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Original article

Factors Affecting Outcome of Hospitalized Patients with COVID-19

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Abstract:

Background: Coronavirus induced disease-19 (COVID-19), produced by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The emergence and rapid spread of COVID-19 has caused enormous mortality worldwide. Egypt had reported the first case of COVID-19 infection in Africa on February 14, 2020. World health organization (WHO) declared COVID-19 a global pandemic on March 11, 2020. Aim of the work: Analyze factors affecting prognosis and outcome in COVID - 19 Egyptian patients who were admitted to Mansoura Health Insurance Hospital. **Patients and methods:** This current study is a combined retrospective and prospective. The retrospective part included 100 patients and the prospective part included 275 patients. All the included cases (or their records) were reviewed to obtain data about general history, clinical examination and investigations. The cases (or the records) were followed up to determine the study outcomes including (intensive care unit admission, length of hospital or ICU admission, need of mechanical ventilation and mortality. **Results:** Significant more cases in the second wave were transferred to ICU than first wave cases (p=0.02). There was statistically significant difference between the two waves regarding mortality rate which was significantly higher among the second wave patients (p=0.001). During the first wave, with multivariate regression analysis, older age, male sex, higher respiratory rate, presence of CKD, cancer or DCL at admission were associated with increased odds of death. During the second wave, with multivariate regression analysis, older age, male sex, hypertensive, presence of CLD, cancer, dyspnea, DCL, higher respiratory rate, lower platelet level, higher D-dimer, lower albumin level, higher urea level, lower SO2 level at admission were associated with increased odds of death. **Conclusion:** The second wave of COVID-19 in Egypt was linked to more severe disease and higher mortality rates. During both waves, COVID-19 mortality was independently predicted by age, male gender, and poor comorbidity.

Keywords: COVID-19, Egypt, Wave, Mortality.

Introduction

SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) a novel coronavirus causing COVID-19 was identified in December 2019 [1]. The virus spread around the whole world in a short time and World Health Organization (WHO) declared the pandemic status by 11 March 2020 [2].

COVID-19 is a serious respiratory infection marked by fever, dry cough, and dyspnea [3]. While mild symptoms are encountered by most infected people, who do not need hospitalization, a considerable percent of admitted patients were complicated with acute hypoxemia and needed assisted ventilation in ICU [3-5].

Many researches have reported prolonged ICU care and high death rate in critically ill patients with COVID-19 [6-8]. Critically ill patients with COVID-19 are marked by severe respiratory failure caused by SARS-CoV-2 infection [9].

The clinical spectrum can range from mild symptoms (e.g., fever and malaise) to severe hypoxic respiratory failure, sepsis, multiorgan involvement and death. The infection appears to induce an inflammatory reaction with pulmonary infiltrates generating hypoxemia secondary to intraparenchymal shunt and ventilation/perfusion mismatch, favoured by endothelial damage and dysfunction, and altered regulation of perfusion and associated with macroembolism and/or microembolism [10, 11].

Many of the affected countries in 2020 adopted the recommended lockdown policies and succeeded to downward slope of the epidemic curve and restrain the first wave of COVID-19 [12]. Unfortunately, most countries rushed out to mitigate the lockdown measures despite all the warnings about the consequences of early lockdown lifting. Thus, they were hit by a second COVID-19 wave. For instance, many countries were affected by a second wave of COVID-19 since September 2020 [13].

It was expected that these countries had learned the lesson from the first wave and would manage the second wave more appropriately. However, these countries had gone through a worse situation as they had more COVID-19 positive cases, ICU admissions, and deaths [14].

For this, the current study was conducted to analyze factors affecting prognosis and outcome in COVID - 19 Egyptian patients who were admitted to Mansoura Health Insurance Hospital. The current study mainly concentrated on the differences between the two waves regarding patients' characteristics and different outcomes.

Patients and methods

This is a combined retrospective and prospective descriptive and analytical study that was conducted at Mansoura Health Insurance Hospital, Mansoura, Egypt.

The retrospective part included 100 patients from period from May 2020 to September 2020 (first wave of COVID-19) while the prospective part included 275 patients who were recruited from December 2020 until the end of the Quarantine measures in the Hospital (second wave of COVID-19).

The study included COVID - 19 positive patients who were diagnosed based on clinical symptoms and signs (fever, cough, breathing difficulties or organ failures [15]), laboratory findings (elevation of inflammatory biomarkers as (CRP, Ferritin, Lactate dehydrogenase, D-dimer and INR, decrease in lymphocyte count and decrease in serum K level [16]), positive result of reverse transcription polymerase chain reaction (RT-PCR) in nasopharyngeal swab specimens [17] and CT chest finding (patchy ground-glass opacities (GGO) and patchy consolidation which were mainly distributed in the middle and outer zone of the lung [18].

The cases with the following criteria were excluded; age < 18 years, negative for COVID -19, patients with no available clinical or laboratory data confirming the

diagnosis of COVID-19 and presence of any contraindication to radiation exposure such as pregnant women.

The study is conducted in accordance with Helsinki Standards as revised in 2013 [19].

The study was conducted after obtaining the approval from the local ethics committee, Faculty of Medicine, Benha University (Ms.5.3.2021) and after obtaining a written/oral informed consent from the included cases (or their relatives).

The cases (or by reviewing the medical records) were subjected to the following: history taking (including the demographic data and history of present illness) and clinical examination.

Patients were allocated in COVID-19 units according to admission severity based on the best respiratory supportive option to maintain an acceptable SO_2 (>93%) and respiratory rate as follows, 0 points in case of spontaneous breathing, 1 point in case of need for conventional oxygen therapy, 2 points in case of need for High Flow Nasal Cannula (HFNC), 3 points in case of need for non-invasive ventilation (NIV) and 4 points in case of need for intubation [20].

Laboratory investigations were done including complete blood count, liver and kidney functions, serum electrolytes, arterial Blood Gas (ABG), serum level of D. DIMER, serum Ferritin, CRP.

Radiological studies included chest x-ray and chest computerized tomography (CT).

COVID-19 severity was classified as mild (presence of constitutional and/or upper respiratory tract symptoms with none or mild changes on chest radiography or CT), moderate to severe (lower respiratory tract symptoms and evidence of pneumonia and/or sign of respiratory failure such as dyspnea, respiratory rate >30 cpm, pulse oximetry ≤92% or PaO2/FiO2 <300 mm Hg) and critical (severe pneumonia and respiratory or another organ failure requiring ICU admission) [21].

The study outcomes included the primary outcome (mortality rates) and secondary outcomes (disease severity, duration of hospitalization, need for ICU admission, need for mechanical ventilation, duration of ICU admission).

Statistical analysis

The data collected were coded, processed and analyzed with SPSS version 26 for Windows® (Statistical Package for Social Sciences) (IBM, SPSS Inc, Chicago, IL, USA). Qualitative data as number (frequency) and percent was presented. The Kolmogorov-Smirnov test tested quantitative data for normality. Data was shown as median ± SD or median (interquartile range) according to normality.

To compare two groups with categorical variables, Chi-Square test (or Fisher's exact test/Monte-carlo test) were used. To compare two groups with normally distributed quantitative variables, independent samples (student's) t-test was used and Mann-Whitney U-test was used if the data were abnormally distributed .

Correlation of numeric data was done by Pearson's or Spearman correlation (r). Univariate and multivariate logistic regression analysis were used for prediction of risk factors for death or ICU admission. For all tests, *p* values <0.05 are considered significant.

Results

The current study included 375 patients with COVID-19 associated pneumonia. The mean age of the studied group was 63.36 ± 12.85 SD and ranged from 19 to 91 years. The studied patients included 247 males (65.9%) and 126 females (34.1%). One hundred patients (26.7%) of the study group infected with COVID-19 in the first wave and 275 (73.3%) caught COVID-19 infection in the second wave.

Table (1): Comparison between the cases during the first and second waves.

Variables		Group I (Patients in the 1st wave of COVID-19) (N=100)		Group II (Patients in the 2nd wave of COVID-19) (N=275)		Statistics	*p*
		N	**%**	**N**	**%**		
Age	*Median (Q_1, Q_3)*	64.5 (55, 72)		65 (58, 72)		0.87	0.38*
Sex	Female	39	39%	89	32.4%		
	Male	61	61%	186	67.6%	1.44	0.32
Smoking	Non-smoker	72	72%	196	71.3%	0.019	0.89
	Smoker	28	28%	79	28.7%		
Transfer to ICU	No	68 (68%)		149 (54.6%)		5.42	0.02*
	Yes	32 (32%)		124 (45.4%)			
Its cause	ARDS	13/32 (40.6%)		74/124 (59.7%)		6.74	0.19
	Cardiac injury	4/32 (12.5%)		13/124 (10.5%)			
	Liver dysfunction	0/32 (0%)		2/124 (1.6%)			
	AKI	3/32 (9.4%)		3/124 (2.4%)			
	DKA	1/32 (3.1%)		4/124 (3.2%)			
	DCL	11/32 (34.4%)		28/124 (22.6%)			

ICU= Intensive care unit; ARDS= Acute respiratory distress syndrome; AKI= Acute kidney injury; DKA= Diabetic keto acidosis; DCL = Disturbed conscious level; *p* values were calculated by Mann-Whitney U test* or χ^2 test† as appropriate

Table (1) shows insignificant differences between COVID-19 patients in the first and second waves as regard age, sex, smoking history or comorbidity history ($p>0.05$). There were statistically significant differences between COVID-19 cases in the first and the second waves regarding chest tightness and DCL

The median temperature was significantly higher in first wave patients. Significantly more patients scored higher heart rate > 100 beats per min in the second wave (26.5%) compared with 18% in the first wave ($p=0.03$). Blood oxygen saturation (SO_2) % was significantly lower among second wave patients 87% compared with 89% ($p=0.001$) with more patients scored $SO_2 \leq 93\%$ (77.5% compared with 62%) ($p=0.003$). A significant increased white blood cell count was found among COVID-19 patients of the second wave ($p = 0.001$). Mean CRP was significantly more elevated in first wave patients mean 80.4 compared with mean 45.6 in the second wave ($p=0.001$). Serum albumin was decreased ($\leq$ 3.5 g/L) in 17% and 30.5% of patients of first and second waves respectively with highly statistically significant difference between both graft ($p>0.009$). Urea level was significantly more elevated in COVID-19 patients of second wave Calcium level was significantly lower in patients of second wave 8.8 compared with 10 in the patients of the first wave. Regarding ABG, PH of second wave patients was significantly lower than first wave patients. CO_2 was significantly higher in the second wave and SO_2 was significantly lower in the second wave patients. HCO3 was significantly higher in patients of the second wave. (Data not shown).

There are more significant cases in the second wave which were transferred to ICU than first wave cases (45.4%, 32%) ($p=0.02$). The major cause for ICU transmission in both waves was developing ARDS (40.6%, 59.7%). Nasal cannula or mask was needed in 36% and 40.4% of cases of first and second waves respectively. There was statistically significant difference between the two waves regarding mortality rate which was significantly higher among the second wave patients (40.4% compared with 22% in the first wave) ($p=0.001$).

Table (2): Comparison between deaths and survivors of the first wave as regard demographic data, clinical, laboratory and radiological findings (n=100).

Variables		Recovery of first wave (N=78)		Death of the first wave (N=22)		Statistics	p
Demographics							
Age (years)		62 (51, 69)		70 (65, 75)		3.68	**0.001***
Sex	*Female*	35	44.9%	4	18.2%		
	Male	43	55.1%	18	81.8%	5.14	**0.023**†
Smoking	*Non-smoker*	57	73.1%	15	68.2%	0.204	0.652†
	Smoker	21	26.9%	7	31.8%		
Comorbidity	*Chronic kidney disease*	3	3.8%	6	27.3%	11.5	**0.001**†
	Cerebrovascular disease	0	0%	6	27.3%	22.63	**0.001**†
	Cancer	1	1.3%	6	27.3%	17.81	**0.001**†
Laboratory findings							
Hemoglobin (g/dL)		12.3 (11.7, 13.5)		11.1 (9.7, 13.1)		2.47	**0.014***
White blood cell count × 10⁹ per L		7.55 (5.53, 10.7)		11.25 (8.9, 16.5)		3.6	**0.001***
Neutrophils (%)		71.6 (67.18, 77)		80.2 (73.8, 85.2)		2.44	**0.015***
Lymphocytes (%)		22.85 (16.95, 26.2)		13.3 (10.8, 18.4)		2.98	**0.003***
Neutrophil-lymphocyte ratio (NLR)		3.1 (2.5, 4.33)		5.8 (3.6, 7.9)		2.81	**0.005***
Platelet-lymphocyte ratio (PLR)		10.1 (6.58, 16)		14.9 (10.03, 22.2)		2.16	**0.031***
D-dimer (ng/mL)		463 (341.5, 832.5)		1255 (672.7, 2152.5)		3.55	**0.001***
S-ferritin (ng/mL)		477.5 (225.3, 912)		931 (636.2, 1267.5)		3.55	**0.001***
CRP (mg/dL)		48 (24, 96)		96 (48, 196)		3.86	**0.001***
LDH (IU/L)		390.9 (240, 482)		855.5 (491.5, 946)		5.26	**0.001***
INR		1.2 (1.1, 1.3)		1.41 (1.18, 1.8)		3.25	**0.001***
AST (IU/L)		34.6 (23, 51.3)		42 (26.2, 127.5)		2.17	**0.03***
Serum Albumin (g/L)		3.9 (3.7, 4.3)		3.7 (3, 4.2)		2.32	**0.02***
Total bilirubin (mg/dL)		0.495 (0.4, 0.795)		0.91 (0.41, 2.42)		2.47	**0.014***
Direct bilirubin (mg/dL)		0.125 (0.11, 0.21)		0.22 (0.12, 0.81)		2.39	**0.016***
Creatinine (mg/dL)		1.13 (0.89, 1.4)		1.65 (1.35, 2.9)		4.17	**0.001***
Urea (mg/dL)		40 (28.8, 48.5)		96.5 (75.9, 146.9)		4.94	**0.001***
Calcium (Ca) (mEq/L))		10 (8.9, 10.2)		9.1 (8.1, 10.2)		2.17	**0.03***
PH		7.43 (7.36, 7.48)		7.32 (7.23, 7.42)		3.89	**0.001***
Po_2		61 (53, 77)		48.5 (45.5, 56.7)		3.77	**0.001***
So_2		91 (86.7, 96)		82 (79.7, 85.3)		4.68	**0.001***
HCo_3		19 (17.7, 22)		15.5 (12.9, 18.3)		3.89	**0.001***
Imaging features							
	Consolidation	17 (21.8%)		0 (0%)		18.39	**0.001**†
	Ground glass opacity	36 (46.2%)		9 (40.9%)			
	Mixed	24 (30.8%)		7 (31.8%)			
	Bilateral pulmonary Infiltration	1 (1.3%)		6 (27.3%)			

*CRP= C-reactive protein; LDH= Lactate dehydrogenase; INR= International normalized ratio; AST= Aspartate transaminase; PO2= Partial pressure of oxygen; SO2= Oxygen saturation; HCO3: Sodium Bicarbonate; Data presented as or n/N (%)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 (2) shows that from 100 COVID-19 patients admitted to the hospital during the first wave, 22 patient died and 78 patients survived. The non-survived patients were significantly older than survived patients with median age 70 compared with 62 (p = 0.001). The higher percentage of the non-survived patients were males 81.8% (p=0.023). Chronic kidney disease, cerebrovascular diseases and cancer were more prevalent among non survivors (p=0.001). Chest tightness, DCL and coma were significantly more prevalent among non survivors (59.1%, 31.8%, 27.3% respectively) (p=0.001). Respiratory rate was significantly higher among non survivors (31 compared to 22) (p=0.001) and blood oxygen saturation was significantly lower (82 compared to 91) (p=0.001). Regarding laboratory finding, non survivors showed significant increase in WBC count (p=0.001), Neutrophil % (p=0.015), Neutrophil-lymphocyte ratio (p=0.005), platelet-lymphocyte ratio (p=0.031), D-dimer (p=0.001), serum ferritin (p=0.001), CRP (p=0.001), LDH (p=0.001), INR (p=0.001), AST (p=0.03), total bilirubin (p=0.014), direct bilirubin (p=0.016), serum urea (p=0.001) and creatinine (p=0.001). In addition, they showed significant decrease in HB level (p=0.014), lymphocyte % (p=0.003), serum albumin (p=0.02), Ca (p=0.03), PH (p=0.001), PO_2 (p=0.001), SO_2 (p= 0.001) and HCO_3 (p=0.001). Bilateral pulmonary infiltration was significantly more prevalent in non survivors (27.3%) (p=0.001).

Table (3) shows that in univariable analysis, older age, male sex, chronic kidney disease, cancer, chest tightness, DCL, higher respiratory rate and lower blood oxygen saturation were significant predictors for death from COVID-19 in the first wave (p<0.05). Regarding laboratory finding, low hemoglobin level, higher WBC level, higher platelet-lymphocyte ratio, increased D-dimer, serum ferritin, CRP, LDH, INR, AST, total and direct bilirubin, lower serum albumin, higher urea and creatinine level, hypocalcemia, decreased PO2, SO2 and HCO3 levels were significant predictors for death from COVID-19 in the first wave (p<0.05). In the multivariable logistic regression model, we found that older age, male sex, higher respiratory rate, presence of CKD, cancer or DCL at admission were associated with increased odds of death (p<0.05).

Table (4) shows that from 275 COVID-19 patients admitted to the hospital during the second wave, 111 patients died and 164 patients survived. The non-survived patients were significantly older than survived patients with median age 68 compared with 63 (p = 0.001). Most non survived patients were males (75.7%) compared with 62.2% among survived (p=0.019). Hypertension, CLD, Chronic kidney disease, lung disease and cancer were more prevalent among deaths (66.7%, 26.1%, 21.6%, 17.1%, 13.5%) compared with (47%, 9.1%, 11.6%, 8.5%, 1.8%) (p= 0.001, 0.001, 0.025, 0.032, 0.001).

Dyspnea, chest pain, chest tightness, DCL and coma were more prevalent among deaths (74.3%, 35.1%, 65.5%, 45.9%, 9.9%) compared with (40.9%, 13%, 23.8%, 3%, 0%) (p= 0.001, 0.001, 0.001, 0.001, 0.001).

Systolic and diastolic blood pressure were significantly lower among deaths (110 (100, 130) compared with 120 (110, 130) and 70 (60, 80) compared with 70 (70, 80)) (p=0.001, p=0.008). Respiratory rate and heart rate were significantly higher among non survivors (33 compared with 22 and 98 compared with 90) (p=0.001, p=0.007) and blood oxygen saturation was significantly lower among deaths (79 compared with 89.5) (p=0.001). Regarding laboratory finding, non survivors showed significant increase in WBC count (p=0.001), Neutrophil % (p=0.001), Neutrophil-lymphocyte ratio

(0.001), platelet-lymphocyte ratio (*p*=0.003), D-dimer (*p*=0.001), serum ferritin (*p*=0.001), CRP (*p*=0.001), LDH (*p*=0.001), INR (*p*=0.001), ALT (*p*=0.022), AST (*p*=0.001), total bilirubin (*p*=0.001), direct bilirubin (*p*=0.001), serum urea (*p*=0.001) and creatinine (*p*=0.001) and CO_2 (*p*=0.003). In addition, they showed significant decrease in platelets level (*p*=0.007), lymphocyte % (*p*=0.001), serum albumin (*p*=0.001), Ca (*p*=0.001), PH (*p*=0.009), PO_2 (*p*=0.001) and SO_2 (*p*= 0.001).

Bilateral pulmonary infiltration was significantly more prevalent in non survivors (18.9%) (*p*=0.001).

Table (3): Logistic regression for predictors and risk factors associated with COVID-19 deaths in the first wave (n=100).

Variables		Univariable OR (95% CI)	*p* value	Multivariable OR (95% CI)	*p*
Demographics and clinical characteristics					
Age (years)		0.92 (0.874 – 969)	**0.002**	0.912 (0.862- 0.965)	**0.001**
Male sex (vs female)		3.66 (1.14-11.82)	**0.03**	5.49 (1.35 – 22.26)	**0.017**
Current Smoker (vs non-smoker)		1.26 (0.453-3.53)	0.652		
Comorbidity present (vs not present)					
Chronic kidney disease		9.37 (2.12-41.5)	**0.003**	16.44 (2.96-91.16)	**0.001**
Cancer		28.87 (3.25 -256.5)	**0.003**	74 (7.6-719.5)	**0.001**
Clinical manifestations	Chest tightness	9.8 (3.34-28.9)	**0.001**		
	DCL	35.9 (4.1-314)	**0.001**	14.8 (1.13-193)	**0.04**
	Respiratory rate	0.75 (0.66-0.85)	**0.001**	0.65 (0.47-0.89)	**0.008**
	Blood oxygen saturation (SO2) %	1.2 (1.1-1.3)	**0.001**		
Laboratory findings	Hemoglobin (g/dL)	1.4 (1.1-1.8)	**0.013**		
	White blood cell count × 10^9 per L	0.84 (0.76-0.94)	**0.002**		
	Platelet-lymphocyte ratio	0.97 (0.95-0.99)	**0.033**		
	D-dimer (ng/mL)	1 (0.99-1)	**0.047**		
	S-ferritin (ng/mL)	0.99 (0.99-0.1)	**0.001**		
	CRP (mg/dL)	0.99 (0.98-0.99)	**0.001**		
	LDH (IU/L)	0.99 (0.99-0.1)	**0.001**		
	INR	0.07 (0.01-0.4)	**0.003**		
	AST (IU/L)	0.98 (0.97-0.99)	**0.005**		
	Serum Albumin (g/L)	3.2 (1.4-7.1)	**0.005**		
	Total bilirubin (mg/dL)	0.22 (0.09-0.5)	**0.001**		
	Direct bilirubin (mg/dL)	0.07 (0.01-0.37)	**0.002**		
	Creatinine (mg/dL)	0.29 (0.14-0.62)	**0.001**		
	Urea (mg/dL)	0.96 (0.95-0.98)	**0.001**		
	Calcium (Ca) (mEq/L))	1.9 (1.1-3.3)	**0.015**		
	Po_2	1.09 (1.03-1.15)	**0.001**		
	So_2	1.2 (1.09-1.3)	**0.001**		
	HCo_3	1.27 (1.09-1.5)	**0.002**		

DCL= Disturbed conscious level; CRP= C-reactive protein; LDH= Lactate dehydrogenase; INR= International normalized ratio; AST= Aspartate transaminase; PO2= Partial pressure of oxygen; SO2= Oxygen saturation; HCO3: Sodium Bicarbonate; OR=odds ratio; CI = Confidence interval; *p* values were calculated by Mann-Whitney U test*and χ^2 test or FET† as appropriate..

Table (4): Comparison between recovery and deaths of COVID-19 patients in the second wave as regard demographic data, clinical, laboratory and radiological findings (n=275).

Variables		Recovery of second wave (N=164)		Death of the second wave (N=111)		Statistics	*p*
Demographics							
Age (years)		63 (55, 69.75)		68 (61, 74)		3.72	**0.001***
Sex	Female	62	37.8%	27	24.3%		
	Male	102	62.2%	84	75.7%	5.5	**0.019**†
Comorbidity	Hypertension	77	47%	74	66.7%	10.4	**0.001**†
	CLD	15	9.1%	29	26.1%	14.2	**0.001**†
	Chronic kidney disease	19	11.6%	24	21.6%	5.1	**0.025**†
	Lung disease	14	8.5%	19	17.1%	4.61	**0.032**†
	Cancer	3	1.8%	15	13.5%	14.8	**0.001**†
Laboratory findings							
	White blood cell count × 10^9 per L	8.95 (5.9, 14.45)		13.2 (10.4, 18)		5.13	**0.001***
	Platelets (10^9/L))	218 (165.5, 269.8)		184 (109, 257)		2.68	**0.007***
	Neutrophils (%)	77 (69, 84)		83.6 (77.1, 88.2)		4.93	**0.001***
	Lymphocytes (%)	15.6 (10.1, 22.8)		9.7 (6.9, 14.8)		5.83	**0.001***
	Neutrophil-lymphocyte ratio (NLR)	4.95 (2.9, 8.6)		8.6 (5.2, 12.8)		5.61	**0.001***
	Platelet-lymphocyte ratio (PLR)	13 (7.2, 23)		18 (10.2, 31)		2.94	**0.003***
	D-dimer (ng/mL)	595 (327, 960)		1150 (542, 2270)		5.56	**0.001***
	S-ferritin (ng/mL)	362.5 (172.5, 871.8)		769.8 (369.8, 1319.2)		3.84	**0.001***
	CRP (mg/dL)	24 (12, 96)		48 (24, 96)		4.32	**0.001***
	LDH (IU/L)	418 (251, 512)		612 (480, 817)		6.46	**0.001***
	INR	1.12 (1.04, 1.32)		1.4 (1.15, 1.7)		5.58	**0.001***
	ALT (IU/L)	30.3 (19.2, 47)		38.5 (20.1, 72.6)		2.29	**0.022***
	AST (IU/L)	33 (21, 52)		51 (26, 95)		4.28	**0.001***
	Serum Albumin (g/L)	3.9 (3.6, 4.2)		3.52 (3.06, 3.96)		5.87	**0.001***
	Total bilirubin (mg/dL)	0.53 (0.373, 0.838)		0.75 (0.51, 1.28)		4.005	**0.001***
	Direct bilirubin (mg/dL)	0.14 (0.10, 0.20)		0.225 (0.120, 0.420)		5.23	**0.001***
	Creatinine (mg/dL)	1.05 (0.87, 1.35)		1.48 (0.99, 2.19)		4.09	**0.001***
	Urea (mg/dL)	44.4 (31, 77.3)		88 (57, 141)		7.22	**0.001***
	Calcium (Ca) (mEq/L))	8.9 (8.3, 9.2)		8.2 (7.8, 8.9)		4.83	**0.001***
	PH	7.38 (7.34, 7.44)		7.36 (7.28, 7.42)		2.63	**0.009***
	Co_2	32 (29, 36.8)		36 (29, 42)		2.95	**0.003***
	Po_2	61 (50, 71.8)		48 (42, 60)		6.26	**0.001***
	So_2	89.5 (85, 94)		79 (71, 88)		7.95	**0.001***
Imaging features							
	Consolidation	31 (18.9%)		7 (6.3%)		52.8	**0.001**†
	Ground glass opacity	99 (60.4%)		41 (36.9%)			
	Mixed	34 (20.7%)		42 (37.8%)			
	Bilateral pulmonary infiltration	0 (0%)		21 (18.9%)			

DCL= Disturbed conscious level; CRP: C-reactive protein; LDH= Lactate dehydrogenase; INR= International normalized ratio; PLR= Platelet-lymphocyte ratio; ALT= alanine transaminase; AST= Aspartate transaminase; PO2= Partial pressure of oxygen; NLR= Neutrophil-lymphocyte ratio; SO2= Oxygen saturation; HCO3= Sodium Bicarbonate; Data presented as or n/N (%) 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 (5): logistic regression for predictors and risk factors associated with COVID-19 deaths in the second wave (n=275)

Variable		*Univariable OR (95% CI)*	*p value*	*Multivariable OR (95% CI)*	*p*
Demographics and clinical characteristics					
Age (years)		0.959 (0.938 – 0.981)	**0.001**	0.961 (0.939-0.983)	**0.001**
Male sex (vs female)		1.89 (1.11-3.23)	**0.02**	1.76 (1.01-3.05)	**0.045**
Comorbidity present (vs not present)					
Hypertension		2.26 (1.37-3.73)	**0.001**	2.7 (1.5-4.7)	**0.001**
CLD		3.51 (1.78-6.93)	**0.001**	3.7 (1.7-7.8)	**0.001**
Chronic kidney disease		2.11 (1.09-4.07)	**0.027**		
Lung disease		2.21 (1.06-4.63)	**0.035**		
Cancer		8.39 (2.37-29.7)	**0.001**	5.12 (1.4-19)	**0.015**
Clinical manifestations	*Dyspnea*	4.2 (2.5-7.1)	**0.001**	2.6 (1.16-5.8)	**0.02**
	Chest pain	3.6 (1.9-6.6)	**0.001**		
	Chest tightness	6.1 (3.6-10.3)	**0.001**		
	DCL	27 (10.3-71)	**0.001**	16.9 (4.6-62)	**0.001**
	Systolic blood pressure (mmHg)	1.02 (1-1.03)	**0.007**		
	Diastolic blood pressure (mmHg)	1.03 (1-1.05)	**0.011**		
	Respiratory rate	0.81 (0.77-0.85)	**0.001**	0.82 (0.73-0.92)	**0.001**
	Heart rate	0.98 (0.96-0.99)	**0.01**		
	Blood oxygen saturation (SO_2) %	1.16 (1.11-1.21)	**0.001**		
Laboratory findings	*White blood cell count × 10^9 per L*	0.92 (0.88-0.96)	**0.001**		
	Platelets (10^9/L)	1.004 (1.001-1.006)	**0.005**	1.007 (1-1.014)	**0.035**
	Neutrophils (%)	0.96 (0.94-0.98)	**0.001**		
	Lymphocytes (%)	1.06 (1.03-1.09)	**0.001**		
	Neutrophil-lymphocyte ratio (NLR)	0.86 (0.82-92)	**0.001**		
	Platelet-lymphocyte ratio (PLR)	0.97 (0.96-0.99)	**0.002**		
	D-dimer (ng/mL)	0.999 (0.999-1)	**0.001**	1 (0.999-1)	**0.01**
	S-ferritin (ng/mL)	1 (0.999-1)	**0.007**		
	CRP (mg/dL)	0.99 (0.981-0.994)	**0.001**		
	LDH (IU/L)	0.997 (0.996-0.998)	**0.001**		
	INR	0.197 (0.094-0.415)	**0.001**		
	ALT (IU/L)	0.994 (0.990-0.998)	**0.007**		
	AST (IU/L)	0.985 (0.979-0.992)	**0.001**		
	Serum Albumin (g/L)	4.8 (2.9-8.1)	**0.001**	2.8 (1.18-6.86)	**0.02**
	Total bilirubin (mg/dL)	0.478 (0.314-0.728)	**0.001**		
	Urea (mg/dL)	0.978 (0.982-0.992)	**0.001**	0.991 (0.984-0.997)	**0.007**
	Calcium (Ca) (mEq/L))	1.71 (1.23-2.38)	**0.001**		
	PH	110 (7.4-1644)	**0.001**		
	Co_2	0.965 (0.943-0.988)	**0.003**		
	Po_2	1.05 (1.03-1.07)	**0.001**		
	So_2	1.14 (1.1-1.19)	**0.001**	1.2 (1.1-1.31)	**0.001**

*DCL= Disturbed conscious level; CRP= C-reactive protein; LDH: Lactate dehydrogenase; INR= International normalized ratio; PLR= Platelet-lymphocyte ratio; ALT= alanine transaminase; AST= Aspartate transaminase; PO2= Partial pressure of oxygen; NLR= Neutrophil-lymphocyte ratio; SO2= Oxygen saturation; HCO3= Sodium Bicarbonate; OR=odds ratio; CI = Confidence interval; p values were calculated by Mann-Whitney U test*and χ^2 test or FET† as appropriate..*

Table (5) shows that in univariable analysis, older age, male sex, hypertensive, CLD, chronic kidney disease, lung disease, cancer, dyspnea, chest pain, chest tightness, DCL, higher systolic blood pressure, higher diastolic blood pressure, higher respiratory rate, higher heart rate and lower blood oxygen saturation were significant predictors for death from COVID-19 in the second wave (p<0.05).

Regarding laboratory finding, higher WBC level, lower platelet level, higher neutrophil %, lower lymphocyte %, higher neutrophil-lymphocyte ratio, higher platelet-lymphocyte ratio, increased D-dimer, serum ferritin, CRP, LDH, INR, ALT, AST, total bilirubin, and higher urea and CO2 level, lower serum albumin, , hypocalcemia, decreased PH, PO2 and SO2 levels were significant predictors for death from COVID-19 in the second wave (p<0.05).

In the multivariable logistic regression model, we found that older age, male sex, hypertensive, presence of CLD, cancer, dyspnea, DCL, higher respiratory rate, lower platelet level, higher D-dimer, lower albumin level, higher urea level, lower SO2 level at admission were associated with increased odds of death (p<0.05

Discussion:

The current study was conducted to analyze factors affecting prognosis and outcome in COVID - 19 Egyptian patients who were admitted to Mansoura Health Insurance Hospital. The current study mainly concentrated on the differences between the two waves regarding patients' characteristics and different outcomes. This current study included 375 patients with COVID-19 associated pneumonia. In the current study, there were insignificant differences between COVID-19 patients in the first and second waves as regard age, sex and smoking history (p=0.38, 0.32, 0.89 respectively).

In the current study, there were statistically significant differences between COVID-19 cases in the first and the second waves regarding chest tightness and DCL where chest tightness and DCL were more prominent among COVID cases of the second wave.

This agreed with another study, who showed that the most common clinical manifestation among the deceased were dyspnea in both waves, followed by fever and cough. Symptoms in the form of cough, sore throat, and loss of taste and smell were more common among deceased in second wave. The difference was statistically significant for cough (p< 0.000), sore throat (p<0.002), AMS (p< 0.002), headache (p< 0.025) and loss taste and smell (p< 0.001) among the two groups [22].

In the current study, there is a significant increased white blood cell count among COVID-19 patients of the second wave (p = 0.001), with about two-thirds (69.1%) of second wave patients showed white blood cell count > 8 (× 10^9 per L) (p=0.001).

This disagreed with a previous study, who showed that the total leukocyte counts were lower in the second wave **[23]**.

Also, Contou et al.,(2021) reported no differences in laboratory parameters except a higher platelet count in the second wave; however, this was a single-center, very small study, with only 50 patients in the second wave [24].

An elevated NLR, as in other viral infections, carried a poor prognosis, serving as a surrogate indicator for survival and the need for ventilator support. [25, 26].

In the current study, there is a significant more cases in the second wave had transferred to ICU than first wave cases (45.4%, 32%) (p=0.02). The major cause for ICU transmission in both waves was developing ARDS (40.6%, 59.7%).

This agreed with another study who conducted a study between February 25 th, 2020 and April 30 th, 2021, 678 235

patients were admitted with a positive RT-PCR for SARS-CoV-2, with 325 903 and 352 332 patients for the first and second wave, respectively **[27]**.

In the current study, there was no statistically significant difference between the cases during the first and the second waves regarding the mode of ventilation. The need of invasive mechanical ventilation (IMV) was 6% in the first wave and 9.1% in the second wave.

Also, Meschiari et al.,(2022)reported that the cumulative proportion of patients requiring respiratory support, both invasive and non-invasive, was lower in the second wave as compared with the first period of the pandemic (35.5% vs 45.9%, p=0.002) [28].

The reason for this difference in our cohort could be due to the fact that alternative means of providing oxygen support were used more often in ICU patients **[29]**.

The use of HFNO increased by >3-fold during the second wave also for logistic reasons. Moreover, during the second wave, there was extensive use of pronation, which may slow respiratory deterioration in selected COVID-19 spontaneously breathing patients, thus reducing the need for noninvasive ventilation (NIV) or invasive mechanical ventilation (IMV) as compared with standard oxygen **[30, 31]**.

There was statistically significant difference between the two waves regarding mortality rate which was significantly higher among the second wave patients (40.4% compared with 22% in the first wave) (p=0.001).

The current findings came in accordance with an Egyptian study by that utilized the official daily reports of the Egyptian Ministry of Health. The results of that study showed that the mean number of weekly reported cases infected with COVID-19 was 870.3±612.26 in the first wave with a median of 869. This number increased significantly to 6016.4 ±3343.12 in the second wave with a median of 8136.00 (p <0.001). The mean number of deaths/weeks was 67.33 ± 36.25 (median= 69) in the first wave. This number increased significantly in comparison with the second wave to be 272.28 ± 121.70 (median= 268) with p value of 0.007 **[32]**.

This came in agreement with Zirpe et al., (2021) who included 3,498 ICU patients. In the first wave, 1,921 patients needed ICU admission, while in the second wave, 1,577 patients. They found that the ICU and hospital mortality at both 7 and 14 days was significantly higher in patients who developed COVID-19 and were admitted to the ICUs of tertiary care units in western Maharashtra during the second wave of the pandemic [23].

The difference could be as during the first wave, clinicians had a lower threshold for admitting, whereas by the second wave, fitter patients and those with no or minimal comorbidities were managed at home. [33].

The changes in the mortality rates during the course of the pandemic around the world could be difficult to interpret due to the fact that COVID-19 waves occurred in different stages, periods of time, and among patients with diverse underlying medical conditions [34].

On the contrary, the current results disagreed with who showed that admission NEWS was significantly higher in the first wave compared with the second wave. Also, the proportion of deaths after diagnosis with COVID-19 was higher in the first wave than in the second wave **[35]**.

A reduction in the 90-day mortality has also been observed over time in critically ill COVID-19 patients in a multicenter study conducted in three European countries [36].

It was reported that COVID-19 case fatality rates have fallen in the second wave in 43 of the 53 countries with the highest total COVID-19-related deaths **[37]**.

In the current study, with univariable analysis, older age, male sex, chronic kidney disease, cancer, chest tightness, DCL, higher respiratory rate and lower blood oxygen saturation were significant predictors for death from COVID-19 in the

first wave (p<0.05). Regarding laboratory finding, low hemoglobin level, higher WBC level, higher platelet-lymphocyte ratio, increased D-dimer, serum ferritin, CRP, LDH, INR, AST, total and direct bilirubin, lower serum albumin, higher urea and creatinine level, hypocalcemia, decreased PO2, SO2 and HCO3 levels were significant predictors for death from COVID-19 in the first wave (p<0.05). In the multivariable logistic regression model, we found that older age, male sex, higher respiratory rate, presence of CKD, cancer or DCL at admission were associated with increased odds of death (p<0.05).

This result was agree with who reported that the predictors for mortality in the first wave were older age, fever, dyspnea, acute respiratory distress syndrome, type 2 diabetes mellitus, and cancer [38].

Also, found SARS-CoV-2 infection during the first wave, comorbidity, and mechanical ventilation to be the predictors of mortality [39].

In the current study, with univariable analysis, older age, male sex, hypertensive, CLD, chronic kidney disease, lung disease, cancer, dyspnea, chest pain, chest tightness, DCL, higher systolic blood pressure, higher diastolic blood pressure, higher respiratory rate, higher heart rate and lower blood oxygen saturation were significant predictors for death from COVID-19 in the second wave (p<0.05). Regarding laboratory finding, higher WBC level, lower platelet level, higher neutrophil %, lower lymphocyte %, higher neutrophil-lymphocyte ratio, higher platelet-lymphocyte ratio, increased D-dimer, serum ferritin, CRP, LDH, INR, ALT, AST, total bilirubin, and higher urea and CO2 level, lower serum albumin, and SO2 levels were significant predictors for death from COVID-19 in the second wave (p<0.05).

In the multivariable logistic regression model, we found that older age, male sex, hypertensive, presence of CLD, cancer, dyspnea, DCL, higher respiratory rate,lower platelet level, higher D-dimer, lower albumin level, higher urea level, lower SO2 level at admission were associated with increased odds of death (p<0.05). This coincided with who reported the predictors for mortality in the second wave were age, male gender, , acute respiratory distress syndrome, and chronic neurological diseases on the same hand [38].

In study reported that males were more likely to die than females during the second wave (OR: 1.969, 95% CI: 1.292; 3.000, p <0.002) [23].

A large multinational study from 14 countries, most of them were high-income countries, found that there was no difference in age in patients infected in the first and second wave; however, mortality was higher during both waves, as the age of the patients increased [40].

Various studies established a linear relationship between the severity of COVID-19 and the increasing number of comorbidities in the same individual, supplemented by advancing age [41, 42].

In a study by Blanc et al. age emerged as the strongest predictor of mortality, along with the severity of lung involvement, in both waves and in the combined population. **[43]**.In the current study, male was associated with higher risk of mortality in both waves. This agreed with the results of a meta-analysis of the 3 111 714 globally reported COVID-19 cases indicates that males have a higher chance of contracting the disease and having death as outcome [44].

In the current study, dyspnea, chest pain and chest tightness were associated with higher odds for mortality.

This was in accordance with the study by who showed that dyspnea was the most common presenting symptom among the patients in both the waves. Presence of associated comorbidities were associated with mortality in the two waves [22].

In the study by it was revealed that the diabetic patients with concomitant elevated

renal parameters were the most likely to succumb to COVID-19 [45].

The mortality rate was less than one percent in the absence of any comorbidity while patients with solid organ transplants formed the other end of the spectrum having the greatest causality [46] diabetes, COPD, and hypertension have been reported as important determinants of survival in various other studies [41].

The current results came in agreement with who showed a high prevalence of comorbidities among patients who died and increased mortality between the first and second waves. The most prevalent comorbidity in their study was cardiovascular disease, followed by diabetes [27].

Also survival analysis performed in Italian cohort studies showed an association between older age and decreased glomerular filtration rate with a higher risk of death [47].

Certain symptoms like fever, cough, abdominal pain and vomiting were non-committal in predicting survival similar to the report by [25].

In the current study, the prevalence of fever was statistically significantly higher in the dead subjects during the two waves.

This was in agreement with who showed that regarding the reported symptoms, fever and cough were significantly more frequent among the survivors than non-survivors. However, this may be due to the poorer availability of data on baseline symptoms in patients who were at the critical stage of COVID-19 at admission and should be interpreted with caution [48].

In the current study, regarding laboratory finding, higher WBC level, lower platelet level, higher neutrophil %, lower lymphocyte %, higher neutrophil-lymphocyte ratio, higher platelet-lymphocyte ratio, increased D-dimer, serum ferritin, CRP, LDH, INR, ALT, AST, total bilirubin, and higher urea were associated with mortality.

Lymphopenia at presentation was reported as one of the reasons for poorer prognosis in COVID-19 as per one of the Korean studies [49].

Another meta-analysis reported that leukocytosis was more prevalent in non-survivors of COVID-19 with a weighted mean difference of 3.66 [95%, CI (2.58-4.74)] [50, 51].

In the current study, during the first wave, bilateral pulmonary infiltration was significantly more prevalent in non survivors (27.3%) (p=0.001). Also, in the second wave, bilateral pulmonary infiltration was significantly more prevalent in ICU patients (27.3%) (p=0.001).

This came in agreement with who showed that the percentage of lung involvement on CT was significantly higher and lung involvement of at least 50% was more frequent in the non-survivors than in survivors [48].

As a general rule, the variations between the studies based on several factors. A non-standardized definition of waves was used; exact inclusion criteria were often unclear; follow-up was short; and none provided transparent and reasonable assumptions regarding the underlying causal structural of the data. Indeed, it is also important to remark that the heterogeneity of study designs, including censoring time and the severity of population collected (critical or severe), varies widely and these factors could strongly influence the estimated mortality and its predictors.

Conclusion:

The COVID-19 pandemic was associated with great impact on the health system and the economy. In Egypt, the second wave of COVID-19 was associated with more disease severity and increasing mortality. Increasing age, male gender and bad general condition on admission were reported as the independent predictors for mortality from COVID-19 during both waves.

Conflict of Interest

Authors declare no conflicts of interest.

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