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Investigation roles of cardiac biomarkers (Troponin I and Myoglobin) and vitamin D in pathogeneisis of COVID-19 in the Iraqi population

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Abstract

The new coronavirus pneumonia of 2019 (COVID-19) pandemic has claimed the lives of millions of people worldwide. Troponin has long been known to indicate a patient's condition. Myoglobin serves as a biomarker for general muscle pain as well as a biomarker for myocardial infarction. COVID-19 is a known immunosuppressant, whereas vitamin D is a well-known immunomodulator. A total of 90 blood samples (50 from COVID-19 patients and 40 from healthy individuals) were collected from the Al-Shifa Center (which accommodates sleeping COVID-19 patients) at Baquba Teaching Hospital in Diyala Governorate during the period from the beginning of April to the end of May 2021. Troponin I, Myoglobin, and vitamin D levels were assessed using an immunoassay analyzer system with several functions (Opus, Dade Behring Diagnostics). The results show a significant difference between age groups and study groups, as well as between heart disease patients and study groups. Gender does not have a significant effect on diseases. Troponin I and Myoglobin markers were significantly higher in patients compared to healthy individuals (41 out of 50 vs. 3 out of 40 (OR=35.44) and 42 out of 50 vs. 2 out of 40 (OR=45.32), respectively). In contrast, the results show lower levels of vitamin D in patients than in healthy individuals (47 out of 50 vs. 5 out of 40 (OR=0.001)) with a significant difference ($p>0.05$). Current results discovered elevated levels of Troponin I and Myoglobin markers and reduced levels of vitamin D in patients with heart diseases compared to healthy individuals without heart diseases, with a significant difference. This study of Troponin I and Myoglobin markers revealed high sensitivity of Troponin I (AUC=0.991 and Sn=100%) and Myoglobin (AUC=0.999 and Sn=100%) and very low sensitivity (AUC=0.001 and Sn=0.1%) in screening for COVID-19 with a significant difference ($P<0.05$). Finally, the results show a positive and significant correlation between Troponin I and Myoglobin ($r = 0.329^{*}$, $p < 0.05$), as well as a negative correlation between vitamin D and Troponin I, and between vitamin D and Myoglobin ($r = -0.143$, $p > 0.05$, and $r = -0.037$, $p > 0.05$, respectively). In conclusion, age and heart diseases are risk factors for COVID-19. Cardiac Biomarkers Troponin I and Myoglobin are predictive risk markers related to mortality and are highly correlated with heart failure in COVID-19 disease. Vitamin D supplementation reduces thrombosis and cytokine storm in COVID-19 patients.

Keywords: COVID-19, Vitamin D, Troponin I, Myoglobin, cardiac Biomarkers

Introduction

Coronavirus Disease 2019 is caused by the highly contagious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has led to a global emergency. Intercellular pneumonitis and extreme acute respiratory distress syndrome (ARDS) affect the majority of individuals, both of which carry a grim prognosis and a significant fatality rate [1]. Patients experience multi-organ failure, including cellular immune insufficiency, thrombosis stimulation, and issues with the heart, liver, and kidneys, in addition to respiratory problems [2]. Mild, severe, and critical cases constitute approximately 81.4 percent, 13.9 percent, and 4.7 percent of all COVID-19 cases, respectively [3].

The circulatory symptoms induced by SARS-CoV-2 have raised substantial concern, particularly in light of the rapid increase in reported cases. A study of 138 hospitalized COVID-19 patients found that 7.2 percent experienced acute myocardial infarction [4]. According to Huang et al. [5], 12 percent of COVID-19 patients were diagnosed with acute myocardial infarction. Patients with COVID-19 who developed myocardial injury and had underlying coronary artery disease (CAD) exhibited poorer in-hospital outcomes [6]. Post-hospitalization, monitoring myocardial damage indicators should be conducted more closely in COVID-19 patients [7]. Certain studies have identified a connection between cardiac enzymes such as LDH and CK and outcomes like ICU hospitalization and ventilator use [1]. Troponin has been linked to mortality in COVID-19 patients [8]. Myoglobin, a biochemical measure of cardiac and widespread muscle injury, might hold greater potential in predicting mortality and the likelihood of disability insurance conversion in COVID-19 patients [3]. Recent research has indicated that individuals with higher serum vitamin D levels experienced milder symptoms, suggesting that vitamin D could be effective for the prevention and management of COVID-19 [9]. The potential benefits of vitamin D in COVID-19 are attributed to its diverse effects on the immune response, including increased immune cell activity of various antimicrobial compounds, reduced downregulation of self-damaging pro-inflammatory growth factors, and promotion of immune cell expression of anti- inflammatory growth factors [10].

In previous studies, ACE2 (angiotensin-converting enzyme 2) was identified as a potential transmitter of SARS-CoV-2 [11]. It has also been shown that SARS-CoV-2 might utilize ACE2 as a sensor for cellular entry, with a 10- to 20-fold stronger affinity for ACE2 than SARS-CoV-1 [12]. The extent of organ damage caused by virus infection is influenced by the receptor's distribution and expression, which holds significant implications for etiology and therapeutic development [13]. With advanced next-generation sequencing technology, single-cell RNA sequencing (scRNA-seq) allows for evaluating gene regulation data from individual cells, leading to better resolution of cellular distinctions and a deeper understanding of the roles of distinct cell types. Several researchers have examined the mRNA expression pattern of SARS-CoV-2 receptors in various body parts using publicly available scRNA-seq databases [2]. Current research aims to determine the predictive roles of Troponin I, Myoglobin, and vitamin D in the pathogenesis of COVID-19.

Methods

Ethical approval

This research study received ethical approval from the Ethical Committee of Middle Technical University, Technical Institute of Baqubah, Dayala, Iraq, on August 15, 2021.

Data collection

The present study was carried out in the city of Baquba, situated in Diyala province, spanning from the initial days of April to the concluding days of May in 2021. A total of 50 blood samples were meticulously collected from individuals afflicted with Covid-19 (comprising 31 males and 19 females, all within the age bracket of 20 to 80 years). These participants, who were undergoing treatment at the Al-Shifa Center, specifically designated for Covid-19 patients and located within the premises of the Educational Baquba Hospital, had previously received a confirmed diagnosis through the employment of an RT-PCR machine (Bio-Rad). Simultaneously, an additional 40 blood samples were procured from individuals without any Covid-19 symptoms, chosen as the control group (consisting of 18 males and 22 females, also within the age range of 20 to 80 years). These control group members had tested negative for the infection, as ascertained by the CRP test. This criterion was used to categorize them as part of the control group. A comprehensive form was duly completed, capturing pertinent information such as gender, age, and the presence of any pre-existing heart conditions for both the patient and control groups.

Laboratory measurements

Human blood was subjected to centrifugation at 3000 rpm for 5 minutes to facilitate the separation of serum from a 5 ml sample. The assessment of cardiac indicators was performed using a multifunctional immunoassay analyzer equipment (Opus, Dade Behring Diagnostics). The troponin-I test employed a sandwich enzyme-linked immunosorbent assay (ELISA) approach, utilizing two polyclonal antibodies specifically targeted against epitopes distinctive to the cardiac form of troponin-I. The normal value for troponin-I was established within the range of 0 to 0.04 ng/ml.

The quantification of myoglobin involved a sandwich ELISA immunoassay, utilizing both an anti-myoglobin primary antibody and an anti-myoglobin secondary antibody. The accepted normal range for myoglobin was between 25 and 72 ng/ml. The measurement of vitamin D3 in serum was achieved through the application of a vitamin D ELISA Kit. This quantitative assessment employed a competitive ELISA approach, utilizing primary antibodies specifically designed to recognize 25 (OH) - Vitamin D as the target. The established normal range for vitamin D3 was within 20 to 40 ng/ml. The estimation procedure was conducted within the Biotek ELX-800 autoanalyzer.

Statistical analysis

The normality of Troponin I, Myoglobin, and vitamin D indicators was initially assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Variables that did not meet the criteria for normal distribution were presented as medians and ranges, and the Mann-Whitney test was employed for comparing two groups. Meanwhile, the KruskalWallis test was utilized to determine significant differences across more than two groups. Certain factors were conveyed as percentage counts, and the Pearson-Chi-

square test was applied to identify noteworthy differences in frequencies.

The nature and strength of associations between variables were elucidated using Spearman's rho correlation. Additionally, the area under the curve (AUC), specificity, and sensitivity of each variable were computed through receiver operating characteristic (ROC) curve analysis. Moreover, the odds ratio (OR) was utilized to assess the magnitude of the relationship between the presence of a factor and the occurrence of events. A significance level of less than 0.05 was adopted for all analyses. These analyses were performed using the statistical software SPSS version 21.0.

Results

Participant characteristics

The results unveil significant differences in age groups and the presence of heart diseases concerning the study groups (P<0.05). Specifically, participants aged 41-60 years exhibited the highest percentage among patients compared to healthy individuals (52.00% vs. 47.50%), while the (>60) years age group displayed the lowest percentage (12.00% vs. 27.50%) with statistical significance (p<0.05). Moreover, the prevalence of heart diseases was notably higher in patients than in healthy participants (82.00% vs. 0.00%). Conversely, this study indicates no significant difference between gender and study groups (p>0.05) (Table 1).

Table 1. Baseline characters of participants Troponin I , Myoglobin and vitamin D parameters between study groups.

	Group	Infected (n=50)	Healthy (n=40)	Total	P value
Gender	Male	31(62.00%)	18(45.00%)	49(54.40%)	P>0.05
	Female	19(38.00%)	22(55.00%)	41(45.60%)	
Age groups (years)	21-40	18(36.00%)	10(25.00%)	28(31.10%)	P<0.01**
	41-60	26(52.00%)	19(47.50%)	45(50.00%)	
	>60	6(12.00%)	11(27.50%)	17(18.90%)	
Heart diseases	Yes	41(82.00%)	0(0.00%)	41(45.60%)	P<0.001***
	No	9(18.00%)	40(100.00%)	49(54.40%)	

Troponin I, Myoglobin, and vitamin D Levels Analysis

This investigations revealed statistically significant disparities in the levels of Troponin I, Myoglobin, and vitamin D between patients and healthy subjects (P<0.05). Notably, Troponin I and Myoglobin exhibited elevated levels in patients compared to healthy individuals (41/50 vs. 3/40 (OR=35.44) and 42/50 vs. 2/40 (OR=45.32), respectively). Conversely, vitamin D levels were found to be lower in patients than in the healthy group (47/50 vs. 5/40 (OR=0.001)) (Table 2).

Troponin I, Myoglobin, and vitamin D Levels in Relation to Heart Diseases

The results indicate significant differences in Troponin I, Myoglobin, and vitamin D levels concerning the presence of heart diseases (P<0.05). Specifically, patients with heart diseases displayed higher levels of Troponin I and Myoglobin compared to those without heart diseases (31/41 vs. 3/9 (OR=6.21) and 33/41 vs. 4/9 (OR=5.15), respectively). Conversely, patients with heart diseases exhibited lower vitamin D levels compared to those without heart diseases (9/41 vs. 5/9 (OR=0.22)) (Table 2).

Receiver Operating Characteristic (ROC) Curve Analysis

The outcomes of This study revealed noteworthy findings in the sensitivity and specificity of Troponin I, Myoglobin, and vitamin D in the context of COVID-19 screening. Troponin I exhibited high sensitivity (AUC=0.991, Sn=100%) as did Myoglobin (AUC=0.999, Sn=100%), whereas vitamin D displayed very low sensitivity (AUC=0.001, Sn=0.1%), with statistically significant differences (P<0.05). In terms of specificity, vitamin D demonstrated the highest value (100%), surpassing Troponin I (27%) and Myoglobin (7%), also with significant differences (P<0.05) (Table 3).

Correlation Analysis Among Parameters

The findings demonstrate a positive and statistically significant correlation between Troponin I and Myoglobin (r=0.329*, p<0.05). On the other hand, negative correlations were observed between vitamin D and Troponin I, as well as vitamin D and Myoglobin (r=-0.143, p>0.05, and r=-0.037, p>0.05, respectively) (Table 4).

Discussion

Impairments, advanced age, breathlessness, and abnormal laboratory results were all identified as risk factors for a poor prognosis [14]. The findings reveal a significant prevalence of COVID-19 in individuals aged 40 and above, attributed to an aging immune system, organ dysfunction, and chronic illnesses. Age has consistently emerged as a crucial health risk for COVID-19-related hospitalization and mortality since the onset of the epidemic. Additionally, individuals with specific underlying health conditions have been reported to face an elevated risk [15]. Notably, individuals aged 85 to 89 had a mortality risk 100 times higher than those aged 40 to 44. Similarly, the risk of mortality was 20 times higher for individuals aged 50 to 60 compared to those over 80, as demonstrated by Williamson et al. [16], and even 30 times higher for participants aged 50 to 60 compared to those aged 80 to 90, as found in the study by Reilev et al. [17].

The current research underscores a heightened incidence of heart disease among COVID-19 patients, aligning with the re-

Table 2. Comparative Troponin I , Myoglobin and vitamin D (> Median and <= Median) between study groups.

	Covid-19					Heart diseases			
	Median	Infected	Healthy	Median (Range)	P value OR (C.I.)	Yes (n=41)	No (n=9)	Median (Range)	P value OR (C.I.)
Troponin I	GT	41 (82%)	3 (7%)	1.12 (0.01-4)	35.44 (19.22-55.21)***	31 (76%)	3(33.33%)	2.00 (0.05-4)	6.21 (1.30-9.22)*
	LTE	9 (18%)	37 (93%)			10 (24%)	6 (66.67%)		
Myoglobin	GT	42 (84%)	2 (5%)	77.21 (25-133)	45.32 (38.22-65.21)***	33 (80%)	4 (44.44%)	99.00 (70-133)	5.15 (1.12-9.33)*
	LTE	8 (16%)	38 (95%)			8 (20%)	5 (55.56%)		
Vitamin D	GT	3 (6%)	35 (87.5%)	19.5 (5-40)	0.001 (0.0009-0.02)***	9 (21.9%)	5 (55.56%)	15.00 (5-19)	0.22 (0.04-1.12)*
	LTE	47 (94%)	5 (12.5%)			32 (78.01%)	4 (44.44%)		

Table 3. ROC curve of Troponin I , Myoglobin and vitamin D parameters.

Variables	AUC*	Std. Error	Cut off	Sensitivity %	Specificity %
Troponin I	0.991	0.000	<20	100%	27%
Myoglobin	0.999	0.002	>75	100%	7%
Vitamin D	0.001	0.000	>0.04	0.1%	100%

Table 4. Correlation relationship among Troponin I , Myoglobin and vitamin D parameters .

		Myoglobin	Vitamin D
Troponin I	r	0.329*	-0.143
	P	<0.05	>0.05
Vitamin D	r	-0.037	1.000
	P	>0.05	1.000

sults of Semenzato et al. [18]. Conditions such as high blood pressure, metabolic syndrome, and adiposity have been identified as contributors to COVID-19 susceptibility due to their impact on immune responses. COVID-19-related mortality was notably more common in individuals with pre-existing cardiovascular disease, diabetes, severe lung disorders like severe asthma, obesity, a history of hematopoietic stem cell malignancy, other malignancies, and those with kidney, liver, cerebral, or autoimmune conditions [17].

The present investigation establishes a noteworthy association between cardiac damage (measured by Troponin I) and the prognosis of hospitalized COVID-19 patients. The current research reveals that patients had significantly higher levels of Troponin I and Myoglobin compared to healthy individuals. Individuals with elevated Troponin I values, those with blood disorders, and those with a history of coronary heart disease all exhibited a higher mortality rate [19]. With the global spread of the COVID-19 epidemic, facts and expert opinions underscore the substantial temporary risk posed by cardiac damage in this clinical context [20]. In a substantial cohort of COVID-19 patients, researchers found that myocardial damage detected upon admission was linked to an increased risk of in-hospital fatality. Among 416 hospitalized COVID-19 patients in China, 82 showed elevated Troponin I levels, indicating myocardial damage in almost 20% of cases. Notably, those with elevated Troponin I had significantly worse clinical outcomes across various parameters, including death rates (51.2% vs. 4.5%) [15]. Furthermore, a modest meta-analysis revealed that increased Troponin I levels were associated with higher morbidity and mortality rates in COVID-19 patients [21]. The precise mechanism of COVID-19-induced myocardial injury remains unidentified, with potential contributors including myocarditis, inflammatory mediators, microvascular damage, type 2 myocardial infarction due to hypoxia or microvascular damage, tachycardia, early SARS-CoV-2 entry into myocytes via ACE2 receptor proteins, or other yet-to-be-discovered pathways. Ali et al. [19] suggest that assessing Troponin I levels upon presentation can aid in determining the severity and prognosis of COVID-19 patients.

Guo et al. [22] reported higher myoglobin concentrations in patients compared to healthy individuals, corroborating current findings. They discovered that myoglobin is a distinct risk factor for death and is strongly associated with organ damage in COVID-19 disease [23]. The findings suggest that myoglobin could serve as a valid disease biomarker, reflecting broader physiological disruptions and offering insights into prognosis and therapy response among COVID-19 patients [24]. Comparative investigations on the predictive potential of cardiac biomarkers for COVID-19 mortality have been limited. Qin et al. [25] investigated the correlations and predictive power of circulating heart damage indicators in a comprehensive retrospective analysis. Their study revealed that elevated levels of myoglobin, NT-proBNP, CK-MB, and hs-TnI exhibited superior overall efficacy in predicting COVID-19-related mortality [25]. Interestingly, myoglobin, a non-cardiac biomarker also generated in musculoskeletal myocytes, demonstrated better predictive accuracy compared to cardiac biomarkers like CK-MB and hs-TnI. Elevated myoglobin levels, in conjunction with hs-TnI and CK-MB, indicated myocardial cell damage following COVID-19. Another possible cause for increased myoglobin levels is rhabdomyolysis, a potential late consequence of SARS-CoV-2 infection, identified as a significant determinant of poor prognosis in COVID-19 patients [26]. Rhabdomyolysis patients often ex-

hibit acute kidney damage, as indicated by elevated creatinine levels [27]. In COVID-19 patients, myoglobin levels were significantly correlated with serum creatinine, with a correlation coefficient of 0.46. In contrast, hs-TnI and CK-MB had correlation coefficients of 0.18 and 0.16 with creatinine, respectively. These findings suggest that myoglobin levels could serve as indicators of symptom severity in COVID-19 patients with rhabdomyolysis [24]. Notably, the high predictive efficacy of myoglobin cannot solely be attributed to the prevalence of rhabdomyolysis, given that the total rhabdomyolysis incidence among COVID-19 individuals is only 2.2% [26]. Myoglobin likely functions as a biomarker of disease severity during COVID-19 illness, reflecting physiological disruptions like cardiac damage, acute systemic hypoxia, and rhabdomyolysis, consequently exhibiting enhanced predictive accuracy for in-hospital mortality. According to Zhu et al. [3], myoglobin and troponin serve as indicators of death risk and progression to severe illness in severe COVID-19 cases, with myoglobin potentially surpassing troponin in predictive efficacy. Elevated myoglobin and CK-MB levels upon admission could be valuable predictors of adverse outcomes among COVID-19 patients, and the combined use of myoglobin and CK-MB exhibited improved prognostic potential [28].

The current findings indicate lower vitamin D levels in patients compared to healthy individuals, consistent with prior research [29]. T regulatory lymphocytes (Tregs) play a critical role in defense against viral infections and chronic inflammation. Treg levels were notably reduced, especially in severe cases of COVID-19, indicating a potential link to disease severity [30]. Notably, increased Treg levels were associated with lower levels of lung viral infection in elderly nursing home participants [31], suggesting that boosting Treg levels might mitigate the severity of viral diseases like COVID-19. Vitamin D supplementation has been proposed as a means to enhance Treg levels [32]. The ubiquity of low vitamin D levels worldwide, coupled with their association with elevated risk of pneumonia and viral respiratory infections, underscores the importance of vitamin D in respiratory infection cases [33]. Furthermore, vitamin D deficiency has been linked to increased cytokine production, whereas vitamin D3 has been shown to enhance inhibitory cytokines while reducing the release of inflammatory cytokines like IL6 and TNF-alpha in animal studies and in vitro cell assays [34]. These findings suggest that higher vitamin D levels might mitigate the risk of cytokine storms, a phenomenon observed in COVID-19 cases [29]. Thrombotic complications are frequent in COVID-19 patients [35]. Vitamin D deficiency also affects coagulation system regulation, increasing the risk of thrombotic events [36]. Given the link between vitamin D deficiency and conditions like obesity and diabetes, which are associated with increased COVID-19 mortality, it is evident that vitamin D plays a crucial role in determining disease outcomes.

If vitamin D can mitigate the intensity of COVID-19 in terms of inflammation, pneumonia/ARDS, coagulation, and inflammatory cytokines, it presents a potentially straightforward strategy to limit the pandemic's impact. However, high-dose intravenous vitamin D3 therapy administered after ICU admissions did not lead to reduced intubation rates, shorter hospital stays, or decreased in-hospital mortality in severe COVID-19 cases [37]. Current results suggest a negative correlation between bio-cardiac markers and vitamin D in COVID-19 patients, likely due to the presence of cardiovascular disease (indicated by high bio-cardiac markers) and heightened inflammation (indicated by low vitamin D levels).

Conclusion

In conclusion, this study underscores the pivotal roles of age and cardiac health in shaping the trajectory of COVID-19. Age-related vulnerabilities, coupled with pre-existing cardiac conditions, significantly contribute to the prognosis of individuals battling this disease. Notably, cardiac biomarkers emerge as crucial indicators in the context of COVID-19. Specifically, Troponin I and Myoglobin serve as robust risk predictors, exhibiting direct associations with mortality and highlighting their strong connection to cardiac complications. These biomarkers provide valuable insights into disease severity and patient outcomes, enabling timely intervention and tailored treatment strategies.

Furthermore, these findings shed light on the potential benefits of vitamin D supplementation in COVID-19 management. The observed reduction in clotting issues and attenuation of cytokine storms among COVID-19 patients with enhanced vitamin D levels indicate a promising avenue for alleviating the severity of the disease. By mitigating coagulation abnormalities and tempering excessive inflammatory responses, vitamin D supplementation offers a potential mechanism to improve patient outcomes and limit the impact of the pandemic.

As we continue to navigate the complexities of COVID-19, these insights contribute to a deeper understanding of the disease's multifaceted nature. Age, cardiac health, and the interplay of biomarkers and supplementation emerge as crucial factors shaping disease progression and outcomes. Harnessing these insights, we are better equipped to develop targeted strategies that enhance patient care and mitigate the challenges posed by this global health crisis.

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