Peripheral Blood Elements as Prognostic Biomarkers for Mortality in Hemodialysis Populations

Zienab Fathy Ahmed Yousef[1], Essam Elden Mahmoud Lotfy Omar [2], Khaled Mohamed Talaat Mohamed [3], George Emad Shaker[4]

1. Resident Nephrologist in 6th October Health Insurance Hospital,
2. Professor of Internal Medicine, Faculty of Medicine - Zagazig University,
3. Professor of Internal Medicine, Faculty of Medicine - Zagazig University,
4. Professor of Internal Medicine, Faculty of Medicine - Zagazig University

Corresponding Author: Zienab Fathy Ahmed Yousef

Received: 28 October 2024, **Accepted:** 17 November 2024, **Published:** 20 November 2024

Abstract

Background: Patients undergoing maintenance hemodialysis (HD) experience persistently high morbidity and mortality rates despite advances in renal replacement therapy. Cardiovascular disease, infection, chronic inflammation, malnutrition, and immune dysregulation are major contributors to adverse outcomes in this population. There is increasing interest in identifying simple, cost-effective, and routinely available biomarkers that can aid in early risk stratification and prognostication. Peripheral blood elements, including red blood cell indices, leukocyte subtypes, platelet parameters, and derived inflammatory ratios, are universally measured in HD patients and reflect underlying inflammatory, nutritional, and hematologic disturbances. Emerging evidence suggests that these parameters may provide valuable prognostic information beyond traditional clinical risk factors.

Aim: This review aims to comprehensively evaluate the prognostic value of peripheral blood elements and derived hematologic indices in predicting all-cause and cardiovascular mortality among patients receiving maintenance hemodialysis. We focus on established and emerging markers, including hemoglobin levels, red cell distribution width, white blood cell count and differentials, platelet count and volume, and composite inflammatory ratios such as neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio. Additionally, we explore the biological mechanisms linking these hematologic abnormalities to adverse outcomes and discuss their potential role in clinical risk stratification.

Conclusion: Accumulating evidence indicates that routine peripheral blood parameters are independently associated with mortality risk in hemodialysis populations. Many of these biomarkers reflect the complex interplay between chronic inflammation, malnutrition, oxidative stress, anemia, and immune dysfunction that characterizes end-stage kidney disease. Their widespread availability, low cost, and reproducibility make them attractive tools for longitudinal monitoring and prognostic assessment. However, heterogeneity in study designs, cut-off values, and confounding variables limits their immediate translation into standardized clinical practice. Future prospective studies and integrative risk models are needed to validate these markers, define clinically meaningful thresholds, and determine whether interventions guided by hematologic indices can improve patient outcomes. Incorporating peripheral blood elements into multidimensional prognostic frameworks may enhance personalized care and risk stratification in hemodialysis patients.

Keywords: *Peripheral Blood Elements, Prognostic Biomarkers, Hemodialysis*

Introduction

Patients with end-stage kidney disease (ESKD) receiving maintenance hemodialysis (HD) continue to experience unacceptably high mortality rates, despite significant advances in dialysis technology and supportive care. Annual mortality among HD patients remains several-fold higher than in the general population, with cardiovascular disease and infections accounting for the majority of deaths, followed by malignancy and other non-cardiovascular causes [1]. This excess risk reflects the complex pathophysiological milieu of ESKD, characterized by chronic inflammation, oxidative stress, immune dysfunction, protein–energy wasting, anemia, and accelerated atherosclerosis, all of which interact to worsen clinical outcomes [2].

Risk stratification in HD populations is central to improving outcomes, guiding therapeutic interventions, and optimizing resource allocation. Traditional prognostic factors such as age, dialysis vintage, diabetes, cardiovascular comorbidity, serum albumin, and markers of mineral bone disease provide important information but remain insufficient to fully capture individual mortality risk [3]. Consequently, there is growing interest in identifying additional biomarkers that are objective, reproducible, inexpensive, and routinely available in clinical practice.

Peripheral blood elements fulfill many of these criteria and are universally measured in HD patients as part of standard care. Red blood cell parameters, including hemoglobin concentration and red cell distribution width (RDW), reflect anemia management, erythropoiesis, inflammation, and nutritional status. White blood cell counts and differentials provide insight into immune activation and chronic inflammatory burden, while platelet indices are increasingly recognized as markers of inflammation, thrombosis, and endothelial dysfunction [4,5]. Moreover, derived hematologic ratios such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) integrate multiple immune pathways and have emerged as promising prognostic indicators in various chronic diseases, including chronic kidney disease and dialysis populations [6].

From a mechanistic standpoint, abnormalities in peripheral blood parameters are not merely epiphenomena but may actively participate in disease progression. Chronic low-grade inflammation and uremic toxin accumulation disrupt erythropoiesis, alter leukocyte function, and promote platelet activation, thereby contributing to cardiovascular events, infection susceptibility, and mortality [7]. These hematologic changes may therefore serve as accessible surrogates of the underlying biological processes driving adverse outcomes in HD patients.

Despite a rapidly expanding body of observational evidence, the clinical application of peripheral blood elements as prognostic biomarkers in HD remains inconsistent. Studies vary widely in design, populations, statistical adjustment, and proposed cut-off values, and there is no unified framework integrating these parameters into routine prognostic models [8]. This heterogeneity has limited their translation from research findings to bedside decision-making.

Aim and Research Gap

The aim of this review is to critically synthesize current evidence on the prognostic value of peripheral blood elements and derived hematologic indices in predicting mortality among hemodialysis populations. By integrating mechanistic insights with clinical data, this review seeks to clarify which blood-based markers have the strongest and most consistent associations with outcomes, identify gaps in existing research, and highlight areas where future prospective studies and interventional trials are needed to support their incorporation into clinical practice.

Pathophysiological Basis Linking Peripheral Blood Abnormalities to Mortality in Hemodialysis

Chronic inflammation is a central and unifying pathophysiological feature of end-stage kidney disease (ESKD) and is strongly implicated in the excess mortality observed among hemodialysis (HD) patients. Persistent exposure to uremic toxins, bioincompatible dialysis membranes, recurrent vascular access infections, endotoxemia, and oxidative stress drives a state of low-grade systemic inflammation. This

inflammatory milieu directly alters peripheral blood elements, including leukocyte activation, impaired lymphocyte function, disordered erythropoiesis, and platelet hyperreactivity. Numerous studies have demonstrated that elevated inflammatory markers correlate with adverse outcomes in HD patients, underscoring the biological plausibility of hematologic indices as prognostic biomarkers [9].

Anemia is one of the most prevalent hematologic abnormalities in HD and reflects a multifactorial process involving erythropoietin deficiency, iron dysregulation, inflammation-mediated erythropoietin resistance, and reduced red blood cell survival. Beyond low hemoglobin levels, qualitative alterations in erythrocytes—captured by indices such as red cell distribution width (RDW)—have gained increasing attention. RDW reflects anisocytosis and is influenced by inflammation, malnutrition, oxidative stress, and bone marrow dysfunction. These same processes are independently associated with cardiovascular disease and mortality in HD patients, suggesting that abnormal red blood cell indices may act as integrative markers of systemic disease burden rather than isolated hematologic abnormalities [10].

Immune dysregulation in HD patients is characterized by a paradoxical coexistence of immune activation and immune deficiency. Neutrophils often exhibit enhanced activation and oxidative burst capacity, while lymphocyte apoptosis and impaired adaptive immunity are common. This imbalance contributes to increased susceptibility to infections and impaired immune surveillance, both of which are major contributors to mortality. Peripheral leukocyte counts and differentials therefore reflect not only inflammatory activity but also immune competence. Elevated total white blood cell count and neutrophilia have been associated with increased cardiovascular and all-cause mortality, whereas lymphopenia has been linked to poor nutritional status and adverse outcomes in HD populations [11].

Platelets play an increasingly recognized role at the intersection of inflammation, thrombosis, and atherosclerosis in ESKD. Uremia induces platelet activation and alters platelet size and function, contributing to both bleeding and thrombotic complications. Platelet indices such as mean platelet volume (MPV) and platelet count are influenced by inflammatory cytokines and bone marrow response and have been associated with cardiovascular events and mortality in dialysis patients. Activated platelets also interact with leukocytes and endothelial cells, amplifying inflammatory and prothrombotic pathways that are central to cardiovascular morbidity in HD [12].

Importantly, derived hematologic ratios such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) integrate multiple aspects of immune activation and suppression into single, easily obtainable metrics. These composite markers may better reflect the global inflammatory and immunologic state than individual cell counts alone. Mechanistically, elevated NLR and PLR signify heightened innate immune activation coupled with impaired adaptive immunity, a pattern consistently associated with adverse outcomes in chronic inflammatory conditions, including ESKD [13].

Collectively, the pathophysiological alterations affecting peripheral blood elements in HD patients are closely linked to the same biological processes—chronic inflammation, oxidative stress, immune dysfunction, malnutrition, and endothelial injury—that drive cardiovascular disease, infection, and mortality. This strong mechanistic foundation supports the growing interest in peripheral blood parameters as prognostic biomarkers and provides a rationale for their evaluation in risk stratification models for HD populations [14].

Red Blood Cell Parameters and Mortality in Hemodialysis

Anemia is a near-universal complication in patients receiving maintenance hemodialysis (HD) and remains a central therapeutic focus in nephrology practice. Reduced erythropoietin production, iron deficiency (absolute and functional), shortened red blood cell lifespan, and inflammation-driven erythropoietin resistance all contribute to anemia in end-stage kidney disease (ESKD). Numerous large observational studies have demonstrated a strong association between low hemoglobin levels and increased all-cause and cardiovascular mortality in HD patients, particularly at the extremes of anemia severity [15]. Although anemia management with erythropoiesis-stimulating agents (ESAs) has improved quality of life and reduced transfusion requirements, hemoglobin concentration alone incompletely captures mortality risk.

Beyond absolute hemoglobin levels, variability in hemoglobin over time has emerged as an important prognostic marker. Fluctuations in hemoglobin reflect unstable erythropoiesis, inflammation, iron dysregulation, and inconsistent ESA responsiveness. Several cohort studies have shown that greater hemoglobin variability is independently associated with higher mortality, even after adjustment for mean hemoglobin levels and comorbidities. This suggests that dynamic instability in red blood cell production may be more deleterious than stable, moderately reduced hemoglobin concentrations [16].

Red cell distribution width (RDW), a measure of variability in erythrocyte size, has gained increasing attention as a powerful and independent predictor of mortality in HD populations. RDW is influenced by multiple pathological processes prevalent in ESKD, including chronic inflammation, oxidative stress, malnutrition, iron deficiency, and impaired bone marrow response. Large-scale observational studies have consistently demonstrated that elevated RDW is strongly associated with all-cause and cardiovascular mortality in HD patients, independent of hemoglobin, iron parameters, and inflammatory markers [17]. Importantly, RDW appears to integrate information from multiple biological pathways, making it a particularly robust prognostic biomarker.

The prognostic value of RDW extends beyond baseline measurements. Longitudinal increases in RDW over time have been associated with progressively higher mortality risk, suggesting that worsening anisocytosis may reflect deteriorating systemic health. Unlike hemoglobin, RDW is not a direct target of therapy, which may reduce confounding by treatment effects and enhance its value as a risk stratification tool in observational studies [18]. This characteristic makes RDW especially attractive for prognostic modeling in HD populations.

Iron metabolism abnormalities further complicate the interpretation of red blood cell parameters in HD patients. Functional iron deficiency driven by inflammation-induced hepcidin elevation leads to impaired iron utilization despite adequate or elevated iron stores. This state contributes to ESA hyporesponsiveness, persistent anemia, and increased RDW. Studies have demonstrated that markers of ESA resistance, including higher ESA dose requirements relative to hemoglobin response, are independently associated with increased mortality, reinforcing the link between disordered erythropoiesis and adverse outcomes [19].

Collectively, red blood cell parameters provide valuable prognostic information that extends well beyond traditional hemoglobin targets. Hemoglobin variability, RDW, and ESA responsiveness reflect the cumulative burden of inflammation, nutritional status, iron dysregulation, and bone marrow dysfunction in HD patients. Integrating these parameters into clinical assessment may enhance mortality risk stratification and identify high-risk patients who could benefit from closer monitoring and individualized management strategies [20].

White Blood Cell Count, Differentials, and Inflammatory Ratios

Total white blood cell (WBC) count is one of the most accessible biomarkers in routine care, yet in hemodialysis (HD) it carries prognostic information even when values fall within the “normal” laboratory range. Inflammation is highly prevalent in end-stage kidney disease (ESKD), and mild leukocytosis may represent ongoing exposure to uremic toxins, vascular access inflammation, recurrent micro-infections, endotoxemia, and oxidative stress. Observational studies in maintenance HD populations have shown that higher WBC counts—sometimes still within the reference range—are associated with increased long-term mortality, reinforcing that “normal” values do not necessarily imply low risk in dialysis patients [21]. This aligns with the broader concept that low-grade chronic inflammation in HD is clinically meaningful and often underrecognized if interpreted using general-population reference ranges [21].

Differential leukocyte patterns add a deeper layer of risk stratification beyond total WBC count. In a landmark analysis from a large HD cohort, higher neutrophil counts and lower lymphocyte counts were independently associated with increased mortality risk, even after accounting for confounding clinical variables. Importantly, these leukocyte patterns strongly tracked with surrogates of malnutrition and inflammation, supporting their role as integrative markers of the “malnutrition–inflammation complex”

in dialysis [22]. From an internal medicine perspective, neutrophilia often signals innate immune activation and inflammatory stress, while lymphopenia reflects impaired adaptive immunity, poor nutritional reserve, and systemic catabolism—an especially lethal combination in HD patients [22].

Lymphocyte metrics—particularly lymphocyte percentage—have also been repeatedly linked to adverse outcomes. Earlier cohort data demonstrated that a low lymphocyte percentage predicted both mortality and hospitalization among maintenance HD patients and appeared to function as a sensitive marker of nutritional and anti-inflammatory status [23]. Mechanistically, lymphopenia in dialysis is not simply a passive laboratory finding; it may reflect increased lymphocyte apoptosis and uremia-associated immune dysfunction, which plausibly contributes to the high burden of infection-related mortality and poor vaccine responsiveness observed in ESKD populations [24]. Clinically, persistently low lymphocyte indices should therefore prompt a broader assessment for protein–energy wasting, chronic inflammation, occult infection, and inadequate dialysis or access complications [23,24].

Composite inflammatory ratios derived from differential counts—particularly the neutrophil-to-lymphocyte ratio (NLR)—have emerged as pragmatic markers of risk because they integrate two biologically distinct immune axes in a single metric. Multiple cohort studies have identified NLR as a robust predictor of all-cause mortality in incident and prevalent HD patients, independent of traditional risk factors and, in some analyses, beyond standard inflammatory markers [25]. The prognostic logic is biologically coherent: elevated NLR reflects heightened innate immune activation (neutrophil predominance) coupled with relative suppression or depletion of adaptive immunity (lymphopenia), capturing the "inflammation + immune impairment" phenotype typical of high-risk HD patients [25].

Other ratios, especially the platelet-to-lymphocyte ratio (PLR), may further refine prognostication by incorporating platelet-mediated inflammation and thrombosis. In prevalent HD cohorts, PLR has been associated with all-cause mortality and, in some studies, cardiovascular mortality; notably, one study suggested PLR may outperform NLR for mortality prediction in HD, potentially reflecting the central role of platelet activation in endothelial dysfunction and atherothrombosis in uremia [26]. That said, the relative performance of NLR versus PLR varies across cohorts due to differences in populations, dialysis vintage, comorbidity burden, competing risks, and statistical adjustment—highlighting the need for standardized cutoffs, repeated-measure approaches, and integration into validated multivariable risk models rather than reliance on single baseline measurements [25,26].

Platelet Parameters (Count, MPV, PDW) and Mortality in Hemodialysis

Platelets are increasingly recognized as active participants in the "inflammation–thrombosis–endothelial dysfunction" axis that drives cardiovascular events and mortality in end-stage kidney disease (ESKD). Chronic kidney disease is associated with altered platelet activity and signaling, with a paradoxical phenotype of both bleeding tendency and prothrombotic risk depending on the clinical context, comorbidity burden, and exposure to extracorporeal circuits. Reviews of platelet biology in CKD highlight that uremic milieu and vascular inflammation can promote platelet activation and contribute to heightened cardiovascular risk, providing strong biological plausibility for platelet indices as prognostic biomarkers in dialysis populations [27].

Platelet count itself appears to have a non-linear relationship with outcomes in hemodialysis (HD). A large contemporary analysis reported a **U-shaped association**, where both low and high platelet counts were independently linked to increased risks of all-cause and cardiovascular mortality, even after multivariable adjustment. This is clinically intuitive: thrombocytopenia may reflect inflammation, infection, bone marrow suppression, liver disease, or consumptive processes, whereas thrombocytosis may indicate inflammatory activation and heightened thrombotic propensity [28]. In practice, platelet count is attractive as a prognostic signal because it is universally available and easily tracked over time, but interpretation requires careful clinical correlation to avoid over-attribution to a single pathologic pathway [28].

Thrombocytopenia deserves special attention in HD populations because it is common, multifactorial, and sometimes iatrogenic. A multicenter analysis of Chinese HD patients found that thrombocytopenia

was associated with higher all-cause mortality, supporting platelet depletion as a marker of vulnerability in dialysis. Causes may include inflammation-related consumption, chronic viral infections, hypersplenism, bone marrow dysfunction, and dialysis-related platelet activation; importantly, anticoagulation exposure also makes **heparin-induced thrombocytopenia (HIT)** a critical diagnosis not to miss, given its high thrombotic risk and management implications [29,30]. From an internal medicine perspective, low platelets in HD should trigger a structured evaluation (trend pattern, access thrombosis, new thrombosis/skin necrosis, timing relative to heparin, infection markers, liver/spleen assessment) rather than being dismissed as "uremia-related" [29,30].

Beyond platelet count, **platelet size indices** may better reflect platelet activation biology. **Mean platelet volume (MPV)** has been studied as a marker of platelet reactivity, with larger platelets generally considered more metabolically and prothrombotically active. In a national incident HD cohort, higher MPV was associated with increased mortality risk, supporting the concept that platelet activation states—captured by routine indices—carry prognostic information beyond conventional risk factors [31]. Mechanistically, chronic endothelial dysfunction and inflammatory signaling in CKD create a milieu favoring platelet activation and platelet–leukocyte interactions, which plausibly links higher MPV to cardiovascular events and death in dialysis populations [27,31].

Platelet distribution width (PDW) is another platelet morphology index reflecting heterogeneity in platelet size and, indirectly, activation and turnover. In HD cohorts, higher baseline PDW has been independently associated with increased all-cause and cardiovascular mortality, suggesting PDW may capture a platelet activation phenotype relevant to atherothrombosis and systemic inflammation in ESKD [32]. A practical advantage of PDW is that it is often reported automatically with complete blood counts, enabling low-cost longitudinal monitoring. However, PDW is sensitive to pre-analytical factors and analyzer variability, so its clinical use requires awareness of laboratory standardization and preference for within-lab serial comparisons rather than single absolute cutoffs across different centers [32].

Finally, platelet indices often perform best when interpreted as part of **composite immune–platelet biomarkers**, particularly the platelet-to-lymphocyte ratio (PLR). PLR integrates platelet activation/inflammation with adaptive immune suppression (lymphopenia), both of which are common in HD and mechanistically linked to mortality. Cohort data indicate PLR is associated with all-cause (and in some studies cardiovascular) mortality in maintenance HD, and one classic study suggested PLR may outperform NLR for mortality prediction—highlighting the potential relevance of platelet-mediated pathways in ESKD outcomes [33,34]. Overall, platelet parameters (count, MPV, PDW) and platelet-derived ratios appear promising for risk stratification, but the field still needs harmonized cutoffs, repeated-measure modeling, and validation within multivariable prognostic tools before routine implementation as decision triggers in clinical pathways [31-34].

Single peripheral blood parameters (e.g., RDW, NLR, platelet count) are often statistically significant predictors of mortality in hemodialysis (HD), but their **clinical utility increases when interpreted in integrated frameworks** that reflect the multidimensional biology of end-stage kidney disease (ESKD). The HD phenotype that drives poor outcomes is rarely explained by one pathway; rather, it is a convergent state involving inflammation, immune dysfunction, malnutrition/protein–energy wasting, anemia biology, and thrombosis risk. The **malnutrition–inflammation complex syndrome (MICS)** concept is particularly relevant here, because it describes how chronic inflammation and nutritional depletion co-evolve, worsen cardiovascular risk, and increase hospitalization and mortality in dialysis patients [35]. This creates a strong rationale for multimarker approaches that combine hematologic indices with established inflammatory–nutritional constructs instead of relying on isolated CBC variables [35].

A classic example of an integrated clinical-biological framework is the **Malnutrition-Inflammation Score (MIS)**, which was developed to quantify the malnutrition–inflammation burden and has been shown to correlate strongly with morbidity and mortality in maintenance HD populations [36]. MIS is

not a "blood-only" score, but it provides a clinically validated anchor for interpreting CBC-derived markers: lymphopenia, elevated neutrophils, high RDW, and platelet abnormalities often track with the same inflammatory–nutritional derangements captured by MIS. In practice, combining CBC markers (particularly NLR and RDW) with MIS or albumin-based risk assessment can help distinguish patients with transient abnormalities from those with sustained systemic deterioration who need intensified evaluation for inflammation sources, access problems, underdialysis, and protein–energy wasting [36].

Within CBC-derived composites, **inflammatory ratios** have been among the most studied for integration into risk stratification models. A systematic review focusing on HD populations concluded that **NLR is strongly associated with mortality**, supporting its role as a low-cost biomarker suitable for risk enrichment and longitudinal surveillance [37]. However, risk prediction improves when NLR is used alongside other "orthogonal" measures (e.g., RDW or platelet indices) because NLR captures immune balance, while RDW captures erythropoiesis integrity and systemic stress biology. This multimarker logic aligns with contemporary prognostic modeling, where combining markers from distinct physiological domains often improves discrimination and calibration compared with any single marker alone [37].

Several studies have explored **combined or hybrid CBC indices** that incorporate multiple cell lines into a single prognostic signal. For example, work in HD populations has examined combinations involving NLR and red cell/platelet-derived measures (such as RDW-based ratios) to predict cardiovascular outcomes, reinforcing the concept that **simultaneous immune activation and disordered erythrocyte/platelet biology** identifies a particularly high-risk phenotype [38]. While many of these studies focus on cardiovascular endpoints rather than mortality alone, cardiovascular events are a dominant pathway to death in HD, making these multimarker composites clinically relevant as upstream risk indicators [38].

An underappreciated issue is that CBC biomarkers are **dynamic**, and their prognostic meaning often depends on persistence, trajectory, and context. Many associations are stronger when modeled as **time-varying or repeated-measure exposures** rather than single baseline values. For example, RDW has been shown to predict mortality robustly in HD cohorts, and its prognostic value is biologically plausible as a cumulative marker integrating inflammation, malnutrition, oxidative stress, and impaired erythropoiesis [39]. In clinical practice, this supports an approach where clinicians track *trends* (e.g., rising RDW, rising NLR, falling lymphocyte count, drifting platelet count toward extremes) and interpret them in conjunction with clinical events (access infection, hospitalization, ESA hyporesponsiveness) rather than reacting to isolated measurements [39].

Finally, integrating platelet indices into multimarker models may refine cardiovascular and mortality risk estimation. Recent evidence indicates a **U-shaped association between platelet count and both all-cause and cardiovascular mortality** in HD, emphasizing that both thrombocytopenia and thrombocytosis can signal danger—albeit through different biological mechanisms (consumption/infection/marrow suppression vs inflammatory activation/thrombosis propensity) [40]. When platelet count (or MPV/PDW where available) is interpreted alongside NLR and RDW, clinicians can better triangulate whether risk is dominated by inflammation/immune imbalance, erythropoiesis failure/systemic stress, or platelet-driven thrombo-inflammatory pathways—helping prioritize investigations and interventions [40].

Practical Clinical Use of RDW, PDW, and NLR in Mortality Risk Stratification (Hemodialysis)

RDW (red cell distribution width) is one of the most consistently replicated CBC-derived predictors of mortality in maintenance hemodialysis (HD). In a large HD cohort analysis, higher RDW showed a graded, independent association with mortality and in some analyses demonstrated stronger prognostic performance than traditional anemia-related labs, suggesting RDW acts as an integrated "stress biomarker" reflecting inflammation, malnutrition, oxidative stress, iron dysregulation, and impaired erythropoiesis rather than anemia severity alone. Clinically, RDW is most useful when interpreted longitudinally: a persistently high RDW or a rising RDW trend over months should prompt evaluation

for chronic inflammation sources (access-related issues, occult infection), protein–energy wasting, iron handling problems, and ESA hyporesponsiveness rather than reflexive anemia-only interventions. Importantly, RDW can remain elevated despite acceptable hemoglobin, so it may identify "hidden risk" among patients who look stable by hemoglobin targets alone. [41]

How to operationalize RDW at the bedside: avoid rigid universal cutoffs and prioritize (1) *trajectory* and (2) *context*. A practical approach is to flag patients who move upward across their lab's distribution (e.g., from mid-range to persistently high RDW) and integrate that with albumin, CRP (if available), interdialytic weight gain, access events, hospitalization, and ESA dose escalation. Confounders to account for include recent transfusion, acute bleeding, major changes in iron therapy, hemolysis, and concurrent hematologic disease—each can distort RDW's meaning. Still, because RDW is inexpensive and ubiquitous, it is a strong candidate for routine "risk enrichment" lists in dialysis units, especially when combined with immune markers (e.g., NLR) to identify patients with simultaneous dysregulated erythropoiesis and inflammation. [41]

PDW (platelet distribution width) reflects heterogeneity in platelet size and is often interpreted as a surrogate of platelet activation and turnover—processes that are highly relevant in uremia where thrombo-inflammation and endothelial dysfunction drive cardiovascular events. In chronic HD cohorts, higher PDW has been associated with increased all-cause and cardiovascular mortality, supporting its use as a platelet-based prognostic biomarker. PDW's bedside strength is that it can capture a "platelet activation phenotype" even when the platelet count is not dramatically abnormal, which may be helpful because platelet count alone can be influenced by many competing etiologies. However, PDW is sensitive to pre-analytical variation (timing to analysis, EDTA effects) and analyzer differences, so serial within-lab trends are more reliable than comparing absolute PDW values across centers. [42]

How to operationalize PDW: use PDW to *contextualize cardiovascular and inflammatory risk*, not as a stand-alone trigger. A high or rising PDW should raise suspicion for active thrombo-inflammatory biology (e.g., access inflammation, systemic inflammation, atherosclerotic instability) and can justify closer surveillance for ischemic symptoms, access dysfunction, and inflammatory drivers. Interpretation must account for platelet count extremes, active infection, liver disease, malignancy, and medication effects (antiplatelets), all of which can change platelet indices. PDW becomes more clinically actionable when paired with NLR (immune axis) and RDW (erythropoiesis/systemic stress axis), because concordant abnormalities across these three markers typically indicate a more global and persistent pathobiological risk state rather than a transient lab fluctuation. [42]

NLR (neutrophil-to-lymphocyte ratio) is a simple integrated marker of innate immune activation (neutrophils) and adaptive immune suppression or nutritional/inflammatory stress (lymphopenia). In HD cohorts, elevated NLR has been associated with higher cardiovascular and all-cause mortality, even after adjustment for common confounders, supporting its use as a pragmatic inflammation–immune balance biomarker. From an internal medicine perspective, NLR is particularly appealing in HD because infection and cardiovascular disease are the two dominant mortality pathways, and NLR biologically tracks with both (immune dysregulation and vascular inflammation). Clinically, NLR interpretation should emphasize persistence and upward drift rather than a single value, since acute intercurrent infection, steroid exposure, or hospitalization can transiently inflate NLR. [43]

Evidence synthesis and practical thresholds: meta-analytic work in HD populations supports the association between higher NLR and increased all-cause and cardiovascular mortality, but studies differ in the cutoffs used (often cohort-derived) and in adjustment strategies, which limits immediate universal threshold adoption. A pragmatic clinical strategy is to treat NLR as a "risk flag" when it is persistently elevated relative to the patient's baseline and the dialysis unit's distribution, especially when accompanied by rising RDW and/or high PDW—an alignment that strongly suggests chronic inflammation with immune dysfunction and systemic stress. Operationally, this triad can be embedded into monthly review: (1) confirm no acute transient driver, (2) screen for access infection/stenosis and underdialysis, (3) reassess nutrition/protein intake and inflammation markers, and (4) reconsider

cardiovascular risk surveillance and volume management intensity. [44,45]

Evidence Synthesis and How to Apply RDW, PDW, and NLR in HD Mortality Risk Workflows

RDW—strength of evidence and interpretation. Among CBC-derived markers in hemodialysis, RDW has one of the strongest and most replicated associations with mortality. A large observational study by Vashistha et al. reported a graded relationship between higher RDW and higher mortality risk in HD, and importantly suggested RDW may outperform traditional anemia markers as a mortality predictor—supporting RDW as an integrative biomarker of illness burden rather than a simple anemia metric [1]. Smaller cohort studies in maintenance HD similarly report worse survival in patients with higher RDW, reinforcing consistency across settings and populations [2,3]. Clinically, RDW becomes most meaningful when interpreted as a **persistent phenotype** (chronically high) or a **trajectory phenotype** (rising over time), which is more likely to reflect progressive inflammation/malnutrition/iron restriction than a transient perturbation [1-3].

RDW—what it "means" biologically in dialysis patients. RDW reflects heterogeneity of RBC size (anisocytosis), but in HD it also functions as a surrogate for intertwined processes: inflammation-driven iron sequestration, oxidative stress and RBC membrane injury, reduced RBC lifespan, nutritional deficiency, and bone marrow stress. These processes are common in ESKD and track with the same pathways that drive cardiovascular events and infection-related mortality, which helps explain why RDW remains predictive even after adjustment for hemoglobin and comorbidity in several studies [1-3]. A practical nephrology takeaway is that **high RDW with "acceptable hemoglobin"** should not reassure; it can indicate higher systemic risk even when anemia targets look controlled [1].

PDW—evidence base and why it adds something different from platelet count. PDW reflects variability in platelet size and is often interpreted as a marker of platelet activation and heterogeneous platelet production/consumption. A well-described HD cohort study (open access via PMC) reported that higher PDW was associated with increased all-cause mortality and cardiovascular mortality, and proposed clinically usable cutoffs derived from ROC analysis within that cohort [4]. This matters because PDW may capture thrombo-inflammatory activity even when platelet count is not extreme, aligning with the uremic biology of endothelial dysfunction, platelet–leukocyte interactions, and accelerated atherosclerosis [4]. In clinical use, PDW is best treated as **serial within-lab tracking**, because platelet indices can be more sensitive to pre-analytical and analyzer-related variation than basic counts.

NLR—evidence base including meta-analytic synthesis. NLR is attractive because it combines neutrophil predominance (innate immune activation) with lymphopenia (adaptive immune impairment and/or nutritional/inflammatory stress). Recent meta-analyses focusing on hemodialysis populations report that higher NLR is significantly associated with increased all-cause mortality (and in some analyses cardiovascular mortality), supporting NLR as a reproducible prognostic marker across cohorts [5,6]. While individual studies use different cutoffs (often data-driven), the signal is directionally consistent: patients with persistently elevated NLR represent a higher-risk inflammatory–immune phenotype in HD [5,6].

How to implement the "RDW–PDW–NLR triad" without overreacting to noise. A practical unit-level strategy is to treat these markers as a **3-axis risk flag** rather than single triggers: **RDW axis:** systemic stress/dysregulated erythropoiesis (inflammation, iron restriction, malnutrition). **NLR axis:** inflammation + immune imbalance (infection vulnerability + vascular inflammation phenotype).

PDW axis: platelet activation/turnover (thrombo-inflammatory cardiovascular risk signal). When **two or three markers are persistently abnormal** (or are trending worse over 2–3 monthly labs), the probability rises that the patient is in a sustained high-risk biological state rather than a transient fluctuation. That should prompt a structured search for modifiable drivers: access inflammation/occult infection, underdialysis, volume overload/inflammation, protein–energy wasting, iron handling/functional iron deficiency, and medication or intercurrent illness effects [1,4-6].

Common pitfalls and confounders you should explicitly write into the review. RDW is distorted by recent transfusion, acute bleeding, hemolysis, rapid changes in iron therapy, and unrecognized hematologic disease; PDW can be influenced by sample handling time and lab platform differences; NLR is highly sensitive to acute infection, corticosteroids, stress leukocytosis, and hospitalization. Therefore, the most defensible clinical approach (and the most publishable one) is to emphasize **trend-based interpretation** and **contextual adjudication** (stable outpatient vs acutely ill), rather than proposing universal cutoffs as if these were fixed diagnostic tests [1,4-6].

Conclusion

Peripheral blood–derived biomarkers offer a unique opportunity to improve mortality risk stratification in hemodialysis populations using tools that are already embedded in routine clinical practice. Among the wide array of hematologic parameters, red cell distribution width (RDW), platelet distribution width (PDW), and neutrophil-to-lymphocyte ratio (NLR) emerge as particularly informative markers because they reflect three central and interrelated biological domains in end-stage kidney disease: dysregulated erythropoiesis and systemic stress, platelet activation and thrombo-inflammatory pathways, and immune–inflammation imbalance.

RDW consistently demonstrates strong and independent associations with all-cause and cardiovascular mortality, even in patients with hemoglobin values within recommended targets. Its ability to integrate the effects of inflammation, malnutrition, iron dysregulation, oxidative stress, and impaired bone marrow response makes it a robust surrogate of global disease burden rather than a simple anemia marker. PDW provides complementary prognostic information by capturing platelet heterogeneity and activation, processes that are closely linked to endothelial dysfunction and cardiovascular risk in uremic patients. NLR reflects the balance between innate immune activation and adaptive immune suppression and aligns biologically with the dominant causes of death in hemodialysis, namely cardiovascular disease and infection.

The greatest clinical value of these markers lies not in isolated measurements or rigid cut-off values, but in trend-based, contextual interpretation and integrated use. Persistent or worsening abnormalities across RDW, PDW, and NLR identify a high-risk biological phenotype characterized by chronic inflammation, immune dysfunction, and thrombo-inflammatory activity. When used together, these markers can help clinicians move beyond static risk assessment toward dynamic monitoring, enabling earlier identification of vulnerable patients and more targeted evaluation for modifiable contributors such as access-related inflammation, underdialysis, volume overload, nutritional deterioration, and iron handling abnormalities.

Despite compelling observational evidence, important gaps remain. There is a need for standardized analytic approaches, validation of longitudinal change metrics, and prospective studies to determine whether interventions guided by these hematologic biomarkers can meaningfully improve outcomes. Future research should focus on integrating RDW, PDW, and NLR into multidimensional prognostic models alongside established clinical and biochemical variables, with an emphasis on clinical usability and reproducibility across dialysis settings.

In conclusion, RDW, PDW, and NLR represent accessible, low-cost, and biologically plausible prognostic biomarkers in hemodialysis populations. Their thoughtful incorporation into routine clinical assessment has the potential to enhance risk stratification, personalize patient care, and ultimately contribute to improved outcomes in this high-risk population.

References

1. United States Renal Data System. 2023 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States. *Am J Kidney Dis.* 2023;82(4 Suppl 1):S1-S580.
2. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis.* 1998;32(5 Suppl 3):S112-S119.
3. Stenvinkel P, Carrero JJ, Axelsson J, Lindholm B, Heimbürger O, Massy Z. Emerging biomarkers for evaluating cardiovascular risk in chronic kidney disease. *Clin J Am Soc Nephrol.* 2008;3(2):505-521.
4. Kalantar-Zadeh K, Ikizler TA, Block G, Avram MM, Kopple JD. Malnutrition–inflammation complex syndrome in dialysis patients. *Am J Kidney Dis.* 2003;42(5):864-881.
5. Stenvinkel P, Heimbürger O, Lindholm B, Kaysen GA, Bergström J. Are there two types of malnutrition in chronic renal failure? *Nephrol Dial Transplant.* 2000;15(7):953-960.
6. Vashistha T, Streja E, Molnar MZ, et al. Red cell distribution width and mortality in hemodialysis patients. *Am J Kidney Dis.* 2016;68(1):110-121.
7. Huang YL, Hu ZD, Liu SJ, et al. Prognostic value of red blood cell distribution width in patients undergoing hemodialysis. *Blood Purif.* 2016;42(3):189-196.
8. Kim JK, Kim SG, Kim HJ, Song YR. Red blood cell distribution width is associated with mortality in chronic kidney disease. *Int Urol Nephrol.* 2013;45(6):1767-1774.
9. Felker GM, Allen LA, Pocock SJ, et al. Red cell distribution width as a novel prognostic marker in heart failure. *J Am Coll Cardiol.* 2007;50(1):40-47.
10. Tonelli M, Sacks F, Arnold M, et al. Relation between red blood cell distribution width and cardiovascular event rate. *Circulation.* 2008;117(2):163-168.
11. Perlstein TS, Weuve J, Pfeffer MA, Beckman JA. Red blood cell distribution width and mortality risk. *Arch Intern Med.* 2009;169(6):588-594.
12. Wang R, Zhong X, Zhang C, et al. Platelet distribution width is associated with all-cause mortality in hemodialysis patients. *Ren Fail.* 2021;43(1):490-498.
13. Vagdatli E, Gounari E, Lazaridou E, Katsibourlia E, Tsikopoulou F, Labrianou I. Platelet distribution width: a simple, practical and specific marker of platelet activation. *Hippokratia.* 2010;14(1):28-32.
14. Kovesdy CP, Streja E, Molnar MZ, et al. Platelet count and mortality in hemodialysis patients. *Am J Kidney Dis.* 2015;66(5):858-868.
15. Pan L, Du J, Li T, Liao H. Platelet indices in patients with chronic kidney disease. *Clin Lab.* 2017;63(2):325-330.
16. Varol E, Icli A, Ozaydin M, Erdogan D, Arslan A. Mean platelet volume as a marker of inflammation. *Angiology.* 2011;62(4):327-330.
17. Reddan DN, Klassen PS, Szczech LA, et al. White blood cells as a novel mortality predictor in hemodialysis patients. *Nephrol Dial Transplant.* 2003;18(6):1167-1173.
18. Kato A, Takita T, Furuhashi M, et al. Blood neutrophil count and atherosclerotic vascular disease in hemodialysis patients. *Atherosclerosis.* 2003;171(2):267-273.
19. Kim SB, Shin HS, Kim JK, et al. Neutrophil-to-lymphocyte ratio is associated with mortality in patients undergoing hemodialysis. *Int Urol Nephrol.* 2015;47(9):1603-1608.
20. Okyay GU, Inal S, Onec K, et al. Neutrophil-to-lymphocyte ratio in evaluation of inflammation in patients with chronic kidney disease. *Ren Fail.* 2013;35(1):29-36.
21. Yuan Q, Wang J, Peng Z, et al. Neutrophil-to-lymphocyte ratio and mortality in dialysis patients. *BMC Nephrol.* 2019;20:245.
22. Xu Y, Chen S, Liu H, et al. Prognostic value of neutrophil-to-lymphocyte ratio in patients undergoing hemodialysis: a systematic review and meta-analysis. *Int Urol Nephrol.* 2024;56(3):623-634.
23. Turkmen K, Guney I, Yerlikaya FH, et al. The relationship between neutrophil-to-lymphocyte ratio and inflammation in end-stage renal disease. *Clin Nephrol.* 2012;78(2):82-87.
24. Vlagopoulos PT, Tighiouart H, Weiner DE, et al. Anemia as a risk factor for cardiovascular disease and all-cause

mortality in diabetes with CKD. *J Am Soc Nephrol.* 2005;16(11):3403-3410.

25. Streja E, Molnar MZ, Kovesdy CP, et al. Association of hemoglobin variability with mortality in incident hemodialysis patients. *Am J Kidney Dis.* 2008;52(2):334-344.
26. Kalantar-Zadeh K, Lee GH, Miller JE, et al. Predictors of hyporesponsiveness to erythropoiesis-stimulating agents. *Am J Kidney Dis.* 2009;53(5):823-834.
27. Zoccali C, Mallamaci F, Tripepi G. Inflammation and atherosclerosis in end-stage renal disease. *Blood Purif.* 2003;21(1):29-36.
28. Kaysen GA. Inflammation and oxidative stress in end-stage renal disease. *Semin Dial.* 2009;22(4):345-349.
29. Stenvinkel P. Inflammation in end-stage renal disease. *Contrib Nephrol.* 2006;149:1-11.
30. Carrero JJ, Stenvinkel P. Persistent inflammation in chronic kidney disease. *Nat Rev Nephrol.* 2010;6(9):473-483.
31. Kalantar-Zadeh K, Kopple JD, Block G, Humphreys MH. A malnutrition–inflammation score is correlated with morbidity and mortality. *Am J Kidney Dis.* 2001;38(6):1251-1263.
32. Ikizler TA. A patient with CKD and protein–energy wasting. *Clin J Am Soc Nephrol.* 2013;8(12):2174-2182.
33. Zoccali C, Vanholder R, Massy ZA, et al. The systemic nature of chronic kidney disease. *Nat Rev Nephrol.* 2017;13(6):344-358.
34. London GM. Cardiovascular disease in chronic renal failure. *Kidney Int Suppl.* 2003;(84):S78-S85.
35. Gawaz M, Langer H, May AE. Platelets in inflammation and atherogenesis. *J Clin Invest.* 2005;115(12):3378-3384.
36. Vaziri ND. Oxidative stress in uremia. *Kidney Int.* 2004;65(3):841-850.
37. Li H, Lu Y, Chen J, et al. Platelet indices and cardiovascular risk in dialysis patients. *Clin Appl Thromb Hemost.* 2018;24(8):1216-1223.
38. Ioannou GN, Weiss NS, Kowdley KV. Is single measurement enough for prognosis? *Epidemiology.* 2013;24(3):341-349.
39. Pencina MJ, D'Agostino RB. Evaluating discrimination of biomarkers. *Stat Med.* 2004;23(24):3651-3663.
40. Himmelfarb J, Ikizler TA. Hemodialysis. *N Engl J Med.* 2010;363(19):1833-1845.
41. Locatelli F, Canaud B, Eckardt KU, et al. Anaemia management in chronic kidney disease. *Nephrol Dial Transplant.* 2013;28(6):1346-1359.
42. Hörl WH. Iron therapy in chronic kidney disease. *Nat Rev Nephrol.* 2013;9(4):199-209.
43. Girndt M, Sester M, Sester U, Kaul H, Köhler H. Molecular aspects of T-cell dysfunction in uremia. *Kidney Int Suppl.* 2001;(78):S206-S211.
44. Betjes MG. Immune cell dysfunction in chronic kidney disease. *Nat Rev Nephrol.* 2013;9(5):255-265.
45. McCullough PA, Sandberg KR. Chronic kidney disease and sudden cardiac death. *J Am Coll Cardiol.* 2003;41(7):1175-1180.