Determination of ICU prognosis of COVID-19 Patients (January to April 2021)

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ABSTRACT

Background: Since the end of 2019, a new type of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) disease, named coronavirus disease *2019* (COVID-19), has spread all over the world and ever since has been designated as a pandemic that originated in Wuhan, China. The World Health Organization (WHO) has declared that the coronavirus outbreak has become a global health concern. **Patients and methods:** This retrospective cohort study was conducted at Covid Isolation Sednawy Hospital, Zagazig University during the period from 1/1/2021 to 30/4/2021. The study included 300 cases as a comprehensive sample; the patients were selected as severe to critical covid-19 patients in that work, according to the criteria of Egyptian protocol for management of COVID-19 patients (May, 2020). All patients had a laboratory diagnosis of COVID-19 based on real-time polymerase chain reaction (RT-PCR) in respiratory tract materials. **Results:** The Mean age of admitted patient 57±15.6 where male are more affected, There is statistically significant relation between severity and hemoglobin on admission within critical cases (P<0.001*).also, there is significant positive correlation between IL-6 and CRP value on admission. There is high statistical significant relation between severity and albumin and total protein on discharge. While increase mortality in critical cases, the best cutoff of neutrophil/lymphocyte ratio in prediction of mortality among patients is ≥8.8615 with area under curve 0.622, sensitivity 67.9%, specificity 50%, positive predictive value (PPV) 48.4%, negative predictive value (NPV) 69.3% and overall accuracy 57.3% (p<0.001). **Conclusion:** Admission characteristics were associated with the need for ICU admission; laboratory findings in the first day of hospitalization could be predictor factors of severity and mortality in ICU-admitted COVID-19 patients.

Keywords: COVID-19; ICU admission, Covid-19 Prognostic factors, IL6, CRP**.**

INTRODUCTION

The coronavirus pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This is a highly pathogenic human coronavirus first reported in Wuhan, China, where pneumonia of unknown cause was detected in December 2019 was declared a global pandemic on March 11, 2020. As of April 10, 2022, over 496 million cases including over 6.1 million deaths have been reported worldwide. Mortality secondary to COVID-19 is highly variable and related to age, severity of disease, and comorbidities [(1)].

The requirement of intensive care among COVID-19 hospitalized patients varies between countries from 5% to 32%. In some studies, it has been reported that many factors including age, sex, and comorbidities are associated with the severity of disease and ICU admission According to these studies, severe disease is accompanied by acute kidney injury, acute respiratory distress syndrome (ARDS), myocarditis, cardiac shock and septic shock. Hence, ICU admission plays a crucial role in the care of COVID-19 patients and also is effective in decreasing the mortality rate [(2)].

Various studies reported high mortality rates among COVID-19 patients admitted to the Intensive Care Unit (ICU). These rates appear to be higher than reported among ICU patients with other types of viral pneumonia. During the COVID-19 pandemic in the Netherlands, many ICUs were scaled up above their maximum capacity. Of note, the Netherlands healthcare system has less ICU beds per capita than other European countries [(3)].

This combined with both the high number of patients and their longer length of stay (when compared to average ICU patients) caused a limitation in the numbers of available ICU beds. This potentially has had adverse effects on the quality of care, and may have increased the mortality risk. To utilize ICU beds most effectively, preventing overload due to new cases of high emergency (related or not related to COVID-19), ICU patients were transferred between regional and (inter)national ICUs [(4)]. Relocation is not risk free, especially for mechanically ventilated patients [(5)].

Currently, our ICU resources are limited and typically more than 50% of its capacity is full under normal conditions. Therefore, in emergency conditions such as the COVID-19 pandemic, we encountered a lack of capacity. Under this condition, we have to focus more on distinguishing critical patients to save more ICU capacity and classify ICU-needed from non-ICU-needed patients. To achieve this goal, it is vital to identify the factors related to ICU admission and those that are significantly different between ICU and non-ICU admitted COVID-19 patients [(6)].

The aim of the present study was to evaluate prognostic risk factors for ICU admission among COVID-19 hospitalized patients.

PATIENTS & METHODS

This retrospective cohort study was conducted at Covid Isolation Sednawy Hospital, Zagazig University during the period from 1/1/2021 to 30/4/2021. The study included 300 cases as a comprehensive sample, the patients were selected as severe to critical covid-19 patients according to the criteria of Egyptian protocol for management of COVID-19 patients (May, 2020).

The study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans (6883-11-4-2021).

All patients had a laboratory diagnosis of COVID-19 based on real-time polymerase chain reaction (RT-PCR) in respiratory tract materials.

Inclusion Criteria: Patients admitted in isolation hospitals that were:

- Laboratory-confirmed COVID-19
- Age ≥18 years.
- Severe-Critical covid-19 cases.

Definition of COVID-19 based on Egyptian protocol in to mild, moderate, severe or critical groups:

1. Cases were considered mild if they were asymptomatic or symptomatic with leucopenia or lymphopenia and no evidence of pneumonia in the radiological image.
2. Moderate cases were symptomatic with pneumonia on radiology and/or leucopenia or lymphopenia.
3. Severe cases were presented with either; respiratory rate >30 breaths/min; SpO_2 ≤92% on room air, PaO_2/FiO_2 ratio <300 or CT was showing more than 50% lesion or progressive lesion within 24–48 hours.
4. Critical cases were defined as cases who had respiratory rate >30 breaths/min, SpO_2 ≤92% on room air or PaO_2/FiO_2 ratio <300 despite O_2 therapy.

Exclusion Criteria:

Baseline data including Age, Sex, PCR, Date of admission, Date of discharge, Medications , Comorbidies and chronic diseases, chest computed tomography (CT), severity admission criteria, length of hospital stay and outcome (survival or non-survival).

Patients with negative SARS-CoV-19 test and

Patients with incomplete files were excluded from this study or with missing any data.

Baseline routine laboratory test results included: CBC with differential counts, CRP, (At admission, after 4 days and at discharge), Procalcitonin, D-Dimer, and IL6.

Statistical analysis:

The Statistical Package for Social Science (SPSS) was used to generate the results (version 26). Means and standard deviations (SD) or medians and ranges were used to describe quantitative numerical data. Frequencies and percentages were used to describe qualitative data. The Mann-Whitney –U test, the Chi-square test, or Fisher's exact test were used to do comparisons. Stepwise logistic regression was used to estimate the risk for the relevant factors in the univariate analysis, and the odds ratio (OR) and its 95% confidence intervals (CI) were obtained. A p-value of ≤ 0.05 was judged significant.

RESULTS

Table (1): relation between time of admission and demographic data:

Parameter	Number of cases (n=300)
Age (year)	57.01 ± 15.6
Gender: **Female** **Male**	 101 (33.7%) 199 (66.3%)

The mean age of patient admitted in this period 57.01±15.6.Where male the highest gender affected.

Table (2): Correlation between IL-6 and CRP on admission:

	IL-6	
	r	p
CPR	0.358	<0.001**

r Spearman rank correlation coefficient

There is high significant positive correlation between IL-6 and CRP value on admission.

Table (3): Status of acute phase reactants parameters at given period:

Parameter	Number of cases ,Mean (n=300)
CRP (Mean):	61(3-331)
N(for CRP) **Negative** **Positive**	300 5 (1.7%) 295 (98.3%)
Procalcitonin (Mean):	0.2 (0.07-0.43)
N (for PCT) **Negative** **Positive**	27 3 (11.1%) 24 (88.9%)
D dimer (Mean):	1.4(0.2 – 9.4)
N (for d-dimer) **Negative** **Positive**	182 37 (20.3%) 145 (79.7%)
IL-6 (Mean): **N(for IL6)** **Negative** **Positive**	49.6 (6.8-123.5) 300 132 (44%) 168 (56%)
Albumin/IL-6 ratio (Mean):	0.07(0.02-0.57)
Neutrophil/lymphocyte ratio (Mean):	10.25 (0-45)

The Mean of CRP is 61, where percentage of positive cases (98.3%) and percentage of negative cases (1.7%), Mean of procalcitonin 0.2, where (88.9%) percentage of cases positive and (11.1%) percentage of cases negative.
Mean of D-dimer 1.4, where (79.7%) percentage of cases positive and (20.3%) negative cases, Mean of IL6 49.6 where percentage of positive cases (56%) and (44%) percentage of negative cases.

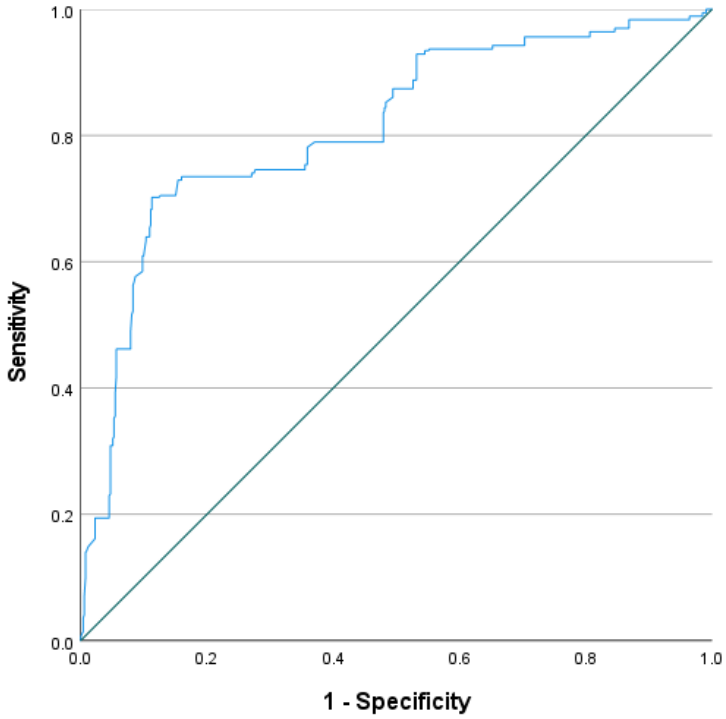

Figure (1) ROC curve showing **Performance of albumin/IL-6 in prediction of mortality among the studied patients**

Figure (1) Showed The best cutoff of albumin/IL-6 ratio in prediction of mortality among patients is ≤0.0802 with area under curve 0.812, sensitivity 73.5%, specificity 75.2%, positive predictive value (PPV) 67.1%, negative predictive value (NPV) 80.5% and overall accuracy 74.5% (p<0.001).

Table (4): Percentage of mortality and severity in a given period :

Parameter	Number of cases (n=300)
Duration (day)	11 (1 – 31)
Mortality:	
No	127 (42.3%)
Yes	173 (57.7%)
Severity:	
Critical	182 (60.7%)
Severe	118 (39.3%)

There is statistically significant relation between time of admission and mortality, There is statistically significant relation between time of admission and disease severity with highest percentage of critical patient**.**

Table (5): relation between different CBC data in given period :

Parameter	Number of Cases (n=300)	P
Hemoglobin:	Mean±SD	
Baseline	13.17±2.35	0.149
Day 4	13.45±2.7	
Final	13.08±2.56	
WBCs:		
Baseline	9.6(4.2-31.4)	0.006*
Day 4	11.6(1.2-26.8)	
Final	11.35(3.1-27.3)	
Lymphocytes:		
Baseline	1(0.2-2.7)	0.0147
Day 4	0.9(0.2-3.1)	
Final	1 (0.2-3.6)	
Neutrophil:		
Baseline	8.2 (0-29.6)	0.003*
Day 4	10.6(0.4 – 25.4)	
Final	9.5 (2 – 25.2)	
Monocytes:		
Baseline	0.4 (0-1.5)	0.002*
Day 4	0.5(0 – 1)	
Final	0.4 (0 – 1.5)	
Platelet :		
Baseline	184(27-479)	0.001*
Day 4	238.8(19-514)	
Final	173(20-476)	

There is no statistical significant difference value regarding hemoglobin, between baseline, day 4, and final readings (0.149).

There is statistical significant difference value regarding WBCs between baseline and 4 day and final readings (0.006*).

There is no statistical significant difference value regarding Lymphocytes between baseline and 4 day and final readings (0.147).

There is statistical significant difference value regarding Neutrophil between baseline, 4 day and final readings (0.003*).

There is high statistical significant difference value regarding Monocytes, between baseline, day 4, and final readings (0.002*)

There is highly statistical significant difference value regarding platelet, between baseline, day 4 and final readings (0.001**).

Table (6) Relation between severity and laboratory data baseline and on follow up of the studied patients:

Parameter	Severity		Test	
	Critical	Severe	t	p
	Mean ± SD	Mean ± SD		
Albumin				
Baseline	3.21 ± 0.48	3.23 ± 0.43	-0.708	0.469
Final	2.99 ± 0.41	3.09 ± 0.46	-3.364	<0.001**
p	<0.001**	<0.001**		
Protein				
Baseline	6.16 ± 0.77	6.15 ± 0.7	0.233	0.816
Final	5.87 ± 0.71	6.06 ± 0.7	-3.692	<0.001**
p	<0.001**	<0.001**		

t independent sample t test *p<0.05 is statistically significant

There is statistically significant relation between severity and albumin and total protein on discharge. There is significant change in albumin and protein over time.

Table (7): Relation between severity and CBC baseline and on follow up of the studied patients:

Parameter	Severity		Test	
	Critical	Severe	t	p
	Mean ± SD	Mean ± SD		
Hemoglobin				
Baseline	12.82 ± 2.39	12.48 ± 1.88	2.202	0.028*
Day 4	13.09 ± 2.82	12.43 ± 1.91	3.882	0.086
Final	12.54 ± 2.62	12.3 ± 2.1	1.458	0.101
p	<0.001**	<0.001**		
	Median (range)	Median (range)	Z	p
WBCs:				
Baseline	11.5(2.6 – 31.4)	10.4 (2.3 – 31.4)	-2.586	0.01*
Day 4	14.2 (1.2 – 31.2)	11.2 (2.8 – 32.9)	-6.685	<0.001**
Final	13.5 (3.1 – 31.8)	12.2 (2.8 – 31.8)	-3.545	<0.001**

p	<0.001**	<0.001**		
Lymphocytes:				
Baseline	0.8 (0.1 – 3.1)	1.1 (0.2 – 2.7)	-5.8	<0.001**
Day 4	0.32 (0.1 – 4.2)	1.1 (0.1 – 3.5)	-6.508	<0.001**
Final	0.9 (0.2 – 3.6)	1.2 (0 – 6.5)	-7.022	<0.001**
p	0.069	<0.001**		
Neutrophil:				
Baseline	10.1 (0 – 29.6)	9.1 (1.4 – 29.6)	-2.631	0.009*
Day 4	11.4 (0.4 – 29.6)	9.1 (1.4 – 29.9)	-7.333	<0.001**
Final	12.3 (2 – 28.5)	9.7 (2 – 28.5)	-5.046	<0.001**
p	<0.001**	0.179		
Monocytes				
Baseline	0.5 (0 – 1.9)	0.4 (0 – 1.8)	-2.102	0.036*
Day 4	0.5 (0.1 – 1.8)	0.5 (0 – 3.4)	-2.132	0.033*
Final	0.5 (0 – 1.7)	0.5 (0 – 4)	-3.182	<0.001**
p	0.585	0.013*		
Platelet:				
Baseline	174 (27 – 581)	198 (30 – 581)	-3.279	<0.001**
Day 4	191 (12 – 499)	217 (29 – 516)	-5.332	<0.001**
Final	158 (20 – 656)	211 (33 – 656)	-6.293	<0.001**
p	<0.001**	<0.001**		

Z Mann Whitney test t independent sample t test *p<0.05 is statistically significant

There is statistically significant relation between severity and hemoglobin on admission within critical group. Also, there is significant change in WBC, neutrophil and platelet (P<0/001).

While there is non-significant change in Neutrophil within severe group, there is significant change in WBCS, lymphocytes, hemoglobin, platelet and monocytes.

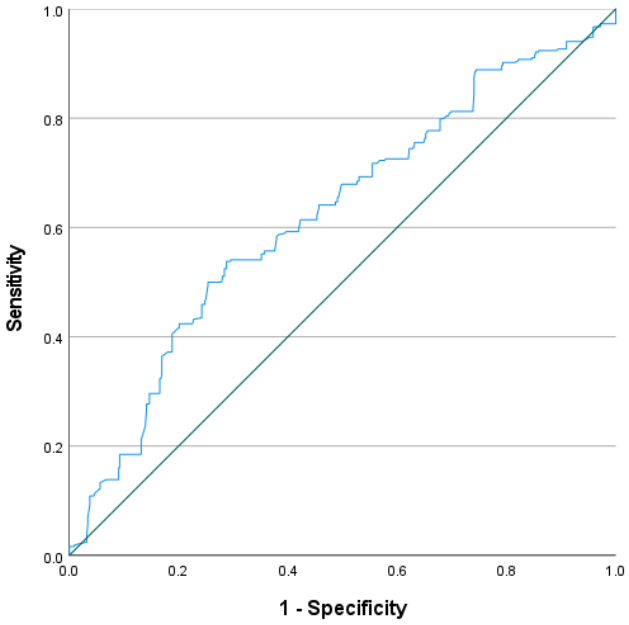

Figure (2) ROC curve showing Performance of neutrophil/lymphocyte ratio in prediction of mortality among patients

Figure (2) showed that the best cutoff of neutrophil/lymphocyte ratio in prediction of mortality among patients is ≥8.8615 with area under curve 0.622, sensitivity 67.9%, specificity 50%, positive predictive value (PPV) 48.4%, negative predictive value (NPV) 69.3% and overall accuracy 57.3% ($p<0.001$).

DISCUSSION

In December 2019, a severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that caused severe disease clusters was first reported in Wuhan, the capital of China's Hubei province. This viral disease, which is reported to originate from a seafood market where wild animals are illegally sold, has been transmitted among humans worldwide through close contact. Given the growing number of infected people worldwide and the disastrous consequences in all aspects of life, COVID-19 is a serious public health issue that requires special attention. In some countries, the epidemic curve of infection which was in the plateau phase or decreasing phase during the lockdown period increases day by day since the reopening, indicating the second phase of contamination. **(7)**.

Critically ill patients with COVID-19 are characterized by progressive respiratory failure due to lung infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Recent evidence suggested that SARS-CoV-2 might directly dysregulate the normal functions of the kidney, liver and peripheral blood components, which increases the risk of multiple organ failure. To our knowledge, some potential high-risk factors of

death were speculated in small sample-sized studies on COVID-19 **(8)**. In another study exploring the risk factors of death, only 11 (8%) were treated in ICUs and only 3 (2%) received mechanical ventilation during hospitalization in the survivor group, and severe complications during the progression of COVID-19, including acute respiratory syndrome (ARDS), acute cardiac injury, acute kidney injury (AKI), and liver dysfunction, were not considered at all **(9).**

Few months after the first reports of coronavirus disease 2019 (COVID-19), it was declared a pandemic. Given its high transmissibility, SARS-CoV-2 has infected millions of people worldwide and has placed a huge burden on the healthcare system **(10)**. Some infected patients develop acute respiratory distress syndrome (ARDS), multiple organ failure, pulmonary embolism, and heart failure (**11)**. ARDS is the most common reason for intensive care unit (ICU) admission in these patients. For patients requiring intensive care, ICU admission occurs about 10 days after the onset of symptoms and 14 days after infection. After a rapid surge in COVID-19 cases, the need for intensive care and aggressive treatment has been dramatically increased around the world. The in-ICU mortality rate of COVID-19 is twice that of other causes of viral pneumonia that require ICU admission **(12).**

This Retrospective cohort study was conducted at Covid Isolation Sadnawy Hospital, Zagazig University during the period from 1/1/2021 to 30/4/2021 to detect the Outcome and survival of COVID-19 Patients admitted at Zagazig University Hospital.

In the present study, showed that mean age of patient admitted in this period 57.01±15.6SD, where male the highest gender affected.

In agreement with our study, **We et al. (13)** demonstrated that there was a high statistical difference in the male to female ratio between studied patients ($P < 0.0001$). Also, **Wang et al. (14)** demonstrated that of the total 80 patients, 39 (49%) were females and 41 (51%) were males. The mean age (SD) was 53 years for COVID-19 (+) patients a high statistical significant difference regarding age and sex distribution.

In the current study, there is significant positive correlation between IL-6 and CRP on admission.

This came in agreement with **Du et al. (15)** who demonstrated that there was high significant correlation between CRP and IL-6 in the studied patients ($P < 0.0001$).

CRP is considered a sensitive biomarker of infection, inflammation, and tissue damage. During the acute inflammatory responses, the CRP level increases rapidly (**19).**

The current study showed there is high statistical significant difference value regarding platelet, Monocytes, Neutrophil and WBC between baseline, day 4, and final readings (<0.001**, 0.002*, 0.003* and 0.006* respectively). While there is no statistical significant difference value regarding hemoglobin and lymphocyte between baseline and 4 day readings which in agreement with the study of **Blasco** et al., (16) who concluded similar results.

In the present study there is statistically significant relation between severity and albumin and total protein, there is significant change in albumin and protein over time.

This came in agreement with **Zayed et al. (17)** who demonstrated that laboratory assessment of patients on admission revealed the followings in more sever group compared to less sever group; more lymphopenia (16.18% ± 7.13% for group B vs 42.1% ± 7.78% for group A P < 0.001), higher MPV (12.76 ± 7.13 (fL) vs 10.51 ± 7.78 (fL), P < 0.001), higher ESR (60.4 ± 17.7 (mm/h) vs 39 ± 19.6 (mm/h), P < 0.001), higher CRP (119.5 ± 45.6 mg/L vs 59.6 ± 39.5 mg/L, P < 0.001), higher serum ferritin (954 ± 138 ng/ml vs 447 ± 166 ng/ml, P < 0.001), more positive D-dimer (75.8% vs 20.7%, < 0.001), higher LDH (604 ± 220 U/L vs 384 ± 183 U/L, P-value < 0.001), higher AST (69 ± 37 U/L vs 51.7 ± 25.4 U/L, P = 0.01), higher ALT (59.5 ± 17.7 U/L vs 48.2 ± 26.5 U/L, P = 0.01), higher creatinine (1.25 ± 0.65 mg/dL vs 0.83 ± 0.2mg/dL, P = 0.01), and higher CPK-MB (24.27 ± 5.82 IU/L vs 16.4 ± 4.87 IU/L, P < 0.001).

There is statistically significant relation between severity and hemoglobin on admission within critical group. Also, there is significant change in WBC, neutrophil and platelet (P<0/001), While there is non-significant change in Neutrophil within severe group, there is significant change in WBCS, lymphocytes, hemoglobin, platelet and monocytes.

Lippi G et al., (18) Considered the Hb level in severe COVID-19 patients was significantly lower than those with milder forms. Suggested that in severe COVID-19 patients compared to milder forms of the disease, Hb levels essentially decreased that needs clinical studies to investigate the effectiveness of blood transfusion support in prevention of progress to severe disease and death.

CRP is considered a sensitive biomarker of infection, inflammation, and tissue damage. During the acute inflammatory responses, the CRP level increases rapidly (**19).**

The best cutoff of albumin/IL-6 ratio in prediction of mortality among patients is ≤0.0802 with area under curve 0.812, sensitivity 73.5%, specificity 75.2%, positive predictive value (PPV) 67.1%, negative predictive value (NPV) 80.5% and overall accuracy 74.5% (p<0.001).

Kumar et al.,(20) Demonstrated that it is important to point out that the results from univariate logistic regression analysis revealed age, CRP, and lymphocytes at admission to hospital as predictors of mortality in patients admitted to ICU, while serum albumin, D-dimer, IL-6, and CT severity score were significant predictors of mortality at admission to the ICU. Final multivariate analysis revealed serum albumin, IL-6, and D-dimer at admission to ICU as independently associated with mortality, Hypoalbuminemia (serum albumin levels below 35 g/L) is more severe in critically ill patients and is associated with poor outcomes.

In agreement with our study, **Chen et al. (8)** found that CRP suggested as an efficient marker in assessing COVID-19 severity. This study revealed that CRP was associated with disease severity and clinical outcome.

Kermali et al. (21) reported that biomarkers that included CRP, IL-6, LDH and IL-10. IL-6 and CRP with significantly correlated with the WHO severity score. Il-6 and CRP

were both closely associated with increased fraction of inspired oxygen delivery (FiO2) requirements and radiological evidence of acute respiratory distress syndrome (ARDS).

Also, **El-Shabrawy et al. (22)** assessed the IL-6 levels in COVID-19 patients. The patients with severe COVID-19 had higher levels of IL-6 in comparison with non-severe patients. Regards IL-6 diagnostic performance criteria, IL-6 seems to be a useful marker for early recognition of severe disease. IL-6 showed significantly predictive power even after adjustment to different models that include clinical and laboratory significant parameters. So, IL-6 can be considered as an independent predictor of COVID-19 severity.

There is statistically significant relation between severity and mortality where mortality was higher among critical cases.

Ismail et al. (23) demonstrated that non-survivors were older, more likely to have comorbidities like ischemic heart disease and chronic renal disease, less likely to complain of malaise and headache as the initial symptoms of COVID 19 disease, and had greater APACHE II score than survivors.

Regarding performance of neutrophil/lymphocyte ratio in prediction of mortality among the studied patients, The best cutoff of neutrophil/lymphocyte ratio in prediction of mortality among patients is ≥8.8615 with area under curve 0.622, sensitivity 67.9%, specificity 50%, positive predictive value (PPV) 48.4%, negative predictive value (NPV) 69.3% and overall accuracy 57.3% ($p<0.001$).

Zayed et al. (17) demonstrated that multivariate regression of potential predictors of COVID-19 severity and mortality revealed the following predictors: age, MPV, and IHD with. The overall results of the ROC analysis regarding MPV and serum ferritin as predictors of COVID-19 severity.

Jimeno et al. (24) demonstrated that in a multivariable logistic regression, age, cardiovascular disease, CRP at admission and Peak NLR were significantly associated with death. Peak NLR and mortality were positively correlated (Pearson coefficient regression 0.332, $P < .001$), as well as Peak NLR and age (Pearson coefficient regression 0.258, $P = .005$). In a multivariable logistic regression, mortality was significantly associated with an elevated Peak NLR > 6.

Yang et al. (25) reported that the multivariate multivariable logistic regression showed that IL-6 ($P < 0.001$), CRP ($P < 0.001$), and PCT ($P = 0.002$) could be used as independent factors to predict the severity and mortality of COVID-19.

Conclusion: Admission characteristics were associated with the need for ICU admission. Laboratory findings in the first day of hospitalization could predictor factor severity and mortality rate prediction in ICU-admitted COVID-19 patients.

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