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Clinical laboratory parameters and comorbidities associated with severity of coronavirus disease 2019 (COVID-19) in Kurdistan Region of Iraq

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ABSTRACT

Background: The pandemic coronavirus disease (COVID-19) dramatically spread worldwide. Considering several laboratory parameters and comorbidities may facilitate the assessment of disease severity. Early recognition of disease progression associated with severe cases of COVID-19 is essential for timely patient triaging. Our study investigated the characteristics and role of laboratory results and comorbidities in the progression and severity of COVID-19 cases.

Methods: The study was conducted from early-June to mid-August 2020. Blood samples and clinical data were taken from 322 patients diagnosed with COVID-19 at Qala Hospital, Kalar, Kurdistan Region of Iraq. Biological markers used in this study include complete blood count (CBC), D-dimer, erythrocyte sedimentation rate (ESR), serum ferritin, blood sugar, C-reactive protein (CRP) and SpO2.

Results: The sample included 154 males (47.8%) and 168 females (52.2%). Most females were in the mild and moderate symptom groups, while males developed more severe symptoms. Regarding comorbidities, diabetes mellitus was considered the greatest risk factor for increasing the severity of COVID-19 symptoms. As for biological parameters, WBC, granulocytes, ESR, Ferritin, CRP and D-Dimer were elevated significantly corresponding to the severity of the disease, while lymphocytes and SpO2 showed the opposite pattern. Higher RBC was significantly associated with COVID-19 severity, especially in females.

Conclusion: Gender, age and diabetes mellitus are important prognostic risk factors associated with severity and mortality of COVID-19. Relative to non-severe COVID-19, severe cases are characterized by an increase of most biological markers. These markers could be used to recognize severe cases and to monitor the clinical course of COVID-19.

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1. Introduction

Currently, the novel coronavirus disease (COVID-19) has affected more than 223 countries, territories and regions around the world. As of first of June 2022, more than 528 million people (2,328,264 people in Iraq) have been infected and nearly 6.3 million have died including 25,219 in Iraq [1]. Based on clinical symptoms and laboratory test results, patients are categorized as mild, moderate, severe, and critical cases [2,3]. The clinical symptoms of patients with mild COVID-19 include fever, fatigue, dry cough and myalgia, while moderate cases also display dyspnea and pneumonia. In severe cases, affected patients may experience acute respiratory failure, multiorgan and systemic dysfunctions in terms of sepsis and septic shock failure that in critical cases might culminate in death [2,4–6]. Most affected patients (81%) suffer from mild to moderate cases. Severe and critical cases comprise 14% and 5% of infected cases, respectively, and require hospitalization [7].

The use of biological markers (biomarkers) allows more confident interpretation of the progression of the disease [8]. Thus, instant identification of clinical laboratory predictors of disease progression is urgently needed for clinicians to be able to stratify risks, distinguish and differentiate severe cases from mild to moderate ones, follow-up patients, and guide treatment and therapeutic monitoring [9,10].

Since the COVID-19 pandemic outbreak, a vast number of studies have investigated laboratory changes in confirmed COVID-19 patients. However, the association between routine laboratory tests and disease severity has received less attention [9,11,12]. A large number of confirmed COVID-19 patients have shown laboratory fluctuations in complete blood count (CBC) variables, coagulation parameters, and inflammation-related factors [13,14].

Laboratory findings in COVID-19 patients also may include lymphopenia and elevated levels of white blood cells (WBCs), erythrocyte sedimentation rate (ESR), d-dimer, C-reactive protein, and ferritin [15–19].

This article explores the role of different biomarkers in the disease prognosis of COVID-19 and assesses variations in their levels depending on the severity of the disease. By doing so, it gives clinicians a tool to group patients and predict prognosis and mortality. These biomarkers include WBCs, lymphocytes, granulocytes, platelets, RBCs, CRP, D-dimers, ESR, serum Ferritin, and SpO2.

2. Materials and methods

2.1. Study design and patients

This cross-sectional study was conducted from early-June to mid-August 2020. Blood samples and clinical data were taken from 322 patients (154 males and 168 females) diagnosed with COVID-19 at Qala Hospital, Kalar Kurdistan Region, Iraq.

2.2. Laboratory tests

Laboratory testing for SARS-CoV-2 infection was done by using reverse transcription-polymerase chain reaction (RT-PCR). A nasopharyngeal swab sample was collected for extracting viral RNA. After collection, the total RNA was automatically extracted within 45 min using the Qiagen EZ1 Advanced XL system (Qiagen, Hilden, Germany). Then, the presence of SARS-CoV-2 was detected by real-time RT-PCR amplification of SARS-CoV-2 open reading frame 1 ab (ORF1ab) and envelope (E) genes fragments using Power Chek SARS-CoV-2 Real-Time PCR Kit (Kogenebiotech, Seoul, Korea) [20].

The biological markers examined in this study included CBC, D-dimer, ESR, serum ferritin, blood sugar, and CRP. The CBC was primarily performed using a Medonic M-Series hematology analyzer (Medonic M32, Boule Medical AB, Stockholm, Sweden). Biochemistry tests were conducted on an automated multiparametric analyzer Cobas C111 (Roche Diagnostics, Mannheim, Germany). Ferritin levels were measured with Roche Elecsys 2010 (Roche Diagnostics, Mannheim, Germany) and ESR was tested by the Westergren method [21].

2.3. COVID-19 severity case category

The clinical classification of patients was based primarily on the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7) developed by the National Health Committee of the People's Republic of China [National Health Commission of the People's Republic of China home page. Available from: http://www.nhc.gov.cn [22]. Classifications are characterized as follows [1]: mild type: only mild clinical symptoms with no sign of pneumonia in imaging features [2]; moderate type: complicated with fever, respiratory symptoms and imaging features of pneumonia [3]; severe type: complicated with any of the following: respiratory distress; respiratory rate $\geq$30 beats/min, mean oxygen saturation $\leq$93% at rest, or ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO2:FiO2) $\leq$ 300 mmHg (1 mmHg = 0.133 kPa).

2.4. Ethics declarations

All methods were carried out in accordance with relevant guidelines and regulations. We confirm that all experimental protocols were approved by the Ethics Licensing Committee of the Kalar Technical Institute at the Sulaimani Polytechnic University (No. 02 on June 02, 2020). In addition, informed consent was obtained from all participants or from a parent or legal guardian if participants were under the age of 18.

2.5. Statistical analysis

Pearson correlations, polynomial regressions and ANOVA tests were employed to investigate the relationships between different parameters among the mild, moderate and severe groups.

3. Results

The study population consisted of 322 COVID-19 confirmed patients. The median age was 47 years with a range of 11–91 years, with 154 (47.8%) male and 168 (52.2%) female participants. Fig. 1A shows that mild symptoms were more frequent in females, while male were more likely to develop severe symptoms. Patients in the under-17 age group had the lowest number of cases, and no severe cases. The majority of patients in the 18–34 years age group were mild cases. Patients over 70 years of age had more severe cases relative to other age groups (Fig. 1B).

Of the 322 patients, 287 (89.1%) were non-smokers and 35 (10.9%) were smokers. This study illustrates that COVID-19 cases at all levels of severity spread more numerously among non-smoker in comparison to smokers (Fig. 2).

Diabetic patients were more likely to show severe symptoms, while no hypothyrodic patients showed severe symptoms. Hypertension had a synergistic effect when paired with diabetes on increasing the severity of symptoms. Slightly more than half of patients with no comorbidities had mild symptoms (Fig. 3).

In all COVID-19 patients, regardless of case severity, we found a strong positive correlation ($R2 = 0.88$ in mild, 0.91 in moderate and 0.94 in severe) between total white blood cells (WBC) and granulocyte cell number. We also found a significant correlation ($R2 = 0.77$ in mild, 0.61 in moderate and 0.76 in severe) between the total number of red blood cells (RBC) and hematocrit level. Patients with mild symptoms exhibited a significant correlation ($R2 = 0.67$) between the total number of WBC and lymphocytes. In patients with moderate symptoms, an increase in CRP was correlated positively ($R2 = 0.66$) with an increase of ESR (Supplementary - 1).

Our study found that WBC count, including granulocytes, was elevated significantly ($p < 0.001$) with the severity of disease, while lymphocyte numbers decreased in the severe group (1.5×10^9 cells/liter) in comparison with the mild (2.0) and moderate (1.8) groups ($p = 0.01$) (Fig. 4A).

The scatter plot in Fig. 5 shows the follow up of the main parameters for all COVID-19 symptomatic patients (mild, moderate, and

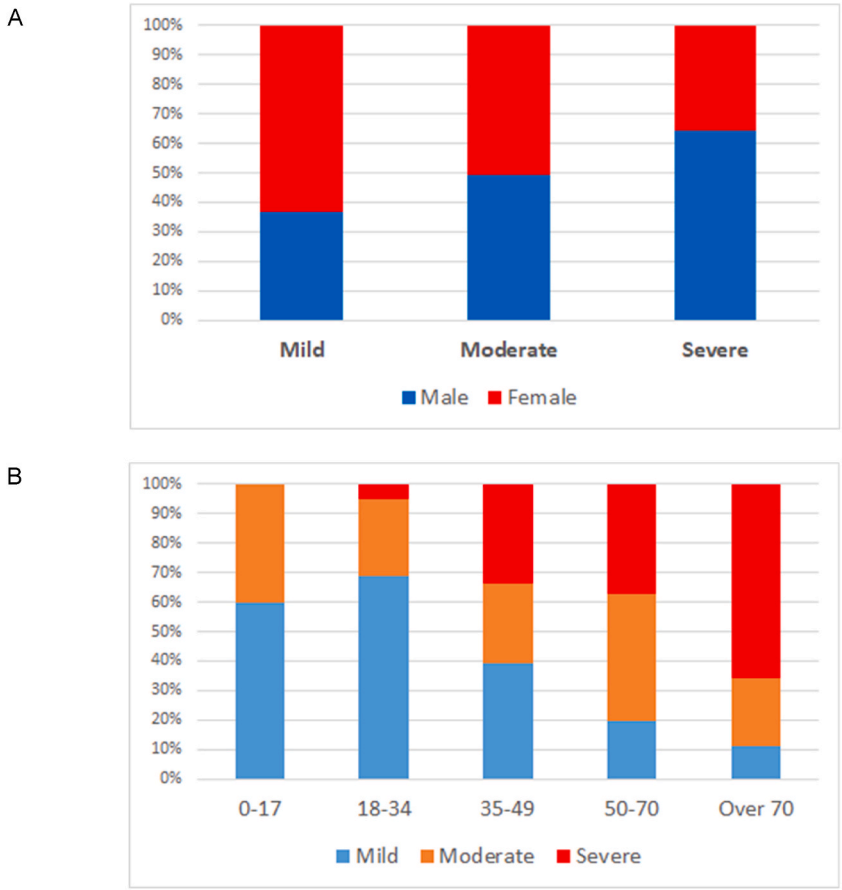

Fig. 1. Distribution of COVID-19 severity (mild, moderate, severe) in patients by gender (A) and age (B).

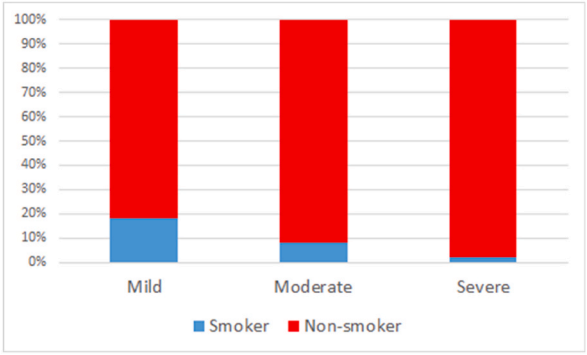

Fig. 2. Smoking behavior and severity of COVID-19 symptoms.

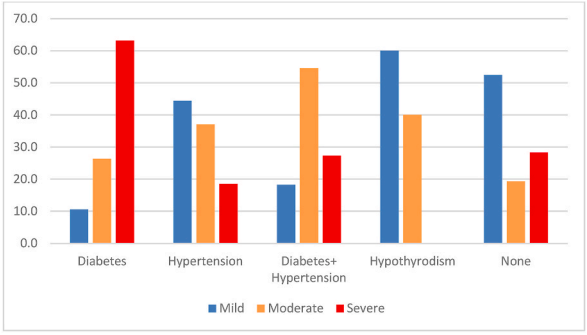

Fig. 3. Patient comorbidity and level of severity of symptoms.

severe) across symptomatic days. We found that ESR, ferritin, CRP, D-Dimer, WBC and granulocyte were increasingly elevated with symptomatic dates, reaching a maximum on day 15 then declining. An exception was ESR, which continued increasing. However, SpO2 steadily decreased until day 20. In addition, lymphocytes fluctuated, reaching a minimum (1.6) on day 15 and then increasing to reach a maximum (1.9) on day 20.

The RBC level in severe cases was higher relative to mild and moderate cases; this difference was significant in female cases ($p = 0.02$) (Fig. 6).

A schematic key diagram in Fig. 7 illustrates the vital role of SpO2 in the direction of the COVID-19 patient symptoms. Patients with SpO2 levels greater than 93 were most likely to be classified as moderate or mild cases. In the same groups (moderate/mild, SpO2 >93), the symptomatic date can be a crucial parameter to determine the severity of the cases for patients with CRP >59.73. When the symptomatic date is less than 5 days, symptoms are likely to be mild; when the symptomatic date is longer than 5 days, symptoms may become moderate. However, when CRP <59.73, WBC can indicate the severity of the cases (WBC >11.1 = moderate). When WBC is below 11.1, and granulocyte number is higher than 2.7 and/or D-dimer is less than 220, the patient's case can be considered mild. If D-dimer is greater than 220, the patient's case is categorized as moderate.

All cases with SpO2 level under 91 are treated as severe cases, but when the level of SpO2 is between 91 and 93, the combined red blood cell count and D-dimer can indicate severe cases (RBC >5.57, D-dimer > 630). Otherwise, when D-dimer is less than 630, the CRP level determines whether cases are considered severe (CRP >103.3) or moderate (CRP <103.3).

4. Discussion

Identifying risk factors associated with poor patient outcomes will help appropriate resource allocation and patient management during the COVID-19 pandemic. In the early stages of the pandemic, clinical characteristics such as patient's age and presence of comorbidities were suggested as predictive factors for patient outcomes [22,23].

The pandemic is having enormous health, social and economic impacts which could continue for months and possibly years to come. Several studies have examined gender differences in relation to the disease's severity and fatality [5,24]. Our study found that males were 1.8 times more likely to develop severe symptoms than females. This increased risk could possibly be due to differences between male's and female's innate and adaptive immune responses, such as the effect of sex-specific inflammatory responses from X-chromosomal inheritance, which contain immune-related genes [25]. Other studies have suggested males have a higher level of ACE2 [26]. Additionally, age can be considered a risk factor that increases the severity of COVID-19 symptoms. Younger people are less likely to develop severe symptoms [27], while older people are prone to develop severe symptoms. In older people, viral alert signals

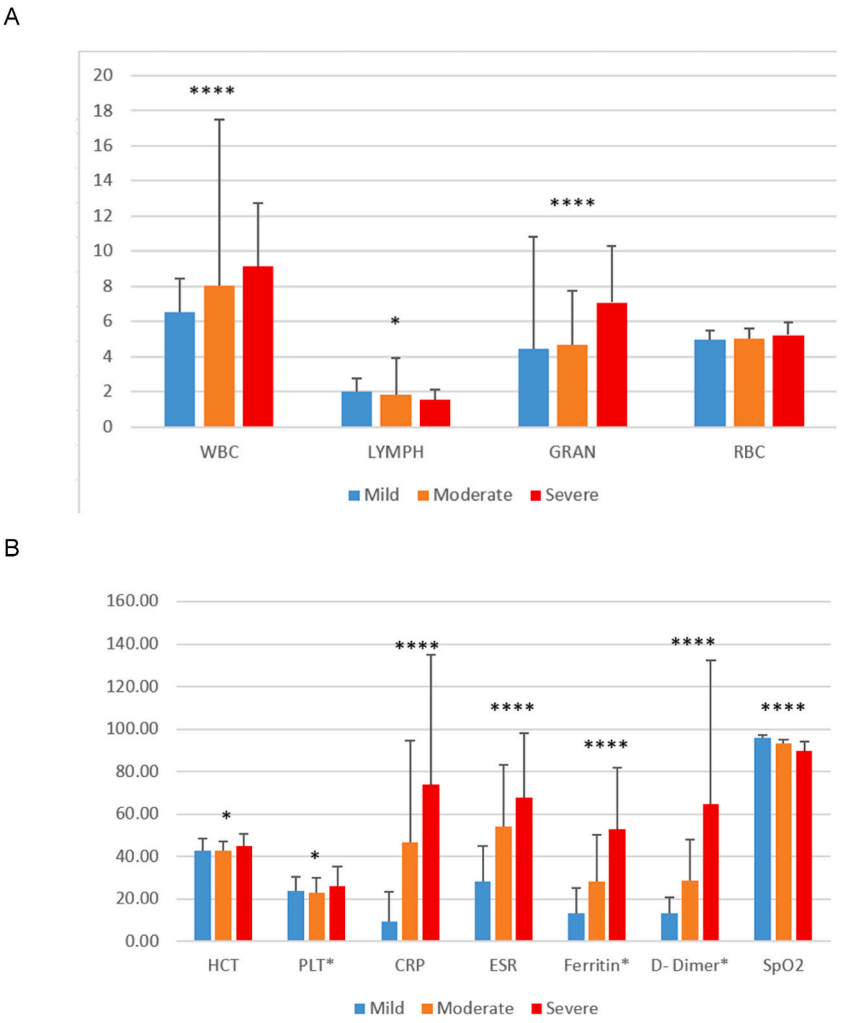

Fig. 4. Values of parameters in different severity groups. **A**. WBC (x10^9 cells/liter) ($p < 0.001$); LYMPH, lymphocyte (x10^9 cells/liter) ($p = 0.01$); GRAN, granulocyte (x10^9 cells/liter) ($p < 0.001$); RBC, red blood cell (x10^{12} cells/liter). **B.** HCT, hematocrit (%) ($p = 0.01$); PLT, platelet (x10^{10} cells/liter) ($p = 0.01$); CRP, C-reactive protein (gm/L) ($p < 0.001$); ESR, erythrocyte sedimentation rate (mm/hour) ($p < 0.001$); Ferritin (x10 ng/ml) ($p < 0.001$); D-Dimer (x10 ng/ml) ($p < 0.001$); SpO_2 (%) ($p < 0.001$). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

and immune responses (immune senescence) are significantly slower and the number of specific immune cells decrease, allowing the virus to replicate at a higher level [28]. Another study reported that changes in lung anatomy and muscle atrophy in the aged population can affect physiological function and reduce lung reserve and airway clearance [29]. Finally, studies have shown that the immune cross-protection from other coronaviruses or nonspecific protection from other respiratory viruses occurs more frequently in children than other age groups [27].

Regardless of the ratio of smokers to nonsmokers in the studied population, the current study found that smokers were least represented in severe cases and highest in mild cases. Results of a preliminary meta-analysis based on Chinese patients suggest that active smoking does not seem to be significantly associated with increased risk of progression toward severe disease in COVID-19 [30]. However, other studies reported that smoking was clearly associated with the severity of COVID-19 symptoms [31,32].

Comorbidities also have been reported to be associated with the severity of COVID-19 progression. Cardiovascular conditions have been reported to be related to poor condition in COVID-19 patients [33]. In particular, hypertension has been shown to increase the risk of the severity of the disease [34]. This effect may possibly be due to the widely used antihypertensive treatment (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) by this group which can increase ACE2 expression [35]. In general, diabetic patients are at risk of increasing infection because of defects of their innate immune system. Individuals with type-2 diabetes may develop secondary diseases such as cardiovascular disease and homeostasis dysfunction, which lead to more severe symptoms and fatality outcomes in COVID-19 [36]. Accordingly, we found that patients with both hypertension and type-2 diabetes were more likely to develop severe symptoms.

Our study found no severe COVID-19 cases among hypothyroid patients. Similarly, a retrospective cohort study showed that

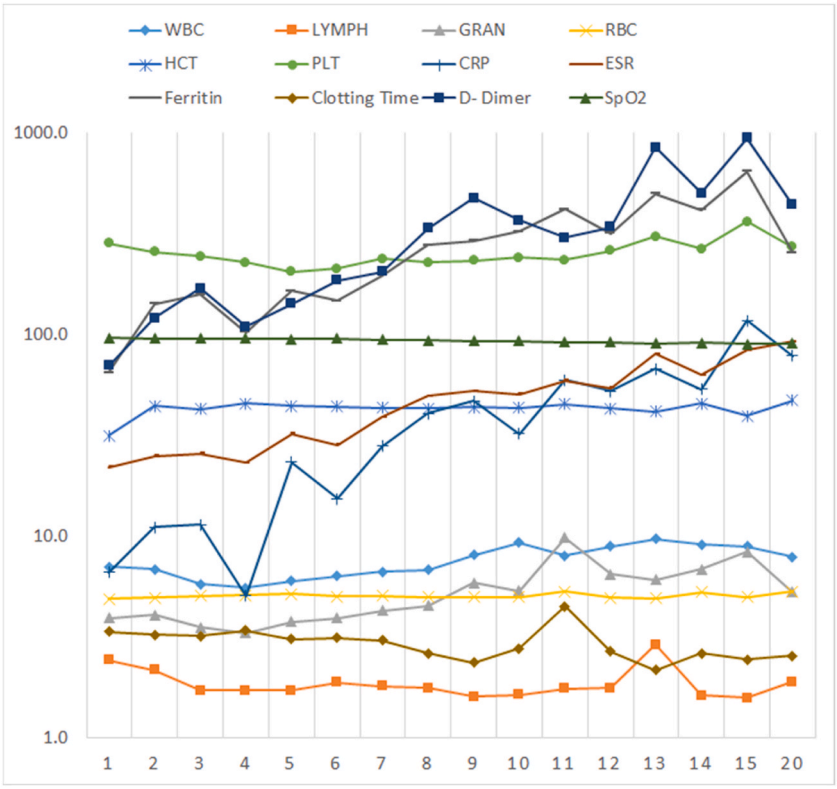

Fig. 5. Scatter plot of blood parameters (Y axis) and symptomatic date in days (X axis). ESR, erythrocyte sedimentation rate (mm/hour); Ferritin (ng/ml); CRP, C-reactive protein (gm/L); D-dimer (ng/ml); SpO_2 (%); WBC ($x10^9$ cells/liter); GRAN, granulocyte ($x10^9$ cells/liter); LYMPH, lymphocyte ($x10^9$ cells/liter).

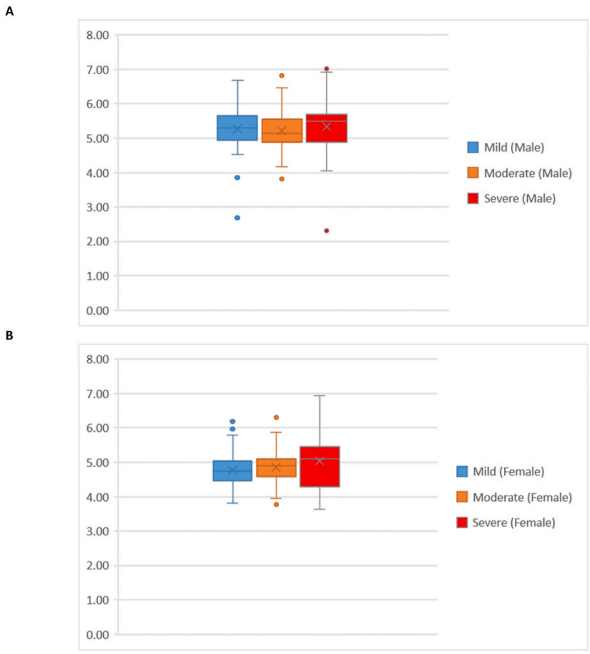

Fig. 6. Box and whisker graph of RBC (red blood cell ($x10^{12}$ cells/liter) levels by gender in different severity groups in male (A) and female (B) COVID-19 patients (*$p = 0.02$)AA. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

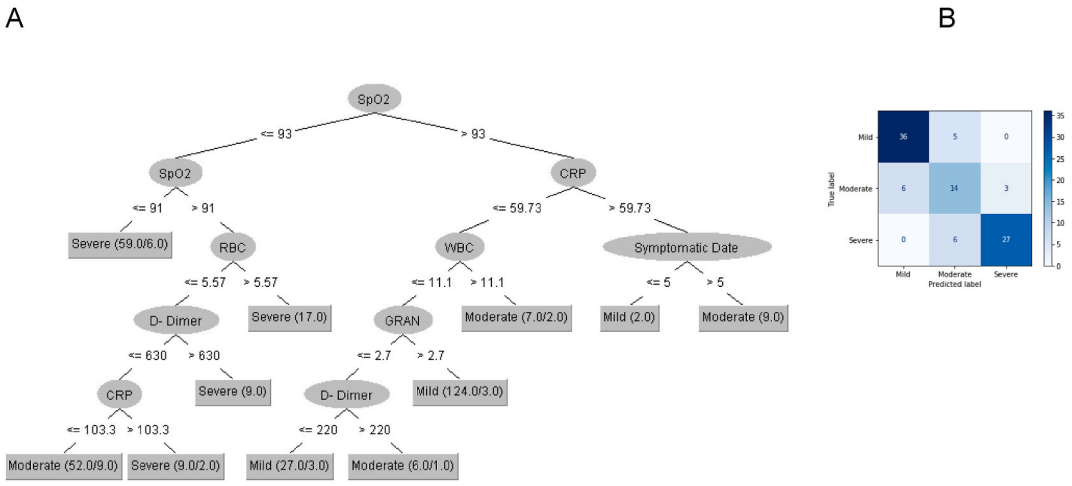

Fig. 7. A. Schematic diagram of blood parameters in relation to severity of COVID-19 symptoms. B. Confusion Matrix–Truth Table depicting accuracy of COVID-19 case severity determinations based on the decision tree produced.

hypothyroidism was not associated with increased risk of COVID-19-related hospitalization or worse outcomes [37]. However, another study showed that excess or deficient thyroid hormone levels observed in thyroid disease lead to dysregulation of the innate immune response. Additionally, innate immune responses were thought to be the greatest contributor in the pathogenesis of COVID-19, as they are the frontlines of the body defense system to fight SARS-CoV-2, the virus responsible for COVID-19 infection [38].

Biomarkers are used clinically in studies as quantitative measurements to reflect pathological progress. Physicians can benefit from using biomarkers to assess patients with COVID-19 infections to prescribe treatment and close monitoring [39]. In this study, CRP, SpO2, D-dimer, WBC and granulocytes had the strongest relationships with severity of the disease. Levels of CRP usually begin low, as through acute inflammatory responses, then increase rapidly and significantly alone or in combination with other biomarkers, indicating bacterial or viral infection [40–42]. The role of CRP as a marker to differentiate the severity of COVID-19 infection has been demonstrated by studies conducted in China, in which severe cases commonly showed a higher level of CRP compared to non-severe cases. These studies suggest CRP levels are a strong indicator of the presence and severity of COVID-19 infection [42,43]. Our study explored the relationship between CRP and COVID-19 and found that patients with CRP >103.3 mg/L were more likely to develop severe disease.

The elevation of serum CRP level in patients with COVID-19 infection had been seen by other researchers in conjunction with elevation of other blood markers like D-dimer and ferritin [44]. Fig. 7 shows that D-dimer greater than 630 μg/L independently indicates severe cases. Studies have found an association between COVID-19 and haemostatic abnormalities [45]. A retrospective cohort study of 191 patients found that D-dimer levels >1000 ng/ml were associated with increased mortality among COVID-19 patients [46].

Serum ferritin is used as a clinical biomarker to assess depletion or overload of iron stores. However, ferritin also represents an acute-phase-protein that is upregulated and elevated in both infectious and non-infectious inflammation [47,48]. Our study demonstrated that ferritin is a strong biomarker for assessing the severity of COVID-19 infection; recently, several studies have reported that serum ferritin seems to be relevant for assessing disease severity and patient outcome [11,49]. Furthermore, a study found that elevated ferritin levels due to secondary hemophagocytic lymphohistiocytosis (sHLH) and cytokine storm syndrome have been reported in severe COVID-19 patients [50].

Another prognostic risk factor for case severity was SpO2 $\leq$ 91%. Similarly, other studies reported that SpO2 less than 90% with shortness of breath and respiratory rate of more than 30 per minute have been suggested as evidence of severe pneumonia in COVID-19 patients [51,52]. Low blood oxygen saturation has also been used to identify severe COVID-19 pneumonia in admitted patients [53]. In certain guidelines, this parameter has been used to identify high-risk patients who need hospital admission [54]. SpO2 has also previously been shown to be a valuable prognostic tool in community-acquired pneumonia with good specificity for poor outcome [55] based on our findings, patients with SpO2 $\leq$ 91% were considered severe cases.

Our study demonstrated that patients with high RBC are more prone to severe cases, especially in the second week of infection. Studies also showed that patients with polycythemia are deemed high-risk groups with or without a history of thrombosis. These patients with polycythemia are prone to develop thrombotic and sometimes bleeding complications [56,57]. In addition to an increase in total leukocyte, lymphopenia can be considered as a main haematological sign associated with the severity of the disease [58,59].

Generally, most of the studied parameters steadily return to recovery after 2 weeks of symptomatic dates. One exception is ESR, which continues to increase. This increase may possibly be due to low albumin level in severe cases, which have been reported to have a negative correlation with ESR in those patients ([60,61]).

5. Conclusion

Male patients were more likely to develop severe symptoms. Patients over 70, of both genders, were also more likely to develop severe symptoms. In addition, fewer patients with a history of smoking were observed in severe cases. Hematological markers such as WBC, granulocyte, ESR, ferritin and other markers, CRP and D-dimer were increased with the severity of the disease. SpO2 and lymphocyte decreased with the progression of the disease severity. Follow-up and evaluation of the parameters studied is vital to monitor and determine disease progression.

Author contribution

HNA contributed to data collection, KMA performed experiments, designed the study and wrote the manuscript, AMA performed experiments, HMR has contributed in the writing and data analysis. MHF and HMT have contributed to the manuscript preparation, GF has analyzed the data. All authors approved the final version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.plabm.2022.e00294.

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