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Review Article

The Role of Inflammatory Markers for Risk Stratification and Prognosis in Dialysis Patients: A Narrative Review

Siti Liyana Mohd Nor[1], Mohd Radzniwan A. Rashid[1,2], Faizul Helmi Addnan[1], Siva Gowri Patmanathan[1], Nizam Baharom[1,2], Sharifah Najwa Syed Mohamad[1,2], Ruslinda Mustafar[3], Saharudin Ahmad[3], Arifa Mustika[4], Minidian Fasitasari[5], and Lusito Lusito[5]

[1]Faculty of Medicine and Health Sciences, Universiti Sains Islam Malaysia, Nilai, 71800, Malaysia.

[2]Department of Primary Care, Faculty of Medicine and Health Sciences, Universiti Sains Islam Malaysia, 71800, Malaysia.

[3]Faculty of Medicine, Universiti Kebangsaan Malaysia, Cheras,56000 Kuala Lumpur, Malaysia.

[4]Department of Anatomy, Histology, Faculty of Medicine, Universitas Airlangga, Surabaya, 60115, Indonesia.

[5]Medical Faculty of Universitas Islam Sultan Agung, Semarang, 50112, Indonesia.

Correspondence should be addressed to:
Mohd Radzniwan Abdul Rashid; mradzniwan@usim.edu.my

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***Abstract*— Chronic inflammation is a prevalent condition among dialysis patients and is associated with adverse health outcomes. This narrative review aims to provide a comprehensive analysis of the types and roles of inflammatory markers in risk assessment and their impact on the prognosis of dialysis patients. The associations between various inflammatory markers, including C-Reactive Protein (CRP), anti-inflammatory markers (IL-4, IL-10), and pro-inflammatory markers (TNF-α, IL-1, IL-6, IL-12), are evaluated in relation to their ability to predict mortality and cardiovascular complications in this population. Additionally, the potential of these markers for individualized risk stratification is discussed, aiding proper clinical decision-making and improving patient care. This review synthesizes current knowledge on inflammatory markers and their impact on the outcomes of dialysis patients, offering insights for improved prognostic assessment and therapeutic strategies.**

***Keywords*— dialysis, inflammatory markers; risk stratification; prognosis, cardiovascular complications**

I. INTRODUCTION

End-Stage Renal Disease (ESRD) is defined as an estimated Glomerular Filtration Rate (eGFR) of below 15 ml/min/1.73 m², where Renal Replacement Therapy (RRT) such as dialysis or transplantation becomes necessary. The transition from acute kidney injury to Chronic Kidney Disease (CKD) and eventual ESRD involves a complex cascade of maladaptive repair mechanisms. Following initial acute injury, failed recovery leads to continuous inflammation, oxidative stress, and activation of fibrotic pathways [1,2]. At the cellular level, this progression is driven by nephron loss, sustained inflammatory responses, and myofibroblast activation resulting in excessive extracellular matrix deposition [1].

Key pathogenic mechanisms include chronic low-grade inflammation, lipotoxicity, and oxidative stress mediated through NLR family pyrin domain–containing 3 (NLRP3) inflammasome signaling, mitogen-activated protein kinase (MAPK) pathways, and Renin-Angiotensin-Aldosterone System (RAAS) activation [1]. Notably, macrophages play a pivotal role in this progression through phenotypic switching that promotes tissue fibrosis via Transforming Growth Factor-beta 1 (TGF-β1)/Smad3 signaling [3]. Specifically, the fibrotic

process encompasses tubular atrophy, interstitial inflammation, glomerulosclerosis, and vascular rarefaction, creating a self-perpetuating cycle of injury and repair that ultimately culminates in ESRD [2,4]. Hence, understanding these pathophysiological mechanisms is important for appreciating how dialysis treatment may take over the function in ESRD patients. Once ESRD is reached, dialysis is the next best treatment option other than a renal transplant.

Dialysis serves as a life-saving treatment for ESRD patients, and it replaces the loss of kidney function in filtering waste products and excess fluids from the bloodstream. Two primary modalities exist: (i) hemodialysis, involving the extracorporeal purification of blood, and (ii) peritoneal dialysis, which employs the peritoneal membrane as a filter. Dialysis patients are prone to various complications, particularly in the areas of cardiovascular disease, infections, and inflammation, which significantly impact their prognosis, survival, and quality of life [5].

In the realm of dialysis patient care, understanding the role of inflammatory markers is paramount as they offer valuable insights into disease progression and prognosis. Among the array of inflammatory markers studied, C-Reactive Protein (CRP), interleukin-6 (IL-6), and Tumor Necrosis Factor-alpha (TNF-α) have emerged as important poor indicators in prognosticating outcomes among dialysis patients. Elevated levels of CRP, for instance, have been consistently correlated with increased cardiovascular morbidity and mortality rates within the dialysis population [6]. Thus, this correlation underscores the potential of CRP as a robust risk stratification and prognostic tool in identifying high-risk patients who may benefit from targeted interventions to mitigate cardiovascular risks. Furthermore, TNF-α, another key inflammatory mediator, has been implicated in the pathogenesis of various complications in dialysis patients. Stenvinkel et al. highlighted TNF-α's role in the development of cachexia and cardiovascular disease, both of which contribute significantly to morbidity and mortality in this patient population [7].

Similarly, IL-6, a pro-inflammatory cytokine, has obtained attention due to its association with adverse outcomes as well. There is a significant link between elevated IL-6 levels and increased mortality rates, as well as a decline in kidney function among individuals undergoing dialysis[7,8].

On the contrary, other interleukins such as IL-4, IL-10, and IL-12 have been implicated in the inflammatory milieu of dialysis patients positively. IL-4, known for its anti-inflammatory properties, plays a role in modulating the inflammatory response and mitigating adverse outcomes in dialysis patients. Furthermore, IL-10, an anti-inflammatory cytokine, has been demonstrated to attenuate inflammatory cascades and potentially mitigate the progression of inflammation-related complications in dialysis patients[9,10] Moreover, IL-12, a pro-inflammatory cytokine, has been reported in CKD not to be associated with arterial stiffness, a surrogate marker of cardiovascular disease [11]. Hence, understanding the roles of these interleukins alongside CRP, IL-6, and TNF-α is essential for comprehensively assessing the inflammatory status and prognosis of dialysis patients.

The significance of these inflammatory markers lies in their ability to serve as crucial indicators of systemic inflammation, a pervasive condition in dialysis patients. Chronic inflammation is a consequence of renal dysfunction and a contributor to disease progression and complications in this population. Therefore, by monitoring and evaluating inflammatory markers mentioned above, clinicians can gain valuable insights into the inflammatory burden experienced by dialysis patients and tailor treatment strategies accordingly.

Nonetheless, there are various other types of inflammatory markers being reported. These will be discussed in the next section, where some of them still require further clarification and investigation of their role and how they may be implicated in the chronic inflammation process, as well as the survival of the dialysis population. Additionally, studies exploring the effectiveness of interventions targeting inflammation, such as anti-inflammatory medications or lifestyle modifications, are crucial in refining treatment approaches apart from improving outcomes in this vulnerable population. Figure 1 illustrates the key inflammatory markers relevant to dialysis patient management, highlighting both pro-inflammatory (CRP, IL-6, TNF-α) and anti-inflammatory interleukins (IL-4, IL-10, IL-12), along with their roles in systemic inflammation, prognosis, and potential as therapeutic targets. Whereas Figure 2 illustrates the interplay of pro- and anti-Inflammatory cytokines in dialysis patients and their clinical consequences.

However, although serum interleukin levels are useful indicators of systemic inflammation, recent evidence highlights that urinary interleukins are also associated with both urinary tract infections and broader systemic disorders [12]. Markers such as IL-8, IL-18, and IL-1β appear particularly promising for diagnosing urinary tract infections and related conditions. Nonetheless, their clinical application remains challenging, and further research is required to enhance aspects such as sensitivity and measurement speed [12].

Accordingly, a narrative review of inflammatory markers for risk stratification and prognosis in maintenance dialysis was conducted. Searches were performed in PubMed, Embase, Scopus, and Web of Science using terms for dialysis, inflammatory biomarkers, and prognostic outcomes, supplemented by reference screening. Eligible studies included adult dialysis, evaluating inflammatory markers with prognostic endpoints, while non-dialysis, pediatric, transplant-only, animal, and non-English/Malay studies were excluded. Additionally, the selection was purposive, and findings are presented thematically by inflammatory marker types.

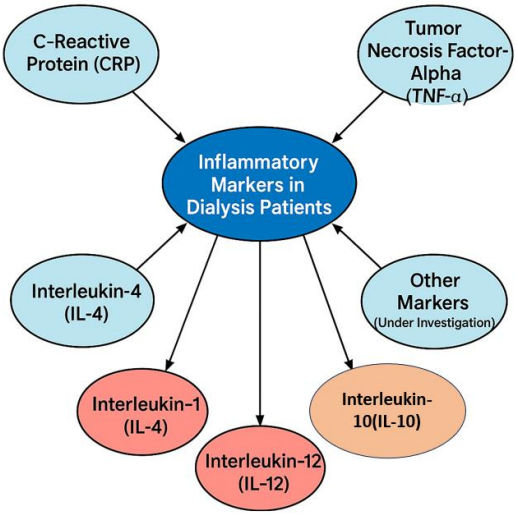

Figure 1. Key inflammatory markers and their roles in dialysis patients.

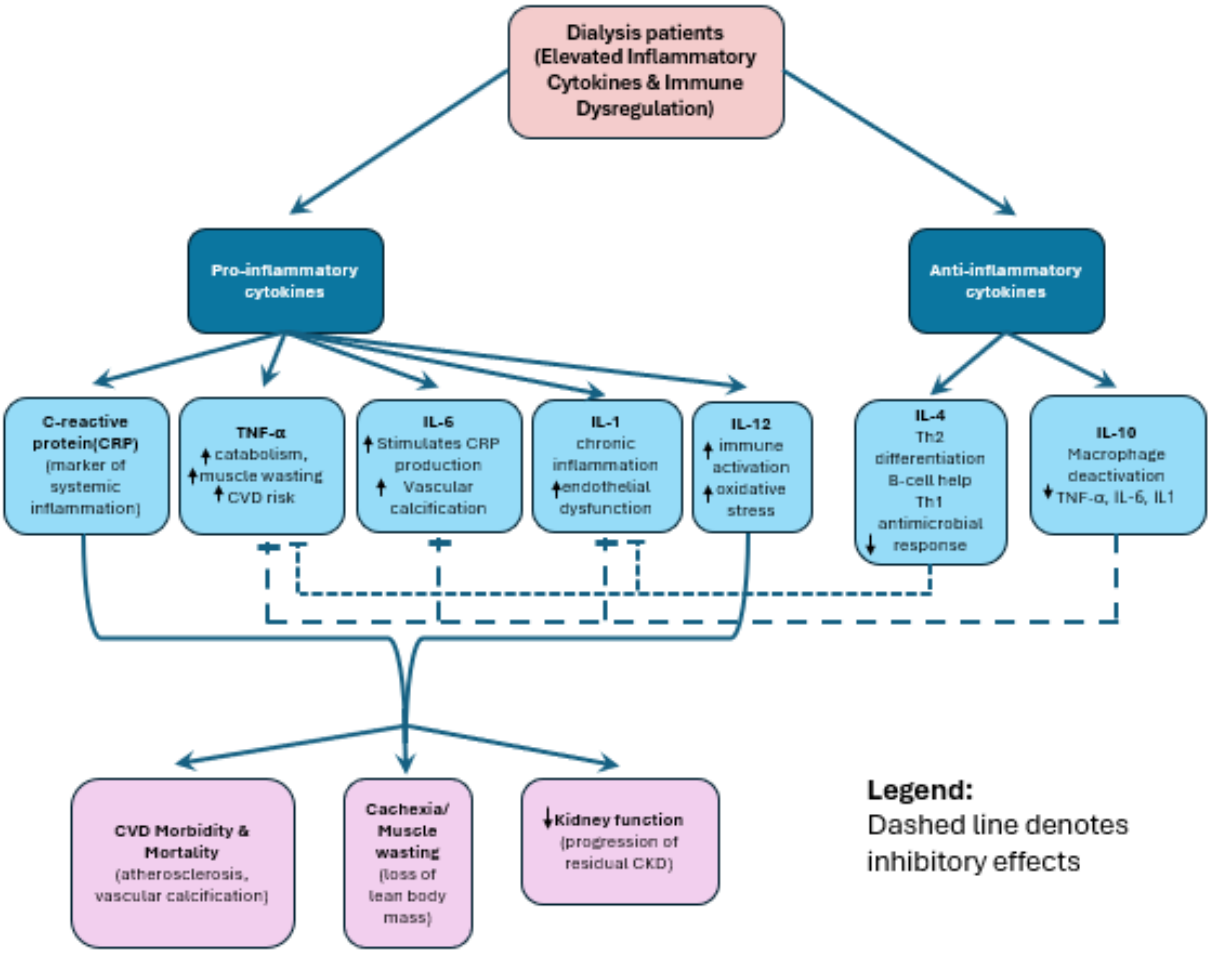

Figure 2. Interplay of pro- and anti-inflammatory cytokines in dialysis patients and their clinical consequences.

II. COMMON INFLAMMATORY MARKERS IN DIALYSIS PATIENTS

Dialysis patients frequently have chronic inflammation due to several factors, such as uremia, comorbidities, and the dialysis procedure itself. This is largely attributable to persistently elevated inflammatory markers, reflecting the frequent occurrence of systemic inflammatory disorders in this population [13,14] . Consequently, cardiovascular events, the progression of kidney disease, impaired motor function and protein energy wasting, cognitive decline, and other adverse effects such as anemia, insulin resistance, CKD mineral and bone issues, are some of these unfavorable outcomes [15].

The term "inflammatory markers" refers to a broad range of molecules that indicate the existence and degree of inflammation in the body. Specifically, these markers include CRP, the interleukin (IL) family (e.g., IL-1β, IL-1 receptor antagonist, IL-6), and TNF-α. These are the common types of inflammatory markers, and they are inversely associated with kidney function but positively associated with albuminuria [16,17]

In contrast, other cytokines like IL-4, IL-10, and IL-12 have emerged as potential prognostic indicators, reflecting the complex interplay between pro- and anti-inflammatory processes in dialysis [18,19]. These cytokines have generated attention because of their potential anti-inflammatory properties in dialysis patients. The following are common inflammatory markers revealed in patients undergoing dialysis:

A. C-Reactive Protein (CRP)

CRP, an acute-phase reactant protein synthesized in the liver, is an inflammatory marker that is frequently linked to CKD. Notably, elevated CRP is increasingly recognized as a biomarker of systemic inflammation in CKD and has been linked to adverse clinical outcomes, including higher morbidity and mortality [20,21]. In CKD patients, an elevated CRP level is a known predictor of cardiovascular events and an independent factor for all-cause mortality in ESRD. Some literature also highlights that CRP can be produced by many inflammatory cells, such as the intrinsic renal cells, namely the tubular and endothelial cells, and macrophages, which is more apparent in patients with renal disease [22,23]. The pathogenesis of renal inflammation and fibrosis in renal diseases has also been linked to high CRP [24].

As such, in dialysis patients, CRP levels are often higher than normal due to the chronic inflammation associated with ESRD and multiple comorbid conditions. This persistent inflammatory state contributes significantly to the high morbidity and mortality rates in this population. For example, elevated CRP has been strongly implicated in the pathogenesis of cardiovascular disease, which remains the leading cause of death in dialysis patients. In a study by Bazeley et. al, among patients on hemodialysis of more than 90 days, Japan demonstrated the lowest CRP median (1.0 mg/L; Interquartile Range [IQR], 0.5 to 3.1) compared to European, Australian, and New Zealand countries (ANZ; 6.0 mg/L; IQR 3.0 to 14.0) [25]. At the biomolecular level, CRP is seen to promote endothelial dysfunction by impairing nitric oxide bioavailability, initiating the inflammatory cascade within the vascular endothelium, and promoting the adhesion of leukocytes to the endothelial surface [26]. Thus, these processes ultimately lead to vascular inflammation, atherosclerosis, and an increased risk of cardiovascular events.

Furthermore, CRP is closely associated with markers of malnutrition and inflammation in dialysis patients. Hypoalbuminemia, a common finding in this population, reflects both malnutrition and inflammation and is inversely correlated with CRP levels [27]. Additionally, elevated CRP levels are also associated with increased levels of pro-inflammatory cytokines such as IL-6 and TNF-α, further perpetuating the inflammatory cascade and contributing to adverse outcomes [28].

Notably, knowing the benefit of reducing inflammation, a recent Anti-Cytokine Therapy for Hemodialysis InflammatION (ACTION) trial, a pilot, multicenter, randomized, placebo-controlled trial of an IL-1 receptor antagonist, anakinra, has been conducted, and the safety, tolerability, and feasibility have been achieved. The trial demonstrated promising results, with a median decrease in hsCRP from baseline to week 24 of 41% in the anakinra group and 6% in the placebo group [29].

Many clinical investigations have revealed the importance of CRP as a predictive factor in dialysis patients. Raised CRP levels are a poor prognostic predictor in dialysis patients as a biomarker for systemic inflammation as well as mortality prediction in hemodialysis patients [25,30]. Similarly, even after controlling for conventional cardiovascular risk factors, a prospective cohort study by Ducloux et al. reported that higher baseline CRP levels were predictive of mortality in hemodialysis patients [31].

In summary, CRP serves as a valuable biomarker for assessing systemic inflammation and predicting poor outcomes in dialysis patients. Its association with cardiovascular disease, malnutrition, and inflammation emphasizes its importance in risk stratification and therapeutic decision-making in this high-risk population. Additionally, CRP measurement offers a practical and cost-effective approach to routine monitoring compared to other inflammatory markers. The inclusion of CRP in the overall risk assessment of dialysis patients is an added value that further emphasises its clinical applicability.

B. Tumor Necrosis Factor-alpha (TNF-α)

TNF-α is mostly produced by activated T lymphocytes and macrophages, while it can also be produced by endothelial cells, fibroblasts, and adipocytes [32]. It functions as a major immune response mediator and is essential for controlling inflammation, cell division, proliferation, and apoptosis. Initially secreted as a transmembrane protein precursor, TNF-α is subsequently converted to its physiologically active soluble form by the metalloprotease TNF-α Converting Enzyme (TACE) [33].

Moreover, TNF-α has been linked to the development of chronic inflammation in dialysis patients, which is a defining characteristic of ESRD. Elevated levels of TNF-α are inversely associated with the function of the kidneys [34]. Patients on dialysis frequently have elevated TNF-α levels, which are linked to higher rates of morbidity and mortality.

TNF-α uses a variety of methods to negatively impact health. First, TNF-α causes the synthesis of pro-inflammatory

cytokines of interleukin-1 beta (IL-1β) and IL-6, as well as the activation of immune cells of neutrophils and macrophages, which prolongs the inflammatory cascade [34,35]. Conversely, chronic inflammation plays a role in the onset and advancement of infections, cardiovascular disease, and other comorbidities that are frequently seen in dialysis patients.

Furthermore, TNF-α is essential in causing endothelial dysfunction, which is a critical step in the development of cardiovascular problems in dialysis patients. TNF-α causes apoptosis and endothelial cell activation, interferes with the function of the endothelium barrier, and increases the expression of adhesion molecules like Intercellular Adhesion Molecule-1 (ICAM-1) and Vascular Cell Adhesion Molecule-1 (VCAM-1) that aid in the adhesion and recruitment of leukocytes to the vascular endothelium and encourage thrombosis and atherosclerosis [36].

Additionally, TNF-α has a role in the emergence of insulin resistance and metabolic disorders seen in dialysis patients. Hence, it disrupts insulin signaling pathways, impairing the absorption and utilization of glucose, and encourages lipolysis and malfunction of adipose tissue, which exacerbates dyslipidemia and the metabolic syndrome [37]. However, it is undeniable that dialysis patients are more susceptible to cardiovascular disease and mortality as a result of these metabolic abnormalities. Due to this, recent advances in medicine promote anti-TNF-α treatment strategies that could tackle insulin resistance and the development of type 2 diabetes.

TNF-α also causes muscular atrophy and suppresses erythropoiesis, which all contribute to the anemia and Malnutrition-Inflammation Complex Syndrome (MICS) that are frequently seen in dialysis patients. In this cohort, lower quality of life, higher morbidity, and mortality are linked to anemia and MICS [38].

Overall, TNF-α emerges as a key mediator of inflammation, endothelial dysfunction, metabolic abnormalities, and erythropoiesis inhibition in dialysis patients, contributing to the risk and development of cardiovascular disease, infections, anemia, and malnutrition. Therefore, targeting TNF-α and its attenuating signaling pathways may represent a promising therapeutic approach for mitigating inflammation and improving outcomes in this vulnerable population.

C. Interleukin-1

A cytokine called interleukin-1 (IL-1) is important in the control of inflammation and immunological responses. According to Dinarello et al., IL-1 is essential for several physiological functions, such as hematopoiesis, host defence, and inflammation resolution [39]. Hundreds of secondary inflammatory mediators are synthesized and expressed by IL-1, a pro-inflammatory mediator of both acute and chronic inflammation (39)(40). In particular, there are two isoforms of IL-1. (i) IL-1α and (ii) IL-1β, which are produced by different cells such as monocytes, macrophages, and dendritic cells. IL-1 receptor antagonist or IL-1RN has been revealed to have a protective effect on renal function [41].

Since dialysis patients frequently suffer from cardiovascular disease and Systemic Inflammatory Response Syndrome (SIRS), IL-1 has drawn attention in the context of dialysis for its role in inflammation-related problems [42]. Moreover, patients on hemodialysis have been reported to have high levels of IL-1β, which may be a factor in the chronic inflammatory state that is typical of ESRD [43,44].

On the other hand, Vanholder et al. suggested that dialysis-associated inflammatory stimuli and immunological dysfunction caused by uremia could be the cause of the elevated IL-1 production in these individuals [42]. Thus, to reduce inflammation and enhance outcomes for dialysis patients, methods for modifying IL-1 signaling have been investigated.

Genetic studies demonstrated that cytokine gene polymorphisms, especially IL-1 receptor antagonist, are strongly associated with susceptibility to ESRD (45). Several single-nucleotide gene polymorphisms, such as IL-1B -5887, IL-1B -3953, IL-1RN + 8006, and the IL-1RN 86 bpVNTR polymorphisms, have been associated as potential risk factors for developing ESRD. Therefore, understanding the role of the IL-1 gene cluster in chronic inflammation may be key to slowing the decline in kidney function observed in ESRD.

In summary, IL-1 plays a significant role in inflammation and immune regulation, with implications for dialysis patients. Thus, future research is warranted to elucidate the precise mechanisms underlying IL-1 dysregulation in the context of dialysis and to explore targeted therapeutic approaches.

D. Interleukin-4 (IL-4)

The main producers of the multifunctional cytokine interleukin-4 (IL-4) are mast cells, basophils, and activated T lymphocytes. It is essential for controlling immunological responses, especially when it comes to allergic reactions and the host's ability to fight off parasites [46]. Hence, by attaching to a particular receptor, IL-4 activates signaling pathways that are subsequently implicated in immunological regulation, cell proliferation, and differentiation.

Due to immunological dysfunction and chronic inflammation linked to ESRD, IL-4 levels are frequently dysregulated in dialysis patients. However, despite being able to inhibit pro-inflammatory reactions and encourage the development of T-helper 2 (Th2) cells, IL-4 is generally regarded as an anti-inflammatory cytokine. Nevertheless, its function in dialysis patients is more complicated [50]. Consequently, research has indicated that different subgroups of dialysis patients may have higher or lower amounts of IL-4, depending on whether they have compromised Th2 cell function or concurrent allergy diseases or parasite infections [47].

The probable involvement of IL-4 in regulating immune responses and inflammation makes it significant for dialysis patients. Immunoglobulin class flipping to IgE and IgG4 subclasses, which are involved in allergic responses and immunological tolerance, respectively, has been linked to IL-4's control of B cell function [48]. Dialysis patients may be more susceptible to infections and allergy reactions due to dysregulation of IL-4-mediated immune responses.

Furthermore, the primary cause of death for dialysis patients, cardiovascular disease, may be influenced by IL-4. IL-4 is widely thought to be anti-atherogenic due to its ability to limit the production of pro-inflammatory cytokines and inhibit the expression of adhesion molecules. However, under some circumstances, investigations have revealed that IL-4 may actually accelerate the development of atherosclerosis [49].

The intricate interaction between immunological responses and cardiovascular function in dialysis patients is highlighted by the dual effects of IL-4.

Moreover, IL-4 might affect how dialysis patients react to standard therapy methods, including immunosuppressive drugs and Erythropoiesis-Stimulating Agents (ESAs). Notably, IL-4 may play a part in the treatment of anemia in dialysis patients as it has been demonstrated to regulate erythropoiesis by boosting erythropoietin receptor expression and encouraging the differentiation of erythroid progenitor cells [50]. Furthermore, by controlling T cell activation and differentiation, IL-4 may impact the safety and effectiveness of immunosuppressive treatments, hence affecting the risk of infection and rejection in transplant recipients.

Overall, IL-4 emerges as a multifaceted cytokine with diverse roles in modulating immune responses, inflammation, and cardiovascular health in dialysis patients. Thus, further research is needed to elucidate the precise mechanisms underlying the effects of IL-4 in this population and to explore its potential as a therapeutic target for improving outcomes in dialysis patients.

E. Interleukin-6 (IL-6)

Interleukin-6 (IL-6) is an important cytokine that has multiple functions. It promotes inflammation by acting on the immune response and inflammation [51]. In reaction to a variety of stimuli, such as infection, injury, and inflammation, it is produced by a variety of cell types, including leukocytes, macrophages, and endothelial cells [52]. By attaching itself to a particular receptor, IL-6 activates signaling pathways that are subsequently implicated in tissue repair, inflammation, and immunity.

Additionally, elevated IL-6 levels are commonly seen in dialysis patients and are a sign of chronic inflammation, which is a characteristic of ESRD. Increased IL-6 levels in dialysis patients have repeatedly been linked to unfavorable clinical outcomes, such as cardiovascular events, infections, and death [27]. Previous reports have revealed that high IL-6 values are associated with coronary artery calcification and mortality among dialysis patients [53]. Hence, this highlights the significance of IL-6 as a prognostic marker in this high-risk group, as demonstrated by this connection.

However, IL-6 has a negative impact on health by various mechanisms. IL-6 stimulates hepatocytes to produce acute-phase proteins, like CRP, which intensifies the inflammatory response and adds to the systemic inflammatory state seen in dialysis patients [26]. As cardiovascular disease is the primary cause of death in this population, CRP exacerbates inflammation and plays a role in its pathophysiology.

Furthermore, endothelial dysfunction is induced by IL-6. Atherosclerosis and thrombosis are encouraged by endothelial dysfunction, which is characterized by decreased nitric oxide bioavailability, elevated adhesion molecule expression, and increased vascular permeability [54]. Additionally, vascular endothelial cells produce Reactive Oxygen Species (ROS) in response to IL-6 stimulation, which results in oxidative stress, endothelial dysfunction, and vascular damage.

Moreover, IL-6 is a major factor in the immunological dysregulation that dialysis patients experience. It alters the way that T cells, B cells, and macrophages function, which compromises immunological responses and makes people more vulnerable to infections [54]. The high number of infections seen in dialysis patients is partly caused by this dysregulated immune response, which exacerbates morbidity and mortality rates.

Overall, IL-6 emerges as a key mediator of inflammation and immune dysregulation in dialysis patients, contributing to the pathogenesis of cardiovascular complications, infections, and mortality. Targeting IL-6 and its downstream signaling pathways may represent a promising therapeutic strategy for mitigating inflammation and improving outcomes in this vulnerable population.

F. Interleukin-10 (IL-10)

Interleukin-10 (IL-10) is an important anti-inflammatory cytokine that is vital for immune response regulation and maintaining immunological homeostasis. It is produced by immune cells such as T cells, B cells, macrophages, and dendritic cells when the body encounters inflammatory stimuli. Consequently, by attaching to its particular receptor, IL-10 binds to its target and activates downstream signaling pathways that decrease the production of pro-inflammatory cytokines, prevent the presentation of antigens, and enhance immunological tolerance [55].

Moreover, because of its immunomodulatory and anti-inflammatory properties, IL-10 may have an impact on the cardiovascular health of dialysis patients. It has been demonstrated that IL-10 reduces endothelial dysfunction and atherosclerosis by suppressing the expression of adhesion molecules and the synthesis of pro-inflammatory cytokines in vascular endothelial cells [56]. Furthermore, IL-10 may inhibit foam cell production and macrophage activation, two important processes in the etiology of cardiovascular disease.

Overall, it appears that IL-10 plays a crucial role in controlling inflammation and immunological responses in dialysis patients, which may have consequences for the treatment of immune-related problems and cardiovascular disease. However, immune-mediated problems like autoimmune disorders and infections, which are frequently observed in dialysis patients, may give rise to the dysregulation of IL-10-mediated immune responses. Therefore, despite being able to reduce tissue damage and suppress pro-inflammatory responses, IL-10 is not able to play its role well.

Nonetheless, its function in dialysis patients is more complicated [57]. Research has indicated that while IL-10 levels may be reduced in some dialysis patients, indicating immunological dysregulation and compromised regulatory T cell activity, they may be raised in other subsets of patients, especially those with concurrent infections or autoimmune disorders [58]. Thus, additional investigation is required to clarify the exact processes that underlie IL-10's effects in this particular population and to investigate its potential as a therapeutic target to enhance dialysis patients' health outcomes.

G. Interleukin-12 (IL-12)

Interleukin-12 (IL-12), a heterodimeric cytokine, is made up of two subunits, p35 and p40 [59]. It is generated in response to microbial pathogens and other inflammatory stimuli. Antigen-presenting cells, such as macrophages, dendritic cells, and monocytes, are essential for controlling

both innate and adaptive immune responses, especially when it comes to cell-mediated immunity and Th1 cell development.

The potential involvement of IL-12 in regulating immune responses and inflammation makes it significant for dialysis patients. IL-12 is essential for naive T cells to polarize towards the Th1 cell lineage, which in turn triggers the generation of Interferon-gamma (IFN-γ) and activates cell-mediated immune responses against intracellular pathogens [60].

Furthermore, IL-12 may affect how dialysis patients react to standard therapy methods, including immunosuppressive drugs and ESAs. It has been demonstrated that IL-12 influences T cell activation and differentiation, which may have an impact on transplant recipients' safety and effectiveness when receiving immunosuppressive treatments [66]. Notably, by encouraging the development of erythroid progenitor cells, IL-12 may regulate erythropoiesis, which may have implications for the treatment of anemia in dialysis patients [61].

In addition, due to its effects on inflammation and immunological responses, IL-12 may have an impact on dialysis patients' cardiovascular health. It has been demonstrated that IL-12 induces endothelial cell activation and dysfunction and promotes the production of pro-inflammatory cytokines, including TNF-α and IL-6, which gives rise to the pathophysiology of cardiovascular disease [68]. Furthermore, IL-12 may promote the activation and multiplication of vascular smooth muscle cells, which could result in atherosclerosis and vascular remodeling.

In dialysis patients, IL-12 is generally demonstrated to be a crucial regulator of immunological responses and inflammation, with possible ramifications for the treatment of immune-mediated problems and cardiovascular disease. Hence, to fully understand the processes underlying IL-12's impacts in this group and investigate its potential as a therapeutic target to improve dialysis patient outcomes, more research is required.

However, dialysis patients may have dysregulated levels of IL-12 due to immunological dysfunction and chronic inflammation, including infections and autoimmune illnesses, that accompany ESRD. Nevertheless, despite being widely regarded as a pro-inflammatory cytokine due to its capacity to stimulate Th1 cell differentiation and IFN-γ production, IL-12 has a complicated role in dialysis patients [69]. Additionally, research has indicated that while IL-12 levels may be reduced in some dialysis patients, indicating immunological dysregulation and compromised Th1 cell function, they may be raised in other subsets of patients, especially those with concurrent infections or inflammatory diseases [62].

H. Neutrophil and lymphocyte count, Neutrophil-to-Lymphocyte Ratio, and Platelet-to-Lymphocyte Ratio

Numerous studies and discussions have highlighted the pro-inflammatory function of neutrophils and lymphocytes in immune system modulation as a significant inflammatory signal [63,64]. As an illustration, higher rates of lymphocyte apoptosis have been linked to unfavorable cardiovascular events, elevated infection risk, and systemic inflammation [65,66]. Studies by Mureşan et al, which included 461 end-stage kidney disease patients, demonstrated the detrimental effects of elevated neutrophil counts and decreased lymphocyte numbers [64].

Moreover, literature from recent years has established the predictive role of biomarkers for both the course of CKD and its adverse outcomes. This finding highlights the correlation between high Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) values and the development of CKD into ESKD, and consequently, a high mortality rate in multiple studies (67)(68)(69). Furthermore, platelets are crucial for both immunological responses and the inflammatory process [70.71]

III. OTHER CHRONIC INFLAMMATORY MARKERS

Fibrinogen is an acute-phase reactant that is elevated in response to inflammation. Chronic elevation of fibrinogen levels is associated with increased cardiovascular risk and mortality in dialysis patients. Conversely, serum albumin level is another inflammatory marker. However, although primarily regarded as a marker of nutritional status, low serum albumin levels also reflect chronic inflammation and are associated with increased mortality risk in dialysis patients. Additionally, elevated levels are commonly observed in dialysis patients and may reflect chronic inflammation, iron overload, or both.

On the other hand, recent research using National Health and Nutrition Examination Survey (NHANES) 2001–2018 data demonstrated that the Neutrophil Percentage-to-Albumin Ratio (NPAR) is linked to both all-cause and cardiovascular mortality in CKD [72]. Consequently, the findings highlight a non-linear relationship with all-cause mortality and a positive association with cardiovascular mortality. As a simple, low-cost marker, NPAR outperformed traditional inflammatory indicators in predicting mortality, making it a valuable tool for risk stratification and personalized management [72].

High ferritin levels have been associated with increased cardiovascular risk and mortality in this population. Erythrocyte Sedimentation Rate (ESR) is a nonspecific marker of inflammation that may be elevated in chronic inflammatory conditions. ESR, although less commonly used in clinical practice, can provide additional information about the inflammatory status of dialysis patients.

IV. NEWLY STUDIED CHRONIC INFLAMMATORY MARKERS

There is no limit in science, and so is the development and recovery of new findings in chronic inflammatory markers. Hence, several studies have been conducted, revealing important inflammatory markers that may play a significant role in the prognostication of dialysis patients. These include high-sensitivity troponins, Pentraxin-3, and soluble ST2.

A. High-sensitivity troponins

Multiple mechanisms cause troponin levels to increase in CKD patients. Among them are increased small vessel coronary artery obstruction, transmural pressure, intracellular oedema, endothelial dysfunction, and the direct cytotoxicity of uremia. Furthermore, the troponin elevation in dialysis patients is partly due to the rapid exchange of fluid through the dialysis

membrane. This process reduces the perfusion of coronary flow and thus encourages microvascular damage or obstruction. In addition to that, because the kidneys help clear troponin from the circulation, its levels are elevated in ESRD due to the inability to clear it due to insufficient kidney function.

Moreover, the highly sensitive cardiac troponin (hs-cTn) measurement can detect small troponin concentrations and produce small changes in biomarkers. Elevated hs-Tn levels may indicate myocardial injury or damage, which can occur in dialysis patients due to cardiovascular disease or other complications. Thus, the elevation due to cardiac injury as a result of myocardial infarction still needs to be ruled out. Nonetheless, high-sensitivity troponins, traditionally used for the diagnosis of myocardial infarction, have demonstrated promise as prognostic markers for cardiovascular events and mortality in dialysis patients. As a result, these markers provide insights into myocardial injury and may assist in identifying patients at higher risk of poor cardiovascular outcomes.

B. Pentraxin-3

Pentraxin-3, a member of the pentraxin family, is a novel inflammatory marker associated with cardiovascular disease and endothelial dysfunction in ESRD. Recent studies have investigated the prognostic value of pentraxin-3 in dialysis patients, suggesting its potential utility in risk stratification and monitoring of inflammatory status.

Pentraxins are a family of proteins involved in the acute-phase response to inflammation. However, while CRP is the most well-known pentraxin, other members of this family, such as Pentraxin-3 (PTX3), are being investigated for their roles as inflammatory markers in various disease states, including CKD.

C. Soluble ST2

A member of the IL-1 receptor family known as soluble ST2 (sST2) has emerged as a promising tool for the prognosis and risk assessment of chronic diseases, including heart failure and CKD. sST2 levels are associated with inflammation, cardiovascular events, and all-cause mortality in dialysis patients, making it a valuable marker for identifying individuals at risk. Furthermore, it has also been reported that soluble sST2 is a promising marker of adverse cardiovascular events in patients undergoing dialysis.

Additionally, further research is needed to validate these novel inflammatory markers and elucidate their role in improving risk stratification and guiding therapeutic interventions in dialysis care. Table 1 depicts different types of inflammatory markers and how they relate to dialysis patients. It explains their functions, examples of each type, and how they can help predict health problems and guide treatment plans.

Table 1. Inflammatory markers and their prognostic implications in dialysis patients

Category	Markers	Function / Role	Clinical Implication
Established Prognostic Markers	C-Reactive Protein (CRP) Interleukin-6 (IL-6) Tumor Necrosis Factor-alpha (TNF-α)	Pro-inflammatory cytokines Reflect systemic inflammation	Strong association with mortality, cardiovascular events, and disease progression
Anti-Inflammatory / Modulatory Interleukins	Interleukin-4 (IL-4) Interleukin-10 (IL-10) Interleukin-12 (IL-12)	Modulate immune response Act in opposition to pro-inflammatory markers	Potentially protective, need further investigation
Emerging Biomarkers	High-sensitivity Troponins Pentraxin-3 Soluble ST2	Novel biomarkers indicating cardiovascular stress and inflammation	Promising tools for improved risk stratification and personalized therapy

V. INTERACTION OF INFLAMMATORY MARKERS IN DIALYSIS PATIENTS & RELATIONSHIP BETWEEN INFLAMMATORY MARKERS AND DIALYSIS OUTCOMES

As has been described above, it is an undeniable fact that elevated inflammatory markers in CKD and chronic dialysis patients are associated with poor clinical outcomes.

In this section, the interaction of IL-4, IL-6, IL-10, IL-12, TNF-α, and CRP and their implications for the health outcomes of dialysis patients are examined.

IL-6, a pro-inflammatory cytokine, stands out as a key mediator in the inflammatory cascade observed in dialysis patients. Elevated levels of IL-6 have been consistently associated with adverse outcomes, including increased mortality rates and a decline in kidney function among individuals undergoing dialysis [8].

In contrast, IL-10, an anti-inflammatory cytokine, plays an important role in counteracting the pro-inflammatory effects of cytokines like IL-6 and TNF-α. IL-10 exerts immunomodulatory effects by reducing the production of pro-inflammatory cytokines and inhibiting the activation of immune cells.

Similarly, IL-4, another anti-inflammatory cytokine, exerts immunomodulatory effects by promoting the differentiation of Th2 cells and inhibiting the activation of pro-inflammatory pathways. IL-4 has been demonstrated to mitigate inflammation and tissue damage in various disease models, including CKD. In the context of dialysis patients, IL-4 may play a beneficial role in modulating the immune response and reducing the risk of inflammation-related complications. However, further research is warranted to elucidate the specific mechanisms underlying the protective effects of IL-4 in dialysis patient outcomes.

Conversely, IL-12, a pro-inflammatory cytokine, promotes the differentiation of T-helper 1 (Th1) cells and enhances the production of pro-inflammatory cytokines such as IFN-γ. Furthermore, in the context of CKD and ESRD, dysregulated IL-12 signaling may exacerbate the inflammatory response and contribute to the development of cardiovascular disease and other comorbidities. Thus, while IL-12 serves as a critical mediator of immune responses, its excessive activation may predispose dialysis patients to adverse health outcomes.

TNF-α, another pivotal inflammatory mediator, exerts pleiotropic effects on immune cells and tissues, contributing to the pathogenesis of various inflammatory conditions. In dialysis patients, TNF-α has been implicated in the development of cachexia, cardiovascular disease, and other complications associated with chronic inflammation [7]. The dysregulation of TNF-α signaling may exacerbate systemic inflammation and contribute to poor health outcomes in dialysis patients. However, TNF-α also plays a role in immune surveillance and host defence mechanisms, highlighting the complex and multifaceted nature of its effects in dialysis patient care.

Elevated levels of CRP have been consistently correlated with increased cardiovascular morbidity and mortality rates in this population [28]. CRP may serve as a valuable prognostic tool in identifying high-risk patients who may benefit from targeted interventions to mitigate cardiovascular risks. However, the exact mechanisms underlying the association between CRP and adverse health outcomes in dialysis patients remain to be fully elucidated.

In conclusion, the interaction of inflammatory markers such as IL-4, IL-6, IL-10, IL-12, TNF-α, and CRP plays a critical role in shaping the health outcomes of dialysis patients. Nevertheless, while IL-10 and IL-4 exhibit anti-inflammatory properties and may confer protective effects against inflammation-related complications, IL-12 and TNF-α may exacerbate systemic inflammation and contribute to poor health outcomes. Additionally, CRP serves as a valuable prognostic marker but requires further investigation to clarify its mechanistic link to adverse health outcomes in dialysis patients. Therefore, a comprehensive understanding of the interplay between these inflammatory markers is essential for developing targeted therapeutic strategies and improving outcomes in this vulnerable dialysis population.

VI. USE OF INFLAMMATORY MARKERS IN RISK STRATIFICATION AND PROGNOSTICATION

The utilisation of inflammatory markers in risk stratification and prognostication among dialysis patients is paramount, facilitating the identification of individuals at increased risk of adverse outcomes. For instance, elevated levels of well-established inflammatory markers, including CRP, IL-6, and TNF-α, provide valuable prognostic insights that go beyond conventional risk factor assessments [34].

CRP in particular can play a very important role in guiding clinicians in the management, as its measurement is widely available and can be easily incorporated into the usual clinical review of dialysis patients. In addition, beyond their role in predicting mortality, cardiovascular events, and hospitalisations, these markers also hold significance as adjuncts in anticipating other adverse outcomes among dialysis patients. These outcomes include cardiovascular disease progression, vascular access dysfunction, and reduced quality of life. Moreover, recognition of these associations allows clinicians to implement timely preventive or therapeutic strategies aimed at mitigating these risks, improving overall quality of care.

By integrating inflammatory markers into existing risk stratification algorithms, healthcare providers can evaluate more precisely the comprehensive risk profile of dialysis patients, enabling tailored interventions. For instance, patients exhibiting elevated CRP levels may necessitate intensified surveillance for cardiovascular events and could potentially benefit from more aggressive management of cardiovascular risk factors. However, while therapies specifically aimed at lowering inflammatory markers have not yet demonstrated clear clinical utility in dialysis patients, recognition of elevated inflammatory markers remains clinically relevant. Their presence should prompt the optimization of established measures aimed at minimizing complications, including strict cardiovascular risk factor control, appropriate dialysis strategies, and comprehensive management of comorbid conditions. Table 2 provides a structured summary of the role of inflammatory markers in risk stratification and prognostication among dialysis patients. It outlines the purpose, key biomarkers, predictive value, clinical integration into risk algorithms, and potential management strategies, thereby emphasizing their clinical utility in improving patient outcomes.

It is important to note that across kidney failure cohorts, inflammation chiefly predicts survival rather than access to transplantation. In incident waitlisted candidates, a one-standard-deviation increase in log IL-6, soluble TNF Receptor-1 (sTNFR1), and CRP raised the subdistribution hazard of waitlist mortality by 68%, 38%, and 23%, respectively. In dialysis meta-analyses, higher IL-6 and NLR consistently tracked increased all-cause mortality. Conversely, adjusted associations with time-to-transplant have not been demonstrated, and transplantation is typically treated as a competing outcome [73,74,75].

Table 2 . Use of inflammatory markers in risk stratification and prognostication

Aspect	Details
Purpose	Identify dialysis patients at higher risk of adverse outcomes
Key Markers	- C-Reactive Protein (CRP) - Interleukin-6 (IL-6) - TNF-α
Predictive Value	- Mortality - Cardiovascular events - Hospitalizations - Disease progression - Vascular access issues - Reduced quality of life
Clinical Integration	Included in risk stratification algorithms to improve overall risk evaluation
Tailored Interventions	- More frequent monitoring for high-risk individuals - Intensive management of risk factors
Management Strategies	- Anti-inflammatory medications - Lifestyle modifications to reduce inflammation

VII. POTENTIAL FOR PERSONALIZED TREATMENT STRATEGIES

Inflammation presents itself as a promising avenue for intervention in CKD, as reviewed by Shacham et al. (76). Both pharmaceutical and non-pharmacological therapies have demonstrated their effectiveness in mitigating chronic systemic inflammation in patients with CKD and chronic dialysis requirements. Notably, the measurement of inflammatory markers presents an opportunity for personalized treatment strategies in dialysis patients. Hence, by assessing the inflammatory status of individual patients using markers, healthcare providers can tailor treatment approaches to address underlying inflammation and mitigate associated risks. For example, through observational studies and clinical trials, specific exercises and stress reduction techniques have proven effective in reducing inflammation.

Furthermore, agents, such as statins and RAAS blockers, which include Angiotensin-Converting Enzyme (ACE) inhibitors, have promise in lowering inflammatory markers and improving outcomes in dialysis patients. Other pharmacological therapies that have an additional anti-inflammatory advantage include finerenone and pentoxifylline. Additionally, finerenone reduces the risk of kidney function decline and cardiovascular death in patients associated with type 2 diabetes, while pentoxifylline improves renal function in CKD and reduces proteinuria. However, the latter two therapies are yet to be proven for use in dialysis patients.

By meticulously addressing inflammation in a targeted manner, personalized treatment approaches have the potential to improve outcomes, diminish complications, and optimize the quality of life in dialysis patients. Notably, this approach offers a potentially unique and alluring avenue that promises improved prognosis among the dialysis population. Nevertheless, while evidence suggests that various treatment modalities can reduce systemic inflammatory indicators, further research is warranted to provide robust proof that interventions targeting inflammation within the population can indeed lead to better clinical outcomes.

VIII. CHALLENGES AND LIMITATIONS IN CLINICAL APPLICATION POTENTIAL FOR PERSONALIZED TREATMENT STRATEGIES

In the field of dialysis patient care, understanding inflammatory markers provides crucial insights into pathophysiology and prognosis. However, their clinical application faces formidable challenges and limitations. One major hurdle lies in the lack of standardization across the measurement and interpretation of these markers. While assay methods are seldom standardized, studies also document high within and between-patient variability even among stable individuals [77,78]. With variability in assay methods, reference ranges, and cut-off values, achieving comparability and reproducibility across studies and clinical settings becomes difficult.

Moreover, the dynamic nature of inflammation poses another obstacle. Interpretation of inflammatory marker levels over time is complicated by fluctuations due to acute illnesses, infections, or interventions, which can obscure baseline levels and impede risk stratification efforts. Research reveals that up to 30% of patients shift CRP tertiles over short periods, with acute events provoking rapid marker increases [77,79]. Additionally, the lack of specificity in predicting particular outcomes further hampers their clinical utility. Nonetheless, while markers like CRP and IL-6 are linked to adverse outcomes, their inability to pinpoint individual risk factors or diseases complicates the differentiation between inflammation-driven pathology and other causes [80,81].

Furthermore, the diversity within dialysis populations, encompassing variations in age, comorbidities, and dialysis modalities, further complicates the interpretation and generalizability of inflammatory marker data [82]. Conversely, emerging evidence suggests that dialysis modality and nutritional status significantly influence inflammatory marker levels and their variability over time. For instance, in a prospective cohort study, hemodialysis patients demonstrated both higher median levels and greater fluctuations of IL-6 and CRP compared to peritoneal dialysis patients. Furthermore, protein-energy wasting independently predicted this variability, even after adjusting for age, comorbidities, and dialysis vintage (82). The inherent temporal instability of inflammatory markers due to intermittent exposures further complicates interpretation. Meuwese and colleagues highlighted that patients with ESRD experience significant intra-individual variability in serum inflammation, which is driven by transient infections, comorbid episodes, and the intermittent physiological stress of dialysis, suggesting that reliance on single measurements may misrepresent true inflammatory burden [78].

In summary, as depicted in Figure 3, the clinical application of inflammatory markers is hampered by challenges related to variability in standardization, influence from diverse etiologies, limited outcome validation, and the dynamic nature of inflammation. However, despite these challenges, ongoing research endeavors are focused on standardizing assay methods, elucidating inflammation's underlying mechanisms, and discovering novel biomarkers. These efforts offer promising avenues for overcoming these limitations and enhancing the clinical relevance of inflammatory markers in dialysis care.

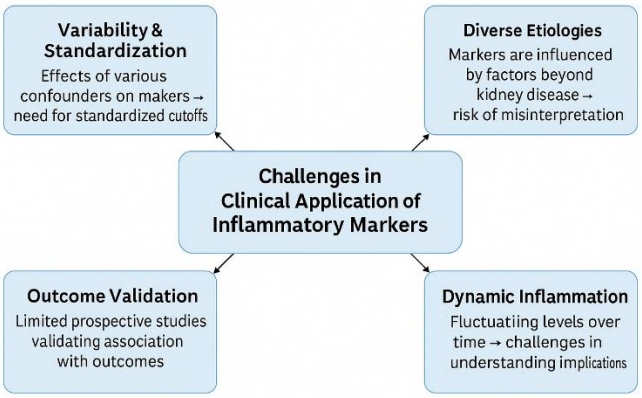

Figure 3. Challenges in the clinical application of inflammatory markers among dialysis patients

IX. CONCLUSIONS

This narrative review has explored the role of inflammatory markers in prognostication among dialysis patients. The review highlights a significant association between elevated inflammatory markers and adverse outcomes, including mortality, cardiovascular events, and other adverse outcomes in this population. Based on this review, key inflammatory markers such as CRP, IL-6, and TNF-α remain as valuable prognostic indicators, providing insights into the inflammatory state and disease progression in dialysis patients. Consequently, these markers, along with IL-4, IL-10, and IL-12, which exert opposite effects, warrant further investigation. Moreover, novel biomarkers such as high-sensitivity troponins, pentraxin-3, and soluble ST2 demonstrate promise for improving risk stratification and guiding therapeutic interventions in the dialysis population. Thus, understanding the mechanisms underlying the effects of these interleukins on inflammation and disease progression is essential for developing targeted therapeutic interventions to improve outcomes. Therefore, further research is needed to unravel the nuanced roles of interleukins and refine therapeutic strategies aimed at mitigating inflammation and improving health outcomes in this vulnerable patient population.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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