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Research Article

Evaluating Serum Troponin as A Mortality Predictor in COVID-19: Two-Center Prospective Study

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Abstract

Background: Acute Respiratory Syndrome Coronavirus 2 is induced by a combination of the virus protein and an angiotensin-converting enzyme 2, which is expressed in the heart and lungs, causing myocardial injury with increasing serum Troponin. The finding of a significant cardiac involvement requires follow-up during hospitalization or after COVID-19 recovery.

Objectives: evaluating serum troponin as a mortality predictor in COVID-19: a two-center prospective study.

Methods: A prospective observational study was carried out in Al Yarmouk Teaching Hospital and Dar Al-Salam Hospital, Al-Karkh, Baghdad, Iraq from the 1st of January 2021 to the 30th of June 2021 and involved (85) patients confirmed to have COVID-19 by RT-PCR, then screened for cardiac-specific biomarkers as reflected by elevated serum troponin. Microsoft Excel 2010 and the Statistical Package for Social Sciences version 23 were used for data entry. Chi-square and *the t*-test were used to compare proportions, analyzing data, and show any significant difference in the mean age.

Results: In this study, 24 (28.2%) patients were with high serum troponin levels, and the majority, 61 (71.8%) had normal serum troponin levels. The highest proportion of high serum troponin was among smokers and ex-smokers [55.6% (5) and 66.7% (2), respectively]. 12 (46.2%) of patients with diabetes had high serum troponin levels (P=0.015). 62.5% (15) of hypertensive patients were significantly with high troponin levels. There was a strong association between COVID-19 severity and serum troponin level, whereas in patients with critical COVID-19, 60.9% (14) were within a high serum troponin level. There was a significant difference between the outcome of COVID-19 patients and serum troponin level, where the higher serum troponin level was in 14 (60.9%) of patients who ended up with death.

Conclusion: The study showed a significant relationship between high serum troponin levels and mortality in critical COVID-19 patients. High serum troponin level was significantly associated with diabetes mellitus, hypertension, ischemic heart disease, and smoking. There was no significant association between high serum troponin levels and age, sex, asthma, or malignancy.

Keywords: Diabetes Mellitus; COVID-19; Hypertension; Myocardial Ischemia; Troponin;

Introduction:

Severe acute respiratory syndrome coronavirus 2 infection is induced in the body cells by binding the spike protein of the virus to the angiotensin-converting enzyme receptor 2 (ACE2), which is strongly expressed in the heart, lungs, and blood vessels (1). Therefore, SARS-CoV-2 can cause acute myocardial injury, which may be reflected by the increase in serum troponin levels that have been identified among patients with COVID-19(2). The mechanisms include direct infection causing myocardial injury, specific binding to functional receptors on cardiomyocytes, or immune-mediated myocardial injury (3). Rupture of the plaque, cytokine storm, hypoxic injury, coronary vasospasm, microthrombosis, or direct endothelial injury can cause myocardial damage in patients with COVID-19. Those patients who develop Cardiac ischemia was found to have poorer in-hospital outcomes (4). Finding the cause of acute myocardial injury or ischemia may participate to explain the evolution of the severe SARS-CoV-2 infection and apply management according to the type of myocardial injury (5).

The severity of cardiac damage is variable, which depends on the age of the patient, past medical history, and preexisting cardiac disease. Cardiac biomarkers increase in most of the critical cases of COVID-19 patients, given their prognostic power for the worst outcome, and the lower threshold of the biomarkers would be applicable for diagnosis and prognosis (6)

A comprehensive assessment of cardiac biomarkers may be necessary to differentiate high-risk patients from low-risk, and the identification of a significant cardiac involvement might activate a cardiology unit for work-up with serial troponin level and Echocardiogram study during hospitalization and after COVID-19 recovery. The need for such a study in our hospitals will open the door for the use of such

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assessment as a routine workup for those patients. The study aimed to evaluate serum troponin as a mortality predictor in patients diagnosed with COVID-19 in Baghdad City.

Patients and methods:

Study design, Study setting, and period: A prospective study was carried out in Al Yarmouk Teaching Hospital and Dar Al-Salam Hospital, Al-Karkh side of Baghdad-Iraq from 1st of January 2021, to 30th of June 2021.

Study Population The target population was represented by COVID-19 patients who were admitted to a specified isolated center in Al Yarmouk Teaching Hospital and Dar Al-Salam Hospital, confirmed by positive RT-PCR, then screened for cardiac-specific biomarkers as reflected by elevated troponin levels. Inclusion criteria: All COVID-19 patients aged > 18 years, confirmed by positive RT-PCR. Exclusion criteria: Patients with negative RT-PCR, patients with renal failure, stroke, and subarachnoid hemorrhage. Classification of COVID-19 severity was according to the World Health Organization WHO COVID-19 severity definitions (7).

Data collection and sampling: The data were collected by using a questionnaire paper, which researchers filled with direct interviews. A convenience sample was used, depending on the investigation available in the hospital and data collected during two consecutive months, three days/ week. Questionnaires included sociodemographic, clinical features, and cardiac-specific biomarkers (age, gender, symptoms, associated signs, comorbidities, s. troponin). The affected group (with high serum troponin levels) is compared with other patients with normal serum troponin levels in terms of demographic age, gender, clinical features, and comorbidity.

Ethical consideration: The approval of the committee of the Iraqi Board of Medical Specializations was obtained before the start of the study. The official agreement from the Ministry of Health (MOH) and Al-Karkh health directorate was obtained before starting the research. The Administration of Al-Yarmook Teaching Hospital and Dar Al-Salam Hospital were informed about the nature and scope of the study, and verbal consent was obtained from participants before participating and filling up the questionnaire. The collection of data will be kept confidential and not revealed except for the study purpose.

Statistical analysis:

Microsoft Excel 2010 and Statistical Package for Social Sciences (SPSS) version 23 were used for data entry and statistical analysis. The Chi-square test of association was used to compare proportions and analyzing data. The Independent sample *t*-test was used to define the significant difference in the mean age. Data frequencies and percentages were presented by tables and figures. *P* value ≤0.05 was considered statistically significant.

Results:

In this study, the total participants was 85, of (45) patients among the elderly aged≥ 60 years. Male patients were the majority, 49 (57.6%). Non-smokers count for 73 (85.9%). Most of the study patients were non-diabetic, not asthmatic, and non-hypertensive [59 (69.4%), 80 (94.1%), and 49 (57.6%), respectively]. There were 5 (5.9%) patients with malignant disease. Patients with a medical history of ischemic heart disease were 8 (9.4%), Arrhythmia were 3 (3.5%), and patients with a negative history of cardiac problems were 74 (87.1%). The variations are shown in Table 1:

Table 1: Baseline demographic characteristics of study COVID-19 patients (n=85)

Variable		No.	%
Age (yr.)	(20-39)	8	9.4
	(40-59)	32	37.6
	≥ 60	45	53
Sex	Male	49	57.6
	Female	36	42.4
Smoking	Smoker	9	10.6
	Non-smoker	73	85.9
	Ex-smoker	3	3.5
Diabetes Mellitus	Yes	26	30.6
	No	59	69.4
Hypertension	Yes	36	42.4
	No	49	57.6
Asthma	Yes	5	5.9
	No	80	94.1
Malignancy	Yes	5	5.9
	No	80	94.1
Heart Disease	IHD	8	9.4
	Arrythmia	3	3.5
	Negative	74	87.1
Severity of COVID-19	Moderate	48	56.5
	Severe	14	16.5
	Critical	23	27.1

The serum Troponin level showed a significant association with the smoking history (*P*= 0.041), history of DM (*P*= 0.015), history of hypertension (*P* value = 0.018), history of IHD (*P* value 0.008), critical COVID-19 cases (*P* value = < 0.001) without significant relationship with age, gender, asthma or malignancy. According to the smoking history, the highest proportion of smokers and ex-smokers, 55.6% (5) and 66.7% (2) respectively, were of high Troponin levels, while the highest proportion of non-smokers, 76.7% (56), were with normal Troponin levels. About half of the patients who have diabetes mellitus 12 (46.2%), with high Troponin levels, while the highest proportion of patients without diabetes mellitus 79.7% (47) with normal serum Troponin levels, and this difference was significant (*p*=0.015). The highest proportion of patients having hypertension, 62.5% (15), were with high Troponin levels, while the highest proportion of patients without hypertension, 65.6% (45), were within normal serum Troponin levels, and this difference was significant (*P*=0.018). The majority of patients with ischemic heart disease 6 75 75 75%) had high serum Troponin levels, while patients with negative ECG findings 17, 23%) were within normal serum Troponin levels, and this finding was significant (*P* 0.008). Regarding the severity of COVID-19, there was a significant association with serum troponin levels where the highest proportion of patients with moderate and severe COVID-19 cases, the troponin was within the normal level [91.7% (44), and 71.4% (10) respectively], while the highest proportion of patients with critical COVID-19 60.9% (14) was associated with high serum troponin level as illustrated in Table (2).

Table 2: The distribution of Troponin level among study COVID-19 patients (n=85)

Variable		Total	Normal Troponin level		High Troponin level		*P*-value
			N.	%	N.	%	
Age (yr.)	(20-39)	8	4	50.0	4	50.0	0.477
	(40-59)	32	23	71.9	9	28.1	
	≥ 60	45	34	75.0	11	25.0	
Sex	Male	49	34	69.4	15	30.6	0.570
	Female	36	27	75.0	9	25.0	
Smoking	Smoker	9	4	44.4	5	55.6	0.041*
	Non-smoker	73	56	76.7	17	23.3	
	Ex-smoker	3	1	33.3	2	66.7	
Diabetes Mellitus	Yes	26	14	53.8	12	46.2	0.015*
	No	59	47	79.7	12	20.3	
Hypertension	Yes	36	21	34.4	15	62.5	0.018*
	No	49	40	65.6	9	37.5	
Asthma	Yes	5	3	60.0	2	40.0	0.547
	No	80	58	72.5	22	27.5	
Malignancy	Yes	5	2	40.0	3	60.0	0.104
	No	80	59	73.8	21	26.3	
Heart Disease	IHD	8	2	25.0	6	75.0	0.008*
	Arrhythmia	3	2	66.7	1	33.3	
	Negative	74	57	77.0	17	23.0	
COVID-19 Severity	Moderate	48	44	91.7	4	8.3	<0.001*
	Severe	14	10	71.4	4	28.6	
	Critical	23	9	39.1	14	60.9	

* *Chi-square is significant at the < 0.05 level.*

The highest frequency of patients with normal troponin levels was with normal ECG, sinus tachycardia, and atrial fibrillation, whereas the highest frequency of patients with high troponin levels was with ECG abnormalities as ST elevation and ST depression, and this difference was significant (*P* = 0.013). As illustrated in Table 3.

Table 3: The distribution of Troponin level with the ECG finding among study COVID-19 patients (n=85)

Variable		Total	Normal Troponin level		High Troponin level		*P*-value
			N.	%	N.	%	
ECG finding	Normal	50	39	78.0	11	22.0	0.013*
	ST elevation	7	1	24.3	6	85.7	
	ST depression	2	0	0.0	2	100.0	
	T wave inversion	2	2	100.0	0	0.0	
	sinus tachycardia	17	12	70.6	5	29.4	
	AF	4	3	75.0	1	25.0	
	ectopic beat	2	2	100.0	0	0.0	
	RBBB	1	1	100.0	0	0.0	

* Fisher's exact is significant at the < 0.05 level

Serum Troponin level was significantly associated with outcome, where the highest proportion of patients, 60.9% (14), ended up with death, high serum Troponin levels, and the highest proportion of patients who recovered and were discharged 83.9% (52) with normal serum Troponin levels (P = < 0.001). As illustrated in Table 4 and Figure 1.

Table 4: Serum Troponin Level about the outcome of a sample of COVID-19 patients

Variable	Outcome					
Serum Troponin Level	Death	Discharge	Total	Crude odds ratio	95% C.I.	*P*- value
High	14 (60.9%)	10 (16.1%)	24 (28.2%)		2.756 -	
Normal	9 (39.1%)	52 (83.9%)	61 (71.8%)	8.089	23.740	*< 0.001**
Total	23 (27.1%)	62 (72.9%)	85 (100%)			

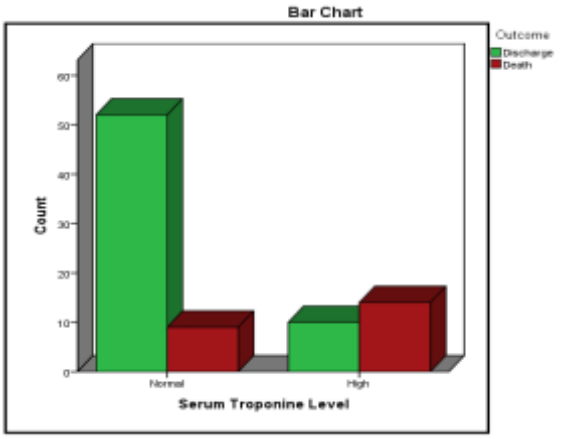

Figure 1: Distribution of serum Troponin level among study COVID-19 outcome

Discussion:

This study involved 85 COVID-19 hospitalized patients; more than half of them were males, of age ≥ 60 years, the majority were nonsmokers, and more than one-third of them had comorbid chronic diseases like DM and hypertension.

Previous multiple studies have demonstrated that male cases are more numerous than female COVID cases, and males usually tend to have a more severe infection in critical situations (8). Nevertheless, there is no precise explanation for this gender preponderance of COVID-19 infection among males. This gender difference can be due to some comorbidities like DM, HTN, which may increase the risk of infection and severity among males, while female sex hormones may have influenced the regulation of immune response (9). This is in agreement with a study done in Baghdad in 2020 on a sample of 99 COVID patients attending Baghdad Teaching Hospital, in whom 43.4% (43/99) of PCR-positive patients were aged >50 years with male, and a significant percentage had a chronic illness like hypertension and asthma (10). The high serum Troponin level in this study showed a significant association with smoking, diabetes mellitus, ischemic heart disease, and critical cases. The high troponin level was also associated with abnormal ECG findings. This is in agreement with a study done in Kurdistan, Iraq, 2021, by Ayad *et al.* (11), investigating the correlation of troponin, CRP, D-dimer, and other biomarkers within COVID-19 survivors. Troponin and D-dimer were significantly higher in COVID-19 patients who died than in COVID-19 survivors. Also, the high troponin and abnormal WBC count were significantly associated with families who lost more than one family member. This study revealed that a normal ECG was the initial ECG finding among 59% of patients, while the most common abnormal findings were sinus tachycardia in 20%. Followed by ST elevations, ST depression, and arrhythmias, respectively. Gur *et al.* in their study in 2021 exposed different results, they stated that ECG findings are crucial to diagnose COVID-19 disease as early as possible, sinus tachycardia was the commonest presentation in COVID-19 patients in that study, but they didn't find specific - characteristic ECG finding for COVID-19 apart from some non-significant ST changes (12); which was also in consistence with Angeli *et al.* study who found in 50 in patients with COVID-19, a wide spectrum of ECG abnormalities in COVID patients during hospitalization, these changes include persistent ST-T changes, bradytachy- syndrome, and atrial fibrillation (13). Cardiac injury had been reflected in the current study, 28% of patients had raised levels of troponin, one-third of patients died from myocardial injury, and about half of the studied samples were discharged home without the need for ICU or CCU wards. Interestingly, different outcomes in COVID-19 patients could be well predicted through cardiac biomarkers. This is consistent with the results of Pzizzini *et al.* (14) and Yange *et al.* (15), who reported higher mortality associated with high cardiac enzymes. As evident in many previous studies in the last couple of years, the rate of abnormal cardiac enzyme levels in COVID-19 positive cases urged clinicians to measure serum troponin levels when they suspected acute myocardial infarction. In comparison, our findings demonstrated that serum troponin acted as a marker of severity in COVID-19 infection and was raised in around one-third of the studied patients. This confirms the findings of an earlier study in Wuhan city, which declared that patients with comorbid conditions and high cardiac enzymes had higher death rates, especially for diabetes, chronic respiratory disease, and hypertension (16).

Limitations:

1- Sample size.
2- Number of centers

Conclusions:

COVID-19 could cause a cardiac injury, as our study showed that most of the critical COVID-19 patients

had a significantly elevated troponin level. Serum troponin was significantly higher among smokers and diabetic patients, whereas about half of them had high serum troponin levels. Two-thirds of hypertensive patients had high troponin levels, which suggests a significant association between them. The history of ischemic heart disease has a significant association with high troponin levels. Two-thirds of COVID-19 patients who died had high serum troponin levels, while the overwhelming majority of recovered COVID-19 patients had normal troponin levels.

Measuring serum troponin levels at admission for COVID-19 patients may give a prediction of the course of COVID-19 severity and outcome. Further studies should be conducted on a larger sample size to assess the probability of using serum troponin levels in the prediction outcome of COVID-19 patients, and the probability of cardiac injury.

Authors' contributions:

Study conception & design: (Abbas Naji Al-Sharifi). Literature search: (Muhanned M. Jawad). Data acquisition: (Muhanned M. Jawad). Data analysis & interpretation: (Abbas Naji Al-Sharifi). Manuscript preparation: (Muhanned M. Jawad). Manuscript editing & review: (Abbas Naji Al-Sharifi).

Authors' declaration:

We confirm that all the Figures and Tables in the manuscript belong to the current study. Besides, the Figures and images, which do not belong to the current study, have been given permission for re-publication attached to the manuscript. Authors sign on ethical considerations' Approval-Ethical Clearance: The project was approved by the local ethical committee in Al-Yarmook Teaching Hospital. According to the code number (122) on (10/12/2020).

Conflict of Interest: None

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تقييم التروبونين في مصل الدم كمؤشر للتنبؤ بالوفاة في مرضى كوفيد-19: دراسة مستقبلية في مركزين

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مقدمة: متلازمة الجهاز التنفسي الحادة الوخيمة فيروس كورونا 2 الناجم عن مزيج من البروتين الشوكي للفيروس والإنزيم المحول للأنجيوتنسين 2، والذي يتم التعبير عنه بقوة في القلب والرئتين، مما يسبب إصابة عضلة القلب الحادة مع زيادة مستوى التروبونين في الدم. قد يؤدي تحديد الإصابة القلبية الكبيرة إلى تنشيط متابعة اطباء القلب أثناء العلاج في المستشفى أو بعد التعافي من كوفيد-19.
الهدف من الدراسه : تقييم مصل التروبونين كمتنبئ للوفيات لدي مرضى كوفيد -19: دراسه استطلاعيه مركزيه.
طريقة العمل : أجريت دراسة استطلاعية في مستشفى اليرموك التعليمي، جانب الكرخ من بغداد، العراق في الفترة من 1 كانون الثاني (يناير) 2021 إلى 30 حزيران (يونيو) 2021 ، وأجريت على (85) مريضا تأكدت إصابتهم بـ الكوفيد-19 بواسطة RT -PCR بعد ذلك يتم فحصها بحثا عن المؤشرات الحيوية الخاصة بالقلب كما ينعكس ارتفاع مستوى التروبونين.
النتائج: في هذه الدراسة ، كان 24 (28.2%) مريضا لديهم مستوى تروبونين مصل مرتفع ، وكانت الغالبية (61) 71.8% بمستوى تروبونين مصل طبيعي. كانت أعلى نسبة تروبونين في مصل الدم بين المدخنين وغير المدخنين السابقين (5) 55.6 % و (2) 66.7% على التوالي. كان 12 (%) من مرضى السكري معنويا مع ارتفاع مستوى التروبونين في الدم كان 62.5% (15) من مرضى ارتفاع ضغط الدم معنويا بمستوى تروبونين كان هناك ارتباط كبير بين شدة COVID-19 ومستوى تروبونين المصل بينما في المرضى الذين يعانون من COVID-19 الحرج ، كان 60.9 % (14) ضمن مستوى تروبونين المصل المرتفع. كان هناك فرق كبير بين نتيجة مرضى COVID-19 ومستوى تروبونين المصل ، حيث كان تروبونين المصل الأعلى في 14 (60.9%) من المرضى الذين انتهى بهم الأمر بالموت.
الخلاصة: قد يتسبب مرض كوفيد -19 في إصابة القلب. أظهرت الدراسة ارتباطا كبيرا بين ارتفاع مستوى التروبونين في الدم مع وجود COVID-19 الحرج والوفيات. ارتبط ارتفاع مستوى التروبونين في الدم بشكل كبير بمرض السكري وارتفاع ضغط الدم ومرض نقص تروية القلب والتدخين. لم يكن هناك ارتباط معنوي بين ارتفاع مستوى التروبونين في الدم والعمر والجنس والإصابة بالربو والأورام الخبيثة.
الكلمات المفتاحية: الانزيم المحول للانجيوتنسين 2, الكوفيد-19 , السارس كوفيد2, منظمه الصحه العالميه, متفاعل البولمريز المتسلسل.