Biochemical, Hematological, and Immunological Biomarkers as Predictors for Intensive Care Unit Admission in Patients with COVID-19

Zakariya Al Aamri[1]*, Fahad Zadjali[2], Nafila AL-Riyami[2], Feryal Al Lawati[3], Samata Al Dowaiki[3] and Manal Al Kindi[4]

[1]Clinical Biochemistry Residency Training Program, Oman Medical Specialty Board, Muscat, Oman

[2]Biochemistry Department, Sultan Qaboos University Hospital, Muscat, Oman

[3]Infectious Disease Department, Royal Hospital, Muscat, Oman

[4]Biochemistry Department, Royal Hospital, Muscat, Oman

***Received**: 11 December 2021*

***Accepted**: 24 May 2022*

**Corresponding author*: zakariya.alaamri@gmail.com

DOI 10.5001/omj.2022.99

Abstract

Objectives: To find out the biochemical, hematological, and immune biomarkers on admission that can predict intensive care unit (ICU) admission in patients with COVID-19.

Methods: This is a retrospective cohort study conducted on all confirmed COVID-19 cases hospitalized at Royal Hospital, Oman from February 24, 2020 to July 30, 2020. The demographic, clinical, and laboratory data were collected from the hospital information system. Patients were divided into two groups: non-intensive care unit (ICU) admitted group and ICU admitted group.

Results: Out of 445 patients, 276 (62.0%) were males and 169 (38.0%) were females; 259 (58.2%) patients were admitted to COVID-19 general wards whereas 186 (41.8%) were admitted to ICU. Admission to ICU was more likely when patient had following co-morbidities: diabetes (odds ratio (OR) = 1.84, 95% confidence interval (CI): 1.26–2.69), liver diseases (OR = 2.18, 95% CI: 1.10–4.3), and respiratory diseases (OR = 2.0, 95% CI: 1.1–3.7). Among ICU versus non-ICU patients, there were remarkable differences ($p < 0.001$) in on-admission laboratory blood/serum parameters: total white blood cells (WBC) count, lymphocytes count, C-reactive protein (CRP), ferritin, corrected calcium, interleukin 6, D-Dimer, alanine transaminase (ALT), lactate dehydrogenase (LDH), albumin, and troponin ($p < 0.050$).

Conclusions: The current study identified presence of the co-morbidities (i.e. diabetes, liver diseases and respiratory diseases) and on-admission changes in laboratory blood and serum parameters (i.e. WBC, lymphocytes, CRP, ferritin, corrected calcium, IL-6, D-diameter, ALT, LDH, albumin, and troponin) that are associated with ICU admission.

Keywords: COVID-19, progression, severity, Intensive Care Unit, prediction, biomarkers, risk factors

Introduction

Since the start of 2020, the world undergoes a great health burden as a consequence of Coronavirus disease 2019 (COVID-19) pandemic. The first case of COVID 19 was identified in December, 2019 in Wuhan, China and from there its spread continued to involve the whole globe.[1] The impact of the pandemic exceeded to affect multiple life aspects; politically, economically, socially, mentally and health services. The first two reported cases in Oman

were diagnosed on 24th of February, 2020. Since that time, the number of cases increased dramatically and accounted to be 389 thousand cases on April 2022 with a total number of around 4285 deaths.[2]

Coronavirus disease 2019 (COVID-19) is caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] There are seven coronavirus strains that are known to cause illness in human in which four of them (i.e. 229E, NL63, OC43, and HKU1) are associated with mild course of common cold but the other three strains (i.e. MERS-CoV, SARS-CoV, and SARS-CoV-2) are attributed to a severe disease.[3] SARS-CoV-2 is a single-stranded RNA virus that is characterized by its high transmission rate compared to other coronavirus family members.[4,5]

Clinical presentation of COVID-19 ranges from asymptomatic to a critical form of the disease. Depending on the clinical presentation, the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7) has classified COVID-19 cases into four categories; mild, moderate, severe and critical.[6] The severity and progression of COVID-19 is associated with multiple biomarkers changes including hematologic, biochemical, and immunological markers.[7-10] A metanalysis published by Henry et al.,[9] (2020) concluded that platelets count, white cell count (WCC), lymphocyte count, ferritin, and interleukin-6 levels predict the progression of COVID-19 cases to critical presentation. Furthermore, C-reactive protein (CRP), procalcitonin, cytokines, coagulation parameters, lactate dehydrogenase (LDH), liver enzymes, and cardiac biomarkers were studied as possible predictors for the disease progression & severity.[11-15] The current study aimed to identify possible predictors of intensive care admission for COVID-19 in a cohort of patients form Oman.

Method

Study Design

The study was approved by the Research and Ethical Review and Approve Committee (RERAC) at Royal Hospital-Ministry of Health (SRC#110/2020). Clinical data were retrospectively collected from all PCR-confirmed COVID 19 cases in a single tertiary hospital in Oman (Royal Hospital) from February 24th, 2020 to July 31st, 2020. Demographic information, clinical history details (i.e. signs, symptoms, contact history, radiographic findings, hospitalization duration and comorbidities), and laboratory investigations were collected. Laboratory data included complete blood count, coagulation parameters, liver profile, Lactate dehydrogenase (LDH), cardiac markers, and inflammatory markers. Data were collected on admission. Progression severity of COVID-19 was assessed by admission to intensive care units (ICU) based on clinical management of the patient. The ICU admission was based on oxygen peripheral saturation (SpO2) and/or dyspnea and/or mental confusion. To study predictors of COVID-19 severity, patients were categorized into ICU and non-ICU admission. The inclusion criteria include: 1) Adult and children with a confirmed diagnosis of COVID-19 by molecular tests. 2) Patients with available baseline clinical and laboratory data. The exclusion criteria include: Patients with primary or secondary immune deficiency.

Data Analysis

The data were analyzed using Statistical Package for the Social Sciences software version 25.0 (IBM, Chicago, IL). In the case of categorized variables, the chi-square test was used. The continuous variables follow the normal distribution pattern the ANOVA was used to compare means. Otherwise, Mann–Whitney U-test was used in the variables that do not follow the normal distribution. P-value <0.05 was considered significant. The predictability of studied variables was determined using receiver operating characteristic (ROC) curves followed by Youden index to identify the best predicting cut-off value of each biomarker.

Results

Demographic data of study population

Table 1 summarizes the demographics and other characteristics of the COVID-19 patients based on ICU admission. Out of 445 patients, 276 (62.0%) were males with a median age of 49 (18-87) years and 169 (38.0%) were females with a median age of 53 (15-94) years. Omani patients represented 55.7% (248 patients) of total study subjects. Of the patients in the study population, 46.1% had diabetes (DM), 46.7% had hypertension (HTN),

and 24% had dyslipidemia. In addition, 11% of patients reported respiratory problems, 18.4% cardiac problems, 8.3% liver disease and 20.2% chronic kidney disease (CKD).

Table 1: Demographics and characteristics of patients with COVID 19 admitted in non-ICU and ICU wards.

	Total	**Non-ICU**	**ICU**	**P-value**
N	445	259 (58.2%)	186 (41.8%)	
Gender				
Male	276 (62.0%)	152 (55.1%)	124 (44.9%)	NS
Female	169 (38.0%)	107 (63.3%)	62 (36.7%)	NS
Demographics				
Median Age (min.-max.)	51 (15-94)	51 (16-94)	50 (15-80)	NS
Omani Nationality	248 (55.7%)	186 (75%)	62 (25%)	<0.0001
Comorbidities				
Diabetes	205 (46.1%)	103 (50.2%)	102 (49.8%)	0.002
Hypertension	208 (46.7%)	123 (59.1%)	85 (40.9%)	NS
Dyslipidemias	107 (24%)	59 (55.1%)	48 (44.9%)	NS
Respiratory Disease	49 (11%)	21 (42.9%)	28 (57.1%)	0.031
Cardiac conditions	82 (18.4%)	45 (54.9%)	37 (45.1%)	NS
Liver disease	37 (8.3%)	15 (40.5%)	22 (59.5%)	0.035
Chronic Kidney Disease	90 (20.2%)	56 (62.2%)	34 (37.8%)	NS

**NS: Not significant*

Patients admitted to the intensive care unit (ICU) had a higher mortality at odds ratio (95% CI): 3.39 (2.0-5.6), sepsis 3.5 (1.6-7.4), intubation 31.2 (18.2-53.7), and Acute respiratory distress syndrome (ARDS) 41.57 (20.4-84.8), figure 1.

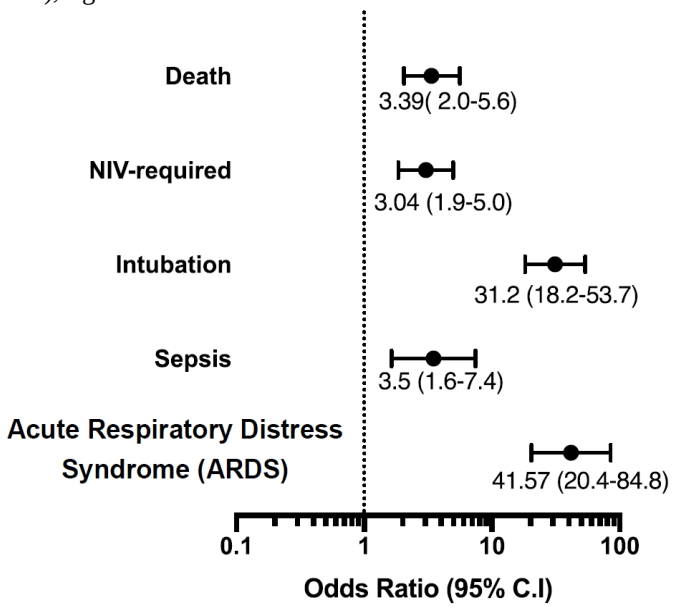

Figure 1: Complications associated with ICU admission with Odds Ratio (95% confidence interval) for each one.

On-admission factors associated with critical care admission in patients with COVID-19

Out of 445 patients, 259 patients (58.2%) were admitted into COVID-19 wards whereas 186 patients (41.8%) were admitted to ICU. Figure 2 summarizes the association of co-morbidities at the time of diagnosis upon admission to intensive care. Patients with liver diseases presented an odds ratio of 2.18 (95% C.I 1.10–4.3). Furthermore, the following patients were significantly more likely to be admitted to ICU: diabetes [1.84 (1.26–2.69)], and respiratory diseases [2.0 (1.1–3.7)]. In contrast, having hypertension, chronic kidney disease, cardiac conditions, and dyslipidaemia at diagnosis were not associated with a higher risk to be admitted to ICU.

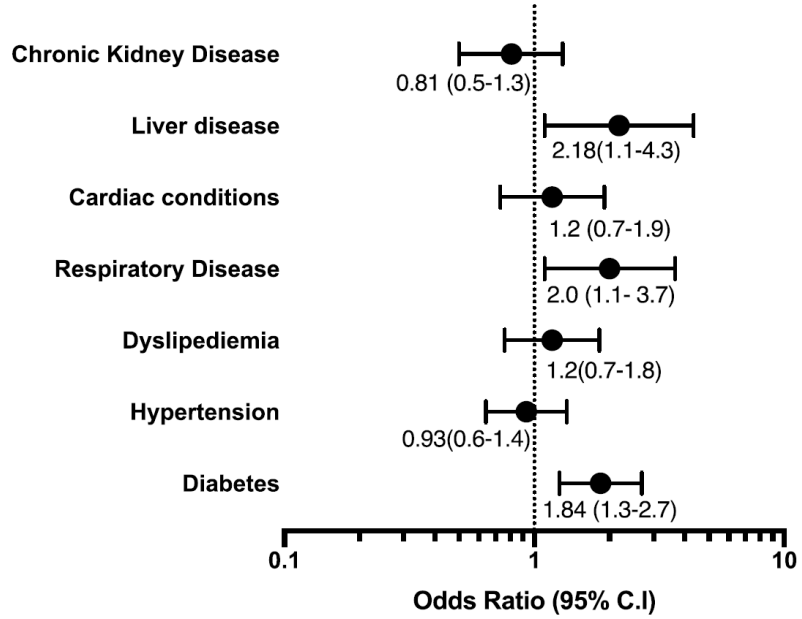

Figure 2: On admission comorbidities associated with ICU admission with Odds Ratio (95% confidence interval) for each comorbidity.

We then studied other patients' parameters that are associated with ICU admission in patients with COVID-19, Figure 3. The age of patients was not associated with ICU- admission (51+/-16 years vs 50+/-14 years). Longer hospital stay was significantly associated with ICU admission (8.3+/- 9.1 vs 17.5+/-12.9 days, P-value < 0.001), Figure 3. In addition, on admission high values of each of following parameters: white blood cell count (WCC), C-reactive protein (CRP), ferritin, IL-6, D-Dimer, ALT, LDH, and troponin were significantly associated with ICU admission ($p < 0.001$ for all parameters except troponin; $p < 0.050$). Furthermore, Low values for lymphocytes count, corrected calcium levels, and albumin were markedly associated with ICU admission ($p < 0.001$ for all three parameters), Figure 3. Levels of vitamin D in patients was not associated in ICU admission.

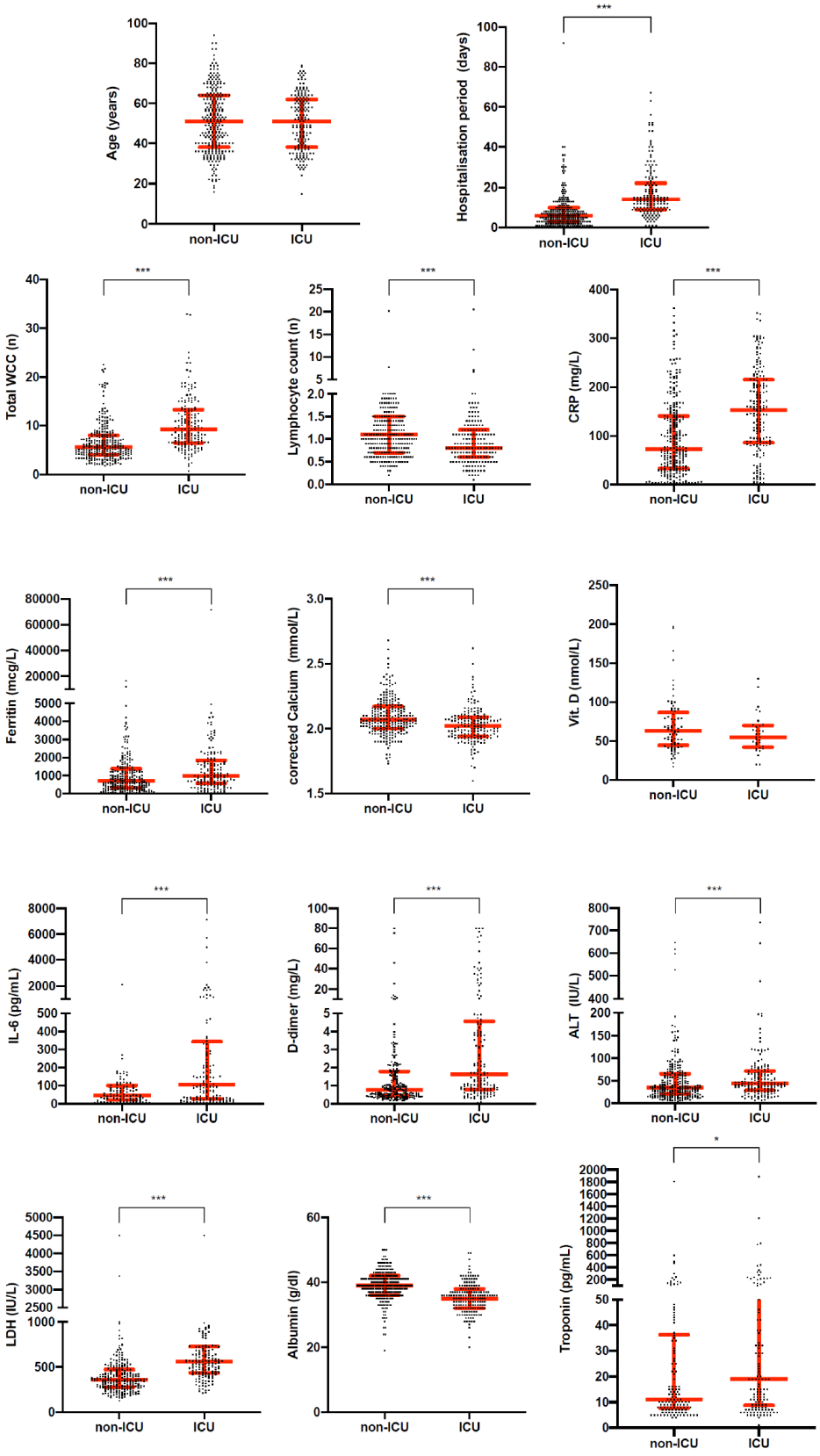

Figure 3: Factors associated with ICU admission; age, hospitalization period, and biomarkers. Mann Whitney U test was applied and values are significant at *p<0.05, **p<0.01, and ***p<0.001.

Optimum cut-off points for biomarkers predicting ICU-admission in COVID-19 patients

We used ROC curve to assess the predictivity of each significant biomarker in figure 3. Figures 4 and 5 show the area under the curve (AUC), optimum cut-off point, and odds ratio of at admission biomarkers. LDH Levels of more than 419.5 IU/L was the most predictive biomarker for ICU admission with AUC of 78% and OR (95% CI) of 7.34 (4.6-11.5). In addition, the other biomarkers showed variable significant predictivity as follows: WCC > $6.35x10^9$/L: AUC: 74% (OR (95% CI) 5.35 (3.5-8.2)), albumin < 37.5 g/L: 74% (5.30 (3.5-8.0)), IL-6 >121.4 pg/mL: 65% (4.53 (2.4-8.5)), CRP > 78.0 mg/L: 69% (4.50 (2.9-6.9)), D-Dimer > 0.69 mg/L: 69% (3.4 (2.1-5.4)), ferritin > 666.5 mcg/L: 60% (2.35 (1.5-3.6)), corrected Ca < 2.0 mmol/L: 64% (2.21 (1.4-3.4), and lymphocytes < 0.95 x109/L: 61% (1.93 (1.3-2.8)).

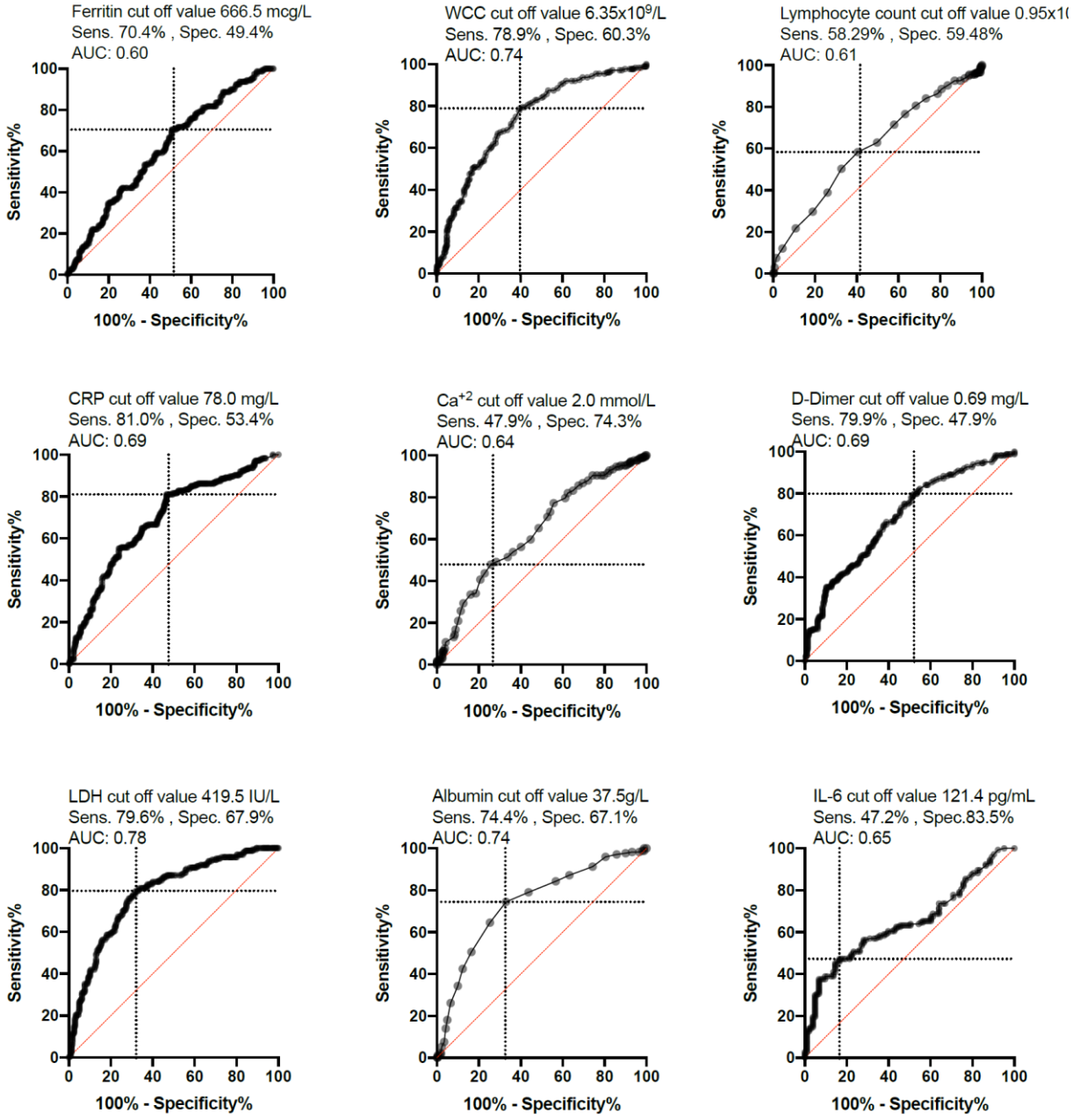

Figure 4: Receiver operator characteristic curves (ROC) presenting the predictive potential of different on admission biomarkers to predict COVID-19 progression. Area under curve (AUC), sensitivity, specificity, and optimum critical cut-off values are shown. AUC ≥ 0.6 was considered significant. Youden's index was used to find out optimum cut-off values.

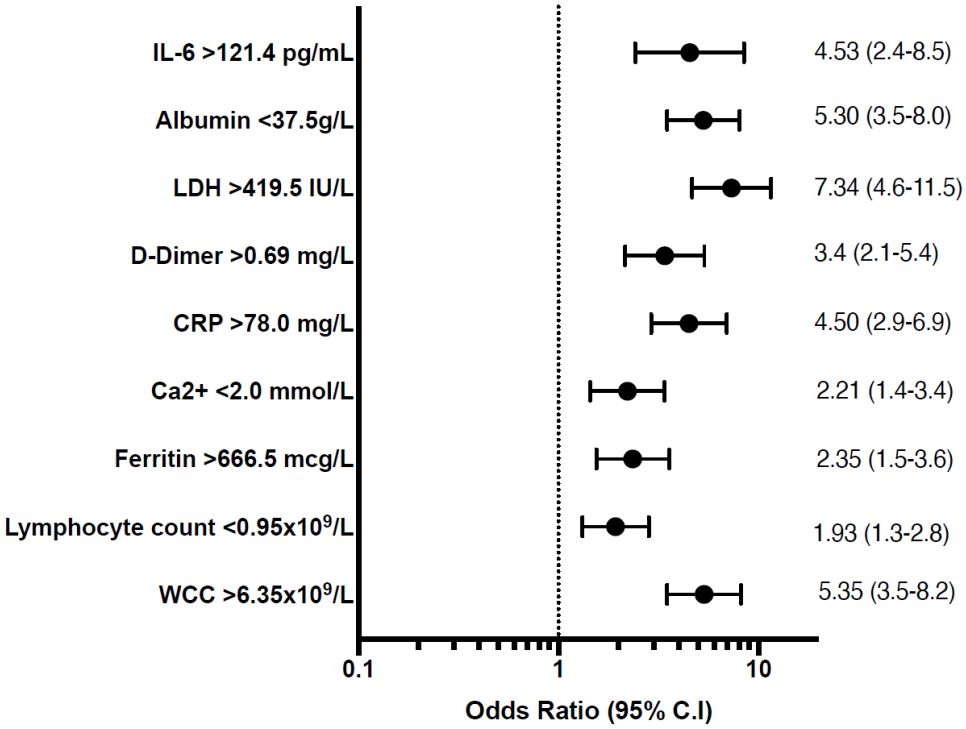

Figure 5: Forrest plot showing Odds Ratio (95% confidence interval) of on admission biomarkers associated with ICU admission.

Discussion

Predicting the progression and severity of COVID-19 is considered as a crucial step in patients' management. Therefore, many studies were conducted to find out the most optimal predictive factor and associated co-morbidities that can be used in clinical practice. Diabetes, hypertension, liver disorders, respiratory diseases, renal illnesses, immunodeficiencies and malignancies were studied extensively.[16-18] Initial data from China, showed that likelihood to develop severe COVID-19 presentation is higher in individuals with hypertension, diabetes, respiratory diseases and cardiovascular diseases with odds ration >2.30.[19] Most recent data from India, showed that hypertension or diabetes was present in more than 98% of patients who died form COVID-19.[20] Moreover, other studies were aimed to find out the best predictive biomarker/s for COVID 19 progression and LDH, WCC, CRP, D-dimer, ferritin, lymphocytes, procalcitonin, electrolytes, cardiac enzymes, hepatic enzymes, cytokines (IL-6, IL-10, and etc.), coagulation, and others were all investigated.[12,21-23] Mortality from COVID-19 was associated with leukocytosis, neutrophilia, lymphocytopenia, high urea and creatinine and increased levels of CRP, LDH, ferritin and D-dimer.[22]

In the current study, we found that 41.8% of COVID 19 patients were admitted in ICU which is relatively higher than Guan et al.,[24] (2020) findings in which 5% of 1099 patients were admitted in ICU. However, this can be attributed to the difference in the sample size and our study was conducted in a single tertiary hospital. Moreover, we identified that some preexisting comorbidities including diabetes, liver diseases, and respiratory diseases were significantly associated with COVID-19 progression ending up to ICU admission. On the other hand, hypertension, chronic kidney disease, cardiac conditions, and dyslipidaemia were not contributed to ICU admission. Previous metanalysis showed that diabetes, malignancy, cerebrovascular disease, respiratory system disease, hepatitis B infection, and digestive diseases are markedly associated with COVID-19 severity.[17] Unlike our present results, Fang et al.,[17] (2020) found that age, HTN, cardiac diseases, and CKD were significant contributors on disease severity that can be related to the sample size, demographics, and multiple coexisting comorbidities. In addition, cardiac disorders (i.e. myocarditis, myocardial infarction, and exacerbated heart failure) are also reported to be associated with a severe form of COVID 19.[25]

The effect of diabetes on COVID-19 severity can be attributed to multiple factors including the presence of DM complications, and increased expression of both angiotensin-converting enzyme-2 (ACE2) and dipeptidyl peptidase 4 (DPP4).[16,26,27] Beside altered immune function, DPP4 has been noticed in increased concentrations in

some hepatic disorders which as well can explain the relationship between liver illnesses and COVID 19 progression.[16,28] Apparently, raised expression of some molecules (i.e. SLC2A1 (GLUT1), SLC7A5(CD98), transmembrane protease serine 2 (TMPRSS2), ITGA3, and ITGA6), a limited pulmonary reserve and restrictive ventilatory impairment associated with pulmonary disorders can elucidate the progression of COVID 19 patient to ICU admission.[28]

Our study showed that multiple biomarkers have noticeable predictivity which can be used as indicators for COVID 19 progression in which the critical upper limit was produced. Current results revealed LDH > 419.5 IU/L as the most predictive biomarker for ICU admission with OR (95% CI) of 7.34 (4.6-11.5). This finding is consistent with previous studies that reported LDH as a strongest predictor for COVID-19 severity.[22,23]

Likewise, WCC > 6.35x10^9/L, albumin < 37.5 g/L, IL-6 > 121.4 pg/mL, CRP > 78.0 mg/L, D-Dimer > 0.69 mg/L, ferritin > 666.5 mcg/L, corrected Ca < 2.0 mmol/L and lymphocytes < 0.95 x10^9/L were all significantly associated with COVID 19 progression and ICU admission. Since the beginning of the pandemic, many studies were conducted and showed that the above-mentioned biomarkers were markedly associated with COVID 19 progression, severity, and fatality. Henry et al.,[9] (2020) demonstrated the significant association of high WCC, IL-6, IL-10, ferritin, cardiac enzymes, coagulation indicators, and decreased lymphocyte and platelet counts to both severe and fatal COVID-19. A study was conducted by Wang, L.,[29] (2020) showed the noticeable correlation between increased CRP level and COVID 19 severity. Moreover, other studies meant to find out the optimum biomarkers for prediction of COVID 19 progression and severity and all of them revealed the remarkable association of these biomarkers with COVID 19 progression; Tan et al.,[30] (2020) (CRP and ESR), Zeng et al.,[12] (2020) (CRP, PCT, IL-6 and ESR), Zhang et al.,[31] (2020) (D-Dimer), Gao et al.,[28] (2020) (IL-6 and D-Dimer), Pan et al.,[21] (2020) (lymphocyte, CRP, PCT, and LDH), Asghar et al.,[22] (2020) (LDH, PCT, D-dimer, CRP, and ferritin), Han et al.,[32] (2020) (IL-6 and IL-10), Lagadinou et al.,[33] (2020) (LDH, d-dimers, CRP, fibrinogen and ferritin), and Liu et al.,[34] (2020) (IL-6 and CRP).

Although the markers associated with COVID 19 severity were reported by many others, identifying the cut-off values for these biomarkers is unique and the data is from Oman. The limitation of the study is being a retrospective cohort study, data was collected from those already admitted to the hospital and the collected data may not include all COVID 19 variants.

In conclusion, the current study identified that the presence of following co-morbidities; diabetes, liver diseases and respiratory diseases associated with higher admission to ICU in patients with COVID-19. Furthermore, some on-admission laboratory blood and serum parameters (i.e. WBC, lymphocytes, CRP, ferritin, corrected calcium, IL-6, D-diameter, ALT, LDH, albumin, and troponin) provide useful guide for predicting ICU admission in patients with COVID-19.

Disclosure

The authors declare that they have no competing interests. No funding was received for current study.

Abbreviations

ICU: Intensive Care Unit, COVID-19: Coronavirus disease 2019, WBC: white cells count, CRP: C-reactive protein, IL-6: Interleukin 6, ALT: Alanine Transaminase, LDH: lactate dehydrogenase, ACE2: angiotensin-converting enzyme-2, DPP4: dipeptidyl peptidase 4, TMPRSS2: transmembrane protease serine 2.

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