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Post-Hospitalization, Levels of D-dimer, C-Reactive Protein, Ferritin, And Lactate Dehydrogenase in Recovered COVID-19 Iraqi Patients

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Abstract

This study was performed to evaluate concentration of D-dimer, C-reactive protein (CRP), ferritin, and lactate dehydrogenase (LDH) to monitor treatment response of COVID -19 patients at the post hospitalization period. Results of present study revealed that there significant increases in patients showing abnormal values for the LDH, CRP, and ferritin; but not for D-dimer that decreased significantly. Higher elevation ($P<0.0001$) in concentration of blood biomarkers was detected among the group of abnormal values when compared to the group of normal values of study patients. In addition, the concentration of D-dimer had showed a significant higher concentration in patients with abnormal values. Concerning time-required recovery and age factors, we showed that the patients required 4-30 (13.35±0.65) days for recovery; while the age of study population was ranged 26-95 (54.85±1.57) years and the percentage of COVID-19 patients were increased with the advancing of age. Relation to gender factor, abnormal values of study biomarkers reported that there no significant differences ($P>0.05$) between males and females. Among three study age groups (≤39, 40-59, and ≥60 years), the findings of study biomarkers showed insignificant differences ($P>0.05$) in concentration of D-dimer, CRP, and LDH; but not in concentration of ferritin that increased significantly ($P\leq0.0065$) at the group of 40-59 years. As well as the findings of time-required recovery found that there insignificant variation ($0\leq0.084$) between the study age groups. In conclusion, our study found a significant prevalence of abnormal values and significant elevation in concentration of blood biomarkers, particularly Di-dimer, in recovered COVID-19 patients indicating the potential high risk of infection. Therefore, the discovery of how different biomarkers behave post the course of the disease could help in identifying severe disease and subsequently improve prognosis. Nevertheless, we urge for more research across the globe to corroborate these findings.

Keywords: Coronavirus, Blood, Biomarkers, Wasit province, Iraq.

INTRODUCTION

Over the past two decades, coronaviruses have been associated with significant disease outbreaks in East and Middle East Asia which began as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) in 2002 and 2012, respectively (**1, 2**). At the end of 2019, a series of pneumonia cases of unknown cause emerged in Wuhan (Hubei, China) (**3**). In January 2020, deep sequencing analysis from lower respiratory tract samples identified a novel virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or 2019-nCoV) as the causative agent for that observed pneumonia cluster (**4**). On February 2020, the World Health Organization (WHO) named the disease as COVID-19, and by March, 2020 when the number of countries involved was 114, with more than 118,000 cases and over 4000 deaths, the WHO declared the pandemic status (**5**).

Coronavirus Disease 2019 (COVID-2019) is an RNA virus, with a typical crown-like appearance under an electron microscope due to the presence of glycoprotein spikes on its envelope (**6**). Based on molecular characterization, COVID-19 is considered as a new *Betacoronavirus* belonging to the subgenus *Sarbecovirus* (**7**). Although pathophysiology and virulence mechanisms of COVID-19 have links to the function of the structural and non-structural proteins (nsps), the pathogenic mechanism that produces disease seems to be particularly complex (**8, 9, 10**). In addition, there are no specific clinical features that can yet reliably distinguish COVID-19 from other viral respiratory infections. The clinical spectrum of COVID-19 varies from asyptomatic or paucisymptomatic forms to clinical conditions characterized by severe respiratory failure, sepsis, septic shock, and multiple organ dysfunction syndromes (**5, 11**). Therefore, a number of diagnostic techniques are utilized to identify the positive cases in patients with suspected infection such real-time polymerase chain reaction (RT-PCR) to detect nucleic

acid of virus in nasal and oral swab samples, imaging findings-chest computed tomography (CT-scan) to demonstrate ground-glass opacification, consolidative abnormalities, pleural effusion, pleural thickening, and lymphadenopathy (**12, 13**). Apparently, the findings of hematology, serum liver enzymes, and blood biomarkers have the potential to discriminate between mild and severe disease and possibly may be used as prognostic markers (**14**). Various biomolecules such as D-dimer, CRP, ferritin, and LDH has been increased in COVID-19 critical patients in comparison with those no-severe infected cases (**15**). Post hospitalization, data available on the rate and characteristic of blood biomarkers in the recovered COVID-19 patients are few. Hence, the present study aims to detect the level of D-dimer, CRP, ferritin, and LDH in the cured COVID-19 patients for monitoring treatment response for first time in Iraq.

MATERIALS AND METHODS

Ethical approval

The current study was performed under the license of the College of Science, Wasit University, Wasit, Iraq. All collected data as well as samples were approved by the scientific and Ethical Committee of the College of Science, Wasit University. In addition, agreement of the study population to participate in this study was obtained prior an initiating of the study.

Samples and data

The present study, performed during May to July 2020 in Wasit province (Iraq), was involved an overall 89 recovered COVID-19 patients had severe worsening condition during hospitalization, and confirmed recently as recovered individuals. During follow-up post hospitalization, 2.5 ml of venous blood samples were drained from each patient and the sera were tested targeting four blood biomarkers; D-dimer, CRP, ferritin, and LDH. Time-required recovery, age, and gender were documented as possible risk factors.

Measurement of blood biomarkers

Following the manufacturer instructions of D-dimer (Genrui, China), CRP (Genrui, China), ferritin (ELIITech Group, France), and LDH (ELIITech Group, France) kits, study sera were prepared, analysed, and calculated.

Statistical analysis

GraphPad Prism (version$^{6.0.1.298}$) software was used to data analysis of blood biomarkers. The *t*-test was applied to detect significant differences at a $P<0.05$ between abnormal and normal values of study population; whereas, one-way Analysis of Variance (ANOVA) was used to detect significant variation between abnormal values among categories of risk factors (**16**). Values are mean (M) ± standard errors (SE) and range (R).

RESULTS

Of 89 recovered COVID-19 patients, significant increases (P<0.05) were showed in patients with abnormal values to LDH (83.15%), CRP (78.65%), and ferritin (69.66%); whereas, significant decreases (P<0.05) were reported in study patients with abnormal values to D-dimer (43.82%). In comparison to normal values, significant abnormal higher values were detected in all studied blood biomarkers; D-dimer (918.43 ± 67.35), CRP (40.56 ± 4.79), ferritin (446.45 ± 32.93), and LDH (372.67 ± 16.23), (Table 1).

Table 1. Total study results of blood markers among study population

Test	Unit	Abnormal		Normal		*t-test*	*P-value*
		No. (%)	Concentration	No. (%)	Concentration		
D-dimer	µg/L	39 (43.82)	918.43 ± 67.35 (510-2180)	50 (56.18) *	282.96 ± 18.92 (90-500)	10.3482	0.0001 S****
CRP	mg/L	70 (78.65) *	40.56 ± 4.79 (4.01-173.26)	19 (21.35)	2.73 ± 0.03 (2.5-2.9)	3.9623	0.0002 S***
Ferritin	µg/L	62 (69.66) *	446.45 ± 32.93 (211-1629)	27 (30.34)	108.18 ± 9.33 (11.8-192.4)	6.8804	0.0001 S****
LDH	U/L	74 (83.15) *	372.67 ± 16.23 (644-224)	15 (16.85)	172.14 ± 9.45 (107-217)	5.2847	0.0001 S****

The findings showed that the time-required for recovery was ranged (4-30) days with M±SE (13.35 ± 0.65), and age of the study population was ranged (26-95) years at M±SE of 54.85 ± 1.57. In details, 47 (52.81%) of study patients were required 10-20 (14.13 ± 0.46) days to be recovered; while 30 (33.71%) and 12 (13.48%) were required respectively to < 10 and > 20 days to be recovered (Figure 1). Concerning age, significant increases (P<0.05) in percentage of study population were reported in patients with advancing of their ages (Figure 2).

Relation to gender factor, the study population was involved 51 males (57.3%) and 38 female (42.7%). In males, significant increases (P<0.05) in patients showing abnormal values were reported in LDH (92.16%), CRP (78.43%), and ferritin (78.43%); while, significant decrease (P<0.05) was detected in abnormal values of D-dimer (37.25%). In comparison with the normal concentration of blood biomarkers, higher significant abnormal values were seen in concentration of D-dimer (797.74 ± 67.79) and ferritin (430.16 ± 38.48), (Table 2).

Table 2. Results of blood markers among males of the study population (Total No: 51)

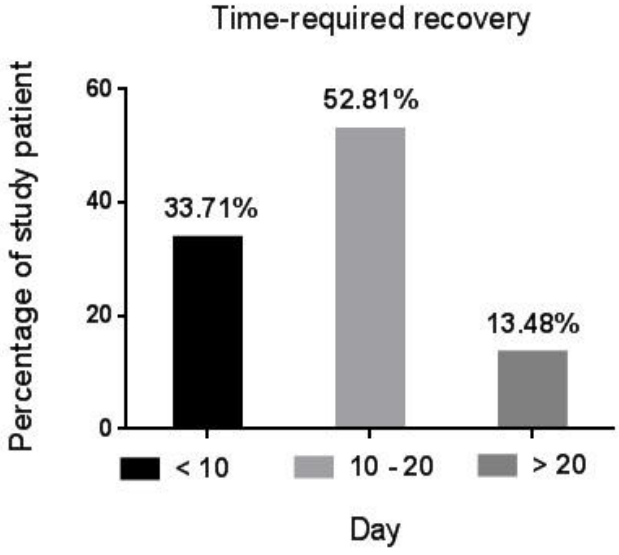

Figure 1. Distribution of study patients according to the time required recovery (Total

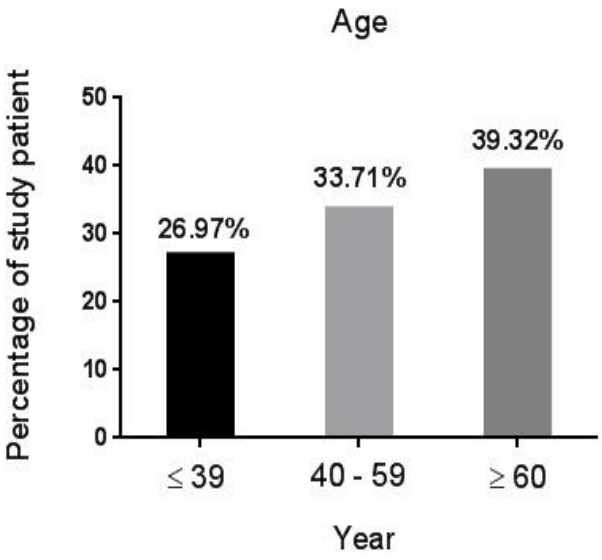

Figure 2. Distribution of study patients according to their ages (Total No: 89)

Test	Unit	Abnormal		Normal		*t-test*	*P-value*
		No. (%)	Concentration	No. (%)	Concentration		
D-dimer	µg/L	19 (37.25)	797.74 ± 67.79 (510-14330)	32 (62.75) *	270.22 ± 22.04 (90-490)	8.8973	0.0001 S****
CRP	mg/L	40 (78.43) *	35.96 ± 5.88 (4.01-161)	11 (21.57)	2.72 ± 0.04 (2.5-2.9)	2.9437	0.0049 S**
Ferritin	µg/L	40 (78.43) *	430.16 ± 38.48 (217.04-1250)	11 (21.57)	99.54 ± 13.61 (28.1-192.4)	4.4527	0.0001 S****
LDH	U/L	47 (92.16) *	361.53 ± 20.82 (224-868)	4 (92.16)	172 ± 17.06 (128-211)	2.6264	0.0115 S*

In females, significant increases (P<0.05) in patients showing an abnormal values were detected in values of CRP (78.95%), LDH (71.05%), and ferritin (57.89%); while, no significant difference (P>0.05) was observed in patients having normal and abnormal values for D-dimer. In comparison with the normal concentration of blood biomarkers, D-dimer (1000.1 ± 106.34), ferritin (500.35 ± 69.66), and LDH (397.26 ± 26.22) were showed, significantly, the higher concentration (Table 3).

Table 3. Results of blood markers among females of the study population (Total No: 38)

Test	Unit	Abnormal		Normal		*t-test*	*P-value*
		No. (%)	Concentration	No. (%)	Concentration		
D-dimer	µg/L	20 (52.63)	1000.1 ± 106.34 (490-2180)	18 (47.37)	294.11 ± 35.25 (100-500)	6.0284	0.0001 S****
CRP	mg/L	30 (78.95) *	47.55 ± 8.1 (4.85 – 173.26)	8 (21.05)	2.72 ± 0.03 (2.6-2.88)	2.8309	0.0075 S**
Ferritin	µg/L	22 (57.89) *	500.35 ± 69.66 (211-1629)	16 (42.11)	103.32 ± 14.13 (11.8-172.2)	4.7912	0.0001 S****
LDH	U/L	27 (71.05) *	397.26 ± 26.22 (229-760)	11 (28.95)	175.73 ± 11.33 (107-217)	5.2732	0.0001 S****

In comparison between males and females, there no significant differences (P>0.05) were detected in abnormal values of all tested blood biomarkers; D-dimer, CRP, ferritin, and LDH (Table 4).

Table 4. Distribution of abnormal results concerning gender factor

Test	Unit	Male	Female	*t-test*	*P-value*
		Concentration	Concentration		
D-dimer	µg/L	797.74 ± 67.79 (510 - 14330)	1000.1 ± 106.34 (490 - 2180)	1.586	0.1212 NS
CRP	mg/L	35.96 ± 5.88 (4.01-161)	47.55 ± 8.1 (4.85 – 173.26)	1.1885	0.2388 NS
Ferritin	µg/L	430.16 ± 38.48 (217.04 - 1250)	500.35 ± 69.66 (211 - 1629)	0.96	0.3409 NS
LDH	U/L	361.53 ± 20.82 (224 - 868)	397.26 ± 26.22 (229 - 760)	1.0537	0.2956 NS

Regarding time-required recovery and age factors, no significant differences (P>0.05) were seen between males and females of study patients (Table 5, Figures 3 and 4).

Table 5. Association of time-required recovery and age factors to gender factor

Factor	Unit	Value: M ± SE (R)		*t-test*	*P-value*
		Male	Female		
Time-required curing	Day	13.27 ± 0.8 (4 - 27)	13.79 ± 1.08 (4 -30)	0.3915	0.6964 NS
Age	Year	52.39 ± 2.09 (26 - 95)	57.58 ± 2.21 (28-82)	1.6804	0.0965 NS

Relation to age factor, the study population was divided into 3 age groups; 24 patients of ≤ 39 years, 30 patients of 40 – 59 years, and 35 patients of ≥ 60 years. In a group of ≤ 39 years, the percentage of patients showing abnormal values was increased significantly (P<0.05) in CRP (70.83%), LDH (70.83%), and ferritin (62.5%); and decreased significantly in D-dimer (33.33%). In comparison with the normal values, significant higher concentration were observed in D-dimer (954 ± 139.54) and ferritin (404.49 ± 59.09), (Table 6).

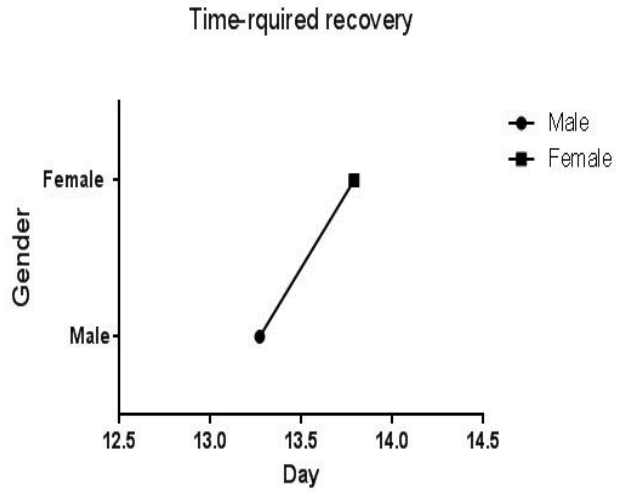

Figure 3. Association between gender and time-required recovery factor

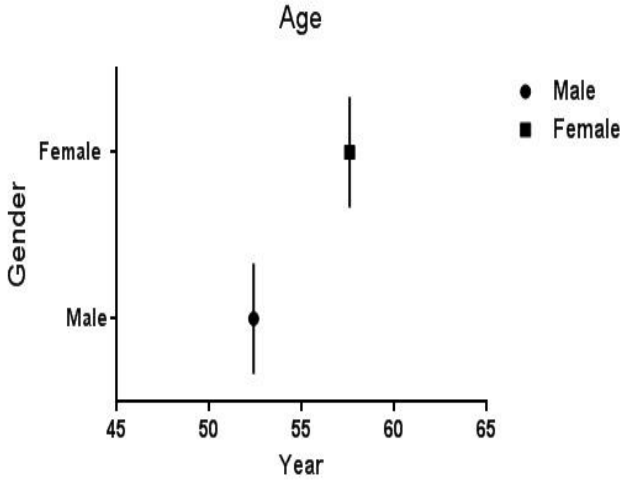

Figure 4. Association between gender and age factor

Table 6. Results of blood markers among age group of ≤ 39 years of study population (Total No: 24)

Test	Unit	Abnormal		Normal		*t-test*	*P-value*
		No. (%)	Concentration	No. (%)	Concentration		
D-dimer	µg/L	8 (33.33)	954 ± 139.54 (550 - 1500)	16 (66.67) *	249.56 ± 33.69 (90 - 490)	6.5364	0.0001 S****
CRP	mg/L	17 (70.83) *	42.43 ± 11.01 (7.57 - 161)	7 (29.17)	2.74 ± 0.05 (2.5 - 2.88)	2.2838	0.0324 S*
Ferritin	µg/L	15 (62.5) *	404.49 ± 59.09 (227 - 1001)	9 (37.5)	90.27 ± 15.84 (17.35 - 155)	4.0327	0.0006 S***
LDH	U/L	17 (70.83) *	400.71 ± 48.46 (224 - 868)	7 (29.17)	160.57 ± 14.35 (107 - 211)	3.1168	0.005 S**

In an age group of 40-59 years, significant increases (P<0.05) in percentage of patients showing abnormal values were reported in CRP (86.67%), LDH (83.33%), and ferritin (73.33%); while, significant decreases (P<0.05) were observed in patients showing abnormal values to D-dimer (33.33%). In comparison with the normal values of blood biomarkers, higher significant abnormal values (P<0.05) were reported in D-dimer (837 ± 158.88), ferritin (653.8 ± 11.28), and LDH (385.4 ± 28.62), respectively; but not in values of CRP (Table 7).

Table 7. Results of blood markers among age group of 40 - 59 years of study population (Total No: 30)

Test	Unit	Abnormal		Normal		*t-test*	*P-value*
		No. (%)	Concentration	No. (%)	Concentration		
D-dimer	µg/L	10 (33.33)	837 ± 158.88 (540 - 2180)	20 (66.67) *	283.4 ± 32.11 (98 - 500)	4.6345	0.0001 S****
CRP	mg/L	26 (86.67) *	41.75 ± 7.92 (4.01 - 142)	4 (13.33)	2.73 ± 0.06 (2.6 – 2.9)	1.9052	0.0671 NS
Ferritin	µg/L	22 (73.33) *	653.8 ± 11.28 (211 - 1629)	8 (26.67)	85.28 ± 15.01 (11.8 - 154)	3.376	0.0022 S**
LDH	U/L	25 (83.33) *	385.4 ± 28.62 (229 - 760)	5 (16.67)	179 ± 16.14 (124 - 217)	3.1636	0.0037 S**

In an age group of ≥ 60 years, abnormal values was increased significantly (P<0.05) in study patients having abnormal values to all tested blood biomarkers; LDH (94.29%), CRP (80%), ferritin (74.29%), and D-dimer (57.14%). In comparison with the concentration of normal blood biomarkers, higher significant (P<0.05) abnormal values were seen in D-dimer (933.35 ± 83.55) and ferritin (374.57 ± 21.64), (Table 8).

Table 8. Results of blood markers among age group of ≥ 60 years of study population (Total No: 35)

Test	Unit	Abnormal	Normal	*t-test*	*P-value*

		No. (%)	Concentration	No. (%)	Concentration		
D-dimer	µg/L	20 (57.14) *	933.35 ± 83.55 (510 - 1700)	15 (42.86)	318 ± 31.78 (100 - 500)	6.1149	0.0001 S****
CRP	mg/L	28 (80) *	38.31 ± 7.27 (4.85 – 173.26)	7 (20)	2.71 ± 0.05 (2.5 – 2.9)	2.4205	0.0212 S*
Ferritin	µg/L	26 (74.29) *	374.57 ± 21.64 (221 - 690)	9 (25.71)	117.88 ± 18.17 (28.1 – 192.4)	6.6568	0.0001 S****
LDH	U/L	33 (94.29) *	348.58 ± 16.71 (230 - 642)	2 (5.71)	195.5 ± 7.5 (188 - 203)	2.2238	0.0331 S*

In comparison between abnormal values of the three study age groups, the findings of blood biomarkers were showed insignificant differences (P>0.05) in concentration of D-dimer, CRP, and LDH; but not in concentration of ferritin which increased significantly (P≤0.0065) at an age group of 40-59 years (653.8 ± 11.28), (Table 9).

Table 9. Distribution of abnormal results among the study age groups (Total No: 89)

Test	Unit	Age group			*ANOVA* R^2	*P-value*
		≤ 39	40 - 59	≥ 60		
D-dimer	µg/L	954 ± 139.54 (550 - 1500)	837 ± 158.88 (540 - 2180)	933.35 ± 83.55 (510 - 1700)	0.013	0.7948 NS
CRP	mg/L	42.43 ± 11.01 (7.57 - 161)	41.75 ± 7.92 (4.01 - 142)	38.31 ± 7.27 (4.85 – 173.26)	0.0021	0.09312 NS
Ferritin	µg/L	404.49 ± 59.09 (227 - 1001)	653.8 ± 11.28 (211 - 1924)	374.57 ± 21.64 (221 - 690)	0.1546	0.0065 S**
LDH	U/L	400.71 ± 48.46 (224 - 868)	385.4 ± 28.62 (229 - 760)	348.58 ± 16.71 (230 - 642)	0.05426	0.0581 NS

Also, the findings of time-required recovery were showed insignificant variation (0≤0.084) throughout the three study age groups; ≤ 39 [14 ± 1.24 (6 - 25)], 40-59 [13.2 ± 1.02 (4 - 27)], and ≥ 60 [13.06 ± 1.14 (4 - 30)] years (Figure 5).

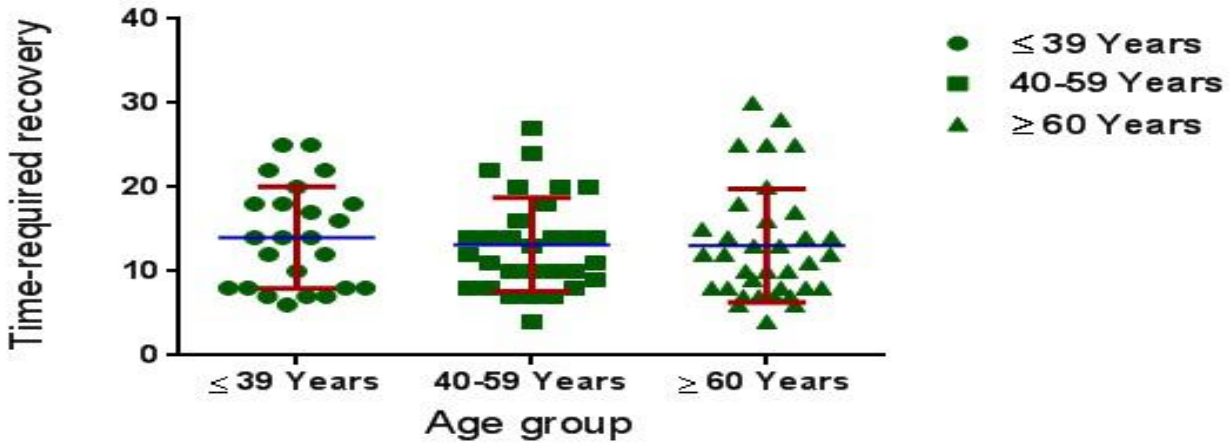

Figure 5. Total results of time-required recovery among three study age groups

DISCUSSION

COVID-19 is an emerging viral illness that has rapidly transmitted throughout the world. During the course of hospitalization, some patients may reveal severe clinical symptoms that important in recognition of disease progression and decision the point concerning intensive management. Post hospitalization, clinical management requires a whole-patient perspective which intended for careful examination and primary selective blood testing (**17**). Clear pattern of inflammatory, hematologic, biochemical and immune biomarker abnormalities have been found by many studies. Hence, general clinical profile of blood biomarkers can play a predictive role in identifying people at high risk of mortality so as to make appropriate clinical decision (**18, 19, 20**). In this study, our findings demonstrated significant prevalence of abnormal values among the recovered COVID 19 patients. As well as, there high concentration of blood biomarkers (D-dimer, CRP, ferritin, and LDH) was detected in the recovered patients post hospitalization. Our findings were in agreement with that detected recently (**21, 22, 23, 24**). We also found that most patients required approximately 14 days for recovery, and that the percentage of infection was increased with advancing age, while the concentration of D-dimer and ferritin was elevated significantly at all age groups. D-dimer testing is performed as a diagnostic algorithm for excluding the diagnostic thrombosis caused by any process (**25**). Many studies have demonstrated that D-dimer level is associated with the severity of COVID-19 and clinical outcome (**26, 27, 28**). Yao et al suggested that an elevated D-dimer level on admission (> 2.14 mg/L) may identify patients at higher risk for mortality and therefore inform physicians about suitable candidates for intensive care and early intervention (**28**).

Although the exact function in patients with COVID-19 remains unclear (**29**), an elevated concentration of CRP detected in this study might be the indication of excessive inflammatory stress and contribution to severe / critical illness or death. Positive correlation between concentration of CRP and the lung lesion in COVID-19 infected patients has been demonstrated (**30**); whereas, Koozi et al reported that increased level of CRP associate with 30-days mortality rate (**31**). Moreover, it showed that level of CRP level can use to monitor the progression and improvement of COVID-19 patients (**32**). Despite its value in predicting a poor outcome, different factors can affect level of CRP, involving liver injury, blood pressure, lipid level, weight, smoking

status as well as gender and age (**33**).

Along with other biomarkers included in this study, we also found that a higher serum ferritin was detected in recovered COVID-19 patients. Serum ferritin is a well-known inflammatory marker which can be increased significantly in response to systemic and pulmonary inflammation, as well as to a variety of diseases including COVID-19 (**22**). The mechanisms responsible for the association of an elevated ferritin level and severity of infection in COVID-19 patients are unclear; however, several possibilities for this including pro-inflammatory cytokines that may increase ferritin synthesis (**34**), cellular damage originated due to inflammatory process that promotes leaking of intracellular ferritin (**35**), and liberation of iron from ferritin due to microvascular environment and increase production of ROS which causing further cellular damage (**36**). Wang et al mentioned that hepatic dysfunction in severe COVID-19 is accompanied by greater activation of coagulative and fibrinolytic pathways, relatively depressed platelet counts, climbing neutrophil counts and neutrophil to lymphocyte ratios and high ferritin levels (**37**). This alteration in immune balance had demonstrated to be elevated with increase age, and older patients might therefore be expected to fare worse, with greater reliance on this pathway (**38, 39**).

Among the risk factors we investigated in this study, the findings revealed that the prevalence of LDH was increased significantly among abnormal values of recovered COVID-19 patients, and the concentration was elevated greatly. Several studies have reported elevated levels of LDH with COVID-19 severity (**40, 41, 42**). It has proposed that COVID-19 causes direct liver injury via a viral hepatitis as well as from immune interactions involving intrahepatic cytotoxic T cells and Kupffer cells (**43, 44**). Based on the findings Han *et al* (**21**) suggested that either there a strong correlation between LDH and lung damage as well as disease severity, or that the myocardial and liver injury caused COVID-19 is due to the direct damage of the virus to targeted organ but not because the hypoxia induced by lung injury. It was also found that LDH increases production of lactate leads to enhancement of immune suppressive cells and inhibition of cytolytic cells which strongly correlated with the severity of disease (**45, 46**).

In this study, the recovery time in confirmed cases of COVID-19 patients is found to be high. This meaning that stress on the medical resource increased, and time taken recovery required for proper arrangement and utilization of available resources. However, treatment applied protocol involving the using of Remdesivir had superior effects in shortening the time required recovery as well as in decreasing of lower respiratory tract infection (**47**). Nonetheless, patients recovering from COVID-19 might show variable organ abnormalities particularly in lung which possibly prolong the time required recovery. Also, older patients possibly required an additional time to be recovered. Regarding age factor, many studies reported that COVID-19 tends to affect older patients more severely, and those who survive are at high risk complications (**48, 49, 37**). Although Niu et al mentioned that the case fatality rate of infected COVID-19 was estimated 2-5%, Wu and McGoogan reported that this percentage can increase to 8% and 14.8% in aged 70-90 years and older than 80 years patients respectively (**49, 50**). Multiple factors lead to a higher proportion of elderly patients with severe situation such as senior, co-morbidities, low immune functions and so on (**51, 49**). There is no doubt that old severe patients are more likely to die, therefore, special attention should be improved to decrease the case fatality rate of severe patients. In addition, the first cases of re-infection by COVID-19 were reported among older adults (**52**).

CONCLUSIONS

The COVID-19 pandemic is rapidly spreading and increasing the healthcare burden worldwide. The variable course of illness and complications makes it crucial to collect strong evidence to determine the patient's condition in a timely manner and predict complication. Our findings highlighted the importance of D-dimer, CRP, ferritin, and LDH as possible biomarkers for mortality of recovered COVID-19 patients during post hospitalization period. Chronic diseases and secondary infection in correlation with aging might exert effects on the increased concentration of blood biomarkers; therefore, the discovery of how different biomarkers behave post the course of the disease could help in identifying severe disease and subsequently improve prognosis. Nevertheless, we urge for more research across the globe to corroborate these findings.

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COMPETING INTEREST

No conflicts to be interested

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