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PRELIMINARY STUDY: CLINICAL CHARACTERISTIC OF PATIENTS WITH MILD TO MODERATE COVID-19 PNEUMONIA EGYPTIAN EXPERIENCE REGARDING MANAGEMENT, MORBIDITY, MORTALITY

Running Title: Factors Determine Survival Probability In Covid-19.

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ABSTRACT:

Objectives: The coronavirus outbreak causes a wide range of disease severity. Our study aimed to identify factors affecting the survival of patients with mild to moderate COVID-19 pneumonia by evaluating inflammatory markers, anti-IL6 treatment, clinical parameters, oxygen levels, hospital stay duration, and mortality.

Material and Methods: a prospective cohort study that included 96 patients hospitalized for COVID-19 pneumonia. they underwent a thorough history review, vital signs assessment, and measurement of TNFα and IL6 by ELISA and CT chest.

Results: The median CT chest severity score was 5. Anti-IL-6 therapy was administered to 22 patients (22.92%). The median hospital stay was 9 days, with a 13.54% mortality rate. Higher oxygen levels at admission were associated with increased survival probability ($p<0.001$). Conversely, lower TLC, CRP, and IL-6 levels at admission were significantly linked to survival ($p=0.04$, 0.04, and 0.001, respectively). A smaller CT chest score was also associated with a higher survival probability ($p<0.001$). the mean survival time of patients receiving anti-IL-6 treatment was 21 days, while patients not receiving the drug was 26 days ($p=0.01$).

Conclusion: Patients treated with anti-IL-6 and received oxygen treatment showed early survival time compared to those who did not. This suggests that disease severity may significantly impact survival outcomes.

Keywords: Corona virus Disease of 2019, Tumor necrosis factor-alpha, C-reactive protein, anti- interleukin 6.

1. INTRODUCTION

According to the most recent World Health Organization data, SARS-COV-2, a novel human coronavirus, first emerged in December 2019 and has infected more than 500 million people through March 2023. (1)

Droplet infection, aerosols, and intimate contact are all widely established mechanisms of SARS-CoV-2 transmission. COVID-19's rapid dissemination, illness burden, and symptom pattern, on the other hand, have raised the possibility of other routes of transmission, such as fecal-oral. A significant proportion of SARS-CoV-2 infected persons experienced diarrhea. SARS CoV-2, like other coronaviruses, has been found in fecal samples. The presence of SARS-CoV-2 in feces could be explained by the presence of ACE-2 receptors, which SARS-CoV-2 binds to in the gastrointestinal mucosa. (2)

Pathological findings from a severe COVID-19 patient revealed pulmonary bilateral diffuse alveolar damage with cellular fibro myxoid exudates, hyaline membrane formation, interstitial mononuclear inflammatory infiltrates, and desquamation, which is consistent with acute respiratory distress syndrome (ARDS) and similar to lung pathology seen in severe Middle Eastern respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS). (3)

Lung damage causes a significant drop in the number of CD4+, CD8+ T lymphocytes, and natural killer cells. Elevated levels of IL-6, enhanced T-helper 17 in CD4+ T lymphocytes, and cytotoxicity of CD8+ T cells are thought to boost the immune response and trigger cytokine release syndrome (CRS), which eventually leads to ARDS and multiorgan failure. (4)

Macrophage activation syndrome is a condition characterized by systemic hyperinflammation that is typically encountered in patients with infections or malignancies. In patients with severe COVID-19 pneumonia, IL-1, IL-2, IL-6, IL-7, IL-17, and TNF levels were significantly raised. In COVID-19 patients, not only hypercytokinemia but also high ferritin, CRP, and D-dimer

levels indicate the development of macrophage activation syndrome-like severe inflammation and fibrinolysis. [5]

Coughing is a common symptom of COVID-19. Chest discomfort and dyspnea usually appear later in the illness. Pneumonia and ARDS are examples of respiratory problems. [6]
According to the Egyptian Ministry of Health's COVID-19 diagnosis and treatment recommendations, COVID-19 is classed as a mild sickness, with symptoms of COVID-19 but no evidence of pneumonia or hypoxia. Patients with mild fever, respiratory symptoms, and radiological signs of pneumonia, regardless of whether they have one or more risk factors (obesity, pregnancy, active malignancy, age > 65, chemotherapy, immunosuppressants, or uncontrolled comorbidities). Patients with severe cases have any of the following conditions: breathing difficulty, breathing less than 30 times per minute, arterial oxygen saturation (SaO2) 92%, arterial oxygen pressure (PaO2)/oxygen concentration (FiO2) in arterial blood 300, and computerized tomography of the chest (CT chest) affection >50% that has progressed in the previous 24-48 hours. Cases in point: Patients with one of the following conditions: Because of respiratory failure, mechanical ventilation is necessary. Admission to the intensive care unit (ICU) due to severe organ failure and/or shock. SARS-CoV-2 has been associated with innate immunity activation, with an increase in neutrophils, mononuclear phagocytes, and natural killer cells, as well as a decrease in T lymphocytes composed of CD4 + and CD8. [7]
It is noteworthy that during the SARSCoV-2 infection, an increase in the secretion or production of IL-6 and IL-8 is seen in COVID-19 patients along with a decrease in CD4+ and CD8+ and T cells in general. [8]
Studies have shown that IL-6 and ferritin levels were higher in patients who lost their lives due to COVID-19 than in patients who recovered. [9]
TNF is predominantly generated by activated macrophages, T lymphocytes, and natural killer cells. TNF and interleukin (IL)-1 are proinflammatory cytokines involved in the pathogenesis of rheumatoid arthritis (RA). TNF has a substantial impact on bone remodeling; it directly regulates osteoclast precursor levels in the bone marrow by upregulating c-fms expression, and it activates osteoclasts by enhancing RANK signaling. It also contributes significantly to infection control. TNF production by macrophages appears to be necessary for granuloma development and maintenance, as well as for defending intracellular organisms against invasion. [10]
Increasing the secretion and activity of IL-6 in the bloodstream can increase blood pressure and subsequent complications. [11]
High levels of interleukin-6 and COVID-19 have a very high risk of developing severe respiratory failure. [12]
Our research intends to assess the influence of numerous inflammatory mediator parameters, including TNFα and IL 6, and the severity of COVID-19 infection. It also aims to study the relationship between Tocilizumab and survival rate, which may have a significant impact on patient's clinical outcomes.

2. METHODS

The present study was a prospective cohort analytical study that was carried out during the period between November 2021 and August 2022. The study included 96 hospitalized patients diagnosed with COVID-19 infection based on real-time polymerase chain reaction (PCR) for COVID-19. Patients with non-available PCR results or those under the age of 18 years were excluded. The study was approved by the Institutional Review Board of the Faculty of Medicine (IRB No. (MD-6-2022) and was conducted by the principles of the Declaration of Helsinki. Written informed consents were obtained from all participants before enrollment in the study. We enrolled all hospitalized COVID-19 pneumonic patients, both sexes were

included. The exclusion criteria were any subjects with age less than 18 years, mild cases of COVID-19 patients, and non-hospitalized COVID-19 patients. All patients were subjected to full history taking including; age, sex, smoking status, history of present illness, and co-morbidities. Vital signs were checked including blood pressure measurement, pulse, temperature, and oxygen saturation on room air and after oxygen therapy if needed. laboratory investigations were done including complete blood count (CBC) & lymphocyte percentage, renal and liver function tests, C-reactive protein (CRP), D-dimer, LDH, Procalcitonin, serum Ferritin, serum interleukin 6 (IL6), Tumor necrosis factor-α (TNF-α). Also, resting arterial blood gases (ABG) during room-air breathing was done.

All initial chest CT scans were performed on the day the patient was admitted. The patients were lying down and asked to hold their breath while the scans were taken. The scanning parameters were as follows: scan direction (from head to toe), tube voltage (120 kV), tube current (100–600 mA), rotation time (0.5 s), and scan length (60.00–1300.00 s). For the CT image analysis, the scans were first assessed to see if they showed typical findings of COVID-19 pneumonia, such as bilateral, multilobe, and posterior peripheral ground-glass opacities. Then, the severity was evaluated using a scoring system based on the visual assessment of each affected lobe.

Measurement of serum TNF-α and IL6 serum levels by an enzyme-linked immunosorbent assay (ELISA)*, It is a sandwich kit for the accurate quantitative detection of human tumor necrosis factor-α and IL6 in serum. The plates have been pre-coated with Human TNF-α and IL6 antibodies. TNF- α and IL6 present in the sample were added and bound to antibodies coated on the wells then biotinylated Human TNF-α, and IL6 antibodies were added and bound to TNF-α and IL6 in the sample.

Eight ml venous blood sample was taken and allowed to clot for 10-20 minutes at room temperature, centrifuge at 2000-3000 RPM for 20 minutes. The supernatant was collected without sediment and stored at - 20℃ till the time of assay.

Statistical Methods

The statistical analysis for this study was conducted using Minitab 17.1.0.0 for Windows (Minitab Inc., 2013, Pennsylvania, USA). The normality of the data was assessed using the Shapiro-Wilk test. Continuous data were presented as medians and interquartile ranges, while categorical data were expressed as numbers and percentages. Non-parametric numerical data were compared using the Mann-Whitney test, and frequencies were compared using the Fisher Exact test. Furthermore, multiple logistic regression analysis with stepwise selection methods was utilized to predict the factors associated with in-hospital COVID-19 survival. The receiver operating characteristic curve was used to determine the utility of some inflammatory markers and oxygen saturation in predicting the good prognosis of COVID-19 patients.

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Kaplan-Meier test was employed to estimate the in-hospital survival probability of patients with COVID-19 pneumonia. All tests were two-sided, and a p-value of less than 0.05 was considered statistically significant.

3. RESULTS

The current study was conducted on 96 hospitalized patients who were diagnosed with COVID pneumonia attending, during the period between November 2021 and August 2022. **Table (1)** summarizes their demographic and clinical characteristics. The median age of the patients was 65 years (IQR: 56-72 years), with males comprising 60.42% of the sample. The most common comorbidities were hypertension (54.17) and diabetes mellitus (44.79%). The median time from symptom onset to hospital admission was 7 days (IQR: 5-10 days). Upon admission, only

23 patients (23.96%) required oxygen supplementation, with conventional devices being the most frequently used (20.83%), while only 3 cases required mechanical ventilation. The severity score of CT-Chest was mild to moderate; the median was 5 and the IQR was from 4-7. Anti-IL-6 therapy was initiated for 22 patients (22.92%). The median length of hospital stay was 9 days (range: 6-14 days), with a mortality rate of 13.54%.

Table (1): Characteristics of COVID-19 patients:

Factors	**Total (n=96)**		
	Median	Q1	Q3
Disease onset (days)	7	5	10
Comorbidity	N	%	
HTN	52	54.17	
DM	43	44.79	
Renal	21	21.88	
Hepatic	8	8.42	
IHD	28	29.79	
SO2 (%) on room air	88	82	94
Lab.	Median	Q1	Q3
TLC ($\times 10^9$)	8.5	5.4	11.1
Hb (mg/dL)	11.75	10	13.8
PLT ($\times 10^9$)	216.5	149.3	277.8
Lymphocyte (%)	782	500	1200
CRP (mg/L)	58.5	23	125
Ferritin (ng/mL)	650	286	1100
IL-6 (pg/mL)	44	23.25	79.75
TNF-alpha (pg/mL)	77.3	62	110.3
LDH (U/L)	450	262	666
D-DIMER (µg/mL)	0.9	0.5	1.875
PROCALCITONIN (µg/mL)	0.29	0.1	0.4
CT-chest (score)	5	4	7
Treatment	N	%	
A. Oxygen supply	23	23.96	
A.1. Conventional oxygen	20	20.83	
A.1.1. high-velocity nasal cannula	3	3.13	
A.1.2. FM	8	8.33	
A.1.3. NP	4	4.17	
A.1.4. NRM	5	5.21	
A.2. Invasive	3	3.13	
A.2.1. CPAP	1	1.04	
A.2.2. MV	2	2.08	
B. Ant-IL-6	22	22.92	
Outcome	N	%	
Survival	83	86.46	
Mortality	13	13.54	
	Median	Q1	Q3

LOS (days)	8.5	6.25	14

N: number, Q1: quartile 1: Q3: quartile 3, the numerical data presented as median and inter-quartile range (Q1-Q3), LOS: length of hospital stay, and categorical data as number and percentage.

In the univariate analysis Table (2), the survival probability increased significantly in patients with high oxygen saturation levels on room air at admission ($p<0.001$). Conversely, low TLC, CRP, and IL-6 levels at admission were significantly associated with survival ($p=0.04$, 0.04, and 0.001, respectively), while elevated TNF-α levels increased the survival probability ($p=0.05$). Additionally, a smaller CT chest score was associated with a higher survival probability ($p<0.001$). The frequency of patients requiring oxygen supply and anti-IL-6 treatment was significantly lower in the survival group compared to the mortality group ($p=0.001$ for both). The median length of hospital stay was significantly shorter in the survival group compared to the mortality group ($p<0.001$).

Table (2): Factors associated with COVID-19 survival:

Factors	**Survival (n=74)**			**Mortality (n=22)**			**p**
	Median	Q1	Q3	Median	Q1	Q3	
Age (years)	65	53	72	62	58	71	0.71
	Median	Q1	Q3	Median	Q1	Q3	
Disease onset (days)	7	5	10	7	4	13	0.77
Comorbidity	N	%		N	%		
HTN	8	61.54		44	53.01		0.56
DM	7	53.85		36	43.37		0.48
Renal	3	23.08		18	21.69		0.91
Hepatic	6	7.32		2	15.38		0.33
IHD	5	38.46		23	28.4		0.51
Clinical signs	Median	Q1	Q3	Median	Q1	Q3	
SO2 (%) on room air	89	84	94	60	42	78.5	<0.001†
Lab.	Median	Q1	Q3	Median	Q1	Q3	
TLC ($\times 10^9$)	8.3	5.4	10.3	11.55	5.88	15.33	0.04†
Hb (mg/dL)	11.6	10	13.8	12.7	10.9	13.7	0.55
PLT ($\times 10^9$)	203	142	277	243	191	303.5	0.14
Lymphocyte (%)	800	500	1200	720	450	1302	0.85
CRP (mg/L)	55	22	120	117	54.5	156	0.04†
Ferritin (ng/mL)	669	300	1102	353	237	662	0.24
IL-6 (pg/mL)	42	22	71	112	47	244	0.001†
TNF-alpha (pg/mL)	80.1	64.3	113.5	62.3	48.25	89.1	0.05†
LDH (U/L)	427	261	670	550	439	715.5	0.21
D-DIMER (µg/mL)	0.9	0.5	1.8	1.4	0.94	2.2	0.14
PROCALCITONIN (µg/mL)	0.26	0.1	0.4	0.37	0.125	0.715	0.13
CT-chest (score)	5	3	6	9	5	13.5	0.003†
Treatment	N	%		N	%		
Oxygen supply	16	19.28		7	53.85		0.001*
Ant-IL-6	12	14.46		10	76.92		0.001*
	Median	Q1	Q3	Median	Q1	Q3	
LOS	7	6	14	14	14	21	<0.001†

N: number, Q1: quartile 1: Q3: quartile 3, the numerical data presented as median and inter-quartile range (Q1-Q3), and categorical data as number and percentage. †: The test of significant: Mann Whitney test, *: The test of significance: Fisher Exact test, $p<0.05$ considered significant.

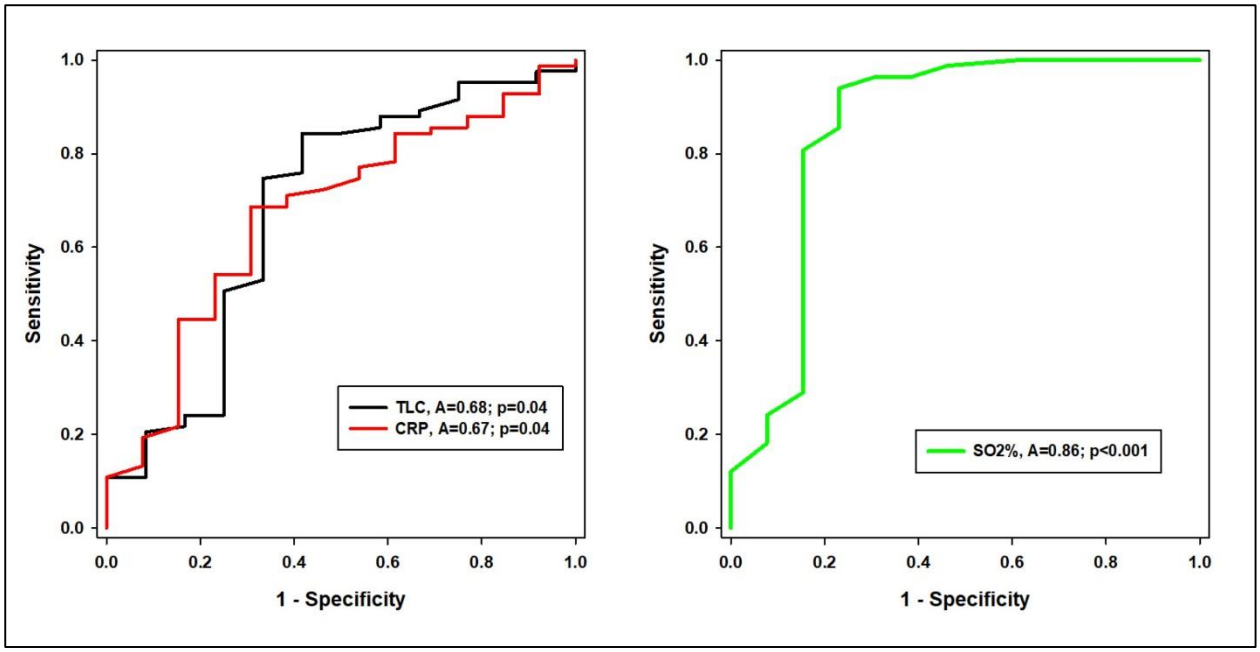
The independent predictors of survival are summarized in **Table (3)**. The likelihood of mortality increased by 35 times in patients with DM, and 0.05 in patients with HTN (OR=35.46 and 0.05, respectively, p=0.04 for both). Moreover, for every one-unit increase in oxygen saturation at room air, the likelihood of survival doubled (OR=1.56, p=0.001). Additionally, for every one-unit increase in TLC, particularly lymphocyte percentage, the likelihood of survival increased by two and one-fold, respectively (OR=1.68 and 1, p=0.01 for both). Conversely, for every one-unit decrease in PLT and CRP, the likelihood of survival increased (OR=0.98 and 0.97, respectively, and p=0.03 and 0.01, respectively).

Table (3): Predictors of survival of COVID-19 pneumonia:

Factors	**CE**	**OR**	**95% CI**	**p**
Age	0.09	1.09	(0.9557, 1.2526)	0.12
Female-Sex	-1.10	0.33	(0.0167, 6.6390)	0.45
HTN	3.02	0.05	(0.0014, 1.7622)	0.04
DM	-3.57	35.46	(0.4843, 2596.1861)	0.04
Disease onset (days)	-0.13	0.88	(0.6788, 1.1438)	0.32
SO2 (%) on room air	0.43	1.54	(1.0576, 2.2309)	0.001
CT-chest (score)	-0.55	0.58	(0.2482, 1.3372)	0.17
TLC ($\times 10^9$)	0.52	1.68	(0.8114, 3.4742)	0.01
Hb (mg/dL)	-0.23	0.79	(0.3262, 1.9275)	0.61
PLT ($\times 10^9$)	-0.02	0.98	(0.9666, 1.0012)	0.03
Lymphocyte (%)	0.001	1.00	(0.9920, 0.9999)	0.01
CRP (mg/L)	-0.03	0.97	(0.9364, 1.0022)	0.01
Ferritin (ng/mL)	0.001	1.00	(0.9984, 1.0005)	0.41
IL-6 (pg/mL)	0.03	1.03	(0.9908, 1.0642)	0.11
LDH (U/L)	0.001	1.00	(0.9965, 1.0080)	0.42
PROCALCITONIN (µg/mL)	-0.87	0.42	(0.1178, 1.4897)	0.24

CE: Coefficient, OR: odd ratio, CI: confidence interval, the sign before CE denoting the direction of relationship, the test of fitness: Hosmer-Lemeshow test, $X^2=4.3$, p=0.81, the test of significance: Multiple logistic regression test with stepwise selection and adjustment for age, sex, and comorbidity, $p<0.05$ considered significant.

The ROC curves for TLC, CRP, and SO2% Fig. (1) demonstrated good to very good discrimination power between the survival and mortality groups, with AUCs of 68%, 67%, and 86%, respectively (p=0.04, 0.04, and <0.001, respectively). The cut-off points for TLC and CRP, less than 11.45 and 95 mg/L respectively, yielded sensitivities and specificities of approximately 84% and 58%, and 69% and 69%, respectively. Conversely, the cut-off value for SO2% above 76% resulted in a sensitivity of 94% and a specificity of 77% (Table 4).



A: area under curve, p<0.05 considered significant.
Fig. (1): ROC curve of TLC, CRP, and SO2%.

Table (4): Utility of TLC, CRP, and SO2% at room air in detecting survival probability:

Factors	Cutoff	Sensitivity	95% CI	Specificity	95% CI	PPV	NPV
TLC ($\times 10^9$)	<11.45	84%	0.7471 to 0.9139	58%	0.2767 to 0.8483	67 %	79 %
CRP (mg/L)	<95	69%	0.5756 to 0.7841	69%	0.3857 to 0.9091	69 %	69 %
SO2%	>76	94%	0.8650 to 0.9802	77%	0.4619 to 0.9496	80 %	93 %

CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value.

In Fig. (2), the average in-hospital survival time for COVID-19 pneumonia patients was 24 days, with a 24% survival probability by day 28. Among patients treated with anti-IL-6, the mean survival time was 21 days, resulting in a 38% survival probability by day 21. Conversely, those who did not receive the drug had an extended mean survival time of 26 days, with a survival probability of approximately 57% by day 21 (p=0.01). Furthermore, patients who received oxygen treatment had a mean survival time of 17 days, with a 44% survival probability by day 21. In contrast, those who did not receive oxygen had a longer mean survival time of 25 days, with a 24% survival probability by day 28 (p=0.03). However, concerning disease severity determined by CT-Chest score, data showed that patients with mild COVID-19 pneumonia had a mean survival time of about 25 days, with a 31% survival probability by day 28, while those with moderate pneumonia had a mean survival time of about 20 days with a 21% survival probability by day 21 (p=0.31).

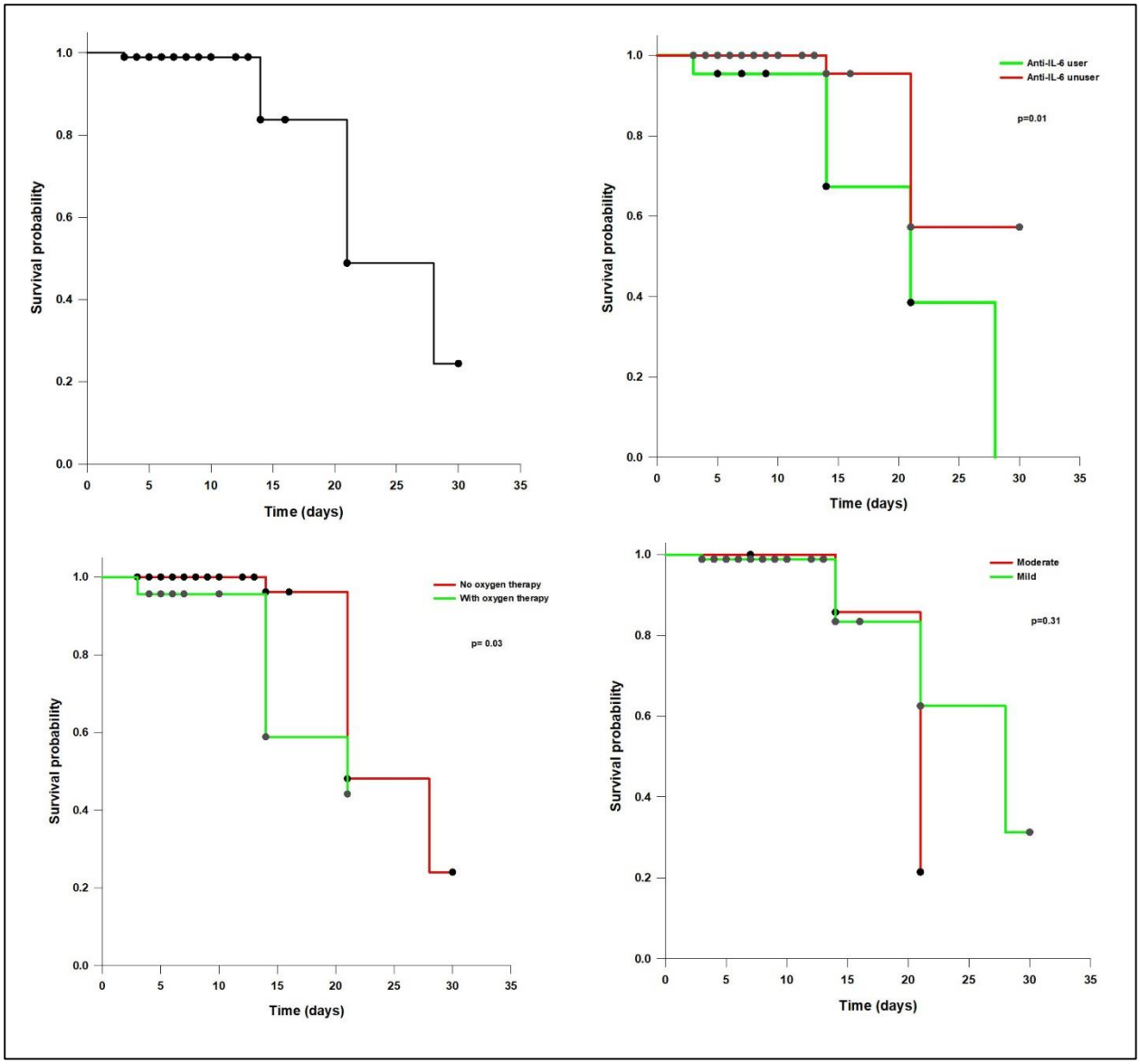


Fig. (2): Survival probability of patients with COVID-19 pneumonia.

4. DISCUSSION

This article was a prospective cohort study which was conducted on 96 hospitalized patients who were diagnosed with COVID pneumonia and admitted to the hospital, during the period between November 2021 and August 2022.

The study aimed to determine the factors influencing the survival probability of patients with mild to moderate COVID-19 pneumonia through evaluation of the level of the inflammatory mediators associated with SARS-CoV-2 infection including; TNF-α, and IL6, treatment with anti-IL6 and to identify their relation to clinical parameters, arterial oxygen saturation, duration of hospital stay, and mortality.

The median age of the patients was 65 years (IQR: 56-72 years), with males comprising 60.42% of the sample. The most common comorbidities were hypertension (54.17) and diabetes mellitus (44.79%). The median time from symptom onset to hospital admission was 7 days (IQR: 5-10 days).

Similarly, a study was done by **Jia and his colleagues (2021)** on 149 patients with severe or critical COVID-19 pneumonia who were hospitalized in the Sino-French New City Branch of

Tongji Hospital from 30 January to 30 March 2020. The mean age of their patients was 64 ±13.29 years with male predominance accounting for 69.1%. Most of their patients had hypertension (40.3%) followed by diabetes (16.8%) followed by coronary artery disease (14.8%). [14]

Another Egyptian study was conducted on 46 COVID-19 patients who were admitted to the Internal Medicine Isolation hospital from November 2020 to March 2021, their study included 28 males and 18 females (M: F 1.6:1) with a mean age of 57.76 ±12.49 years. About 69.6% of them had co-morbidities. [15]

Also, a prospective cross-sectional study was conducted on 50 patients with COVID-19 at Loghman Hospital in Tehran (Iran) from March 26 to April 22/ 2020. The mean age was 42.7 ± 12.4 years (19–78). The highest proportion of the patients were males (57.1%). [16]

We found that cough was the most prevalent presentation (n=72 patients, 75%) followed by fever (n=70 patients, 72.9%), then fatigue (n=63 patients, 65.6%). However, Jia and his colleagues (2021) reported that fever (88.6%), cough (68.5), and dyspnea (34.9%) were the most common symptoms. [14]

Also, a retrospective, single-center cohort study was conducted on 308 patients diagnosed with COVID-19 from 10 January 2020 to 13 February 2020 at Tongji Hospital, Huazhong University of Science and Technology (Wuhan, China). The authors detected that the most common symptom was fever followed by cough. [17]

A single-center retrospective cohort study was conducted on 80 hospitalized patients in Beijing You'an Hospital. This study detected that the most common symptom of patients with COVID-19 was fever (86.3%), which was followed by cough (71.3%), expectoration (42.5%), shortness of breath (37.5%), fatigue (37.5%) and anorexia (30.0%). [18]

In our study, the severity score of CT-Chest was mild to moderate; the median was 5 and the IQR was from 4-7. Additionally, a smaller CT chest score was associated with a higher survival probability ($p<0.001$).

An Italian study by Francone et al.reported that the Chest CT score values were significantly higher in critically ill patients than in mildly ill patients, and in late-onset patients than in early-onset patients ($p < 0.0001$). [13]

In our study, the median TLC was 8.5 with an IQR of 5.4 - 11.1, the median lymphocyte number was 782 and the IQR was 500-1200. The median CRP was 58.5 with IQR 23-125. The median IL6 was 44 with an IQR of 23.25 – 79.75, and the median TNF α was 77.3 with an IQR of 62 – 110.3.

Jia and his colleagues (2021) found that the mean WBCs was 9.52±5.82 $\times 10^9$/L with the mean lymphocytes 0.77±0.47 $\times 10^9$/L. The mean LDH was 488.36±311.44 IU/L. The mean IL-6 was 31.8 pg/ml and the mean TNF- α was 9.2 pg/ml. [14]

Saleh and his colleagues (2022) detected that the median TLC was 6.94 (4.5-8.7) 10^3/cmm with median lymphocytes 13.5 (7-31) %. The median CRP was 20.5 (6-71) mg\L. The median ferritin was 499.5 (165-1247) ng/mL. The median D-dimer was 0.88 (0.53-2.2) µg/mL. The median LDH was 437 (311-541) U\L. The median PCT was 0.13 (0.08-0.4) ng/mL. The median IL-6 was 108.6 (25.8-262) ng/mL. The median TNF-α was 77.95 (29.2-513.3) pg/mL. [15]

Also, **Mardani and his colleagues (2022)** revealed that the mean CRP was 8.70, the mean lymphocytes was 37, the mean TNF-α was 66, and the mean IL−6 was 20. [16]

The high levels of IL6 and TNF-α shown in our study as well as others are in harmony with the exaggerated production of pro-inflammatory cytokines in COVID-19 patients. [20] [21]

High serum levels of cytokines and chemokines in infected patients have been reported to be associated with the disease severity and adverse outcomes, highlighting the potential function of hyper-inflammatory reactions in COVID-19 progression. [22] [23]

Recently, it has been suggested that the cytokine storm and immunological dysfunction were linked to rapid illness progression. Researchers discovered that the levels of infection-related biomarkers were critical in severe instances of COVID-19. Furthermore, prior research found that lower lymphocyte counts, particularly lower levels of T lymphocyte subsets, were associated with severe cases, as were elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6). These revealed that immunological dysfunction and cytokine dysregulation could play crucial roles in the course of the disease. **(24, 25, 26, 27)**

Regarding the correlation between laboratory findings and their impact on the outcome, our study low TLC, CRP, and IL-6 levels at admission were significantly associated with survival (p=0.04, 0.04, and 0.001, respectively), while elevated TNF-α levels increased the survival probability (p=0.05).

Jia and his colleagues detected that the levels of TNF-α, and IL-6, elevated in patients who died, whereas the level of IL-1β in the patients who died was lower than that of those who survived **(14)**.

Also, **Mardani and his colleagues** revealed that the correlation between IL-6, TNFα, and CRP levels along with other factors and the disease severity was significant. **(16)**

Similar to a study by **Huang and his colleagues** who found that IL-6 and TNFα levels were associated with the severity of COVID-19. **(28)**

Another meta-analysis conducted **by Aziz and his colleagues** involved nine studies (1426 patients), and it confirmed that a higher serum level of IL6 was associated with an increased risk of complicated COVID-19 and death. **(29)**

Among patients treated with anti-IL-6 in Fig. (2), the mean survival time was 21 days, resulting in a 38% survival probability by day 21. Conversely, those who did not receive the drug had an extended mean survival time of 26 days, with a survival probability of approximately 57% by day 21 (p=0.01).

The frequency of patients requiring anti-IL-6 treatment was significantly lower in the survival group compared to the mortality group (p=0.001).

Conrozier and colleagues published a retrospective case series of 40 patients with ARDS treated with tocilizumab (anti-IL6), with 30 surviving and 10 dying. Compared to the case fatality rate of 22.8% (94/413) among all COVID-19 patients at their center during the same period. The authors proposed that tocilizumab resulted in favorable evolution in instances with COVID-19 ARDS. (30)

Similarly, in another retrospective case series from South Italy, the IL-6 receptor antagonist sarilumab was prescribed to 15 patients with COVID-19. In 10 of 15 patients, respiratory function improved rapidly, and inflammatory indicators were normalized. The case fatality rate for this cohort was 33%. **(31)**

The independent predictors of survival **Table (3)**. The likelihood of survival increased by 35 times in patients with DM, whereas HTN decreased the likelihood of survival (OR=35.46 and 0.05, respectively, p=0.04 for both). Moreover, for every one-unit increase in oxygen saturation at room air, the likelihood of survival doubled (OR=1.56, p=0.001). Additionally, for every one-unit increase in TLC, particularly lymphocyte percentage, the likelihood of survival increased by two and one-fold, respectively (OR=1.68 and 1, p=0.01 for both). Conversely, for every one-unit decrease in PLT and CRP, the likelihood of survival increased (OR=0.98 and 0.97, respectively, and p=0.03 and 0.01, respectively).

Khalil, 2023 a retrospective cross-sectional study was conducted to analyze the survival of COVID-19 patients and the factors associated with COVID-19 deaths in the hospitals of Ilam Province. The sample size was 774 COVID-19-positive patients from Ilam Province. Measuring survival and risk probabilities in one-week intervals was performed using Cox regression. Most patients were male (55.4%) and 55.3% were over 45 years old. Of the 774 patients, 87 (11.2%) died during the study period. The mean hospital length of stay was 5.14

days. The median survival time with a 95% confidence interval was four days. The probability of survival of patients was 80%, 70%, and 38% for 10, 20, and 30 days of hospital stay, respectively. There was a significant relationship between the survival time of patients with age, history of chronic lung diseases, history of diabetes, history of heart diseases, and hospitalization in ICU ($p < 0.05$). The risk of dying due to COVID-19 disease was higher among men, older age groups, and patients with a history of chronic lung diseases, diabetes, and heart disease. According to the results, taking preventive measures for elderly patients and those with underlying conditions to prevent the infection of COVID-19 patients is of potential interest. Efficiency in the management of hospital beds should also be considered. **(32)**

Wen Lu, 2022 study included 239 patients who were diagnosed with COVID-19, they were divided into the *improvement* group and the *death* group according to their outcome, Clinical characteristics and laboratory parameters were collected from medical records. The time-dependent area under curves (AUC) based on white blood cell count, lymphocyte count, neutrophil count by age, blood urea nitrogen, and C-reactive protein were plotted. Efficacy evaluation indicated that 99 (41.4%) patients had deteriorated, and 140 (58.6%) patients had improved. Oxygen saturation, hemoglobin levels, infection-related indicators, lymphocyte and platelet counts, C-reactive protein, serum albumin, liver and kidney function, and lactate dehydrogenase in the improvement group were statistically significant between the *improvement* and *death* groups. A survival analysis revealed that comorbidities, lymphocyte counts, platelet count, serum albumin, C-reactive protein level, and renal dysfunction may be risk factors in patients with COVID-19. **(33)**

Ahmed and Somasundram, 2022 studied 236 participants comprising 153 (77.54%) survivors and 53(22.46%) non-survivors. Most participants were female (59.75%) with a mean age of 53.08 (16.96) years. The non-survivor group demonstrated a significantly lower median/mean for admission oxygen saturation (%) [87(78–95) vs. 96(90–98)], Age, oxygen saturation, respiratory rate, glucose, and diastolic BP were found to be significantly associated with mortality on univariate analysis. A log-rank test revealed significantly lower survival rates in patients with an admission oxygen saturation of $< 90\%$ compared with $\geq 90\%$ ($p = 0.001$). Multivariate logistic regression revealed a significant relationship between age and oxygen saturation with in-hospital mortality (OR 1.047; 95% CI 1.016–1.080; $p = 0.003$ and OR 0.922; 95% CI 0.880–0.965; $p = 0.001$ respectively). A ROC curve analysis generated an area under the curve (AUC) of 0.778 ($p < 0.001$) when evaluating the predictive ability of oxygen saturation, respiratory rate, glucose, and diastolic BP for in-hospital death. This improved to an AUC of 0.832 ($p < 0.001$) with the inclusion of age. **(34)**

Some limitations also need to be addressed. First, the cytokine changes throughout the hospitalization duration were not analyzed because most of the patients underwent a single cytokine test only. Additionally, the patients enrolled in our study were moderate, severe, or critical cases only, the potential role of TNF-α in disease prognosis might not be directly applicable to asymptomatic and convalescent cases. Finally, the relatively small sample size.
So, we recommended, that further longitudinal multi-center studies with larger sample sizes are required to detect predictively of cytokines and to analyze the efficacy of immunomodulatory treatment. Also, Serial cytokines measurements and long-term follow-up of COVID-19 have to be performed. Taking into consideration that serum cytokine especially IL-6 is a promising biomarker of COVID-19 severity and outcome. Also, Proper understanding of the cytokine response pattern in COVID-19 would contribute to the improved development of more effective immunomodulatory therapies for COVID-19 in the future.

5. CONCLUSION

These results indicate several important findings regarding the impact of treatments and disease severity on survival outcomes in COVID-19 pneumonia patients. Firstly, patients treated with anti-IL-6 had a shorter mean survival time compared to those who did not receive the drug, but they exhibited a higher survival probability by day 21, suggesting a potential benefit in terms of early survival despite the shorter mean survival time. Conversely, patients who did not receive anti-IL-6 treatment had a longer mean survival time but a lower survival probability by day 21. Similarly, patients who received oxygen treatment had a shorter mean survival time compared to those who did not receive oxygen, but they showed a higher survival probability by day 21, indicating potential short-term survival benefits. However, patients with moderate pneumonia had a shorter mean survival time compared to those with mild pneumonia, although the difference was not statistically significant. This suggests that disease severity, as determined by CT-Chest score, may have a notable impact on survival outcomes, with moderate pneumonia being associated with poorer survival. These findings underscore the importance of considering both treatments and disease severity in managing COVID-19 pneumonia patients to optimize survival outcomes.

List of Abbreviations:
COVID-19: coronavirus disease 2019
ARDS: acute respiratory distress syndrome
IL6: interleukin 6
TNFα: tumor necrosis factor α
MERS: Middle East respiratory syndrome
CRS: cytokine release syndrome
PCR: polymerase chain reaction.

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34. Declaration Ethics approval and consent to participate.
35. The study was approved by the Institutional Review Board of Faculty of Medicine, Cairo University (IRB No. MD-6-2022) and was performed in accordance with the principles of the Declaration of Helsinki. Written informed consents were obtained from all participants before the enrollment to participate in the study.
36. Consent for publication Not applicable.
37. AVAILABILITY OF DATA and MATERIAL
38. The datasets generated during the current study are not publicly available due to the hospital policy and because the data will be used in future multi-center research to generate a nationwide statistic. However, these datasets are available from the corresponding author (Hala Ashraf) on reasonable request.
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43. Author Contributions
44. NMM was the idea founder, shared in the patient collection, SZK and SSA were the supervisor in all the steps. AAH shared in the patient collection did the data analysis, HAH, MHM and wrote and revised the manuscript and supervise in all steps. HAH did the laboratory work and is the submitting and corresponding author. NMM shared in the patient collection. All authors read and approved the final manuscript.
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