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Systemic inflammatory response index in IgA nephropathy; a review to recent findings

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Abstract

Numerous studies have shown that patients with IgA nephropathy (IgAN) exhibit a range of systemic inflammatory indicators that correlate with clinical outcomes. Elevated neutrophil-to-lymphocyte ratios and systemic immune inflammation index scores have been associated with poorer renal survival and strengthened risk of progression to end-stage renal disease (ESRD). The relationship between systemic inflammation and IgAN progression provides valuable insights into potential therapeutic strategies and prognostic implications for cases suffering from this disease. However, this tool has some limitations which should be respected following its application.

Introduction

IgA nephropathy (IgAN) is regarded as a chronic kidney disorder which characterized by the deposition of immunoglobulin A (IgA) in the glomeruli (1). The accumulation of this immunoglobulin leads to an inflammatory process, which is followed by damage to the kidney structure which finally perturb kidney function (2). This disease begins across with the abnormal production and accumulation of IgA in the mesangial area of the glomeruli (3). The triggering factors would be genetic predispositions, infections, and environmental influences (4). Following mesangial IgA deposition, it instigates an inflammatory response, which results in hematuria and proteinuria. In IgAN glomerular inflammation and resultant proteinuria or hematuria, will attribute to renal function disturbance and poor long-term outcomes (5). Several studies pointed out that elevated proteinuria not only serves as a clinical marker of disease severity but also as a predictor of cardiovascular diseases, which are frequently detected in individuals with chronic renal failure due to IgAN (6). Additionally, patients with IgAN have an increased risk for developing high blood pressure and heart diseases (7). One of the typical points of IgAN is a gradual onset and progress over several years. When this disease progresses, it can lead to irreversible kidney disease which finally results to the end-stage renal disease (ESRD) (8). Recently, the systemic inflammatory response index (SIRI) is considered as a new prognostic indicator that serves as an effective tool in the assessment of systemic inflammation(9). It is derived from the ratio of peripheral neutrophil, monocyte, and lymphocyte counts measured through routine blood tests, and is calculated using the formula: SIRI = (neutrophil count × monocyte count)/ lymphocyte count (10). This index reflects the body's inflammatory status along with a significant potential in predicting clinical outcomes across various medical conditions, including infections, cancers, and other chronic conditions (11). The calculation of SIRI integrates three critical components of the immune response; neutrophils, monocytes and lymphocytes, while elevated neutrophil levels often indicate acute inflammation or infection. Besides monocytes play an essential role in tissue repair; since, their numbers can increase in response to systemic inflammation (12). Finally, a decrease count in lymphocyte can suggest an overwhelmed immune responses or chronic inflammation, providing crucial

Key point

The systemic inflammatory response index (SIRI) has emerged as a hopeful biomarker for assessing systemic inflammation and predicting clinical outcomes across various diseases. By integrating neutrophil, monocyte, and lymphocyte counts into a single ratio, SIRI provides insight into the inflammatory state of an individual. This essay explores the significance of SIRI in diverse medical conditions, emphasizing its critical role in the context of IgA nephropathy, a common form of chronic kidney disease (CKD) characterized by immune-mediated renal injury.

context when analyzing inflammation. The interplay of these cell types allows SIRI to reflect a comprehensive view of the inflammatory state in the body (13).

Search strategy

For this review, we searched PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ) and Embase, using different keywords like; systemic inflammatory response index, IgA nephropathy, biomarker, chronic kidney disease and end-stage renal disease.

A short look to the SIRI

The clinical relevance of SIRI lies in its ability to act as a prognostic marker. Prior studies indicated that elevated SIRI levels are significantly associated with increased mortality and adverse outcomes in critically ill patients, particularly those with conditions such as sepsis and acute ischemic stroke (14,15). In acute ischemic stroke patients, higher SIRI levels correlate with a 90-day elevated possibility of all-cause mortality (16). Moreover, SIRI is being actively researched in the context of chronic conditions like chronic renal failure and heart disorder (17). Previous authors have demonstrated that heightened SIRI levels in individuals with chronic kidney disease (CKD) are independently linked to several adverse outcomes (17), establishing it as a potential target for intervention (18). This index also capable to predict the extend to heart disease as well, where elevated SIRI correlates with higher incidences of myocardial infarction (17,18), and stroke (19). For example, the study by Vallianou et al illustrated that chronic renal failure individuals with elevated SIRI not only had higher rates of CKD progression but also faced increased cardiovascular mortality risks, further compounding the severity of their condition (20). Furthermore, increased SIRI can serve as a reliable indicator of patients' inflammatory status, guiding clinical decision-making and management strategies (21). Besides, in cancers, SIRI has been linked to tumor progression and poorer survival rates, underscoring the role of inflammation in malignancy (22). The utility of SIRI as a readily accessible and cost-effective marker derived from routine blood tests renders it particularly appealing in diverse diagnostic settings (23). Recent studies also focus on the interaction of systemic inflammation and kidney involvement, through the activation of inflammatory cytokines and the innate immune response. Meanwhile, high levels of pro-inflammatory cytokines, such as tumor necrosis factor-alpha, interleukin-6, and C-reactive protein have been associated with renal tissue damage (24). Further, inflammation typically leads to increased vascular permeability in renal vasculature, contributing to glomerular damage and dysfunction (25). The presence of inflammatory cells, such as macrophages and T lymphocytes, infiltrates renal tissues and exacerbates inflammatory responses, culminating in oxidative stress and renal fibrosis (26). This process not only impairs glomerular filtration rate but also promotes interstitial fibrosis and scarring, further complicating kidney function (27). Therefore, this index could facilitate timely interventions which may significantly alter patient outcomes across various disease spectrums (28). In a recent study by Petrou et al, kidney failure or death was detected. In half of their IgAN patients in a period follow-up of 5.9 years. They found that systemic inflammation was one of the key indicators of poor prognosis (29). In another comprehensive cohort study by Tang et al on 1420 pre-dialysis patients, higher SIRI levels independently predicted the progression of CKD. This study also showed that patients in the highest quartile of SIRI experienced a significantly increased risk of progressing to advanced-stage CKD. The odds ratio calculated in this analysis was 1.59 (95% confidence interval $P < 0.001$), underscoring the association of elevated SIRI with advanced CKD stages and highlighting its reliability as a predictor independent of other confounding factors (30).

Systemic inflammation in IgAN

More recent studies talk on the critical role of systemic inflammation in the pathophysiology of IgAN. Previous studies noted that the development of IgAN initiates with an abnormal immune response, leading to the production of galactose-deficient IgA1 molecules. Then the altered IgA molecules are recognized as a foreign structure by the immune system, triggering inflammatory pathways following immune complex deposition which culminate in glomerular injury (31,32). In fact, mesangial accumulation of immune complexes induced a cascade of inflammatory events. The deposition also activates the complement system, leading to the generation of complement split products, such as C3a and C5a, which are powerful anaphylatoxins that recruit immune cells and promote inflammation. These complement products facilitate the recruitment of inflammatory cells consisting macrophages and neutrophils into the glomerular causing injury along with exacerbation of inflammatory responses (33,34). The cascade of inflammatory response in this disease also pursued by the production of various pro-inflammatory cytokines that drive renal injury

and fibrosis (35). Activated complement components stimulate mesangial and endothelial cells to release cytokines like tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β), interleukin-6 (IL-6), and other inflammatory mediators (36). TNF-α, for instance, enhances the expression of adhesion molecules on endothelial cells, promoting the recruitment and infiltration of leukocytes into the glomeruli (37). Similarly, IL-6 is crucial for driving the differentiation of B cells and T cells, influencing the immune response and amplifying inflammation in the kidney (38). The activation of the NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) signaling pathway is a hallmark of inflammation within the renal context. NF-κB is a transcription factor that, when activated, leads to the expression of other inflammatory cytokines (39). Another player of this cascade are macrophages, which can adopt pro-inflammatory (M1) or anti-inflammatory (M2) phenotypes, are essential players in renal inflammation. M1 macrophages are typically activated by pro-inflammatory cytokines and contribute to tissue injury through the release of reactive oxygen species (ROS) and additional inflammatory mediators. In conditions of sustained inflammation, such as in chronic renal failure, the prevalence of M1 macrophages increases, driving renal injury and fibrosis (40-42). Similarly, T cells, predominantly CD8+ cytotoxic T cells and CD4+ T helper cells, are integral to the immune response in the renal system. They can aggravate kidney injury by releasing cytokines that sustain inflammation and promote immune-mediated injury (43,44). For example, Th1 cells produce IFN-γ, which activates macrophages, leading to further inflammation and renal injury. The cumulative effect of these mediators contributes to mesangial cell proliferation and the excessive deposition of the extracellular matrix, resulting in glomerulosclerosis and a progressive decline in renal function (45,46). In addition to immune-mediated damage, the renin-angiotensin system (RAS) is implicated in the inflammatory processes of IgAN (47). Activation of RAS leads to the secretion of angiotensin II, a potent vasoconstrictor that increases glomerular pressure and contributes to proteinuria. Angiotensin II also promotes inflammation by stimulating the release of inflammatory cytokines from mesangial and tubular epithelial cells, further exacerbating injury and fibrotic changes (48,49).

Fibrosis is a significant consequence of chronic inflammation in IgAN, wherein TGF-β plays a central role in mediating fibrogenesis. It promotes the proliferation of fibroblasts and the synthesis of collagen and other extracellular matrix components, leading to progressive scarring within the kidney (50,51). Persistent inflammation also leads to glomerulosclerosis, interstitial fibrosis, and tubular atrophy. if this process not controlled efficiently, the fibrotic response can culminate in CKD and end-stage renal failure (52,53). Hence, systemic inflammation seems more than a byproduct of IgAN; since it is integral to understanding disease severity and tailoring treatment approaches.

Limitations of SIRI in IgAN

Despite the potential benefits of this tool, its clinical utility and specificity of SIRI for identifying and managing IgAN have some limitations. One of them addressed its lack of specificity for IgAN compared to other inflammatory conditions. Since this index is calculated from the counts of neutrophils, lymphocytes, and monocytes, all of which can be influenced by numerous factors unrelated to IgAN, including infections, cancer, and autoimmune disorders. Thereby, elevated SIRI level may not lonelily indicate disease progression or activity specific to IgAN; while it may simply reflect a generalized inflammatory reaction. Therefore, it may lead to misinterpretation of SIRI as an indicator of IgAN activity when it affected by other underlying disease (54,55). The second one is confounding factors that significantly affects its clinical applicability. For example, age, sex, ethnic background, comorbidities, and lifestyle choices can influence white blood cell counts and, consequently, SIRI level. Likewise, older adults often exhibit higher inflammatory markers, which may result in elevated SIRI levels regardless of their kidney function (56,57). Another critical limitation of SIRI in this disease is the absence of widely accepted cut-off values for its interpretation. Several studies have proposed varying thresholds for SIRI levels that arguably predict poor outcomes in different patient cohorts, which adds to the ambiguity surrounding its clinical application. Without standardized cut-off values, clinicians may struggle to determine when elevated SIRI levels warrant clinical action or intervention in IgAN management. Consequently, the decision-making process regarding patient care may be hindered due to uncertainty about how to utilize SIRI scores effectively (58,59). Finally, integrating SIRI into routine clinical practice causes challenges too (60,61). Lack of standard protocols for measuring and interpreting SIRI level, across with the complexity of obtaining and understanding complete blood counts and the dynamic nature of inflammation necessitate a full understanding of patient history and current status to accurate SIRI assessment (60).

Conclusion

Systemic inflammation is intricately linked to the pathophysiology of IgAN, influencing disease progression, prognosis, and treatment strategies. It serves not only as a predictor of renal outcomes but also as a target for therapeutic interventions. While this tool provided potential insight into inflammation and clinical outcomes in IgAN, its limitations in clinical applicability and specificity must be carefully considered. The lack of diagnostic specificity, variability stemming from

confounding factors, absence of accepted cut-off values, and challenges related to its integration into clinical workflows all contribute to the complexities surrounding SIRI's use in IgAN. Addressing these limitations through continued research and development of standardized protocols will be essential for enhancing the clinical value of SIRI and improving the management of patients with IgAN in practice.

Authors' contribution

Conceptualization: Seyed Yousef Mojtahedi, Paniz Pourpashang.
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Writing–original draft: Paniz Pourpashang.
Writing–review and editing: All authors.

Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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