Original Article

Predictive Role of High Sensitive Troponin and IL-37 Markers in the Evaluation of Patients with Covid-19

Maysam Adnan Mezher[1], Bahaa Abdullah Ali[2], Muhammed Salih Allawi[3]

[1]College of Pharmacy/tikrit University. Email: maysam.adnan@tu.edu.iq
[2]Salahaddin General Hospital Email: drbahaaaljubory@gmail.com
[3]College of Medicine/ tikrit university Email: m.s.alawi2019@gmail.com

Abstract

Background: The COVID-19 has infected more than 140 million people worldwide, killing more than three million people. The existing studies lack research on the relationship between IL-37 and Hs-Troponin markers with COVID-19 syndrome. Thus, the present study aimed to investigate the predictive roles of IL-37 and Hs-Troponin markers in examining patients with COVID-19. **Material and Methods:** The present study was conducted in Salahalddin General Hospital, Iraq. A total of 45 blood samples were collected from hospitalized COVID-19 patients, and 45 blood samples were collected from healthy people who considered as a control group. Commercial ELISA kits for the quantitative determination of IL-37 (CUSABIO, China) and Hs-Troponin (Abbott, USA) were used. **Results:** Maximum patients belonged to the age group of 30-39 (33.3%) and 40-49 years (28.9%). Significantly higher levels of IL-37 were found in patients (179.97± 86.12) than in healthy controls (40.29±13.50). Similarly, significantly higher levels of Hs-Troponin were also observed in patients (50.59± 22.19) than in healthy group (15.64± 5.47) ($P \leq 0.05$). ROC curve showed that in screening patients with COVID-19, both IL-37 and Hs-Troponin showed 100% sensitivity while specificity was found to be97% and 95% respectively ($p<0.05$). Moreover, Pearson's correlation test showed a negative correlation between IL-37 and Hs-Troponin. **Conclusions:** We concluded that the severity of diseases increase with age which might be due to the fact that age progression results in weaker immunity. The increase in age makes people vulnerable to almost all types of infections. In such a situation, any challenging or intense disease can be threatening to one's life. Both IL-37 and Hs-Troponin are good prognostic markers in screening patients with COVID-19.

Keywords: COVID-19, SARS-COV-2, IL-37, Hs-Troponin.

Introduction

Severe Acute Respiratory Syndrome (SARS) is a life-threatening respiratory condition. Coronavirus disease of 2019 (COVID-19) has spread to nearly every country on the planet and has become a global pandemic.[1] The symptoms of the disease may vary in different individuals depending on the immunity of a person as every patient entails a distinct immunity to fight against the disease. According to a study, trouble in breathing, persistent pressure or chest pain, unable to wake or stay awake, blue-colored skin, gray or pale lips, etc., are some of the common symptoms identified in these patients. Some clinicians have declared COVID-19 to be equivalent to diseases related to respiratory disorders as this disease also affects the lungs and causes breathing problems. A person apparently cannot differentiate between flu and COVID-19 symptoms as they are relatively the same. Since 8 December 2019, several cases of pneumonia of unknown etiological origin occurred in Wuhan, Hubei province, China. This issue has become the subject of global attention due to clinical presentations and its resemblance to an unidentified cause of viral pneumonia.[2] A novel coronavirus was detected on 7 January 2020 in a patient's throat swab sample by the Chinese Center for Disease Control and

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Address for Correspondence: College of Pharmacy/tikrit University. Email: maysam.adnan@tu.edu.iq

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Prevention (CDC). As the novel virus spread quickly to over 100 countries around the globe, the world health organization (WHO) declared it as a pandemic on 11 March 2020. The UK Advisory Committee on Dangerous Pathogens assigned SARS-CoV-2 as a hazardous group-3 organism, which means that it can cause serious human diseases.[3] This new virus is highly contagious and has quickly spread globally and caused more than 124,037,128 cases in the world so far.[4]

Coronaviruses are a large family of viruses which are strong enough to infect people as well as animals too. The virus is released when an infected person sneezes, coughs, or talks and can also transmit by touching any surface that is not sanitized or has the virus on it. The infected person, if touches that surface and afterward touches one's nose, eyes, or mouth, can be detected with the disease. Research has been conducted to find better ways for the treatment of COVID-19 and for its prevention. SARS-CoV-2 infection may be asymptomatic, mild or moderate, severe (showing symptoms such as breathlessness, increased respiratory rate, and oxygen need), or critical (showing symptoms such as shock or other organ dysfunction requiring intensive support). The main signs and symptoms of mild to moderate COVID-19 are a troublesome dry cough i.e. unusual coughing for an hour or three or more coughing episodes in 24 hours, fever of 37.8 °C or higher, diarrhea, headache, breathlessness with light exertion, muscle pain, fatigue, and loss of taste and smell.[5] COVID-19 is a systemic disease that affects a wide spectrum of tissues and cell types; thus, infected patients display extremely variable severity. In this regard, a lot of biological, physiological, hematological, and serological markers may reflect a critical view of disease severity.[6]

Interleukin-37 (IL-37), also referred as "interleukin-1 family member 7 (IL-1F7), is a well-known anti-inflammatory cytokine that suppresses the inflammatory response by inhibiting the release of proinflammatory cytokines. It entails an important metabo-regulatory and anti-inflammatory influence, which dramatically decreases the cytokine secretion in dendritic cells and macrophages. The absence of IL-37-mediated immune response has recently been suggested as a predictor of a poor clinical prognosis in COVID-19 patients.[7] Numerous mechanisms, including microvascular thrombosis, increased risk of coronary plaque destabilization, myocarditis, endothelial dysfunction, damage by systemic inflammatory response, and supply-demand imbalance, have been hypothesized for myocardial injury in COVID-19.[8] Although elevated troponin may signify myocardial damage and is predictive of mortality, yet, its prognostic performance and whether its value is affected by various comorbidities in COVID-19 patients are not known.[9] The present study aimed to investigate the predictive role of IL-37 and Hs-Troponin markers in the evaluation of patients with COVID-19 because there is a lack of studies on the relationship between these two markers with COVID-19 syndrome.

Material and Methods

Data Collection

After the approval from Institutional Review Board, the present study was conducted at Salahalddin General Hospital in Iraq. A total of 45 blood samples were collected from hospitalized COVID-19 patients (25 males and 20 females of the age group 20-65 years). Also, blood samples from 45 healthy individuals were collected and considered as a control group (25 males and 20 females of age group 20-65 years). A form containing information on gender and age was filled out by the two groups. Their names and personal identities were not made part of demographic information to maintain confidentiality standards. In addition, before conducting the study, a consent from the management of the Salahalddin General Hospital was also obtained.

Inclusion and Exclusion Criteria

Patients who were 18 years or older and were admitted to the Salahalddin general hospital in Iraq were included. TheirSARS-Cov-2 virus infection was confirmed through the polymerase chain reaction (PCR) test of a nasopharyngeal sample. The included patients were finalized on the basis of the assessment of serum troponin measured within 48 hours after getting admitted. Whereas, the patients with chronic diseases and renal disease at serious stage were excluded from this study. These patients were ensured to be identified with renal diseases based on the Global disease classification-10 codes at the time of admission, along with the potential for elevated troponin because of impaired renal clearance and independent of myocardial disease. Patients having serious comorbidity, which determined the existence of two or more serious diseases, were also excluded from this study.

Sample Preparation

To isolate the serum, 5 ml of human blood was spun at 3000 rpm for 5 minutes. Levels of IL-37 and Hs-Troponin in the sera samples were measured by sandwich - Enzyme-Linked Immunosorbent Assay (ELISA) at the wavelength of 450 nm. Commercial ELISA kits for the quantitative determination of IL-37 (CUSABIO, Chine) and Hs-Troponin (Abbott, USA) were used and the test was performed following the protocol provided by the manufacturers.

Statistical Analysis

The statistical software package SPSS version 25.0 and GraphPad Prism version 6 were used for analyzing the data. The normality of the concentration of IL-37 and Hs-Troponin was assessed by Kolmogorov-Smirnov and Shapiro-Wilk tests. Student T test and F test

(ANOVA) were used to compare the means of the numerical variables. The Pearson-Chi-square test was used to determine whether there were any significant differences in the percentage frequencies of the other parameters. To describe the nature and intensity of the association between the variables, Pearson correlation (R) was used. Each parameter was given its receiver operating characteristic (ROC) curve from which the area under the curve (AUC), sensitivity, and specificity were inferred.

Results

Demographic Features of Study Participants

In the current study, maximum patients belonged to the age group 30-39 (33.3%) and 40-49 years (28.9%). Likewise, 35.6% of healthy individuals also belonged to the age group 30-39and 28.9% were of age group 40-49 years. Table 1 shows that 2 patients and 1 healthy individual belonged to the age group of 20-29 years. Moreover, total 15 patients (33.3%) and 16 healthy individuals (35.6%) were in the age group of 30-39. The age category of 40-49 years had an equal number of patients and healthy individuals (n=13, 28.9%). Similarly, equal number of participants from both groups (n=7, 15.6%) belonged to the age group 50-59 years. Remaining individuals i.e. 16 (8 from each group) were more than 59 years old. Regarding the gender distribution, both groups had an equal number of male participants i.e. 25 each and female participants i.e. 20 each.

Table 1: Demographic features of study participants.

			Groups		Total
			Patients	Healthy	
Age groups (years)	20-29	n	2	1	3
		%	4.4%	2.2%	3.3%
	30-39	n	15	16	31
		%	33.3%	35.6%	34.4%
	40-49	n	13	13	26
		%	28.9%	28.9%	28.9%
	50-59	n	7	7	14
		%	15.6%	15.6%	15.6%
	>59	n	8	8	16
		%	17.8%	17.8%	17.8%
Gender	Males	n	25	25	50
		%	55.6%	55.6%	55.6%
	Females	n	20	20	40
		%	44.4%	44.4%	44.4%

Levels of IL-37 and Hs-Troponin in study groups

As shown in table 2 and figure 1, significantly higher levels of IL-37 were observed in patients (179.97± 86.12) than in healthy controls (40.29±13.50). Similar results were obtained with levels of Hs-Troponin in patients (50.59± 22.19) and in controls (15.64± 5.47).

Table 2: Comparison of IL-37 and Hs-Troponin between study groups by using the student t-test.

Groups		N	Mean	Std. Deviation	P value
IL-37	Patients	45	179.97	86.12	P<0.001***
	Healthy	45	40.29	13.50	
Hs- Troponin	Patients	45	50.59	22.19	P<0.001***
	Healthy	45	15.64	5.47	

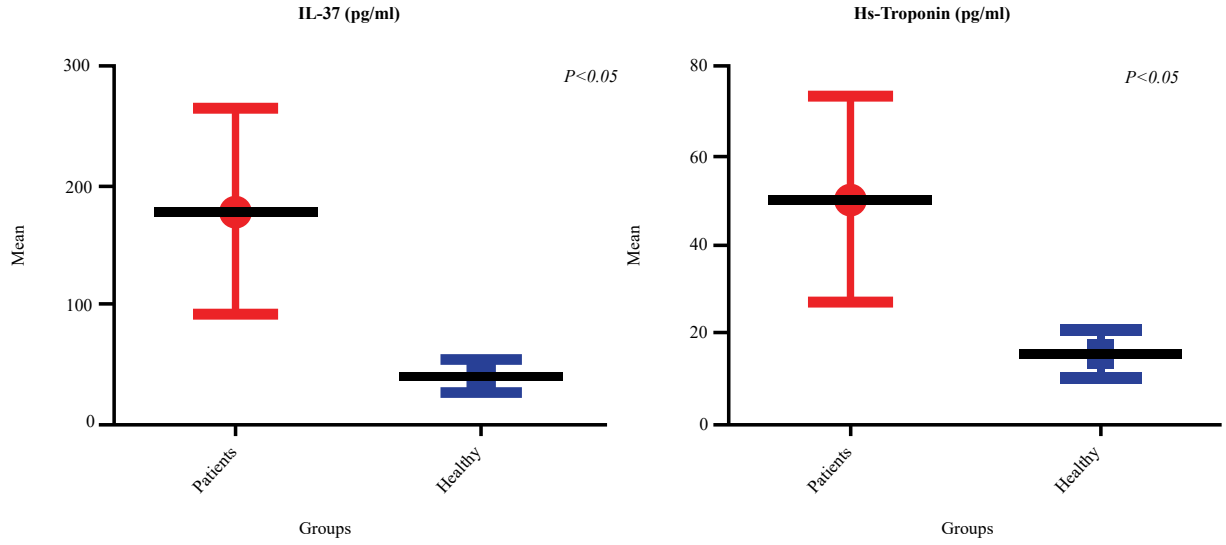

Figure 1: Mean levels of IL-37 and Hs-Troponin in study groups

Receiver operator characteristic (ROC) curve of parameters

An ROC curve is a graph which depicts the performance concerning the classification model at all the threshold classifications. Table 3 and figure 2 shows that in screening COVID-19 patients, both IL-37 and Hs-Troponin showed 100% sensitivity. While specificity for IL-37 and Hs-Troponin were found to be 97% and 95%, respectively (p<0.05). The resulting p-value for IL-37 was 0.001***, indicating a perfect significance with 100

percent sensitivity and 97% specificity. Similar results of the ROC curve were obtained for Hs-Troponin with a p-value of 0.001***.

Table 3: ROC curve, sensitivity, and specificity of IL-37 and Hs-Troponin.

Parameters	AUC	St. error	P value	Sensitivity %	Specificity %
IL-37	1.000	.001	0.001***	100	97
Hs-Troponin	1.000	0.000	0.001***	100	95

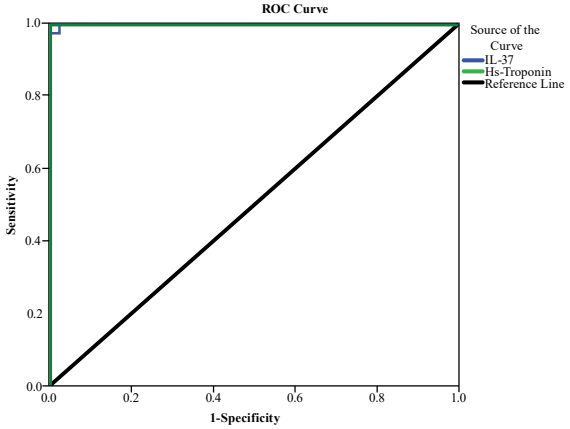

Figure 2: ROC curve of IL-37 and Hs-Troponin

Relation of IL-37 and Hs-Troponin with age groups of patients.

The present study showed no significant difference (p>0.05) in IL-37 and Hs-Troponin in different age groups of patients as measured by ANOVA test. The results are presented in table 4.

Table 4: The relation of IL-37 and Hs-Troponin with age groups of patients

	Age groups (years)	N	Mean	Std. Deviation	P value
IL-37	20-29	2	109.94	42.60	p>0.05
	30-39	15	201.24	88.22	
	40-49	13	177.94	70.89	
	50-59	7	147.65	61.59	
	>59	8	189.18	96.25	
Hs-Troponin	20-29	2	68.33	14.35	p>0.05
	30-39	15	57.74	20.27	
	40-49	13	48.33	18.20	
	50-59	7	50.00	18.53	
	>59	8	49.11	13.44	

Relation of IL-37 and Hs-Troponin with the gender of patients.

With the student t-test, the present study showed no significant differences (p>0.05) between IL-37 and Hs-Troponin with the gender of patients (table 5). Similar levels of IL-37 were observed in males (174.54±85.36) and in females (186.76±88.80). Likewise, no significant difference was found for Hs-Troponin levels between males (51.39±24.12) and females (49.59±20.11).

Table 5: The relation of IL-37 and Hs-Troponin with the gender of patients.

Gender		N	Mean	Std. Deviation	P value
IL-37	Males	25	174.54	85.36	p>0.05
	Females	20	186.76	88.80	
Hs-Troponin	Males	25	51.39	24.12	p>0.05
	Females	20	49.59	20.11	

Correlation between IL-37 and Hs-Troponin

The present study showed a negative significant correlation (r=-0.331*) between IL-37 and Hs-Troponin as measured by Pearson's correlation (table 6).

Table 6: The correlation relationship between IL-37 and Hs-Troponin.

		Hs-Troponin
IL-37	Pearson coefficient (r)	-0.331*
	p-value	0.026

Discussion

In the present study, maximum COVID-19 patients belonged to the age group 30-39 and 40-49 years, which is in accordance with the results of another study by Al-Bayati *et al*.[10]. The reason of having this age group might be because that people with weaker immunity persistently catch the symptoms of COVID-19 as compared to the young individuals. Age is an important element for the evaluation of immunity and disease absorption rate because the probability of disease intensity can be controlled through age. This finding is similar to many studies which believe that age is a significant risk factor for the evaluation COVID-19 or its severity. For example, a study by Al-Bayati *et al*.[10] demonstrated that age can be considered as a death-associated risk factor in this pandemic because elderlies tend to have a higher prevalence of chronic diseases like cardiovascular diseases and diabetes. Another study[11] showed higher frequency of COVID-19 in the age group of 30-39 years, which, might be because this age group is most susceptible to transmission of infection. Studies have shown that reduced production of B and T cells in primary lymphoid organs and the declining function of mature lymphocytes in secondary lymphoid tissues have also been associated with aging.[12] In kids, lower Angiotensin-converting enzyme 2 (ACE-2) production throughout the nasal epithelium may be the cause of reduced SARS-CoV-2 sensitivity, hence, COVID-19 disease in infants is minimal or non-existent.[13] COVID-19 fatality is more age-dependent than in other fatalities, and males have an increased risk relative to women.[14]

The present study showed high levels of IL-37 in patients than in healthy individuals and these results are opposite to the findings of other studies which depicted that levels of IL-37 are inversely associated with disease severity.[15,16] IL-37 acts as an anti-inflammatory cytokine and through its down-regulation, it inhibits the production

of several proinflammatory cytokines like IL-1a IL-1b, IL-6, IL-17, IL-23, TNFa, and IFN-Y.[17,18] A study showed as IL-37 a strong inhibitor of IL-1 which could have a therapeutic effect on COVID-19 patients.[19] Recently, a group of researchers showed that black fungus, diabetes, and COVID-19, all have a dysregulated immune response in common, which partly could also be attributed to IL-37.[20] IL-37 also plays a significant immuno-regulatory role in the inhibition of the release of most of the common inflammatory mediators such as CRP, proinflammatory cytokines, neutrophils, eosinophils, and other granulocytes.[21]

The ROC of the present study showed high sensitivity (100%) and specificity (97%) of IL-37 in screening patients with COVID-19. According to a study by Li *et al*.[7], IL-37 plays a protective role by antagonizing inflammatory responses while retaining type I interferon, thereby maintaining the functionalities of vital organs. IL-37, IL-8, and C-reactive protein can be formulated as a precise prediction model for screening severe clinical cases and have good value in clinical practice.[7] A study showed that gender, body mass index, blood group, and chronic disease status may also affect IL-37 levels,[15] however, the present study showed no significant effects of gender and age groups on levels of IL-37 in patients with COVID-19.

In the current study, high levels of Hs-Troponin were observed in patients than in healthy group and these results are compatible with the results of Papageorgiou *et al*.[22]. Hospitalized COVID-19 patients frequently suffer from acute cardiac injury (ACI) and later, many survivors suffer from chronic heart injuries. The recovery status of ACI can be accurately predicted at 2.5 months after COVID-19 by utilizing a few easily accessible laboratory markers i.e. troponin, creatinine, lymphocyte, salt, and lactate dehydrogenase. Early detection of people who are susceptible to chronic ACI would allow proper follow-up care to prevent long-term heart damage and other cardiovascular issues.[23] Troponin appears to be a predictor of both cardiovascular and non-cardiovascular events and outcomes in COVID-19 patients, and may have an impact on patient management.[22] Recent research revealed a greater risk of death in pregnant women with COVID-19 due to elevated troponin T levels. Therefore, myocardial biomarkers should be assessed in COVID-19-positive pregnant patients who need to be admitted to the hospital for risk assessment.[24]

A recent study reported significantly higher levels of troponin in COVID-19 patients who died than in those who survived. High troponin especially within the second week of admission has been found more commonly in families that lost more than one member due to COVID-19 when compared with the unrelated COVID-19 patients.[25] Another study showed significantly higher survival rate of COVID-19 patients with negative troponin as compared to those with positive troponin. Also, the study demonstrated an independent association between troponin positivity and increased short-term mortality in COVID-19 patients.[26]

In contrast to patients with myocardial ischemia (MI), cardiac troponin T (cTnT) is often elevated to higher levels than cardiac troponin I (cTnI) in COVID-19 patients indicating that the release of cardiac troponin has a different cause in these patients.[27] One possibility is that troponin elevations are due to long-term cardiac stress following high ventilation pressures, right ventricular strain, right ventricular Takotsubo syndrome, fast atrial flutter, or other sustained periods of tachycardia.[28] A recent study found that inflating a balloon in the left anterior descending artery for 0.5 to 1.5 minutes can control MI and cause cTnT levels to rise to similar or greater levels as cTnI levels.

The ROC of the present study showed high sensitivity (100%) and specificity (95%) of Hs-Troponin in screening patients with COVID-19, and these results are similar to that of another study.[22] It has been found that high troponin levels in these patients may be associated with a poor clinical prognosis. Troponin can be used as a predictor of prognosis with more comprehensive studies and long-term follow-up results in the future.[29] Since cTn is a diagnostic marker of disease activity and a strong independent predictor of negative events, its usage in emergency rooms may well be advantageous. Elevated levels of cTn may indicate hospitalization.[30] The present study showed no significant effects of gender and age on levels of troponin in patients with COVID-19, and these results matched with the results of Mukhopadhyay *et al*.[8]. Moreover, negative correlation was found between troponin and IL-37 in COVID-19 patients. In conclusion, the severity of COVID-19 increased with age progression. Also, IL-37 and Hs-Troponin are good prognostic markers in screening patients with COVID-19.

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