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Evaluation of Hematological blood tests among COVID-19 patients with chronic disease history

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We aimed to appraise the relationship between hematological laboratory tests and the severity of COVID-19 in patients with pre-existing chronic diseases to predict the disease severity. This case-control retrospective study was conducted at Dr. Soliman Fakeeh Hospital, Jeddah, Saudi Arabia, from April to August 2020. Laboratory blood test data of 270 patients with confirmed COVID-19 and admitted to the hospital were enrolled in the study. On the other hand, patients with a respiratory infection, newly diagnosed with a chronic disease, and patients on an anticoagulant were excluded. Patients with no history of chronic disease were grouped into a control group, while the case group included patients with chronic disease. The variances between groups were analyzed by unpaired t-test, while within the groups was paired t-test using SPSS version 19. COVID-19 patients with comorbidities had a higher risk of severe and critical COVID-19 clinical manifestations. Red blood cell and lymphocyte counts were significantly different between the groups at admission (P = 0.012 and 0.027, respectively). Additionally, D-dimer and C-reactive protein (CRP) levels were higher in the comorbid COVID-19 group (64% and 60%, respectively) than in the non-comorbid COVID-19 group. Severe reduction in lymphocyte count and elevation in D-dimer and CRP levels could be potential indicators of COVID-19 severity. These indicators might be helpful in managing patients with chronic diseases.

Keywords: COVID-19, Chronic disease, laboratory biomarkers, CBC, CRP, D-dimer

INTRODUCTION

Syndrome coronavirus (MERS-CoV) in Saudi Arabia in 2012 (Azhar et al. 2019) (Hui and Zumla 2019) (Guo et al. 2020). The coronavirus family affects the respiratory system, particularly the upper respiratory tract, causing mild to severe pneumonia (Hui and Zumla 2019).

The disease has a wide range of clinical symptoms ranging from asymptomatic and mild to severe conditions resulting in acute respiratory distress syndrome, sepsis, shock, and multi-organ failure (Wu and McGoogan 2020) (Yang et al. 2020). The new coronavirus disease 2019 (COVID-19) has become a serious disease impacting people all over the world and is considered a pandemic disease by the World Health Organization (WHO). COVID-19, which was first identified in Wuhan, Hubei, China, involves a series of previously discovered coronaviruses, including severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) in China in 2002 and Middle East respiratory syndrome (MERS) (Yu et al. 2020). Clinical observation is classified into three types: mild disease, severe disease, and critical disease. The mild disease is usually associated with no symptoms of mild pneumonia, whereas the severe disease comes with dyspnea and severe pneumonia. A serious onset of respiratory failure called acute respiratory distress syndrome (ARDS) develops in the critical phase, requiring noninvasive or invasive ventilation (Chen et al. 2020) (Wang et al. 2020).

The demographic distribution of COVID-19 has revealed a high risk for severe clinical conditions among certain people, leading to hospitalization and mortality increase (Cecconi et al. 2020) (Chen et al. 2020). Asymptomatic cases are mostly observed in children and young adults. In contrast, critical cases are more common in older people, predominantly those with pre-existing medical conditions such as cardiovascular disease, diabetes mellitus, hypertension, chronic respiratory disease, and oncological diseases (Chen et al. 2020) (Wang et al. 2020). It has been reported that children below 15 years old with COVID-19 were asymptomatic, whereas patients over 45 years had pneumonia symptoms (Yang et al. 2020). The severity of cases correlates with chronic diseases, as observed by Wu et al., who reported

that roughly 50% of COVID-19 cases admitted to the intensive care unit (ICU) were suffering from chronic diseases (Wu and McGoogan 2020).

Laboratory test results of some biomarkers, particularly the lymphocyte count, D-dimer, lactated dehydrogenase (LDH), ferritin, and C-reactive protein (CRP), reportedly correlate with disease severity (Chen et al. 2020) (Han et al. 2020) (Spiezia et al. 2020). In this study, we aimed to estimate the correlation between hematological laboratory biomarkers and the severity of COVID-19 cases with pre-existing chronic diseases to elucidate the pathophysiology and predict disease severity by using routine blood tests to identify an optimal treatment strategy as supporting clinicians in disease monitoring.

MATERIALS AND METHODS

This retrospective study has recruited COVID-19 patients who were admitted to Dr. Soliman Fakeeh Hospital (DSFH) between April and August of 2020. The Institutional Review Board committee approved the study of Fakeeh College for Medical Sciences (FCMS) and DSFH (code #: 155).

Data from 270 confirmed cases of COVID-19 was collected using the non-probability consecutive sampling method from patients' records at the hospital. An online sample size calculator was used to estimate the required samples, considering the margin error, confidence level, and prevalence of chronic disease were 5%, 95%, and 50%, respectively. Newly diagnosed patients with any chronic disease at admission or suffering from a respiratory bacterial infection and under an antibiotic medication were excluded from the study. In addition, patients on aspirin or any anticoagulant medication were exempt.

Eligible COVID-19 cases were categorized into two groups based on whether or not they had a history of chronic disease history: comorbid group (case group; with pre-existing chronic diseases such as hypertension, diabetes mellitus, both diabetes mellitus and hypertension, and other chronic diseases) and the non-comorbid group (control group; without a history of any chronic diseases).

COVID-19 participants were categorized into two groups according to the presence or absence of chronic disease history: the comorbid group (case group; with pre-existing chronic diseases such as hypertension, diabetes mellitus, both diabetes mellitus and hypertension, and other chronic diseases) and the non-comorbid group (control group; without a history of any chronic diseases). COVID-19 severity was classified based on WHO guidelines into mild, moderate, severe, and critical (World Health 2020).

Laboratory blood data were collected retrospectively according to the patients' medical records. The collected laboratory biomarkers were Complete Blood Count (CBC), D-dimer, LDH, and CRP, which were drawn in EDTA tube, Sodium Citrate tube, and Lithium Heparin, respectively. These parameters are reported as mean with ± standard deviation (SD) for each group. After that, the results were compared between the two groups at admission and 10 days after treatment using non-paired *t*-tests. The parametric paired t-test performed the comparisons between the blood results within the same group. On the other hand, the chi-square test was used to compare the severity of disease among the two groups. The SPSS version 19 (SPSS, Chicago, IL) for Windows was used to analyze the data, and the statistically significant is considered when *P* value <0.05.

RESULTS

A total of 270 patients who were COVID-19 positive were divided into control and case groups. In the control group, 125 were enrolled, and 54% had mild and moderate clinical symptoms. The case group was composed of 145 patients with chronic diseases, and 47% had severe and critical clinical manifestations (Figure 1). The chi-square test showed a significant association between the two groups at the point of disease severity ($P < 0.005$). Furthermore, obesity was linked to a 2.5-fold increased risk of developing an adverse condition of COVID-19 (Table 1). Hypertension with diabetes mellitus, hypertension with other chronic diseases and hypertension alone were allied with a high risk of developing severe COVID-19, with ORs of 1.55, 1.14, and 1.15, respectively.

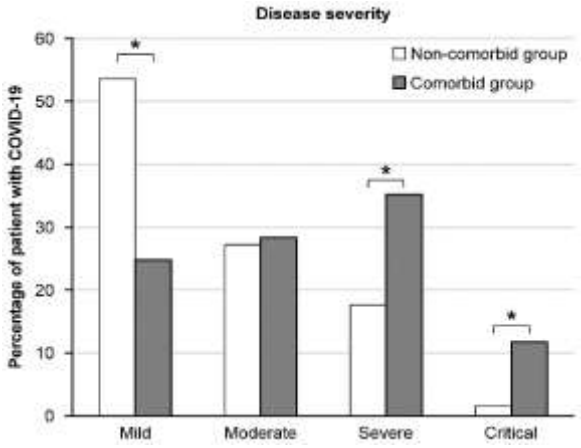

Figure 1: The distribution of COVID-19 cases according to the severity of disease among the control and case groups. * *P* value is <0.05

According to the hematological covariates at admission, both groups had normal RBC count and hemoglobin levels. However, the case group had lower levels of RBCs and hemoglobin than the control group ($P = 0.012$, $P < 0.005$, respectively) (Table 2). In addition, the total and differential WBC counts were not significantly different between the two groups at admission (Table 2).

Table 1: Distribution of chronic diseases in the comorbid group according to clinical severity.

Clinical Diagnosis	Number of cases (n = 145)	Percentage	Mild (Median age in years)	Moderate (Median age in years)	Severe (Median age in years)	Critical (Median age in years)	OR	95% CI:
Lung and Respiratory Disease	12	8.28	4 (37)	4 (43.5)	2 (53.5)	2 (56.5)	0.54	0.1548–1.8768
Cardiac Disease	2	1.38	0	1 (45)	0	1 (38)	1.13	0.0696–18.4911
Diabetes Mellitus	32	22.07	11 (44)	7 (45)	9 (52)	5 (55)	0.85	0.3857–1.8724
Diabetes Mellitus + Other Chronic Disease	9	6.21	2 (32.5)	3 (53)	3 (43)	1 (58)	0.90	0.2316–3.4969
Hypertension	14	9.66	5 (55)	2 (57.5)	6 (65)	1 (54)	1.15	0.3810–3.4560
Hypertension + Other Chronic Diseases	10	6.90	0	5 (65)	5 (64)	0	1.14	0.3162–4.1306
Hypertension, Diabetes Mellitus	54	37.24	12 (59)	13 (58)	23 (65)	6 (68.5)	1.55	0.7858–3.0442
Hypertension, Obesity	2	1.38	0	2 (39)	0	0	0.22	0.0104–4.6732
Obesity	3	2.07	0	1 (38)	2 (37.5)	0	2.30	0.2042–25.9786
Others*	7	4.83	2 (32)	3 (44)	1 (80)	1 (56)	0.44	0.0819–2.3262

The OR describes the strength of severity of chronic diseases listed above.

*****Breast cancer, celiac disease, systemic lupus erythematosus, chronic kidney disease, hyperthyroidism, hypothyroidism, solitary kidney, isolated thrombocytopenia, and dyslipidemia. CI, confidence interval; OR, odds ratio.

Table 2: Comparison of laboratory results between the non-comorbid (control) and comorbid (case) groups at admission and after treatment.

#	Laboratory Parameters	At Admission			10 days after treatment		
		Control Group	Case Group	*P* value	Control Group	Case Group	*P* value
		Mean (±SD)	Mean (±SD)		Mean (±SD)	Mean (±SD)	
1	**Hemoglobin, mg/dL**	14.08 (±1.64) **(n = 125)**	13.23 (±1.82) **(n = 145)**	**<0.005***	13.92 (±1.49) **(n = 26)**	12.34 (±2.36) **(n = 67)**	**0.002***
2	**RBC count × 10^6/μL**	5.00 (±0.55) **(n = 125)**	4.80 (±0.69) **(n = 145)**	**0.012***	4.90 (±0.60) **(n = 26)**	4.70 (±0.92) **(n = 67)**	0.298
3	**WBC count × 10^3/μL**	6.33 (±2.68) **(n = 125)**	6.77 (±3.23) **(n = 145)**	0.230	8.33 (±3.66) **(n = 28)**	8.84 (±4.75) **(n = 67)**	0.613
4	**Neutrophils × 10^3/μL**	4.23 (±2.48) **(n = 125)**	4.66 (±3.00) **(n = 145)**	0.208	5.96 (±3.79) **(n = 28)**	6.47 (±4.55) **(n = 67)**	0.601
5	**Monocytes × 10^3/μL**	0.52 (±0.31) **(n = 125)**	0.62 (±0.93) **(n = 145)**	0.267	0.56 (±0.20) **(n = 28)**	0.54 (±0.35) **(n = 67)**	0.854
6	**Lymphocytes × 10^3/μL**	1.45 (±0.68) **(n = 125)**	1.30 (±0.55) **(n = 145)**	**0.027***	1.96 (±0.86) **(n = 28)**	1.64 (±1.48) **(n = 67)**	0.302
7	**Platelet count × 10^3/μL**	229.21 (±76.95) **(n = 125)**	221.46 (±84.63) **(n = 145)**	0.435	354.46 (±127.68) **(n = 28)**	278.51 (±123.50) **(n = 66)**	**0.008***
8	**D-dimer, mg/L**	0.66 (±0.59) **(n = 77)**	1.88 (±5.30) **(n = 104)**	**0.047***	1.02 (±1.33) **(n = 6)**	1.73 (±3.46) **(n = 20)**	0.628
9	**LDH, U/L**	347.90 (±147.98) **(n = 77)**	369.70 (±174.64) **(n = 116)**	0.254	323.00 (±49.40) **(n = 6)**	452.60 (±260.76) **(n = 20)**	0.244
10	**CRP, mg/L**	25.77 (±31.54) **(n = 119)**	64.25 (±72.30) **(n = 131)**	**<0.005***	5.29 (±5.65) **(n = 12)**	15.38 (±13.45) **(n = 32)**	**0.016***

*The *P* value represents the statistical significance between the mean values of the two groups.

However, both groups showed lymphocytopenia, with significantly lower WBC levels in the case group than in the control group (P = 0.027). Meanwhile, D-dimer and CRP levels were higher in the case group than in the control group (P = 0.047 and P < 0.005, respectively) (Table 2). After treatment, the hemoglobin level, platelet count, and CRP levels were significantly different between the two groups (Table 2). The mean CRP value was within the normal range in the control group, but it increased above the normal range with a significant reduction in the case group after treatment (P < 0.005).

In the control group, the hematological laboratory results at admission and after treatment showed significant improvement in the total WBC, neutrophil, lymphocyte, and platelet counts (P < 0.005, P = 0.043, P < 0.005, and P < 0.005, respectively). The CRP returned to normal and reached 5.29 mg/L after treatment (P = 0.016). In the case group, the total WBC, neutrophil, and platelet counts had also improved after treatment (P < 0.005); despite that the improvement in lymphocyte count was not significant, the level was slightly increased from 1.5×10^3/µL to 1.6×10^3/µL.

DISCUSSION

Patients with chronic disease were more likely to be in severe and critical conditions than those without any pre-existing chronic disease based on data collected from hospitalized COVID-19 patients during the first wave of the pandemic. Patients with a history of chronic diseases, such as diabetes mellitus and hypertension, had a higher median age. However, the overall median age of our participants was 49 years, which is lower than that reported in other studies conducted in Spain, Italy, and the UK (Chen et al. 2020) (Han et al. 2020) (Spiezia et al. 2020). In Saudi Arabia, around 4.2% of the population is at 60 years, which could explain the difference between the other populations. Our study demonstrated that advanced age people with chronic diseases were more likely to experience adverse symptoms of COVID-19, similar to other studies conducted in Spain, the UK, and Italy (Borobia et al. 2020) (Docherty et al. 2020) (Livingston and Bucher 2020). Furthermore, our study showed that hypertension, diabetes and obesity were associated with high rates of serious conditions of COVID-19, while in the US, UK, and China, obesity and cardiac disease are the most common predictors of hospitalization (Cai et al. 2020) (Docherty et al. 2020) (Petrilli et al. 2020). For example, in a study conducted on Chinese patients, obesity increases the risk of developing severe pneumonia by 2.42-fold (Cai et al. 2020).

However, the pathologic mechanism of hypertension and obesity in COVID-19 severity remains unclear. Nonetheless, researchers have proposed that patients with obesity had an altered respiratory system because of fat formation in the mediastinum and abdomen, leading to a loss in chest elasticity, respiratory muscle weakening, and diaphragm excursion reduction, followed by attenuated gas exchange and surfactant dysfunction (Aghili et al. 2021). The immune system in patients with obesity is also disrupted through imbalanced mediation caused by the increased release of cytokines and adipokines. As a result, the pro-inflammatory state is over-activated, and the cytokines accumulate, leading to vascular hyper-permeability and multi-organ failure (Aghili et al. 2021). Regarding hypertension, the coronaviruses have more affinity to alveolar epithelial cells in patients taking angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (Kuster et al. 2020).

In our study, laboratory tests such as CBC, D-dimer, CRP, and LDH, which are inexpensive, could predict the severity of COVID-19 patients with or without pre-existing chronic diseases. At admission, the RBC count, lymphocyte count, D-dimer level, and CRP level were significantly different between the control and case groups. Although both groups had normal hemoglobin levels, the case group was 4% lower than the control group. A previous study classified patients with COVID-19 into three groups according to disease severity; the hemoglobin level was within the normal range, but the level in severe cases was 3% lower than that in mild and moderate cases (Wan et al. 2020).

Generally, anemia of chronic disease (ACD) is related to an immune or inflammatory response that disrupts the regulation of iron metabolism (Madu and Ughasoro 2017). In ACD, erythropoiesis decreases when cytokines such as IL-6 inhibits TNF and induces ferritin formation, accumulate (Kumar and Bhoi 2016). Ferritin increase leads to iron storage increase through the upregulation of hepcidin, which is a small peptide involved in iron trafficking (Banchini et al. 2020). In COVID-19 pathogenesis, disease severity is linked with inflammatory response activation (“cytokine storm”), which increases the IL-6 level. Consequently, the IL-6 activates hepcidin production, thereby increasing the ferritin level and reducing the production of erythrocytes (Banchini et al. 2020) (Banchini et al. 2021). This pathway could explain the elevated level of ferritin in the comorbid group.

Moreover, lymphocytopenia occurred in both groups, consistent with previous studies reporting a positive correlation between lymphocytopenia and COVID-19 (Huang et al. 2020) (Terpos et al. 2020). In our research, the degree of lymphocytopenia was reported to be lower in the case group than in the control group. This observation is similar to other studies that found that 72% of severe cases or patients requiring ICU support had a lower lymphocyte count than mild cases or those patients in the isolated room (Chen et al. 2020) (Fan et al. 2020) (Yang et al. 2020). However, we found that the lymphocyte count was increased significantly in the control group but in the case group was mildly elevated, possibly because of the risk stratification of COVID-19 among these patients.

Patients with ARDS have a significantly high level of

CRP, which is linked to adverse COVID-19 prognosis (Poggiali et al. 2020) (Wu et al. 2020) (Zhu et al. 2020). D-dimer and CRP levels were also high in the case group (64% and 60%, respectively), indicating that severe COVID-19 is associated with increased inflammatory response, leading to pro-coagulant pathway activation and thrombin formation. Subsequently, vascular endothelial and endothelial injuries occur, leading to severe clinical symptoms of the disease.

The other hematological and biochemical laboratory results were not significantly different between the control and case groups. However, the LDH level was slightly increased in the case group than in the control group. LDH as an inflammatory marker is an enzyme involved in glycolysis pathway that produces adenosine triphosphate (ATP) by converting lactate into pyruvate. It has been reported to increase acute and chronic damage in COVID-19; LDH and CRP levels correlate with P_cO_2/F_iO_2 value (Poggiali et al. 2020).

This study has some limitations. Considering that our data were collected retrospectively, some laboratory tests were not performed. These tests could have strengthened and consolidated our findings in determining disease severity. Among these tests are fibrinogen, ferritin, and IL-6 levels, which were unexploited in this study and could possibly support disease risk. In addition, the correlation of hematological and biochemical laboratory results at admission and throughout the treatment period was not examined because of the insufficient sample size.

CONCLUSION

COVID-19 patients with pre-existing chronic diseases are more likely to have adverse clinical symptoms. The RBC count, D-dimer, and CRP are the main parameters showing a significant difference between patients with and without chronic diseases. Lymphocytopenia was observed in both study groups, but it was more evident in the case group. These laboratory results could be helpful in determining disease severity and could serve as a guide when introducing an anti-inflammatory agent to the standard protocol to minimize cytokine storm.

CONFLICT OF INTEREST

The authors declared that the present study was performed without any conflict of interest.

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AUTHOR CONTRIBUTIONS

Haitham Qutob is the sole owner who meets the authorship criteria listed as the author who developed the study, including the concept, design, analysis, writing, and manuscript revision. The author read and approved the final version.

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