Biomarker for cardiorenal syndrome risk in patients with liver cirrhosis and type 2 diabetes in Saudi Arabia

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ABSTRACT

الأهداف: تقييم العلاقة بين السمات المختلفة ومستويات المؤشرات الحيوية واحتمالية الإصابة بمتلازمة القلب الكلوية (CRS) لدى المرضى الذين تم تشخيص إصابتهم بداء السكري من النوع 2 (T2DM) وتليف الكبد (LC). تشير الفرضية إلى أن أمراض الكبد قد تكون مرتبطة باختلال وظائف الكلى، واختلال وظائف القلب، وتطور متلازمة القلب الكلوي.

المنهجية: قامت الدراسة الحالية بتقييم السجلات الطبية بأثر رجعي للمرضى الذين تم تشخيصهم بـ LC وT2DM وتم إدخالهم إلى المستشفى في مستشفيات المدينة المنورة في عام 2022م و 2023م.

النتائج: قام هذا البحث بدراسة مرضى T2DM الذين أكد الطبيب إصابتهم بـ LC. تتم الإشارة إلى ضعف التحكم في نسبة السكر في الدم من خلال قراءات ارتفاع نسبة الجلوكوز في الدم والهيموجلوبين السكري (HbA1c) لدى المشاركين في البحث. ارتفاع ضغط الدم، ومؤشر البلازما تصلب الشرايين (AIP)، والسمنة عانى بها معظم هؤلاء الأفراد. كان ارتفاع الكرياتينين وانخفاض معدل الترشيح الكبيبي المقدر (eGFR) والارتفاع المتواضع في الزلال البولي إلى الكرياتينين (UACR) هي المتغيرات الأكثر انتشارًا في مرضى LC وT2DM. تم تحديد عوامل خطر الإصابة بمتلازمة القلب والأوعية الدموية، بما في ذلك ارتفاع ضغط الدم ومستويات الدهون الثلاثية ومؤشر كتلة الجسم (BMI) وتركيزات البروتين التفاعلي C عالي الحساسية (hs–CRP)، من خلال الانحدار اللوجستي. وقد ثبت أن انتشار عوامل الخطر هذه يزداد مع تقدم العمر؛ قد تكون النساء أكثر عرضة للإصابة بـ CRS. صنفت تقييمات المؤشرات الحيوية المحددة 108 (22.6%) من مرضى LC وT2DM المعرضين لخطر كبير للإصابة بأمراض الكلى المزمنة (CKD)، و100 (20%) معرضين لخطر الإصابة بأمراض القلب والأوعية الدموية (CVD)، و91 (18.2%) معرضين لخطر الإصابة بـ CRS.

الخلاصة: التقييم الحالي شمل 500 مريض يعانون من T2DM وLC. اشتملت عوامل الخطر لCRS التي تم تحديدها في هذه الدراسة على ارتفاع مستويات الكوليسترول والدهون الثلاثية، وارتفاع مؤشر كتلة الجسم، وارتفاع ضغط الدم، مع كون العمر عاملاً مهمًا، خاصة في المرضى الإناث. إن التحديد المبكر لهذه الخصائص لدى المرضى الذين يعانون من LC وT2DM يمكن أن يساعد في التخفيف من تطور الأمراض المزمنة والمضاعفات المرتبطة بها.

Objectives: To evaluate the correlation between different attributes, levels of biomarkers, and the probability of developing cardiorenal syndrome (CRS) in patients who have been diagnosed with type 2 diabetes mellitus (T2DM) and liver cirrhosis (LC). The hypothesis suggests that liver illness may be linked to renal impairment, cardiac dysfunction, and the development of cardiorenal syndrome

Methods: The current study retrospectively assessed the medical records of patients who had LC and T2DM diagnoses and were hospitalized at Al Madina Al Munwara hospitals in 2022 and 2023.

Results: This research investigated T2DM patients with physician-confirmed to have LC. Poor glycemic control is indicated by high blood glucose and glycated hemoglobin (HbA1c) readings in research participants. High blood pressure, atherogenic plasma indicator (AIP), and obesity plagued most of these individuals. High creatinine, moderate estimated Glomerular Filtration Rate (eGFR) decline, and a modest urinary albumin-to-creatinine (UACR) rise were the most prevalent variables in LC and T2DM patients. Cardiorenal syndrome risk factors, including elevated blood pressure, triglyceride levels, body mass index (BMI), and high-sensitivity C-reactive protein (hs-CRP) concentrations, were identified through logistic regression. It has been demonstrated that the prevalence of these risk factors increases with age; women may be at a greater risk for developing CRS. Specific biomarker evaluations classified 108 (22.6%) LC and T2DM patients at high risk for chronic kidney disease (CKD), 100 (20%) at risk for cardiovascular disease (CVD), and 91 (18.2%) at risk for CRS.

Conclusion: The current assessment included 500 patients with T2DM and LC. The risk factors for CRS identified in this study included elevated cholesterol and triglyceride levels, high BMI, and elevated blood pressure, with age being a significant factor, particularly in female patients. Early identification of these characteristics in patients with LC and T2DM could aid in mitigating the progression of chronic illnesses and their associated complications.

Keywords: biomarkers, cardiorenal, syndrome, liver cirrhosis, Saudi

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Recent research has established a strong correlation between cardiovascular disease (CVD) and liver disease. The diseases at issue share risk factors, including dyslipidemia, diabetes, and obesity. In addition, the progression of atherosclerotic cardiovascular disease (ASCVD) is closely associated with the deterioration of metabolic conditions in patients with liver disease.[1-6] Moreover, it has been reported that cirrhosis exacerbates the impairment of natriuresis, potentially resulting in increased cardiac preload and obstruction in patients with HF, cardiac dysfunction, and pulmonary hypertension due to portal hypertension.[7,8] In contrast, persistent HF may lead to hepatic impairment as a consequence of hepatic congestion, ultimately leading to hepatic fibrosis and cirrhosis.[8]

For a considerable duration, it has been firmly established that the prognosis of cirrhosis is substantially affected by kidney function.[1,2] Functional hepatorenal syndrome (HRS) is a characteristic of advanced cirrhosis, but it is not the only cause of acute kidney injury (AKI) in this scenario.[3,4] Multiple mechanisms contribute to the development of hepatorenal syndrome (HRS), including circulatory alterations, renal variables, and systemic inflammation.[5,6]

Individuals diagnosed with type 2 diabetes mellitus (T2DM) may experience the presence of various coexisting medical conditions and an increased risk of premature death as a result of ASCVD, hospitalization stemming from HF, or CKD.[9,10] Diabetes mellitus (DM) is associated with an increased susceptibility to HF and a more unfavorable prognosis. Moreover, it is worth noting that nearly half of individuals diagnosed with DM will develop CKD, thereby establishing DM as the primary etiological factor contributing to kidney failure.[9,10]

Diabetes can lead to both CVD and kidney disease, making it a significant risk factor for CRS. The coexistence of CRS and diabetes has been widely recognized as a significant factor contributing to heightened rates of hospitalization and mortalit.[11] Considering the interrelationship between cardiac function, kidney function, and liver disease, the evaluation of their respective biomarkers is significant in the current era of aging. Several biomarkers have been identified as potential factors in the development of cardiorenal disease over the past decade. Cardiorenal syndrome refers to a group of conditions that impact both the heart and the kidneys, in which acute or chronic dysfunction in one organ can contribute to dysfunction in the other organ.[12,14] Cardiorenal syndrome describes the complex bidirectional relationship between heart and kidney dysfunction. Therefore, 5 subtypes comprise CRS: Type 1 is an acute decline in renal function precipitated by a precipitous decline in cardiac function. Chronic cardiac dysfunction that causes a sustained decline in renal function is classified as Type 2. Type 3 is an acute reduction in cardiac function due to a precipitous decline in renal function. Chronic cardiac dysfunction is the consequence of Type 4 renal dysfunction. Systemic diseases that cause cardiac and renal dysfunction are classified as Type 5.

Every variant possesses a distinct pathophysiology, which necessitates distinct approaches to treatment and a range of prognoses.[14] Type 1 CRS is the most prevalent and extensively studied variety.

The risk factors for developing CRS involve a combination of cardiovascular and renal conditions, as well as other health and lifestyle factors. Understanding these risks is crucial for prevention and management. Generally, LC and T2DM have been recognized as the primary factors initiating various pathophysiological mechanisms that directly impact multiple organs, including the kidneys and heart. However, recent research indicates that there is a potential link between the heart and detrimental renal consequences, or vice versa, which is referred to as CRS. Therefore, the purpose of this research is to identify biomarkers associated with the progression of renal and cardiac dysfunctions in patients with LC and T2DM. Cirrhosis of the liver can initiate a series of systemic complications, including cardiac dysfunction and renal impairment, both of which may play a role in the progression of CRS. Many of these problems get worse for people with T2DM because of the effects of high blood glucose and insulin resistance working together, which causes both microvascular and macrovascular damage. Analyzing biomarker levels is critical to understanding the complex association between liver disease, renal impairment, and cardiac dysfunction. This knowledge is vital in the development of precise diagnostic and therapeutic approaches for individuals with T2DM, with the potential to enhance clinical outcomes and quality of life.

Methods. A retrospective review of medical records was carried out on a sample of 1200 patients (600 females and 600 males) who were referred to King Fahad Hospital in Al Madina Al Munawara, Saudi Arabia's endocrinology and diabetes unit between January 2022

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and December 2023 and were diagnosed previously with T2DM. Medical records were obtained from the hospital's electronic health records (EHR) system. The inclusion criteria were patients (30-80 years old) with a confirmed diagnosis of liver cirrhosis (LC) (based on clinical, imaging, or biopsy data), patients with a documented diagnosis of T2DM, and availability of comprehensive medical records, including laboratory results, imaging studies, and biomarker levels relevant to renal and cardiac function. The exclusion criteria were patients with incomplete medical records; patients with coexisting chronic illnesses that could independently affect renal or cardiac function (such as, chronic obstructive pulmonary disease, and active malignancy); and patients who have undergone major surgery or transplants during the study period. A random sampling method was used to select a representative cohort from the eligible patient pool with T2DM. To ensure diversity and comprehensiveness, stratified sampling was employed based on age, gender, and severity of LC (such as Child-Pugh score).

The sample size was calculated using the equation provided below:

$$S = (P\ (1\text{-}P) \div d2)\ x\ (Z1\text{-}\alpha/2)2$$

With a 95% level of confidence, $Z1\text{-}\alpha/2 = 1.96$, $d = 0.05$, and P = population proportion (0.5 or 50% is assumed).

Relevant data was extracted from the EHR, including demographic information, medical history, and laboratory test results.

The study employs a rigorous selection methodology to guarantee the validity, dependability, and generalizability of the results to a wider cohort of patients afflicted with LC and T2DM. In total, 500 patients (270 males and 230 females) who had received a diagnosis of these diseases were included in the present investigation (**Figure 1**).

The severity of LC was conclusively diagnosed in the patients, after which the Child-Pugh scores were calculated. The Child-Pugh score is commonly employed as a method for evaluating the severity of hepatic cirrhosis in a clinical context. The Child-Pugh classification score encompasses various factors, including ascites, hepatic encephalopathy (HE), total bilirubin, albumin, and international normalized ratio (INR).[15] Upon completion of the score calculations, liver disease is categorized into 3 distinct groups: A, B, or C. The score was calculated using the provided methodology outlined in MDCalc.[16]

In Class A, the disease is classified as mild, typically exhibiting a range of symptoms totaling 5 to 6 points. Within the context of Class B, a disease is classified as moderate when it attains a score falling within the range of 7 to 9 points. Within the context of Class C, a disease is deemed to be severe when it exhibits a cumulative score falling within the range of 10 to 15 points.

Various parameters, including fasting blood glucose (FBG), C-reactive protein (hs-CRP), alanine transaminase, aspartate transaminase, total bilirubin, albumin (blood and urine), creatinine (serum and urine), estimated glomerular filtration rate (eGFR), blood urea nitrogen, INR and lipid profile (total cholesterol (TC), low-density lipoprotein-C (LDL-C), high- density lipoprotein-C (HDL-C), triglycerides (TG). The data were obtained from patient records and assessed based on the reference range values utilized by the laboratories of Madinah Hospital in Al Madina Al Munawara region of Saudi Arabia. The mean of FBG values from the year of cohort entry (2022) was calculated and classified into 4 categories (7 mmol/L to <7.7 mmol/L, 7.7 mmol/L to <8.9 mmol/L, 8.9 mmol/L to <10 mmol/L, and ≥10 mmol/L) incorporating cutoffs for prediabetes and T2DM.[17]

The typical range for serum creatinine levels in adults with normal kidney function is approximately 0.5 to 1.3 mg/dL. Elevated levels of creatine beyond the established normal range have been observed to exhibit a negative correlation with glomerular filtration rate (eGFR), thereby serving as an indicator of impaired renal function.[18,19]

The baseline level for creatinine in a patient with a normal eGFR is 1 mg/dL. A creatinine level of 2 mg/dL corresponds to a 50% decrease in eGFR. A creatinine level of 4 mg/dL corresponds to a decrease in glomerular filtration rate ranging from 70% to 85%. A reduction in glomerular filtration rate of 90 to 95% is observed at a creatine level of 8 mg/dL.[18,19]

To identify the presence of proteinuria, hematuria, and glucosuria, dipstick urinalysis was performed on random urine samples. The data were acquired from patient records and evaluated by employing established methodologies to determine the sensitivity, specificity, and positive and negative predictive values of the dipstick tests.[20]

Using the Modification of Diet in Renal Disease (MDRD) equation, the eGFR was computed.[18,19] 175 x (creatinine, mg/dl) - 1.154 x (Age, years) = eGFR (mL/min/1.73 m^2). This formula can be used to calculate the eGFR. The eGFR stages (classification of CKD): G1=90, normal or elevated, G2=60 to 89, slightly reduced, G3a=45 to 59, moderately to mildly decreased, G3b=30 to 44, moderately to drastically diminished, G4=15 to 29 significantly decreased,

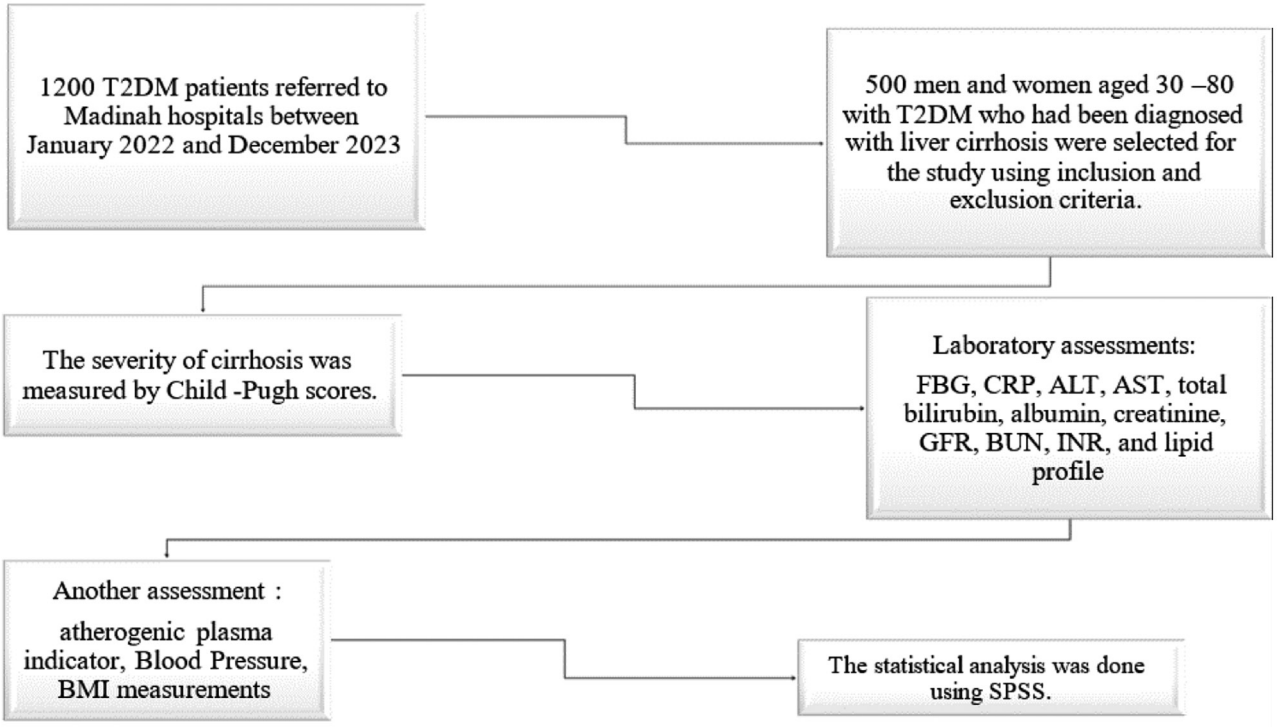

Figure 1 - The study protocol's graphic is presented.

G5=15, renal insufficiency.

The diagnostic criterion for albuminuria was defined as a spot urinary albumin-to-creatinine ratio (UACR) equal to or greater than 30 mg/g. Albuminuria can be categorized based on UACR. Category A1 is defined as having a UACR of <30. Urinary albumin-to-creatinine ratio levels ranging from 30 to 300 are indicative of a normal to slightly elevated condition, this is denoted by A2. The UACR value exceeding 300 indicates a moderate increase or severe increase, this is denoted by A3.[21,22]

The atherogenic plasma indicator was assessed using the AIP (log10TG/HDL-C). The AIP classification divides individuals into three categories based on their risk for CVD: low risk (AIP score of 0.1), medium risk (AIP score between 0.1 and 0.24), and high risk (AIP score greater than 0.24).[23]

Three separate readings of arterial pressure were obtained at 5-minute intervals, and the mean value was computed and documented. The determination of blood pressure (BP) cutoffs was established in accordance with the 2017 guidelines outlined by the American College of Cardiology (ACC) and the American Heart Association (AHA).[24] The standard range for BP is considered to be less than 120/80 mm Hg, whereas BP readings falling between 120-129 mm Hg systolic and 80 mm Hg diastolic are classified as "Elevated". Individuals were identified as having stage I hypertension, commonly referred to as prehypertension, if their systolic blood pressure (SBP) or diastolic blood pressure (DBP) fell within the range of 130-139 mm Hg or 80-89 mm Hg, respectively and high BP is considered to be 140/90 mmHg or higher.

The study obtained data on age, gender, and anthropometric dimensions, including height, weight, and body mass index (BMI). The BMI was ascertained based on established criteria, utilizing the weight-to-height squared formula, and subsequently classified into three categories: normal (18.5-25.0Kg/^{2}), overweight (25.0-29.9Kg/m^2), or obese (>30.0Kg/m^2).[25]

Ethical approval: The study was conducted with the appropriate ethical clearance obtained from the Ethical Committee at the College of Applied Medical Sciences, Taibah University, Al Madinah Al Munawara. Additionally, ethical approval was granted by the Institutional Review Board (IRB), General Directorate of Health Affairs in Al Madina Al Munawara, with the approval code IRB022-22. The ethics committee excluded the retrospective analysis of medical records from informed consent while ensuring that all data was anonymized.

Statistical analysis. The statistical analysis was

conducted utilizing the Statistical Package for the Social Sciences, version 26, (IBMCorp, Armonk, NY, USA). Quantitative data is typically conveyed through statistical measures such as frequencies, percentages, mean values, and standard deviations. The Chi-square test was employed to assess variations among categorical variables (p-values of ≤0.05 are considered significant). The study carried out a logistic regression analysis to determine the relationship between various characteristics, biomarker levels, and the likelihood of developing CRS. In this analysis, the outcome variable represents the risk of developing CRS in a participant throughout the course of the study. Considered predictor variables consist of age, BMI, gender, BP, elevated TC, elevated TG, elevated UACR, and elevated hs-CRP. Through the examination of these variables, we aim to determine which factors might elevate the likelihood of CRS in patients with T2DM and LC.

Logistic regression formula:

$\text{logit}(P)=\ln(P\ 1\text{-}P)=ß0+ß1X1+ß2X2+ß3X3+\ldots+ßkXk$

$\text{logit}(P)=\ln(1\text{-}PP)=ß0+ß0+ß1X1+ß2X2+ß3X3+\ldots+ßkXk$

Where: P is the probability of the occurrence of CRD. logit (P) is the log-odds of the probability P. ß0 is the intercept term. ß1, ß2, ß3…,ßk,ß1,ß2,ß3,…,ßk are the coefficients for the predictor variables. X1,X2,X3,…,XkX1,X2,X3,…,Xk are the predictor variables.

Study model: We have the following predictor variables:

X1: Age, X2: Gender (coded as 0 for male, 1 for female), X3: BP, X4: TC, X5: Triglycerides, X6: BMI, X7: Albumin-to-creatinine ratio UACR, X8: Elevated hs-CRP

The relationships between variables and outcomes were expressed as odds ratios (ORs) and 95% confidence intervals. Statistical significance is attributed to values of p≤0.05 or p≤0.001.

Results. Table 1 presents the baseline characteristics of the patients in our study who had both T2DM and LC (500 individuals [41.7%] in the study population). It is noteworthy that a significant proportion of these patients were aged 50 years or older. In the present investigation, there was a greater representation of males, accounting for 54% of the total sample, compared to females, who constituted 46% of the sample. The current study focused on the diagnosis of LC in patients, which had been previously confirmed based on physician reports. The severity of hepatic cirrhosis was assessed using Child-Pugh scores. Our findings revealed that 243 individuals (48.6%) were classified as Class B, indicating a moderate to severe level of cirrhosis. The study participants exhibit increased fasting blood glucose (FBG) levels, as well as increased levels of HbA1c, indicating poor glycemic control. Additionally, there are observed alterations in lipid levels and liver enzyme activity among the participants. The majority of these patients exhibited elevated blood pressure, were overweight, and had a high risk of CVD, as indicated by their atherogenic index of plasma value 0.4±0.2. Furthermore, there is evidence of abnormalities in renal function tests, particularly in creatinine levels, which are associated with a decrease in eGFR and an increase in albumin-to-creatinine ratio (ACR) values (Table 1).

In our study, the most prevalent biomarkers for CKD in patients with LC and T2DM were elevated creatinine levels, a moderate decrease in eGFR, and a modest increase in UACR levels, which were found in 51%, 51%, and 60% of patients, respectively. In contrast, alterations in the lipid profile level, particularly increasing cholesterol and triglyceride levels, are observed in 42% and 44% of patients, respectively, with 30% of them being overweight (Table 2).

The logistic regression analysis found the risk variables linked with developing CRS in individuals with LC and T2DM. The risk variables identified were higher blood pressure, increased triglyceride levels, high body mass index (BMI), and elevated high-sensitivity C-reactive protein (hs-CRP) levels. These risk factors were shown to be more prevalent with increasing age, as seen in Table 3. Current findings indicate that females may have a higher likelihood of developing CRS. However, the underlying reasons for gender variations in CRS are not yet fully comprehended.

Discussion. Cardiorenal syndrome pathophysiology developments played a role in the identification of new biomarkers that could be helpful in the diagnostic process and the definition of suitable therapies in CRS.[26] Cardiorenal syndrome is divided into five types according to the direction of action and whether the triggering injury is acute or chronic.[27] It is due to complex pathophysiologic processes. There are three major pathophysiology beliefs for the development and progression of cardiac and renal interactions. Firstly, the hemodynamic changes resulting from the decreased left ventricular ejection fraction or altered venous return.[28,29] The renal function depends on renal plasma flow and filtration fraction, therefore, inconsistent renal perfusion due to impaired cardiac output will lead to disruption of the renal auto-regulation.[28] Also, the increase of central venous pressure, apart from changes in the right atrial pressure, stimulates sympathetic nerve activation as well as dysregulates the neuro-hormonal axis of the heart

Table 1 - Clinical and biochemical characteristics of patients with liver cirrhosis and T2DM.

Parameter	Patients with liver cirrhosis & T2DM, N=500	Reference range
Age (years)	52.54±10.12	-
Gender (male/female)	270(54%)/230(46%)	-
Duration of diabetes	11±5.13	-
Duration of liver cirrhosis	4.5±1.5	-
Child-Pugh score	7.5 ± 1.21**	5-15 points
Child-Pugh classification	147(29.4%) Class A 243(48.6%) Class B** 110(22%) Class C	Class A=5-6 Class B=7-9 Class C=10-15
FBG (mmol/L)	**8.81±1.66**	3.89 - 5.50
HbA1c (%)	**7.53±1.78**	4.3% - 6.0%
Blood pressure(systolic/diastolic)	**125/80***	Systolic: less than 120 mm Hg Diastolic: less than 80 mm Hg
LDL-C (mmol/L)	3.81±0.72	2.6 - 4.11
HDL-C (mmol/L)	**1.02±0.61**	1.04 - 1.6
Total cholesterol (mmol/L)	**6.7±1.71**	<5.17
Triglycerides (TG) (mmol/L)	**3.16±1.19**	<1.6
BMI (kg/m^2)	**26.5±7.51§§**	18.5 - 24.9
AIP = log (TG/HDL-C).	**0.4±0.2§**	<0.11
hs-CRP(mg/L)	**3.4±1.33**	<1.0
Albumin (g/dL)	**10.4±1.66**	30- 50
Total Protein (g/dL)	**5.4±1.5**	**6.3 - 7.9**
AST (IU/L)	**85.22±10.21**	**8 - 48**
ALT(IU/L)	**75.90±11.54**	**7 - 55**
ALP (IU/L)	**144±11.26**	**40 - 129**
INR	**1.8±0.56**	**≤1.1**
Total bilirubin (mg/dL)	**1.5±0.51**	
Serum creatinine(mg/dL)	**1.9±0.71**	0.5- 1.3 mg/dL
BUN (mg/dL)	22.5±7.43	6-24 mg/dL
CK (U/L)	**180±13.65**	30- 170 U/L
Urine creatinine (mg/dL)	105±16.44	20 – 320 mg/dL
Urine Albumin (mg/dL)	**45.5±10.12**	<30 mg/dl
eGFR (mL/min/1.73m^2)	**55±9.10†**	90- 120 mL/min/1.73 m^2
Urinary Albumin-to-creatinine ratio (UACR) mg/g	**120.5±10.15‡**	<30 mg/g
Proteinuria (+ve)	35(7%)	+ve
Hematuria (+ve)	20(4%)	+ve
Glucosuria (+ve)	90(18%)	+ve
Glucosuria + Proteinuria (+ve)	125(37%)	+ve
Proteinuria + Hematuria (+ve)	50(10%)	+ve
All Glucosuria Hematuria Proteinuria tests (+ve)	320(64%)	+ve
All Glucosuria Hematuria Proteinuria tests (-ve)	180(36%)	-ve

Values are presented as mean ± standard deviation, frequency, and percentage (%). Bold is used to indicate values that are either higher or lower than the reference ranges. The reference range values utilized in this study were derived from data obtained from the laboratories of Madinah Hospital, located in the Al Madina Al Munawara, Saudi Arabia. *120-129 mm Hg systolic and 80 mm Hg diastolic are classified as Elevated. **Child-Pugh score= the severity of liver cirrhosis was considered moderate. §AIP >0.21, high risk of CVD, §§BMI (25.0-29.9Kg/m^2) overweight. †G3a=eGFR (45-59), there was a mild to moderate decrease. ‡A2= ACR (30–300) there was a moderate increase. T2DM: Type 2 diabetes mellitus, FBG: Fasting blood glucose, HbA1c: hemoglobin A1c, HDL-C: high density lipoprotein, and LDL-C: low-density lipoprotein, hs-CRP: high-sensitivity C-reactive protein, BMI: body mass index, AIP: Atherogenic Index of Plasma, AST: aspartate transaminase, ALT: alanine transaminase, ALP: alkaline phosphatase, international normalized ratio, BUN: blood urea nitrogen, CK: creatinine kinase, eGFR: estimated glomerular filtration rate

and the kidney.[30,31] Moreover, the sympathetic nervous system over-activation will aggravate HF progression.[32] Finally, other factors contributing to cardiac and renal worsening include immunity, metabolic disorders such as diabetes, metabolic syndrome, and obesity, oxidative stress, uremic molecules, as well as epigenetic factors.[33]

In CRS patients, biomarkers can have a prognostic impact, offer an understanding of the pathophysiology, and ultimately play a role in the guidance of therapeutic methodologies.[34,35] Some biomarkers reflect hemodynamic changes, and cardiac and renal damage or dysfunction. On the other hand, other biomarkers are expressions of alterations in collagen turnovers in the extracellular matrix of both the heart and kidneys,

Table 2 - Evaluation of biomarkers levels in CKD and CVD in patients with LC and type 2 diabetes mellitus (N=500).

Risk factors	n (%)
Chronic renal disease (CKD)	
FBG (mmol/L)	
7 mmol/L to <7.7 mmol/L	67(13.4%)
7.7 mmol/L to <8.9 mmol/L	241(48.2%)*
8.9 mmol/L to <10 mmol/L	166(33.2%)
≥10 mmol/L	26(5.5%)
Blood pressure (systolic/diastolic)	
<120/80 mm Hg (Normal)	240(48.0%)
120/80 mm Hg (Elevated)	230(46.0%)
>120/80 mm Hg (High)	30(6.0%)
Serum creatinine (mg/dL)	
Creatinine 1 mg/dL is normal eGFR	155(31.0%)
Creatinine 2 mg/dL is a 50% decreasing in eGFR	255(51.0%)*
Creatinine 4 mg/dL is a 70 to 85% decreasing in eGFR	90(18.0%)
Creatine 8 mg/dL is a 90 to 95% decreasing in eGFR	0
eGFR stages	
G1 = 90 (Normal)	55(11.0%)
G2 = 60 to 89 (Slightly reduced)	100(20.0%)
G3a = 45 to 59 (Moderately to mildly decreased)	255(51.0%)*
G3b = 30 to 44 (Moderately to severely reduced)	90(18.0%)
G4 = 15 to 29 (Significantly decreased)	0
G5 = 15 (Renal insufficiency)	0
Urinary albumin-to-creatinine ratio mg/g	
UACR1 <30 (Normal)	140(28.0%)
UACR2 = 30 to 300 (Slightly elevated)	300(60.0%)*
UACR3 >300 (Moderate increase or severely increased)	60(12.0%)
Cardiovascular disease (CVD)	
LDL-C (mmol/L)	
<2.6 (Optimal)	344(69.0%)
>4.11(Borderline high)	156(31.0%)
HDL-C (mmol/L)	
<1.04 (at risk)	190(38.0%)
>1.6 (Desirable)	310(62.0%)*
Total cholesterol (mmol/L)	
<5.17 (Normal)	190(38.0%)
5.17 to 6.18 (Borderline high)	210(42.0%)*
>6.21 (High)	100(20.0%)
Triglycerides (TG) (mmol/L)	
<1.6 (Normal)	180(36.0%)
1.6 to 5.6 (Moderately high)	220(440.%)*
≥5.6 mmol/L (Very high)	100(20.0%)
BMI (kg/m^2)	
18.5-25 (Normal)	107(21.0%)
25.0-29.9 (Overweight)	245(49.0%)*
>30 (Obese)	150(30.0%)
hs-CRP(mg/L)	
<1.0 (Low risk)	106(21.0%)
1.0-3.0 (Moderate risk)	245(47.0%)*
>3.0 (High risk)	150(32.0%)

Values are frequency and percentage (%). FBG: fasting blood glucose, HDL-C: high density lipoprotein, LDL-C: low-density lipoprotein, hs-CRP: high-sensitivity C-reactive protein, BMI: body mass index, eGFR: estimated glomerular filtration rate. *P≤0.05 was obtained from the Chi-square test.

Table 3 - ELogistic regression analysis used to assess the possibility of developing Cardiorenal syndrome (CRS) in patients with T2DM and LC.

Variables	Odd ratio	(95% CI)	*P*-value
Age (years)			
30-50	3.13	(1.10–4.31)	>0.05
51-70	**5.7**	**(2.11–6.9)**	**0.05***
>71	**6.9**	**(2.12–7.41)**	**0.04***
Gender			
Females	**5.5**	**(2.41–7.5)**	**0.04***
Males	3.5	(1.16–4.51)	>0.05
Elevated blood pressure	**5.54**	**(2.10–6.41)**	**0.04***
High cholesterol	1.12	(0.10–1.31)	>0.05
High Triglycerides	**5.62**	**(2.22–7.23)**	**0.03***
BMI= 25.0-29.9 (Overweight)	**6.34**	**(2.10–7.84)**	**0.03***
Elevated UACR	1.12	(0.10–1.31)	>0.05
Elevated hs-CRP	**5.29**	**(2.12–7.56)**	**0.04***

The statistically significant data are indicated in bold, p≤0.05 or 0.001. Logistic regression analysis, *P<0.05, CI: confidence interval. BMI: body mass index, UACR: Albumin-to-creatinine ratio

and others may reflect oxidative stress-induced cell damage.[26] Based on our search, this is the first study to investigate the biomarkers related to renal and cardiac impairments' progression in patients with LC and T2DM and their associations with CRS risk, in Saudi Arabia. The study found that the risk factors associated with CRS in patients with LC and T2DM included elevated blood pressure, increased triglyceride levels, high BMI, and increased hs-CRP levels. In a retrospective study assessing the risk factors of CRS type 1 in elderly Chinese patients, basic estimated glomerular filtration (eGFR <60 ml/(min 1.73 m^2), as well as diuretics use, were associated with the higher risk factors of CRS1 in patients, however, higher basic eGFR and serum albumin were both protective factors for CRS1.[36] Our results are in line with the literature, in terms of obesity being a predisposition for CRS.[37] The adipocytes secrete cytokines, and consequently cause heart and kidney injury. As an example, interleukin (IL)-6 and tumor necrosis factor alpha (secreted by adipocytes) have been associated with cardiac and renal diseases. Also, IL-6 production via abdominal adipocytes into the portal circulation and transit to the liver is the main stimulus for hs-CRP levels. Therefore, hs-CRP levels are highest in obese people,this also supports our results of increased hs-CRP levels being a risk factor associated with CRS in patients with LC and T2DM.[38,39] Moreover, previous research reported that the CRS association was dependent on hypertriglyceridemia and oxidative stress.[40] Lee et al[41] observed that proteinuria and renal dysfunction were risk enhancers for hospitalization for HF in T2DM patients, which was in line with

Table 4 - The incidence of developing CVD or CKD, or the co-occurrence of both conditions (CRS) in individuals diagnosed with T2DM and LC based on biomarker levels (N=500).

The prevalence of patients at high risk of having CVD	108(21.6%)
The prevalence of patients at high risk of having CKD	100(20%)
The prevalence of patients at high risk of having CRS	91(18.2%)
Total	299(59.8%)

Frequency and percentage (%). The patient frequency was determined by assessing the presence of risk factors associated with the development of CVD, CKD, or (CRS). CVD: cardiovascular disease, CKD: chronic kidney disease, CRS: cardiorenal syndrome, T2DM: type 2 diabetes mellitus

previous studies.[42] Also, in patients without proteinuria and decreased eGFR, MAFLD significantly increased the risk of hospitalization for HF, signifying that active diagnostic and interventional policies should be available for T2DM patients, minimally in those who concurrently have diabetic kidney disease or MAFLD.[43]

Our findings stated that the most prevalent risk factors for CKD in LC and T2DM patients were increased creatinine levels, a moderate decrease in eGFR, and a modest increase in ACR levels. This was consistent with the literature, as among the renal function biomarkers, serum creatinine and GFR levels are widely used for identifying kidney impairment and they also have a prognostic value in patients with renal diseases and are possibly useful in identifying the increased prevalence of renal dysfunction in patients with HF.[26] On the other hand, it was reported that serum creatinine levels might not reflect GFR accurately, as it could be impacted by non-renal factors, for example, sarcopenia, which is detected in 20% of CHF patients.[43] Therefore, other more accurate renal dysfunction biomarkers have been identified, including cystatin C, which has been considered a more accurate surrogate marker of GFR in comparison to serum creatinine levels. This was due to its less dependency on age, nutrition, and BMI.[44] In addition to this, cystatin C might stratify the risk of cardiovascular events, such as coronary artery disease, and acute as well as chronic HF. Moreover, it might increase the NT-proBNP accuracy in CRS type 1.[26] Another biomarker includes the kidney injury molecule 1 (KIM1),which might identify AKI or CKD progression in HF patients.[26] Also, KIM1 is associated with HF, cardiovascular events, and AKI and CKD mortalities.[45]

It was recently reported that CRS was prevalent in 0.40% of the whole population, and in 2.3% of T2DM patients.[46] There is limited data regarding the incidence and prevalence of CRS risk in LC and T2DM patients in Saudi Arabia. This study found that, during the study period, 18.2% (91 people) were at risk of developing CRS in this population. The study also revealed that 22.6% had CKD, and 20% had CVD risk. This study provides insights about biomarkers for CRS risk in LC and T2DM patients in Saudi Arabia, which could open doors for better understanding and ultimately better diagnosis, and prognosis. Future research is recommended which could also focus on novel biomarkers which might provide more accurate results.

Study limitations. The study conducted was characterized by a single-center design and a limited sample size. The presence of selection bias and the absence of comprehensive documentation of treatment history were observed. Additionally, patients who demonstrated improvement in renal and cardiac function during their hospitalization but were subsequently discharged, as well as patients who passed away during the study period, did not have comprehensive follow-up data collected. This omission was identified as a limitation of the research and underscored the necessity for further investigations in this area. Therefore, it is recommended that further follow-up studies be conducted to evaluate the long-term outcome.

In conclusion, patients with LC and T2DM, elevated creatinine, a moderate decrease in eGFR, and a slight increase in ACR were the most common risk factors for CKD. Moreover, the risk variables for CRS in LC and T2DM patients included raised blood pressure, lipids, BMI, eGFR, and hs-CRP as risk factors. During the research period, 22.6% of the sample had CKD. Approximately 20% were at risk of CVD, while 18.2% were at risk CRS. These findings indicate that early necessary investigations in LC and T2DM patients may enhance treatment and avert complications. Nevertheless, additional research is required to comprehend the efficacy of biomarker levels associated with kidney, cardiac, and liver functions in forecasting all-cause that enhances the possibility of CRS in patients with liver cirrhosis.

It is recommended that forthcoming longitudinal investigations provide comprehensive monitoring and examination of the enduring effects of these

constituents on subgroups of vulnerable adults. This will aid in enhancing the categorization of risk for the management of chronic illnesses.

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