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Original article

Prevalence and Associated Risk Factors of Mortality among COVID-19 Patients

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Abstract

Background: COVID-19 pandemic has had a significant impact on global health, with a high mortality rate among infected individuals. **Methods:** This retrospective study included 400 patients- who were PCR positive for COVID-19- admitted at hospital either ward or ICU and it was conducted at Benha University hospital isolation department, in the period between April 2021to April 2022. **Results:** 20% (80 patients) died while 80% (320 patients) survived. The patients who died were significantly older and had higher rates of comorbidities such as hypertension, diabetes mellitus, cardiovascular disease, chronic kidney disease, liver disease, and cancer. All patients -who died- were admitted to the ICU, compared to 12.5% of the survived patients. Significant differences were observed in laboratory findings, including; lymphocyte count, TLC, D-dimer, serum ferritin, urea, creatinine levels, ALT, AST levels, and SPO2. CT chest findings also showed differences in CORAD distribution between the groups. Multivariable analysis identified older age, diabetes mellitus, chronic kidney disease, higher serum ferritin level, and elevated serum urea level- as independent predictors of death. Various factors, such as; age, lymphocyte count, TLC, serum ferritin level, D-dimer, serum creatinine, urea, ALT, AST levels, and SPO2- had predictive value for mortality. These findings provide valuable insights into the prevalence and risk factors associated with mortality among COVID19 patients, aiding in better patient management and outcomes. **Conclusions:** There is a high mortality rate among hospitalized COVID-19 patients, particularly among older individuals with comorbidities such as hypertension, diabetes, and cardiovascular disease.

Keywords: Mortality; Risk Factors; COVID-19 Patients.

Introduction

Corona virus disease (COVID-19) is an infectious disease caused by the most recently discovered RNA virus named corona virus, formerly referred to as severe acute respiratory syndrome-corona virus-2 (SARS-CoV-2). It causes

respiratory tract infections within the human and animal bodies, presents with fever, cough, cold, and sometimes patients may die due to acute respiratory distress syndrome or pneumonia
(1).

The first case of COVID-19 disease was identified on December 2019, in Wuhan, Since COVID-19 disease emergence first in China, it is rapidly become a worldwide threat and it is declared as a pandemic by World Health Organization (WHO). From that time, this disease has spread to 216 countries and territories around the world (2).

Patients with COVID-19 present primarily with various symptoms like fever, cough, dyspnea, myalgia, and fatigue (3). Although most of the COVID-19 infected patients are thought to be recovered after few days, male patients, older patients (age greater than 60 years) and patients with various chronic diseases- may have fatal outcomes (4).

Several factors are responsible for the severity and mortality of COVID- 19 disease such as hypertension, diabetes mellitus, acute respiratory distress syndrome (ARDS), cardiovascular disease, cancer, COPD, asthma, renal disease, kidney disease, liver disease, pneumonia, obesity, and history of smoking- were responsible for the development of the disease or death (5).The mortality rate of COVID-19 patients varies among the intensive care unit (ICU) and non- ICU patients and also for severe and non- severe patients with higher rate among ICU admitted patients and severe patients compared to non-ICU and non-severe patients (6).

Low and middle-income countries, COVID-19 disease is sort of a threat to health and economic sectors. Proper social distancing is not possible for a large number of populations-which is essential to prevent this disease-because of having no proper treatment or medicine to treat coronavirus infected patients- and vaccine to prevent it. Numerous requiring ICU care and mechanical ventilator, which is difficult to arrange for many developing countries. Proper steps should be taken to prevent this disease and reduce the mortality rate (7).

This study aimed to observe the prevalence of mortality among hospitalized COVID-19 infected patients and associated risk factors for death.

Patients and Methods

This retrospective study included 400 patients who were PCR positive for
COVID-19 and admitted at hospital either ward or ICU and were conducted at Benha
University hospital isolation department, in the period between April 2021to April 2022.

This study was done after approval ethical committee of faculty of medicine Benha university .

Inclusion criteria were all patients who were admitted at BUH isolation department.

Exclusion criteria were pediatric patients and patients who have

heterogeneous infection in CT CHEST similar to Covid 2019.

All patients were subjected to a) Full medical history, b) Physical examination: general and local chest examination, c) Routine laboratory investigation: Complete blood count (CBC) with differential leucocytic count. Liver function tests including serum alanine transaminase (ALT), serum aspartate transaminase (AST), serum albumin, Renal function tests including Creatinine and Urea, D-Dimer, C - reactive protein (CRP), Erythrocyte sedimentation rate (ESR), serum ferritin level, SPO2 by pulse oximetry and PCR test: polymerase chain reaction test for covid-19 is amolecular test that analyzes upper respiratory specimen looking for genetic material (RNA) of SARs-COV2, the virus that causes covid-19, scientists use the PCR technology to amplify small amounts of RNA from specimens into DNA which is replicated until SARS-COV2 is detectable if present. The PCR test has been the gold standard test for diagnosing COVID19, its accurate and reliable.

Radiological investigations: HRCT chest, CORADS classification: Based on the CT findings, the level of suspicion of COVID-19 infection is graded from very low or CO-RADS 1 up to very high or CO-RADS 5.

The severity and the stage of the disease are determined with remarks on comorbidity and a differential diagnosis. CORADS-1 has a high negative predictive value in patients with complaints for four or more days. The interobserver variation of CORADS 2-4 is still high and has a poor negative and predictive value. The interpretation of the CT findings has to be combined with the clinical symptoms and the duration of the symptoms as a CT can be negative in the first few days of a mild infection.

Approval Code: Ms.9.9.2021

Statistical analysis:

The collected data underwent thorough analysis using IBM SPSS Statistics (Version 26.0). Normality of data distribution was assessed using the Shapiro-Wilk test, with nonparametric data considered significant.

Descriptive statistics included mean and standard deviation for parametric numerical data, and median with interquartile range (IQR) for non-parametric numerical data. Categorical data were presented as frequency and percentage. Analytical statistics involved Student's T-test for comparing means, Mann-Whitney U test for non-parametric variables, and Chi Square test for examining relationships between qualitative variables.

Fisher's exact test was used when expected counts were less than 5 in more than 20% of cells. Univariate and multivariate logistic regression analyses were conducted to predict risk factors for death or ICU admission. Receiver Operating Characteristic (ROC) analysis evaluated the diagnostic performance, determining cut-off points, sensitivity, specificity, and Area Under the Curve (AUC). Statistical significance was set at $P<0.05$, with $P<0.001$ considered highly

significant and P>0.05 deemed nonsignificant.

Results

Table (1) shows characteristics of the studied patients.

Table (2) shows that from 400 COVID-19 patients 80 patients died and 320 patients survived. Died patients were significantly older than survived patients with median age 65.5 years compared with 55 years (p = 0.001). Hypertension, diabetes mellitus, cardiovascular disease, chronic kidney disease, liver disease and cancer- were more prevalent among non survivors compared with survived (p=0.009, 0.001, 0.005, 0.001, 0.01, 0.016). All died patients were admitted to the ICU (100%) while 12.5% of survived patient were admitted to the ICU (p=0.001).

Table (3) shows that there is statistically significant difference between died group and survived one as regard lymphocyte, TLC, D. dimer, serum ferritin, urea and creatinine level, ALT, AST level and SPO2 (P=0,001).

CORAD distribution was significantly different in died patients compared to survived, where all of died patients showed CORAD 4 and 5 on CT 41.2% and 58.8% while survived patients showed CORAD 2 and 3. In contrast, the majority of survived patients showed CORAD 3 and 4 (27.5% and 45.9%) and only 20% and 6.6% of them reported CORAD 4 and 5 respectively (p=0.001), **Figure (1)**.

Table (4) shows that in univariable analysis, older age, hypertensive, diabetics, cardiovascular diseases, chronic kidney disease, and liver diseases- were significant predictors for death from COVID-19 (p<0.05). Regarding laboratory finding, decreased lymphocyte count, higher TLC count, CRP > 10 ng/dL, higher serum ferritin level, increased D-dimer, higher urea, creatinine, ALT, AST levels and SPO2- were significant predictors for death from COVID-19 (p<0.05).

Table (5) shows that ROC curve demonstrated age of 56.5 has 83.8% sensitivity and 59.2% specificity for mortality (AUC: 0.752, p = 0.001).

Table 1: Characteristics of the studied group (N=400).

Variable		(N = 400)	
		No.	**%**
Age (years) *Median* (Q_1, Q_3)	**59.5 (49, 67)**		
Sex	**Male**	180	45%
	Female	220	55%
Smoking	**Non-smoker**	330	82.5%
	Smoker	70	17.5%
Comorbidity	**Hypertension**	188	47%
	Diabetes	156	39%
	Cardiovascular disease	52	13%
	Asthma	18	4.5%
	COPD	24	6%
	Cancer	10	2.5%
	CKD	44	11%
	Liver disease	40	10%
	ICU	190	47.5%
	Ward	210	52.5%
PCR	**PCR +ve**	400	100%
	PCR –ve	0	0%

Table 2: Comparison between deceased and survived patients as regard demographic data and comorbidities (n=400).

Variable		Deceased (N=80)		Survived (N=320)		Statistic s	P
		Demographics					
	Age (years)	65.5 (59, 72)		55 (40, 63)		6.04	**0.001***
Sex	Male	33	41.3 %	147	45.9 %	0.57	0.45†
	Female	47	58.8 %	173	54.1 %		
Smoking	Non-smoker	68	85%	262	81.2 %	0.43	0.51†
	Smoker	12	15%	58	18.1 %		
Comorbidity	Hypertension	48	60%	140	43.7 %	6.78	**0.009†**
	Diabetes	44	55%	112	35%	10.76	**0.001†**
	Cardiovascular disease	18	22.5 %	34	10.6 %	7.98	**0.005†**
	Asthma	4	5%	14	4.4%	0.06	0.81†
	COPD	6	7.5%	18	5.6%	0.4	0.53†
	Cancer	5	6.3%	5	1.6%	5.8	**0.016†**
	CKD	21	26.3 %	23	7.2%	23.8	**0.001†**
	Liver disease	14	17.5 %	26	8.1%	6.25	**0.01†**
	ICU	80	100%	40	12.5 %	233	**0.001†**
	Ward	0	0%	280	87.5 %		

Data presented as number & percentage (%) for qualitative variables or median (Q1, Q3) for quantitative variables, p values were calculated by Mann-Whitney U test*and χ^2 test or FET† as appropriate.

Table 3: Comparison between deceased and survived patients as regard laboratory findings (n=400).

Variable	Deceased (N=80)	Survived (N=320)	Statistics	P
	Median (Q1, Q3)	**Median** (Q1, Q3)		
	Laboratory markers (at the time of admission)			
Lymphocyte count (LC)	0.6 (0.5, 0.98)	0.9 (0.7, 1.2)	4.55*	**0.001***
TLC (× 10^3 per L)	11.8 (7.5, 17)	7 (5, 13)	3.98*	**0.001***
CRP (mg/dL)	48 (12, 63)	48 (12, 84.3)	1.22*	0.22*
ESR	105 (90, 130)	95 (81.3, 130)	1.13*	0.26*
S-ferritin (ng/mL)	646 (462.5, 1140)	350 (235, 400)	9.03*	**0.001***
D-dimer (ng/mL)	1450 (700, 2497)	600 (400, 900)	6.43*	**0.001***
Urea (mg/dL)	71 (45, 120)	30 (20, 38)	10.04*	**0.001***
Creatinine (mg/dL)	1.15 (0.8, 2.08)	0.8 (0.7, 1)	5.8*	**0.001***
ALT (IU/L)	38 (28, 98.3)	34.5 (25, 40.8)	3.7*	**0.001***
AST (IU/L)	52 (30, 119)	25 (19.3, 33)	7.3*	0.001*
	70 (60, 77)	85 (78.25, 90)	8.77*	0.001*

Data presented as median (Q1, Q3), p values were calculated by Mann-Whitney U test*

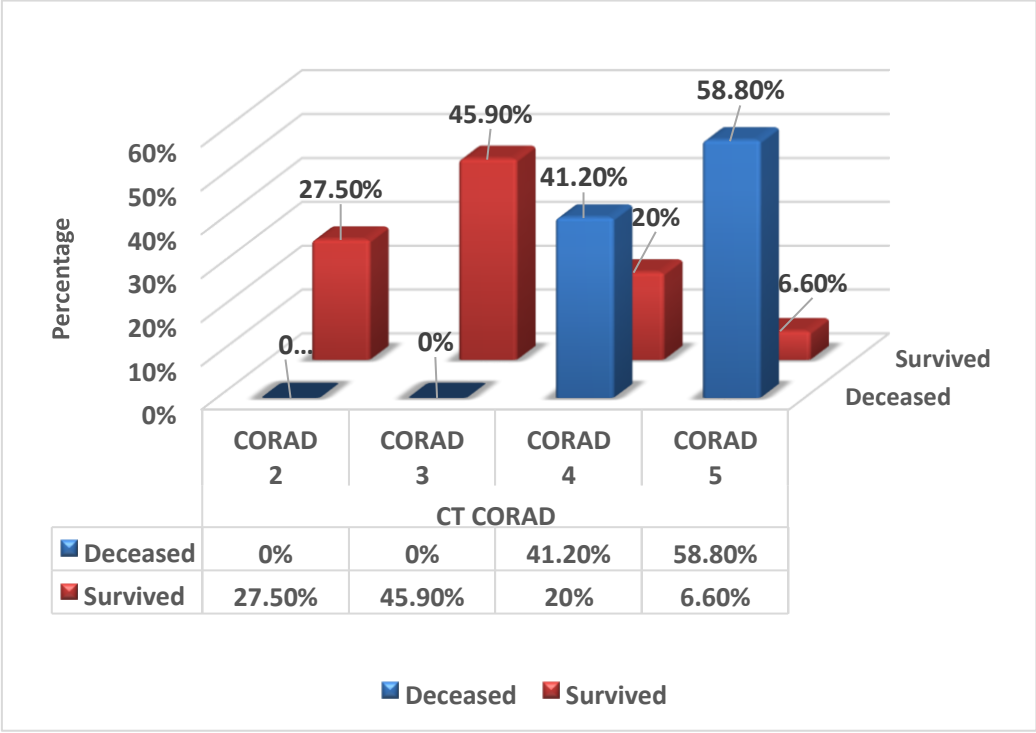

Figure 1: Bar chart shows significant differences between deceased and survived patients CORAD distribution (P=0.001).

Table 4: logistic regression for predictors and risk factors associated with COVID-19 deaths (n=80).

Variable		Univariable OR (95% CI)	P value	Multivariable OR (95% CI)	P
Demographics and clinical characteristics					
Age (years)		1.072 (1.043 – 1.1)	**0.001**	1.09 (1.05-1.13)	**0.001**
Male sex (vs female)		0.776 (0.438-1.37)	0.384		
Current Smoker (vs **nonsmoker)**		1.344 (0.626-2.88)	0.448		
Comorbidity present (vs not present)					
HTN		0.414 (0.232 – 0.740)	**0.003**		
DM		0.232 (0.179 – 0.585)	**0.001**	0.422 (0.187-952)	**0.038**
CVD		0.246 (0.101 – 0.598)	**0.002**		
Cancer		0.000 (0.000 – .)	0.999		
CKD		0.024 (0.003 – 0.180)	**0.001**	0.01 (0.001-0.106)	**0.001**
Liver disease		0.248 (0.091 – 0.677)	**0.006**		
Laboratory findings	Lymphocyte count (LC)	0.324 (0.145-0.723)	**0.006**		
	TLC ($\times 10^3$ per L)	1.094 (1.042-1.15)	**0.001**		
	CRP (>10 ng/dL)	3 (1.077-8.36)	**0.036**		
	S-ferritin (ng/mL)	1.01 (1.007-1.013)	**0.001**	1.03 (1.01-1.05)	**0.001**
	D-dimer (ng/mL)	1.002 (1.001-1.002)	**0.001**		
	Urea (mg/dL)	1.136 (1.09-1.18)	**0.001**	1.27 (1.08-1.49)	**0.003**
	Creatinine (mg/dL)	1.57 (1.15-2.13)	**0.004**		
	ALT (IU/L)	1.04 (1.02-1.05)	**0.001**		
	AST (IU/L)	1.07 (1.04-1.09)	**0.001**		
	SPO2	0.874 (0.840-0.909)	**0.001**		

OR=odds ratio CI = Confidence interval

Table 4: ROC statistics for risk of death in studied group.

Variable state		Cut off value	Sensiti vity	Specifi city	AUC	P value
Demographics	**Age (years)**	56.5	83.8%	59.2%	0.752	**0.001**
Laboratory findings	**Lymphocyte count (LC)**	0.45	70%	34%	0.311	**0.001**
	TLC (× 10^3 per L)	3.5	26%	82%	0.666	**0.001**
	S-ferritin (ng/mL)	425	81.3%	85%	0.877	**0.001**
	D-dimer (ng/mL)	585	82.5%	45.8%	0.768	**0.001**
	Urea (mg/dL)	51.5	66.3%	99.2%	0.919	**0.001**
	Creatinine (mg/dL)	2.05	25%	99.2%	0.739	**0.001**
	ALT (IU/L)	58.5	45%	95%	0.653	**0.001**
	AST (IU/L)	52.5	50%	98.3%	0.805	**0.001**
	SPO2	57.5	76.3%	0.8%	0.134	**0.001**
	CRP	36	60%	43.3%	0.55	**0.233**

AUC = area under the curve

Discussion

The present study agreed with a study showed that the most common chronic disease was hypertension in 10.9% of cases, Diabetes mellitus in 7.5%, Chronic lung diseases in 2.4%, chronic kidney disease in 1.9%, cardiovascular diseases in 2.8% of cases (8).

A research studied COVID-19 and ICU admission associated predictive factors in Iranian patients and showed that, 214 patients with positive CT-scan or PCR-test were admitted, from these patients, 74.30% were admitted in emergency room or ward, and about 25.70% of them had the ICU admission experience during their hospitalization (9).

The present study is parallel to a study evaluated the effect of age on morality and demonstrated that mortality from COVID-19 increased by increasing age as mortality was 1.1% in individuals aged 50 years, and it raised rapidly after that age. Patients over the age of 80 had the highest fatality rate, as expected. When compared to the immediately younger age group, patients aged 60 to 69 years had the greatest increase in mortality risk when compared to those aged 50 to 59 years (10).

Meta-analysis observed that the case fatality rate was higher for ICU admitted patients compared to non-ICU patients. Increased mortality among ICU patients may be due to increased associated risk factors like chronic diseases, limited number of ventilation machines, skilled stuffs, and doctors, critical patients- may be the main reason for this high risk of mortality, and limited numbers of ICUs mainly in developing countries (11).

The present study disagreed with a study found that case fatality risk was 52% for heart disease, 51% for COPD, 48% for chronic kidney disease (CKD), 39% for chronic liver disease (CLD), 28% for hypertension, and 24% for diabetes

among those who died- indicating that mortality from COVID-19 increased by presence of comorbidities (12). This may be due to variation in the population studied and different sample size as well.

A study investigated the association between several biomarkers, including serum C-reactive protein (CRP), D-dimer, and serum ferritin, and COVID-19 severity, supported our results (13).

Research found that there was significant leucocytosis, lymphopenia, and inflammatory markers (CRP and serum ferritin) significantly elevated among COVID-19 patients especially severe cases (14).

The present study was also parallel to research found that non-survivors had considerably higher rates of neutrophilia lymphopenia. Similarly, non-survivors had significantly higher levels of (ALT), blood urea nitrogen, and inflammatory indicators such as serum ferritin, and CRP (15).

Previous cohort study identified several risk factors for death in adults in Wuhan who were hospitalized with COVID-19. In particular, older age, d-dimer levels greater than 1 μg/mL, were associated with higher odds of in-hospital death. Additionally, lymphopenia was more commonly seen in severe COVID-19 illness, which agreed with our results (16).

There is mounting evidence that in critically ill patients, there are characteristics of hyperinflammation, which consist of elevated serum CRP, procalcitonin (PCT), D-dimer, and hyper-ferritinemia. These findings suggest a possibly crucial role of a cytokine storm in COVID-19 pathophysiology (17).

COVID-19 has been reported to be associated with coagulopathy and 3.75–68.0% of the COVID-19 patients have been found to have raised D-dimer levels (18).

A study described that CT can be negative at the early stages of COVID-19, which might be the case for some of COVID-19 patients whose CTs were rated CORADS 1 or 2 by at least one observer. Therefore, a CO-RADS score of 1 and 2 should be interpreted with caution within the first days of disease presence. CO-RADS 3 encompasses a category in which CT alone offers little for the diagnosis of COVID19 (19).

In same line with a study which found that in the univariate Cox regression analysis, the age, presence of heart disease, presence of comorbidities, and neutrophil-lymphocyte ratio were significant predictors for death. Each increased year of age increased the risk of death by 6%. The presence of heart disease increased the risk of death by 3.75 times, the presence of comorbidities by 86%, and the presence of a unit increase in the neutrophil-to-lymphocyte ratio by 18% (20).

A study revealed that both isolated systemic hypertension and cardiovascular disease- showed higher significance in the univariate analysis. However, hypertension did not retain its significance in the multivariable analysis, after adjusting for age and elevated urea (21).

The present study was in harmony with a study showed that lymphopenia as a

marker of severity does not seem to be specific to COVID-19; it has been used to prognosticate other viral pneumonias such as influenza. Neutrophilia may be more specific to severe disease than leukocytosis (22).

A study suggested serum ferritin levels as a key mediator suggesting immune dysregulation. Cytokine storm associated with raised serum ferritin levels has been associated with disease severity and adverse outcomes (23).

Conclusion

There is a high mortality rate among hospitalized COVID-19 patients, particularly among older individuals with comorbidities such as hypertension, diabetes, and cardiovascular disease. This underscores the importance of identifying at-risk patients and implementing effective management strategies to reduce mortality and combat the COVID-19 pandemic.

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