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Correlation between ST2 concentration and Cardiorenal syndrome

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ABSTRACT:
Background: Cardiorenal syndrome, a term used to describe a variety of heart and kidney illnesses, is characterized by the dysfunction of one organ resulting to the dysfunction of the other.
Objective: The aim of the current study to evaluate some biochemical indicators, linking hematologic analysis and kidney function test with interleukin-1 receptor family biomarker
(ST2), and investigating the early diagnosis and prediction of chronic renal syndrome.
Patients and methods: A total of 60 cases were recruited; comprising 20 controls and 40 patients with chronic kidney disease and cardiovascular disease. The patients were aged between 25 and 65 years old. Levels of ST2 were measured in both the case and the control groups. **Result:** In comparison with the control group, patients with cardiovascular diseases had higher concentrations of haematological features than do patients with chronic kidney disease. Also, when compared to controls, those with chronic kidney disease had statistically significant ($P<0.05$) increase in their serum levels of urea and creatinine. When compared to other groups, the levels of the biomarker ST2 were significantly higher in chronic kidney disease patients. **Conclusions:** Adults with chronic kidney disease had higher circulating ST2 levels and a higher mortality rate. RBC negatively affects ST2 levels as a result there is a link between ST2 levels and the risk of anaemia in chronic kidney disease patients.
Keyword: Interleukin-1 receptor family biomarker, ST2 Concentration, Chronic kidney disease, Cardiorenal Syndrome, Case control study, AL-Zahraa University for Women.

INTRODUCTION

The numerous biochemical mechanisms that make up the crosstalk between the heart, kidneys, and vascular system allow these organs to work together to sustain key physiological functions. The term "cardiorenal syndrome" also known as "Reno cardiac syndrome" refers to heart or kidney disease that compromises the other organ and ultimately leads to failure of both. The detrimental effects of one organ on another may be immediate or delayed, and they may involve a complex feedback system that controls hormones, inflammatory substances, and oxidative stress reactions [(1)]. The phrase "cardiorenal syndrome" refers to the progression of renal insufficiency to heart failure (HF) and vice versa [(2)]. Chronic renal syndrome (CRS) is one of the worst prognostic indicators because it worsens morbidity and mortality in individuals with heart failure (HF), acute kidney injury (AKI), or chronic renal illness [(3)].

There are five primary types of CRSs. Acute cardiac failure of Type I, sometimes referred to as abrupt CRS, causes renal injury. Chronic Type II CRS, also known as chronic heart failure, harms the kidneys. Acute kidney injury that causes acute heart failure, like uremic cardiomyopathy, is one of the features of Type III or acute nephrocardiac illness. Chronic kidney disease that leads to diastolic heart failure and kidney failure is the defining feature of Type IV, also known as chronic nephrocardiac sickness. The most severe type of diabetes, type IV, is caused by a systemic infection and leads to kidney and heart failure [(4)].

The endothelial cells lining the LV and aortic outflow tract produce the decoy protein ST2 in response to biomechanical load. Cardio myocytes and satellite cells include the IL-33 (interleukin-33) receptor, which ST2 binds to. This contact leads to in myocyte dysfunction and tissue fibrosis instead of a positive signal transduction. ST2 monitors complement natriuretic peptide levels and is especially unaffected by renal function in predicting HF-related mortality and hospitalizations [(5)].

The aim of the current study to evaluate some biochemical indicators, linking hematologic analysis and kidney function test with ST2, and investigating the early diagnosis and prediction of chronic renal syndrome.

PATIENTS AND METHODS

From April 2021 to June of 2021, the current study was conducted in Iraq. This investigation was carried out at the Artificial Kidney Unit of the Al-Kafel Hospital in the Province of Karbala.

Study Design: A case control study included 60 samples; of which 40 patients had chronic kidney disease (CKD) and cardiovascular disease (CVD) and 20 represented the control group. The patients were aged between 25 and 65 years old. Patients and controls were recruited daily till fulfilling the sample size.

Collection of Blood Samples: Using 5 millilitres of sterile synergies, blood samples were drawn from the vein. Sample put into test tube as instructed. When blood was extracted, it was allowed to clot for ten minutes at room temperature, centrifuged for fifteen minutes at 6,000 rpm, and the serum was then taken out and immediately frozen at -80 °C for use in the study's laboratory analysis.

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Biochemical Parameters

Blood urea concentration evaluation: A colorimetric calculation was used to determine the serum urea content. A special kit for determining the amount of urea in human serum was provided by France's Biolabo SA.

Measuring the concentration of serum creatinine: A colorimetric reaction was used to ascertain the level of creatinine in the serum. French company Biolabo SA provided the serum creatinine level.

Ethical Consideration:

The Ethical Institutional Review Board at AL-Zahraa University for Women approved the study. After explaining our research objectives, written informed consent was obtained from all study participants. This study was conducted in compliance with the code of ethics of the world medical association (Declaration of Helsinki) for human subjects.

Statistical Analysis:

The collected data were introduced and statistically analyzed by utilizing the Statistical Package for Social Sciences (SPSS) version 20 for windows. Qualitative data were defined as numbers and percentages. Pearson Chi-Square test and Fisher's exact were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by Kolmogorov-Smirnov test. Normal distribution of variables was described as mean and standard deviation (SD), and independent sample t-test was used for comparison between groups. The correlation between CKD and sociodemographic and clinical data was determined using Spearman's correlation. P value ≤0.05 was considered to be statistically significant.

RESULTS

Demographic Characteristics of the Subject of the Study: Table 1 summarizes the sociodemographic of the studied groups. The age difference between patients with CKD and CVD, in contrast to the control group's age is statistically significant.

Table 1. Clinical study on the variations between the patient and control groups.

Characteristics		
Disease	**CKD**	54.8%
	CVD	41.9%
Age (year)	**CKD**	53.5 ± 3.05*
	CVD	60 ± 2.98*
	Control	21.2 ± 0.66
Gender	**Male**	87.1%
	Female	12.9%
Anemia	**Anemic patient**	61.3%
	Non-anemic	38.7%

Haematological Characteristics of the Research Subject

Figures 1 and 2 show that individuals with CKD had a significant decrease in haematological characteristics (Hb and RBC) compared to the other research groups.

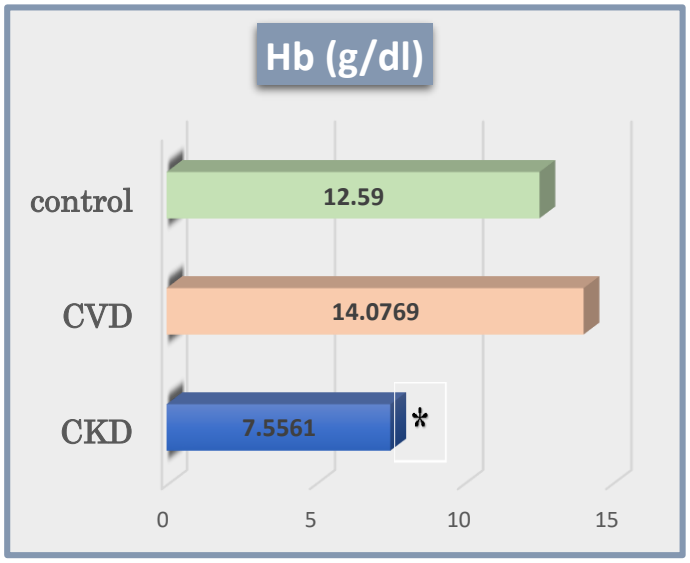

Figure 1. Comparison of Haemoglobin (g/dL) between the Study Groups.

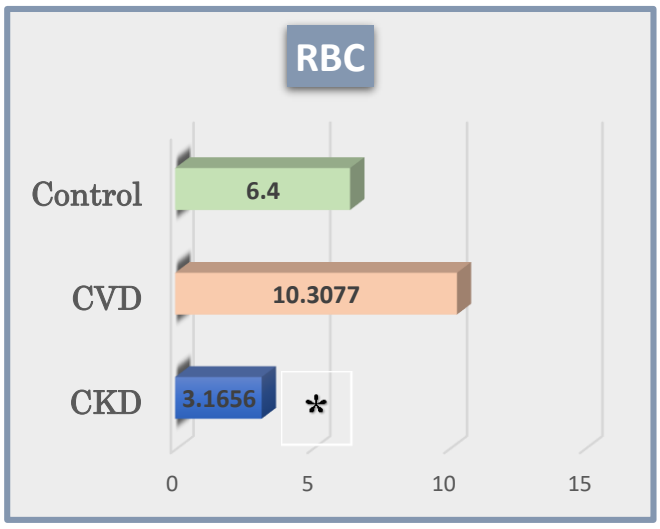

Figure 2. RBC count comparison between groups of patients with Chronic Kidney Disease and a Healthy Control Group.

* P<0.05 statistically significant with control group.

Evaluation of the subject's kidney function

Figures 3 and 4 illustrate the differences in kidney function test results between the groups tested. Serum concentrations of urea and creatinine are significantly higher (P<0.05) in individuals with CKD compared to other research groups, as depicted in these data. Comparing patients with CVD to controls, kidney function tests found no statistically significant difference (P>0.05).

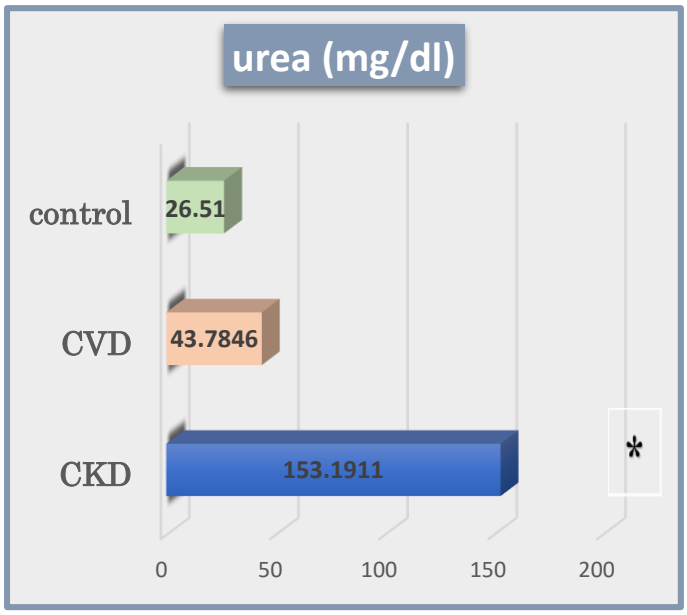

Figure 3. Comparison of urea (mg/dl) between Groups of patients with CKD and the Healthy Group.
* P<0.05 statistically significant with control group.

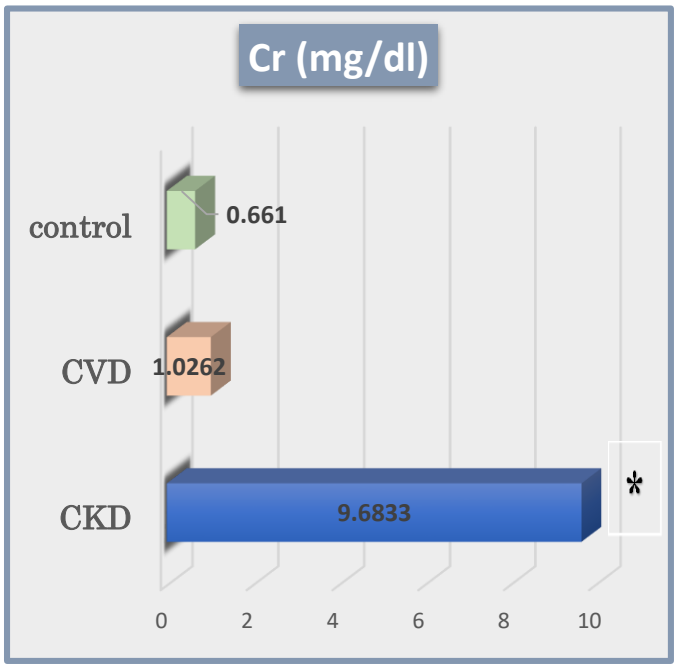

Figure 4. Comparison of the Creatinine (mg/dl) between Groups of Patients with Chronic Kidney Disease and Healthy Individuals.

* P<0.05 statistically significant with the control group.

ST2 concentration

Figure 5 depicted the values of specific biomarker tests between the study groups. ST2 levels were significantly higher (P<0.05) in patients with CKD compared to other research groups, as indicated by the data presented. Comparing patients with CVD to controls, kidney function tests found no statistically significant difference (P>0.05).

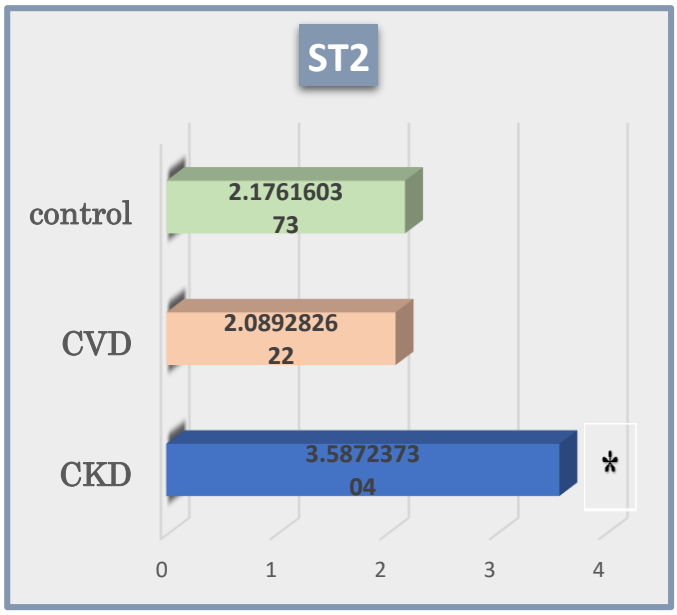

Figure 5. Comparison of ST2 (mg/dL) between the Study Groups.
* P<0.05 statistically significant with the control group.

There was a substantial positive correlation between ST2 and serum creatinine among patients with CKD and CVD, as shown by the association and linear regression results (**Table 2**). In contrast to what the other finding of the same table suggested, there was a substantial negative connection between ST2 and RBC in patients with CKD.

Table 2. Correlation between CKD patients and sociodemographic and clinical data.

ST2	Correlations	Age	S. Creatinine	Urea	Hb	RBC
	Pearson Correlation	0.172	.435**	0.232	-0.237	-.344*
	Sig. (2-tailed)	0.283	0.004	0.145	0.136	0.027

* At the 0.05 level, correlation is significant (2-tailed).

DISCUSSION

The term "cardiorenal syndrome" means a number of illnesses that affect the heart and kidneys. It involves the confluence of heart-kidney interactions across many media, hemodynamically, through alterations in neurohormonal markers, and increased venous and renal pressure [(6)]. Our study's findings show that CKD patients have significantly lower levels of Hb and RBC than the other study groups. These findings supported those of Almahdi and Co-workers (2016), who found that the haemoglobin levels of Libyan CKD patients were significantly lower than those of the control group [(7)].

Haemoglobin concentration dropped as renal failure increased. It has been shown that the severity of anaemia is closely associated with the stage of CKD [(8)]. The findings of this study were in line with the previous study's findings, which indicated that patients' red blood

cell counts were much lower than those of the control group [9].

One of the main reasons for a decrease in RBC count is a lack of kidney-produced erythropoietin, which slows erythropoiesis [10]. Uraemia also enhanced the production of phosphatidylserine on the outer cell surface of red blood cells, which accelerated RBC destruction by macrophages and lowered cell survival. These combined effect lead to both a decreased RBC count and a reduced RBC life spin [11]. It has not yet been established if a haemoglobin level in and of itself, or one that is within a physiological range, has any impact on the occurrence of CVD. Additionally, few researches that were published looked into the connection between a haemoglobin level and the incidence of cardiovascular disease in Asian populations [12].

According to a recent study from Norway, AMI was solely linked to increased haemoglobin levels in men [13]. It is well recognized that higher haematocrit levels or haemoglobin concentrations increase blood viscosity, which raises peripheral resistance and decreases blood flow and perfusion [14].

Haemoglobin concentrations are known to be higher among cigarette smokers, which could enhance oxidative assaults to the cell [15]. High haemoglobin concentrations have different effects on different subtypes of CVD, though [16]. Additionally, there are emerging signs of urea's toxicity. Urea was discovered to disrupt cellular processes both directly and indirectly by increasing oxidative stress [17], which inhibits glucose absorption in adipocytes [18].

Some investigations analysed blood urea and serum creatinine and found that urea was the first organic solute discovered in the blood of patients with chronic kidney disease [19]. The inability of the kidney to clear nitrogenous wastes from the blood, resulting in the accumulation of urea and creatinine in the blood, causes an increase in urea and creatinine levels in individuals with chronic renal disease [20].

The patients in this study had a significantly lower haemoglobin concentration than the control group. Anaemia is a symptom of chronic kidney disease. Numerous studies demonstrated that anaemia is the most prevalent consequence of advanced chronic renal failure. This result concurred with earlier research [21].

According to the current study, persons with CKD had a ST2 level that was significantly higher than that of other research groups. These outcomes found that despite the haemoglobin levels of CKD patients dropped, their ST2 levels considerably rose. Haemoglobin and ST2 levels are discovered to be connected by a correlation analysis [22].

Compared to healthy controls, patients with chronic renal disease have higher ST2 levels. As a result, increasing IL-33/ST2 levels in people with chronic renal illness are a sign of increased inflammation, compromised endothelial function, and cardiovascular events [23]. Increased sST2 levels in CKD patients have been demonstrated to be able to predict their all-cause mortality, CVD mortality, and CVD events. Several organs and cells produce ST2, a member of the interleukin-1 (IL-1) receptor family, in response to stress, inflammation, and other stimuli [23, 24]. The two important ST2 isoforms are membrane-linked ST2L (ST2L) and soluble ST2 (sST2) [25].

The cytokine guards against fibrosis, cardiomyocyte hypertrophy, and apoptosis via interacting with IL-33, a member of the IL-1 cytokine family and a crucial ST2L ligand. The cytokine guards against apoptosis, fibrosis, and cardiomyocyte hypertrophy by working with IL-33, a member of the IL-1 cytokine family and a significant ST2L ligand. In contrast, sST2 inhibits ST2L's cardio protective actions by competitively binding to IL-33 [26, 27].

CONCLUSIONS

All disorders involving the heart and kidneys' reciprocal interactions, in which one organ's failure can have a significant impact on the other, are included in CRS. Furthermore, we draw conclusions from this work. Our analysis found strong evidence that cardiovascular disease (CVD) would occur in CKD patients with cardiorenal syndrome. The study sheds more light on how anaemia, which is defined by low haemoglobin and high levels of urea and creatinine, raised the risk of death for CRS patients. However, anaemia needs to be treated. The death rate was greater in adults with CKD and higher blood ST2 concentrations.

A higher prevalence of CRS was likewise linked to elevated ST2 levels. More study is required to clarify the processes relating these circulating biomarkers to CVD in CKD patients. RBC controls ST2 in an unfavourable way. As a result, there is a link between ST2 levels and the risk of anaemia in CKD patients. In patients with CRS, there is a connection between ST2 and S. creatinine.

As a result, the increase in ST2 has a big impact on how CVD develops in CKD patients. Our research indicates that renal disorders and ST2 have a clinically relevant relationship. Consequently, increased sST2 levels could forecast all-cause death, CVD mortality, and CVD events in CKD patients.

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