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Mean Platelet Volume, Adropin, and Inflammatory Markers in Maintenance Hemodialysis: A Comprehensive Review

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ABSTRACT

Background: Chronic kidney disease (CKD) is a progressive condition characterized by a gradual loss of renal function, ultimately leading to end-stage renal disease (ESRD) in many patients. Maintenance hemodialysis (HD) remains the primary renal replacement therapy for ESRD, significantly improving patient survival. However, HD patients are at elevated risk for numerous complications, most notably cardiovascular disease (CVD), which is the leading cause of mortality in this population. Emerging evidence has highlighted the role of inflammatory processes, hemostatic disturbances, and novel biomarkers in mediating this risk.T his comprehensive review aims to critically examine the current evidence regarding the interplay between mean platelet volume (MPV), adropin, and inflammatory markers in patients undergoing maintenance hemodialysis. The review further explores the role of these markers in the context of CKD complications, malnutrition, and heightened cardiovascular risk observed in the HD population. Additionally, the review synthesizes current findings on the regulatory functions of adropin in vascular homeostasis and discusses how its serum levels may be associated with risk factors for cardiovascular disease in HD patients. A growing body of literature suggests that MPV serves as a surrogate marker for platelet activation and systemic inflammation, contributing to the elevated cardiovascular risk in CKD and HD populations. Adropin, a relatively novel peptide hormone, has been implicated in metabolic regulation and endothelial function, with emerging data indicating its potential as a protective factor against vascular injury and inflammation. The interaction between MPV, adropin, and classical inflammatory markers offers new insights into the multifactorial mechanisms underlying cardiovascular complications in HD patients. Nonetheless, significant gaps remain regarding the precise mechanisms, prognostic value, and therapeutic implications of these markers. Further large-scale, prospective studies are warranted to validate their clinical utility and to elucidate their roles in risk stratification and personalized management strategies for HD patients. This review integrates recent advances and highlights the need for continued research to optimize cardiovascular outcomes in this vulnerable population.

Keywords*: Mean Platelet Volume, Adropin, CKD, Hemodialysis*

INTRODUCTION

Chronic kidney disease (CKD) is a major global health problem, affecting an estimated 10–15% of the world's population and contributing significantly to morbidity and mortality rates [1]. Progression to

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end-stage renal disease (ESRD) necessitates renal replacement therapy, with hemodialysis (HD) being the most widely adopted modality. While HD effectively manages the metabolic derangements of kidney failure, it does not fully mitigate the high risk of cardiovascular disease (CVD) and related complications that persist in this patient population [2]. CVD remains the leading cause of death among individuals on maintenance HD, underscoring the urgent need for improved risk stratification and novel therapeutic strategies [3].

Recent research has focused on the roles of inflammation and hemostatic dysfunction in mediating the excessive cardiovascular risk observed in HD patients. Mean platelet volume (MPV), a simple and accessible measure of platelet size and activation, has emerged as a promising marker linked to both thrombosis and inflammation [4]. Meanwhile, adropin—a recently identified peptide hormone involved in energy homeostasis and endothelial function—has attracted increasing attention due to its potential regulatory effects on vascular health and metabolic balance [5]. Additionally, traditional inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) remain central to risk assessment in CKD and HD populations, although they often lack specificity for cardiovascular complications [6].

The aim of this review is to provide a comprehensive synthesis of the current evidence on the association between MPV, adropin, and inflammatory markers in maintenance HD patients. Special attention is given to the clinical implications of these biomarkers in the context of CKD complications, malnutrition, and cardiac risk. Despite considerable advances, a significant research gap remains regarding the mechanistic interplay between these markers and their potential integration into routine clinical practice. This review seeks to identify and address these gaps, offering recommendations for future research and highlighting areas of translational potential in the management of HD patients [7].

Chronic Kidney Disease (CKD) and Its Complications

Chronic kidney disease (CKD) is a progressive condition defined by the gradual loss of kidney function over months or years, frequently culminating in end-stage renal disease (ESRD) that necessitates renal replacement therapy such as hemodialysis or transplantation [8]. The global prevalence of CKD is rising, driven by the increasing burden of diabetes mellitus, hypertension, and an aging population. CKD is stratified into five stages based on glomerular filtration rate (GFR), with stage 5 corresponding to ESRD. The insidious nature of early-stage CKD often results in delayed diagnosis, enabling the progression of systemic complications before therapeutic interventions can be effectively implemented [9].

One of the most significant complications associated with CKD is cardiovascular disease (CVD), which represents the leading cause of morbidity and mortality in this patient population. CKD itself is now recognized as an independent risk factor for atherosclerosis, heart failure, and arrhythmias. The increased cardiovascular risk in CKD patients is multifactorial, involving a complex interplay between

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traditional risk factors (such as hypertension and dyslipidemia) and non-traditional factors (such as chronic inflammation, endothelial dysfunction, and vascular calcification) [10]. These non-traditional risk factors are particularly pronounced as renal function deteriorates, and they are further amplified by the metabolic and hemodynamic disturbances inherent to advanced CKD.

Beyond cardiovascular complications, CKD is associated with a host of systemic sequelae that contribute to overall disease burden and diminished quality of life. These include mineral and bone disorders, anemia, malnutrition, and an increased susceptibility to infections. Uremic toxins accumulate as renal clearance declines, contributing to oxidative stress, impaired immune responses, and chronic low-grade inflammation. Malnutrition and protein-energy wasting are common in advanced stages of CKD, exacerbated by metabolic acidosis, anorexia, and chronic inflammation, which collectively drive a catabolic state [11].

The persistent low-grade inflammatory milieu in CKD not only accelerates the progression of renal dysfunction but also underpins many of the extra-renal complications observed in these patients. Inflammatory cytokines, oxidative stress markers, and acute-phase reactants such as C-reactive protein (CRP) are frequently elevated in CKD, correlating with poorer cardiovascular and overall outcomes. This inflammatory state is thought to play a pivotal role in endothelial dysfunction, atherosclerosis, and the heightened risk of thrombotic events [12]. As such, understanding and managing the myriad complications of CKD remains a major clinical challenge, with ongoing research focused on identifying novel biomarkers and therapeutic targets to improve patient prognosis [13].

Hemodialysis: Principles and Hemodialysis-Related Complications

Hemodialysis (HD) is the most widely utilized form of renal replacement therapy for patients with end-stage renal disease (ESRD). The principle of HD involves the extracorporeal removal of uremic toxins, excess fluid, and electrolytes via a semipermeable membrane, thereby partially substituting for the excretory functions of the failing kidneys. HD sessions are typically performed three times per week, and each session lasts between three and five hours. While HD is lifesaving, it is not a cure for kidney failure; rather, it serves to maintain metabolic stability and prolong survival [14].

Despite its efficacy, HD is associated with a variety of procedure-related and long-term complications. Vascular access dysfunction is one of the most common issues, often due to thrombosis, infection, or stenosis of arteriovenous fistulas or grafts. These complications can lead to repeated hospitalizations and increased morbidity. HD patients are also susceptible to intradialytic hypotension, muscle cramps, and dialysis disequilibrium syndrome, all of which can negatively impact quality of life [15]. The repeated exposure to bioincompatible dialysis membranes and potential contamination with endotoxins may exacerbate systemic inflammation and oxidative stress, further contributing to cardiovascular risk [16].

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Long-term HD is linked to chronic inflammatory activation, malnutrition, and a distinct pattern of cardiovascular disease characterized by accelerated atherosclerosis, vascular calcification, and left ventricular hypertrophy. The process of HD itself may amplify inflammatory responses due to the activation of leukocytes and complement pathways. Chronic inflammation is further aggravated by non-traditional factors such as fluid overload, the presence of uremic toxins, and frequent infections. Together, these factors result in a persistently heightened inflammatory state, which is closely associated with the development and progression of cardiovascular disease in HD patients [17].

Furthermore, HD-related complications extend beyond the cardiovascular system. Patients are at increased risk for mineral and bone disorders, anemia, pruritus, and cognitive dysfunction. These comorbidities, along with the psychosocial burden of a lifelong dependency on dialysis, significantly impair health-related quality of life. Addressing HD-related complications remains a key priority in the holistic care of patients with ESRD, and ongoing research continues to seek ways to mitigate these risks and improve long-term outcomes [18].

Malnutrition and Cardiac Risk in Hemodialysis Patients

Malnutrition, particularly protein-energy wasting (PEW), is a prevalent and critical concern among patients undergoing maintenance hemodialysis (HD). The pathogenesis of malnutrition in this population is multifactorial, involving inadequate dietary intake, metabolic acidosis, chronic inflammation, hormonal imbalances, and nutrient losses during dialysis sessions. Anorexia is a frequent symptom in HD patients, often exacerbated by uremic toxins, gastrointestinal disturbances, and psychological stress. Inflammatory mediators such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) play a substantial role in promoting a catabolic state and suppressing appetite, further worsening nutritional status [19].

The consequences of malnutrition in HD patients are profound and far-reaching. Malnutrition is a well-established independent predictor of mortality, largely due to its strong association with cardiovascular disease (CVD). Malnourished HD patients are more susceptible to cardiac events, arrhythmias, and sudden cardiac death. Several mechanisms underpin this association, including the impact of chronic inflammation, oxidative stress, endothelial dysfunction, and the direct effects of nutritional deficiencies on cardiac muscle integrity and vascular health. Loss of lean body mass and hypoalbuminemia, common findings in malnourished individuals, are both linked to poor cardiovascular outcomes [20].

Malnutrition also contributes to the phenomenon known as the malnutrition-inflammation-atherosclerosis (MIA) syndrome, a triad that characterizes the heightened cardiovascular risk in the HD population. The MIA syndrome underscores the interconnectedness of nutritional status, inflammatory burden, and the development of atherosclerotic cardiovascular disease. This relationship is further complicated by the frequent presence of additional comorbidities such as diabetes,

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hypertension, and mineral-bone disorder, all of which synergistically increase the risk of cardiac morbidity and mortality [21].

Addressing malnutrition in HD patients requires a multidisciplinary approach that includes dietary counseling, individualized nutritional support, and aggressive management of underlying inflammation and metabolic derangements. Early identification and correction of malnutrition are essential to improving both short- and long-term outcomes, particularly in reducing the burden of cardiovascular disease. The integration of novel biomarkers, such as mean platelet volume (MPV) and adropin, into nutritional and cardiac risk assessment may offer further insights and enhance personalized care strategies in this vulnerable group [22].

Mean Platelet Volume (MPV) in Cardiovascular Diseases

Mean platelet volume (MPV) is an accessible and routinely reported parameter on automated blood analyzers, reflecting the average size and activity of circulating platelets. Larger platelets are more metabolically and enzymatically active, containing higher concentrations of prothrombotic and inflammatory mediators. Consequently, MPV has emerged as a surrogate marker of platelet reactivity, with elevated MPV values indicating increased platelet activation and a higher propensity for thrombosis [23]. In recent years, substantial evidence has linked elevated MPV with the development and progression of various cardiovascular diseases (CVD), including coronary artery disease, myocardial infarction, and stroke.

Several studies have demonstrated that patients with acute coronary syndromes or stable coronary artery disease often present with significantly higher MPV values compared to healthy controls. Elevated MPV has been independently associated with worse clinical outcomes, such as increased rates of major adverse cardiovascular events and higher mortality [24]. The mechanistic basis for these associations is grounded in the observation that activated platelets not only contribute to thrombus formation but also release inflammatory cytokines and growth factors, exacerbating vascular injury and promoting atherogenesis.

Beyond acute vascular events, elevated MPV has also been implicated in chronic processes such as atherosclerosis and endothelial dysfunction. Inflammatory stimuli, including those prevalent in CKD and HD, can stimulate megakaryocyte proliferation and the production of larger, more reactive platelets, thereby increasing MPV. This relationship underscores the close interplay between systemic inflammation, platelet activation, and cardiovascular risk in both the general population and those with underlying renal dysfunction [25]. Moreover, high MPV values have been proposed as a useful adjunct to traditional risk factors in stratifying cardiovascular risk, particularly in patients with complex comorbidities such as CKD.

The clinical utility of MPV as a biomarker lies in its ease of measurement, cost-effectiveness, and ability to provide additional prognostic information. Despite these advantages, standardization of

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measurement techniques and reference ranges remains a challenge, as various pre-analytical and analytical factors can influence MPV values. Nevertheless, MPV continues to garner attention as a promising marker for identifying patients at increased risk for cardiovascular complications and as a potential target for future therapeutic interventions [26].

Mean Platelet Volume (MPV) in Hemodialysis

In the context of hemodialysis (HD), mean platelet volume (MPV) gains additional clinical significance due to the unique hemostatic challenges faced by these patients. HD is associated with profound alterations in platelet function, stemming from both uremic toxins and the dialysis procedure itself. Uremic milieu promotes platelet activation and aggregation, while repetitive extracorporeal circulation and exposure to artificial surfaces during HD sessions further stimulate platelet consumption and turnover [27]. This environment leads to dynamic fluctuations in platelet count and MPV, often resulting in elevated MPV values in HD patients compared to healthy individuals.

Several observational studies have reported a strong association between elevated MPV and adverse cardiovascular outcomes in the HD population. Patients with higher MPV levels tend to exhibit an increased risk of thrombotic events, vascular access thrombosis, and all-cause mortality. Elevated MPV in HD patients is also linked to the presence and severity of atherosclerotic vascular disease, as well as markers of systemic inflammation such as C-reactive protein (CRP) and interleukin-6 (IL-6) [28]. These findings highlight the role of MPV as both a marker and a potential mediator of the heightened cardiovascular risk inherent to chronic HD.

The interplay between inflammation and platelet activation is particularly relevant in HD, where chronic low-grade inflammation is ubiquitous and tightly linked to complications such as malnutrition, vascular calcification, and cardiac dysfunction. Pro-inflammatory cytokines stimulate megakaryopoiesis and the release of larger, more reactive platelets, reflected in increased MPV. Furthermore, intradialytic events—including hypotension, bioincompatible dialyzer membranes, and repeated vascular access interventions—can further aggravate platelet activation and contribute to MPV elevation [29].

Given the prognostic implications, routine monitoring of MPV in HD patients has been suggested as a valuable tool for identifying individuals at higher risk for cardiovascular and thrombotic complications. However, challenges remain regarding the interpretation of MPV values in this setting, as factors such as anemia, concurrent medications, and individual variability must also be considered. Standardized approaches to MPV measurement and integration with other biomarkers may improve its utility in risk stratification and personalized management for HD patients [30].

Regulation of Vascular Function by Adropin

Adropin is a recently discovered peptide hormone encoded by the energy homeostasis associated (ENHO) gene, with prominent roles in the regulation of metabolic processes and vascular function.

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Initially identified in the context of energy balance and glucose metabolism, adropin has since been implicated in maintaining endothelial health and modulating vascular tone. Experimental studies have shown that adropin exerts protective effects on the vascular endothelium by promoting nitric oxide (NO) synthesis, enhancing endothelial cell survival, and inhibiting oxidative stress [31]. Through these mechanisms, adropin helps preserve endothelial integrity and contributes to vasodilation, thereby counteracting processes that lead to vascular dysfunction and atherogenesis.

The relationship between adropin and vascular health is further supported by evidence linking low serum adropin levels with impaired endothelial-dependent vasodilation and increased arterial stiffness—two key risk factors for cardiovascular disease. Adropin appears to directly regulate endothelial nitric oxide synthase (eNOS) activity, fostering the bioavailability of NO, which is essential for vascular relaxation and anti-inflammatory effects. Additionally, adropin downregulates the expression of adhesion molecules and pro-inflammatory cytokines, thereby reducing leukocyte adhesion and vascular inflammation [32].

In animal models, adropin deficiency has been associated with the development of hypertension, insulin resistance, and accelerated atherosclerosis, while administration of exogenous adropin can ameliorate endothelial dysfunction and reduce blood pressure. These findings suggest a crucial role for adropin as a modulator of vascular tone and an inhibitor of early atherogenic processes [33]. Notably, factors common in chronic kidney disease (CKD) and hemodialysis (HD) patients—such as oxidative stress, inflammation, and metabolic dysregulation—are also known to suppress adropin expression, potentially linking low adropin levels to the heightened vascular risk observed in these populations.

The emerging recognition of adropin as a regulator of vascular homeostasis has prompted interest in its utility as a biomarker and therapeutic target in conditions marked by endothelial dysfunction, including CKD and HD. Further clinical studies are required to clarify the mechanistic pathways through which adropin influences vascular health and to determine whether modulation of adropin levels could yield benefits in reducing cardiovascular morbidity and mortality in high-risk groups [34].

Serum Adropin Levels and Cardiovascular Disease Risk Factors in Hemodialysis Patients

Serum adropin levels have emerged as a novel biomarker of metabolic and cardiovascular health, garnering particular interest in the context of hemodialysis (HD) patients, who are at high risk for adverse cardiovascular events. Multiple studies have documented significantly lower adropin concentrations in individuals with chronic kidney disease (CKD) and those receiving maintenance HD compared to healthy controls. This reduction in adropin is believed to result from the persistent inflammation, oxidative stress, and metabolic imbalances characteristic of advanced renal failure and HD therapy [35].

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In HD patients, low serum adropin levels have been associated with a range of cardiovascular risk factors, including arterial stiffness, impaired endothelial function, left ventricular hypertrophy, and increased carotid intima-media thickness. These associations are independent of traditional risk factors such as hypertension, diabetes, and dyslipidemia, suggesting that adropin may provide additive predictive value for cardiovascular risk stratification in the HD population [36]. Moreover, adropin levels show inverse correlations with established markers of inflammation, including high-sensitivity C-reactive protein (hsCRP) and interleukin-6 (IL-6), supporting its role as a mediator of vascular inflammation and dysfunction.

The interplay between adropin deficiency and metabolic abnormalities—such as insulin resistance, dyslipidemia, and obesity—further compounds the cardiovascular burden faced by HD patients. Adropin has been shown to enhance insulin sensitivity and promote favorable lipid profiles, and its deficiency may accelerate the development of atherosclerosis and other cardiovascular complications. Clinical investigations have demonstrated that lower adropin levels in HD patients are associated with poorer nutritional status, higher rates of protein-energy wasting, and increased all-cause and cardiovascular mortality [37].

Given these findings, serum adropin measurement may serve as a valuable tool in identifying HD patients at greatest risk for cardiovascular events, enabling more personalized risk reduction strategies. Nonetheless, further research is needed to establish standardized reference ranges, determine the effects of HD modality and duration on adropin levels, and explore the potential therapeutic benefits of restoring or augmenting adropin in this high-risk population [38].

MPV, Adropin, and Inflammatory Markers: Interrelations and Mechanistic Insights

The interplay between mean platelet volume (MPV), adropin, and inflammatory markers presents a complex but critical landscape in understanding the heightened cardiovascular risk among hemodialysis (HD) patients. Elevated MPV, indicative of increased platelet activation and turnover, is frequently observed in HD and correlates strongly with markers of systemic inflammation such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) [39]. This relationship is believed to be bidirectional, as inflammatory cytokines promote the production of larger, more reactive platelets, while activated platelets release pro-inflammatory mediators that further perpetuate vascular inflammation.

Adropin, conversely, acts as a counter-regulatory peptide with anti-inflammatory and vasoprotective properties. In the HD population, reduced serum adropin levels are consistently linked to higher MPV values and increased concentrations of inflammatory biomarkers. Several studies suggest that low adropin status may amplify the pro-thrombotic and pro-inflammatory milieu, exacerbating endothelial dysfunction and accelerating atherosclerotic processes [40]. This synergy likely contributes to the malnutrition-inflammation-atherosclerosis (MIA) syndrome so prevalent in HD patients.

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Mechanistically, the convergence of high MPV, low adropin, and elevated inflammatory markers is thought to fuel a cycle of vascular injury. Activated platelets adhere to dysfunctional endothelium, releasing growth factors and cytokines that attract leukocytes and drive further inflammation. Simultaneously, adropin deficiency impairs nitric oxide (NO) production, diminishing endothelial repair and favoring vasoconstriction and plaque formation [41]. The combined effect of these processes is a marked increase in the risk for major cardiovascular events, vascular access thrombosis, and overall mortality in the HD setting.

Understanding these interrelationships opens the door to innovative risk assessment and management strategies. Integrating measurements of MPV, adropin, and inflammatory markers may enhance prognostic accuracy beyond traditional risk factors alone. Moreover, therapeutic interventions aimed at reducing platelet activation, controlling inflammation, or restoring adropin levels hold promise for mitigating cardiovascular complications in this vulnerable group. However, further research is needed to clarify causality and identify optimal strategies for targeting these interconnected pathways [42].

Clinical Implications and Future Perspectives

The evolving understanding of the roles of mean platelet volume (MPV), adropin, and inflammatory markers in hemodialysis (HD) patients has significant clinical implications. The integration of these biomarkers into routine clinical practice could enhance risk stratification and enable more personalized management of cardiovascular disease (CVD) in this high-risk group. For example, elevated MPV—readily measured through routine complete blood counts—may serve as a practical, cost-effective tool for identifying HD patients at increased risk for thrombotic events and poor cardiovascular outcomes. Similarly, serum adropin measurement, though less established in clinical settings, offers promise as an early indicator of endothelial dysfunction and nutritional status [43].

The recognition of the malnutrition-inflammation-atherosclerosis (MIA) syndrome further underscores the need for multidimensional risk assessment strategies. Incorporating MPV, adropin, and established inflammatory markers like C-reactive protein (CRP) and interleukin-6 (IL-6) into composite risk scores could improve prognostic accuracy and inform targeted interventions. Such an approach could enable early identification of patients who might benefit from intensified nutritional support, anti-inflammatory therapies, or interventions aimed at modulating platelet activity [44].

Therapeutically, strategies to modulate platelet activation, reduce systemic inflammation, and restore adropin levels are emerging as attractive avenues for research and clinical application. Potential interventions include the use of anti-platelet agents, optimization of dialysis techniques to minimize inflammation, and nutritional or pharmacologic agents aimed at augmenting adropin expression. Early studies investigating the cardiovascular effects of adropin supplementation or analogs in experimental models show promise, but translation to clinical practice will require robust trials to establish safety and efficacy in humans, particularly among HD patients [45].

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Future research should focus on large, prospective cohort studies and interventional trials to further elucidate the causal relationships among MPV, adropin, and inflammation, and to validate these biomarkers as targets for therapy. Personalized medicine approaches, leveraging novel biomarker panels, could revolutionize the management of cardiovascular risk in HD populations, ultimately improving survival and quality of life. Ongoing advances in biomarker discovery and mechanistic understanding hold the potential to transform current practice and drive the development of novel therapeutic strategies in the field of nephrology and dialysis care [46].

Conclusion

The interplay between mean platelet volume (MPV), adropin, and inflammatory markers represents a critical axis in understanding the pathophysiology of cardiovascular complications in patients undergoing maintenance hemodialysis (HD). Elevated MPV reflects heightened platelet activation and a prothrombotic state, while low adropin levels signify impaired vascular and metabolic regulation. Both are closely intertwined with the chronic inflammatory milieu that characterizes HD patients, collectively fueling the development of atherosclerosis, vascular calcification, and cardiac dysfunction. Integrating these novel and established biomarkers into routine clinical assessment could enhance risk stratification and facilitate the early identification of patients at highest risk for adverse outcomes. While current evidence strongly supports the prognostic value of MPV and adropin, significant gaps remain regarding their precise mechanistic roles, standardization of measurement, and the impact of therapeutic interventions aimed at modifying their levels. The complexity of cardiovascular risk in HD patients necessitates a multidimensional approach, and future research should prioritize large-scale, prospective studies to validate these biomarkers and determine their potential in guiding personalized management strategies. Ultimately, advances in understanding the interconnections between MPV, adropin, and inflammation may open new avenues for the prevention and treatment of cardiovascular disease in this vulnerable population, improving both longevity and quality of life for those living with end-stage renal disease.

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