ORIGINAL ARTICLE

Parameters linked with Mortality in Egyptian COVID-19 Hospitalized Patients

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ABSTRACT

Background: *The early prediction of COVID-19 mortality is a key in the patient's treatment.* ***Objectives:*** *To assess the parameters that are associated with mortality in COVID-19 patients.* ***Methods:*** *COVID-19 was diagnosed by reverse transcriptase–polymerase chain reaction (RT-PCR) for SARS-CoV-2, from oropharyngeal swabs. Demographic findings, clinical, laboratory, and radiological data were recorded and analyzed. Classification of cases to mild, moderate, or severe was performed according to The World Health Organization Guidelines.* ***Results:*** *Our study involved 66 COVID-19 patients, 48 (72.7%) were classified as severe and 18 (27.3%) as moderate. Male gender represented 60.1% of patients, and 54.5% had one or more medical comorbidities. The outcome of 20 (30%) patients was death.* Computerized Tomography *Severity Score (CT-SS) (r=0.533, p=0.002), age (r=0.300, p=0.016)**,** comorbidity with a cerebrovascular disease (r=0.479, p=0.013) or cancer (r=0.276, p=0.027). Also**,** oxygen saturation <93 (**r**=0.490, p=0.000), and Lactate dehydrogenase (LDH) plasma levels (r=0.525, p=0.006) showed correlations with mortality.* ***Conclusion:*** *Old age, CT Severity Score, elevated LDH, cardiovascular diseases, and cancer were linked with mortality that can aid expecting COVID-19 disease outcome.*

INTRODUCTION

Since February 2020, millions of people in the world have been diagnosed with Coronavirus Disease 2019 (COVID-19), a disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2 virus)[1]. In Egypt, the first case of COVID was on February 14, 2020[2]. Coronaviruses are enveloped positive-sense RNA viruses with spike-like projections on their surface giving them a crown-like an appearance[3].

The clinical presentations of COVID-19 are varied, ranging from an asymptomatic form to acute respiratory distress syndrom[4]. A confirmed case diagnosis is by reverse transcriptase–polymerase chain reaction (RT-PCR) tests on respiratory samples. The chest *computerized tomography* (CT) is considered a sensitive and specific diagnostic tool[5]. Severe COVID-19 is characterized by dyspnea, respiratory frequency of 30 breaths /minute or more, and blood oxygen saturation below 93%, while critical COVID-19 is characterized by respiratory failure, septic shock, and/or multiple organ failure[6]**.** In the United States, among 24 ICU patients, 75% required mechanical ventilation. While in China, 5% required ICU, and 2.3% required mechanical ventilation[7]. Mortality rates were described in patients with severe COVID-19 in the ICU range from 50–65%[8]. The risk of development of severe COVID-19 is related with age and patients' comorbid diseases such as obesity, Hypertension, and diabetes[9].COVID-19 pandemic has placed extraordinary pressure on health systems, and the mortality rate in severe patients with COVID-19 is high. So, the assessment of the factors linked with mortality is needed. This study aimed to analyze demographic, clinical, laboratory, and radiological parameters of COVID-19 Egyptian patients, and assess the parameters linked with the mortality helping to identify and treat severe patients early.

METHODOLOGY

The study was conducted at Fayoum University (FU) isolation Hospital**,** Egypt. Since the 21st of April 2020, the isolation hospital at FU started receiving and treating COVID-19 patients. The study is a prospective, observational cohort study on hospitalized COVID-19 patients. The study involved the individuals aged 18

years or older admitted to FU isolation hospital from November 2020 to April 2021 (second wave of COVID19 in EGYPT) with a confirmed PCR diagnosis for (SARS-CoV-2). The study was approved by the Ethical Committee of the Faculty of Medicine, Fayoum University (Code Number R167). The participants and their attendants were informed about the study aim and objectives.

The study included the newly admitted patients. Oropharyngeal swabs were taken from all suspected cases (by specialized Dacron swabs and preserved into vials containing viral transport medium STOR-F (DNA-Technology, Russia) and transported to the medical microbiology and immunology department faculty of medicine for RT-PCR (DNA-Technology, Russia); after RNA extraction using (Tiagen Bioscience Corporation, Taiwan). The program of real-time PCR (Rotor-Gene Q, 5-Plex-MDX) was adjusted according to the manufacturer's instructions.

Classification of cases to Mild, Moderate and Severe was performed according to World Health Organization guidelines as follows:

- **Mild cases:** when clinical symptoms are minimal without dyspnea, shortness of breath, or abnormal imaging of chest. Mild cases were indicated for home isolation.
- **Moderate Cases**: Individuals who show signs and symptoms of lower respiratory infection and their oxygen saturation was ≥93% on room air at sea level, were admitted to the isolation hospital.
- **Severe Cases**; defined by any of the following criteria: Respiratory rate > 30 breaths/min; Oxygen saturation <93%; Arterial partial pressure of oxygen (PaO_2)/ Fraction of inspired oxygen (FiO2) (P/F) < 300 mmHg or more than 50% progression in the chest radiological findings within 24 to 48 hours[2,9].

Patients diagnosed as a moderate or severe disease were involved in the study. Cases were followed up from the time of admission to hospital until discharged or death. RT- PCR was performed for all patients upon discharge. Patient demographics, presenting symptoms and laboratory findings reported at the time of admission, in addition to radiological data and outcome of all enrolled patients positive for SARS-CoV-2 infection were obtained. The labs included mainly; total lymphocytic count (TLC) and neutrophil/lymphocytic ratio (NLR), Platelet count, International Normalized Ratio (INR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), Creatinine, Urea, C-reactive protein (CRP), D-dimer, ferritin, Lactate dehydrogenase (LDH), albumin, K+, Na+, and blood gases. Also, chest CT-scan was performed in all cases, and were classified according to CT severity score (CT-SS), the 18 segments of both lungs were divided into 20 regions, a scoring of all 20 individual regions in each lung were assigned by the radiologists attributing a score of 0, 1, or 2 to each region, if parenchymal opacification was involved 0%, less than 50%, or equal to or more than 50% of each region, respectively. The CT-SS is the sum of the individual scores in the 20 segment regions and varied from 0 to 40 points. All lesions were evaluated for the following characteristics: a) ground-glass opacity (GGO), consolidation, or mixed pattern; b) involvement of the lung lobes; (c) location: peripheral; central, or both[10].

The (P/F) ratio was calculated to evaluate the levels of respiratory failure. Acute respiratory distress syndrome (ARDS) was diagnosed by the Berlin criteria [11]. For the patient's clinical status**,** Acute Physiology and Chronic Health Evaluation II score (APACHE score) was reported according to Kanus et al[12]. The outcome for all the patients was collected as discharged or death. The COVID-19 protocol of the Ministry of Health in Egypt was applied for the treatment of all hospitalized patients[13].

Statistical analysis:

Demographic data were summarized as frequencies and percentages, while continuous and categorical variables were obtainable as mean and Stander Deviation (SD). A chi-square test/Fisher's exact test was used to recognize the presence of a statistically significant difference between moderate and severe cases. The statistically significant difference was set at a p-value of <0.05. To recognize the relationship between different parameters and severs outcome and mortality in tested groups, the correlation was used. All analyses were performed using SPSS software version 26.

RESULTS

Demographic and comorbid diseases among the studied groups:

The current study included 66 patients. The Demographic data were showed in Table 1. Based on the severity classification of COVID-19 patients, 18 (27.3%) were moderate, and 48 (72.7%) were severe. The mean age, ±SD were 60.9 (±2.9) years with no significant difference between groups. Among all studied COVID-19 patients, 36(54.5%) of patients had one or more medical comorbidities. Common comorbidities were hypertension 18(27.3%) followed by diabetes mellitus 14(21.2%).

Table 1. Demographic data and comorbid diseases of COVID-19 patients

Variable	Total cases (N= 66)	Moderate cases (N=18)	Severe cases (N=48)	*P value*
Age (mean± SD)	60.9 ±2.9	55.1 ±14.3	63.04 ±16.56	0.06
Distribution No. (%)				
<40	8(12.1%)	2(11.1%)	6 (12.5%)	
41–60	18(27.3%)	6 (33.3%)	12 (25%)	
61–80	34(51.5%)	10 (55.5%)	24(50%)	
>80	6(9.1%)	0 (0%)	6(12.5%)	
	N %	N %	N %	
Sex N (%)				
Male	40(60.1%)	8(44.4%)	. 6%)632(6	0.18
Female	26 (39.9 %)	10(55.5%)	16(33.3%)	
Comorbidity (yes)				
DM	14(21.2%)	2(11.1%)	12 (25.0%)	0.90
HTN	18(27.3%)	2(11.2%)	16(33.3%)	0.38
HCV	4 (6.1%)	0(0%)	4(8.3%)	0.20
CKD	10(15.2%)	0(0.%)	10(20.8%)	0.08
IHD	2 (3.0%)	0(0 %)	2(4.2%)	0.37
Cancer	6(9.1%)	2(11.1%)	4(8.3%)	0.72
≥1 Comorbid diseases	36(54.5%)	4(22.2%)	32(66.6%)	

Abbreviations: **DM,** diabetes mellitus; **HTN**, hypertension; **HCV**, hepatitis C virus. **CKD**, chronic kidney disease; **IHD**, ischemic heart disease; <, less than; >, more than. Independent t test #Chi-square test, P considered significant if P < 0.05

Clinical findings of the studied groups

The commonest symptom on admission was cough (69.7%) followed by fever (60.6%) as shown in Table 2. Compared with the moderate group, fever (70.8%) was significantly more dominant in the severe groups (*p<0.005*). O_2 saturation on admission, ARDS, CT-SS, and APACHE II score were significantly greater in the severe group compared to the moderate group (*p<0.05*). Regarding outcome: death was reported only for severe cases (*p=0.028*).

Table 2: Clinical characteristics of the studied groups on admission

Variable	Total cases (N= 66)	Moderate cases (N=18)	Severe cases (N=48)	*P value*
	N %	N %	N %	
Symptoms				
Cough	44 (66.7%)	12 (66.6%)	32(66.7%)	0.743
Fever	40(60. 6 %)	6(33.3%)	34(70.8%)	**0.005**
Fatigue	18(27 .3%)	4(22.2%)	14 (29.2%)	0.573
Difficulty breathing	34(51.5%)	6(33.3%)	28(58.3%)	0.070
Gastrointestinal symptoms	2(3.0%)	0(0%)	2(4.2%)	0.379
O2 saturation on admission		.55±1.0994	79.8±14.3	**0.000**
Initial support				
Nasal cannula	22(33.3%)	12(66.6%)	10(20.8%)	
Face mask	14 (21.2%)	6 (33.3%)	8(16.7%)	
Non-rebreathing mask	30 (45.5%)	0(0%)	30(62. 5%)	
C-PAP	(12.1%)8	0 (0%)	8(16.7%)	
Intubated, ventilated	(15.1%)10	0 (0%)	10(20.8%)	0.030
P/F ratio				
100-200	(57.6%)38	16(88.8%)	22(45.8%)	
Less than 100	(39.4%)26	2 (11.1%)	24(50%)	0.339
ARDS development	26(39.4%)	2(11.1%)	24(50%)	**0.008**
CT findings				
Pattern:				
GGO	34(51.5%)	12(66.6%)	22(45.8%)	0.131
GGO consolidation:	32(48.5%)	6 (33.3%)	26(54.2%)	
Distribution				
Peripheral	44(66.7%)	18(100%)	26(54.2%)	**0.000**
central, peripheral	22(33.3%)	0(0%)	22(45.8%)	
affected lobe				
upper	22(33.3%)	2(11.1%)	20(41.7%)	**0.019**
lower	66(100%)	18(100%)	48(100%)	
CTSS (mean ±SD)		9.3 ±5.08	15.7 ±3.08	**000.0**
APACHE II (mean ±SD)		5.6±2.9	.3±7.510	**0.018**
Outcome				
Discharge	(69.7%)46	(100%)18	(58.3%)28	**0.002**
Died	(30.3%)20	0(0%)	(41.7%)20	

CPAP: Continuous positive airway pressure **P/F** is the ratio of arterial oxygen partial pressure (PaO2 in mmHg) to fractional inspired oxygen (FiO2 expressed as a fraction, not a percentage**)** **ARDS** Acute respiratory distress syndrome **GGO**: Ground-glass opacification CTSS CT severity score **APACHE II** Acute Physiology and Chronic Health Evaluation
Independent t test #Chi-square test, P considered significant if P < 0.05

Laboratories markers of the studied groups

As shown in **Table 3**, our results revealed significant increased levels of TLC, NLR, INR, ALT, and K+ in the severely ill group versus moderately ill group (*p<0.05*).

Table 3: Laboratories markers of COVID-19 patients

Variable	Reference rang	Rang	Total cases Mean ±SD	moderate Mean ±SD	Severe Mean ±SD	*P value*
CRP	**0·0–5·0**	6-96	52.13± 29.94	52.2 ± 27.962	52.1±30.39	990.0
LDH	**140-250u/l**	1920-267	726.5 ± 488	5 93.9 ± 000	737.3±456.5	0.1340
TLC	**4-11 x 10 / ul.**	25.5-3	.6± (6.19)10	6±1.8	12.3±6.3	**00.00**
NLR	**1.3-1.7**	5.2.-.20	.91± -0.500	1.18±0.53	0.82±0.46	**0.035**
PLT	**150-250x10/ul**	93-510	79.13 ±278	27 9 ±67.0	268 ±82.7	0.609
INR	**1.1**	0.9.1-1	1.16±0.22	1.07±0.06	1.2±0.25	**0.016**
Ferritin	**20–275 ng/mL**	46.00-3891.00	1.19389 ±76.76520	791.6±824.8	1299.6±982.5	0.141
D-dimer	**< 0.5mg/ml**	0.1-5.00	1.1667±1.10387	1.16±0.351	1.216±.1	0.997
Creatinine	**0.84 to 1.21 mg/dL 8-**	1.0- 4.300	1.1714±0.75810	0.93 ± 0.38	1.2 ±0.814	0.076
Urea	**23 mg/dL**	32.00-153.0	38.199± 66.67	52.5±24.7	73.7±41.1	0.131
AST	**7-40 mU/mL**	26.00-1562.00	16.85 ± 403.534	28±0000	179±409.4	0.071
ALT	**10.0-40.0 mU/mL**	17.00-1360.00	18.077± 354.8135	30±000	192± 359.12	**0.030**
Albumin	**3.5-5.5 g/dL**	2.60-4.00	3.3308±.36306	.45 ±3.3	3.3± 33	0.746
K	**3.5-5.5 mEq/L**	3.60-15.30	6.0222± 3.55274	4.0±000	6.27± 3.58	**0.023**
Na	**135-145 mEq/L**	122.00-190.00	141.62± 21.30686	132±000	143± 21.7	0.081
PaO2	**75 to 100 (mm Hg)**	22.00-71.00	41.8889± -14.18106	10.5 ± 40.1	42.5±15.15	0.528
PaCO2	**38-42 (mm Hg)**	22.00-60.00	41.8889 ± -9.79534	39.0±9.9	42.9± 9.52	0.216
H2CO3	**22-27(mEq/L)**	16.00-36.00	24.4815± -5.83998	26.5±5.19	23.7± 5.86	0.103
PH	**7.38 - 7.42**	7.29-7.50	7.3459± -.05264	7.3±.06	7.3±0.047	0.428

CRP:C-reactive protein **LDH**, lactate dehydrogenase **. TLC** total lymphocytic count **NLR**: neutrophils to lymphocyte ratio. **INR**, international normalized ratio. **AST**: aspartate aminotransferase; **ALT:** alanine aminotransferase;, P-value < 0.05 was considered statistically Independent t test #Chi-square test, P considered significant if P < 0.05.

Parameters that are related to mortality

Twenty (30.3%) patients died, being old age (r=0.300, p=0.016), having a cerebrovascular disease (r=0.479, p=0.013) or cancer (r=0.276, p=0.027). were conditions linked with mortality. Also decreasing oxygen saturation<93 on room air (r=0.490, p=0.000), and elevated LDH (r=0.525, p=0.006) showed a correlation with mortality. In addition, there was a significant positive correlation between CT-SS (r=0.533, p=0.002) with patient mortality. Whereas there was no correlation (p = 0.06) between Acute Physiology and Chronic Health Evaluation (APACHE) score II and mortality Table 4.

Table 4. Correlations between the parameters of COVID19 patients and Mortality

Parameter / Mortality	P value	*R*
Age	*0=0.016*	0.300
Cerebrovascular disease	*p*<0.013	0.479
Cancer	*p*<0.027	0.276
Decrease oxygen saturation (less than 93% on room air)	*p* = 0.000	0.490
LDH	*p*<0.006	0.525
CT SS	*p*<0.002	0.533

CTSS: CT severity score **LDH**: lactate dehydrogenase
APACH II score: Acute Physiology and Chronic Health Evaluation II score

DISCUSSION

It is preferable to identify severe COVID-19 patients earlier, to improve the recovery rate and reduce mortality rate[14]. In the current study, data analysis of 66 hospitalized adult Egyptian COVID-19 patients were presented. About (27.3%) were moderately ill, and (72.7%) were severely ill. Wang et al [15]. reported that with increasing age here is a reduction in humoral and cell-mediated immune responses. Our results revealed that the mean age of our patients was 60.9 (±2.9) years. These results are consistent with the preceding reports from Florida[14] and Egypt[16] that found the severe patients were significantly older compared to their matching groups. Females' innate and acquired immune responses may be stronger than males', making them less susceptible to infections[17]. Among our 66 participants, the most patients were males (60.1%). Karthick et al. from India[18], Wang et al from china[19], and Marcolino et al. from Brazil[20] also reported that the most COVD 19 patients (74.7%, 50.9%, 51.0%, and 50.9% respectively) were male. About 54.5% of our patients had more than one of medical comorbidities. Our findings are largely consistent with many previous studies. Sanyaolu et al[21] found that 40% of COVID 19 patients had comorbid conditions. Previous research reported that the commonest comorbidities were hypertension (range from 52.4 to 64.1%), diabetes mellitus (range from 25.3 to 41.2%), and obesity (17.2%) [14]. Also, Souza et al[22] reported that cardiac disease, diabetes mellitus, obesity, kidney disease, and lung diseases were the most prevalent comorbidities.

Our results revealed that on admission, the commonest symptoms were cough (69.7%), followed by fever (60.6%). Previous studies agree with these results as they found the most frequent symptoms were cough, shortness of breath, and fever[23,24]. Fever was a significant prominent feature among the severe cases in our study, a previous meta-analysis research found that dyspnea, was prominent feature among the severe cases[25]. Among our patients', overall ventilated patients were (15%). These findings were consistent with King et al[26] who found that (16.0%) were managed with mechanical ventilation. Most COVID-19 patients receiving invasive ventilation due to had moderate or severe acute respiratory distress syndrome[27]. CT scan can be a valuable tool in evaluating the individual disease problem[28]. Marcolino et al[20] and Al-Mosawe et al[29] found that ground-glass opacities were a common frequent finding (89.2%),(79%) respectively in COVID-19 patients, this was comparable to our results in which many of patients had ground- glass opacities (51.5%). Among our severe cases the mean of the total CT score was 15.7 with a statistically significant difference compared with moderate cases (p=0.00). In agreement with our results, Islam et al [30] reported that symptomatic presentations were higher (85.21%) when the CT severity index >15.

The overall mortality in the current study was 30% with a statistically significant difference between severe and moderate cases (p=0.002). This result agreed with Ahmed et al[31] who reported the mortality rate was 33%, but greater than that reported in another study which estimated the overall mortality was 22%[20]. Also, Souza et al[22] reported that mortality in the UK (33%), USA (29%), and Italy (26%).

Severe disease and death are linked with high levels of inflammatory parameters[32]. In our study, we revealed that the patients with severe disease have a significant difference of TLC (p=0.000) and Neutrophil Lymphocytes Ratio (p = 0.035), ALT (p = 0.03), and INR (p = 0.016). Liu et al[33] reported that the levels of lymphocyte count, CRP, and D-dimer were linked to the disease severity. In addition, Suleiman et al[34] reported significant leukocytosis in severe COVID-19 patients. Zhu et al[35] found the neutrophil-to-lymphocyte ratio was the most frequent statistically significant laboratory parameter in expecting the severity of the disease (96%).The higher levels of CRP may cause cytokine storms and affect liver function. Therefore, hepatic abnormalities worse the situation of COVID 19 patients[36]. The APACHE-II scoring system was found useful for classifying patients according to their disease severity[37]. We revealed a significant high APACHE score among severe cases compared with moderate cases (p=0.018).

In the present study we obtained a significant positive correlation between the age (r=0.300, p=0.016), decreasing oxygen saturation<93 on room air (r=0.490, p=0.000), having a cerebrovascular disease (r=0.479, p=0.013), or cancer (r=0.276, p=0.027) and elevated LDH (r=0.525, p=0.006) and mortality. Similar results were found by Karthick et al[18] who found that the patients aged >70 years identified as independent risk factors for mortality. Also, Bairwa et al[38] found Oxygen saturation ($P < 0.05$), elevated LDH ($P < 0.05$) had a significant association with mortality. While in studies done by Wang et al[19] and Zhu et al[35] suggests that acute blood urea was significantly associated with severity of COVID-19. This difference could be due to the differences in the study population between different countries or different viral genotypes.

Francone et al.[39] reported that the CT score ≥ 18 has shown to be highly predictive of patient mortality. This was comparable to our findings, there was a significant positive correlation between CT severity score (r=0.533, p=0.002) with patient mortality. Although we reported no correlation (p = 0.06) between (APACHE) score II and mortality. Nagar et al[40] suggested that the APACHE IV model better predicted mortality than the scoring system APACHE II in ICU.

CONCLUSION

Among the altered parameters, being old age**,** having a cerebrovascular disease or cancer, decreasing oxygen saturation<93 on room air**,** and elevated LDH, CT severity score showed a correlation with the mortality of COVID-19. These parameters might help to evaluate the treatment plan early and to improve the outcome and decrease mortality.

This manuscript has not been previously published and is not under consideration in the same or substantially similar form in any other reviewed media. I have contributed sufficiently to the project to be included as author. To the best of my knowledge, no conflict of interest, financial or others exist. All authors have participated in the concept and design, analysis, and interpretation of data, drafting and revising of the manuscript, and that they have approved the manuscript as submitted.

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