Lupus nephritis

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Abstract

Background

Lupus nephritis, one of the most serious manifestations of systemic lupus erythematosus (SLE), usually arises within 5 years of diagnosis; however, renal failure rarely occurs before American College of Rheumatology classification criteria are met. Lupus nephritis is histologically evident in most patients with SLE, even those without clinical manifestations of renal disease. The symptoms of lupus nephritis are generally related to hypertension, proteinuria, and renal failure. With the advent of more aggressive immunosuppressive and supportive therapy, rates of renal involvement and patient survival are improving.

Keywords: LN, SLE.

INTRODUCTION:

Systemic lupus erythematosus (SLE) is an autoimmune disease that can involve any structure of the body and exhibits a large spectrum of clinical manifestations including cutaneous, joint, renal, hematological, and central nervous system disease. The renal disease represents a frequent manifestation of SLE as well as an important outcome predictor in these patients. [1]

Cardiovascular disease is recognized as the leading cause of death in systemic lupus erythematosus (SLE) patients with and without nephritis. Although traditional cardiovascular risk factors contribute to early-onset atherosclerosis in SLE, the phenomenon is not fully explained by a higher frequency of smoking habits, hypertension, or dyslipidemia in this population but may be due to chronic inflammatory state. [2]

A close pathophysiologic relationship between the kidney and the heart is well known (cardio-renal syndrome). Cardio-renal syndrome encompasses a spectrum of disorders involving both the heart and kidneys in which acute or chronic dysfunction in 1 organ may

fraction (LVEF). Uremic cardiomyopathy (type 4 CRS) is characterized by the significant burden of LV hypertrophy on which FGF-23 (fibroblast growth factor-23) has recently been shown to have an independent causal effect. [3]

Prediction models such as the Framingham equation based on traditional cardiovascular risk factors are less accurate at identifying cardiovascular risks in systemic lupus erythematosus (SLE) patients as compared to the general population. Thus, identification of biological markers able to better stratify cardiovascular risks in SLE patients is needed. [2]

High sensitivity troponin (Hs-TnT) is established as a diagnostic and prognostic marker for myocardial injury. Elevated levels are associated with a higher risk of death. [3]

Aim of the study

Was to determine whether lupus nephritis (LN) is a risk factor for myocardial injury, whether Hs-TnT and CKMB had a rule in early detection of myocardial injury in lupus nephritis (LN) patients and to determine if the prevalence of myocardial injury is higher in lupus nephritis (LN) than systemic lupus erythematosus (SLE) patients.

induce acute or chronic dysfunction in the other organ. It represents the confluence of heart-kidney interactions across several interfaces. The overlap of cardiovascular and kidney disease extends across several interfaces. These include the hemodynamic interactions of the heart and kidney, the impact of atherosclerotic disease across both organ systems, neurohormonal activation, cytokines, the biochemical perturbations across the anemia–inflammation–bone mineral axis in chronic kidney disease (CKD), and structural changes in the heart unique to kidney disease progression. Several non-hemodynamic pathways that exacerbate cardiac or kidney injury are operative in cardio-renal syndrome (CRS), central to which is the activation of the sympathetic nervous system, chronic inflammation, imbalance in the proportion of reactive oxygen species/nitric oxide production, and persistent renin angiotensin aldosterone system (RAAS) activation. Circulating levels of tumor necrosis factor-α (TNF-α), IL-1 (interleukin-1), and IL-6 (interleukin-6), which are elevated in experimental models of acute kidney injury (AKI), have direct cardio depressant effects such as a reduction in left ventricular ejection

taking the age, gender, levels of total cholesterol and HDL-c, cigarette smoking, presence or absence of DM, levels of systolic blood pressure and the use of antihypertensive drugs as variables. Considering as low risk values <10%, moderate 10–19% and high ≥20% [24]. Renal biopsy was done for all lupus nephritis (LN) patients. For all patients, the following investigations were evaluated: electrocardiogram (ECG), transthoracic echocardiography (ECHO), pelvi-abdominal ultrasonography, erythrocyte sedimentation rate (ESR) (Estimation was done by the weastergen method recorded in mm/hr. The reading of the first hour was taken [21], C- reactive protein (CRP) (by Latex agglutination test), complete blood count (CBC), complete urine analysis, urinary albumin to creatinine ratio (UACR), serum creatinine, serum albumin, serum sodium, serum potassium, fasting blood glucose, postprandial blood glucose, lipid profile, antinuclear antibody (ANA) (by immunoflourescence technique [22], anti double stranded DNA (anti-ds DNA) antibodies (by indirect fluoresecent antibody test.), antiphospholipid antibodies, complement 3 (C3) and complement 4

Patients and methods:

This prospective study was carried out at the nephrology unit, internal medicine department, Benha University Hospitals on 50 patients divided into 2 groups (30 patients with LN, and 20 patients with SLE). After approval of the ethics committee of Benha university hospital, the patients were informed about the nature of the study, and a written consent was obtained from each patient. Patients who fulfilled four or more of Systemic Lupus International Collaborating Clinics (SLICC) criteria and asymptomatic for cardiovascular disease (CVD) were included in this study. Exclusion criteria included patients with other preexisting disease precipitating cardiac problems (e.g Diabetes mellitus (DM) diagnosed before the onset of lupus and patients with collagen vascular diseases other than SLE). Baseline characteristics of all patients were collected using self-reported standardized questionnaires that included demographics, medical history, and medication use. Full physical examination was done. The cardiovascular risk was calculated using the modified Framingham score, which assesses the risk for cardiovascular event that a person may suffer from over the next 10 years,

$$\text{Phosphocreatine} + \text{ADP} \xrightarrow{CK} \text{Creatine} + \text{ATP}$$

$$\text{ATP} + \text{Glucose} \xrightarrow{HK} \text{ADP} + \text{Glucose-6-phosphate}$$

$$\text{G6P} + \text{NADP} \xrightarrow{G6P-DH} \text{6-Phosphogluconate} + \text{NADPH} + \text{H}$$

The rate of NADPH formation, measured photometrically, is proportional to the catalytic concentration of CK-B present in the sample. The reference range was < 25 ug /L**.**

We predefined 3 categories of hs-TnT concentrations. The lowest category consisted of those participants with concentrations below 3 ng/L: undetectable hs-TnT), and the remaining distribution of measurable hs-TnT were divided into 2 categories [{those with concentrations between (3-13.9 ng/L): minimally elevated troponin} and {those with concentrations (≥14ng/L): significantly elevated troponin}].

Also, CKMB in LN patients was categorized into 2 groups: high CKMB group with level ≥25 ug /L and low CKMB group with level <25 ug/L).

The clinical data were recorded on a report form. These data were tabulated

(C4) (by Enzyme Linked ImmunoSorbent Assay (ELISA). [23]

Hs-TnT measurements were performed on the Cobas e602 Immuno module analyzer (Roche Diagnostics GmbH, SandhoferStrasse 116, D-68305 Mannheim) using the Hs-TnT Elecsys®2018 immunoassay. This assay is based on a sandwich principle; with electrochemiluminescent revelation. The total duration of the assay is 9 minutes**.** 50 µL of the sample is incubated with an anti-cTnT monoclonal antibody labeled with ruthenium complex and streptavidin-coated microparticles and with a biotinylated monoclonal anti-cTnT antibody**.** According to the manufacturer, the measurement range of the assay is 3 to 10,000 ng/L. The 99th percentile value is 14 ng/L, and the 10% coefficient of variation (CV) value is 13 ng/L (data from the manufacturer)**.**

CKMB measurements were performed on Biosystem BTS.350 analyzer (Biosystem. Barcelona, España) using Reactivos GPL**.** This assay is based on an antibody to the anti CK-M inhibits completely CK-MM and subunit (M) of the CK-MB. The activity of the non-inhibited CK-B subunit is then assayed by the following series of reactions:

biopsy-proven LN who fulfilled the SLICC criteria for SLE were selected for this study with a mean age (35.3±7.98 years versus 32 ± 9.51 years for LN and SLE respectively) and (88%) were females. Our results demonstrated no significant difference between LN and SLE as regard traditional and SLE related risk factors {SLE duration, disease activity index (SLEDAI-2K), antiphospholipid antibody (APL ab) and steroid dose and duration}, so apparently, both groups in our study were at low to moderate risk for developing CVD according to the classic cardiovascular risk factors {framingham score {a mean (9.3± 4.16) versus (6.6± 2.6) in LN and SLE respectively with a (p-value 0.12)}(Table 1, fig 1).

Twenty-eight LN patients (93.3%) versus 10 SLE patients (50%) had detectable Hs-TnT with a mean (29.77± 18.22) ng/L versus (7.2± 6.21) ng/L for LN and SLE respectively. The mean CKMB was (23.9±18.6 ug/L and 14.8± 9.4 ug/L in LN and SLE patients respectively).

Twenty four lupus nephritis (LN) patients (80%) versus 7 SLE patients (35%) had positive ECHO and ECG findings so this higher cardiovascular injury in LN patients can be explained

and analyzed using the computer program SPSS (Statistical package for social science) version 20 to obtain: mean and standard deviation $(\pm SD)$. Data were compared using student's *t*-test for comparing the mean of two groups with parametric quantitative data and chi-square test (X^2-value) and Fisher exact test (FET) for categorical variables. Comparisons among more than 2 groups were made using one-way factorial ANOVA (analysis of variance). ROC curve was used to show in a graphical way the connection /trade–off between clinical sensitivity and specificity for every possible cut-off for a test. To explain the relationship between one continuous dependent variable and two or more independent variables, we used multiple linear regression analysis (a form of linear regression analysis used as a predictive analysis). A *P*-value <0.05 was considered statistically significant**,** while >0.05 was considered statistically insignificant. A *P*-value <0.01 was considered highly significant in all analyses.

RESULTS:

This prospective study included twenty systemic lupus erythematosus (SLE) patients and thirty patients with

interventricular septum thickness in diastole (IVSD), ejection fraction (EF), left ventricular hypertrophy (LVH) and higher grades of diastolic dysfunction (DD) with a p-value <0.05 but no statistically significant difference between groups as regard right ventricular hypertrophy (RVH), regional wall motion abnormality (RWMA) and electrocardiographic changes suggesting ischemia. (Fig 4,5)

Our study revealed that 28 LN patients (93.3%) had detectable hs-TnT ≥3ng/l {twelve patients (40%) in the minimally detectable group with a mean (12.34 ± 1.14) ng/L and 16 patients (53.3 %) in the significantly detectable group with a mean (45.18 ± 8.27) ng/L}. None in the undetectable group, 66.7% of the minimally detectable group and all patients in the significantly detectable group were found to have positive ECHO findings with a p-value <0.01.

We found 8 LN patients (26.7%) had high CKMB (≥25 ug). All of them had positive ECHO findings. 22 LN patients (73.3%) had normal CKMB (<25 ug) with 16 patients (72.7%) of them had positive ECHO findings. (Fig 9,10)

We found a statistically significant higher mean CKMB level in the high CKMB group (50.1± 15.8 ug/L versus mainly by renal factors (Table 1, fig 2,3).

Our study revealed that the cut off value of Hs-TnT was 3 ng/L. The sensitivity and specificity of Hs-TnT in LN patients in detecting myocardial injury were 85.7 and 100% respectively. Our study revealed that the cut off value of CKMB was 25 ug/L. The sensitivity and specificity of CKMB in LN patients in detecting myocardial injury were 33.3% and 100% respectively.

Factors independently associated with elevated hs-TnT (≥3 ng/L) and high CKMB (≥25 ug/L) in LN patients were older age, greater BMI, abnormal blood pressure, abnormal lipid profile, higher Framingham risk score, longer SLE duration, SLEDAI-2K, higher anti ds DNA titer and prevalence, higher APL ab prevalence, higher ESR, higher CRP, lower C3, C4, lower e-GFR and higher UACR (Table 2, 3, Fig 6, 7, 8).

Besides these well- known risk factors for CVD in LN, detectable hs-TnT was also associated with a higher prevalence and abnormal left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter (LVESD), left ventricular posterior wall dimensions (LVPWD), left atrial diameter (LAD),

To further characterize the link between CKMB and myocardial injury in LN patients, multilinear regression analysis was done and revealed a highly statistically significant inverse correlation between CKMB and e GFR and EF (P-value <0.001).We found a highly statistically significant positive correlation between CKMB and urinary ACR (P value 0.006) (Table 5).

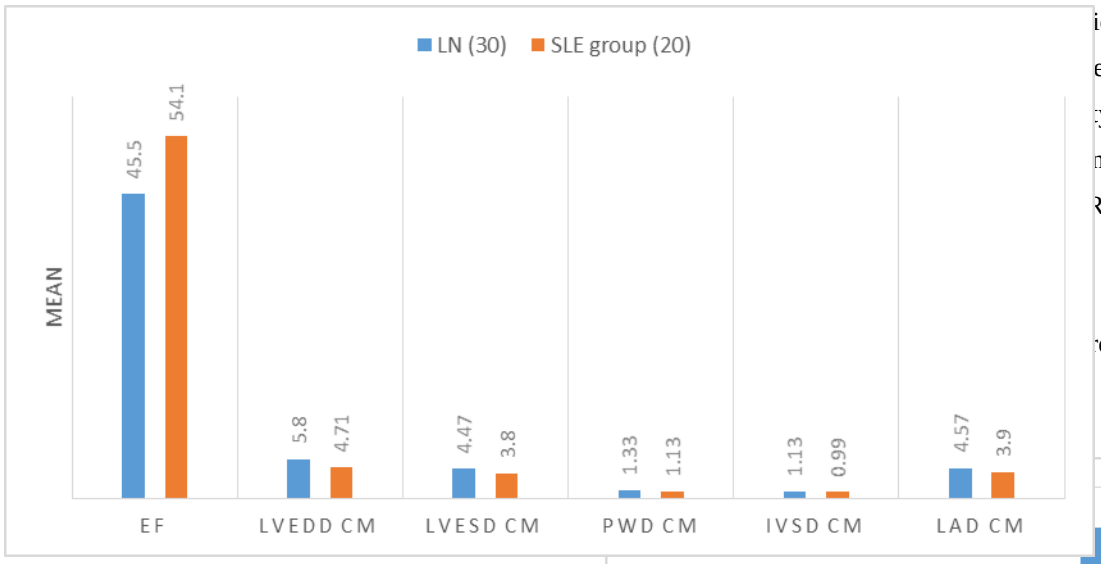
Table 1: Comparison between LN and SLE groups as regards the demographic and risk factors

14.4±6.4 ug/L for the high and normal CKMB groups respectively with a (p-value <0.001)).

To further characterize the link between HS-cTnT and myocardial injury in LN patients, multilinear regression analysis was done and revealed a statistically significant positive correlation between the serum levels of troponin and each of LVH, LVDD, LVEDD, LVESD and urinary ACR ($p < 0.05$). A highly significant inverse correlation existed between troponin level and e GFR and EF ($p < 0.001$). (Table 4)

	LN group (30)		SLE group (20)		P-value
	Mean	**±SD**	**Mean**	**±SD**	
Age (y)	35.3	7.98	32.0	9.51	0.19
Gender N (%) Male Female	 6 24	 20.0 80.0	 0 20	 0.0 100	 0.07
Smoking N (%)	6	20.0	0	0.0	0.07
SLE duration (y)	4.05	3.09	4.03	2.03	0.97
SLEDAI-2k	5.9	1.7	5.7	1.9	0.77
ESR 1st hour (mm/hr)	43	19.2	23.95	10.5	<0.001**
C3(mg/dl)	42.5	29.9	72.85	21.3	<0.001**
C4 (mg/dl)	7.3	2.78	10.5	29	<0.001**
CRP (mg/L)	34.97	12.19	19.73	10.99	<0.001**
Anti dsDNA titre	106.0	73.1	80.0	85.9	0.21
APL Ab N(%)	6	20.0	4	20.0	1.0
BMI (kg/m2)	25.47	3.76	23.83	2.63	0.098
FBG (mg/dl)	87.3	7.31	84.05	9.57	0.18
SBP (mmhg)	139.27	21.39	128.6	14.88	0.059
DBP (mmhg)	77.83	12.9	79.85	8.57	0.54
Cholesterol (mg/dl)	257.6	27.84	246.6	12.92	0.11
TG (mg/dl)	218.1	48.07	201.55	24.27	0.16
LDL (mg/dl)	148.0	35.55	144.95	15.96	0.72
HDL (mg/dl)	48.7	11.26	51.85	9.94	0.32
Framingham Risk Score	9.3	4.16	6.6	2.61	0.12
e GFR (ml/min/1.73m2)	63.6	25.5	98.51	4.614	<0.001**
Urinary ACR(mg/g)	3600.0	1369.87	19.8	6.97	<0.001**
Serum albumin gm/dl	3.13	0.73	4.13	0.30	<0.001**
Active urinary sediment (RBCS casts)(n) %	9	30.0	0	0.0	0.007**

C3,C4: complement 3,4, Anti ds DNA: Anti double stranded DNA, APLab: antiphospholipid ab , BMI: Body mass index, SLE: Systemic lupus erythematosus, SLEDAI: SLE disease activity index, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate,



EF: ejection fraction, LVEDD: Left ventricular end diastolic diameter, LVESD: Left ventricular end systolic diameter, PWD: Posterior wall diameter, IVSD: Interventricular septum diameter, LAD: left atrial diameter

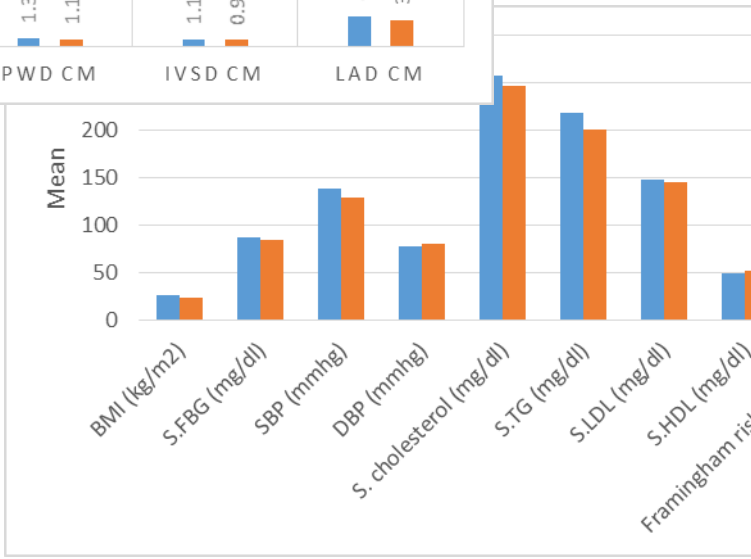
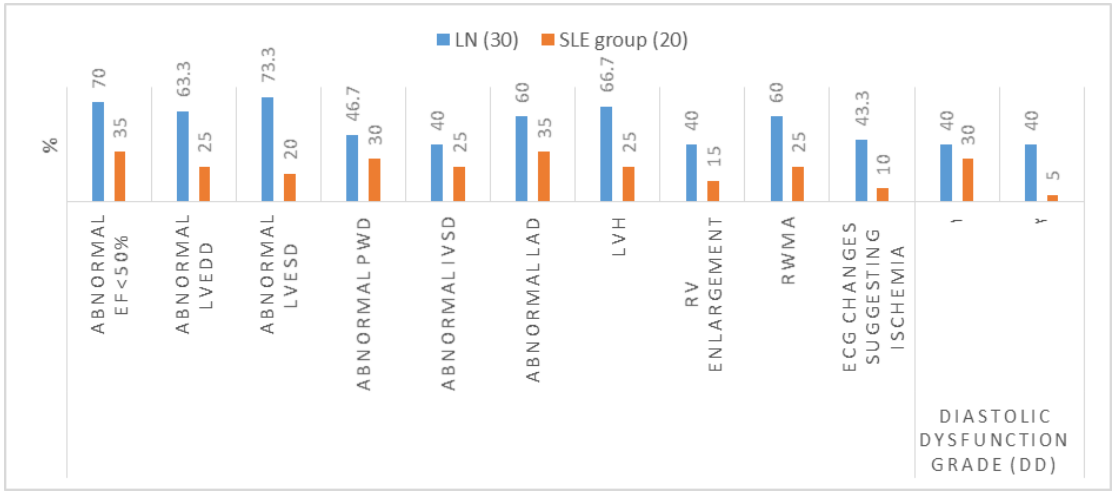


Fig 3: prevalence of myocardial injury in SLE and LN



EF: ejection fraction, LVEDD: Left ventricular end diastolic diameter, LVESD: Left ventricular end systolic diameter, PWD: Posterior wall diameter, IVSD: Interventricular septum diameter, LAD: Left atrial diameter, LVH: Left ventricular hypertrophy, RV: Right

cardiovascular risk factors and renal factors:

	Undetected (2)		Minimally detected (12)		Significantly detected (16)		Undetected versus minimally detected troponin(p value)	Undetected versus significantl y detectable troponin (p value)	Minimally detectable versus significantl y detectable troponin(p value)
	Mean	±SD	Mean	±SD	Mean	±SD			
	18.0	0.0	22.8	2.7	28.2	0.7	<0.001**	<0.001**	<0.001**
	77.0	0.0	81.5	3.09	92.94	4.61	0.13	<0.001**	<0.001**
	105.0	0.0	122.33	14.58	156.25	5.92	0.09	<0.001**	<0.001**
	50.0	0.0	71.25	9.97	86.25	5.92	<0.001**	<0.001**	<0.001**
	216.0	0.0	234.58	11.73	280.06	14.31	0.17	<0.001**	<0.001**
	150.0	0.0	181.92	15.7	253.75	35.57	0.32	<0.001**	<0.001**
	100.0	0.0	119.92	7.66	175.06	26.09	0.41	<0.001**	<0.001**
	69.0	0.0	57.6	5.96	39.5	8.3	<0.001**	<0.001**	<0.001**
x	3.55	0.2	6.03	1.5	12.5	2.8	0.34	<0.001**	<0.001**
2	99.3	0.0	84.96	14.96	43.0	2.5	<0.001**	<0.001**	<0.001**
ng/g	1350.0	212.13	2491.67	739.11	4712.5	496.49	0.154	<0.001**	<0.001**
l	4.0	0.0	3.5	0.31	2.63	0.20	<0.001**	<0.001**	<0.001**

BMI: Body mass index, FBG: Fasting blood glucose, SBP: Systolic blood pressure, DBP: diastolic blood pressure, TG: Triglyceride, LDL: Low density lipoprotein, HDL: high density lipoprotein, ACR: albumin creatinine ratio, e GFR: Estimated glomerular filtration rate.

Fig 4: Comparison of the three Hs-TnT detection groups according ECHO and ECG findings

ventricle, RWMA: Regional wall motion abnormality, ECG: Electro cardio gram, DD: diastolic dysfunction

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according to

	Mean	±SD	Mean	±SD	Mean	±SD	Undetected versus minimally detected troponin (p value)	Undetected versus significantlly detectable troponin (p value)	Min dete vers sign dete trop valu
Age (y)	20.0	0.0	29.5	4.76	41.56	2.58	<0.001**	<0.001**	<0.0
SLE duration (y)	0.5	0.0	1.8	0.8	6.2	2.71	Insignificant0.68	<0.001**	<0.0
SLEDAI-2k	3.3	2.5	4.6	0.5	7.3	0.6	<0.001**	<0.001**	<0.0
ESR (mm/h)	10.5	15.5	27.7	7.7	57.9	11.9	0.28 Insignificant	<0.001**	<0.0
CRP (mg/L)	496.49	1.0	26.08	3.65	44.63	6.18	<0.001**	<0.001**	<0.0
C3 (mg/dl)	20.0	115	57.5	23.01	22.2	4.4	<0.001**	<0.001**	<0.0
C4 (mg/dl)	12.5	0.71	9.25	1.54	5.19	1.32	<0.05	<0.001**	<0.0
Anti ds DNA titre	10.0	0.0	47.5	46.3	161.9	38.16	0.47	<0.001**	<0.0

SLE: Systemic lupus erythematosus, SLEDAI: SLE disease activity index, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, C3,C4: complement 3,4, Anti ds DNA: Anti double stranded DNA.

Table 3: Comparison of the three Hs-TnT groups according to traditional

abnormality, ECG: Electro cardio gram, DD: diastolic dysfunction

Table 4: Multilinear regression for hsTnT

LN group (30)	Beta	T	P-value
Age (y)	0.18	1.14	0.29
Anti ds DNA titre	0.25	1.42	0.19
SLE duration(Y)	0.27	2.35	0.05
SLEDAI-2k	0.18	1.11	0.29
ACEI/ ARBS(%)	0.04	0.68	0.51
BMI(Kg/m2)	0.116	0.89	0.40
SBP(mmHg)	0.15	1.08	0.31
DBP(mmHg)	0.104	0.74	0.48
Serum Cholesterol(mg/dl)	0.18	1.11	0.29
Serum HDL(mg/dl)	-0.17	0.79	0.45
Serum LDL(mg/dl)	0.58	1.34	0.21
Framingham (%)	0.08	0.75	0.46
CRP(mg/L)	0.044	0.91	0.39
CKMB (ug/L)	0.12	0.70	0.50
LVH (%)	6.22	7.44	<0.001**
LVEDD Cm	1.2	2.6	0.02*
EF (%)	–0.62	–5.39	<0.001**
LVDD	0.746	3.1791	0.003**
LVESD cm	2.0	2.1	0.04*
PWD cm	0.11	0.79	0.45
RWMA (%)	0.18	1.11	0.29
LAD (cm)	0.17	1.12	0.28
e GFR (ml/min/1.73m2)	-4.02	5.18	<0.001**
Urinary Albumin creatinine ratio (U ACR) mg/g	1.4	3.0	0.006**
Serum albumin (gm/dl)	0.18	1.11	0.29

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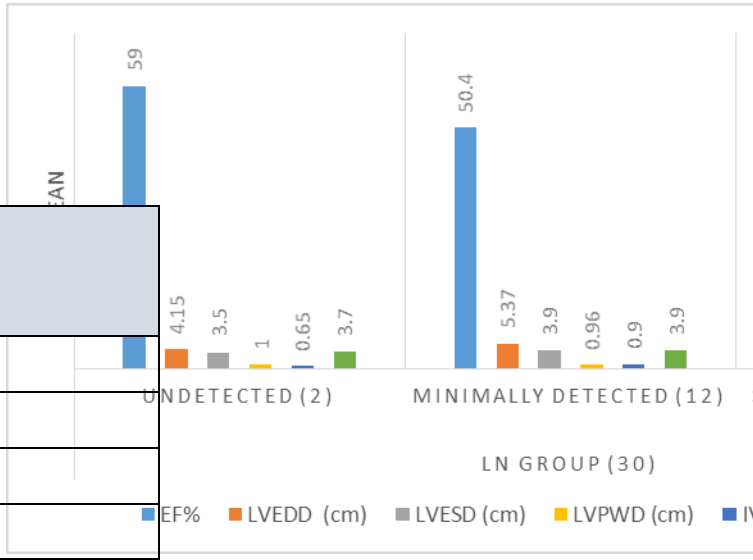
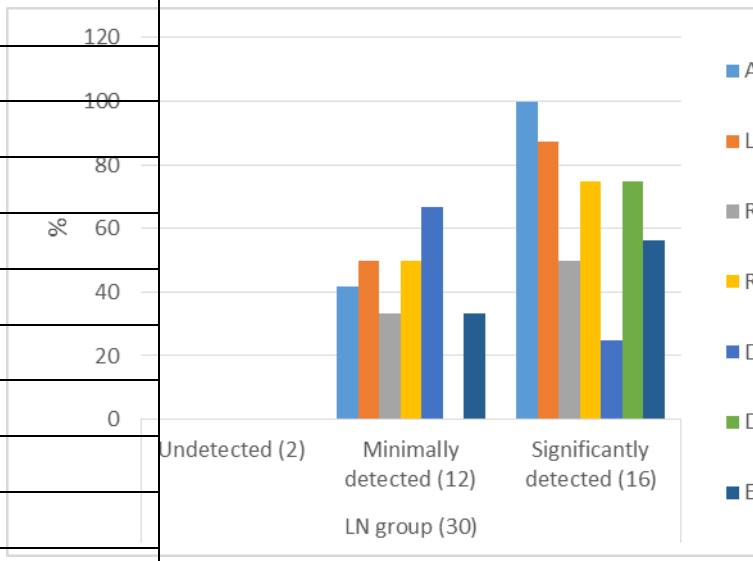


EF: ejection fraction, LVEDD: Left ventricular end diastolic diameter, LVESD: Left ventricular end systolic diameter, PWD: Posterior wall diameter, IVSD: Interventricular septum diameter, LAD: Left atrial diameter.

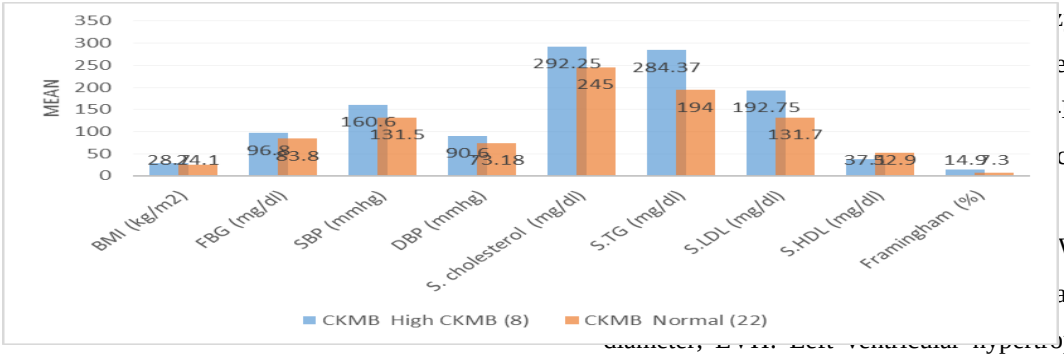
Fig 5: Comparison of the three Hs-TnT detection groups according ECHO and ECG findings



LVH: Left ventricular hypertrophy, RV: Right ventricle, RWMA: Regional wall motion

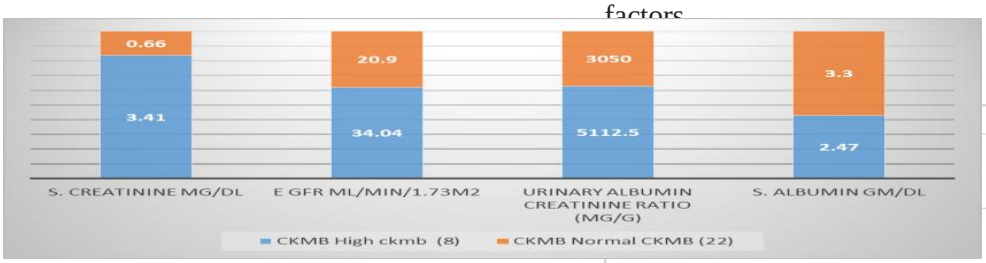
DNA, ESR: Erythrocyte sedimentation rate, C3,C4: complement 3,4..

Fig 7: comparison between high CKMB and normal CKMB groups as regard traditional cardiovascular risk factors



BMI: Body mass index, SBP: Systolic blood pressure, DBP: diastolic blood pressure, FBG: fasting blood glucose, LDL: Low density lipoprotein, HDL: high density lipoprotein, TG: Triglyceride,

Fig 8: comparison between high CKMB and normal CKMB groups as regard **renal factors**

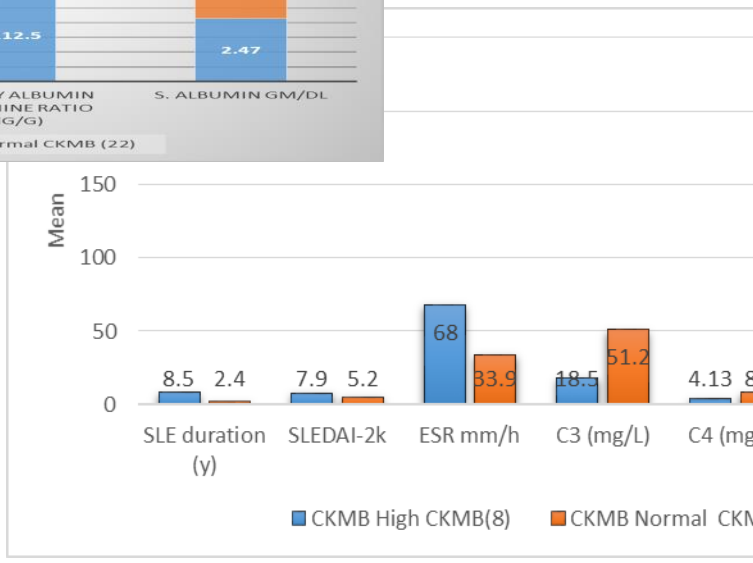


e GFR: Estimated glomerular filtration rate.

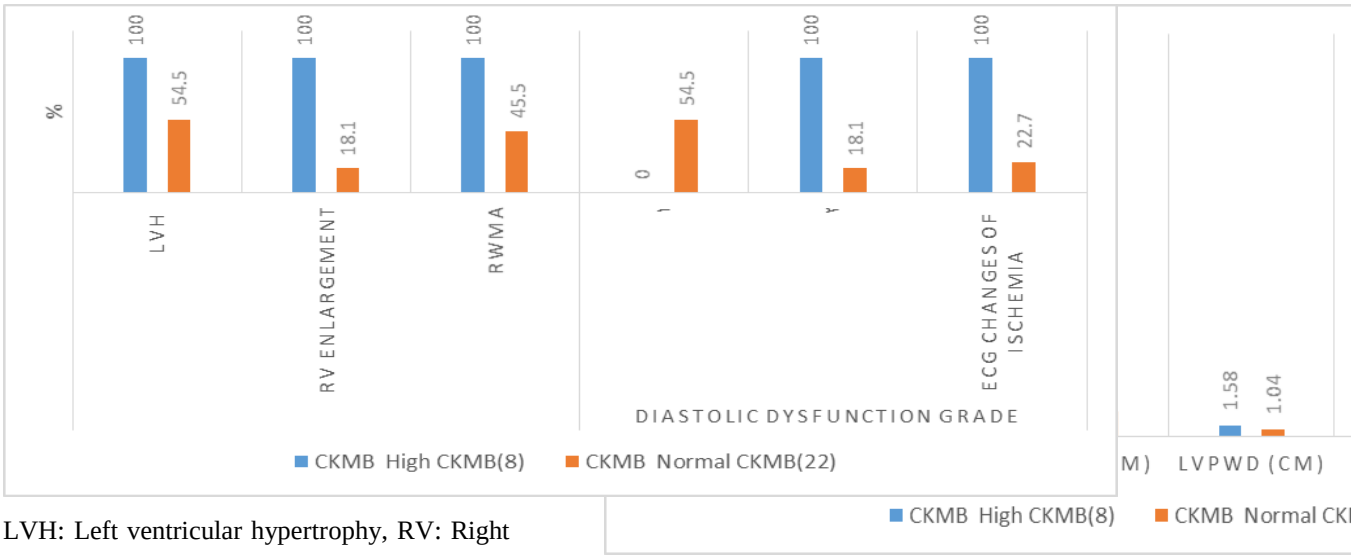
Fig 9: Comparison of the two CKMB groups according to cardiovascular affection:

BMI: Body mass index, SBP: Systolic blood pressure, DBP: diastolic blood pressure, LDL: Low density lipoprotein, HDL: high density lipoprotein, ACR: albumin creatinine ratio, e GFR: Estimated glomerular filtration rate, yme eptor MB, cular Left WD: atrial phy, RWMA: Regional wall motion abnormality, LVDD:Left ventricular diastolic dysfunction, SLE: Systemic lupus erythematosus, SLEDAI: SLE disease activity index, CRP: C-reactive protein, Anti ds DNA: Anti double stranded DNA

Fig 6: comparison of the two CKMB groups according to immunological risk factors



SLE: Systemic lupus erythematosus, SLEDAI: SLE disease activity index, CRP: C-reactive protein, Anti ds DNA: Anti double stranded



LVH: Left ventricular hypertrophy, RV: Right ventricle, RWMA: Regional wall motion abnormality, ECG: Electro cardio gram, DD: diastolic dysfunction.

Table 5: Multilinear regression analysis for CKMB

EF: ejection fraction, LVEDD: Left ventricular end diastolic diameter, LVESD: Left ventricular end systolic diameter, PWD: Posterior wall diameter, IVSD: Interventricular septum diameter, LAD: Left atrial diameter.

Fig 10: Comparison of the two CKMB groups according to the prevalence of cardiovascular affection:

Case group (30)	Beta	T	P-value
Hs TnT (ng/L)	-0.17	0.79	0.45
Framingham score	0.104	0.74	0.48
CRP (mg/L)	0.12	0.70	0.50
TG (mg/dl)	0.11	0.79	0.45
Cholesterol (mg/dl)	0.25	0.38	0.71
HDL(mg/dl)	0.193	0.79	0.45
LDL(mg/dl)	1.33	1.54	0.15
LVH(%)	0.07	1.07	0.83
DD (cm)	0.04	0.68	0.51
EF (%)	-1.52	-3.9	<0.001**
RWMA (%)	0.11	0.79	0.45
Urinary albumin creatinine ratio (mg/g)	1.23	3.41	**0.006****
Serum albumin (gm/dL)	0.15	1.08	0.31
e GFR(ml/min/1.73m2)	-0.005	-4.025	<**0.001****
SLEDAI-2k	0.14	0.83	0.42
SLE duration(y)	3.46	1.58	0.13
Bl Pr (mmhg)	2.22	1.43	0.17

DD: diastolic dysfunction, LVH: Left ventricular hypertrophy, EF: ejection fraction, RWMA: Regional wall motion abnormality, LDL: Low density lipoprotein, HDL: high density lipoprotein, TG: Triglyceride, CRP: C-reactive protein, e GFR: Estimated glomerular filtration rate, Bl Pr: blood pressure, SLE: Systemic lupus erythematosus, SLEDAI: SLE disease activity index, Hs TnT: High sensitive troponin

Discussion

A renal disease represents a frequent manifestation of SLE as well as an important outcome predictor in these patients [1]. Cardiac involvement in SLE may affect all anatomical structures of the heart. Accelerated atherosclerosis and premature coronary artery disease represent important comorbidities. [4]

While current markers have greatly improved the diagnosis and the treatment of cardiovascular disease (CVD) patients, there is still room for

increased coagulability, endothelial dysfunction, hypertension and arterial stiffness which were more likely to have a rule in progression of atherosclerosis and cardiovascular disease. Therefore, the combination of SLE and impaired kidney function could result in a higher risk for CVD than SLE alone [9&10].

Our study revealed that the cut off value of serum troponin in LN patients was 3 ng/L. This is concordant with another study as they found that the lower detection limit of the hs-cTnT assay was 3 pg/L [11].

We found (6.7%) of LN patients had undetectable hs-TnT (<3 ng/L), (40%) had minimally elevated troponin (3-14ng/L) and (53.3%) had significantly elevated troponin (≥14ng/L) and this is concordant with many studies as they found nearly all patients have detectable hs-TnT [2, 12&13]. We found none in the undetectable group had positive ECHO findings, 66.7% of the minimally detectable group had positive ECHO finding and all patients in the significantly detectable group had positive ECHO findings and this could be explained as troponin can be released early before structural changes start to appear in the ECHO as ECHO is not a sensitive tool to diagnose early improvement, especially in the area of early detection. [5]

cTnT levels as measured by a highly sensitive assay were detectable in the majority of LN patients in this study [(93.3%) LN versus (50%) of SLE]. This is concordant with **Divard et al** [2] who found that SLE patients with nephritis had higher percent of detectable hs-TnT. We also found higher CKMB mean in LN patients than SLE (23.9±18.6 ug versus 14.8± 9.4 ug in LN and SLE respectively) and this is concordant with ***Wang et al* [11]** who found higher CKMB in patients with CKD.

80% of LN and 35% SLE patients in our study had positive ECHO findings. This was concordant with **Gustafsson** et al [6] and **Elshishtawy** et al [7] who found that cardiovascular affection is more prevalent in LN than SLE without nephritis independent of the traditional cardiovascular risk factors [6&7]. So LN is considered an independent risk factor for cardiovascular disease (CVD). This could be explained by that impaired kidney function and associated nephrotic syndrome in LN had been linked to chronic inflammation, abnormal apolipoprotein levels, elevated plasma homocysteine,

serum creatinine and UACR, and lower e-GFR and serum albumin in the high CKMB group. This is concordant with **Odum** et al [16] who found that high CKMB is associated with higher UACR. We found inverse correlation of CKMB with e-GFR and this could be explained by that cardiovascular morbidity and mortality increase as GFR declines so more release of CKMB **[16].**

We found statistically significant higher mean hs-TnT, the prevalence of RWMA, RV enlargement, LVH, ischemic changes in ECG, higher DD grade, mean of LAD, LVEDD, LVESD, PWD, and IVSD but lower EF in the high CKMB group. This was concordant with **Hajsadeghi et al** [17] who found a significant positive correlation between CKMB and RWMA and diastolic dysfunction [17]. CKMB reflects structural alterations in the myocardium which is released when structural and functional remodeling in ventricular myocardium occurs in response to neurohormonal factors, mechanical stress, and increasing filling pressures so promoting cardiac cell death **[18&19].**

Absence of correlation between troponin (which is a more sensitive marker to myocardial injury) and structural and subclinical changes which are highly prevalent in SLE [14&15].

We found a statistically significant increase in the renal factors (except for a decrease in the e-GFR and serum albumin) in the significantly detectable group**.** This is concordant with others as they explained this as increasing UACR even in the high normal range, hematuria, and impaired renal function lead to both increased sub-clinical myocardial injury with subsequent increased hs-cTnT release as they cause endothelial dysfunction. **[11]**

Our study revealed that the cut off value of CKMB is 25 ug/L. 8 LN patients (33.3%) had high CKMB with a mean (50.1 ±15.8) ug/L. All of them had positive ECHO findings. 22 LN patients (73.3%) had normal CKMB with a mean (14.4 +/- 6.4) ug/L. 16 patients (72.7%) of them had positive ECHO findings. The sensitivity and specificity of CKMB in LN patients in detecting myocardial injury were 33.3% and 100% respectively.

We found a statistically significant higher prevalence of patients with active urinary sediment (red cell cast),

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CKMB suggesting that CKMB is not a sensitive tool for detecting early myocardial injury in LN patients. This is concordant with **Odum** et al [16] who found no significant correlation between CKMB and troponin and this could be explained by the superior discriminatory power of troponin in detecting minor cardiac injury, also troponin persists longer in the circulation and its proportional rise to the discriminator value is higher, enabling the detection of trace amounts of damaged myocardium [16]. Troponin increases above the cutoff value in clinical situations with trace amounts of injured myocardial tissue; it increases in 19% to 64% of patients with unstable angina pectoris, whereas CK-MB usually remains normal **[20].**

Conclusion and recommendations

Detectable Hs-TnT concentration was independently associated with subclinical atherosclerosis in asymptomatic LN patients at apparently low risk for CVD according to traditional risk factors.

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Conflicts of interest

There are no conflicts of interest.

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