PREDICTORS OF MORTALITY AMONG HOSPITALIZED PATIENTS WITH COVID-19 IN EGYPT: A RETROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

The prediction of mortality and risk stratification of severe coronavirus disease 2019 (Covid-19) offers a rational approach for clinical support, health resource allocation, and implementation of protective interventions to optimize the treatment. Clinicians need these predictors that permit them to elderly patients with Covid-19 rapidly during the pandemic. Investigate demographic features, clinical characteristics, laboratory parameters, and pharmacological treatment received by individuals who died due to Covid-19 that may be predictors of mortality. A retrospective observational study. A single-center cohort in Almaza Fever Egyptian Hospital through three years of the pandemic, 2020-2022. About 194 elderly patients with Covid-19 were attendees of the hospital and died through three years of the pandemic, 2020-2022. A total of 64 cases were in 2020, 94 cases in 2021, and 36 cases in 2022. Main outcome measures: Mortality after a short stay of 9 days evaluated by the area under the curve (AUC), determination of the clinical features, and laboratory measures that may be predictors related to mortality over the three years of the pandemic. Our research found a statistically significant variation between the three years (2020, 2021-2022) regarding co-morbidities including IHD, renal and stroke (p-value <0.05), treatment including Iverzine, chloroquine, remedisvir, and SL (p-value <0.001), and symptoms including pneumonia status, cytokine storm, dyspnea, cough, anosmia, loss of taste and GIT symptoms (p-value <0.005). After analysis, there were some predictors, including male sex, age, and hospital stay, that were positively associated with the deterioration of some laboratory measures and biomarkers such as IL-6 with mortality

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after a short period of stay (9 days) over time. The presented study showed a reliable prediction of mortality over time, so, it plays a crucial role in early patients' identification who are at high risk of death. Therefore, the deteriorated cases should be closely monitored.

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INTRODUCTION

The coronavirus disease 2019 (Covid-19) illness, utilizing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pathogenesis, leads to excellent health and societal burdens globally[1]. The early symptoms noted in Covid-19 patients range from mild to severe[2]. Mild symptoms include cough, sore throat, fever, dyspnea, anorexia, and fatigue[3]. A previous study in 552 Chinese hospitals and 30 regions involving 1099 affirmed Covid-19 occurrences. It detected a high percentage of cough (67.7%) and fever (87.9%), and a low percentage of vomiting and diarrhea (less than 5%) occurrence[4]. The virus may cause severe problems in some patients, such as pneumonia, sepsis, acute respiratory distress syndrome (ARDS), hyperinflammation, neurological symptoms, or multisystem organ failure[5].

Our community was significantly impacted by the early Covid-19 pandemic, which seriously affected our everyday routines, financial prudence, and healthcare structures. The adoption of public healthcare programs lowered the rate of infection; however, there is a significant risk that relaxing these regulations will result in the next global epidemic flood, which is already being seen in many nations. The fatality rate of most serious SARS-CoV-2 illnesses transferred to the intensive care (ICU) differs between study results, varying in hospital setting SARS-CoV-2 pneumonia patients (8.1% - 30%) and in intensive care patients (16% - 78%)[6]. Furthermore, 283 million recorded incidents and 5.41 million reported deaths from Covid-19 on 25 December 2021 in over 237 nations, with a worldwide fatality rate of 1.9% and a sharp everyday rise in the number of occasions[7].

Moreover, in the initial Wuhan study, from 41 patients with Covid-19 pneumonia, six (14.6%) patients quickly deteriorated and died due to multiple organ failure;[3] when the study sample size increased to 99 cases, the deaths were 11 (11.1%)[8]. In another Wuhan study, 4.3% (six out of 138) was the total mortality in hospitalized Covid-19 pneumonia patients[9]. Additionally, hospitalization rates, from the first wave in the spring of 2020 until the end of April, increased from 20% to 70%[10].

As of March 2020, numerous investigations on the clinical features of patients with Covid-19 have been publicly released in both minor (n=58[11], n=2006) and major studies (n>50007[12]). However, such research findings found significant differences in patient features that were linked to poor outcomes.

Interestingly, these research findings provide only data about clinical findings and predictors on a group level but not about individual patients' prognoses. Furthermore, Covid-19 mortality predictors were defined in multiple types of research involving advanced age[13], male sex[14], and comorbidities[15] including coronary artery disease, diabetes mellitus, obesity, malignancy, renal diseases, and hypertension.[16] Also, some symptoms included fever[17], cough[17], hemoptysis[13], dyspnea[13], fatigue[17], and loss of consciousness[13], and laboratory measures included high neutrophil-to-lymphocyte ratio (NLR)[13], and high creatinine level[15], lactate dehydrogenase (LDH)[13], direct bilirubin[13] and alanine aminotransferase[15], which indicated disease severity, high biomarkers level like serum ferritin, D-dimer[15], interleukin-6 (IL-6), procalcitonin (PCT), and C-reactive protein (CRP)[14] and reinforces these outcomes[15].

Estimation of fatalities and risk stratification provides a logical strategy for clinical support, health care services allotment, and constructing protective methods to maximize treatments available. The effectiveness of special antiviral and directed immunomodulatory treatment is still enigmatic. Additionally, clinical professionals should have a critical need for mortality-leading indicators that enable rapid management of severe (Covid-19) illness[18].

Despite extensive research currently reporting death rates and risk factors worldwide, in-depth research on the clinical traits and consequences of Covid-19 patients in Egypt is still lacking. Therefore, completing the knowledge gap by comprehending the clinical characteristics of Covid-19 can aid in mapping the illness, identifying patients at high risk, and directing healthcare administration in the future. The main goal of this retrospective non-interventional study was to better map and manage the Covid-19 pandemic by examining the clinical characteristics of the virus and locating potential predictors associated with mortality.

MATERIALS AND METHODS

Design and Population is A retrospective observational study was performed to collect data from the medical records of every individual who died from Covid-19 and was an attendee of Almaza Fever Hospital, through three years of pandemic. The study started on January 2023, and the data were collected retrospectively from records starting from 1/1/2020 till the end of 2022.

Inclusion and Exclusion Criteria only patients who died and had complete laboratory results in their records were included in the study. Patients who didn’t have complete records with laboratory results were excluded.

Data collection our research examined retrospective data collected from medical files in Almaza Fever Hospital to assess the clinical consequences of 194 hospitalized elderly patients who died from Covid-19 through three years of the pandemic, 2020, 2021, and 2022. The positive polymerase chain reaction (PCR) was the confirmation test for the diagnosis of Covid-19 illness according to the SARS-CoV-2 virus testing.

Data of some variables were detected, including; sex, age, comorbidities, length of stay in the hospital, pneumonia and other symptoms,

laboratory results (neutrophils, d-dimers, hemoglobin, C-reactive protein (CRP), urea, alanine aminotransferase (ALT), aspartate aminotransferase (AST), platelets (PLT), TLC, creatinine, ferritin, and IL-6) and treatment medications.

Outcome measures the overall outcome of these admitted Covid-19 elderly patients was the determination of the clinical features and laboratory measures that may be leading indicators for mortality. Patient and public involvement, this study was a reply to a global health crisis, this research was conducted without patients' involvement in any stage of it.

Ethical considerations the research was performed in complete compliance with the ethics of the "Declaration of Helsinki", principles of Good Clinical Practice (GCP), and within the rules and restrictions of "The Ministry of Health" (MOH) in Egypt. Medical records collected were retrospective and did not require informed consent, according to national guidelines and privacy law.

Statistical analysis evaluation was conducted utilizing R version 4.1.1. Median and interquartile range were employed to elucidate numerical factors due to their departure from normal distribution. In the case of non-parametric data, the Kruskal-Wallis rank sum test was employed, followed by the application of the Dunn test for precise identification of groups exhibiting noteworthy distinctions. Categorical variables are presented by count and percentage. Pearson's chi-square test was used for categorical data. Statistical significance is set at 0.05.

RESULTS

Variables description comorbidity and symptom numbers were created using scoring. Those who had any comorbidities or symptoms took a score of 1 and those who haven't taken 0, and the scores are summed to give the numbers. In addition, the pneumonia variable was produced from the CT.1 variable, all the levels containing the word severe, consolidation, or collapse took the value of 1 and all the others took the value of 0.

The length of hospital stay variable was categorized into 2 levels; death after a short hospital stay took a score of 1 and death after a long hospital stay took a score of 0. The cut-off point was the median of the length of stay which was 9 days. Those who stayed in the hospital more than 9 days took 0 and those who stayed less than 9 days and then died took a score of 1, this was the main outcome of the logistic regression and roc curve analysis.

Modeling a generalized estimation equation is a type of regression used to account for the effect of time to analyze the change in the lab results through time. Then, logistic regression is utilized to assess the predictors of fatality after a short stay in the hospital. Finally, roc analysis is used to know the discriminative abilities of the logistic regression model.

There was a statistically significant difference between the three years (2020-2022) in patients who suffered from IHD, renal and stroke co-morbidities (p-value =0.036, 0.008, 0.038 respectively), and in the proportions of patients taking Iverzine, chloroquine, remedisvir, and SL. (p-value <0.001, 0.009, <0.001, <0.001 respectively) Table 1.

Table 1. Demographic characters, comorbidities, and treatment used distributed across the 3 years

Demographic characteristics, Comorbidities, and the treatment used	**Overall**, N = 194[1]	**Year**			**p-value**[2]
		2020 N = 64[1]	**2021** N = 94[1]	**2022** N = 36[1]	
Age	69 (63. 76)	69 (63.74)	70 (62.76)	69 (60.75)	>0.9
Sex					0.8
Female	46 (24%)	14 (22%)	22 (24%)	10 (28%)	
Male	147 (76%)	50 (78%)	71 (76%)	26 (72%)	
Co-morbidities					
Hypertension	118(61%)	39(61%)	63 (67%)	16 (44%)	0.062
Diabetes Mellitus	114(59%)	39(61%)	55 (59%)	20 (56%)	0.9
Cardiac impairment	43(22%)	10(16%)	27 (29%)	6 (17%)	0.10
IHD	30(15%)	4 (6.2%)	20 (21%)	6 (17%)	0.036
Renal impairment	10(5.2%)	0 (0%)	5 (5.3%)	5 (14%)	0.008
Liver cirrhosis	8 (4.1%)	2 (3.1%)	3 (3.2%)	3 (8.3%)	0.4
Stroke	11(5.7%)	1 (1.6%)	5 (5.3%)	5 (14%)	0.038
Length of hospital stay	9 (5.15)	8 (4.14)	11 (6.15)	8 (4.15)	0.5
Treatment					
Iverzine: single dose (*12 mg/day for 3 days*)	79 (41%)	0 (0%)	67 (71%)	12 (33%)	<0.001
Chloroquine: 600 mg first *dose* followed by 300 mg after 12 hours then 300 mg daily till day 5	16 (8.2%)	11 (17%)	4 (4.3%)	1 (2.8%)	0.009
Remdisivir: 200 mg one dose daily as an intravenous infusion and then a total of 100 mg daily for 5-10 days	62 (32%)	18 (28%)	17 (18%)	27 (75%)	<0.001
Sofosbuvir/ledipasvir (SL): 400 mg and 90 mg, orally once a day for 14 days	124 (64%)	49 (77%)	71 (76%)	4 (11%)	<0.001
Actemra (*Tocilizumab)*: (8mg/kg, 800mg) first dose then 2nd dose (4mg/kg, 400mg).	104 (54%)	31 (48%)	51 (54%)	22 (61%)	0.5

[1] Median (IQR); n (%)
[2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test; Fisher's exact test

We also determined that the significance of the IHD co-morbidity was between the years 2020 and 2021(adj. p-value=0.031), the renal co-morbidities significance was between the years 2020 and 2022 (adj. p-value=0.007), and the

stroke co-morbidities significance was between the years 2020 and 2022 (adj. p-value=0.032) Supplementary Table 1.

In addition, the significance of iverzine treatment was between the years (2020 and 2021), (2020 and 2022), and (2021 and 2022) (adj. p-value<0.001, 0.003, <0.001 respectively), chloroquine treatment significance was between the years (2020 and 2021), and (2020 and 2022) (adj. p-value=0.011, 0.036 respectively), Remidisvir treatment significance was between the years (2020 and 2022), and (2021 and 2022) (adj. p-value<0.001, <0.001 respectively), and SL treatment significance was between the years (2020-2022), and (2021-2022) (adj. p-value<0.001,<0.001 respectively).

There was a statistically significant difference between pneumonia status, cytokine storm, dyspnea, cough, anosmia, loss of taste, and GIT symptoms between the 3 years (p-value=0.005, 0.015, <0.01, <0.001, <0.001, <0.001, <0.001 respectively) Table 2.

There was a significant difference in pneumonia status between the years 2021 and 2022 (adj. p-value=0.003), cytokine storm status significance was between the years 2020 and 2022) (adj. p-value=0.011), the significance in dyspnea, cough, anosmia, and loss of taste status was between the years (2020 and 2022) and (2021-2022) (adj. p-value<0.001, <0.001 respectively), and the significance between CIT symptoms status was between the years (2020 and 2021), (2021 and 2022) (adj. p-value =0.0015, <0.001, <0.001 respectively) Supplementary Table 2 and figure from 1 to 12.

Table 2. Pneumonia and other symptoms distributed across the 3 years

Pneumonia and other symptoms	**Overall**, N = 194[1]	**Year**			**p-value**[2]
		2020, N = 64[1]	**2021**, N = 94[1]	**2022**, N = 36[1]	
pneumonia					0.005
Non-severe	77 (47%)	24 (46%)	33 (38%)	20 (74%)	
Severe	88 (53%)	28 (54%)	53 (62%)	7 (26%)	
Symptoms					
Cytokine storm	116 (61%)	33 (52%)	56 (61%)	27 (82%)	0.015
Fever	106 (56%)	35 (55%)	49 (53%)	22 (67%)	0.4
Sore throat	1 (0.6%)	0 (0%)	1 (1.1%)	0	>0.9
Dyspnea	165 (87%)	64 (100%)	89 (97%)	12 (36%)	<0.01
Cough	171 (91%)	64 (100%)	88 (97%)	19 (58%)	<0.001
Fatigue and headache	5 (2.6%)	0 (0%)	4 (4.3%)	1 (3.0%)	0.2
Anosmia	74 (39%)	29 (45%)	44 (48%)	1 (3.0%)	<0.001
Loss of taste	81 (43%)	34 (53%)	47 (51%)	0 (0%)	<0.001
RASH	1 (0.6%)	0 (0%)	1 (1.1%)	0	>0.9
GIT symptoms	84 (44%)	43 (67%)	41 (45%)	0 (0%)	<0.001
Duration of presenting symptoms	4 (3, 5)	3 (3, 4)	4 (3, 5)	4 (2, 5)	0.10

[1] n (%); Median (IQR)
[2] Pearson's Chi-squared test; Kruskal-Wallis rank sum test; Fisher's exact test

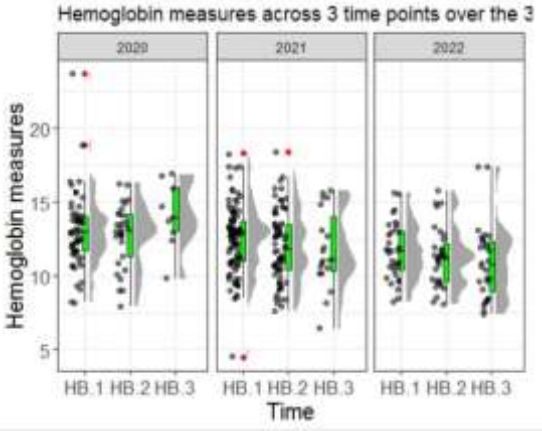

Figure 1. Generalized estimation equation of Hemoglobin measures over time

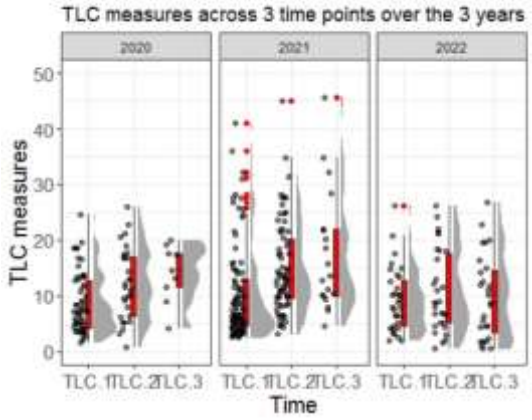

Figure 2. Generalized estimation equation of TLC measures over time

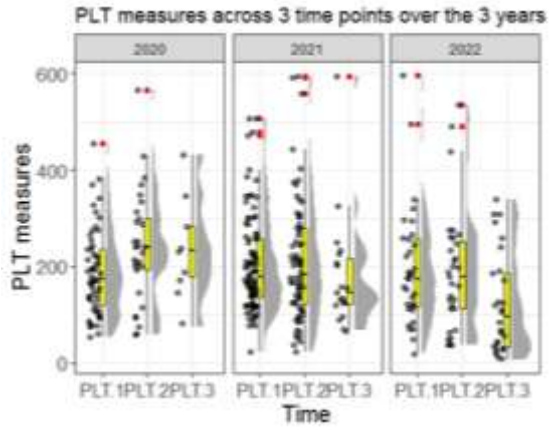

Figure 3 Generalized estimation equation of PLT measures over time

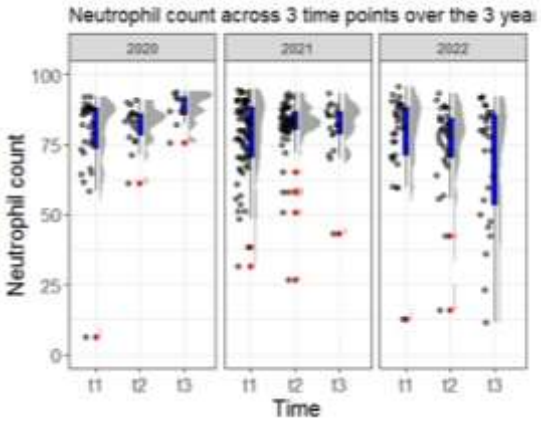

Figure 4. Generalized estimation equation of Neutrophil count measures over time

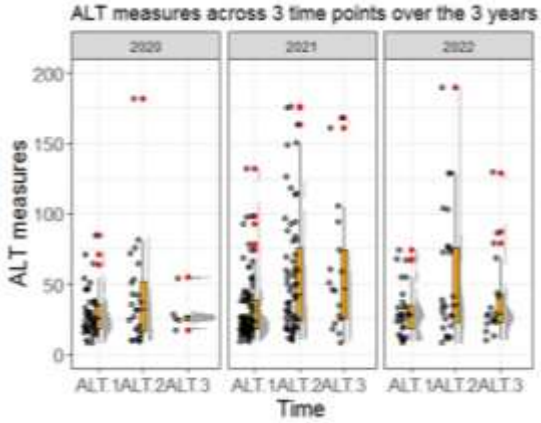

Figure 5. Generalized estimation equation of ALT measures over time

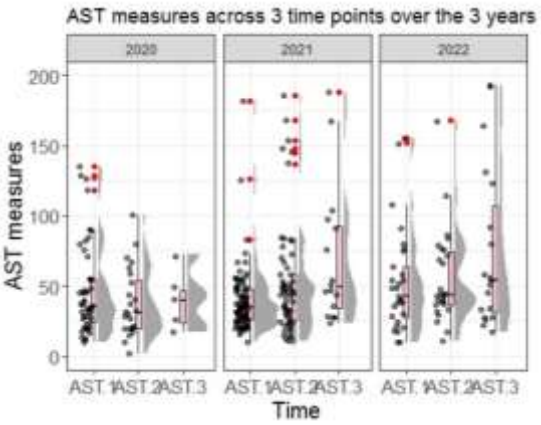

Figure 6. Generalized estimation equation of AST measures over time

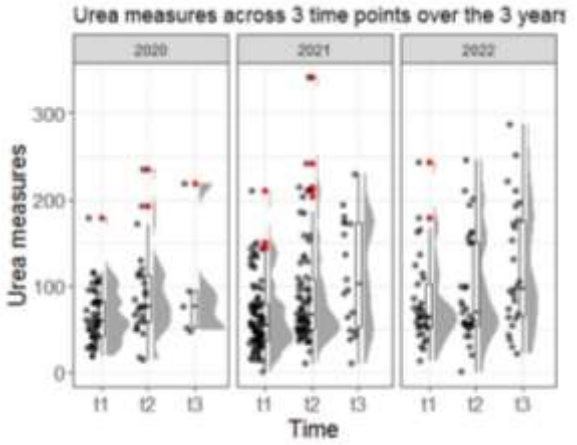

Figure 7. Generalized estimation equation of Urea measures over time

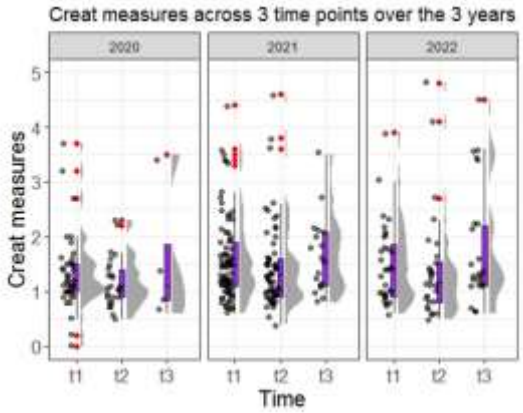

Figure 8. Generalized estimation equation of Creatine measures over time

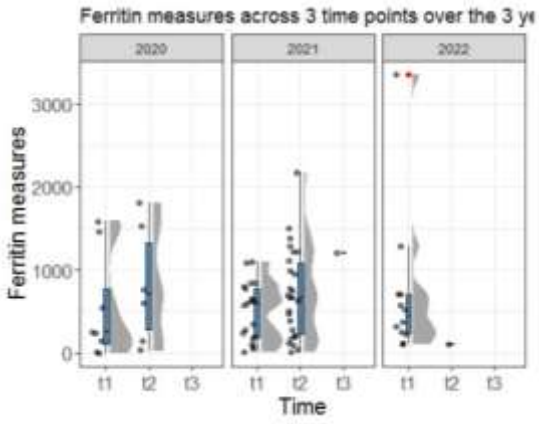

Figure 9. Generalized estimation equation of Ferritin measures over time

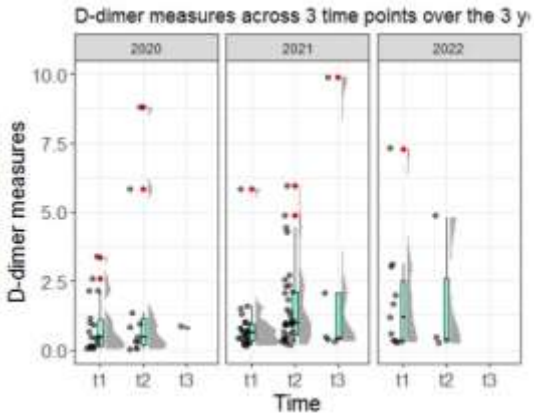

Figure 10. Generalized estimation equation of D-dimer measures over time

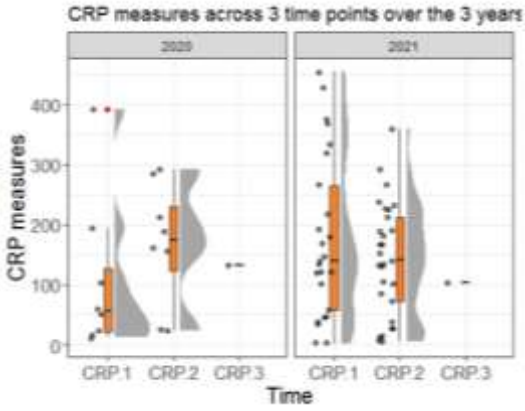

Figure 11. Generalized estimation equation of CRP measures over time

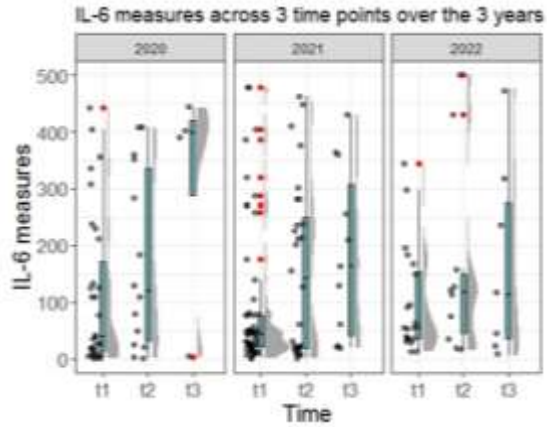

Figure 12. Generalized estimation equation of IL-6 measures over time

By increasing age by 1 year, the hemoglobin measures significantly decreased by 0.02 units adjusted for all the other factors (p-value=0.037). Further, males have significantly higher hemoglobin measures by 1.7 units compared to females when adjusting for all the other factors (p-value<0.001). (Supplementary Table 3)

TLC measures have significantly decreased in the second and third-time measurements by 4.4 and 6.4 units respectively (p-value <0.001, <0.001 respectively). Also, by increasing age by 1 year, TLC measures significantly decreased by 0.11 when adjusting for all the other factors (p-value=0.015). The length of hospital stay has decreased TLC measures by 0.17 units (p-value=0.008). (Supplementary Table 4) There were no significant differences regarding platelet measures. (Supplementary Table 5).

Regarding urea measures, we determined a significant increase in the second and third-time measurements compared to the first time by 27 and 51 units respectively (p-value<0.001, 0.001 respectively). However, by increasing age by 1 year, urea measures significantly increased by 0.97 units when all the other factors were considered (p-value <0.001). (Supplementary Table 6)

Creatinine measures significantly increased in the year 2021 compared to the year 2020 by 0.25 units (p-value=0.025). Males had higher Creatinine measures by 0.28 units compared to females (p-value=0.013). Besides, by increasing the number of comorbidities by 1, creatinine measures increased by 0.09 (p-value=0.031). Also, the length of hospital stay has resulted in a significant decrease in Creatinine measures by 0.02 units (p-value=0.006). (Suplementary Table 7).

Ferritin measures significantly increased in the third time measurement compared to the first time by 596 units adjusted for all the other factors (p-value<0.001). (Suplementary Table 8). D-dimer measures significantly decreased in patients enrolled in the hospital in the year 2022 compared to the year 2020 by 127 units and adjusted for all the other factors (p-value=0.029). Males have significantly decreased D-dimer measures by 116 units compared to females with adjusted all the other factors (p-values=0.041). (Suplementary Table 9). Il-6 measures have significantly increased in the third time measurement by 601 units compared to the first time (p-value=0.027) and this means the deterioration of cases over time. The length of hospital stay significantly decreased IL-6 measures by 31 units (p-value <0.001). Supplementary Table 10

Logistic regression the model was built by the backward selection of the variables, in other words, all the potential predictors were put in the model which made instability of the model removed. All the assumptions were met by pseudo R2 =0.678, and the Hosmer Lemeshow test was not significant (p-value=0.678) reported that the model fit the data very well and there was no colinearity between the independent variables.

When urea measures increased, the adjusted odds of death after a short hospital stay decreased by 4% (p-values 0.004), higher creatinine levels increased the adjusted odds of death after a short hospital stay by 7 the odds (p-value=0.008), and hypertension comorbidities decreased the adjusted odds ratio of death after a short hospital stay by 81% (p-value=0.021). (Table 3).

Table 3. Logistic regression of death after a short stay in the hospital

Dependent= Death after a Short stay at the hospital	AOR[1]	95% CI[1]	p-value
Age	1.07	0.99, 1.16	0.094
Gender			
Female	—	—	
Male	3.21	0.56, 22.0	0.2
HB	0.89	0.66, 1.19	0.4
TLC	1.01	0.92, 1.12	0.8
PLT	1.00	0.99, 1.01	0.6
Lymphocytes	1.00	1.00, 1.00	0.14
ALT	1.00	1.00, 1.01	0.2
Urea	0.96	0.93, 0.98	**0.004**
Creatine	7.00	1.83, 33.4	**0.008**
IL6	1.00	1.00, 1.00	0.4
Comorbidities			
Cirrhosis	0.49	0.02, 10.0	0.6
Stroke	4.31	0.25, 83.7	0.3
HTN	0.19	0.04, 0.75	**0.024**
DM	0.60	0.15, 2.37	0.5
Cardiac	1.64	0.26, 10.4	0.6
IHD	0.10	0.01, 1.08	0.070
Renal	2.38	0.08, 99.0	0.6
TTT with Actemra			
No	—	—	
Yes	1.22	0.22, 7.38	0.8
TTT with Remdisivir			
No	—	—	
Yes	3.98	0.83, 21.6	0.090
TTT with Iverzine			
No	—	—	
Yes	1.25	0.29, 5.64	0.8
Cytokine storm	0.16	0.01, 1.50	0.12
Fever	0.26	0.05, 1.04	0.069
PCR.1			
Negative	—	—	
Positive	0.71	0.09, 5.17	0.7
Anosmia	1.81	0.40, 8.83	0.4
Loss of taste	6.40	1.47, 35.7	**0.021**
GIT Symptoms	0.50	0.08, 2.73	0.4
Pneumonia	2.28	0.65, 8.99	0.2

[1] OR = Odds Ratio, CI = Confidence Interval

ROC analysis the dataset was divided by a ratio of 7:3 into train data (to train the model) and test (to test the model). Additionally, the predictors were statistically significant in the logistic regression which was introduced to the model (full model). Then, a univariate model containing creatinine and hypertension was also built and compared to the full model. Finally, the confusion

matrix and the roc curve showed that the full model had the highest AUC (0.782), as illustrated in **Table 14** and **Figure 13**.

Table 14. The confusion matrix of the models

Statistic parameter	Full model (predictors: creatinine measures, loss of taste, and hypertension comorbidity)	Univariate model by using Creatinine as a predictor	Univariate model by using hypertension comorbidity as a predictor
AUC	0.782	0.631	0.714
Accuracy (CI)	0.705 (0.56-0.83)	0.627 (0.48-0.758)	0.724(0.591-0.833)
Sensitivity	0.709	0.774	0.787
Specificity	0.700	0.400	0.640
PPV	0.785	0.666	0.742
NPV	0.608	0.533	0.695

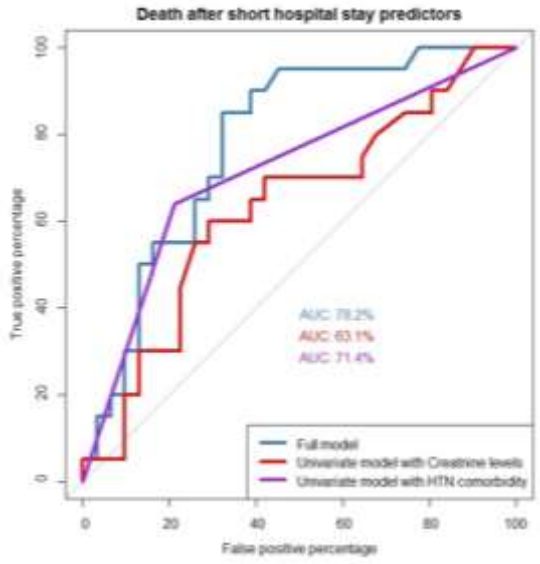

Figure 13. Roc Curve of the models

DISCUSSION

According to our research, we determined and defined elderly patients with COVID-19 who died after a short hospitalization period (9 days). We assessed the relation of many demographics and clinical features to mortality over three years of the pandemic. We noticed similar findings as previous studies[13,19–21] regarding the association of older age, and male gender with deterioration of cases, and mortality. Also, there was an association of clinical features examined during hospitalization, including laboratory measures, symptoms, and comorbidities.

We noticed a statistically significant difference between the three years (2020, 2021, and 2022) in patients who suffered from IHD, renal, and stroke co-morbidities (p-value < 0.05). These findings were supported by another Egyptian study. The research detected that 54.9% of the hospitalized patients were comorbid; mainly DM and HTN comorbidities, which were highly linked with the severe illness cohort versus the non-severe. Due to low nitric oxide levels in such morbidities; hypertension and diabetes[22,23].

Also, we reported statistically significant differences between the three years (2020, 2021, and 2022) in pneumonia status, cytokine storm, dyspnea, cough, anosmia, loss of taste, and GIT symptoms (p-value < 0.01). According to the findings of the systematic review study, fever, cough, dyspnea, malaise, arthralgia, and nasal obstruction were among the top ten

noticed signs and symptoms with the increased mean percentage related to Covid-19 mortality[24].

Moreover, we detected a statistically significant difference between the three years (2020, 2021, and 2022) in the proportions of patients taking Iverzine, chloroquine, remedisvir, and SL treatment (P-value < 0.001). The evidence stated that many hospital treatments were linked to an increased risk of death[25]. These results could be clarified as most medicines were only suggested to be taken by patients suffering from severe illness. Remdesivir and dexamethasone, for example, are suggested for severely ill Covid-19 patients who necessitate supplemental oxygen[26].

Furthermore, our laboratory findings were analyzed over three years regarding some risk factors including age, male sex, and length of stay. Thus, by increasing 1 year of **age**, the hemoglobin and TLC measures significantly decreased, and urea **and creatinine** measures significantly increased, after adjusting for all the other factors (p-values < 0.05). An initial trial in Wuhan, China, included 179 Covid-19 patients and reported that 17(81%) of severe illness patients were older than 65 years old[27]. Also, in a London study, 75 of 229 patients had a severe illness, aged 78 years old[28]. Also, in Spain, 1131 of 4035 patients died, where 85.6% were older than 65[20].

Moreover, our study determined that the male gender has significantly higher hemoglobin and **creatinine** measures and decreased D-dimer measures compared to females when adjusting for all the other factors (p-value < 0.05). The evidence indicated that mortality in men was greater than in women[29], it could be related to a combination of biological and psychosocial differences[30].

Additionally, the length of hospital stay has decreased TLC, IL-6, and creatinine measures (p-value <0.001). As the same, deaths versus survivors in the Saudi Arabia study were more commonly attended to the ICU (65.4% versus 22.6%) with (p-value < 0.001) and practiced 15 days of hospital stay vs. 8 days, (p = 0.003) [31].

This study supported the findings of the role of laboratory results in predicting mortality. A systematic review study of 4659 patients, detected the effect of LDH, CRP, Troponin, Creatinine, and Albumin in higher mortality rates[32]. Also, several vital signs and laboratory results, such as LDH, CRP[25], and D-dimer[33], were associated with serious outcomes and higher death rate likelihood in patients with Covid-19.

In addition, a Turkish study with a 4.5% in-hospital mortality rate, detected the most common leading causes of death including; male sex, older age, concomitant and severe diseases, sepsis, increased BUN, D-dimer and procalcitonin levels and decreased albumin levels. Biomarkers had a larger effect with a strong association with mortality. However, medications as antivirals (including; hydroxychloroquine and azithromycin) weren't linked to persistence. Our research has a strength, the novelty of analyzing data over time and comparing the three years of the Covid-19 pandemic.

There were some limitations. First, some laboratory tests weren't performed for all patients due to the retrospective study design. As a result, we were unable to explore their significance in Covid-19 patients' outcome prediction. Second, the

study had restricted healthcare settings and limited sample size. Additionally, some comorbidities and medications may not have been taken or noted. Moreover, the information used for development is probably not as reflective of Covid-19 hospitalized patients today. It should also be assessed how the models' predictions stack up against the clinical expertise. Finally, the values of the laboratory tests might be biased by previous antiviral treatment.

CONCLUSION

Our research identified some patient demographics and important clinical features linked to Covid-19 mortality in short-period hospitalized elderly patients over the three years of the Covid-19 pandemic. Covid-19 deteriorated cases and mortality were a serious threat and related to risk factors including; old age, male sex, and increasing hospital stays, therefore, such deteriorated cases should be closely monitored. The presented study showed a reliable prediction of mortality over time, so, it plays a crucial role in early patients' identification who are at high risk of death. In addition, this may help healthcare providers in medical management and improve the medical decision. Furthermore, comorbidities should be given special attention by healthcare workers because uncontrolled conditions are related to higher death rates in Covid-19 patients. The next step toward clinical implication would be to address these unanswered questions.

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CONFLICT OF INTEREST

All authors declare that there are no conflicts of interest regarding the publication of this study. All authors have reviewed and approved the final manuscript and affirm that there are no financial or personal relationships that could inappropriately influence or bias the content of this research.

ETHICS CONSIDERATION

The ethical boards of the Supreme Council of University Hospitals approved the study protocol ("Serial Number": NO-0326(V3)).

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Supplementary Table 2. Dunn test (p-value adjusted by using Bonferroni method)

Comparison in IHD comorbidities	Z-value	p-unadjusted	p-adjusted
2020-2021	-2.55	0.01	0.031
2020-2022	-1.37	0.167	0.503
2021-2022	0.64	0.516	1.00
Renal impairment comorbidity			
2020-2021	-1.48	0.138	0.416
2020-2022	-3.00	0.002	0.007
2021-2022	-1.97	0.0485	0.145
Stroke comorbidity			
2020-2021	-0.99	0.317	0.952
2020-2022	-2.55	0.010	0.032
2021-2022	-1.88	0.059	0.0178
Iverzine			
2020-2021	-8.928	<0.001	<0.001
2020-2022	-3.248	0.001	0.003
2021-2022	3.930	<0.001	<0.001
Chloroquine			
2020-2021	2.893	0.003	0.011
2020-2022	2.507	0.012	0.036
2021-2022	0.273	0.784	1.00
Remedisvir			
2020-2021	1.325	0.185	0.555
2020-2022	-4.812	<0.001	<0.001
2021-2022	-6.211	<0.001	<0.001
SL			
2020-2021	0.132	0.894	1.00
2020-2022	6.524	<0.001	<0.001
2021-2022	6.826	<0.001	<0.001

Supplementary Table 3. Dunn test (p-value adjusted by using Bonferroni method)

Pneumonia status	Z-value	p-unadjusted	p-adjusted
2020-2021	-0.885	0.376	1.00
2020-2022	2.352	0.018	0.055
2021-2022	3.234	0.001	0.003
Cytokine storm			
2020-2021	-1.171	0.241	0.724
2020-2022	-2.891	0.003	0.011
2021-2022	-2.114	0.034	0.103
Dyspnea			
2020-2021	0.600	0.548	1.00
2020-2022	8.894	<0.001	<0.001
2021-2022	8.912	<0.001	<0.001
Cough			
2020-2021	0.702	0.482	1.00
2020-2022	6.884	<0.001	<0.001
2021-2022	6.696	<0.001	<0.001
Anosmia			
2020-2021	-0.315	0.752	1.00
2020-2022	4.031	<0.001	<0.001
2021-2022	4.511	<0.001	<0.001
Loss of taste			
2020-2021	0.252	0.8007	1.00
2020-2022	4.995	<0.001	<0.001
2021-2022	5.074	<0.001	<0.001
GIT symptoms			
2020-2021	2.789	<0.001	0.0015
2020-2022	6.292	<0.001	<0.001
2021-2022	4.408	<0.001	<0.001

Supplementary Table 3. Predictors of Hemoglobin measures

Dependent= Hemoglobin measures	Beta	95% CI[1]	p-value
Time of measurement			
Time1	—	—	
Time2	-0.44	-0.99, 0.11	0.12
Time3	-0.47	-1.2, 0.30	0.2
Year			
2020	—	—	
2021	-0.40	-1.1, 0.32	0.3
2022	-0.61	-1.6, 0.33	0.2
Age	-0.02	-0.04, 0.00	0.037
Sex			
Female	—	—	
Male	1.7	1.1, 2.4	<0.001
pneumonia			
Non-severe	—	—	
Severe	0.10	-0.43, 0.64	0.7
Number of comorbidities	0.01	-0.23, 0.25	>0.9
Number of symptoms	0.20	-0.03, 0.42	0.089
Duration of presenting symptoms	0.15	-0.02, 0.33	0.083
Length of hospital stay	0.01	-0.03, 0.04	0.7

[1] CI = Confidence Interval

Supplementary Table 4. Predictors of TLC measures

Dependent= TLC measures	Beta	95% CI[1]	p-value
Time of measurement			
Time 1	—	—	
Time 2	**4.4**	2.6, 6.3	**<0.001**
Time 3	**6.4**	3.3, 9.5	**<0.001**
Year			
2020	—	—	
2021	**2.5**	0.59, 4.4	**0.010**
2022	-2.3	-5.1, 0.46	0.10
Age	**-0.11**	-0.19, -0.02	**0.015**
Sex			
Female	—	—	
Male	0.30	-1.5, 2.1	0.8
pneumonia			
Non-severe	—	—	
Severe	-0.30	-2.1, 1.5	0.7
Number of comorbidities	0.41	-0.38, 1.2	0.3
Number of symptoms	0.07	-0.76, 0.91	0.9
Duration of presenting symptoms	0.29	-0.28, 0.85	0.3
Length of hospital stay	**-0.17**	-0.29, -0.04	**0.008**

[1] CI = Confidence Interval

Supplementary Table 5. Predictors of platelets measures

Dependent: Platelets measures	Beta	95% CI[1]	p-value
Time of measurement			
Time 1	—	—	
Time 2	17	-11, 46	0.2
Time 3	-17	-58, 24	0.4
Year			
2020	—	—	
2021	15	-15, 45	0.3
2022	-28	-66, 11	0.2
Age	-0.53	-1.6, 0.56	0.3
Sex			
Female	—	—	
Male	-21	-51, 9.4	0.2
pneumonia			
Non-severe	—	—	
Severe	5.9	-19, 31	0.6
Number of comorbidities	3.2	-6.9, 13	0.5
Number of symptoms	-4.1	-13, 5.0	0.4
Duration of presenting symptoms	3.4	-6.3, 13	0.5
Length of hospital stay	-0.99	-2.7, 0.72	0.3

[1] CI = Confidence Interval

Supplementary Table 6. Predictors of urea measures

Dependent= Urea	Beta	95% CI[1]	p-value
Time of measurement			
Time1	—	—	
Time2	**27**	14, 39	**<0.001**
Time3	**51**	30, 72	**<0.001**
Year			
2020	—	—	
2021	-5.3	-17, 6.7	0.4
2022	-8.4	-27, 10	0.4
Age	**0.97**	0.53, 1.4	**<0.001**
GENDER			
Female	—	—	
Male	5.0	-7.2, 17	0.4
pneumonia			
Non-severe	—	—	
Severe	-2.2	-14, 9.2	0.7
Number of comorbidities	1.4	-3.1, 5.9	0.5
Number of symptoms	-0.37	-4.8, 4.0	0.9
Duration of presenting symptoms	2.6	-1.3, 6.6	0.2
Length of hospital stay	-0.34	-1.1, 0.38	0.4

[1] CI = Confidence Interval

Supplementary Table 7. Predictors of creatinine measures

Dependent= Creatinine measures	Beta	95% CI[1]	p-value
Time of measurement			
Time 1	—	—	
Time 2	0.05	-0.17, 0.28	0.7
Time 3	0.43	-0.02, 0.88	0.058
Year			
2020	—	—	
2021	**0.25**	0.03, 0.46	**0.025**
2022	0.34	-0.07, 0.75	0.10
Age	0.01	0.00, 0.01	0.2
Gender			
Female	—	—	
Male	**0.28**	0.06, 0.50	**0.013**
pneumonia			
Non-severe	—	—	
Severe	0.02	-0.19, 0.24	0.8
Number of comorbidities	**0.09**	0.01, 0.18	**0.031**
Number of symptoms	0.04	-0.04, 0.12	0.3
Duration of presenting symptoms	0.03	-0.06, 0.11	0.5
Length of hospital stay	**-0.02**	-0.04, -0.01	**0.006**

[1] CI = Confidence Interval

Supplementary Table 8. Predictors of Ferritin measures

Dependent= Ferritin measures	Beta	95% CI[1]	p-value
Time of measurement			
Time 1	—	—	
Time 2	164	-116, 444	0.3
Time 3	596	284, 909	**<0.001**
Year			
2020	—	—	
2021	104	-290, 499	0.6
2022	362	-333, 1,057	0.3
Age	2.0	-10, 14	0.8
Gender			
Female	—	—	
Male	163	-168, 494	0.3
pneumonia			
Non-severe	—	—	
Severe	169	-91, 430	0.2
Number of comorbidities	5.5	-111, 122	>0.9
Number of symptoms	-27	-161, 107	0.7
Duration of presenting symptoms	-30	-135, 75	0.6
Length of hospital stay	11	-12, 34	0.3

[1] CI = Confidence Interval

Supplementary Table 9. Predictors of D-dimer measures

Dependent= D-Dimer measures	Beta	95% CI[1]	p-value
Time of measurement			
Time1	—	—	
Time 2	22	-74, 118	0.7
Time 3	-51	-118, 16	0.13
Year			
2020	—	—	
2021	-3.3	-90, 84	>0.9
2022	-127	-241, -13	**0.029**
Age	-2.2	-5.4, 1.0	0.2
Gender			
Female	—	—	
Male	-116	-227, -4.6	**0.041**
Pneumonia			
Non-severe	—	—	
Severe	-33	-133, 68	0.5
Number of comorbidities	-6.7	-30, 17	0.6
Number of symptoms	-12	-50, 25	0.5
Duration of presenting symptoms	11	-17, 39	0.4
Length of hospital stay	-3.8	-8.3, 0.68	0.10

[1] CI = Confidence Interval

Table 10. Predictors of Ferritin measures

Dependent= Ferritin measures	Beta	95% CI[1]	p-value
Time of measurement			
Time 1	—	—	
Time 2	164	-116, 444	0.3
Time 3	596	284, 909	**<0.001**
Year			
2020	—	—	
2021	104	-290, 499	0.6
2022	362	-333, 1,057	0.3
Age	2.0	-10, 14	0.8
Gender			
Female	—	—	
Male	163	-168, 494	0.3
pneumonia			
Non-severe	—	—	
Severe	169	-91, 430	0.2
Number of comorbidities	5.5	-111, 122	>0.9
Number of symptoms	-27	-161, 107	0.7
Duration of presenting symptoms	-30	-135, 75	0.6
Length of hospital stay	11	-12, 34	0.3

[1] CI = Confidence Interval

Supplementary Table 9. Predictors of D-dimer measures

Dependent= D-Dimer measures	Beta	95% CI[1]	p-value
Time of measurement			
Time1	—	—	
Time 2	22	-74, 118	0.7
Time 3	-51	-118, 16	0.13
Year			
2020	—	—	
2021	-3.3	-90, 84	>0.9
2022	-127	-241, -13	**0.029**
Age	-2.2	-5.4, 1.0	0.2
Gender			
Female	—	—	
Male	-116	-227, -4.6	**0.041**
Pneumonia			
Non-severe	—	—	
Severe	-33	-133, 68	0.5
Number of comorbidities	-6.7	-30, 17	0.6
Number of symptoms	-12	-50, 25	0.5
Duration of presenting symptoms	11	-17, 39	0.4
Length of hospital stay	-3.8	-8.3, 0.68	0.10

[1] CI = Confidence Interval

Supplementary Table 10. Predictors of IL-6 measures

Dependent= IL6 measures	Beta	95% CI[1]	p-value
Time of measurement			
Time 1	—	—	
Time 2	342	-154, 839	0.2
Time 3	601	69, 1,134	**0.027**
Year			
2020	—	—	
2021	193	-81, 468	0.2
2022	1,170	-490, 2,831	0.2
Age	2.8	-12, 17	0.7
Gender			
Female	—	—	
Male	211	-286, 709	0.4
pneumonia			
Non-severe	—	—	
Severe	195	-250, 640	0.4
Number of comorbidities	-106	-280, 69	0.2
Number of symptoms	197	-114, 508	0.2
Duration of presenting symptoms	-26	-96, 45	0.5
Length of hospital stay	-31	-48, -13	**<0.001**

[1] CI = Confidence Interval