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Predictors of mortality among COVID-19 patients in Shebin El Kom Chest Hospital

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***Abstract*---**Background: Determining and classifying predictors of mortality of COVID 19 is of great importance for the most efficient use of healthcare resources and public health guidance and will yield improvement in clinical management and outcomes. Aim of the work: To assess Predictors of mortality among COVID 19 patients. Patients and method: 299 patients of confirmed COVID 19 by PCR rolled in our study each patient underwent detailed history, laboratory investigation, CT chest and treated according to severity regarding to Egyptian Ministry of Health Protocol (MOHP). Result: Univariate analysis revealed that old age (OR 1.061 and P value <0.001) ,ICU admission, (OR 10.052 P value <0.001) HTN (OR 2.412 P value 0.002) ,cardiac diseases (OR 2.687 P value 0.014) tachypnea(OR 1.126 P value 0.002),fever (OR 2.118 P value 0.023) hypoxiemia (OR 0.896 P value <0.001), increased inflammatory markers WBCS(OR 1.080 P value <0.001), CRP(OR 1.015 P value 0.002) ,D-dimer (OR 1.540 P value 0.001) S. Ferritin (OR 1.002 P value 0.002), ESR (OR 1.019 P value <0.001)and corad5 (OR 2.308 P value .250) were predictors for motility while in multivariate analysis elderly patients, tachypnea , hypoxiemia and increased ESR are independent factors of mortality. Anosmia found to be a predictor of good prognosis. P values 0.05 in all previous parameters. Conclusion: Old age, hypoxemia, elevated ESR,

tachypnea and lack of anosmia are independent risk factors of mortality in COVID 19.

***Keywords*---**COVID-19, mortality, PCR.

Introduction

Coronavirus disease 2019 (COVID-19) is defined as illness caused by a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; formerly called 2019-nCoV), which was first identified amid an outbreak of respiratory illness cases in Wuhan City, Hubei Province, China (1). It was initially reported to the WHO on December 31, 2019. On January 30, 2020, the WHO declared the COVID-19 outbreak a global health emergency (2, 3). On March 11, 2020, the WHO declared COVID-19 a global pandemic, Illness caused by SARS-CoV-2 was termed COVID-19 by the WHO. Available evidence indicates that transmission between humans occurs through close contact with infected people through sneezing, coughing, or just talking in the form of respiratory droplets or airborne particles. Transmission through airborne particles is possible by aerosols generated by machines used in clinical care (2; 4).

Respiratory system is the most impacted by the disease, which manifests itself in a variety of clinical manifestations. Most patients have no symptoms, some develop flu-like symptoms or develop mild pneumonia, while others progress to acute lung injury with severe pneumonia, acute respiratory distress syndrome, or even death (5). Early identification of severe COVID-19 is essential for early hospitalization, optimizing the benefit of hospital resources, and limiting unnecessary human and technical consumption. Therefore, determining and classifying the predictors of mortality is of great importance for the most efficient use of healthcare resources and public health guidance and will yield improvement in clinical management (7;8).

This pandemic has created a significant burden in all areas of life, especially economy and health. Different clinical features and risk factors related to hospitalization and mortality such as advanced age, male sex, and obesity, have been defined (9).The length of time from onset of infection until death ranges from 6 to 41 days, with an average of 14 days (10).This period is dependent on several factors (13). The COVID-19 Treatment Guidelines Panel (the Panel) recommends using either a nucleic acid amplification test (NAAT) or an antigen test with a sample collected from the upper respiratory tract to diagnose acute SARS-CoV-2 infection (AIII).(14).Currently, a variety of therapeutic options are available that include antiviral drugs (e.g., molnupiravir, paxlovid, remdesivir),anti-SARS-CoV2 monoclonal antibodies(e.g.,bamlanivimab/etesevimab,casirivimab/imdevimab), anti-inflammatory drugs (e.g., dexamethasone), immunomodulators agents (e.g., baricitinib, tocilizumab) are available under FDA issued Emergency Use Authorization (EUA) or being evaluated in the management of COVID-19 (15).The clinical utility of these treatments is specific and is based on the severity of illness or certain risk factors. The clinical course of the COVID-19 illness occurs in 2 phases, an early phase when SARS-CoV-2 replication is greatest before or soon after the onset of symptoms. Antiviral medications and antibody-based

treatments are likely to be more effective during this stage of viral replication. The later phase of the illness is driven by a hyperinflammatory state induced by the release of cytokines and the coagulation system's activation that causes a prothrombotic state. Anti-inflammatory drugs such as corticosteroids, immunomodulating therapies, or a combination of these therapies may help combat this hyperinflammatory state more than antiviral therapies (16).

Subjects and Methods

This crossectional study was carried out on 299 hospitalized cases in Shebin El kom Chest Hospital in the period from May 2020 to August 2021. The definition of a case was according the WHO criteria of probability: (17)

1. suspect case: A patient who meets the clinical criteria (acute onset of fever, cough, or any three or more of the following: fever, cough, body weakness or fatigue, myalgia, headache, sore throat, dyspnea, coryza, vomiting, diarrhea, altered mental status, and laboratory findings).
2. probable case: A suspect person with chest imaging showing findings suggestive of COVID-19 or A person with recent onset of anosmia (loss of smell) or ageusia (loss of taste) in the absence of any other identified cause and was in contact with a probable or confirmed case.
3. Confirmed case: a person with laboratory confirmation (positive PCR).

We included confirmed cases
Exclusion criteria: referred case, missed data, pregnant women, and children.
They were divided into 2 groups:
Group I: 243 patients, data collected from medical records (retrospective).
Group II: 56 patients' data collected prospectively.

After having an informed consent, each patient underwent. Detailed history taking, Clinical examination and Full routine laboratory investigation in the form of Complete blood picture(CBC), C. reactive protein (CRP) ,Serum ferritin, D. dimer ,Arterial blood gases (ABG) ,Liver functions (AST& ALT) ,Kidney functions (urea &creatinine) ,Random blood sugar(RBS) ,Erythrocyte sedimentation rate (ESR).

Ct chest: Done for clinically suspected cases with symptoms for ≥5days. Findings suggestive of COVID-19 are hazy opacities with peripheral and lower lung distribution on chest radiography, multiple bilateral ground glass opacities with peripheral and lower lung distribution.

Errant chest CT classification systems in COVID-19:CO-RADS RSNA (18)

1. Not interpretable CO-RADS 0: technically insuffient for score
2. Very low CO-RADS 1 - normal scan/non- infectiousNegative for pneumonia Non-COVID
3. Low CO-RADS 2 - typical for other(uncommon/not reported features for COVID)
4. Unsure/equivocal CO-RADS 3: Features compatible with COVID but present in other

5. High CO-RADS 4: suspicious Probable COVID-19
6. Very High CO-RADS 5: Typical appearance for COVID-19
7. Proven CO-RADS 6: confirmed diagnosis: positive PCR

PCR: the gold standard test for diagnosing COVID-19. A positive test result means an infection with SARS-CoV-2. This could be asymptomatic infection or with symptoms. A negative test result means probably no infection with SARS-CoV-2 .
Management regarding case definition (18):

Mild case has no pneumonia, no hypoxia treated with antiviral drug eg molnupiravir within 7 days of symptoms with supportive treatment. If there were risk factors for deterioration monoclonal abs used. Moderate case has pneumonia but no hypoxia treated with Antiviral (molnupiravir or remedisvir), anti-inflammatory (steroid), immunemodulatory and anticoagulant.Severe case has pneumonia with hypoxia responding to oxygen therapy treated with Antiviral (remedisvir), anti-inflammatory (steroid ortoclizumab), immunemodulatory and anticoagulant. Critically ill case has pneumonia with hypoxia not responding to oxygen therapy and /or organ dysfunction treated with Antiviral (remedisvir), anti-inflammatory (steroid ortoclizumab) and anticoagulant

Statistical analysis

Data were collected, tabulated and statistically analyzed using an IBM compatible personal computer with Statistical Package for the Social Sciences (SPSS) version 26 (19). Two types of statistical analysis were performed:

a) Descriptive statistics e.g. qualitative data were expressed as Number (N), percentage (%), while quantitative data were expressed as mean ($\bar{x}$), standard deviation (SD).
b) Analytic statistics e.g. Student's t-test (t) is a test of significance used for comparison of quantitative variables between two groups of normally distributed data, while Mann-Whitney's test (U) was used for comparison of quantitative variables between two groups of not normally distributed data.

Chi-square test (x2) was used to study association between qualitative variables was used. Fisher's exact test for 2 x 2 tables when an expected cell count of more than 25% of cases was less than 5. To investigate risk factors for mortality from COVID infection, the univariate and multivariate logistic regression analyses were performed. Factors with p value <0.05 in univariate analyses were included in multivariate analysis. The results were expressed as adjusted odds ratio with 95% confidence interval.

Odds ratio >1 indicate that association is risky
Odds ratio =1 no association
Odds ratio <1 indicate that association is protective
Probability of error (p value):
Non-significant difference if P > 0.05.
Significant difference if P <0.05.
Highly Significant difference if P <0.001

Result

A crossectional study was carried out on 299 COVID 19 cases confirmed via PCR and divided into 2 groups retrospective and prospective. The result revealed that Mean age was 60 years (range 21-93), 52.5% of population were male and 47.5 % were female, 23.7% of population were smokers and 76.3 % were non-smokers, 23.7% were admitted in ward ,73.9% were admitted in ICU and 3% outpatient. Comorbidities was present in three out of every four patients, 126 diabetic (42.1%), 120 hypertensive (40.1%), 14 malignant (4.7%), 17 Chronic chest diseases (5.7%), 18 hepatic (6%), 14 renal (4.7%), 14 autoimmune (4.7%), 31 cardiac (10.4%).

There were 236 (78.9%) survivors and 63 (21.1%) were died**.** There were significant difference between survivors and no survivors regarding to CT finding. There were significant difference between survivors and no survivors regarding to treatment. Univariate analysis revealed that old age, ICU admission, hypertension, cardiac disease, tachypnea, fever, hypoxiemia, leucocytosis, increased inflammatory markers (ESR, CRP, S. ferritin), and increased D. dimer are predictors of mortality among COVID 19. Multivariate analysis revealed that elderly patients, tachypnea, hypoxiemia and elevated ESR are independent risk factors of mortality. Anosmia found to be a predictor of good prognosis. P value is 0.05 in all previous parameters.

Table (1): Distribution of studied cases as regarding to sociodemographic, site of admission, comorbidities and outcomes. (No. =299)

Variable	Studied cases No.=299	
	No.	%
Age: (Mean ±SD) Range Median(IQR)	59.07±13.82 21-93 60(50-70)	
Sex Male Female	 157 142	 52.5 47.5
Smoking Yes No	 71 228	 23.7 76.3
Site of admission Ward ICU Out patient	 68 221 9	 23.1 73.9 3
DM • Yes • No	 126 173	 42.1 57.9
Hypertension • Yes • No	 120 179	 40.1 59.9

Cardiac disease		
• Yes	31	10.4
• No	268	89.6
Chronic chest disease		
• Yes	17	5.7
• No	282	94.3
Hepatic disease		
• Yes	18	6.0
• No	281	94.0
Renal disease		
• Yes	14	4.7
• No	285	95.3
cancer		
• Yes	14	4.7
• No	385	95.3
Autoimmune disease		
• Yes	14	4.7
• No	285	95.3
Outcomes		
• Survived	236	78.9
• Dead	63	21.1

Table (2): Comparison between survivors and non survivors regarding to sociodemographic data and site of admission (No.=299)

Variable	Survivors No.=236	Non survivors No.=63		Test of significance		P value
	No.	%	No.	%		
Age: (Mean ±SD) Range	57.05±13.86 21 - 88	66.65±10.76 40 - 93		t=5.896		<0.001**
Sex						
Male	118	50	39	61.9	x2=2.826	0.093
Female	118	50	2	38.1		
Smoking						0.098
Yes	61	25.8	10	15.9	x2=2.732	
No	175	74.2	53	84.1		
Site of admission						
Ward	31	13.1	38	60.3	x2=63.024	<0.001**
ICU	196	83.1	25	39.7		
Outpatient	9	3.8	0	0.0		

SD: standard deviation, range: minimum-maximum, No: number, %: percentage
**P value of < 0.001: statistically highly significant.
x2 =Chi squaret = student t test

Table (3): Comparison between survivors and non survivors regarding to vital data (No.=299)

vital data		Survivors No.=236 (Mean ±SD)	Non survivors No.=63 (Mean ±SD)	Test of significance	P value
• Respiratory rate (/min)		26.67±3.56	28.47±4.56	t=2.843	0.006*
• Temperature (°c)		37.29±0.39	37.43±0.45	t=2.313	0.021*
• SBP (mmhg)		120.3±9.6	121.59±10.66	t=0.926	0.355
• DBP (mmhg)		77.54±8.11	77.46±9.15	t=0.069	0.945
• Pulse (b/min)		87.53±9.28	90.13±13.84	t=1.759	0.08
ABG	• PH	7.35±0.72	7.4±0.12	t=0.636	0.525
	• PCO2 (mmhg)	33.4±8.91	36.87±14.9	t=1.765	0.082
	• PO2 (mmhg)	78.73±23.78	70.51±24.18	U=3.584	<0.001**
	• O2 saturation %	86.74±8.68	75.63±11.03	t=7.395	<0.001**
	• HCO3 (mmol/l)	22.65±4.69	24.1±9.32	U=0.347	0.728
CBC	• WBC 109 /1	8.85±5.39	12.75±9.45	U=3.456	0.001*
	• Lymphocytes 109 /1	1.1±0.97	1.57±3	U=1.645	0.1
	• Neutrophils 109 /1	8.44±8.44	10.15±5.41	U= 2.977	0.003*
	• HB (gm/dl)	12.43±2.1	12.88±2.98	t=1.379	0.169
	• Platelet 109 /1	239.8±94.3	213.37±104.8	U=1.649	0.099
Inflammatory markers	• CRP (mg/l)	60.42±32.48	74.89±31.8	U=3.067	0.002*
	• D.dimer (mg/dl)	0.697±0.86	2.16±3.63	U=3.122	0.002*
	• Serum Ferritin (ng/dl)	583.66±182.5	671.65±253.5	U=3.477	<0.001**
	• ESR	49.42±24.96	67.13±40.6	U=2.733	0.006*
Liver Function Test	• ALT (IU/l)	46.04±33.9	58.65±43.37	U=2.219	0.027*
	• AST (IU/l)	44.57±26.32	54.14±46.59	U=1.970	0.049*
Kidney Function Test	• Urea (mg/dl)	49.11±21.69	57.4±23.58	U=2.913	0.004*
	• Creatinine	1.24±0.81	1.31±0.56	U=2.242	0.025*

SD: standard deviation*P value of < 0.05: statistically significant.t = student t test
U= Mann-Whitney test

Table (4): Comparison between survivors and non survivors regarding to associate co-morbidities and CT finding (No.=299)

Co-morbidities	Survivors No.=236		Non survivors No.=63		x2 test	P value
	No.	%	No.	%		
DM Yes No	 93 143	 39.4 60.6	 33 30	 52.4 47.6	3.433	0.064

Hypertension • Yes • No	84 152	35.6 64.4	36 27	57.1 42.9	9.611	0.002*
Cardiac disease • Yes • No	19 217	8.1 91.9	12 51	19 81	6.471	0.011*
Chronic chest disease • Yes • No	13 223	5.5 94.5	4 59	6.3 93.7	0.066#	0.763
Hepatic disease • Yes • No	14 222	5.9 94.1	4 59	6.3 93.7	0.015#	1
Renal disease • Yes • No	12 224	5.1 94.9	2 61	3.2 96.8	0.407#	0.742
cancer • Yes • No	12 244	5.1 94.9	2 61	3.2 98.8	0.407#	0.742
Autoimmune disease • Yes • No	12 224	5.1 94.9	2 61	3.2 96.8	0.407#	0.742
CT finding						
• corad1	19	8.1	2	3.2	1.07	0.2839
• corad2	1	0.4	0	0.0	0.76	0.4466
• corad3	37	15.7	0	0.0	3.14	0.001**
• corad4	70	29.7	13	20.6	1.27	0.2026
• corad5	106	44.9	38	60.3	2.03	0.04*
• corad6	3	1.3	10	15.9	4.69	<0.001**

*P value of < 0.05: statistically significant.x2 =Chi square#= Fisher's Exact Test
**P value of < 0.001: statistically highly significant.x2 =Chi square

Table (5): Comparison between survivors and non survivors regarding to associate clinical presentation (No=299)

Clinical presentation	Survivors No.=236		Non survivors No.=63		total	x2 test	P value
	No.	%	No.	%	no		
Fever • Yes • No	127 109	53.8 46.2	34 29	54 46	161	0.001	0.983
Cough • Yes • No	187 49	79.2 20.8	47 16	74.6 25.4	234	0.628	0.428
Dyspnea					219		

• Yes	169	71.6	50	79.4		1.526	0.217
• No	67	28.4	13	20.6			
Chest pain							
• Yes	93	39.4	24	38.1	117	0.036	0.850
• No	143	60.6	39	61.9			
Bone aches							
• Yes	121	51.3	30	47.6	151	0.265	0.606
• No	115	48.7	33	52.4			
Diarrhea							
• Yes	114	48.3	31	49.2	145	0.016	0.899
• No	122	51.7	32	50.8			
Vomiting							
• Yes	67	28.4	13	20.6	80	1.526	0.217
• No	169	71.6	50	79.4			
Anosmia							
• Yes	111	47	18	28.6	129		
• No	125	53	45	71.4		6.910	0.009*
Headache							
• Yes	75	31.8	23	36.5	98	0.505	0.478
• No	161	68.2	40	63.5			

*P value of < 0.05: statistically significant.
x2 =Chi square#= Fisher's Exact Test

Table (6): Comparison between survivors and non survivors regarding to treatment (No=299)

Treatment	Survivors No.=236		Non survivors No.=63		x2 test	P value
	No.	%	No.	%		
Actemra						
• Yes	4	1.7	16	25.4	44.757	<0.001**
• No	232	98.3	47	74.6		
Remedesvir						
• Yes	5	2.1	20	31.7	56.967	<0.001**
• No	231	97.9	43	68.3		
Colchicines						
• Yes	98	41.5	27	42.9	0.036	0.849
• No	138	58.5	36	57.1		
Iverzine						
• Yes	143	60.6	42	66.7	0.778	0.378
• No	93	39.4	21	33.3		
monoclonalantibodies						
• Yes	24	10.2	0	0.0		
• No	212	89.8	63	100	6.966	0.008*
Hydroxychloroquine						

• Yes	98	41.5	27	42.9		
• No	138	58.5	36	57.1	0.036	0.849
Corticosteroid						
• Yes	188	79.7	57	90.5		
• No	48	20.3	6	6.0	3.93	0.047*
Anticoagulant						
• Yes	208	88.1	63	100		
• No	28	11.9	0	0.0	8.247	0.004
Prophylactic						
• Yes	128	54.2	32	50.8		
• No	108	45.8	31	49.2	0.237	0.626
Therapeutic						
• Yes	80	39.9	31	49.2		0.025*
• No	156	66.1	32	50.8	4.992	
O2. Therapy						
• No	160	67.8	60	95.2	19.261	<0.001
• Yes	76	32.3	3	3		
Type of O2. Therapy						
o2mask						
• Yes	154	65.3	41	65.1	0.001	0.979
• No	82	34.7	22	34.9		
NIV						
• Yes	4	1.7	5	7.9	6.636	0.01*
• No	232	98.3	58	92.1		
IV						
• Yes	3	1.3	17	27	52.674	<0.001**
• No	233	98.7	46	73		

*P vale of < 0.05: statistically significant.**P value of < 0.001: statistically highly significant.

Table (7): Univariate logistic regression analysis for variables significantly associated with increasing mortality from COVID infection

Predictors (Independent variables)	univariate logistic regression		
	Odds ratio	P value	95% CI (lower-upper)
Age	1.061	<0.001**	1.035 – 1.088
Site of admission(Ward vs ICU)	10.052	<0.001**	5.351 – 18.88
Hypertension (no vs yes)	2.413	0.002*	1.370 - 4.248
Cardiac disease (no vs yes)	2.687	0.014*	1.226 – 5.888
Anosmia (no vs yes)	0.450	0.01*	0.246-0.824
Respiratory rate	1.126	0.002*	1.046 – 1.211
Temperature	2.118	0.023*	1.107 – 4.050
PO2	0.985	0.016*	0.972- 0.997
O2 saturation	0.896	<0.001**	0.867 – 0.926
WBCS	1.080	<0.001**	1.036 – 1.126

Neutrophils	1.023	0.161	0.991 – 1.056
CRP	1.015	0.002*	1.005 – 1.024
D. dimer	1.540	<0.001**	1.229 – 1.930
Ferritin	1.002	0.002*	1.001 – 1.004
ESR	1.019	<0.001**	1.009- 1.028
ALT	1.008	0.021	1.001 – 1.015
AST	1.008	0.052	1 – 1.016
Urea	1.003	0.013*	1 -1.026
Creatinine	1.109	0.530	0.803 – 1.532
Corad corad1(reference) corad2 corad3 corad4 corad5 corad6	 6 1.646 1.114 2.308 0.999	 0.035* 0.447 0.876 0.250 1	 1.134 – 31.735 0.455 -5.951 0.287 -4.333 0.556 – 9.579 0.001 -0.004

CI= Confidence interval*P vale of < 0.05: statistically significant. OR= Odds ratio
**P value of < 0.001: statistically highly significant.

Table (8): Multivariate logistic regression analysis for variables significantly associated with increasing mortality from COVID infection

Predictors (Independent variables)	Multivariate logistic regression		
	Odds ratio	P value	95% CI (lower-upper)
Age	1.066	0.002*	1.023-1.111
Site of admission(Ward vs ICU)	1.249	0.674	0.443-3.527
Hypertension (no vs yes)	1.021	0.963	0.417-2.503
Cardiac disease (no vs yes)	1.576	0.494	0.428-5.811
Anosmia (no vs yes)	0.392	0.003*	0.165-0.928
Respiratory rate	1.034	0.005*	0.927 -1.153
Temperature	1.333	0.568	0.497 -3.573
PO2	0.997	0.684	0.980 -1.013
O2 saturation	0.910	<0.001**	0.866 -0.957
WBCS	1.031	0.361	0.965 – 1.103
CRP	1.009	0.188	0.996 – 1.023
D. dimer	1.235	0.131	0.939 -1.624
Ferritin	1.001	0.361	0.999 – 1.003
ESR	1.018	0.008*	1.005 1.031
ALT	0.995	0.641	0.983 – 1.008
Urea	1.003	0.778	0.985 -1.020
Corad corad1(reference) corad2 corad3 corad4 corad5	 6.081 3.540 3.016 3.822	 0.209 0.231 0.523 0.256	 0.363 -10.756 0.447-28.05

corad6	0.0001	1	

CI= Confidence interval*P vale of < 0.05: statistically significant. OR= Odds ratio**P value of < 0.001: statistically highly significant

Discussion

Coronavirus disease-2019 (COVID-19) has rapidly become a global threat .As of 30 April 2020, there have been more than 3.0 million global confirmed cases and greater than 230 000 fatalities due to COVID-19. In 10 December 2021 WHO reported about 5298992 deaths. Deaths has reached now 6501469. (20) Several studies have been done throughout different pandemics of COVID 19 since 2019 for evaluation of different factors that may play a role in prediction of severity and outcomes of COVID 19 patients. Mehraeen et al., a systematic review including 114 studies of about 72 variables but not including treatment protocol they were not able to obtain adequate information to run weighted analysis and draw forest plots. As many of their studies comprised of those with small populations, it was not feasible to analyze according the population density Given that the studies are of case series, cross-sectional design, it was also not possible to pool the data together to estimate the heterogeneity between the studies (21). Du et al., a prospective cohort study of 179 COVID patients hospitalized to Wuhan Pulmonary Hospital included clinical data and laboratory markers but ignored treatment protocol (22).

Regarding the demographic data and comorbidity our study has reported that patients in nonsurvivors were much older than in survivor group. Univariate and multivariate logestic regression analysis revealed age more than 66 years old is a predictor of mortality among COVID -19 patients. This agreed with Mehraeen et al., (21); Du et al., (22); Sanyaolu et al., (23);Mahmoud et al., (24); Elmorshedy et al., (25); Akcicek,(26); Ibrahim et al., (27). Ibrahim et al., noticed that increasing age shows an obvious risk for catching infection or increasing disease severity (27). The age factor was observed since the beginning of the epidemic and that may be for the following: first, the difference in susceptibility to have infection as children were less liable to become infected, and this may be owing to immune cross-protection from other coronaviruses, or from nonspecific immunity resulting from frequent infections by other respiratory viruses, and this is obvious in children. Second, children may have mild or less symptoms of infection more than adults. This variation in severity due to age was observed in other respiratory viruses including SARS (10; 25).

Sanyaolu et al., explained The age-related changes in the geriatric population may be due to the changes in lung anatomy and muscle atrophy which results in changes in physiologic function, reduction of lung reserve, reduction of airway clearance, and reduction of the defense barrier function (21; 29). In our study, we reported that ICU admission is a risk for mortality. All studies either in COVID-19 or other respiratory infections confirmed the high rate of morbidity and mortality among ICU admitted patients (30).The mortality rates among ICU admission cases in different studies are diverse and range from 16% to 67% (31). Sadeghiet al., in Iranian study reported Multivariate analysis of risk factors related to the increased risk of ICU admission: Among the demographic factors, age was an

independent factor for increasing the risk of ICU admission in patients infected with COVID-19. Also, O2 saturation was the only vital sign that could be numbered as an independent predictor for ICU admission in COVID-19 infection. CRP as a biomarker of acute inflammatory phase could independently predict the risk of ICU admission among our patients. The previous studies described a high rate of hyper-coagulopathy during the first days of admission among patients infected with COVID-19. But, it seems that this phase of hypercoagulation is not persisting. However, the second hyperfibrinolysis phase following hypercoagulation is rare among COVID-19 patients (32). The most important issue about the coagulopathies in COVID-19 is its accompaniment with sepsis during the development of COVID-19. The COVID-19 could strongly cause septic shock in critically ill patients (31). Elmorshedy et al., reported that nonsurvivor group had significantly increased duration of ICU stay (25).

In our study we reported that hypertension and cardiovascular diseases were significantly related to nonsurvival group. This was agreed with Yadaw et al.,(33); Sadeghiet al., (32); Mehraeen et al., (21); Du et al., (22); Sanyaolu et al., (23); Ibrahim et al., (27); Mahmoud et al., (24); Akcicek, (26). Mahmoudet al., observed high comorbidity burden in the group admitted with severe illness (24). This is in concordance with previous report on increased vulnerability to severe course of COVID-19 and higher mortality observed in patients having other comorbidities (7).

Mahmoudet al., explained that by Endothelial dysfunction suggested by high neutrophill/ lymphocyte ratio (NLR) plays a pivotal role in disease progression and severity; viral infection amplifies this effect, leading to accelerated cell death and more endothelial dysfunction (24). Patients who suffered endothelial dysfunction (as in hypertension, diabetes, and cardiovascular disease) are more susceptible to a rapid deterioration and earlier hospitalization is required (6; 34; 35). Infection-related demand ischemia and direct viral infection of the myocardium have also been reported in studies among the etiologies of increased mortality in patients with COVID-19 with a prior history of cardiovascular disease.

About hypertension, regular use of medications, including Angiotensin II receptor blockers (ARB) and Angiotensin-convertingenzyme inhibitors (ACEI) upregulates ACE2 expression, therefore facilitating the entry of SARS-CoV-2 into pneumocytes which ultimately increases the severity and fatality of infection. But there is no evidence showing that the termination of ACEI and ARB in patients with COVID-19 infection would be benefcial (36). Regarding to clinical pictures in our study we reported that tachypnea and fever were more in nonsurvivors. Fever was the most reported symptom in severe cases and can be explained by Cytokine storm, aggressive stimulation of immune system, and process of inflammation, all of them play a role in development of fever as documented in previous studies. (5; 37; 39, 40). Moreover, some studies highlighted the risk of missing cases of COVID-19 infection as they reported afebrile form of infection more frequently in COVID-19 relative to other viral infections. (5; 37; 10; 39).

And this was clear in our study as fever documented as a significant sign not a patient complaint and that may be due to low grade fever missed from patient but

detected by measuring body temperature. Du et al., reported that patients in deceased group had a higher respiratory rate than those in the survivor group (22). We reported that anosmia is a good prognostic symptom as it was more in survivors group. ABrazilian study said that the olfactory dysfunction in COVID-19 seems to be more than a symptom of this new infection. The presence of hyposmia/anosmia in patients infected with SARS-CoV-2 may be a predictor of good disease prognosis. It is possibly a spectrum of this disease that affects mostly the upper airways, without significant pulmonary involvement. Therefore, it is reasonable to think that the presence of olfactory dysfunction as a symptom can be associated with a milder clinical picture (41).

In contrast to these findings, Moein et al., and Vaira et al., found no association between the olfactory disorder and disease severity (42 ;43). Vaira stated that alterations in olfaction reported by critically-ill patients can be overlooked in the context of prolonged hospitalization and invasive ventilatory support (42; 43; 44). Another study carried out in the Brazilian population that included patients admitted to the ICU and the hospital ward and participants who received only outpatient treatment also did not identify an association between the presence of olfaction disorder and the severity of the patients' clinical condition (45). Regarding to laboratory markers we reported that lower O_2 saturation was related to nonsurvivor group (mean 75.63) comparing to survivor group (mean 86.74) and this agreed withYadaw et al.,(33).

We reported Leucocytosis, Neutrophillia, elevated CRP, D. Dimer, S. Ferritin and ESR as predictors of mortality and all of them are signs of sepsis and sever inflammation related to cytokine storm. Elevated liver function and kidney function tests are also significantly related to nonsurvivor group. Mahmoud et al., has found total leukocytic count, neutrophils, and inflammatory markers in addition to liver enzymes and kidney function were elevated in the severe group (24).

Some studies reported that increased neutrophils, lower lymphocyte percent, and higher NLR level in the peripheral hemogram can predict progressive course and poor outcome in COVID-19 patients. ***** Wang et al , Zeng et al and Henry et al ., stated that an increase in the total leukocytic count may occur and is driven by the increase in neutrophils; on the contrary, there are decreasing trends for lymphocytes, eosinophils, and monocytes. Higher total leukocytic count in the severe group could be partially explained by the associated secondary bacterial infection due to immunosuppression (11; 46; 47).

Sadeghiet al., repoted a significant association was found between a high level of CRP and ESR as the predictors of the inflammatory phase due to sepsis and ICU admission. Simultaneously, the INR level was significantly higher in ICU-admitted patients (32). These results indicate the inflammatory reactions as one of the main pathophysiology of COVID-19 infection in critically-ill infected patients. Elmorshedy et al., reported severe infection and probably experienced a cytokine storm which was reflected as markedly elevated inflammatory markers (23). Values of D-dimer, ferritin level were higher in the nonsurvivor group. They explained this by the fact that DNA injury and release of virus from the cells is the end result of secretion of oxidative stress markers from neutrophils. Unluckily,

infection with COVID-19 is documented to be associated with significant increase in markers of inflammation released from neutrophils (48; 49) and is also accompanied by inhibition of cellular immunity, with decreased CD4/CD8 T-lymphocyte ratio secondary to systemic inflammation (50).

Mehraeen et al., does not support the role of laboratory results as predictors of mortality (21). Du et al., reported that the deceased group had more white blood cells and neutrophils than did the survivors (22). In fact, lung secondary bacterial infections were documented at a late stage of disease in 10 of the 21 deceased patients, and the aetiological spectrum included Klebsiella pneumoniae, Staphylococcus, Acinetobacter baumannii and Escherichia coli. The reason for liver enzyme abnormalities have been postulated to be multifactorial. Liver histopathology has shown nonspecific findings with steatosis, mild lobular and/or periportal inflammation, and vascular pathology. The potential contributors possibly stem from immune mediated inflammatory response, hepatic congestion, systemic hypoxemia, direct infection of hepatocyte, cytokine release, ischemic hepatitis and venous and arterial thrombosis (51).

Kidney function abnormalities can be explained by hypoxemia, coagulopathies, cardiovascular impairment leading to ischemia, used treatment like actemra and remedsvir and sepsis. Regarding to imaging studies corad 5 has found to be a predictor of mortality. Regarding to treatment we found that actemra and remedsvir couldnot improve the prognosis, on the contrary they were more in non survivor group. High mortality rate with antiviral treatment can be explianed by late administration after 14 days of symptoms onset or due to side effects like acute fulminant hepatitis. The same result has reported by Elmorshedy et al., only 10 patients received tocilizumab owing to their financial situation, and none of them survived (26). Three studies described mortality in patients treated with Remdesivir compare to No-Remdesivir. Wang et al., reported 28-day mortality (12); Beigel et al., described 14-day mortality (52); and Hsu et al., (53) observed a statistically significant reduction of death using Remdesivir (54).

In our study we found that using monoclonal antibodies when used in mild risky cases improve the outcome 100% (no deaths). Lin, revealed that he most important finding of this study is that neutralizing mABs could help to prevent hospitalization or ED visits among COVID-19 patients, as supported by the following evidence. First, the rate of COVID-19-related hospitalization or ED visits was significantly lower among the COVID-19 patients who received neutralizing mABs than in those who received a placebo. Second, the lower rate of hospitalization or ED visits in those who received neutralizing mABs remained unchanged in the sensitivity test and subgroup analyses of patients at high risk and different regimens of neutralizing mABs. Third, neutralizing mABs were associated with a lower risk of COVID-19 related hospitalization than aplacebo. Finally, the risk of death was significantly lower among those receiving neutralizing mABs than the control group (54). These findings are consistent with those of real-world studies and observational cohort studies. Chen et al., reported a significant difference compared to those who received a placebo in the decrease in SARS-CoV-2 viral load from baseline (difference: −0.53; 95% CI: −0.98 to −0.08; $p = 0.02$) (55) .

One study using SARS- CoV-2 virus-like particles (VLP) found that no activity was detected for casirivimab or imdevimab either against Omicron VLPs. Moreover, casirivimab was able to neutralize OmC3 but not OmC1 and imdevimab was able to neutralize OmC1 but not OmC3. All these findings suggested that the failure of these mABs to neutralize Omicron S could be due to the six mutations within the Omicron RBD (K417N, N440K, G446S, G496S, Q498R, and N501Y) (56). Another study using an artificial intelligence model predicted that the efficacy of several neutralizing mABs, such as bamlanivimab and etesevimab, casirivimab and imdevimab against Omicron might largely diminish but the impact of Omicron on the activity of sotrovimab could be mild (55).

The similar findings that bamlanivimab and etesevimab, casirivimab and imdevimab completely lost neutralizing activity against Omicron whereas sotrovimab was only minimally affected, were also reported in an in vitro study in both Vero-TMPRSS2 and Vero-hACE2-TMPRSS2 cells (57). Third, the risk of mutations leading to neutralizing mAB resistance remains a serious concern, particularly for bamlanivimab (6; 58; 59). We found also that mechanical ventilation was more in non survivor group and considered as a predictor of mortality. Many studies have been reported from regions that have seen a rapid rise in SARS-CoV-2–positive patients, leading to significant resource limitation. Owing to the overwhelming number of patients admitted to hospitals in China (Wuhan), Italy (Lombardi Region), and the US (New York), local healthcare systems were over their maximal capacities, possibly leading to intubation avoidance and rationing of medical therapies (6;38; 9).

Conclusion

In this study we found that old age, hypoxia, high ESR and tachypnea are independent predictors of mortality in COVID 19 on the other hand anosmia has found to be a sign of good prognosis.

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	Contributor 1	Contributor 2	Contributor 3	Contributor 4
Concepts	√			
Design	√			√
Definition of intellectual content	√			
Literature search				√
Clinical studies		√		√
Experimental studies		√		√
Data analysis	√		√	√
Statistical analysis	√	√	√	√
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