ORIGINAL ARTICLE

Association of Galectin-3 and IL-33/ST2 Axis with Chronic Kidney Disease Severity: Do They Play A Role in Associated Comorbidities?

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ABSTRACT

Background: *Elevated Galectin-3 (Gal-3) levels and Interleukin 33 (IL-33)/suppression of tumorigenicity 2 (ST2) involved in the pathophysiology of incident chronic kidney disease (CKD), and renal fibrosis. Besides, IL-33 induces fibrosis of pulmonary, hepatic, skin, renal, and pancreatic tissues in a way that is dependent on ST2., whereas, plays a protective role against cardiac fibrosis and atherosclerosis. Objective: the aim of this study was to investigate the association between Gal-3 and the IL-33/ST2 axis with CKD severity and the incidence of associated multi-organ affection.* ***Methodology:*** *Eighty one subjects were enrolled in this study; 69 patients with CKD and 12 age- and sex-matched healthy controls. Disease severity was assessed by estimated glomerular filtration rate (eGFR), and patients were classified as having mild, moderate, or severe CKD. Serum Gal-3, IL-33, and sST2 were tested by ELISA and the expression level of Gal-3 was assessed by Real-time PCR.* ***Results:*** *Serum Gal-3, IL-33, ST2, and the Gal-3 gene expression levels significantly increased as the severity of CKD increases. Correlation analysis showed significant associations between serum creatinine, serum Gal-3, serum IL-33, serum ST2, and the Gal-3 gene level.* ***Conclusion****: Concentrations of Gal-3, IL-33, sST2, and the Gal-3 gene expression were directly proportional with the level of CKD severity highlighting the important role of these mechanisms in the progression of kidney disease. Accordingly, these biomarkers may be useful tools for disease monitoring and individualized therapies to slow the advancement of CKD as well as associated diabetes and heart disease.*

INTRODUCTION

Chronic kidney disease (CKD) is described as abnormalities in kidney structure or function that have been present for more than three months and have an impact on health [1], CKD usually occurs in the context of chronic co-morbid conditions, such as glomerulonephritis, hypertensive nephropathy, interstitial nephritis, and diabetes nephropathy [2].

Studies have suggested that CKD is an immune-inflammatory illness, and that the loss of renal function is accompanied by an increase in inflammatory biomarkers. In addition to contributing to the development of CKD, certain cytokines that are crucial for the control of inflammation are also linked to CKD[3]. Galectins are a family of mammalian B-galactoside binding proteins that share highly conserved carbohydrate recognition domains (CRDs), with fifteen galectins have been found so far [4].

Due to its isolation from many species and laboratories, galectin-3 (Gal-3) is one of the most investigated members of the galectin family, that is also known as Carbohydrate-binding protein 35 (CBP-35) and, immunoglobulin enhancer binding protein (Ig EBP)[5].

It has been reported that Gal-3 is highly expressed in the ureteric bud and its derivatives and that it promotes nephrogenesis. Moreover, it was discovered that a higher concentration of Gal-3 was linked to renal fibrosis and a higher chance of a rapid loss in renal function. and incident CKD [4].

Similarly IL-33 is an important factor in CKD that might have a role in the onset of renal fibrosis and might linked to renal graft damage and lupus nephritis [6]. IL-33 belongs to the interleukin 1 (IL-1) family which contains a variety of members including IL-1, IL-18, IL-36, IL-37, and IL-38. Interestingly, While IL-33 can function to cause fibrosis of the pulmonary, hepatic, cutaneous, renal, and pancreatic tissues in a ST2-

dependent way, it also plays a protective role in cardiac fibrosis and atherosclerosis[7]. IL-33 has pro inflammatory properties in some of diseases, but it has anti-inflammatory properties in other diseases[8]. With IL-33, a persistent fibrotic scar can be formed as a result of an excessive buildup of components of the extracellular matrix brought on by repeated cell damage, persistent inflammation, and healing [9]. IL-33 is the sole recognized ST2 receptor's functional ligand (ST2L), as it binds ST2 to the membrane of the inflammatory cell [10]. The ST2 family of IL-1 receptors includes four splice isoforms arise from a single transcript, L ST2, a membrane receptor; sST2, a soluble factor; ST2V, a variant form of ST2; and ST2LV. Numerous studies showed that fibrotic diseases altered the expressions of ST2 and/or IL-33 [11].

In this investigation, serum concentrations of sST2, IL-33, Gal-3, and Gal-3 gene expression were measured in patients with CKD. The levels were correlated with the severity of CKD, and the role of these biomarkers in concomitant comorbidities was investigated.

METHODOLOGY

Study Population and ethical aspects:

This study is a prospective case-control study that was carried out at the Department of Microbiology and Immunology, Faculty of Medicine in corporation with the Tropical Medicine Department in Assiut University Hospitals. The study was conducted from May 2020 to February 2023 and was approved by the institutional review board (IRB approval number 17101974). All participants received a clear, written consent form indicating the purpose of the study and their freedom to participate or withdraw at any time. A total of 69 subjects were enrolled in the study as well as 12 age- and sex-matched healthy controls. Stages of CKD were determined using estimated glomerular filtration rates (eGFR), and serum creatinine, which were calculated via The CKD-EPI equation [12]. Accordingly, patients were classified as: (17 patients with mild CKD, 19 patients with moderate CKD, 33 patients with severe CKD (under dialysis).

Enzyme-Linked Immunosorbent Assay (ELISA) for Gal-3, IL-33, and soluble ST2 (sST2):

Gal-3, IL-33, and sST2 concentrations were measured in serum using enzyme-linked immunosorbent assay (ELISA) (for Gal-3: Glory science co., Ltd, for IL-33 and sST2: SinoGeneclon Biotech Co., Ltd, kits, China were used). The absorbance for each analyte was measured by spectrophotometry (450 nm) and unknown concentrations determined through a 4-parameter logistic curve fit.

Relative quantification of Gal-3 gene's expression:

The relative quantification of gal-3 genes' expression was determined in CKD patients and controls using quantitative real-time reverse transcription–PCR (qRT-PCR). The primers used were chosen from genetic codes published in Gen Bank (Eurofins) [13] (Table 1). RNA extraction, purification, and reverse transcription of RNA into cDNA were carried out as previously described [14]. cDNA templates were amplified using RT-qPCR on a CFX96 Touch Real-Time PCR Detection System (Bio-Rad, CA, USA) with a SYBR Green RT-PCR Kit (Wizpure, Korea). In a total volume of 25 µl, qPCR relative quantification will be carried out as follows: initial denaturation for 5 minutes at 95 °C, then 40 cycles of denaturation at 95 °C for 30 seconds, followed by annealing at a suitable temperature for 30 seconds (depending on the Tm of the used primer), and an extension step at 72 °C for 30 seconds. To verify the specificity of the amplified products, a dissociation curve (melting curve) was constructed in the temperature range of 60 to 95 °C for each sample. Galectin-3 expression was quantified using the ΔΔCT method, with reference B- actin serving.

Table 1: Primers and melting temperature for detection of Gal-3 and B-actin genes

Genes	Sequence (5`–3`)	*Tm (melting temperature)*	Reference
Gal-3	F 5′-GGGAAATCGTGCGTGACATTAAG-3′ R 5′-TGTGTTGGCGTACAGGTCTTTG-3′	60	[13]
B-actin	F 5′-5CAATACAAAGCTGGATAATAACTGG-3' R 5′-GATTGTACTGCAACAAGTGAG-3′	60	[13]

Statistical analysis:

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 28.0, IBM Corp., Chicago, USA, 2021. Quantitative data after being tested for normality using Shapiro-Walk test described as mean ± SD (standard deviation) as well as minimum and maximum of the range, then compared using ANOVA test. Correlation was tested using Pearson correlation test. The level of significance was taken at p-value <0.050 was significant, otherwise was non-significant.

RESULTS

The present study included 69 CKD patients and 12 healthy controls. Patients were classified as having mild

CKD=17, moderate CKD=19, and severe CKD=33. The associated comorbidities of patients were estimated. There were no significant differences between different CKD groups regarding the occurrence of associated comorbidities (χ^2; p values >.05) (Table 2).

Table 2: Associated comorbidities in CKD patients

Stage of CKD	Associated comorbidity			
	DM	**HT**	**LC**	**CVD**
Mild CKD (17)	3 (4.3%)	5 (7.2%)	0 (00%)	0 (00%)
Moderate CKD (19)	7 (10.1%)	8 (11.٥%)	2 (2.8%)	1 (1.45%)
Severe CKD (33)	9 (13%)	13 (18.8%)	3 (4.3%)	1 (1.45%)
Total (69)	19 (27%)	26 (37.6%)	5 (7.2)	2 (2.9%)
P values	.498	.582	.587	.980

Abbreviations: CKD=chronic kidney disease, CVD=cardiovascular disease, DM=diabetes mellitus, HT=hypertension, LC=liver cirrhosis.

The Gal-3 levels in serum were directly proportional to the disease severity, as levels were significantly the highest in severe CKD group (6.8-21.0 pg/uL), followed by moderate CKD group (2.4-17.5 pg/uL), followed by the mild CKD group (7.1-13.2 pg/uL). The healthy controls had the lowest serum Gal-3 levels (5.8-13.5 pg/uL). The serum levels of Gal-3 were significantly higher in severe CKD patients than all other groups ($p \leq .001$). The Gal-3 levels in serum were considerably higher in moderate and mild CKD group vs the control group (Figure 1).

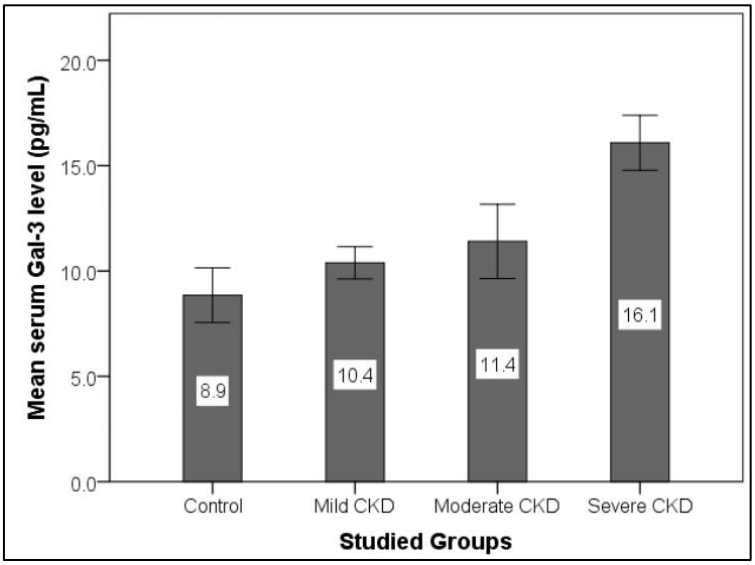

Fig. 1: Mean serum levels of Gal-3 (pg/mL) in CKD, and controls. CKD=chronic kidney disease. ANOVA was used to test the statically significant difference between groups.

IL-33 and ST2 were at the highest levels in severe CKD patients. For IL-33 (ranged from 210.0 to 690.0 ng/L), for ST2 (ranged from 94 to 368 pg/mL) with $p \leq .001$ (severe vs other groups), followed by moderate CKD patients, for IL-33 (ranged from 117.0 to 396.0 ng/L), p=.444 (moderate vs mild), p=.05 (moderate vs controls), for ST2 (ranged from 47 to 191 pg/mL), p= .718 (moderate vs mild), p=.627 (moderate vs controls), and then in mild CKD patients for IL-33 (ranged from 92.0 to 422.0 ng/L), p=.223 (mild vs controls), for ST2 (ranged from 46 to 146 pg/mL), p=.876 (mild vs controls) and the lowest levels were detected in the control group for IL-33 (ranged from 80.0 to 176.0 ng/L), for ST2 (ranged from 51 to 103 pg/mL) (Figure 2).

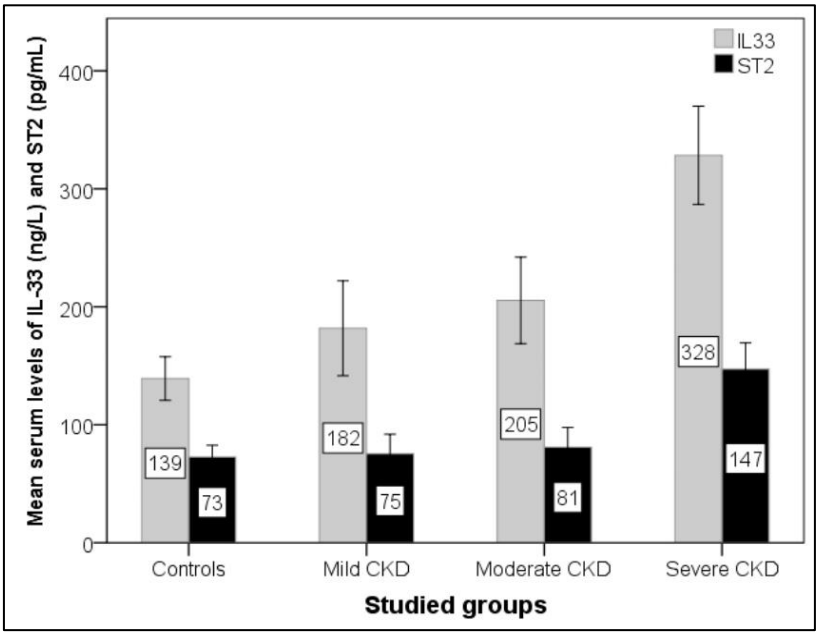

Fig. 2: Mean serum levels of IL=33 (ngl/L) and ST2 (pg/mL) in CKD and controls. CKD=chronic kidney disease. ANOVA was used to test the statically significant difference between groups

Levels of serum creatinine, GFR, Gal-3, IL-33, and ST2 were compared in CKD patients with different comorbidities. Serum Gal-3 levels were significantly higher in CKD patients having DM as well as those with CVD (p=.03 and $p \leq$.001, respectively). On the contrary, serum levels of IL-33 and ST2 were lower in CKD patients without DM, HT, CVD, LC, although that difference did not reach significance (Table 3).

Table 3: Differences in laboratory data in CKD patients with different comorbidities

Parameter	*DM*	*HT*	*CVD*	*LC*
Serum creatinine	Yes: 4.9±3.4 No: 4.2±3.11	Yes: 4.68±3.3 No: 4.2±3.1	Yes: 4.9±3.3 No: 4.38±3.2	Yes: 5.7±3.7 No: 4.3±3.1
p value	.45	.56	.82	.35
GFR	Yes: 25.7±35 No: 32±31.8	Yes: 26±28.6 No: 32.8±34.8	Yes:17.8±16.6 No: 30.6±32.9	Yes: 14.8±13 No: 31.5±33
p value	.48	.38	.46	**.04**
Serum Gal-3	Yes: 14.9±3.2 No: 12.8±4.3	Yes: 13.7±3.48 No: 13.1±4.5	Yes:17.6±0.21 No:١3.2±4.15	Yes: 13.2±3.4 No: 13.4±4.2
p value	**.03**	.59	**≤ .001**	.90
Serum IL-33	Yes: 231.5±121.2 No: 268.6±117.3	Yes: 247±83.6 No: 265.3±136	Yes: 202±٥٤ No: ٢60±١١٩	Yes: 206±67 No: 262±121
p value	.2٥	.49	.3٥	.15
Serum ST-2	Yes: 105.6±71.5 No: 113.4±55.95	Yes: 101±36.3 No: 117±70.6	Yes: 90±31 No: 111±61	Yes: 110±41 No:111±61.6
p value	.6٤	.2٤	.49	.93

Abbreviations: CVD=cardiovascular disease; DM=diabetes mellitus; GFR=glomerular filtration rate; HT=hypertension; IL=33=interleukin 33; LC=liver cirrhosis; ST2=suppression of tumorigenicity 2.

Relative quantification of Gal-3 gene's expression

Gal-3 gene expression levels were at the highest levels in severe CKD patients (ranged from 3.03±0.32), followed by moderate CKD patients (ranged from 1.79±0.35), then in mild CKD patients ranged from (1.461±0.71), and the lowest levels were detected in controls (ranged from 1±0.005) (Figure 3).

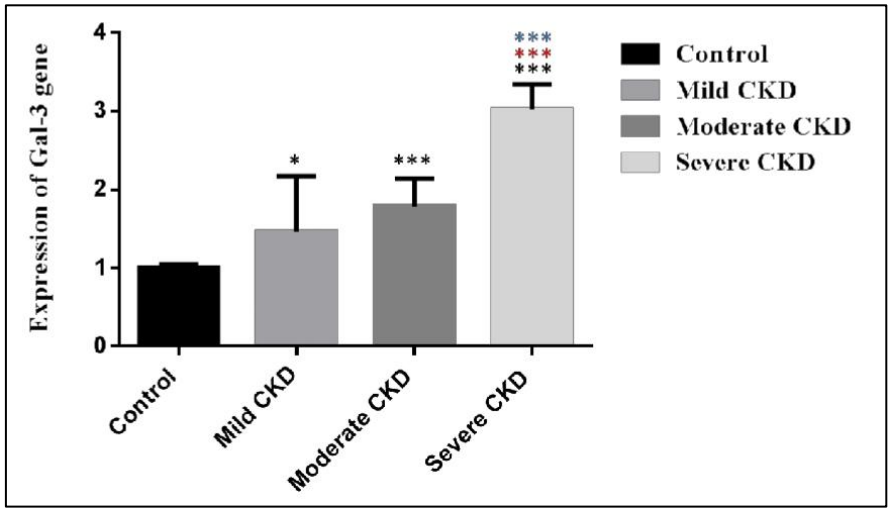

Fig. 3: Exspression of *gal 3* in control, mild CKD, moderate CKD and severe CKD.
***p-value ≤ .001, **p-value < 0.1, * p< .05 when compare with control group, ***p-value ≤ .001
When compare with mild CKD group, ***p-value ≤ .001 when compare with moderate CKD. The values are prsented as mean ± SD (n = 3)

Correlation analysis showed positive correlations were detected between serum creatinine and the levels of serum Gal-3, serum IL-33, serum ST2, and Gal-3 gene (p value ≤.001). Significant negative associations were demonstrated between the GFR and the serum level of Gal-3, serum levels of IL-33, serum ST2, and Gal-3 gene (p ≤.001). The expression level of Gal-3 gene was significantly positively associated with serum levels of creatinine (p ≤.001), Gal-3 (p ≤.001), IL-33 (*p*=0.018), and ST2 (*p*=.003), while it was adversely correlated with the concentrations of GFR (*p*≤ 0.001) (Table 4).

Table 4. Correlations between serum creatinine, GFR, and tested biomarkers in CKD patients.

	Serum creatinine levels (mg/dl)	GFR (ml/min/1.73 m^2)	Gal-3 (pg/mL)	IL-33 (ng/L)	ST2 (pg/mL)	Gal-3 expression by RT-PCR
Creatinine						
R	1.000	-.762**	.602**	.475**	.491**	.599**
P value		**≤.001**	**≤.001**	**≤.001**	**≤.001**	**≤.001**
GFR						
R		1.000	-.487**	-.463**	-.431**	-.637**
p value			**≤.001**	**≤.001**	**≤.001**	**≤.001**
Gal-3						
R			1.000	.223*	.172	.551**
p value				**0.045**	**.124**	**≤.00**١
IL-33						
R				1.000	.891**	.410*
p value					**≤.001**	**.018**
ST2						
R					1.000	.502**
p value						**.003**

DISCUSSION

Since many cytokines are recognized as eliminated by the kidney, CKD disrupts the delicate balance between pro-inflammatory cytokines and their inhibitors [15]. Although, many pro-inflammatory cytokines were found to assist in the occurrence of CKD, However, there are inconsistencies in the related studies on the exact function of cytokines in CKD [16]. Gal-3 is among the cytokines that connected to the etiology of several kidney diseases, including diabetic nephropathy (DN), polycystic kidney disease that is autosomal recessive ,

lupus nephritis, and chronic allograft rejection [17]. In this study our aim was to determine the serum concentrations of Gal-3, IL-33, and ST2 and Gal-3 gene expression among CKD patients suffering from various stages of CKD and to investigate the relationship between these biomarkers with various comorbidities commonly existing in CKD patients. Gal-3 was proven to play a pro-resolution role in tissue inflammation and repair process. It is intensely upregulated in response to ischemic and nephrotoxic acute kidney injury (AKI) [18], thus promoting interstitial fibrotic changes in the kidney with worsening of CKD [19]. Higher concentrations of Gal-3 were also linked in earlier research to the advancement of CKD [19]. Similarly, in the current study, increased Gal-3 levels were linked to an incident CKD in the participating population, and the level was significantly consistent with the severity of the disease. Moreover, serum Gal-3 level was noticeably higher in individuals with DM and those with CVD. The exact mechanism linking elevation of Gal-3 with advancement of CKD is not yet clear. Literatures have proposed that Gal-3 probably affects both the heart and kidneys in a parallel process (REF) or, alternatively, heart disease leading to kidney disease. "Cardiorenal syndrome" is a complex process mediated by intersecting physiologic, neurohormonal, and biochemical derangements and may explain these associations [19]. Gal-3 was discovered to be connected to cardiac fibrosis, remodeling, ventricular dysfunction, and the increase in cardiovascular deaths in individuals who have impaired kidney function and those on hemodialysis [20, 21]. Scientific evidence has proven that Gal-3 had a role in pathogenesis of DN, moreover, suggested that Gal-3 is a mediator of initiation and course of diabetic nephropathy (DN) in type 2 DM patients [17, 18]. They showed that, when compared to other glomerular disorders, the number of Gal-3-positive glomerular cells in the renal biopsy specimens from DN patients was significantly higher. Additionally, there was noteworthy correlation in the individuals with DM between the quantity of Gal-3-positive cells and urine protein excretion in their study.

Recently, the novel IL-1 family member, the IL-33/ST2 axis, has been discovered, and it seems to be a significant factor in several chronic immune inflammatory disorders including asthma, rheumatoid arthritis, and anaphylactic shock. Serum sST2 may also be engaged in the oversight of immune-mediated diseases [22]. In this study, our results showed that serum IL-33 and ST2 levels were highest in severe CKD, followed by moderate CKD, mild CKD, and the lowest level in controls. This was consistent with other previous researches. In a study performed on mice shown that IL-33 increased acute renal damage due to cisplatin and inhibition of IL-33 with sST2 provides functional and histological protection from acute kidney injury caused by cisplatin; so they indicated that IL-33 is a mediator of cisplatin-induced severe kidney damage [23]. The expression of IL-33 was observed to be increased in aortic endothelial cells from a mouse model of CKD. Additionally, higher concentrations of sST2 appeared to be associated with impaired kidney function in a study involving participants with cardiovascular disease. Together, these results suggest that the progressive decline in kidney function is connected to the sST2 and IL-33 levels. [24]. According to earlier reports, our study found a correlation between the disease's severity and the elevated serum levels of IL-33 and sST2 in CKD patients. Gungor *et al.* [25] found that CKD patients had higher concentrations of IL-33 and sST2 than did the general population and patients with other persistent immune inflammatory diseases. Researchers discovered that in patients with advanced stages of CKD, IL-33 and ST2 levels elevated with the condition. They also found that vascular dysfunction was associated with IL-33, ST2, hs-CRP, diabetes, smoking history, proteinuria, and hemoglobin (Hb) levels, which were predictive of cardiovascular events and survival [25]. Prior studies examined the serum levels of sST2 and IL-33 in patients with chronic kidney disease (CKD), a subgroup that included diabetic patients, and linked the levels of ST2 and IL-33 to the severity of the disease. The authors discovered a strong association between concentrations of sST2 and disease severity by examining the connection between sST2 and IL-33 with disease severity [26].

In our work, noteworthy positive associations were detected between creatinine concentration and the concentration of serum Gal-3, serum IL-33, serum ST2, and Gal-3 gene. Significant negative associations were demonstrated between the GFR and the serum levels of Gal-3, serum levels of IL-33, serum ST2, and Gal-3 gene. Also we found strong correlations with between Gal-3, IL-33, ST2 concentrations in serum, and Gal-3 gene level. Our results were in agreement with a previous research by Alam *et al.* [19] where they reported that, every doubling of Gal-3 was significantly associated with a 38% increased risk of progression to eGFR <15 ml/min per 1.73 m2 or ESRD. The authors declared that higher levels of the cardiac biomarker Gal-3 may be linked to the advancement of CKD. Another study by Lukic *et al.* [27], the authors detected a significant positive correlation between serum ST2 and the serum creatinine levels, as detected in our study. Our findings also agreed with the study by Chu *et al.* [4], where they found that the level of serum Gal-3 was significantly correlated with the serum creatinine concentration and inversely correlated with the eGFR. This result indicated that serum Gal-3 level was strongly connected with the advancement of CKD. Another report by Bao *et al.* [26] found a strong relationship between the sST2 serum level and CKD severity.

Our results showed that patients' IL-33 and ST2 concentrations were greater in cases without DM, HT,

CVD, LC, this agreement with previous studies demonstrated that ST2−/− mice, under pressure overload by transverse aortic constriction, showed severe myocyte hypertrophy and interstitial cardiac fibrosis when compared with wide-type littermates. Additionally, treatment with rIL-33 after pressure overload decreased fibrosis and hypertrophy and increased survival in wide-type mice, but not in their ST2−/− littermates [28]. By inhibiting caspase-3 activity and upregulating the protein expression of the "inhibitor of apoptosis" family, IL-33 produces antihypertrophic effects, decreases cardiomyocyte apoptosis and infarct, and enhances ventricular function [29]. The ability of sST2 to block the IL-33's antihypertrophic effects indicates that sST2 functions as a decoy receptor of IL-33 in the myocardium [29]. Thus, in stretched fibroblasts and myocytes of the heart, the signaling pathway IL-33/ST2 probably protects by controlling the myocardial response to biomechanical overload [29]. Moreover, Li *et al*. [30] found that serum from individuals with biliary atresia and the livers and bile ducts of mice with experimental biliary atresia both have greater concentrations of IL-33. The administration of IL-33 to wild-type mice produced a noteworthy and quickening of the extrahepatic bile ducts' enlargement by promoting sustained cell growth and cholangiocyte proliferation. An increase in ILC2s also mediated the IL-33-dependent proliferation; these cells secrete greater amounts of IL-13, which in turn aided in the promotion of cholangiocyte hyperplasia. Consequently, the IL-33/ST2 signaling pathway plays a crucial role in mediating hepatic fibrosis [30].

CONCLUSION

Increased concentrations of the biomarker Gal-3 linked to the advancement of CKD indicate possible new pathways that could accelerate the disease's progression. Patients with CKD have higher serum IL33 and sST2 concentrations, which are correlated with the harshness of the illness. The sST2 may function as a marker of disease severity or play a crucial role in the occurrence of CKD. New cardiac biomarkers may provide insight into the processes that lead to kidney and heart damage. They may also prove to be helpful in disease monitoring and tailored treatments aimed at delaying the advancement of CKD. While IL-33 and ST2 can act to cause fibrosis of the pulmonary, skin, renal, and pancreatic in a ST2-dependent manner, they may also have a defending function in MD, hypertension, cardiac fibrosis, and liver cirrhosis.

Authors' contributions

ROS collected patients' data, clinical specimens, and performed the laboratory investigations. MKK contributed to acquisition of data and collection of patients' clinical specimens. MEM, AAE, and ISS contributed to study concept and design, acquisition of data, the laboratory work, draft and revision of the article, statistical analyses, and interpretation of data. . S. H. performed the protocol for RT-PCR, investigation of RT-PCR experiments, data analysis, and editing of the manuscript. S. A. performed the experimental protocol conceptualization of RT-PCR, supervision of the RT-PCR experiment, the resources, the validation, and the editing of the manuscript. All authors revised and approved the final version of the manuscript

Conflict of interest: The authors declared that no competing interests exist.

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