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Outcome and Survival of Severe to Critical COVID-19 Patients Admitted at Zagazig University Hospitals

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ABSTRACT

Background: More than 356 million people have been infected with the new coronavirus (SARS-CoV-2) that causes COVID-19. **Objective:** to assess outcomes and survival of COVID-19 patients admitted at Zigzag University Hospitals. **Patients and methods:** Retrospective cohort study was conducted at COVID isolation Sednawy Hospital, Zagazig University during the period from Jan 2021 to Dec 2021 including 900 cases as a comprehensive sample, were selected as severe to critical COVID patients according to the criteria of Egyptian protocol for management of COVID-19 patients. All patients had real-time polymerase chain reaction (RT-PCR) in respiratory tract materials.

Results: There was significant relation between severity and overall survival, which was significantly higher in those with severe disease. There was significant relation between comorbidity and overall survival, which was significantly higher in those without comorbidity and overall survival, death was 40.9% of all cases; 84.9% of critical and 12% of severe (P 0.001). Survival was highest in 3rd group 72.8%, while lowest in 1st group 42.3% (P 0.001). Remdesivir was used in 58.4% of critical and 45% in severe cases, while non-used antiviral was in 29% of critical and 27% of severe cases. CRP, IL6, Albumin/IL6 ratio, neutrophil/lymphocytes ratio were all statistically different between critical and severe cases, while PCT and CRP were insignificantly different.

Conclusion: Outcome improving over different groups with time, this means improvement in medical care, different comorbidities, change in the level of acute phase reactant and anti-inflammatory drugs may affect the survival of severe and critically ill COVID 19 patients.

Keywords: COVID-19, Mortality, Outcome and survival, Severity.

INTRODUCTION

Multiple organ damage illness COVID-19 is caused by severe acute respiratory syndrome with the lung as its primary target organ; it can lead to severe pulmonary injury and acute respiratory distress syndrome, which may lead to mortality in severe cases [1, 2]. One of the most difficult aspects of treating COVID-19 patients is determining how severe their sickness is [3].

The identification of parameters related with COVID-19 results is vital in the context of a healthcare system that is already overburdened. When COVID-19 was first discovered, it was initially linked to a cytokine storm [4]. Since then, cytokines, particularly IL-6, have received a lot of interest as possible indicators for disease outcomes. In the past, however, it has been difficult to establish a relationship between poor clinical outcomes and elevated levels of IL-6 in the blood at baseline. Septic shock with or without the acute respiratory distress syndrome has been shown to have lower levels of IL-6 and IL-8 in critically ill patients with COVID-19. As a result, information about the clinical history of COVID-19 may be gleaned from measurements of certain cytokines taken at the time of initial presentation [5].

Many patients died as a result of organ failure caused by their treatment. Toxins generated by activated immune and infected cells contributed to organ failure in SARS patients, as well as COVID-19 mortality, according to that study[6]. There was a high association between the death rate of severe COVID-19 patients and the inflammatory marker procalcitonin as well as the inflammatory marker D-dimer greater than 0.5 mg/mL. Inflammatory responses were thought to be linked to elevated D-dimer levels, which indicate coagulation activity. Since higher disease severity and death were found in COVID-19 patients with lymphopenia, it was assumed that lymphocytopenia was caused by lymphocyte apoptosis in these severely ill Middle East Respiratory Syndrome (MERS) patients. As a result, necrosis or apoptosis of lymphocytes may have also contributed to lymphocytopenia in individuals with severe SARS-CoV-2 infection, as previously suggested [6].

When the severity of lymphocytopenia was severe, it was a potent predictor of mortality in patients with COVID-19. As a result, the percentage of neutrophils reduced, which may be linked to a cytokine storm triggered by virus invasion [7].

It was the goal of this work to detect the outcome and survival of COVID-19 patients admitted at Zagazig University Hospitals.

PATIENTS AND METHODS

At COVID isolation Sednawy Hospital, Zagazig University during the period from 1/1/2021 to 31/12/2021, we conducted this retrospective cohort study.

The study included 900 cases as a comprehensive sample, the patients were selected as severe to critical COVID19 patients, with total number 1204 cases where 304 cases were excluded from study with a lot missing data according to the criteria of

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Egyptian protocol for management of COVID-19 patients (May, 2020).

Ethical consent:

Zagazig University's Research Ethics Committee approved the study as long as all participants signed informed consent forms and submitted them to Zagazig University (ZU-IRB#6659). We adhered to the Helsinki Declaration, the ethical guideline of the World Health Organization for human trials.

A laboratory diagnosis of COVID-19 based on RT-PCR in respiratory tract samples was made in all cases.

Inclusion Criteria: Patients admitted in isolation hospitals that were:

- Aged 18 years or more.
- Confirmed COVID-19.
- Severely critical COVID-19 patients.

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

1. Symptoms with Leukocytosis or lymphocytosis with no signs of pneumonia in the radiological picture or when was asymptomatic was termed mild in cases.
2. Radiology revealed pneumonia and/or leukopenia or lymphopenia in moderate patients.
3. Within 24–48 hours, CT scans showed more than 50% lesion or a growing lesion in more than half of the patients, indicating a more severe episode of respiratory distress.
4. Those who had a respiratory rate of more than 30 breaths per minute, a SpO_2 of less than 92 percent on room air, or a Pa O_2/Fi O_2 ratio of less than 300 despite O_2 therapy, were considered critical.

Exclusion Criteria:

Patients with negative SARS-CoV-19 test.

Patients with incomplete files or with missing any data were excluded from this study, about 304 cases.

Baseline data including age, sex, PCR, date of admission, date of discharge, medications, chest computed tomography (CT), comorbidities and chronic diseases, severity, admission requirements for admission, length of hospital stay, and the outcome (survival or non-survival).

Baseline routine laboratory test results included: CBC with differential counts, CRP, LDH (At admission, after 4 days and at discharge), liver functions test, kidney functions test (At admission and at discharge), ABG, ferritin, procalcitonin, D-dimer, and IL6.

Statistical analysis

SPSS software version 23 was used for statistical analysis. Quantitative data were presented as median and range and were compared by Mann-Whitney test. Qualitative data were presented as frequency and proportions and were compared using the Chi-square test (X^2). P value 0.05 was considered statistically significant. It was judged highly significant when the P value was 0.001.

RESULTS

Table (1) shows that there was statistically significant difference among the 3 groups regarding their distribution according to the date of admission.

Table (1): Patients are grouped into groups based on the day they were admitted

	N=900	%	P
Time for admission during 2021:			
January – April (1st wave)	300	33.3%	<0.001**
May – August (2nd wave)	200	22.2%	
September – December (3rd wave)	400	44.5%	

**: Highly significant P

Table (2) shows that there was statistically significant difference among the 3 groups regarding severity and mortality.

Table (2): Distribution of the studied patients according to severity and outcome

	N=900	%	P
Severity:			
Critical	357	39.7%	<0.001**
Severe	543	60.3%	
Mortality:			
Survived	532	59.1%	<0.001**
Died	368	40.9%	

**: Highly significant P

There was statistically significant relation between severity and mortality where mortality was higher among critical cases (Table 3).

Table (3): Relation between severity and outcome of the studied patients

Parameter	Severity		p
	Critical	Severe	
	N=357 (%)	N=543 (%)	
Mortality:			
Survived	54 (15.1%)	478 (88.0%)	<0.001**
Died	303 (84.9%)	65 (12.0%)	

**: Highly significant P

Table (4) shows that co-morbidity is not statistically linked to the time of admission.

Table (4): Relation between time of admission and presence of comorbidity

Parameter	Time of admission			p
	1st 4months (n=300)	2nd 4months (n=200)	3rd 4months (n=400)	
Comorbidity:				
No	77 (25.7%)	18 (9.0%)	77 (19.3%)	
Yes	223 (74.3%)	182 (91.0%)	323 (80.7%)	0.064

**: Highly significant P

There was significant relation between overall survival and time of admission where the least mortality and longest overall survival occurred in those admitted from first 4 months (Table 5).

Table (5): Relation between time of admission and overall survival

Group	Total	N of death	survival		Survival time		
			N	%	Mean ± St. Error	95% CI	p
First group	300	173	127	42.3%	16.02 ± 0.57	14.91 – 17.12	0.001**
Second group	200	86	114	57.0%	17.39 ± 0.91	15.62 – 19.17	
Third group	400	109	291	72.8%	25.86 ± 1.27	23.36 – 28.35	
Overall	900	368	532	59.1%	19.94 ± 0.63	18.71 – 21.18	

**: Highly significant P

There was statistically significant relation between severity and use of tocilizumab, type of steroid, and antiviral (Table 6).

Table (6): Relation between severity and drug used of the studied patients

Parameter	Severity		p
	Critical	Severe	
	N=357 (%)	N=543 (%)	
Antiviral:			
No	104 (29.1%)	147 (27.0%)	
Favipiravir	62 (17.4%)	110 (20.3%)	
Remdesivir	79 (22.1%)	129 (23.8%)	<0.001**
Favi+ivermectin	4 (1.1%)	69 (12.7%)	
Reme+ivermectin	42 (11.8%)	16 (2.9%)	
Remed+favi	66 (18.5%)	72 (13.3%)	
Tocilizumab:	94 (26.3%)	62 (11.4%)	0.001**
Support:	N=302	N=7	
IMV	233 (77.2%)	7 (100%)	0.214
NIMV	69 (22.8%)	0 (0%)	
Steroid:			
Dexamethasone	287 (80.4%)	482 (88.8%)	<0.001**
Solumedrol	70 (19.6%)	61 (11.2)	

**: Highly significant P

There was statistically significant relation between severity and all of CRP, IL-6, albumin/IL-6 ratio and neutrophil/lymphocyte ratio (Table 7).

Table (7): Relation between outcome and acute phase reactants baseline and on follow up of the studied patients

Parameter	Severity		p
	Critical	Severe	
	Median (range)	Median (range)	
CRP (mg/L)	100 ± 22.54	29 ± 5.81	<0.001**
D dimer	2.1 ± 0.31	1.3 ± 0.21	0.207
IL-6	110.8 ± 24.82	33.4 ± 5.34	<0.001**
Albumin/IL-6	0.03 ± 0.005	0.09 ± 0.011	<0.001**
Neutrophil/lymphocyte ratio	14.2 ± 2.13	8.78 ± 1.73	<0.001**
Procalcitonin PCT	0.29 ± 0.051	0.21 ±0.031	0.325

**: Highly significant P

There was statistically significant relation between presence of comorbidity and mortality (Table 8).

Table (8): Relation between outcome and comorbidities of the studied patients

Parameter	Comorbidity		Test
	Absent	Present	p
	N=172 (%)	N=728 (%)	
Mortality:			
Survived	126 (73.3%)	406 (55.8%)	<0.001**
Died	46 (26.7%)	322 (44.2%)	

**: Highly significant P

There was significant relation between severity and overall survival which was significantly higher in those with severe disease (Figure 1).

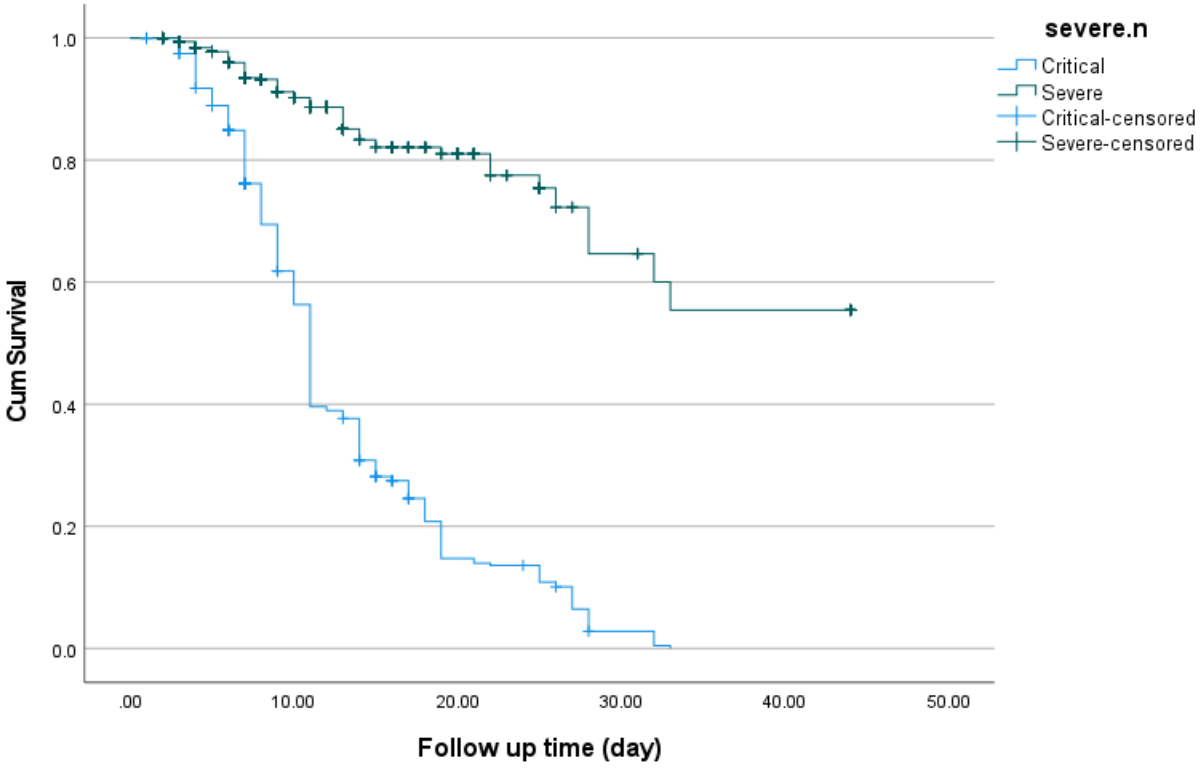

Figure (1): Kaplan Meier plot showing relation between severity and follow up time among the studied patients

There was significant relation between comorbidity and overall survival which was significantly higher in those without comorbidity (Figure 2).

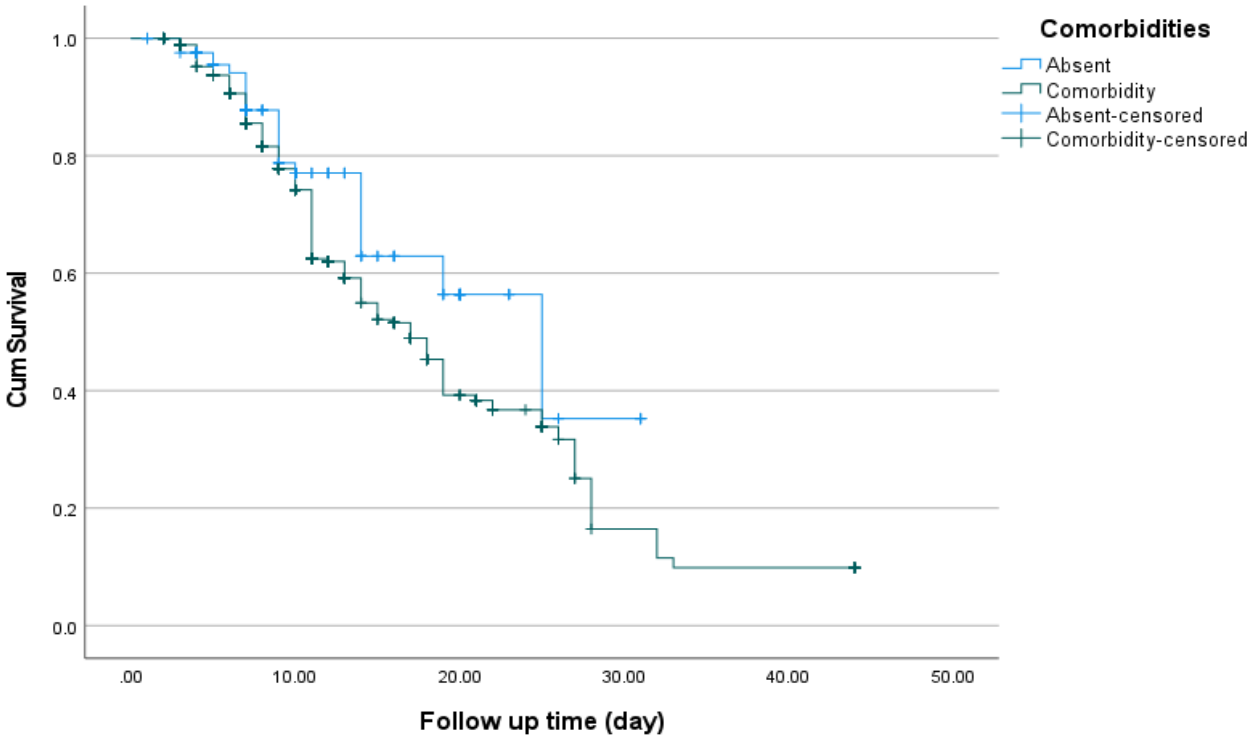

Figure (2): Kaplan Meier plot showing relation between comorbidities and follow up time among the studied patients

DISCUSSION

In January 2020, the WHO declared the COVID-19 virus illness outbreak in China, which began in December of the previous year, to be a pandemic. As of January 29, 2021, there were more than 100,819,363 confirmed cases in 250 countries/regions, with more than 2,176,159 deaths around the world, according to the World Health Organization (WHO) [8].

For those who have come into contact with COVID-19, it is also known that the infection might be mild or even be undetected at all times. Some patients with COVID-19 exhibit symptoms that are not life-threatening or may go unnoticed; in the other half, the predominant symptoms are fever, lethargy, a dry cough, myalgia (muscle soreness), and dyspnea (shortness of breath) [9].

This retrospective cohort study was conducted at isolation Sednawy Hospital, Zagazig University during the period from 1/1/2021 to 31/12/2021 to detect the outcome and survival of COVID-19 patients admitted at Zagazig University Hospitals.

In the current study, 44.5% of patients were admitted from September to December (3rd 4 months), 33.3% were admitted from January to April (1st 4 months) and 22.2% were admitted from May to August (2nd 4 months) with statistically significant difference. There was lesser increase in the duration of stay at home during the third 4 months compared to baseline than that in the first 4 months.

In agreement with our study, **Abdelwanees *et al.*** [10] found that COVID cases increased in the wave in the period from 8 December, 2020 until 19 January than the wave in the period from 21 March 2020 shortly after the start of the official lockdown until 2 May 2020.

The same result was observed by **da Silva *et al.*** [11] who compared March 2020 and December 2020 COVID-19 waves through performing a multi-objective time series analysis of community mobility reduction. The researchers observed that mobility reduction was stronger in March wave compared to the December one; December holidays and shopping seasons had increased mobility in all the studied categories, but contrasting results were recorded for parks (with more mobility reduction) and grocery and pharmacies (with increased mobility). These observations included 5 highly impacted cities by the COVID-19 epidemic: Lombardia, ˆIle-de-France, Birmingham, Berlin, and Toronto.

In the present study, 39.7% of patients had critical illness while 543 patients (60.3%) were with severe illness, while 532 patients survived and 40.9% of patients died by the end of follow up period with statistically significant difference regarding distribution.

In agreement with our study, **Samir *et al.*** [12] found that during the December pandemic wave, the clinical severity had increased by approximately 6.5 percent. As a result, there was a greater incidence of pulmonary and extra-pulmonary complication rates.

In the current study, there was statistically non-significant relation between severity and either age, gender or comorbidities. Comorbidities were higher in critical cases than severe cases but it does not reach a significant difference.

In agreement with our study, **Liu *et al.*** [13] included 140 patients with COVID-19 in their research (one patient was excluded because of massive gastrointestinal hemorrhage). It was found that 107 patients in the study were assigned to the moderate group (MG) and 33 individuals in this group were assigned to severe group (SG). Neither group had a significantly different ratio of males to females. However, they discovered that the average age in the SG was much greater than the average age in the MG. This is in direct conflict with our results.

Also, there was statistically significant relation between severity and albumin and total protein on discharge while there was statistically non-significant relation between severity and either albumin total protein on admission within each group, there was significant change in albumin, and protein over time.

Touma and Bisharat [14] in their study concluded that patients with low albumin levels were more likely to require a second hospital stay and die. Patients with low albumin were shown to have a larger number of co-morbidities at the outset, according to the researchers. **Akirov and colleagues** [15] reported that normalisation of serum albumin decreased rehospitalization and death, not only when serum albumin levels were low. Inflammatory markers may have lowered serum albumin, which is the major plasma anti-oxidant, indicating the severity of COVID-19 in individuals with such co-morbidities.

In the present study there was statistically significant relation between severity and all of CRP, IL-6, neutrophil/lymphocyte ratio and albumin/IL-6 ratio while there was statistically non-significant relation between severity and all of D dimer, or PCT.

Biomarkers of infection, inflammation, and tissue damage can all be detected by measuring CRP levels in the blood. The CRP level rises fast after acute inflammatory reactions. [16].

In agreement with our study, **Chen *et al.*** [17] reported that CRP was proven to be an effective marker for determining the severity of COVID-19. Clinical outcomes and illness severity were linked to elevated levels of CRP in this study.

Also**, Ahnach *et al.*** [18] found that CRP and serum ferritin levels were considerably greater in individuals with severe disease than in patients with moderate disease, according to this research. Because CRP is a protein in the acute phase that serves as an early indicator of infection with COVID-19, these results make sense. With an accuracy of 76.4 percent and a specificity rate of 63.4 percent, the best cutoff value for CRP to predict severe illness was 17.4 mg/L.

Also, there was statistically significant relation between severity and mortality where mortality was higher among critical cases. And regarding relation between severity and overall survival, there was significant relation between severity and overall survival, which was significantly higher in those with severe disease.

In the current study, there was statistically significant relation between presence of comorbidity and mortality where comorbidity was associated with mortality. Also, there was significant relation between comorbidity and overall survival which was significantly higher in those without comorbidity. In addition, there was statistically non-significant relation between severity and gender or age.

In agreement with our study, **El-Shabrawy *et al.*** [19] findings revealed the prevalence in both severe and non-survivor instances of co-morbidities such as high blood pressure, diabetes, cardiovascular, renal, hepatic, and chest problems. The findings of **Yang *et al.*** [6] are in agreement with this one.

Ismail *et al.* [20] demonstrated that non-survivors were older and complications such as ischemic heart disease and chronic kidney disease were more common in patients with COVID 19 disease than in those who survived the disease.

Horby *et al* [21] found that the use of corticosteroids, particularly dexamethasone, in the treatment of severe COVID-19 with viral pneumonia improved the overall survival of patients requiring respiratory support (either mechanical ventilation or oxygen alone). Dexamethasone then became the standard of care for COVID-19 with viral pneumonia patients requiring oxygen support.

Shen *et al.* [22] reported that antiviral medications that target specific steps in the life cycle of SARS-CoV-2 could represent an alternate therapeutic strategy for dealing with this pandemic, if they are made available. Antivirals from the promising classes of fusion inhibitors, protease inhibitors, and transcription inhibitors should be considered. **Mehta *et al.*** [23] revealed that monoclonal anti-IL-6 antibody, a promising possibility for battling the "cytokine storm" and high levels of IL6 in patients with severe lung inflammation and organ damage, has been shown to be effective.

CONCLUSION

Outcome improving over different groups with time means improvement in medical care, where time of admission, different comorbidities, change in the level of acute phase reactant, and anti-inflammatory drugs may affect the survival of severe and critical ill COVID 19 patients.

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