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Association Between Biomarkers of Kidney Disorders and Atrial Fibrillation: A Literature Review

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ABSTRACT

Kidney diseases and atrial fibrillation often occur together. Renal impairment increases the risk of developing incident atrial fibrillation (AF) and is linked to it in a bidirectional manner, making it a prothrombotic and pro-hemorrhagic condition. In Japanese patients with nonvalvular AF, lower creatinine clearance values were associated with thromboembolism, all-cause death, and cardiovascular death, but not with major haemorrhage. Older individuals with elevated serum levels of cystatin C had a significantly higher prevalence of AF. Moderate to severe chronic kidney disease individuals with increased levels of fibroblast growth factor-23 were independently associated with prevalent and incident AF. A higher baseline glomerular filtration rate was associated with an increased risk of AF. Elevated levels of insulin-like growth factor binding protein-7 were also observed in AF patients, while reduced circulating tissue inhibitor of metalloproteinase 2 levels were also associated with an increased risk of AF. Patients with AF had higher levels of non-esterified fatty acids and liver type fatty acid binding protein. Interleukin-18 levels in blood plasma were also found to be higher in AF patients. Furthermore, higher baseline urea/blood urea nitrogen levels were significantly associated with the incidence of AF in women and kidney disease in both men and women.

KEYWORDS: Atrial fibrillation; Biomarkers; Kidney diseases; Pathogenesis, homeopathic.

INTRODUCTION

There appears to be a connection between chronic kidney disease (CKD) and atrial fibrillation (AF). Evidence suggests that AF has a direct impact on renal peptidase/protease expression and kidney function[1]. It is noteworthy that CKD could alter atrial pathophysiology, which could affect the formation of blood clots in the atrium. The decline in renal function appears to affect the outcome for AF patients. However, current AF risk assessment methods do not take into account the actual impact of impaired kidney function[2,3].

According to Olesen et al.[4], renal impairment is a prothrombotic and pro-hemorrhagic condition, which predisposes individuals to incident AF and is linked to it bidirectionally. The two conditions often coexist. Additionally, AF increases

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the risk of developing and worsening CKD and the incidence of renal impairment[5]. According to Zimmerman et al.[6], around 15-20% of CKD patients have coexisting AF, which has been linked to a higher rate of death. On the other hand, another study suggested that CKD may be present in 40-50% of AF patients. Both AF and CKD are connected to an increased risk of thromboembolism, mortality, and morbidity[7,8].

METHODS

According to the literature, there are numerous biomarkers of kidney diseases[9]. However, this review article summarizes the basic role of major biomarkers of kidney diseases including creatinine, cystatin C, fibroblast growth factor-23 (FGF-23), glomerular filtration rate (GFR), insulin-like growth factor binding protein 7 (IGFBP-7), tissue inhibitor of metalloproteinase 2 (TIMP-2), interleukin-18 (IL-18), liver fatty acid binding protein (L-FABP), neutrophil gelatinase-associated lipocalin (NGAL), urea/blood urea nitrogen (BUN), glomerular epithelial protein 1 (GLEPP-1), acute kidney injury molecule-1 (Kim-1), and uromodulin (UMOD) in AF, as explained in Fig. 1.

The researchers utilized various databases, such as ScienceDirect, PubMed, and Google Scholar, to conduct a literature review. The last date of the literature search was March 15, 2023, and keywords such as "Atrial Fibrillation," "Biomarkers," "kidney diseases," and "Pathogenesis" were used. Only clinical studies conducted in English were included in the review, and no time limitations were imposed. In addition to current studies, the researchers also searched through the references of relevant papers to find related articles.

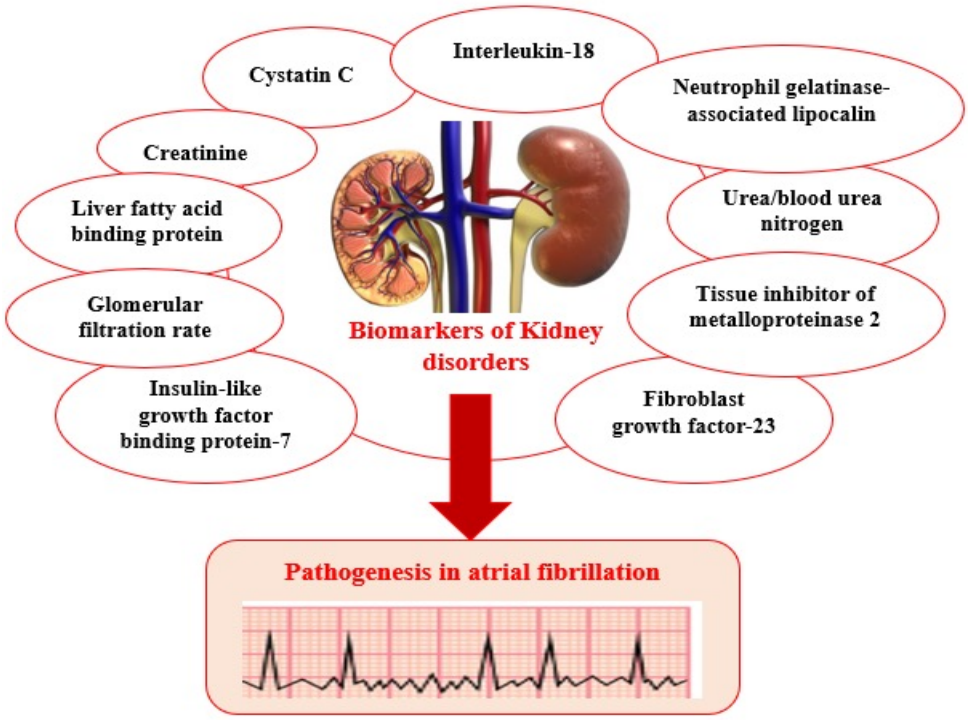

Figure 1. Overall presentation of major biomarkers of kidney diseases in atrial fibrillation.
Source: Elaborated by the authors.

Major biomarkers of kidney diseases in atrial fibrillation

This article only highlighted the creatinine, cystatin c, FGF-23, GFR, IGFBP-7, TIMP-2, IL-18, L-FABP, NGAL, and BUN in AF, as denoted in Fig. 2.

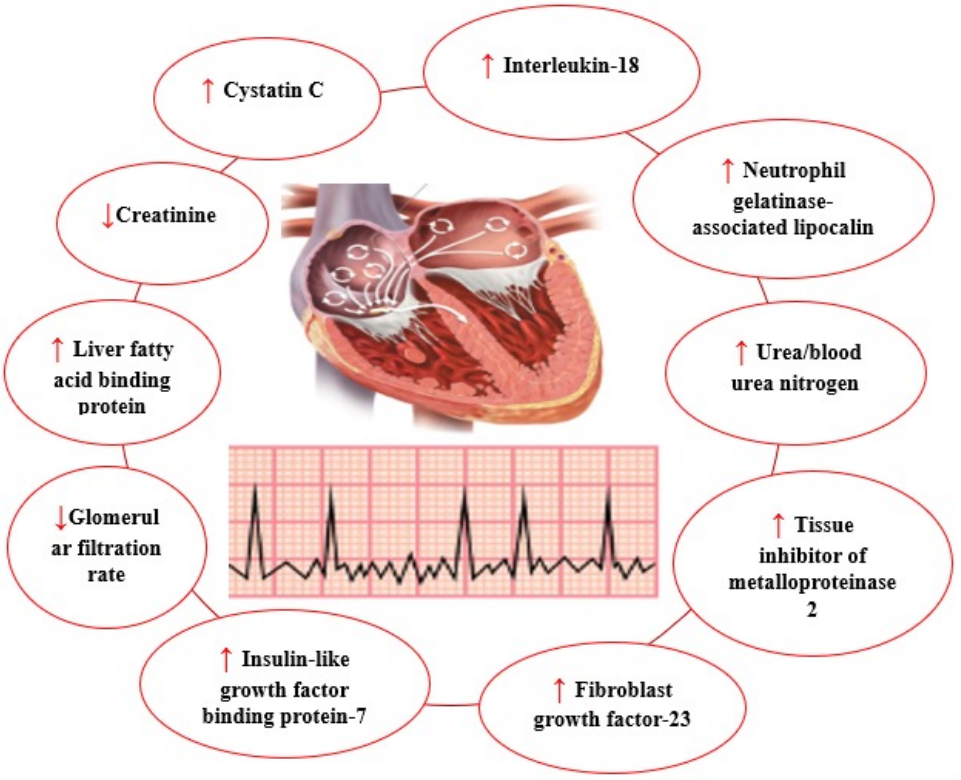

Figure 2. The summary of circulating levels of biomarkers of kidney diseases in atrial fibrillation.
Source: Elaborated by the authors.

Creatinine

Serum creatinine (Cr) is the most commonly used biomarker in nephrology, and it is an endogenous substance that is constantly released into the bloodstream from muscle creatine. Its daily release rate is between 1 to 2% of the body's creatine concentration. Clinical measurement of GFR relies on Cr as the first indicator, and it has a molecular weight of 113 Da. Cr does not bind to proteins, can be easily filtered, is not reabsorbed, and is not metabolized by the kidney. Approximately 25% of urine Cr is released by renal tubules, and medications such as probenecid, penicillin, cimetidine, and trimethoprim can impact this process[10].

According to Auer et al.[11], patients with postoperative AF had a baseline creatinine clearance of 72 ± 22.2 mL/min/1.73 m^2, which was lower than the 78.8 ± 23.5 mL/min/1.73 m^2, observed in patients without AF. Meanwhile, in Chinese nonvalvular AF patients in the emergency department, Wang et al.[12] found that mortality rates increased with decreasing creatinine clearance (CrCl) across all regions. A CrCl of 30 mL/min was not associated with thromboembolism or severe bleeding, but it was linked to all-cause and cardiovascular mortality.

Recent studies have found that moderate to severe renal impairment is a stronger independent predictor of all-cause mortality and bleeding, but not of thromboembolism (TE) in individuals with AF. The two commonly used methods to assess renal function are estimated glomerular filtration rate (eGFR) and CrCl[13]. Furthermore, Kodani et al.[14] found that CrCl was more accurate than GFR in predicting negative outcomes in individuals with nonvalvular AF. In Japanese AF patients, worsening CrCl levels were independently related to TE and all-cause death, but not significantly correlated with severe hemorrhage[15]. Abe et al.[16] and Yuzawa et al.'s[17] research in the Japanese AF registry showed that individuals with lower CrCl were more likely to die, have a cardiovascular event, experience TE, and have significant bleeding.

Cystatin C

To detect the risk of cardiovascular disease and mortality, cystatin C, a cysteine protease inhibitor produced by macrophages and dendritic cells during inflammation[18], has been proven to be a better predictor than creatinine-based

glomerular filtration estimates. Recent research has shown that cystatin C is a better predictor of cardiovascular disease morbidity and mortality compared to glomerular filtration estimates based on creatinine[19,20]. According to Jin et al.[21], pre-ablation cystatin C levels, with an optimal cut-off value of 1.190 mg/L, were linked to AF recurrence after radiofrequency catheter ablation. Cystatin C may be a more accurate indicator of AF return after ablation than changes in heart structure or other inflammatory markers.

Digoxin users tend to be elderly and have a higher likelihood of having reduced muscular mass, and current clinical practice for dosing digoxin only considers the approximated GFR from serum creatinine (eGFRcrea). The purpose of the research was to evaluate digoxin-overdosed older adult patients with AF and estimated GFR (eGFRcrea) and estimated GFR from serum cystatin C (eGFRcys). When adjusting the dosage of digoxin, doctors should take GFR into account. Both the overdosed and the control groups had decreased eGFRcys. Lower digoxin dosages would result from eGFRcys, preventing toxicity[22].

Inflammation is related to atrial abnormal heart rhythms. Cystatin C is a measure of inflammation as well as a reliable indicator of cardiovascular events. Liu et al.[23] investigated the connection between old people's AF and serum amounts of cystatin C. The serum levels of cystatin C demonstrated a substantial association with AF, indicating that elevated cystatin C is associated with a higher prevalence of AF in older individuals.

Another study discovered that there was a substantial difference between the blood cystatin C (Cys-C) levels of the AF and non-AF groups. Clinical kinds of AF varied from one another. The amount of Cys-C increased as AF lasted longer. The authors discovered that blood Cys-C and inflammation were linked to AF as a result of our analysis of the relationships between Cys-C and different clinical markers. AF incidence and growth were strongly associated with inflammation, as evidenced by the positive correlations between markers like hypersensitivity protein, white blood cell count, and neutrophil percentage[24].

The link between different techniques for estimating eGFR and AF in individuals taking anticoagulation was found to vary considerably. Of the various eGFR estimates, those based on cystatin C seemed to be the most dependable for predicting bleeding and mortality. However, a model that factored in the specific components of the eGFR formulas was the most discriminating. These findings may inform how renal function is assessed in future AF research and improve risk stratification for AF patients[25]. It was determined that high-sensitivity C-reactive protein (hsCRP) positively correlates with ischemic stroke escalating AF and may serve as a risk factor for AF alone. Another sign of an elevated chance of AF is a high cystatin C measurement[26].

Fibroblast growth factor-23

Fibroblast growth factor-23 (FGF-23), also known as phosphatonin, is a hormone that controls the renal excretion of phosphorus and has been shown to be an early biomarker for acute kidney injury (AKI) and the prediction of negative results in patients with confirmed AKI[27]. FGF-23, which has a 28 kDa molecular weight, is markedly elevated in the urine and blood of AKI patients, as well as in a variety of animal models, including ischemia/renal reperfusion, folic acid-induced AKI, and rhabdomyolysis. Clinical data demonstrates that infants, children, adults, and the aged with AKI have substantially higher circulating amounts of FGF-23[28].

Elevated levels of FGF-23 have been found to be independently associated with both prevalent and incident AF in individuals with moderate to severe chronic kidney disease. This association may be partly explained by a diastolic dysfunction pathway involving left ventricular hypertrophy, atrial enlargement, and heart failure events. Further studies are needed to investigate whether dietary or pharmacological interventions aimed at lowering elevated FGF-23 levels or blocking FGFR4 in cardiac myocytes to prevent FGF-23-related cardiac injury could be effective therapeutic strategies to reduce the burden of AF in CKD patients[29].

The hormone FGF-23 facilitates urine phosphate elimination and controls vitamin D metabolism. Chronic kidney disease is linked with a definite increase in circulating FGF-23 concentrations and an elevated risk of clinical cardiovascular events. By causing left ventricular enlargement, systolic dysfunction, and left atrial dysfunction, FGF-23 may worsen AF. Higher levels of circulating FGF-23 are linked to episode AF and may help to explain the association between AF and chronic renal disease[30].

AF has been significantly associated with the presence of FGF-23, a hormone produced from bone, in individuals with chronic renal disease. After coronary artery bypass grafting (CABG), the authors hypothesized that FGF-23 could be a very helpful prognostic indicator for atrial remodelling and, consequently, for postoperative AF (POAF). The authors also examined the relationship between heart remodelling in right atrial biopsy, POAF, and the amount of FGF-23. In individuals who have undergone CABG, preoperative FGF-23 levels may predict a possibility of POAF. According to histopathology, POAF incidence was closely linked to the existence of hypertrophic myocytes[31].

Tan et al. demonstrated a significant linear association between serum FGF-23 levels and the risk of AF. Growth differentiation factor-15 (GDF-15) and the chance of AF were not found to be significantly correlated, though. More research is required to determine whether blood FGF-23 levels can be used to forecast the likelihood of AF[32]. Among Japanese cardiac patients, serum FGF-23 had a U-shaped association with the incidence of AF that was unrelated to other calcium/phosphate metabolism-related parameters and eGFR. Further research is required to determine whether there is any pathophysiology underlying the reported connection[33]. Age, sex, and body mass index, measured on a high-throughput platform, along with raised NT-proBNP and elevated FGF-23, consistently identify individuals with AF[34].

Glomerular filtration rate

The eGFR is frequently used to evaluate kidney function, and it is generally regarded as the most comprehensive indicator of kidney function. Chronic kidney disease is defined as kidney abnormalities that persist for more than three months and may affect the structure and/or function of the kidney. Various equations can be utilized to estimate GFR from serum creatinine measurements to produce an estimated GFR[35,36]. Patients with AF in China often experience renal failure, and those without valvular heart diseases (VHDs) have a poorer prognosis when their eGFR is lower. Close monitoring of renal function, adherence to anticoagulation guidelines, and aggressive prevention of renal impairment may improve the outcomes of these patients[37].

Another study explained that lower levels of eGFRcys and eGFRcreat-cys were associated with an increased risk of incident AF. The direction of the association with eGFRcreat suggests an increased risk of incident AF with lower levels of eGFRcreat as well, although the association was less strong and not statistically significant. In cross-sectional and longitudinal analyses, prevalent AF was associated with lower levels of all three GFR estimates, and a faster decline of eGFRcreat with age was revealed in participants with prevalent AF[38].

Patients with valvular AF are more commonly affected by CKD. In individuals with non-valvular AF, a decline in eGFR is linked to the permanent form of AF and elevated CHA_2DS_2VASc and HAS-BLED scores. However, among valvular AF patients, there are no variations in the type of AF between those with and without CKD. CKD is correlated with the continuation of AF, but only in the non-valvular population[39].

Both eGFR and proteinuria appeared to be associated with the persistent form of AF in the current analysis with a cross-sectional design, but their contribution to the pathogenesis does not appear to exceed the atrial stretch and remodeling, represented by left ventricular ejection fraction (LVEF) and left atrial dimension[40]. Another study discovered that renal function could still be improved following radiofrequency catheter ablation in nonvalvular AF patients with a mildly decreased eGFR, even if they had recurrent atrial arrhythmia, by comparing the estimated glomerular filtration before radiofrequency catheter ablation to the eGFR during readmission for recurrence[41].

In this large prospective group of women, there was no substantial correlation between incident AF and less serious decline of renal function, either linearly or crinkly. However, a baseline eGFR of < 60 mL/min/1.73 m2 was found to significantly increase the chance of AF[42].

In a group of patients with AF who visited cardiologists in different parts of Europe, authors discovered that evaluating renal function using the eGFR has significant consequences for the 1-year outcome (all-cause mortality or the composite endpoint stroke/transient ischaemic attack/death). Only about 35% of patients have a normal eGFR, according to the main results, and AF is more often silent in people with seriously impaired eGFR. Second, authors exposed that lesser eGFR categories are linked to higher rates of hospital readmission for non-cardiac causes and a significant increase in all-cause mortality when it comes to results at a one-year follow-up. In fact, a low eGFR category appears to be a reliable

indicator of mortality, transient ischaemic attack, or stroke as the end point, and even minor or intermediate renal function impairments are linked to a markedly elevated risk. Third, the agreement between the various equations for estimating GFR was inconsistent. The Cockcroft-Gault equation adjusted for body surface area had the best discriminant capability for the risk of death, followed by the Cockcroft-Gault equation and the CKD-epidemiology collaboration equation, while the modification of diet in renal disease equation performed the worst[43].

Insulin-like growth factor binding protein-7 and tissue inhibitor of metalloproteinase 2

Kidney epithelial cell division in the G1 phase is disrupted in response to ischemic or septic acute kidney injury. Two biomarkers, IGFBP-7 (29 kDa) and TIMP-2 (21 kDa), both involved in this phase of the cell cycle, have been studied to assess kidney injury. The combined value of these biomarkers did not show any significant difference between healthy males and females. However, certain factors such as diabetes, hyperbilirubinemia, and anemia may affect the accuracy of the results, leading to incorrect positive findings[44].

Hospitalization for congestive heart failure among individuals with AF is a bad prognosis indicator. Higher plasma levels of IGFBP-7 were highly and separately correlated with congestive heart failure hospitalization in AF patients. IGFBP-7 added predictive data to that of N-terminal-pro hormone brain natriuretic peptide (NT-proBNP)[45]. The clinical significance of IGFBP-7, a measure of cellular senescence, in an aged community with numerous comorbidities and a high incidence of asymptomatic cardiovascular ventricular dysfunction, is poorly understood. A characteristic of heart ageing and remodelling is inflammation and fibrosis. The novel biomarker IGFBP-7 was discovered to be associated with cardiac characteristics related to aging, such as left ventricular hypertrophy and mild left ventricular systolic dysfunction, in a cross-sectional epidemiological study that included almost 2,000 community-dwelling elderly people (65-84 years old) living in the region of Rome, Italy, and followed up for 10 years. IGFBP-7 levels were also elevated in patients with AF, larger left atrial area, and E/e' > 8. Both all-cause and cardiovascular death were separately correlated with IGFBP-7[46].

Another study stated the connection between atrial structural remodelling and AF-related levels of matrix metalloproteinase (MMPs) and their tissue inhibitors (TIMPs). The left and right atrial dimensions, as well as the mRNA levels of MMP-3, -7, -9 and TIMP-1, -2, -3, -4, were considerably larger in the AF patients when compared to those in patients with sinus rhythm. Although MMP-1 mRNA increased more in AF patients than it did in patients with sinus rhythm, this variation was not statistically significant. The transcript of MMP-1, -3, -7, -9 and TIMP-1, -2, -3, -4 increases in fibrillating atrial tissue, which may lead to atrial structural remodelling and atrial dilatation in AF patients[47].

Significantly linked with higher risk of AF were elevated tissue mRNA levels of MMP-1 and reduced circulating TIMP-2 levels. Significant publication bias affects the favorable correlations of MMP-2 and MMP-9 with the incidence of AF in blood and atrial tissue. There is a need in this area for prospective biomarker study registries and rigorous adherence to reporting standards[48].

Liver fatty acid binding protein

Scientists have been studying a group of intracellular proteins called fatty acid-binding proteins (FABPs) since their discovery, in 1972. Various subtypes of FABPs have been identified, with different concentrations found in different organs[49]. AF is the most prevalent heart arrhythmia globally, which is related to structural remodeling and disruption of fatty acid metabolism. Increased levels of collagen remodeling biomarkers suggest that AF, which can cause atrial fibrosis, may play a role in upregulating these biomarkers. Patients with AF were found to have increased levels of non-esterified fatty acids and L-FABP. The involvement of these biomarkers in atrial structural remodeling could explain the association between collagen remodeling and dysregulation of fatty acids biomarkers[50].

Interleukin-18

IL-18 is a proinflammatory cytokine that regulates innate and adaptive immunity and was initially discovered as an interferon-inducing proinflammatory factor. It has a molecular weight of 24 kDa and is produced by the dormant progenitor of IL-18 found in the epithelial cells of the proximal tubule and renal collecting ducts, as well as in other organs[51]. Recent research by Rafaqat et al.[52] has emphasized the involvement of major interleukins in the development of AF.

Inflammation plays a significant role in the development and persistence of AF. One key factor in the process of inflammation is a proinflammatory cytokine called IL-18. Another study suggested that patients with AF have higher levels of IL-18 in their blood plasma. The findings support the hypothesis, indicating that AF patients do have elevated levels of IL-18. Other markers of inflammation that are known to be elevated in AF may not be as effective as IL-18 in predicting the presence of AF[53].

According to the findings, AF patients' left atrial diameter was larger, and their left ventricular ejection was lower than in controls. Even after accounting for a number of influencing variables, IL-18 single nucleotide polymorphisms were linked to a lower incidence of AF. Particularly, rs549908 GT genotype and G allele, rs360719 AG genotype and G allele, and rs187238 GC genotype and C allele were linked to a lower incidence of AF[54]. IL-6, but not IL-18, was also associated with increased risk for coronary heart disease, heart failure, and AF after adjustments for cardiovascular risk factors and each other[55].

Neutrophil gelatinase-associated lipocalin

Neutrophil gelatinase-associated lipocalin (NGAL) or lipocalin-2 is a small protein of 25 kDa belonging to the lipocalin family[56]. Its expression is found in neutrophils, kidney, prostate, and epithelia of the respiratory and gastrointestinal systems. In the glomeruli, it is filtered and partly reabsorbed by megalin receptors in the proximal tubule brush border. NGAL has been identified as a biomarker for severe renal damage. However, recent studies have also shown that NGAL levels are elevated in individuals with chronic heart failure[57,58].

In individuals with chronic heart failure and a reduced ejection fraction (HFrEF), AF and renal impairment are two prevalent complications. In addition to assessing the impact of persistent AF on kidney function in HFrEF, the authors looked into the relationships between AF, neutrophil gelatinase-associated lipocalin and neutrophil-to-lymphocyte ratio (NLR) and poor clinical outcomes. The development of renal failure or clinical outcomes (such as all-cause mortality, re-hospitalization, or AF) in individuals with HFrEF are not significantly impacted by the existence of AF. Both NLR and NGAL levels were linked to renal dysfunction in HFrEF, but it appears that systemic inflammation, which is represented by NLR, plays a more significant role in the development of kidney dysfunction[59].

Urea/blood urea nitrogen

Urea/blood urea nitrogen (BUN) is a byproduct of protein breakdown that is converted to urea in the liver and excreted through the kidneys. The concentration of BUN reflects the balance between urea production and renal elimination. The relationship between the heart and kidneys is complex, and it can lead to cardiovascular disease (CVD)[60]. Researchers have found that BUN levels are affected not only by renal function, but also by endocrine diseases. BUN is a measure of neurohumoral activity and kidney function that can reflect the pathophysiological process of CVD. BUN can also serve as an important indicator of other diseases, metabolic disorders, and nutritional status of patients, highlighting the connection between nutritional status, protein metabolism, and renal function[61-63].

Another study observed the prevalence of cardiovascular disease in the older Chinese population and its correlation with blood urea nitrogen levels. The study followed the subjects for a period of four years and recorded incidents of various heart diseases, including heart failure, AF, hypertension, diabetes, metabolic syndrome, and kidney disease. The study found a significant association between higher baseline BUN levels (> 13.51 mg/dL) and the incidence of AF in women and kidney disease in both men and women[64].

CONCLUSION

This review article suggests that certain biomarkers such as creatinine, cystatin c, FGF-23, GFR, IGFBP-7, TIMP-2, IL-18, L-FABP, NGAL, and BUN have a significant role in the AF. However, there is no evidence in the literature to suggest that glomerular epithelial protein-1, acute kidney injury molecule-1, and uromodulin are associated with AF. Biomarkers

that indicate kidney function can be utilized to assess the extent and type of kidney injury. Further research is needed to identify these kidney biomarkers for early diagnosis, allowing for better management of cardiovascular disease related to kidney function.

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DATA AVAILABILITY STATEMENT

Data derived from public domain resources.

AUTHORS' CONTRIBUTION

All authors contributed equally.

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