Clinical Characteristics and Risk Factors of Mortality Among Severe COVID-19 Patients

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Abstract

Background: The novel corona virus is attacking several millions of people worldwide, resulting in death of almost a million and a half-humans. The rational of the current study was to detect clinical characteristics of severe COVID- 19 patients, and assessment of risk factors for death.

Methodology: This retrospective cohort study included all laboratory confirmed COVID-19 patients with severe disease admitted to critical care unit in June and July 2020. All recorded data were collected,which included clinincal, radiological, and laboratory data, in addition to the outcome and duration of ICU stay.Statistical analysis was performed for obtaining descriptive information, comparison between living and dead patients,in addition to regression analysis to identify risk factors for mortality.

Results: One hundred and three patients were included in the current study;cough and fever were the most common clinical presentations, and bilateral ground glass opacity was the most common radiological presentation. Patients had elevated values of neutrophils, neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), serum ferritin, CRP, and D-dimer, also had longer ICU stay ,with reduced values of lymphocytes, and PaO_2/FIO_2 ratio. Most of these variables were more exaggerated in dead patients compared to living ones. Older age, lower values of PaO_2/FIO_2 ratio, and higher values of neutrophils, NLR, and D-dimer were predictors for death.

Conclusion: Cough, fever and bilateral ground glass opacity were the most common clinical and radiological presentation of severe COVID 19. Older age, lower value of PaO_2/FIO_2 ratio, and higher values of D- dimer, neutrophil and NLR were risk factors associated with increased risk of mortality.

Background

The delivery of SARS- COV II (sever acute respiratory syndrome coronavirus II) epidemic first reported in China in December 2019;since that time the virus continues spreading all over the world with a very high rate of infectivity, and also mortality.[1] The vigorous pattern of virus spread all over the world reinforced the World Health Organization (WHO) to consider it as a pandemic where discovery of cases was reported in about one hundred ninety five countries by March 2020.[2] By the last week of May 2020, about 17265 COVID-19 cases were reported in Egypt to be considered as one of five countries with higher incidence of the disease in Africa.[3]

With respect to severity of the disease at the time of presentation, it is documented that eighty percent of cases had mild disease or even were asymptomatic, while fifteen percent had severe disease, and only five percent of cases were reported as critical cases.[4]COVID – 19 patients are classified as mild, moderate, severe, and critically-ill based on clinical, laboratory, and radiological criteria.[4, 5]Mild cases are those who are symptomatic but with normal imaging and oxygenation.

If $SpO_2 \geq 92\%$ in the presence of radiological findings, the patient is considered to have moderate illness, while in the presence of $SpO_2 \leq 92\%$, $PaO_2/FIO_2 < 300$, respiratory rate > 30 breath/minute, or more than 50% radiological infiltrates patient is included in severe disease group[6], Critically ill patients are those with respiratory failure, septic shock, and/or multiorgan failure.[6].The rate of case fatality reported a wide range of variability among countries, which may be related to variation in policies of different governments, acceptance of different population to safety precautions, and errors in the recording of the actual numbers of infected cases.[7]. In Egypt, the rate of case fatality was 2.2% in March 2020 (second week), one month later it markedly increased to a value of (7.5%), which declined slowly to reach 4.8% by the half of May 2020.[8]

The current study was carried out with the aim of studying the clinical, and laboratory chacteristics of severe COVID-19 patients and identifying variations between living and dead cases, also assessment of risk factors associated with increased risk of death in severe COVID-19 patients.

Methodology

Patients

A retrospective cohort analysis was performed on the confirrmed cases of COVID-19, who were admitted to critical care unit, Assiut University Hospital, during June and July 2020. All adult patients ≥18 years were considered in this study. Included patients satisfied at least one of these criteria:respiratory rate≥30 breath /minute, $SpO_2 \leq 92\%$ at rest, $PaO_2/FIO_2<300$, and or radiological infiltration >50% of the lung field. [8] A confirmed case of infection with SARS Cov-II was diagnosed by reverse transcriptase polymerase chain reaction test (RT-PCR) assay on nasopharyngeal and oropharyngeal swabs (CO-RAD 6)[9].

Data collection:

Data were collected from electronic medical records including patient demographic criteria, underlying comorbidities, vital signs, referred symptoms on admission. Acute Respiratory Distress Syndrome(ARDS) was defined as PaO_2/FiO_2 ratio ≤ 300 based on the Berlin Definition [10]. Laboratory tests and radiological data were also collected including complete blood cout, renal and liver functions, D-dimer, serum ferritin, and arterial blood gases.

Statistical analysis:

Data were verified, coded by the researcher and analyzed using IBM-SPSS 24.0 (IBM-SPSS Inc., Chicago, IL, USA)[11]. Descriptive statistics: Means, standard deviations, medians, ranges and percentages were calculated. Test of significances: Chi-square test was calculated to compare the frequencies among groups. Student t-test and Mann-Whitney U test were calculated to test the mean differences in continuous variables between groups (parametric and non-parametric). Significant variables from the univariate analysis were entered in the multivariable logistic regression model to test the independent

predictors of mortality in patients with COVID-19 using odds ratio (OR), 95% confidence interval (CI). A significant p-value was considered when it is less than 0.05.

Sample size calculation

Sample size calculation was carried out using G*Power 3 software[12]**(Faul et al., 2007)**. A calculated minimum sample of 98 COVID-19 patients was needed to detect an effect size of 0.2 (OR ranged between 1.5 and 3.5 in the multivariate Cox Hazard Proportion Regression for the mortality), with an error probability of 0.05 and 80% power on a one-tailed test.

Results

One hundred and three patients satisfying the criteria of severe COVID-19 were included in the present study, with mean age 61.14± 13.4. Male sex represented 53.4% of the patients, where the most frequent clinical presentations were cough, and fever (table1, and figure 1). Associated comorbidities(e.g. diabetes, hypertension, cardiopulmonary diseases, chronic kidney and liver diseases) were observed in 67% of patients. As regard laboratory findings ,most of the patients characterized by near normal leukocyte counts, decreased lymphocyte, and increased neutrophil lymphocyte ratio, CRP, and D-dimer level. Bilateral lung involvement was observed in 68% of patients on radiological evaluation. Multilobar affection in both lungs was found in 40.8% of patients, where isolated ground glass affection was observed in 70.9% of patients (CO-RAD 6)[9]. Death was reported in 78.6% of the studied group (table 1). All included patients were treated according to the Egyptian Ministry of Health protocol which included anticoagulant, Dexamethasone, and antibiotic;because of financial causes ;Tocilizumab was prescribed only in ten patients and non of them survived. Non-invasive ventilation was initiated in all patients, those who did not improve were shifted to invasive mechanical ventilation. By comparing alive and dead patients, it was observed that dead patients had significantly higher age (P-value 0.018), D-dimer level (P-value 0.001), Neutrophil (P-value 0.006), NLR(P- value 0.001), PLR(P- value 0.018), and longer ICU duration (P- value 0.025), PaO_2/FiO_2 ratio was significantly lower in dead patients (P-value 0.001) table (2). Univariate regression analysis of different parameters for idenfication of factors associated with increased mortality revealed that more mortality was associated with increasing each of the following :age, D dimer, Neutrophil, NLR, PLR, and longer ICU stay. Higher mortality was also associated with decreased lymphocyte level, and low PaO_2/FiO_2 ratio. Multivariate regression analysis highlighted that older age, higher D-dimer, neutrophil count and NLR; and lower PaO_2/FiO_2 ratio were associated with higher risk of mortality (table 3).

Discussion

Since the beginning of the outbreak of COVID-19, several studies have emerged on clinical, laboratory, and radiological presentation of patients, followed by summarization of the criteria of mild, moderate, and severe cases.[3, 5, 6]

The current study focused on patients with severe COVID-19 who were admitted to critical care unit, aiming to identify their clinical, and laboratory data, in addition to identify risk factors associated with mortality. The mean age of patients in the present study was 61.14± 13.4, fever and cough were the most frequent clinical presentations(69.9% and 84.5% respectively);while diarrhea was the least one(7.8%), also a large percentage of patients had comorbidities. Several studies came in agreement with these results; they documented that severe COVID-19 disease was associated with older age (more and equal to 51 years), and was more encountered in patients with underlying co-morbidities (hypertension, diabetes, and cardiopulmonary conditions).[13, 14]Other studies highlighted that older groups were more likely to have severe symptoms, and that the presence of co-morbodieties increased the likelihood of developing a poor outcome.[14, 15] In correlation with the current study,several studies documented that fever and cough were the most frequent presentations, and that gastrointestinal symptoms were the least. They related this to the variation in tropism of the virus, they also related fever to the development of a cytokine storm, initiation of inflammation and overstimulation of the immune response.[16- 20] In addition, these studies reported that afebrile illness was more frequent in COVID-19 presentation compared to other corona viruses, and also influenza virus;the finding that may lead to missed cases of COVID -19. [16-19] As regard the radiological pattern of the disease in this study, bilateral affection was observed in 68% of cases with ground glass opacity (GGO) representing the most common finding. In agreement with this finding, a recent study on the radiological presentation of the novel corona virus confirmed that the most common presentation is bilateral, peripheral, ground glass opacity.[21]
Laboratory data of the studied patients revealed that increased NLR, CRP, D-dimer levels, serum ferritin and PLR were significantly higher in dead patients compared to living personnel (as our patients were of the severe form and were in cytokine storm). Longer ICU stay, lower lymphocyte count , and lower PaO_2/FIO_2 ratio were encountered in patients who did not survive. In agreement with our results, several studies reported that raised inflammatory markers (CRP, serum ferritin), higher levels of D- dimer and lymphopenia were observed in severe disease group. [13, 22] These studies also documented that older age, high CRP, presence of comorbidities, and lymphopenia by univariate regression analysis correlated with severe disease and poorer outcome, but after adjusting these variables to multivariate regression analysis lymphopenia was not included[13, 22], which was similar to the present study.A P. Yang, et al[22] stated that NLR is a blood marker that independently predicts prognosis, and also predicts the progression of COVID related pneumonia, and that a NLR value ≥3.3 was associated with disease progression and the need for ICU. They said "large number of reactive oxygen species released from neutrophils resulting in damage of the DNA of the cell, with subsequent viral liberation from the cell. It is observed that under-expression of vascular endothelial growth factor (VEGF) leads to inhibition of damage of tissue and organs; unfortunately COVID -19 infection is found to be associated with increased neutrophil release of these inflammatory markers [24, 25]. In addition , COVID-19 virus produces systemic inflammation that inhibit cellular immunity, with reduced CD4 and increased CD8T lymphocyte.[26] Guisado-Vasco et al[27] stated that factors associated with increased risk of mortality in COVID-19 patients include older age, lower PaO_2/FIO_2, and increased D-dimer levels,which was also noticed in the current study.

High mortality, which reached up78.6% in this study, may reflect late presentation of the patients with progression of disease to critical levels. This observation reflects poor awareness of population about the severity of the disease, and timing at which the patient must don not hesitate and resist hospital admission. In addition to the fact that our hospital is a tertiary hospital received complicated cases from other smaller hospitals after several trials of treatment.

Conclusion

Cough, fever and bilateral ground glass opacities were the most common clinical and radiological presentation of severe COVID-19 infection.Older age, lower value of PaO_2/FIO_2 ratio, and higher levels of D-dimer, neutrophil and NLR were factors associated with increased risk of mortality.

List Of Abbreviations

COVID-19:Corona Virus Disease of 2019

ICU: Intensive Care Unit

NLR: Neutrophil lymphocyte ratio

PLR: Platelet lymphocyte ratio

CRP: C-reactive Protien

PaO_2/FIO_2:Arterial oxygen partial preasure to Fractional inspired Oxygen

SARS- COV II: Sever acute respiratory syndrome coronavirus II

WHO :World Health Organization

SpO_2:Peripheral oxygen saturation

RT-PCR:Reverse transcriptase polymerase chain reaction test

ARDS :Acute Respiratory Distress Syndrome

GGO: Ground glass opacity

VEGF :Vascular endothelial growth factor

Abbreviations

COVID-19
Corona Virus Disease of 2019
ICU

Intensive Care Unit
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PLR
Platelet lymphocyte ratio
CRP
C-reactive Protien
PaO_2/FIO_2
Arterial oxygen partial preasure to Fractional inspired Oxygen
SARS- COV II
Sever acute respiratory syndrome coronavirus II
WHO
World Health Organization
SpO_2
Peripheral oxygen saturation
RT-PCR
Reverse transcriptase polymerase chain reaction test
ARDS
Acute Respiratory Distress Syndrome
GGO
Ground glass opacity
VEGF
Vascular endothelial growth factor

Declarations

Ethics approval and consent to participate

Approval for this study was obtained from the Institutional review board (IRB) of the Faculty of Medicine-Assiut University prior to study execution (IRB no.17300457). In addition, all participants (or their family members) received a written consent form. The informed consent was clear and indicated the purpose of the study, and their freedom to participate or withdraw at any time without any obligation. Furthermore, participants' confidentiality and anonymity were assured by assigning each participant with a code number for the purpose of analysis only. The study was not based on any incentives or rewards for the participants. The study was in line with the Declaration of Helsinki.

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Conflict of Interest: **No Conflict of Intrest**

Financial support and sponsorship: Nil

Authors'contributions:

M.ElKholy : Critical revision of the submitted protocol for important intellectual content

Alaa E: Conception and design,Acquisition of data,Analysis and interpretation of data.

Samiaa H: A major contributor in writing the manuscript.

Shimaa A: Conception and design,Acquisition of data, Analysis and interpretation of data.

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Tables

Table 1: Baseline characteristics of the studied Cohort

Parameter	Category	(n=103)
Age/years	· Mean ± SD	61.14 ± 13.4
	· Median (Range)	62.5 (20-86)
Sex	· Male	55 (53.4%)
	· Female	48 (46.6%)
Main Presenting Symptoms	· Fever	72 (69.9%)
	· Congested Throat	26 (25.2%)
	· Cough	87 (84.5%)
	· Expectoration	43 (41.7%)
	· Dyspnoea	30 (29.1%)
	· Diarrhoea	8 (7.8%)
Comorbidity	· Yes	69 (67%)
Vital signs(mean±SD)	· Temperature	(37.9±3.9)
	· Respiratory rate	(35.7±9.9)
Laboratory Findings	· WBCs	10.5 (2.2-49.9)
	· Neutrophils	10.6 (4.6-25)
	· Lymphocyte	0.6 (0.2-3.8)
	· CRP	76 (7.5-202)
	· D-Dimer	1.9 (0.2-16.5)
	· NLR	16.8 (2-73)
	· PLR	454 (82-1674)
	· Ferritin	1084(53-3540)
	· LDH	521 (204-1500)

Table 1: Baseline characteristics of the studied Cohort.....Continued

Parameter	Category	(n=103)
Blood Gases Parameters	· PaO_2	73.5 (34-260)
	· PaO_2/FiO_2	169 (85-650)
	· $PaCO_2$	28.5 (10-93)
Renal Function Parameters	· B. Urea	12.7 (3.3-46.4)
	· S. Creatinine	87 (1.7-756)
Liver Function Parameters	· Albumin	32 (22-46)
	· T. Protein	57 (39-74)
	· Bilirubin	10 (2.3-66)
	· D. Bilirubin	4 (1-31)
	· ALT	41 (5-1368)
	· AST	35.5 (14-3279)
Radiological Findings	· Bilaterality	70 (68%)
	· Multilobar	42(40.8%)
	· GGO	73(70.9%)
Mortality	· N (%)	81 (78.6%)

Table 2: Correlates of mortality among the studied COVID-19 Patients

	Alive (n=22)	Dead (n=81)	P-value
· **Age/years**	53.22 ± 15.5	63.24 ± 12.1	**= 0.018***
· **Sex (Male/Female)**	10/12	45/36	= 0.237**
· **Ferritin Level (µg/L)**	625 (53 - 1370)	1177 (220 - 3540)	= 0.068***
· **D-dimer**	0.6 (0.2 – 4.1)	2.6 (0.4 – 16.5)	**< 0.001*** **
· **Lymphocyte**	1.2 (0.2 – 3.8)	0.7 (0.1 – 2.4)	**= 0.005*** **
· **Neutrophils**	7.9 (4.6 – 12.5)	10.8 (4.3 - 25)	**= 0.006*** **
· **NLR**	6.6 (2 - 83)	14.7 (3 - 73)	**< 0.001*** **
· **PLR**	205 (75 - 1162)	454 (98 - 1674)	**= 0.018*** **
· **PaO_2/FiO_2**	230 (120 - 650)	155 (85 - 335)	**= 0.001*** **
· **ICU Duration/days**	4 (1 - 28)	8 (3 - 20)	**= 0.025*** **
· **Comorbidity**	14 (63.6%)	55 (67.9%)	= 0.445**

***Independent t-test was used to compare the means among groups**

****Chi-square analysis was used to compare the frequency among groups**

*****Mann-Whitney U-test was used to compare the medians among groups**

Table 3: Predictors of Mortaliry among COVID-19 Patients: Logistic Regression Model

Variable	Univariate		Multivariate	
	OR (95% CI)	P-value	HR (95% CI)	P-value
Age/years	1.054 (1.014–1.095)	**= 0.008**	1.196 (1.015–1.410)	**= 0.033**
D-dimer	2.330 (1.245–4.362)	**= 0.008**	4.037 (1.302–12.519)	**= 0.016**
Lymphocyte	0.281 (0.125–0.631)	**= 0.002**		
Neutrophils	1.286 (1.059–1.561)	**= 0.011**	1.632 (1.005–2.963)	**= 0.031**
NLR	1.078 (1.015–1.146)	**= 0.015**	2.218 (1.057–5.115)	**= 0.021**
PLR	1.001 (1.000–1.003)	= 0.104		
PaO_2/FiO_2	0.984 (0.973–0.995)	**= 0.005**	0.891 (0.801–0.982)	**= 0.022**
ICU Duration/days	1.114 (0.968–1.283)	**< 0.001**		

OR, Odds Ratio; CI, Confidence Interval

Figures

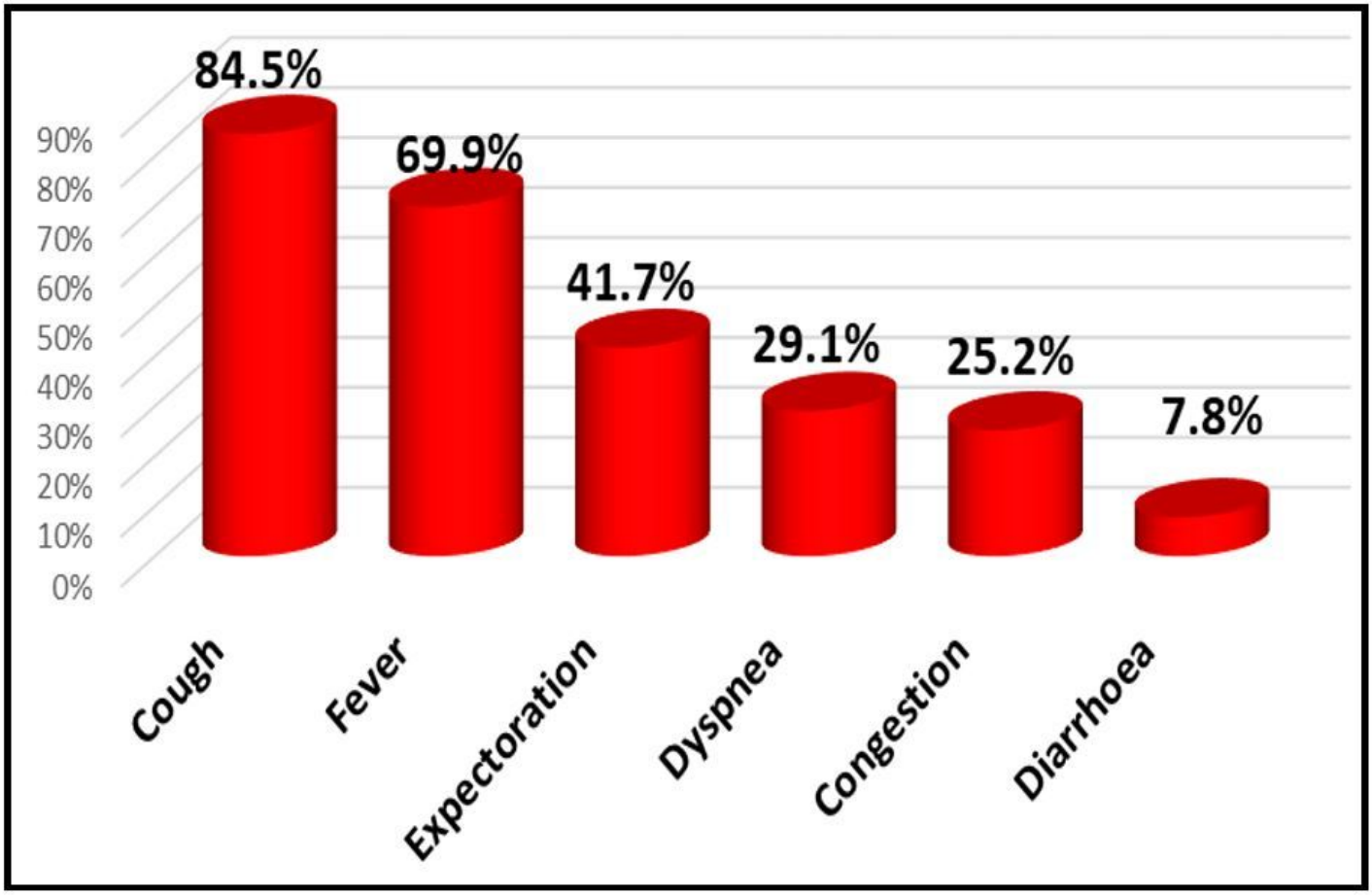

Figure 1

Prevalence of symptoms among severe COVID-19 Patients