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Coronavirus Pandemic

Assessment and outcome of hospitalized patients during delta variant COVID-19 pandemic: A multicenter international study

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Abstract

Introduction: To date, the world has experienced four waves of the Coronavirus disease- 19 (COVID-19) pandemic. Patients infected during the era of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Delta variant were the subject of this study. The objectives were to describe their clinical manifestations, explain their laboratory and radiological findings, conclude factors contributing to clinical outcomes, and evaluate treatment protocols.

Methodology: Relevant data were collected retrospectively from records of patients admitted to six referral centers in four countries. Data included sociodemographic patterns, symptoms, associated comorbidities, physical examination, laboratory and radiologic findings, treatment received, and patient outcomes.

Results: Data analysis identified symptomatology and variables related to acquisition and infection outcome. The most prevalent symptoms were cough (81.5%), body aches (74.1%), and fever (71.6%). Independent risk factors for mortality were age, vomiting, epigastric pain, diabetes, obesity, oxygen saturation less than 90%, leukocytosis, neutrophilia, lymphopenia, thrombocytopenia, elevated creatinine, high glucose level, lung ground glass opacities with consolidation, affection of four lobes and bilateralism. Neither d-dimer nor lactate dehydrogenase nor ferritin foretells death possibility. The efficacy of the medications used was convenient.

Conclusions: Assessing the clinical features of different COVID-19 waves, identifying predictors of outcomes, and concluding the efficacy of treatment protocols provide insight into patients' responses and viral behaviors, which help in the proper diagnosis and treatment of subsequent surges.

Key words: COVID-19 pandemic; outcome predictors; SARS-CoV-2.

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a worldwide pandemic after its first report in Wuhan, Hubei Province of China. So far, many countries have experienced a four-wave pattern of the disease. Like other RNA viruses, SARS-CoV-2 is inclined to undergo genetic transformation while familiarizing itself with its new human hosts. The result could be the evolution over time of mutations, producing variants that may have distinct attributes from their ancestral strains. Emerging variants may produce different degrees of pathogenicity with/ without altered clinical pictures. Due to the increasing number of cases and the growing experience of healthcare providers, management protocols have been updated [1-5].

So far, at least four variants of concern have been circulating globally in the SARS-CoV-2 pandemic

resulting in nearly 180 million documented viral infections and almost 4 million COVID-19 deaths worldwide since December 2019 [6]. The current work is a multicenter assessment of COVID-19 patients infected during the Delta variant era in four countries: Egypt, Romania, Turkey, and Iraq. Challenges related to countries' technical and logistic capabilities in recognizing and diagnosing asymptomatic patients and those with mild symptoms have made population-based evaluation difficult [7]. However, a more accurate study could be carried out on hospitalized patients for whom the disease was confirmed by clinical, laboratory, and radiological investigations.

The effect of newly emerged variants may include variations in the spread, virulence, and mortality rates. The objectives of the current work were to document the clinical features of patients infected with COVID-19 during the Delta variant era of the pandemic, to elucidate the laboratory and radiological findings, to conclude factors contributing to clinical outcomes, whether positive or negative and to evaluate the treatment protocols in the management of infected patients.

Methodology

Ethical approval

The study was ethically approved by the Ethical Research Committee (IRB) of the Faculty of Medicine, Port Said University, Port Said, Egypt. Consent statement was not applicable to this study as data were retrospectively and anonymously collected.

Data collection

The present cross-sectional multicenter research work comprised 482 hospitalized COVID-19-infected patients during the Delta variant era from July 1st to August 8th, 2021. Data were collected from four countries: Egypt (Africa), Iraq (Asia), Turkey, and Romania (Europe) from 6 referral centers; Port Said University Hospital, Zagazig University Hospital, and Altaiseer Private Hospital, Egypt- Kazemia Teaching Hospital, Iraq- Sancaktepe Sehit Prof Dr. Ilhan Varank Training and Research Hospital Turkey and Clinical Hospital for Infectious Diseases, Romania. Adult patients diagnosed to have COVID-19 were included. Those with missing data were excluded. Google form application was used to create an online questionnaire for data collection, and the link was sent to all participating centers.

Data collected included: 1) Sociodemographic patterns: age, gender, residence, marital state, contact with COVID-19 patients, and smoking; 2) Symptoms: cough, body aches, fever, headache, expectoration, sore throat, gastrointestinal; vomiting and epigastric pain, diarrhea, loss of smell/ taste, skin manifestation, eye redness/itching, and duration of symptoms before hospital admission; 3) Co-morbidities: hypertension, diabetes, ischemic heart disease, chronic obstructive pulmonary disease, heart failure, renal failure, hepatic diseases, bronchial asthma, immunosuppressive illness, human immunodeficiency virus (HIV), and others; 4) Physical examination: appearance whether comfortable or distressed, body weight, pallor, cyanosis, lymph nodes enlargement, pulse /min- blood pressure, respiratory rate/min, O_2 saturation; 5) Laboratory tests: total leucocytic count (leukopenia- leukocytosis), neutrophils count (neutropenia- neutrophilia), lymphocytes count (lymphopenia- lymphocytosis), platelets (thrombocytopenia), erythrocyte sedimentation rate (ESR), C- reactive protein (CRP), lactate dehydrogenase (LDH), d- dimer a (ng/mL), ferritin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine, blood glucose level, 6) CT findings: CT pattern (ground glass opacity (GGO), consolidation, number of lobes affected and bilateralism); 7) The treatment received according to the guidelines and management protocols in Egypt [8], Turkey [9], Iraq, and Romania [10]: steroids (dexamethasone), anticoagulants (celxan), antibiotics (ceftriaxone and meropenem) when secondary bacterial infection is suspected, antivirals (ivermectin, remidsivir and favipravir) and others (analgesics and antipyretics, mucolytics, antioxidants, lactoferrin, vitamin D, vitamin C, and Zinc); 8) Outcome: discharged or died.

Statistical analysis

Both COVID-19 raw case fatality rate (CFR) and death percentage rates (DPR) were calculated [11].

$$\text{CFR} = \left(\frac{\text{Number of deaths}}{\text{Total number of cases}}\right)$$

$$\text{DPR} = \left(\frac{\text{Number of fatalities} \times 100}{\text{Total number of cases}}\right)$$

When indicated, the results were displayed as median and minimum/maximum for quantitative data or mean and standard deviation (± SD). Qualitative data were expressed as frequencies and were compared using Chi-square and Fisher exact tests when proper. Binary logistic regression was applied to recognize predictors of unfavorable outcomes among hospitalized COVID-19 patients. A probability (p) value ≤ 0.05 was considered significant. SPSS software version 24 was utilized to perform data analysis.

Results

A total of 482 patients were enrolled in the study. Four hundred twenty-four patients were cured and discharged, while 58 patients died. The raw case fatality rate among the study population was 0.12, and the death percentage was 12.04%.

Baseline sociodemographic characteristics and clinical features

Table 1 demonstrates that most patients were 50 – 69 years old. Older age groups were associated with poorer outcomes as compared to younger age groups. The most frequent occurrence of death was within the age group 70-79 years (25.9%). The number of males

Table 1. Demographic, symptom, and history of COVID 19 patients.

Variable	Total (N = 482); N (%)	Discharged (n = 424); N (%)	Died (n = 58); N (%)	*p* - value
Age				
≤ 29 years	24 (5.0)	23 (5.4)	1 (1.7)	
30-39 years	66 (13.7)	53 (12.5)	13 (22.4)	
40-49 years	78 (16.2)	75 (17.7)	3 (5.2)	**< 0.001***
50-59 years	112 (23.2)	105 (24.8)	7 (12.1)	
60-69 years	112 (23.2)	99 (23.3)	13 (22.4)	
70-79 years	60 (12.4)	45 (10.6)	15 (25.9)	
≥ 80 years	30 (6.2)	24 (5.7)	6 (10.3)	
Gender				
Male	261 (54.1)	231 (54.5)	30 (51.7)	**0.69**
Female	221 (45.9)	193 (45.5)	28 (48.3)	
Residence				
Rural	114 (23.7)	97 (23.5)	17 (29.3)	**0.33**
Urban	356 (73.8)	315 (76.5)	41 (70.7)	
Marital status				
Single	150 (31.1)	133 (31.3)	17 (29.3)	**0.86**
Married	332 (68.9)	291 (68.7)	41 (70.7)	
Contact to COVID 19 case				
No	165 (34.2)	142 (33.5)	23 (39.7)	**0.35**
Yes	317 (65.8)	282 (66.5)	35 (60.3)	
Smoking				
No	322 (66.8)	299 (70.5)	23 (39.7)	**< 0.001***
Yes	160 (33.2)	125 (29.5)	35 (60.3)	
Symptoms				
Cough	393 (81.5)	343 (80.9)	50 (86.2)	0.32
Body aches	357 (74.1)	219 (51.7)	23 (39.7)	0.08
Fever	345 (71.6)	308 (72.6)	37 (63.8)	0.16
Dyspnea	271 (56.2)	231 (54.5)	40 (69.0)	0.03*
Headache	242 (50.2)	313 (73.8)	44 (75.9)	0.73
Expectoration	115 (23.9)	102 (24.1)	13 (22.4)	0.78
Sore throat	155 (32.2)	142 (33.5)	13 (22.4)	0.09
Digestive symptoms				
Epigastric pain and vomiting	22 (4.6)	12 (2.8)	10 (17.2)	< 0.001*
Diarrhea	121 (25.1)	99 (23.3)	22 (37.9)	0.01*
Loss of smell	165 (34.2)	149 (35.1)	16 (27.6)	0.25
Loss of taste	136 (28.2)	119 (28.1)	17 (29.3)	0.84
Skin rash	12 (2.5)	12 (2.8)	0 (0.0)	0.19
Eye redness and itching	12 (2.5)	12 (2.8)	0 (0.0)	0.19
Duration of symptoms before admission				
1-3 days	81 (16.8)	79 (18.6)	2 (3.4)	
4-7 days	232 (48.1)	204 (48.1)	28 (48.3)	0.01*
8-10days	124 (25.7)	103 (24.3)	21 (36.2)	
More than 10 days	45 (9.3)	38 (9.0)	7 (12.1)	
History of illness				
Hypertension	225 (46.7)	195 (46.0)	30 (51.7)	0.41
Diabetes	140 (29.0)	104 (24.5)	36 (62.1)	< 0.001*
Ischemic heart disease	74 (15.4)	64 (15.1)	10 (16.2)	0.67
COPD	52 (10.8)	47 (11.1)	5 (8.6)	0.22
Others [b]	116 (24.1)	104 (24.5)	12(20.7)	0.52

*p value ≤ 0.05; [a] 12 discharged COVID-19 patients residence data were missing (N = 412); [b] Others included heart failure (5.6%); renal disease (8.7%); hepatic disease (8.9%); bronchial asthma (9.3%); Immunosuppressive illness (2.7%); HIV (0.4%); and other illnesses (2.1%).

was slightly higher than that of females. The number of infected patients from urban areas surpassed those from rural ones. Most of the infected persons were married. Many patients had recently been in contact with COVID-19 infected individuals. Smoking was significantly associated with poor outcomes.

The most common symptoms among patients infected in descending order were cough (81.5%), body aches (74.1%), fever (71.6%), dyspnea (56.2%), and headache (50.2%). Duration of symptoms ranged from 4-7 days in many patients (48.1%). Hypertension and diabetes were the most prevalent comorbidities among COVID-19 patients, 46.7% and 29%, respectively.

Physical examination of the studied patients revealed that most looked stressed (68.5%), and a lower number were pale and cyanotic (25.1%, 7.3%, respectively). All these variables were significantly correlated with death (Table 2). Although 41.7% of the infected patients had average body weight, body weight abnormality was significantly associated with death. Deterioration of vital signs (pulse and respiratory rate) and poor oxygen saturation were mainly observed in patients with poor outcomes ($p < 0.001$).

Laboratory parameters, CT imaging, and medications

Table 3 shows that nearly a third of the patients had leukocytosis and neutrophilia, 71.6% had lymphopenia, and 10.8% had thrombocytopenia. All blood cell variables were significantly associated with death outcomes ($p < 0.001$). ESR was elevated in 71% of patients, while almost all patients (94.8%) had raised CRP. LDH and ferritin serum levels were significantly higher in patients with unfavorable outcomes ($p = 0.03$ and 0.004, respectively). Elevated serum creatinine and blood glucose level were significantly associated with poor outcomes ($p < 0.001$). Other laboratory parameters didn't have a significant correlation with unfavorable patient outcomes. GGO, multiple lobes affection (> 3 lobes), and bilaterality of lung disease were remarkable radiologic features encountered with a negative outcome ($p < 0.001$, < 0.001, and 0.009, respectively). Medications including steroids, anticoagulants, antibiotics, antivirals were significantly associated with hospital discharge ($p < 0.001$, $p = 0.001$, $p < 0.001$, and $p < 0.001$, respectively) (Table 3).

Predictors of outcome with binary logistic regression analysis

The binary logistic regression analysis of significant variables calculated by univariate analysis disclosed that: age, smoking, epigastric pain and vomiting, diabetes, obesity, low oxygen saturation (< 90), leukocytosis, neutrophilia, lymphopenia, thrombocytopenia, elevated serum creatinine, hyperglycemia, presence of GGO and consolidation, lung disease affecting >3 lobes, and bilateral lung disease were significant predictors associated with death. The odds ratio of each variable shown in Table 4 determined its chance of predicting an unfavorable outcome.

Table 2. Clinical features of COVID 19 patients.

Variable	Total (N = 482); N (%)	Discharged (n = 424); N (%)	Died (n = 58); N (%)	*p- value*
Appearance				
Comfortable	152 (31.5)	152 (35.8)	0 (0.0)	< 0.001*
Distressed	330 (68.5)	272 (64.2)	58 (100.0)	
Pallor	121 (25.1)	162 (38.2)	27 (46.6)	0.003*
Cyanosis	35 (7.3)	94 (22.2)	5 (8.6)	< 0.001*
Weight				
Normal	201 (41.7)	190 (44.8)	11 (19.0)	
Underweight	31 (6.4)	16 (3.8)	15 (25.9)	0.003*
Overweight	177 (36.7)	158 (37.3)	19 (32.8)	
Obese	72 (14.9)	59 (13.9)	13 (22.4)	
Morbid obesity	1 (0.2)	1 (0.2)	0 (0.0)	
Lymph nodes enlargement	196 (40.7)	30 (7.1)	34 (58.6)	0.67
Pulse /min[a]	90 ± 17	87 ± 16	106 ± 18	< 0.001*
Blood pressure				
Systolic [a] (mmHg)	123.0 ± 19.4	125.0 ± 19.0	115.0 ± 21.0	0.001*
Diastolic [a] (mmHg)	77.5 ± 11.1	78.0 ± 10.0	74.0 ± 16.0	0.003*
Respiratory rate/min [a]	22 ± 5	22 ± 5	29 ± 6	< 0.001*
O2 saturation				
≥ 90	308 (63.9)	304 (71.7)	4 (6.9)	< 0.001*
< 90	174 (36.1)	120 (28.3)	54 (93.1)	

*p value ≤ 0.05; [a] Mean ± SD.

Table 3. Laboratory parameters, Radiological features, and Medications of COVID 19 patients.

Variable	Total (N = 482); N (%)	Discharged (n = 424); N (%)	Died (n = 58); N (%)	*p* - value
Total Leucocytic count				
Leukopenia	89 (18.5)	69 (13.6)	20 (34.5)	< 0.001*
Leukocytosis	154 (32.0)	123 (29.0)	31 (53.4)	
Neutrophils				
Neutropenia	200 (41.5)	168(39.6)	32(55.1)	**< 0.001***
Neutrophilia	238 (49.4)	222(52.3)	16(27.6)	
Lymphocytes				
Lymphopenia	345 (71.6)	291 (68.6)	54 (93.1)	**< 0.001***
Lymphocytosis	28 (5.8)	26 (6.1)	2 (3.4)	
Platelets				
Thrombocytopenia	52 (10.8)	11 (2.5)	41 (70.7)	< 0.001*
ESR				
Normal	140 (29.0)	122 (28.8)	18 (31.0)	**0.72**
Elevated	342 (71.0)	302 (71.2)	40 (69.0)	
CRP				
Negative	25 (5.2)	23(5.4)	2 (3.4)	**0.52**
Positive	457 (94.8)	401(94.6)	56 (96.6)	
LDH [a] (U/L)	275 (5-8222)	264 (5-8222	375.5 (110-1357)	0.03*
D-dimer [a] (ng/mL)	600 (0.1-8230.0)	570 (0.1-4150)	900 (0.74-8230.0)	0.7
Ferritin [a] (ng/mL)	393 (10.5-6666.0)	352.5 (10.5-6666.0	548.5 (140-4000)	0.004*
ALT				
Normal	302 (62.7)	266 (62.7)	36 (62.1)	**0.92**
Elevated	180 (37.3)	158 (37.3)	22 (37.9)	
AST				
Normal	340 (70.5)	297 (70.0)	43 (74.1)	**0.52**
Elevated	142 (29.5)	127 (30.0)	15 (25.9)	
Serum creatinine				
Normal	365 (75.7)	334 (81.1)	31 (53.4)	**< 0.001***
Elevated	117 (24.3)	90 (18.9)	27 (46.6)	
Blood glucose				
Hypoglycaemia	7 (1.5)	3 (0.7)	4 (6.9)	**< 0.001***
Hyperglycaemia	184 (38.2)	153 (36.1)	31 (53.4)	
Radiological findings				
CT pattern				
Presence of GGO and consolidation	222 (46.1)	177 (41.7)	45 (77.6)	
Presence of GGO without consolidation	155 (32.2)	150 (35.4)	5 (8.6)	< 0.001*
Presence of consolidation without GGO	58 (12.0)	50 (11.8)	8 (13.8)	
Number of affected lobes				
One lobe	19 (3.9)	19 (4.5)	0 (0.0)	
Two lobes	95 (19.7)	89 (21.0)	6 (10.3)	
Three lobes	157 (32.6)	156 (36.8)	1 (1.7)	**< 0.001***
Four lobes	126 (26.1)	90 (21.2)	36 (62.1)	
Five lobes	38 (7.9)	23 (5.4)	15 (25.9)	
NA	47 (9.8)	47 (11.1)	0 (0.0)	
Bilateralism				
Unilateral	38 (7.9)	38 (9.0)	0 (0.0)	**0.009***
Bilateral	397 (82.4)	341 (80.4)	56 (96.6)	
NA	47 (9.8)	45 (10.6)	2 (3.4)	
Medications [b]				
Steroids	326 (67.6)	268 (82.2)	58 (17.8)	< 0.001*
Anticoagulants	410 (85.1)	352 (85.9)	58 (14.1)	0.001*
Antibiotics	405 (84.0)	347 (85.7)	58 (14.3)	< 0.001*
Antiviral	386 (80.1)			
Ivermectin	195 (40.5)	158 (81.0)	37 (19.0)	< 0.001*
Remidisvir	42 (8.8)	28 (66.7)	14 (33.3)	< 0.001*
Favipravir	149 (30.8)	120 (80.5)	29 (19.5)	< 0.001*
Others [c]	117 (24.2)	99 (84.6)	18 (15.4)	0.2

**p* value ≤ 0.05; [a] Median (Min- Max); [b] Row percentage was calculated; [c] Other medications included analgesics and antipyretics, antioxidants, lactoferrin, vitamin D, vitamin C, and Zinc.

On the other hand, antiviral medications (ivermectin, remidisvir, and favipiravir) were effective and protective against death outcomes (p = 0.03, p = 0.03, and p = 0.02, respectively) (Table 4).

Discussion

COVID-19, the greatly transmissible infectious illness caused by severe SARS-CoV-2, had disastrous effects on the world's health, leading to more than 2.9 million deaths. After two waves of COVID-19 in 2020, the third and fourth waves were evident in 2021. The four waves have been the primary concern of physicians, public health experts, and researchers. Significant work and rapid investigations of all related aspects have been carried out in all institutions worldwide.

The case fatality rate in the current work was low. Since the study is hospital-based, such a low rate may be due to the launching of extra resources and mobilizing more healthcare teams to COVID-19 isolation hospitals during the pandemic. Moreover, the medical community gained more experience which contributed to providing better diagnosis strategies and treatment regimens. In addition, the application of initial phases of national vaccination programs in the participating countries might be another factor involved to some extent in alleviating COVID-19 infections among the population [12].

The most vulnerable age group identified among studied patients was the same as previously reported, in both the second [13] and third waves [14]. The absence of a significant difference between the number of males and females in the current work supports the findings of Vahidy *et al.* (2021) [15] but opposes that of Eid *et al.* (2021) [14]. Contrary to many studies [16-18], COVID-19 was more prevalent in urban than rural areas. Perhaps rural areas are quieter, less polluted, and uncrowded, and at certain times there is less spread of epidemics and diseases [19]. Our results add to the importance of contact transmission of infection [20] because the prevalence of cases was higher among married than single patients and those exposed to COVID-19 patients. A significant association existed between smoking and death outcomes, as clarified by Mohsin *et al.* (2021) [21].

COVID-19 emerged mainly as a respiratory disease; however, gastrointestinal and neurological symptoms have been described [22]. Cough appeared to be the most prevalent symptom among the current study population, followed by body aches, while fever ranked

Table 4. Logistic regression to detect the predictors of unfavorable outcome.

Variable	B	S.E.	p - value	Odds ratio	95% CI	
					lower	upper
Demographic characteristics						
Age	4.28	2.63	0.03*	2.5	1.5	8.56
Smoking	3.48	1.58	0.02*	2.5	1.6	3.65
Symptoms						
Dyspnea	0.305	0.981	0.75	0.73	1.08	5.03
Diarrhea	0.86	0.80	0.28	0.23	0.49	11.52
Epigastric pain and vomiting	7.42	2.67	0.006*	3.5	2.5	11.11
History of illness						
Diabetes	4.03	2.79	0.01*	2.5	1.5	6.68
Physical Examination						
Obesity	3.48	1.58	0.04*	1.8	1.6	3.45
Pallor	0.05	0.96	0.95	0.94	0.14	6.26
Cyanosis	0.68	0.95	0.47	1.98	0.30	12.94
Oxygen saturation (< 90)	3.06	1.05	0.004*	4.07	2.5	36.9
Laboratory findings						
leukocytosis	1.54	0.66	0.01*	4.69	1.28	17.18
Absolute neutrophilia	1.2	0.34	0.001*	3.32	1.69	6.52
Absolute lymphopenia	0.73	0.38	0.05*	2.09	1.8	4.46
Thrombocytopenia	2.4	1.8	0.04*	2.5	1.9	5.3
Elevated serum creatinine	3.92	1.13	0.001*	2.0	1.5	2.82
Blood glucose level	2.24	0.84	0.01*	2.87	1.7	15.14
Radiologic findings						
CT pattern	1.7	0.65	0.008*	5.53	1.54	19.79
Number of lobes affected	2.04	0.68	0.04*	7.8	3.6	16.6
Bilateral lung disease	2.08	1.4	0.039*	2.95	1.75	49.6
Antivirals						
Ivermectin	-0.72	0.34	0.03*	0.48	0.24	0. 95
Remidisvir	-1.0	0.46	0.03*	0.36	0.14	0.91
Favipravir	-0.79	0.35	0.02*	0.45	0.22	0.90

third. In a meta-analysis of 148 studies from nine countries during the second wave, the cough was rated as the second symptom [23]. In contrast, in a study published in 2021, among third-wave COVID-19 infected patients, the most repeatedly recorded symptom was cough [24]. The occurrence of body aches as the second frequent symptom may be challenging to diagnose, especially if the disease starts in a mild form. It is necessary to diagnose COVID-19 precisely as early as possible, primarily in settings with inadequate medical circumstances, to reduce needless medical waste and rationalize the use of medications. Fever ranked as the third most common symptom. Although patients enrolled were hospitalized due to severe or critical disease courses, all did not present high body temperatures. Perhaps a less frequent occurrence of fever is the coming trend. For confirmation, further studies are needed.

In the current work, expectoration manifested at a rate lower than Xu *et al.* (2020) [25] and fell within the values reported by Al-Swiahb *et al.* (2021) [26]. Emphasis should be placed during hospitalization on applying measures to enhance sputum removal, like posture and physiotherapy, which will improve respiration. Meanwhile, dyspnea was identified at a rate comparable with former studies [27,28]. In addition to the lower respiratory tract-related manifestations, upper respiratory tract-linked symptoms, like sore throat, were common in our work, as found before [29], confirming the broad-spectrum presentation of the coronavirus disease. Clinicians should pay more attention to otolaryngologic symptoms in COVID-19 patients, which can develop early, promoting a quicker diagnosis and treatment [26].

GIT symptoms among our study population were similar to those identified by Dan *et al.* (2020) [30]. However, taste and smell disorders were less common [31]. The current work recognized a small group of symptoms that should not be ignored and can increase the sensitivity of COVID-19 diagnosis (Table 1). They were redness and itching of the conjunctiva and cutaneous manifestations. Nasiri *et al.* (2021) [32] stated that among a total of 8,219 COVID-19 patients, approximately one out of ten showed at least one ocular symptom and Farinazzo *et al.* (2021) [33] concluded that the occurrence of cutaneous manifestations had expanded parallel with SARS-CoV-2 spread.

In addition to symptoms and clinical signs, laboratory investigations and chest CT imaging were made to confirm the diagnosis of the disease and to follow up and monitor the prognosis. Univariate analysis revealed many variants to be associated with death. After introducing all the parameters into the binary logistic regression analysis, independent risk factors for death were determined (Table 4). The association between old age and unfavorable outcomes can be explained by the suboptimal humoral and cell-mediated immunity in the elderly [34]. As described beforehand, the significant correlation between smoking and bad outcomes [13,35-38] calls for a need to mass awareness and cessation campaigns to help smokers refrain from this bad habit.

Reports about the value of GIT symptoms as predictors of disease progression are contradictory. Compatible with the conclusions of He *et al.* (2021) [39], a significant correlation between vomiting and epigastric pain and poor prognosis was evident in our work. On the other hand, Leal *et al.* (2021) [40] reported that the same symptoms were associated with a less severe disease sequence. Whatever the conclusions are, the presence of GIT symptoms raises the possibility of feco-oral transmission of COVID-19.

A significant relationship between diabetes mellitus and mortality was evident in the present work. It is worth mentioning that this correlation was found among patients with uncontrolled diabetes presented by hyperglycemia (Tables 2 and 3). It is universally acknowledged that diabetes mellitus is a risk factor for severe forms of the disease and worse outcomes, including higher mortality. Possible pathological mechanisms include effects on glucose homeostasis, inflammation, different immune status, and activation of the renin-angiotensin-aldosterone system [41]. Contrary to former findings, neither cardiovascular comorbidities nor hypertension had an impact on COVID-19- related death. It is of note that the association between hypertension and mortality is less explicit, and the International Society of Hypertension even has declared that there is none [42-44].

We found that being overweight is significantly connected with bad outcomes in both univariate - and multivariable analyses, which endorses prior information [45,46]. CDC has explained that increased body mass index is associated with undermined immune function and decreased lung capacity and reserve making ventilation more problematic [47]. Our finding and that of Deng *et al.* (2020) [48] of a lower blood oxygen saturation in the death group is logical because progressive hypoxemia often suggests a poor prognosis in pulmonary diseases [42].

As inferred in our work, Neutrophilia, lymphopenia, and thrombocytopenia forecasted death outcomes in COVID-19 patients. Mechanisms

underlying these effects are explained in detail elsewhere [7,49-53].

In the present work, elevated serum creatinine was an independent risk for death. Since the number of patients who had elevated creatinine levels (24.3%) was more than the patients with renal comorbidity (8.7%), and the univariate analysis revealed no association between underlying renal disease and mortality (Tables 1 and 3), it seems that creatinine was elevated due to severe viral infection. A consequence of critical COVID-19 illness was speculated to be kidney damage [54]. The virus causes chronic kidney disease (CKD) and acute kidney injury (AKI) after being attached to angiotensin-converting enzyme 2 (ACE2) expressed in proximal tubule cells [54-56]. Clinicians need to be more alert in monitoring the kidney function of COVID-19 patients to evade terminal-stage renal disease and death. On the contrary, one study illustrated that SARS-CoV-2 neither induces AKI nor CKD aggravation in COVID-19 patients [57].

An interesting result of our work was the absence of a relation between d- dimer and a bad outcome, which supports the findings of only one study in 2021 [13], whereas most data available in the literature concluded that d-dimer value on hospital admission is a reliable biomarker for foretelling mortality in COVID-19 patients [58-62]. This contradiction may be due to a lack of standardization in carrying out the test leading to pitfalls in the analysis and interpretation [63]. Most papers told nothing about the manufacturer and reagent kit used. It was unclear whether d-dimer values were reported in d-dimer units (DDU) or fibrinogen equivalent units (FEU). Furthermore, approximately half the studies did not report normal d-dimer cutoff values [63,64]. Furthermore, the value of other tests like ferritin and lactate dehydrogenase as predictors of clinical outcome could not be verified in our work or by other workers [65].

Imaging tests are profitable for diagnosis, mainly when a concordant clinical presentation and other tests exhibit negative results or are unavailable. Based on the features seen in unenhanced chest CT scans, the COVID-19 Reporting and Data System (CO-RADS) is adopted to determine the degree of suspicion for lung involvement in SARS-CoV-2 infection [66]. In the current study, on performing CT, almost all the recruited patients had PCR–proven SARS-CoV-2 infection, as described elsewhere [67]. Hence, they were classified as CORADS category six. Our study results revealed that the best outcome was associated with negative and milder CT findings, comparable to Yuan *et al.* (2020) [68]. Moreover, the CT findings in the present work support the application value of visual CT scores in assessing COVID-19 severity and prognosis reported by previous studies [69,70].

COVID-19 treatment guidelines have been provided for the proper management of patients. Due to the rapid evolution of evidence-based clinical information about optimal treatment, these guidelines are regularly updated whenever confirmed data and other authoritative facts become available. An example is the recommendations for the application of corticosteroids in the management of COVID-19 issued by WHO [71]. In patients with critical COVID-19 and the absence of co/super bacterial infection, available information is lacking to recommend either for or against empiric broad-spectrum antimicrobial treatment. In cases where antimicrobials are prescribed, their use should be reevaluated daily to lessen the adverse effects and prevent drug resistance's emergence and dissemination [72]. All in all, protocols implemented in all the centers in the countries where data were collected have shown effectiveness.

One limitation of the present study is the lack of immunization data because of the retrospective nature of data collection; immunization programs were at the very beginning, and the immunization data was not recorded or questioned by physicians during history taking. The percentage population who completed the vaccination ranged from 0.8-1.2 % (in Egypt and Iraq) to 18.2- 23.7% (in Turkey and Romania) [12]. A second limitation is the lack of information regarding virus sequencing/strains over the study period. The COVID-19 RNA sequencing was not performed routinely in the referral centers due to limitation of resources or other factors. The presented data regarding SARS-CoV-2 variants depended on WHO Weekly Epidemiological Updates during the study period [6].

Conclusions

The literature provides contrasting data about the majority of variables impacting COVID-19 prognosis, indicating that COVID-19 is still not fully understood and calling for more studies. Currently, the medical community is more efficient in providing sound management of COVID-19 in terms of timely diagnosis and effective treatment. However, we should exert more effort toward rationalizing the use of antibiotics.

Now that the fourth wave has subsided and we are starting to catch our breath after battling this disease, it has become necessary to study the previous waves carefully. It is still unclear if coronavirus will disappear, reemerge in waves, or simmer in the background as an endemic sickness. However, our study and similar work

can help better understand COVID-19, which provides essential insights into healthcare systems' prevention and planning efforts.

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