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The boundaries between survival and nonsurvival at COVID-19: Experience of tertiary care pandemic hospital

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Abstract

Objective: Coronavirus disease 2019 (COVID-19) is an emerging, fast-spreading, highly mortal and worldwide infectious disease. The pulmonary system was defined as the main target of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), but the mortality concept of this disease presented with more severe and systemic disease. The present study investigated the relationship between the patient characteristics at the initial hospital administration and fatality in COVID-19 patients.

Methods: In this retrospective and comparative cohort study, all the 767 hospitalised COVID-19 patients, treated between 18 March and 15 May 2020 in the Covid Clinics of Gulhane Training and Research Hospital in Ankara, Turkey, were evaluated.

Results: The fatality rate was significantly increased in patients with any comorbid disease except asthma. The initial laboratory test results indicated highly significant differences according to the patient's outcome. A multifactor logistic regression analysis was performed to calculate the adjusted odds ratios for predicting patient outcomes. Being older than 60 years increased the death risk with an adjusted OR of 7.2 (95% CI: 2.23-23.51; $P = .001$). The presence of a cancer and the extended duration of intensive care unit treatment were other significant risk factors for nonsurvival. Azithromycin treatment was determined as significantly reduced the death ratio in these patients ($P = .002$).

Conclusion: It was revealed that being older than 60 years, presence of a cancer and extended duration of ICU treatment were the major risk factors for predicting fatality rate in hospitalised COVID-19 patients.

1 | INTRODUCTION

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19) that was first reported in Wuhan, Hubei Province, in January 2020. It has quickly become an emerging, serious, fast-spreading and worldwide health disaster. The 2 487 236 of people had died amongst 112 336 160 infected cases of COVID-19 disease in 218 different countries around the world until 23 February 2021.[1] Mostly the pulmonary system was defined as the main target of SARS-CoV-2, but the mortality concept of this disease presented with more severe and systemic disease including shock, multi-organ failure, pyrexia resistant to treatment and acute lung injury with acute respiratory distress syndrome.[2]

The COVID-19 related fatality rate has been reported into a range between 2% and 20%, mainly depending on the availability of medical resources and economic status of the patient or country in general.[3] One of the most important issues in managing COVID-19 is the accurate and early identification of high-risk patients. Early risk stratification can help medical decision making and resource allocation; for example, transferring the high-risk patients to the intensive care unit (ICU) for close monitoring and organ support at the early stages of the disease could help to decrease the fatality rate. Although several studies have investigated the risk factors for fatality in COVID-19, a standardised systematic effort to develop prediction tools for risk stratification of the patients at an early stage would be needed.

The Centers for Disease Control and Prevention reported that although individuals older than age 65 years comprise 17% of the total population in the United States, they represent 31% of the COVID-19 infections, 45% of hospitalisations, 53% of ICU admissions and 80% of the deaths caused by COVID-19.[4] Wu et al showed that the case fatality rate (CFR) is 2.3% in general population; however, it increases to 8% in 70-80 years old and 14.8% in older than 80 years age group of patients.[5] The physiological changes during ageing, having multiple age-related comorbid conditions such as heart and lung diseases, diabetes, dementia and the increased incidence of polypharmacy, have been associated with poor outcomes in older patients.[6]

Together with the risk factors, several laboratory tests were consistently reported to be related to COVID-19 patient outcomes. For example, elevated C-reactive protein (CRP), creatinine, together with decreased lymphocyte count and reduced magnesium levels upon admission are proposed as the predictors of increased death in COVID-19.[7] In a recent study from our medical centre, Doganci et al showed that increased CRP, white blood cell (WBC) count and neutrophil-to-lymphocyte ratio and decreased prognostic nutritional index could be used as prognostic factors for in-hospital mortality rate of COVID-19 cases.[8]

The present study was designed to investigate the broad range of factors related to fatality rate in COVID-19 cases followed as inpatient in our medical centre. The primary endpoint of the present study is investigating the demographic, clinical and laboratory risk factors for fatality rate in hospitalised COVID-19 patients. The secondary endpoint is evaluating the effects of the applied treatments to the patient outcome. Finally, we aimed to find out the odds ratios (OR) by using multivariate logistic analysis for the selected variables in order to predict nonsurvival patient characteristics in our cohort.

What's known

- Adults over 65 years of age represent 80% of hospitalisations and have a 23-fold greater risk of death than those under 65 years.
- According to the current treatment protocol, favipiravir is accepted as one of several antiviral medications to be used immediately at the onset of symptoms.
- In vitro studies have demonstrated the capacity of azithromycin in reducing production of pro-inflammatory cytokines such as IL-8, IL-6, TNF alpha, reduce oxidative stress and modulate T-helper functions but not described in vivo studies.

What's new

- The presence of a cancer and the extended duration of intensive care unit treatment were the most significant risk factors for nonsurvival together with being older than 60 years.
- Azithromycin was determined as significantly reduced the death ratio in COVID-19 patients.

2 | METHODS

2.1 | Study design and participants

The present study was designed as a retrospective, comparative cohort study. Between 18 March and 15 May 2020, all the patients referred for COVID-19 disease and hospitalised in the Covid Clinics of Gulhane Training and Research Hospital in Ankara, Turkey, were enrolled in the present study. The diagnosis, treatment and management of the patients have been regulated with the valid guides edited and updated by the Science Board of Turkish Republic Ministry of Health since 21 January 2020. The third version of COVID-19 Treatment Guide edited on 11 March 2020 included up-to-date treatments such as suitable antiviral therapies (eg, oseltamivir, favipiravir, lopinavir and ritonavir), oxygen supply, anticoagulant treatmets, supportive medical therapies and indicated antibiotics such as azithromycin. According to this guide, the diagnosis of COVID-19 patients was verified either with a reverse transcription polymerase chain reaction (RT-PCR) test of SARS-CoV-2 virus or having relevant anamnesis, clinical symptoms and signs of typical pulmonary computerised tomography (CT) imaging (even though RT-PCR test is negative).[9] All CT scans were confirmed for the typical signs of

COVID-19 by a radiologist (FC). The typical image features include ground-glass opacities (GGO), consolidation, mixed GGO and consolidation, traction bronchiectasis, bronchial wall thickening, reticulation, subpleural bands and vascular enlargement. The present study was approved by Ankara Provincial Health Directorate (approval number: 2020-05-04T14_24_22) and The Ministry of Health, Gulhane Training and Research Hospital, Noninvasive Local Ethics Committee (approval number: 211/2020) on 19 May 2020. Informed consent was waived as determined by the institutional review board due to the retrospective study design. The study was conducted in accordance to the Declaration of Helsinki.

2.2 | Statistical analysis

The data were represented as the mean ± standard error of mean (SEM). Chi-square or Fisher's exact test was used for analysing the categorical variables and contingency tables. Kolmogrov–Smirnov test performed and the histograms were visually inspected to analyse normal distribution of the continuous variables. The continuous variables were compared for survived and nonsurvived groups by Student's *t* test or Mann–Whitney *U* test, where appropriate. The possible factors identified with univariate analyses were further evaluated by logistic regression analysis to determine the predictors of patient outcome (survival or nonsurvival). A backward elimination method was applied to have a reliable regression model. According to the results of the Wald test, individual parameters are examined, and the least significant effects that do not meet the $P < .2$ levels were removed. Then other probable predictors according to the current literature and clinical practice were added to the model as predictors. Hosmer–Lemeshow goodness of fit was used to assess the model fit. Statistical analyses were performed using the SPSS v.25 Software (IBM Corp., Armonk, NY). The statistical significance was set at $P < .05$. The Bonferroni correction was applied when multliple comparisons were made.

3 | RESULTS

Between 18 March and 15 May 2020, 767 patients were hospitalised with the diagnosis of COVID-19. There were a total of 59 deaths (fatality rate was 7.69%). Demographics, medical comorbidities, chronic drug use of the patients and applied treatments were compared according to the outcomes presented in Table 1. The gender distribution of the patients was similar, and gender had no effect on the outcome ($P > .05$; Table 1). The survived patients were significantly younger compared to nonsurvived patients ($P < .001$; average 50 vs. 74 years). Almost one third of all patients were over 60 years of age, and being in the older group was almost three times more common in the nonsurvived group ($P < .001$; 33% vs. 92%). Other factors such as body mass index (BMI), smoking status and being a health worker had no effect on the patient outcome (*P* values >.05). Hypertension (HT) and diabetes mellitus (DM) were the most frequently recorded comorbidities in the overall patient sample. The death rate was significantly increased in patients with a comorbid disease except asthma (Table 1). Amongst the administered treatments during the hospitalisation, only azithromycin significantly reduced the nonsurvival rate ($P < .001$; Table 1). On the other hand, the death rate seemed significantly increased in patients treated with favipiravir or an anticoagulant drug, possibly due to the differences in treatments according to the disease severity (*P* values <.05). The initial laboratory test results indicated highly significant differences according to the patient outcome (Table 2). In short, initial blood oxygen saturation percentage (SpO_2), haemoglobin and albumin levels were significantly lower; WBC, neutrophil count, aspartate transaminase (AST), alanine transaminase (ALT), urea, creatinine, Lactate dehydrogenase (LDH), potassium (K), lactate, CRP, erythrocyte sedimentation rate, procalcitonin (PCT), ferritin, D-dimer, troponin, N-terminal pro B-type natriuretic peptide (ProBNP) and fibrinogen levels were significantly higher in nonsurvived patients compared to the survivors.

A multifactor logistic regression analysis was performed to calculate the adjusted ORs for predicting patient outcome. Our logistic regression model covers the 92% of the sample and explains the outcome by 62.1%. The older age is the most prominent risk factor for nonsurvival in COVID-19 patients. Being older than 60 years increased the death risk with an adjusted OR of 7.2 (95% CI: 2.23-23.51; $P = .001$; Table 3). Other significant risk factors for nonsurvival were accompanied cancers and number of days spent in ICU (*P* values <.05). On the other hand, azithromycin treatment was determined as it significantly reduced the death ratio in these patients ($P = .002$; Table 3).

Further analyses showed that the most common cancer types in the patients were lung cancer (n = 9) and haematological cancers (n = 5). There was no significant effect of cancer type on survival (*P* values >.05). The half of the cancer patients were followed up at the Stage 4 disease. All the patients had chemotheraphy in the past, and 20 patients (49%) were in a current chemotherapy programme which has no significant effect on patient outcome ($P > .05$). We observed that the cancer patients had significantly more HT, DM, CVD and COPD (*P* values <.05).

4 | DISCUSSION

The fatality rate in hospitalised COVID-19 patients is varied across countries and affected by a lot of distinct measures. There are well-known risk factors, such as older age, accompanied comorbidities, and male gender for predicting fatal outcome and there is an ongoing effort to define more predictors. Also defining the interactions of independent predictors is important to use them in patient evaluation in the clinical setting. The current study had presented the clinical characteristics of the 767 hospitalised patients and defined the risk factors depending on 59 patients who did not survive. Our results showed that the most important risk factor for fatality in hospitalised COVID-19 patients is being older than 60 years old. Together with age, accompanying cancer and staying in ICU for a longer time

TABLE 1 Demographics, medical comorbidities, chronic drug use of the patients and applied treatments compared according to the outcome

	Total (%) or mean ± SEM	Survived (%)	Nonsurvived (%)	*P* value (adjusted)
Gender				.364
Female	339 (47.5)	315 (48.2)	24 (40.7)	
Male	374 (52.5)	339 (51.8)	35 (59.3)	
Mean age (years)	51.99 ± 0.75	49.97 ± 0.78	73.93 ± 1.67	<.001
≥60 years (count)	267 (37.4)	213 (32.6)	54 (91.5)	<.001
BMI	25.9 ± 0.16	25.9 ± 0.17	26.0 ± 0.63	.999
Smoking	80 (12.5)	77 (13.0)	3 (6.8)	.999
Health worker	20 (2.8)	20 (3.1)	0 (0)	–
ICU admission	91 (12.8)	35 (38.5)	56 (61.5)	<.001
Days in ICU	6.02 ± 0.59	4.46 ± 0.54	6.64 ± 0.85	<.001
Mechanical ventilation at ICU	50 (55.5)	4 (8)	46 (92)	<.001
PCR on admission				
(+)	349 (46.2)	328 (50.2)	21 (36.8)	.432
(–)	361 (45.8)	325 (49.8)	36 (63.2)	
Comorbidity				
DM	137 (19.2)	114 (17.4)	23 (39.0)	<.001
HT	220 (30.9)	185 (28.3)	35 (59.3)	<.001
Antihypertensive drug use	167 (75.9)	143 (77.3)	24 (68.6)	.999
ACI or ARB	86 (39.1)	78 (42.2)	8 (22.9)	.384
Diuretic	54 (24.5)	43 (23.2)	11 (31.4)	.999
ß Blocker	47 (21.4)	35 (18.9)	12 (34.3)	.462
Calcium channel blocker	83 (37.7)	75 (40.5)	8 (22.9)	.480
CVD-CCI	113 (15.8)	85 (13.0)	28 (47.5)	<.001
Chronic renal disease	29 (4.1)	20 (3.1)	9 (15.3)	<.001
COPD	43 (6.0)	31 (4.7)	12 (20.3)	<.001
Asthma	58 (8.1)	51 (7.8)	7 (11.9)	.628
Cancer	41 (5.8)	27 (4.1)	14 (22.7)	<.001
Neurological diseases	49 (6.9)	36 (5.5)	13 (22.0)	<.001
Treatments				
Chloroquine	636 (89.2)	588 (89.9)	48 (81.4)	.480
Azithromycin	542 (76.0)	512 (78.3)	30 (50.8)	<.001
Oseltamivir	392 (55.0)	366 (56.0)	26 (44.1)	.800
Anticoagulant	489 (68.6)	441 (67.4)	48 (81.4)	.364
Favipiravir	147 (20.6)	114 (17.4)	33 (55.9)	<.001

Abbreviations: ACI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CCI, cardiac insufficiency; COPD, chronic obstructive pulmonary disease; CVD, chronic vascular disease; DM, diabetes mellitus; HT, hypertension; ICU, intensive care unit.

significantly increased the nonsurvival rates. On the other hand, we showed that other comorbid diseases such as DM, HT, chronic vascular disease (CVD), chronic cardiac insufficiency (CCI), chronic renal disease, chronic obstructive pulmonary disease (COPD) and neurological diseases were more common in dying patients compared to the survived ones. But these comorbid conditions did not produce any significant effect on patient outcomes in the multivariate analysis. Amongst the used drugs in our sample, azithromycin was determined as the only drug that significantly improved the patient outcome.

Our study confirmed that older age is the prominent predictor of fatality in hospitalised COVID-19 patients. It was consistently shown

TABLE 2 Initial laboratory values (mean ± SEM) of the patients compared according to the outcome

	All	Survived	Died	*P* value
SpO_2	94.73 ± 0.18	95.41 ± 0.12	87.13 ± 1.33	<.001
WBC	7.00 ± 0.16	6.66 ± 0.13	10.89 ± 1.2	<0001
Neutrophil count	5.51 ± 0.71	5.24 ± 0.77	8.61 ± 1.1	<.001
Lymphocyte count	1.42 ± 0.74	1.43 ± 0.03	1.25 ± 0.15	.228
Hemoglobin	13.28 ± 0.07	13.36 ± 0.07	12.40 ± 0.33	**.001**
Platelet count	225.15 ± 3.21	226.49 ± 3.31	209.56 ± 12.74	.533
Eosin count	37.02 ± 3.33	36.67 ± 3.45	43.42 ± 13.6	.999
AST	33.51 ± 39.1	30.82 ± 1.00	63.58 ± 13.29	**.017**
ALT	28.28 ± 30.7	27.32 ± 1.01	39.61 ± 8.23	**.003**
Urea	37.43 ± 0.98	33.11 ± 0.7	84.88 ± 6.28	<.001
Creatinine	1.00 ± 0.02	0.95 ± 0.02	1.57 ± 0.13	<.001
Albumin	3.75 ± 0.02	3.83 ± 0.02	3.00 ± 0.09	<.001
LDH	276.57 ± 5.92	259.35 ± 4.36	459.42 ± 47.79	<.001
NA^+	137.56 ± 0.22	137.79 ± 0.15	136.74 ± 0.91	.443
K^+	4.18 ± 0.02	4.16 ± 0.02	4.41 ± 0.11	**.046**
Mg^{++}	1.94 ± 0.02	1.93 ± 0.03	2.00 ± 0.07	.999
Ca^{++}	9.09 ± 0.12	9.2 ± 0.13	8.28 ± 0.11	.443
Lactate	2.39 ± 0.19	2.13 ± 0.15	3.20 ± 0.62	<.001
CRP	46.32 ± 2.63	38.64 ± 2.4	129.39 ± 13.23	<.001
Sedimentation	43.90 ± 1.42	42.37 ± 1.44	59.50 ± 6.1	**.046**
PCT	0.96 ± 0.25	0.32 ± 0.07	7.29 ± 2.55	<.001
Ferritin	227.19 ± 18.32	196.04 ± 15.29	435.62 ± 93.64	**.012**
d-dimer	1.44 ± 0.13	1.14 ± 0.11	3.74 ± 0.62	<.001
Troponin	82.61 ± 32.25	38.9 ± 26.31	520.68 ± 234.91	<.001
ProBNP	4412.60 ± 759.94	2757.40 ± 653.65	9709.23 ± 2169.44	<.001
Fibrinogen	406.23 ± 8.84	397.73 ± 9.09	469.57 ± 30.42	.046

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CRP, C-reactive protein; LDH, lactate dehydrogenase; PCT, procalcitonin; SEM, standard error of mean; WBC, white blood cell.

TABLE 3 Multivariate logistic regression analysis of the variables for predicting the patient outcome

	Odds ratio (adjusted)	95% CI	*P*
Age (≥60 years)	7.235	2.23-23.505	**.001**
Cancer	3.824	1.34-10.94	.012
Days in ICU	1.743	1.47-2.07	<.0001
Azithromycin	0.267	0.12-0.62	.002
Sex	2.050	0.89-4.74	.093
DM	1.975	0.81-4.83	.136
CVD-CCI	1.538	0.63-3.73	.342
Favipiravir	1.348	0.52-3.53	.543
Anticoagulant	0.728	0.34-2.57	.896
COPD	0.972	0.32-3.03	.972
PCR test positive at admission	0.898	0.37-2.21	.814
HT	0.889	0.35-2.28	.807

Abbreviations: CCI, cardiac insufficiency; COPD, chronic obstructive pulmonary disease; CVD, chronic vascular disease; DM, diabetes mellitus; HT, hypertension; ICU, intensive care unit.

that age alone was by far the most significant risk factor for death due to COVID-19. Adults over 65 years of age represent 80% of hospitalisations and have a 23-fold greater risk of death than those under 65.[10] Usually, the increased number and severity of comorbid diseases in an aged population were held responsible for increased death rates. However, our multivariate analysis indicated that only cancer had a significant effect on outcome although DM, HT, CVD/CCI, chronic renal disease, COPD and neurological diseases were significantly more common in nonsurvived patients. Thus, comorbid diseases alone may not explain why age is a risk factor for deaths. Mueller et al proposed that ineffective regulation and gradual deterioration of the immune system (immunosenescence) in the elderly may lead to poor patient outcomes.[10] Their theory describes not only the inability of the immune system for clearing SARS-CoV-2 virus but also increased propensity for the cytokine storm in COVID-19 disease. Thus, the older patients need more intense medical care and treatment support during the hospitalisation.

Our multivariate analysis showed that days spent in ICU is a strong predictor for the poor patient outcome (OR = 1.7; 95% CI: 1.47-2.07; $P < .0001$). The mean number of days spent in ICU was 6.6 days in nonsurvived patients (compared to 4.5 days in survivors). In the present study, the ICU admission criteria consisted of having either of the following signs: respiratory rate >29 per minute, the ratio of arterial oxygen partial pressure (PaO_2 in mm Hg) to fractional inspired oxygen (FiO_2) (PaO_2/FiO_2) < 300, SpO_2 < 90% or PaO_2 < 70 mm Hg despite 5 L/min O_2 treatment, hypotension (systolic blood pressure<90 mm Hg and a decrease from usual systolic blood pressure more than 40 mm Hg, mean arterial pressure <65 mm Hg, heart rate >100 beats/minute, lactate >2 mmol, acute kidney damage, acute liver function test disorder, patients with immunosuppression and development of acute organ dysfunction and acute bleeding diathesis. Reports highlight the high incidences of death rate in critically ill patients transferred to ICU because of COVID-19 disease. An early study including more than 72 000 cases from China reported the CFR as 2.3%, but it increased to 49% in 2087 critically ill patients who needed ICU conditions.[11] Other studies from China and the United States showed that the fatality rate in ICU transferred patients were 62% and 67%, respectively.[12] In the present study, 91 patients were transferred to ICU, and 56 (61.5%) of them did not survive, which is very close to the reported ratios. New treatment options should be developed to decrease these high death rates observed in ICU-transferred patients. Also rearranging the ICU treatment protocols for shortening the ICU stay time could be evaluated, and the cases that exceed the 7 days at ICU should be treated according to the higher fatality risk. Another approach could be transferring the high-risk patients to the ICU at an early stage of the disease. Thus, assessing the predictors for high-risk patients at an early stage and/or adjusting the ICU-transferring criteria for COVID-19 should be evaluated.

We presented that the rate of comorbid diseases, except asthma, significantly increased in nonsurvived patients. However, multivariate analysis revealed that only cancer has a significant effect on poor prognosis. Jianfeng et.al stated that HT was the most common chronic comorbidity amongst COVID-19 patients who nonsurvived.[13] A retrospective study including 191 cases from Wuhan area by Zhou et al showed that 48% of COVID-19 patients had at least one comorbidity, with HT being the most common (30%), followed by DM (19%) and CVD (8%).[14] Our study cohort has very similar comorbidity rates for HT (30.9%) and DM (19.2%), but it has almost two times more CVD rates (15.8%). Resembling our results, Zhou et al showed that having a comorbidity did not have any significant effect on death rates in multivariate analysis, although they were more common in nonsurvived patients in univariate analysis. Interestingly, their cohort comprised only two cases with cancer, both in the survived group.[14] A recent study covering 31 461 confirmed COVID-19 cases from the United States revealed the impact of comorbid conditions on poor outcome in a multivariate analysis.[15] They show that having a comorbid condition significantly increased death. However, when the patients were stratified according to their age groups, only the history of myocardial infarction and renal disease was associated with higher odds of death for all age groups. This approach, stratifying patients according to age seems reasonable to better estimate the impact of comorbidities. However, it could only be performed in large cohorts.

In the present study, cancer is one of the important predictors for death in COVID-19 patients. Our cohort included 41 cancer patients in total (5.8%); 5 of them had haematological malignancy. We combined this group with the solid tumours group during the analyses. A recent systematic review study pooled the result of 52 studies, involving a total of 18 650 patients with both COVID-19 and cancer; a total of 4243 deaths were recorded in this population. The probability of death was calculated as 25.6% (95% CI: 22.0%-29.5%) in this patient population.[16] A meta-analysis covering 13 studies reporting the 2922 hospitalised cancer patients with COVID-19 disease found the 30-day mortality rate as 30% (95% CI: 25%-35%).[17] A prospective study analysed 800 cancer patients with COVID-19 infection and found the fatality rate as 28%. Further analyses indicated that fatality risk was associated with older age, being male and the presence of other comorbidities such as HT and CVD. Moreover, receiving cytotoxic chemotherapy but not immunotherapy, hormonal therapy, targeted therapy or radiotherapy use within the past 4 weeks before testing positive for COVID-19 significantly increased death rates.[18] Our results did not indicate a significant effect of current chemotherapy treatment on patient outcome. However, increased comorbidities in cancer patients such as HT and DM could have an impact on the increased mortality rates. Future studies should investigate how different tumour subtypes, different treatment regimes and more specific timing of anticancer treatments have an impact on the management of COVID-19 infection in cancer patients.

Interestingly, amongst the chronic comorbid diseases observed in the present study, only asthma did not produce a significant increase in death rate even in the univariate analysis. Our study cohort comprised 8.1% of asthmatic patients. Other studies with larger cohorts reported asthma prevalence as 14.5% amongst 17,535 cases in the United Kingdom[19] and 9.4% of 7272 cases in Korea.[20] On the other hand, a study from New York area reported asthma

prevalence as 4.3% in 6245 COVID-19 confirmed cases,[21] and it was even reported as low as 2.1% of 2000 patients in Italy.[22] From the early days of COVID-19 pandemic, patients with asthma attracted attention for disease severity because they were expected to be adversely affected by such a devastating respiratory syndrome. However, large-scale analyses surprisingly did not completely support that expectation. For example, UK study reported a high prevalence of asthma in their cohorts, but their analyses showed that nonasthmatic COPD but not asthma related with mortality rates in hospitalised patients.[19] Similarly, the New York study did not show any significant association between asthma and COVID-19 related in-hospital mortality rates, both in univariate analysis and multivariate analysis adjusted for age, sex, race and COVID-19. A literature review included 15 studies (n = 30 496) and data from local hospitals (n = 436) showed that asthma prevalence amongst the hospitalised COVID-19 patients was similar to asthma prevalence in the population. Asthma also did not appear to be an independent risk factor for intubation amongst these patients, even after adjusting for BMI and age, which are well-known risk factors for severity.[23] Izquierdo et al followed a different approach and analysed the 71 182 patient records with asthma in Spain.[24] They showed that COVID-19 prevalence was 1.41% amongst asthmatic patients, which seems slightly higher than the general population without asthma in the same demographical area (ie, 0.89%), but the manifestation of COVID-19 in asthmatic patients was not severe, with the low rate of hospital admissions. Our study confirmed those large-scale studies. Several factors were proposed to explain the lower prevalence of asthma in COVID-19 patients.[25] For instance, having asthma might protect against COVID-19, perhaps through a different immune response elicited by the chronic disease itself. The previous observations regarding the lower risk associated with rhinitis and eczema in asthma patients were associated with allergic sensitisation, and it was linked to lower expression of ACE-2 receptors in both upper and lower respiratory airways suggesting a potential protective effect.[26] Another possibility is that the therapies used by asthmatic patients could reduce the risk of infection or of developing symptoms leading to diagnosis. In in vitro models, inhaled corticosteroids alone or in combination with bronchodilators were shown to suppress coronavirus replication and cytokine production.[27] Depending on large-scale clinical data, Izquierdo et al concluded that intranasal corticosteroids may decrease the COVID-19 related hospitalisation rate in asthma, and biologics, such as omalizumab and mepolizumab, could be effective in preventing hospitalisations and reducing the death rates in this patient group, even these drugs were used at more severe asthma cases.[21] Prospective clinical studies for testing those observations and better understanding these relationships would be beneficial for developing better preventive approaches and/or treatments.

The biochemical characteristics of the patients measured during initial admission showed significant differences according to their clinical outcome and fatality rate. We tried to create an independent linear regression model for predicting several different clinical outcomes such as length of hospital stays by using laboratory variables. We also tried data transformation approaches, coding the variables as high or low according to their laboratory or calculated cut-off values using receiver operating characteristic curve analysis. But we could not create any valid model because of high variability; thus, we performed only univariate analyses on biochemical variables. Our findings showed that several biochemical parameters during the initial hospital admission could reflect the patient outcome. Previously, the SpO_2 cutoff value was calculated as 90.5% (yielded 84.6% sensitivity and 97.2% specificity) for prediction of survival of COVID-19 patients[28]; our results for SpO_2 as 87.13% in nonsurvived versus 95.41% in survived patients fit this study. Moreover, increased lactate levels in nonsurvivors in the present study could reflect the poor oxygenation in tissues. Blood lactate abnormality has not been widely emphasised in clinical evaluation of COVID-19 patients, but it could be an important factor for indicating organ dysfunction. A recent study measured blood lactate levels on ICU admission and thereafter daily up to 14th day in 45 patients with confirmed COVID-19 pneumonia. Based on 28-day ICU mortality rates, mean daily lactate levels were higher in nonsurvivors, and initial blood lactate was proposed as an independent outcome predictor in ICU-admitted COVID-19 patients.[29]

An increase in LDH has been one of the most replicated laboratory tests in COVID-19. LDH is a marker of various inflammatory states, for example, infections, myocardial infarction MI, sepsis or cardio-pulmonary concession and possibly vascular permeability in immune-mediated lung injury.[30] A systematic review and meta-analysis, including 28 studies comprised 1704 severe and 5088 nonsevere patients, verified the usefulness of LDH as a patient severity predictor in COVID-19 cases.[31] We showed that LDH levels in nonsurvivors were almost two times higher than the survived patients (459 ± 48 vs. 259 ± 4 U/L), and our results support the relationship between increased LDH levels and poor outcome in COVID-19 patients.

Our results were in line with other laboratory test results observed as the indicators of poor prognosis such as, decreased blood albumin levels,[32] decreased hemoglobin,[33] increased ALT and AST,[34] increased urea and creatinine,[35] increased WBC, neutrophil count, CRP levels,[36] highly increased d-dimer[37] and ferritin.[38] In addition to these widely replicated predictors for poor outcome, we observed extremely increased proBNP and troponin levels in nonsurvived patients. In the present study, mean troponin levels increased twofolds in survivors, but in nonsurvivors the increase was 29-folds. For proBNP, we also observed a threefold increase in survivors compared to a 10-fold increase in nonsurvivors. These two parameters indicate myocardial stress and damage. They are frequently elevated amongst patients with severe respiratory illnesses typically in the presence of heart failure, and they are associated with an unfavourable course amongst the COVID-19 patients.[39] Recently, a cohort of 872 confirmed COVID-19 cases was evaluated for cardiac markers, and increased troponin and proBNP levels during initial admission were found as independent and complementary predictors of mortality or the need for mechanical ventilation.[40] That study reported a high prevalence (34.6%) of cardiac injury in COVID-19 patients and

showed that proBNP improved the prognostic accuracy of troponin for the patient outcome. Together with our results, these studies imply that the measurement of biomarkers for cardiac damage, such as troponin and proBNP, during the initial admission may help to identify a subset of patients with a high risk of poor prognosis.

The multivariate analysis indicated that only azithromycin, but not chloroquine, favipiravir, oseltamivir and anticoagulant treatments, significantly improved the patient outcome. The treatments were administered according to the 3rd version of Covid Treatment Guide edited on 11 March 2020 by the Ministry of Health Science Board of Turkey.[9] Together with the fifth version of the treatment guide, high doses of low molecular weight heparin (LMWH) have been administered at an early stage of COVID-19 disease.[41] A previous study from our medical centre investigated the effectiveness of the new treatment algorithm; and using higher than usual doses of LMWH treatment at an early stage of COVID-19 was shown to shorten the length of hospital stay and significantly decreased the ICU transfer rate of the patients.[32] During the time course of the present study, anticoagulants were being used at regular doses and at exacerbated stages of the disease, and we did not find any significant effect of anticoagulant treatment in the present study. Thus, further updates of the treatment guide for regulating the use of anticoagulants seemed to have a significant effect on patient outcome.

Currently, azithromycin is not prescribed to COVID-19 patients according to the treatment guide. However, there are several reports and reviews supporting our observation that azithromycin could be effective in COVID-19. Azithromycin is a macrolide antibiotic, and it is widely used in respiratory tract infections. However, it is also known to have immunomodulating and antiviral properties.[42] Its antiviral activity has been shown in vitro and/or in vivo on a large panel of viruses such as Ebola, Zika, respiratory syncytial virus, influenza H1N1 virus, enterovirus and rhinovirus.[43] In vitro studies have demonstrated the capacity of azithromycin in reducing the production of pro-inflammatory cytokines such as IL-8, IL-6, TNF alpha, reduce oxidative stress and modulate T-helper functions.[44] From the safety perspective, azithromycin was suspected of inducing cardiotoxicity in COVID-19 treatment; further studies indicated azithromycin alone was not associated with a higher risk of adverse events, unlike hydroxychloroquine and its combination with azithromycin.[45] However, investigating the effectiveness of azithromycin in COVID-19 deserves further studies.

Favipiravir is a purine base analogue, selective and potent inhibitor of RNA polymerase of RNA viruses. After RNA viral incorporation, favipiravir-RTP works as a mutagen for coronavirus repair machinery and reduces the number of viral RNA and infectious particles. Viral shedding in SARS-CoV-2 may be seen 1-2 days before symptom onset and may continue beyond 2 weeks in severe cases.[46] A retrospective cohort study in 678 hospitalised COVID-19 patients showed that high viral load was independently associated with mortality and intubation.[47] Thus, early administration of favipiravir should be highly important to achieve a significant effect on viral replication. Our study did not show a significant effect of favipiravir on survival rates of the patients in multivariate analysis. In univariate analysis, favipiravir treated patients were significantly higher in the nonsurvived group, probably because it was prescribed for only severe patients according to the treatment protocol effective during the time period that study performed. According to the current treatment protocol, favipiravir is accepted as one of several antiviral medications to be used immediately at the onset of symptoms.

The present study should be evaluated under several limitations. First, the study was designed as a retrospective cohort study in a single-centre setting; thus, the data were not collected a priori fashion, and we could not evaluate all variables for all the patients. Second, the treatment protocol approved by the Turkish Ministry of Health has been updated several times since the study data were collected, and the results reflect the conditions relatively early and limited time frame of the pandemic. Of note, not all the patients were initially confirmed using PCR test, and the decision to include clinically diagnosed COVID-19 cases was supported by a radiological imaging test, namely, CT scans of lungs.

5 | CONCLUSIONS

The present study confirms that being older than 60 years is the major risk factor for poor outcome in COVID-19 disease. In our sample, more than 90% of the nonsurvived patients were older than 60 years old. Recent observations indicate that the fatality rate is decreasing compared to the initial months of the COVID-19 pandemic. The fast response of the health systems, sharing the scientific information globally and fast, seems to be contributed to the reduction of fatality rates. We also showed that all mentioned comorbidities, except asthma, were more common amongst the nonsurvivors. Multivariate logistic regression analysis revealed that accompanied cancer and length of ICU stay, in addition to being older than 60 years, are the additional risk factors for predicting fatality rate in hospitalised COVID-19 patients. The prominent solution for the COVID-19 pandemic seems to vaccinate more than half of the world population. During that period, patients with high risk for nonsurvival, defined as being older than 60 years and accompanied cancer patients should be immediately evaluated for early diagnosis and current treatments.

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CONFLICT OF INTEREST

All the authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

YA is the guarantor of the content of the manuscript, including the data and analysis. YA, CT, NO, AK and DD designed and performed research; HK analysed the data; YA and HK wrote the manuscript;

YA, DD, NO, AK, TA, RO, FY, MNE., SK, EK, US, FC, GF, GY, NKS, SB, SS and CT collected the data; all the authors (YA, DD, NO, AK, TA, RO, FY, MNE., SK, EK, US, FC, GF, GY, NKS, SB, SS, CT and HK) approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. *Coronavirus Update (Live): 112,336,160 Cases and 2,487,236 Deaths from COVID-19 Virus Pandemic*. Vol 1. 1st ed. Worldometer. 2021:1–111. https://www.worldometers.info/coronavirus/. Accessed February 23, 2021.
2. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in critically ill patients in the seattle region—case series. *N Engl J Med*. 2020;382(21):2012-2022. https://doi.org/10.1056/nejmoa2004500
3. Kranjac AW, Kranjac D. Decomposing differences in coronavirus disease 2019-related case-fatality rates across seventeen nations. *Pathog Glob Health*. 2021;115(2):100-107. https://doi.org/10.1080/20477724.2020.1868824
4. Levi M, Scully M. How I treat disseminated intravascular coagulation. *Blood*. 2018;131(8):845-854. https://doi.org/10.1182/blood-2017-10-804096
5. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18(4):844-847. https://doi.org/10.1111/jth.14768
6. Cangemi R, Casciaro M, Rossi E, et al. Platelet activation is associated with myocardial infarction in patients with pneumonia. *J Am Coll Cardiol*. 2014;64(18):1917-1925. https://doi.org/10.1016/j.jacc.2014.07.985
7. Alamdari NM, Afaghi S, Rahimi FS, et al. Mortality risk factors among hospitalized COVID-19 patients in a major referral center in Iran. *Tohoku J Exp Med*. 2020;252(1):73-84. https://doi.org/10.1620/tjem.252.73
8. Doganci S, Ince ME, Ors N, et al. A new COVID-19 prediction scoring model for in-hospital mortality: experiences from turkey, single center retrospective cohort analysis. *Eur Rev Med Pharmacol Sci*. 2020;24(19):10247-10257. https://doi.org/10.26355/eurrev_202010_23249
9. Turkish Republic Ministry of Health Science Board 3 Rd. Treatment Management of Adult Covid-19 Patients. *MEDICAL GUIDE OF COVID-19 (SARS-CoV2 INFECTIOUS)*. Treatment Management of Adult Covid-19 Patients. Vol 3. 1st ed. Ankara, Turkey: The Science Board of Covid-19 Disease; 2020:1–32.
10. Mueller AL, Mcnamara MS, Sinclair DA. Why does COVID-19 disproportionately affect older people? *Aging*. 2020;12(10):9959-9981. https://doi.org/10.18632/aging.103344
11. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323(13):1239-1242. https://doi.org/10.1001/jama.2020.2648
12. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020;8(5):475-481. https://doi.org/10.1016/S2213-2600(20)30079-5
13. Xie J, Tong Z, Guan X, Du B, Qiu H. Clinical characteristics of patients who died of coronavirus disease 2019 in China. *JAMA Netw open*. 2020;3(4):e205619 https://doi.org/10.1001/jamanetworkopen.2020.5619
14. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062. https://doi.org/10.1016/S0140-6736(20)30566-3
15. Harrison SL, Fazio-Eynullayeva E, Lane DA, Underhill P, Lip GYH. Comorbidities associated with mortality in 31,461 adults with COVID-19 in the United States: a federated electronic medical record analysis. *PLoS Med*. 2020;17(9):1-11. https://doi.org/10.1371/JOURNAL.PMED.1003321
16. Saini KS, Tagliamento M, Lambertini M, et al. Mortality in patients with cancer and coronavirus disease 2019: a systematic review and pooled analysis of 52 studies. *Eur J Cancer*. 2020;139:43-50. https://doi.org/10.1016/j.ejca.2020.08.011
17. Desai A, Gupta R, Advani S, et al. Mortality in hospitalized patients with cancer and coronavirus disease 2019: a systematic review and meta-analysis of cohort studies. *Cancer*. 2021;127(9):1459-1468. https://doi.org/10.1002/cncr.33386
18. Lee LYW, Cazier J-B, Angelis V, et al. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. *Lancet*. 2020;395(10241):1919-1926. https://doi.org/10.1016/S0140-6736(20)31173-9
19. Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO clinical characterisation protocol: prospective observational cohort study. *BMJ*. 2020;369:1-12. https://doi.org/10.1136/bmj.m1985
20. Lee SC, Son KJ, Han CH, Jung JY, Park SC. Impact of comorbid asthma on severity of coronavirus disease (COVID-19). *Sci Rep*. 2020;10(1):1-9. https://doi.org/10.1038/s41598-020-77791-8
21. Lieberman-Cribbin W, Rapp J, Alpert N, Tuminello S, Taioli E. The impact of asthma on mortality in patients with COVID-19. *Chest*. 2020;158(6):2290-2291. https://doi.org/10.1016/j.chest.2020.05.575
22. Caminati M, Vultaggio A, Matucci A, et al. Asthma in a large COVID-19 cohort: prevalence, features, and determinants of COVID-19 disease severity. *Respir Med*. 2021;176:106261 https://doi.org/10.1016/j.rmed.2020.106261
23. Broadhurst R, Peterson R, Wisnivesky JP, et al. Asthma in COVID-19 hospitalizations: an overestimated risk factor? *Ann Am Thorac Soc*.

2020;17(12):1645-1648. https://doi.org/10.1513/annalsats.202006-613rl
24. Izquierdo JL, Almonacid C, González Y, et al. The impact of COVID-19 on patients with asthma. *medRxiv*. 2020. https://doi.org/10.1101/2020.07.24.20161596
25. Halpin DMG, Faner R, Sibila O, Badia JR, Agusti A. Do chronic respiratory diseases or their treatment affect the risk of SARS-CoV-2 infection? *Lancet Respir Med*. 2020;8(5):436-438. https://doi.org/10.1016/S2213-2600(20)30167-3
26. Jackson DJ, Busse WW, Bacharier LB, et al. Association of respiratory allergy, asthma, and expression of the SARS-CoV-2 receptor ACE2. *J Allergy Clin Immunol*. 2020;146(1):203-206.e3. https://doi.org/10.1016/j.jaci.2020.04.009
27. Yamaya M, Nishimura H, Deng X, et al. Inhibitory effects of glycopyrronium, formoterol, and budesonide on coronavirus HCoV-229E replication and cytokine production by primary cultures of human nasal and tracheal epithelial cells. *Respir Investig*. 2020;58(3):155-168. https://doi.org/10.1016/j.resinv.2019.12.005
28. Xie J, Covassin N, Fan Z, et al. Association between hypoxemia and mortality in patients with COVID-19. *Mayo Clin Proc*. 2020;95(6):1138-1147. https://doi.org/10.1016/j.mayocp.2020.04.006
29. Vassiliou AG, Jahaj E, Ilias I, et al. Lactate kinetics reflect organ dysfunction and are associated with adverse outcomes in intensive care unit patients with covid-19 pneumonia: preliminary results from a greek single-centre study. *Metabolites*. 2020;10(10):1-12. https://doi.org/10.3390/metabo10100386
30. Danese E, Montagnana M. An historical approach to the diagnostic biomarkers of acute coronary syndrome. *Ann Transl Med*. 2016;4(10):194. https://doi.org/10.21037/atm.2016.05.19
31. Szarpak L, Ruetzler K, Safiejko K, et al. Lactate dehydrogenase level as a COVID-19 severity marker. *Am J Emerg Med*. 2020;4:11-12. https://doi.org/10.1016/j.ajem.2020.11.025
32. Arslan Y, Yilmaz G, Dogan D, et al. The effectiveness of early anticoagulant treatment in Covid-19 patients. *Phlebology*. 2021;36(5):384-391. https://doi.org/10.1177/0268355520975595
33. Cavezzi A, Troiani E, Corrao S. COVID-19: hemoglobin, iron, and hypoxia beyond inflammation. a narrative review. *Clin Pract*. 2020;10(2):24-30. https://doi.org/10.4081/cp.2020.1271
34. Ali N. Relationship between COVID-19 infection and liver injury: a review of recent data. *Front Med*. 2020;7:1-6. https://doi.org/10.3389/fmed.2020.00458
35. Benedetti C, Waldman M, Zaza G, Riella LV, Cravedi P. COVID-19 and the kidneys: an update. *Front Med*. 2020;7:1-13. https://doi.org/10.3389/fmed.2020.00423
36. Zhao Y, Nie H-X, Hu KE, et al. Abnormal immunity of non-survivors with COVID-19: predictors for mortality. *Infect Dis Poverty*. 2020;9(1):1-10. https://doi.org/10.1186/s40249-020-00723-1
37. Yao Y, Cao J, Wang Q, et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. *J Intensive Care*. 2020;8(1):1-11. https://doi.org/10.1186/s40560-020-00466-z
38. Gómez-Pastora J, Weigand M, Kim J, et al. Hyperferritinemia in critically ill COVID-19 patients—is ferritin the product of inflammation or a pathogenic mediator? *Clin Chim Acta*. 2020;509:249-251. https://doi.org/10.1016/j.cca.2020.06.033
39. Bangalore S, Sharma A, Slotwiner A, et al. ST-Segment elevation in patients with Covid-19—a case series. *N Engl J Med*. 2020;382(25):2478-2480. https://doi.org/10.1056/nejmc2009020
40. Li X, Lai W. Letter to the editor. *Angle Orthod*. 2020;90(4):619. https://doi.org/10.2319/0003-3219-90.4.619
41. Turkish Republic Ministry of Health Science Board 5th. Treatment Management of Adult Covid-19 Patients. *MEDICAL GUIDE OF COVID-19 (SARS-CoV2 INFECTIOUS)*. Treatment Management of Adult Covid-19 Patients. Vol 5. 5th ed. Ankara, Turkey: Turkish Republic Ministry of Health Science Board; 2020:1–98.
42. Pani A, Lauriola M, Romandini A, Scaglione F. Macrolides and viral infections: focus on azithromycin in COVID-19 pathology. *Int J Antimicrob Agents*. 2020;56:106053 https://doi.org/10.1016/j.ijantimicag.2020.106053
43. Bleyzac N, Goutelle S, Bourguignon L, Tod M. Azithromycin for COVID-19: more than just an antimicrobial? *Clin Drug Investig*. 2020;40(8):683-686. https://doi.org/10.1007/s40261-020-00933-3
44. Lin SJ, Kuo ML, Hsiao HS, Lee PT. Azithromycin modulates immune response of human monocyte-derived dendritic cells and Cd4+ T cells. *Int Immunopharmacol*. 2016;40:318-326. https://doi.org/10.1016/j.intimp.2016.09.012
45. Echeverría-Esnal D, Martin-Ontiyuelo C, Navarrete-Rouco ME, et al. Azithromycin in the treatment of COVID-19: a review. *Expert Rev Anti Infect Ther*. 2021;19(2):147-163. https://doi.org/10.1080/14787210.2020.1813024
46. Joshi S, Parkar J, Ansari A, et al. Role of favipiravir in the treatment of COVID-19. *Int J Infect Dis*. 2020;102:501-508. https://doi.org/10.1016/j.ijid.2020.10.069
47. Magleby R, Westblade LF, Trzebucki A, et al. Impact of severe acute respiratory syndrome coronavirus 2 viral load on risk of intubation and mortality among hospitalized patients with coronavirus disease 2019. *Clin Infect Dis*. 2020 Jun 30. https://doi.org/10.1093/cid/ciaa851. [Epub ahead of print]

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