models. Future directions involve dynamic multi-biomarker AI systems validated through prospective trials.

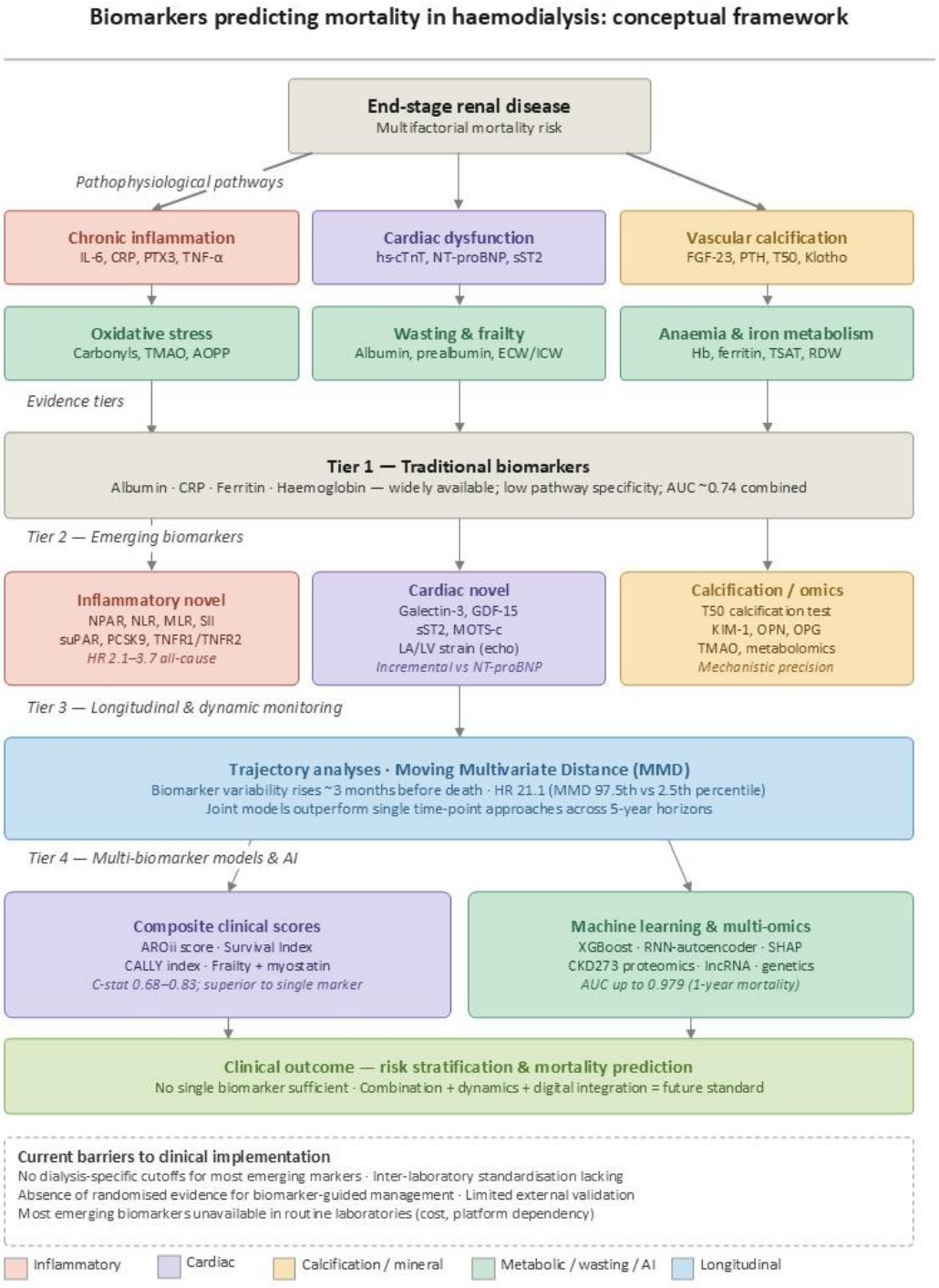

Figure 2 Conceptual framework of biomarker-based mortality prediction in hemodialysis patients

The figure integrates the major pathophysiological pathways contributing to excess mortality in end-stage renal disease, including chronic inflammation, cardiac dysfunction, vascular calcification, oxidative stress, wasting and frailty, and anemia with iron dysregulation. These biological domains are linked to a hierarchical biomarker structure spanning four levels: (i) traditional biomarkers widely used in clinical practice), (ii) emerging pathway-specific biomarkers targeting inflammatory, cardiac, and mineral metabolism processes, (iii) longitudinal and dynamic approaches based on biomarker trajectories and intra-individual variability, and (iv) multi-biomarker models and artificial intelligence approaches, including machine learning, multi-omics, and composite clinical scores. The framework highlights the progressive transition from single-marker assessment to integrated, dynamic, and computational risk stratification models. Barriers to clinical implementation include lack of standardization, absence of dialysis-specific thresholds, and limited interventional evidence.