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Outcome Predictors for ICU Admitted Critically Ill Covid-19 Patients in Fayoum University Hospitals

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Abstract:

Introduction: COVID-19 began as a worldwide public health emergency with a high mortality rate when it started to spread in 2019 in China. It caused millions of deaths within less than two years.

Aim of the study: Evaluation of clinical, laboratory and radiological parameters of COVID-19 patients as well as therapeutic management; and assessment of their impact as outcome predictors.

Subjects and Methods: We investigated 210 patients admitted to the critical care department at Fayoum University hospitals with PCR-confirmed COVID-19, from April 2020 to September 2021. We separated our patients into two groups: survival group (group I) and mortality group (group II).

Results: Our study revealed that among our ICU-admitted patients with COVID-19; those with higher mortality were older, more overweight, and had higher CRP (60.0 ± 54. in group I vs. 78.9 ± 67.2 in group II, $p<0.05$), higher D-dimer level (1.5±1.4 in Group I vs. 2.4±1.9 in Group II, $p<0.01$), higher LDH, higher IL6 (139.9±640.3 in Group I vs. 560.5 ± 1163.7 in Group II, $p<0.05$) and less serum albumin level upon ICU admission. Also, mortality was less in patients with lower CORAD scores in CT chest, less affected lung lobes, and less APACHE II score.

Conclusions: Our study showed that the age and weight of COVID-19 patients together with many laboratory and radiological parameters could be good predictors of mortality upon ICU admission.
Keywords: VID-19; Predictors; Outcome; Intensive Care.

1. Introduction

Coronaviruses (CoVs), the double-stranded RNA viruses, were found to be responsible for the SARS-like disease that started in China in late months of 2019. SARS-CoV-2 virus was identified to cause COVID-19 disease. Then, within a few months, with its high infectivity, virulence and widespread, the WHO stated it was a pandemic in March 2020. Until November 2022, WHO declared more than 6.5 million

deaths from COVID-19 [1]. It has the highest mortality since the Spanish flu pandemic (1914-1918 A.D.) [2].

The pandemic started with the global panic about the shortage of ICU beds for severe COVID-19 patients. Many laboratory and radiological parameters were used to assess patients for categorizing and triaging patients according to disease severity including conventional blood count, renal and liver profile, bleeding profile including D-dimer and acute phase reactants as blood ferritin level. Also, CT chest was used as a diagnostic tool and CORAD score was used to evaluate the probability of COVID-19 infections [3]. Many drugs were added to COVID-19 treatment protocols including many antivirals and immune system modulators including steroids and tocilizumab [4]. Many of these therapeutic options and laboratory tools are to be tested to assess the severity and to anticipate the outcome of these patients in a trial for better evaluation and refining management of COVID-19 patients and improving their outcome.

2. Subjects and Methods

2.1. Subjects

Our study incorporated 210 COVID-19 ICU patients at Fayoum University Hospital, Egypt, from April 2020 to September 2021.

Inclusion criteria

We studied severe and seriously ill COVID-19 patients. We included them if having any of the following: severe dyspnea and high respiratory rate of more than 30; the necessity of the use of mechanical ventilation or PaO2/FiO2 less than 300, multiorgan failure or circulatory shock. We considered the first day of intensive care unit admission as the index date. The endpoint is the patient's improvement, discharge from the ICU or death.

Exclusion criteria

2.2. Patients with chronic lung disease, with missed clinical data or with ICU stay of less than 24 hours were excluded from our study.

2.3. Study design

Our patients were investigated and data was collected within the first 24 hours after ICU admission. All patients had the following:

- Thorough medical history and clinical examination.
- Laboratory investigations: including arterial blood gas analysis (ABG), blood sugar, blood count, serum electrolytes, D-dimer, coagulation profile (PT, PC, INR and PTT), CRP, LDH, serum ferritin, serum albumin, ALT, AST, serum bilirubin, urea, creatinine. These parameters were done within 24 hours of admission and reassessed regularly every 1-3 days as needed. IL6 assessment was done for suspected cases of cytokine storm and repeated as needed.
- APACHE II score was calculated for all of our patients.
- Chest imaging by Computed Tomography: CT chest was assessed for all cases including the presence of ground glass patches or lung consolidations. We used the Dutch Radiological Society-developed CO-RAD score (5) to assess lung affection with a score from 1 to 6.

2.4. Statistical Methods

We made our data analysis by the SPSS software program; version 22. Qualitative data were represented with numerical descriptions and percentages. The differences were evaluated with the test of chi-square. Quantitative data were shown as mean standard deviation and range. An Independent t-test was performed to compare our two groups. A statistically significant *P-value* was considered if it was < 0.05.

3. Results

Demographic features of our study patients: Our study was conducted over 210 PCR-confirmed COVID-19 patients. Our patients had an age range (16- 91 years old) with a Mean ±SD of 57.5 ± 16.1 ($p<0.001$). Although we found a significant relation between death and age and body weight, sex had no difference regarding mortality (**Table 1**).

Table 1: Mortality according to demographic data.

Variable		Group I	Group II	*P-value*
Age (years)		54.9±15.7	62.7±15.8	<0.001*
Body weight (kg)		77.3±8.1	80.6±10.8	0.047*
Sex	Male	75 (64.7%)	41 (35.3%)	0.429
	Female	65 (69.1%)	29 (30.9%)	

Significant

No significant relation was noted between mortality and diabetes or hypertension (p>0.05 for both). Other comorbidities are listed in **Table 2.**

Table 2: Main comorbidities in our study patients.

Variable	Frequency
Diabetes Mellitus	92 (43.8%)
Hypertension	85 (40.5%)
Ischemic heart disease	13 (6.2%)
Chronic kidney disease	13 (6.2%)
Chronic liver disease	11 (5.2%)
Acute kidney Injury	10 (4.8%)
Malignancy	8 (4%)

Data were expressed as Mean ± SD.

A significant relation was found between mortality and both CORAD scores and the number of the affected lung lobes (p<0.05 for both) but not with the presence or absence of consolidation (p>0.05), as shown in **Figure 1.**

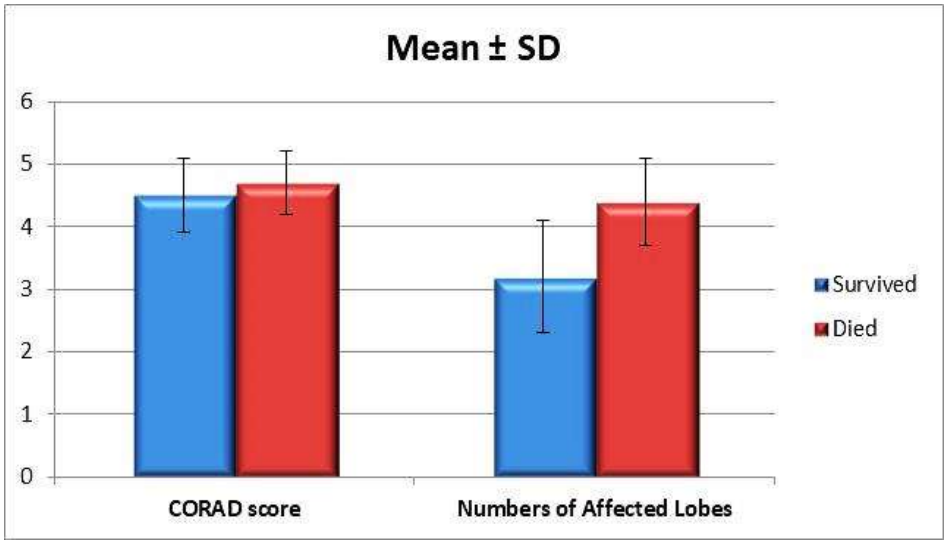

Figure 1: Significant radiological chest C.T. findings in our study patients.

Regarding laboratory data, some laboratory markers on admission were associated with higher mortality including blood level of CRP, D-dimer, LDH, total leucocytic count (TLC), urea, creatinine, albumin and interleukin-6 as listed in **Table 3.**

Table 3: Laboratory findings on admission.

Variable	Group I	Group II	*P-value*
I-Ca (mg/dL)	4.6±0.7	4.5±0.7	0.284
CRP (mg/dL)	60±54	78.9±67.2	0.049*
D dimer (ng/ml)	1.5±1.4	2.4±1.9	0.004*
LDH (U/L)	548.4±319.6	692.3±466.1	0.031*
ALT (U/L)	50±34.7	92.3±202.3	0.097
AST (U/L)	53.2±49.5	82.5±181.2	0.201
Hb (g/dL)	12.8±2	12.2±2.1	0.079
TLC (10^3/ul)	10±5.5	13.3±7.2	0.002*
Lymphocytes (10^3/ul)	1±0.5	0.9±0.5	0.328
Platelets (10^3/ul)	265.2±94.8	243.9±102.2	0.145
Urea (mg/dL)	47.1±34.9	87.8±67.6	0.001*
Creatinine (mg/dL)	1.2±0.9	2.2±2.5	0.004*
Albumin (gm/dL)	3.4±0.5	3.1±0.6	0.001*
INR	1.2±0.3	1.3±0.3	0.051
IL-6 (pg/mL)	139.9±640.3	560.5±1163.7	0.037*

**Significant. I-Ca: ionized calcium, CRP:C-reactive protein; LDH: lactate dehydrogenase; TLC: total leucocytic count; ALT: Alanine transaminase; AST: Aspartate aminotransferase; Hb: haemoglobin; IL-6: Interleukin-6.*

In ABG; PO2 on admission was the only finding that had a significant relation with mortality; (PO2 66.4±31.1for Group I vs. 52.6±22.2 for Group II, $p<0.001$). The main drugs used for treating our COVID-19 patients are listed in **Table 4.**

Table 4: Main drugs for COVID-19 treatment.

Variables		Total	**Group I**	**Group II**	***P-value***
Anticoagulation	No	5 (2.4%)	5 (100%)	0 (0%)	0.172
	Yes	205 (97.6%)	135 (65.9%)	70 (34.1%)	
Anti-viral	No	152 (72.4%)	97 (63.8%)	55 (36.2%)	0.156
	Yes	58 (27.6%)	43 (74.1%)	15 (25.9%)	
Tocilizumab	No	125 (59.5%)	90 (72%)	35 (28%)	0.053
	Yes	85 (40.5%)	50 (58.8%)	35 (41.2%)	

Invasive mechanical ventilation and mortality: Seventy patients (33.3%) who needed invasive mechanical ventilation had a higher mortality rate than those on non-invasive oxygen therapy ($p<0.001$) (**Table 5)**.

Table 5: Relation between mortality and invasive oxygen therapy.

Variable	Group I	Group II	P-value
Patients needed invasive mechanical ventilation	10 (14.3%)	60 (85.7%)	<0.001*

**Significant.*

The discriminative power of Il-6, C-RP and D-dimer in predicting Mortality: By using the ROC curve, we found that IL_6 had an excellent discriminative power for mortality prediction (AUC 0.815 and p <0.001). At the cut-off point of 31.25; sensitivity was 82.6 % and specificity was 70% (**Table 6, Figure 2**).

Table 6: Results of ROC curve IL-6, D-dimer, and CRP in forecasting mortality.

	AUC	***P-value***	**Cut-off point**	**Sensitivity**	**Specificity**
IL-6	0.815	<0.001*	31.25	82.6	70.5
CRP	0.600	0.157	86.5	43.5	83.6
D-dimer	0.620	0.092	1.75	52.2	73.8

**Significant.*

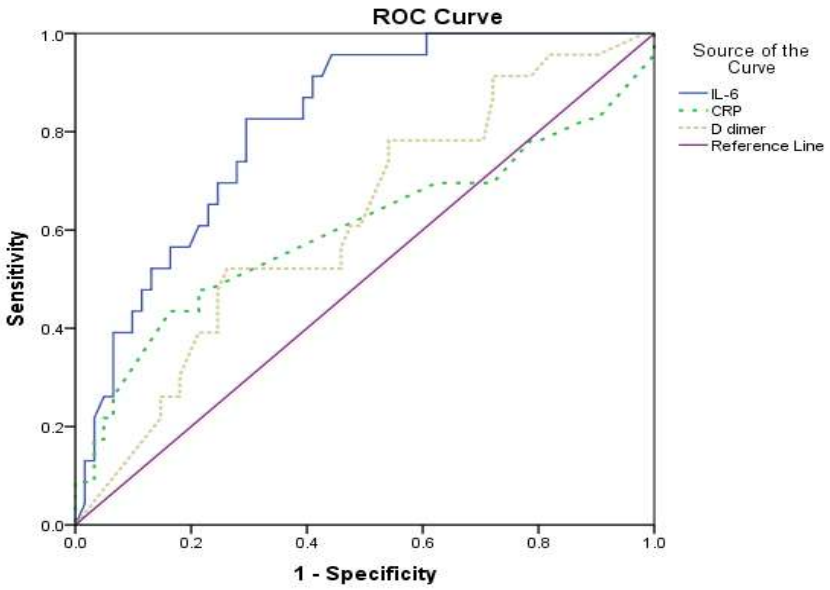

Figure 2: ROC curves of IL-6, D-dimer and C-RP and in predicting death

As identified in multiple logistic regression analysis as in **Table 7**; Age, number of affected lung lobes, PaO2, LDH and IL-6 were significant predictors for mortality. Variables entered were age, CORAD score, numbers of affected lung lobes, PaO2, K, Total Calcium, CRP, D-dimer, LDH, TLC, Urea, Serum Creatinine, Ferritin, Albumin, IL6, APACHE Score.

Table 7: Backward stepwise logistic regression showing significant predictors for mortality.

Variables	B	*P-value*	Odds Ratio (OR)	*95%* C.I.fo1· OR	
				Lower	Upper
Age	0.149	0.008*	1.161	1.039	1.296
Numbers of Affected Lobes	1.823	0.003*	6.188	1.895	20.207
P02-A	-0.068	0.003*	0.934	0.893	0.977
LDH	0.003	0.032*	1.003	1	1005
IL6	0.001	0.033*	1.00 1	1	1.002
Constant	-26.745	0.006*		0	

**Significant. P02_A: arterial oxygen tension, LDH: lactate dehydrogenase, IL6: Interleukin-6.*

4. Discussion

COVID-19 is considered a catastrophic worldwide health crisis that negatively affected not only health systems but also political, social, and economic conditions. Healthcare facilities were overloaded with a large number of seriously ill patients. In this study, we evaluated 210 patients with COVID-19 admitted to the Fayoum University Hospital medical ICU to evaluate their demographic characteristics and to identify mortality predictors that can be used for initial evaluation and identifying high-risk COVID-19 patients.

The mortality rate was found in our patients to be significantly higher with older age patients (Group I patients (Survival group) 54.9±15.7 years Vs. Group II (Mortality group) patients 62.7±15.8 years, P-value <0.001). This agrees with the meta-analyses by Tiruneh et al. [6], and Levin et al. [7], who found an exponential relation when comparing age and infection death rates in their COVID-19 patients.

Regarding weight, in our study, the mortality rate was significantly higher in overweight patients (Group I 77.3 ± 8.1 kg. Vs. Group II 80.6 ± 10.8 kg). This agrees with the meta-analysis by Chu et al. (2020) showed that the Body Mass Index (BMI) of subjects with COVID-19 had a higher probability of mortality [8].

Regarding risk factors of diabetes and hypertension; in our study, we found that DM and HTN did not affect the outcome of our patients. Our diabetic patients followed strict control of blood glucose levels using insulin infusion during their stay and coverage with antibiotics in all patients providing adequate limitation for diabetic adverse effects on our patients in our study and good protection from hyperglycemic complications.

Our findings are concordant with Gupta and colleagues who agreed with our findings and didn’t reveal any effect of both HTN and DM on the outcome; HTN (OR, 1.06; 95% CI, 0.83-1.36), DM (OR, 1.14; 0.91-1.43) [9].

However, our study disagreed with de Almeida-Pititto and colleagues who found that DM and HTN are significant risk factors for the severity of the disease and death [10].

In a CT scan of the lungs, we found that the higher the CORAD score, the

higher the mortality rate (Group I 4.5±0.6 vs. Group II 4.7 ± 0.5). This agrees with the study by INANC et al. (2020), who found that the 4-week fatality rate was higher in patients who had CO-RADS score ≥ 4 than in those who had a score ≤ 3 and (97% vs. 2.7%) [11].

Also, in our study population, the mortality rate was significantly greater in those with an increased number of affected lung lobes (Group I 3.2±0.9 lung lobes vs. Group II 4.4 ± 0.7) which agrees with the study by Tekcan et al. (2021) showing that the necessity for ICU admission is proportional to the number of the affected lung lobes [12].

Regarding laboratory data, we noted that the higher the level of IL-6, the higher the mortality (Group I 139.9±640.3 vs. Group II 560.5 ± 1163.7). This agrees also with the meta-analysis by Halim et al. (2022) which found that the blood level of IL-6 implicates increased COVID-19 morbidity and mortality. This proposes that severity of the COVID-19 may be related to cytokine storms [13]. These findings support the need for more clinical trials to reveal the role of immunomodulatory drugs specifically through IL-6 inhibitory drugs in such patients. Using the ROC curve for testing IL-6 for predicting mortality; we found that IL-6 had an excellent discriminative power for predicting mortality (AUC=0.815); with a high sensitivity of 82.6% and sensitivity of 70.5 % at the cut-off point of 31.25 pg/mL.

Among our patients, a significantly higher mortality rate was noticed in those with low levels of serum albumin level (Group I 3.4±0.5 Vs. Group II 3.1 ±0.6). This agrees with (Acharya R. et al., 2021) showing that the low serum albumin group had higher mortality in comparison to the normal albumin group (13.87% vs. 2.38%) and was coupled with poor prognosis and more complications [14]. We suggest more research on the therapeutic role of albumin infusion in COVID-19 [15]. We also noted that the mortality rate increased significantly with higher levels of D-dimer (Group I 1.5±1.4 μg/mL vs. Group II 2.4±1.9 μg/mL). This agrees with the study of Soni et al. (2020) showing that D-dimer levels higher than 2 μg/mL can forecast mortality [16].

Also, mortality in our patients was significantly higher in those treated by invasive oxygen therapy (mechanical ventilation). Their mortality rate was 85.7% compared to 7.1% in those treated only by

non-invasive oxygen therapy. However, all our patients were put on non-invasive oxygen therapy.

This agrees with the multicenter large study by Roedl et al. (2021) that showed the mortality was 75% in the 223 ICU-admitted COVID-19-infected patients who needed invasive MV [17]. These high mortality rates could be attributed to inappropriately trained or overwhelmed staff, inadequate ventilation settings adjustment, and incomplete understanding of COVID-19-induced lung pathology especially in the first waves of COVID-19, and this has to be investigated.

We found that treatment with tocilizumab does not affect mortality in our ICU-admitted critically ill COVID-19 patients. This agrees with the meta-analysis by Avni et al. (2021), who found that mortality was not changed when tocilizumab was given with corticosteroids to critically ill COVID-19 (RR = 0.94, 95% CI 0.74-1.19) [18]. Additional research should help in detecting subgroups of patients that may benefit from tocilizumab, different doses, especially with concomitant use of steroids and the best timing for initiating it in COVID-19 patients.

Regarding APACHE II Score; we found that the APACHE II score on admission was less in the survival group when compared to the mortality group (8.0±3.6 vs. 15.0 ±6.9, respectively). This agrees with the study by Karthick et al. (2020), who found that the APACHE II score was higher in deceased patients with a mean score (of 22.21 ± 6.05) than in patients who survived COVID-19 (9.87 ± 4.40). They also found that APACHE II scored more than the cut-off value of 17 predicted mortality (at 96% sensitivity and 86% specificity) [19].

Regarding LDH, the mortality rate was higher significantly in those with higher levels of serum LDH (Group I 548.4 ± 319.6 Vs vs. Group II 692.3 ± 466.1). This agrees with the pooled analysis of 8 studies by Huang et al. (2022), who found that higher LDH levels were concomitant with 16 folds higher mortality compared to patients with LDH below the cut-off value that was in the range (245 - 253.2 U/L) in the different pooled studies [20].

Also, we noted that higher levels of serum CRP were associated significantly with higher mortality (Group I 60.0 ± 54.0 Vs. Group II 78.9 ± 67.2), this agrees with the study directed by Stringer et al. (2021)

showed that 31.9% was the mortality of the patients whose CRP levels were ≥40 mg/L versus 15.0% for those with CRP less than 40 mg/L [21].

Conclusion

Our study showed that ICU-admitted patients with COVID-19 have higher rates of mortality, especially those who are elderly, overweight, have higher blood levels of CRP, IL-6, LDH, D-dimer, CORAD score, APACHE II score, a higher number of affected lung lobes in CT chest upon ICU admission.

Ethical approval and consent to participate: approved by faculty of medicine, Fayoum university ethical committee on 09/05/2021, session number 82. Written and informed consents for patients participating in our study were taken and signed by the eligible relatives.

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Conflicts of Interest: All authors declare they have no conflicts of interest.

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