RESEARCH

THE PREDICTORS OF IN-HOSPITAL MORTALITY IN HYPERTENSIVE ELDERLY INTENSIVE CARE UNIT PATIENTS WITH CORONAVIRUS DISEASE 2019

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Abstract

Introduction: Advanced age is an important prognostic indicator for the mortality of coronavirus disease 2019, especially in patients over 65. Patients with chronic underlying conditions such as hypertension showed the worst outcomes. This study aimed to identify predictors of mortality in elderly hypertensive patients hospitalized in intensive care units.

Materials and Methods: Demographic, clinical, treatment, and laboratory data were extracted from electronic medical records and compared between survivors and non-survivors. Univariate and multivariate logistic regression methods were used to explore the indicators of in-hospital mortality.

Results: One hundred and ninety-eight patients with a median age of 75 years (65–94 years) were included in this study, of whom 95 were discharged from the intensive care units, and 103 died. Shortness of breath [hazard ratio (HR): 1.65, 95% confidence interval (CI): 1.04–2.61, p: 0.034], C-reactive protein (CRP)/albumin ratio (>51.32) (HR: 1.83, 95% CI: 1.12–2.97, p: 0.015), serum creatinine (>1.62 mg/dl) (HR: 2.04, 95% CI: 1.13–3.33, p: 0.001), aspartate transaminase (>34 u/l) (HR: 1.99, 95% CI: 1.28–3.09, p: 0.002), D-dimer (>781 ng/ml) (HR: 1.59, 95% CI: 1.04–2.43, p: 0.031), leukocyte (>12,000´ 10^3/µl) (HR: 1.68, 95% CI: 1.09–2.59, p: 0.018) and lymphocyte count, (≤660´ 10^3/µl) (HR: 1.76, 95% CI: 1.17–2.63, p: 0.006) were independent predictors for mortality in elderly hypertensive patients.

Conclusion: Using these predictors with cut-off values can identify patients at risk of death and needing aggressive intervention earlier in the disease course.

Keywords: Aged; COVID-19; Hypertension; Mortality; Patient admission; Prognosis.

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INTRODUCTION

The 2019 novel coronavirus disease (COVID-19), which emerged in December 2019 and was declared a pandemic in March 2020, remains a global public health concern. There is a wide spectrum of clinical presentations, ranging from asymptomatic status to respiratory failure requiring respiratory support to death. Specifically, older patients (>65 years) with comorbidities are at high risk of death, and older age may independently predict 60-day mortality after admission to the intensive care unit (ICU) (1, 2).

Several studies have shown that hypertension may be associated with a poor prognosis in COVID-19 (3-5). It has been reported that after adjusting for confounders, compared with non-hypertensive patients, hypertensive patients continue to have a two-fold increased risk of COVID-19 mortality (6). Nevertheless, the fact that hypertension is often associated with advanced age and other cardiovascular diseases in the general population and that this condition may contribute to COVID-19 causes its independent role to be debated. There is insufficient data on the factors determining prognosis, especially in elderly patients with hypertensive COVID-19.

This study aimed to identify predictors of in-hospital mortality among older hypertensive patients with COVID-19 by investigating the potential prognostic roles of age, gender, COVID-19 related symptoms, comorbidities, and specific laboratory markers on admission.

MATERIALS AND METHODS

Study design and participants

The training cohort participants were consecutive patients diagnosed with COVID-19 by at least two positive nasopharyngeal or oropharyngeal SARS-CoV-2 reverse-transcriptase-polymerase-chain-reaction tests (SARS-CoV-2 (2019-nCoV) with a qPCR Detection Kit and Bio-Speedy) in the Manisa Merkezefendi State Hospital (Pandemic Hospital). Among these patients, those aged ≥ 65 years who were diagnosed with hypertension before hospitalization, it was noted that at least one antihypertensive drug was used, and they were followed up in the ICU and were included in the study. Indications for ICU hospitalization were determined according to the COVID-19 treatment guideline of the Republic of Turkey Ministry of Health. Indications included uncontrollable fever, respiratory rate > 30/minutes, severe respiratory distress, SpO2 < 90% on room air, bilateral multilobar ground-glass opacities, intense consolidations on computed tomography, and need for mechanical ventilation due to respiratory failure. All data were extracted from the electronic medical records of patients hospitalized between April 1st, 2020, and December 31st, 2020. One hundred and ninety-eight patients with an outcome (discharged or dead) were enrolled in the study.

The study protocol was approved by the Manisa Celal Bayar University Clinical Research Ethics Committee (Decision No.85252386-050.04.04.04) and followed the Declaration of Helsinki. Written informed consent was not obtained because the data were anonymous, and the study was observational. However, patients or relatives were verbally informed that their data would be used anonymously for medical studies, and their permission was obtained.

Process of data extraction

We obtained demographic data, epidemiological characteristics, clinical features, disease severity, laboratory tests, and treatment results from the medical record system. Hypertension and treatment were stratified according to medical history or medications administered prior to infection. The laboratory data of patients within the first 24 h after admission to the hospital were evaluated. Data were collected and analyzed once all included patients died or were discharged from the ICU.

Statistical Analyses

Statistical analyses were performed using SPSS Statistics version 26.0 (IBM Corp. Released 2019.

IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). Figures were constructed using GraphPad Prism version 8.0.0 for Windows (GraphPad Software, San Diego, California, USA, www.graphpad.com). Categorical variables were summarized using frequencies and proportions and compared using Pearson's chi-square or Fisher's exact test in cases where applicable conditions were unmet. The Shapiro-Wilk test was used to check whether the continuous variables were normally distributed. Continuous variables were reported as mean values ± standard deviations (SD) or medians (minimum-maximum) for non-normally distributed data and compared using Student's t-test or the non-parametric Mann-Whitney U test. The predictive value of the variables was evaluated by measuring the area under the receiver operating characteristic (ROC) curve. The optimal threshold value for clinical stratification (cut-off value) was obtained by calculating the Youden index. The Kaplan–Meier method was used for univariate survival analysis, and the log-rank test was used to assess the statistical significance between the survival curves of the models. All variables with p values of ≤ 0.20 from the Cox univariate analyses were entered into a multivariate analysis using the backward stepwise Cox regression model. We considered a p-value < 0.05 as statistically significant for all analyses.

RESULTS

During the study period, 489 COVID-19 patients hospitalized in the ICU were evaluated. Of these, 307 were aged ≥65 years. Among the 307 patients, 198 diagnosed with hypertension and using at least one antihypertensive drug were included in the study. The baseline demographic and clinical characteristics of all participants at admission are presented in Table 1 based on ICU survival. The median age of the non-survivor group was significantly higher than that of the survivor group (77 vs. 74 years, p = 0.002). While 55.3% of the non-survivor group was male, 38.9% of the survivor group was male (P = 0.021). The prevalence of symptoms on admission, such as fever, headache, diarrhea, fatigue, muscle ache, or taste dysfunction, was also similar between the two groups. However, shortness of breath was more common among the non-survivors. Shortness of breath was the most common symptom in all the patients (62.6%). In contrast, cough and chest pain were more common among survivors. Renal failure was more common in the non-survivors than in the survivors (41.7% vs. 21.1%, p = 0.002). However, there were no statistically significant differences between the hemodialysis groups. However, the incidence of diabetes mellitus was twice as high in the survivors (42.1% vs. 20.4%, p = 0.001). The other comorbid conditions were similar in both groups. While 97.1% of the non-survivors required invasive mechanical ventilation, this rate was 48% in the survivor group (p < 0.001). Non-survivors had a shorter length of in-ICU stay than survivors did. The median length of stay in the intensive care unit for non-survivors was 8 (min-max, 1–33) days, while the median stay in the intensive care unit for survivors was 14 (min-max, 5–37) days (p < 0.001).

Laboratory parameters and medications used are listed in Table 1. Higher urea, serum creatinine, uric acid, aspartate transaminase, alanine transaminase, D-dimer, troponin, ferritin, leukocyte, CRP, and CRP/albumin ratios were the laboratory parameters measured in non-survivors. Albumin and lymphocyte levels were lower in the non-survivors than in the survivors. The use of angiotensin-converting enzyme (ACE)/angiotensin-receptor blockers (ARB) class drugs for antihypertensive treatment was higher in the survivor group (71.6% vs. 56.3%, p:0.026). In addition, the use of dihydroxycalcium canal blockers was higher in the survivor group (46.6% vs. 31.6%, p = 0.031). Both groups were similar in beta-blockers, non-dihydroxycalcium canal blockers, and aldosterone antagonists. It was observed that more favipiravir, immunosuppressive agents, and steroids were used in non-survivors than survivors during their stay in the intensive care unit.

Table 1. Baseline characteristics, laboratory parameters and medications of study population.

	Total (n:198)	Elder Hypertensive Survivors (n:95)	Elder Hypertensive Non-Survivors (n:103)	p-value
Age, years	75.0 (65.0-94.0)	74.0 (65.0-89.0)	77.0 (65.0-94.0)	**0.002**
Gender (male), n (%)	94 (47.5)	37 (38.9)	57 (55.3)	**0.021**
Body mass index, kg/m^2	24.9 (18.2-35.4)	25.3 (18.3-35.0)	24.4 (18.2-35.4)	0.245
Systolic blood pressure, mmHg	114.5 (70.0-196.0)	145.0 (75.0-190.0)	144.0 (70.0-196.0)	0.452
Diastolic blood pressure, mmHg	87.5 (30.0-126.0)	88.0 (45.0-126.0)	87.0 (30.0-120.0)	0.309
Symptoms at admission, n (%)				
Fever	109 (55.1)	52 (54.7)	57 (55.3)	0.932
Cough	59 (29.8)	35 (36.8)	24 (23.3)	**0.037**
Shortness of breath	124 (62.6)	49 (51.6)	75 (72.8)	**0.002**
Headache	9 (4.5)	5 (5.3)	4 (3.9)	0.641
Diarrhoea	17 (8.6)	12 (12.6)	5 (4.9)	0.051
Fatigue, tiredness	15 (7.6)	11 (11.6)	4 (3.9)	0.041
Palpitation	5 (2.5)	2 (2.1)	3 (2.9)	0.718
Muscle ache	20 (10.1)	12 (12.6)	8 (7.8)	0.256
Sore throat	5 (2.5)	3 (3.2)	2 (1.9)	0.672
Chest pain	5 (2.5)	5 (5.3)	0 (0.0)	**0.024**
Inability to taste	7 (3.5)	6 (6.3)	1 (1.0)	0.057
Comorbidities, n (%)				
Diabetes Mellitus	61 (30.8)	40 (42.1)	21 (20.4)	**0.001**
Anemia	51 (25.8)	21 (22.1)	30 (29.1)	0.259
Renal failure	63 (31.8)	20 (21.1)	43 (41.7)	**0.002**
Dialysis	20 (10.1)	6 (6.3)	14 (13.6)	0.090
Coronary Artery Disease	46 (23.3)	19 (20.0)	27 (26.2)	0.301
Peripheral vascular disease	4 (2.0)	4 (4.2)	0 (0.0)	0.051
Chronic heart failure (HFrEF)	24 (12.1)	10 (10.5)	14 (13.6)	0.509
COPD	33 (16.7)	15 (15.8)	18 (17.5)	0.750
Hyperlipidemia	21 (10.6)	12 (12.6)	9 (8.7)	0.374
Malignancy	11 (5.6)	4 (4.2)	7 (4.2)	0.427
CVA/TIA	19 (9.6)	8 (8.4)	11 (10.7)	0.590
Smoking	28 (14.1)	12 (12.6)	16 (15.5)	0.558
Invasive mechanic ventilation, n (%)	115 (58.1)	15 (48.0)	100 (97.1)	**<0.001**
Length of in-ICU stay (days)	10.0 (1.0-37.0)	14.0 (5.0-37.0)	8.0 (1.0-33.0)	**<0.001**

Laboratory parameters					
	Urea, mg/dl	65 (18-398)	54 (18-258)	85 (27-398)	**<0.001**
	Serum creatinine, mg/dl	1.1 (0.4-7.7)	0.9 (0.4-6.6)	1.3 (0.4-7.7)	**<0.001**
	Serum potassium, mmol/l	4.2 (2.6-7.2)	4.1 (2.6-6.3)	4.2 (2.8-7.2)	0.165
	Serum calcium, mg/dl	8.3 ± 0.7	8.4 ± 0.7	8.3 ± 0.8	0.342
	Uric acid, mg/dl	6.1 (1.8-66)	5.6 (2.1-15.6)	6.9 (1.8-66)	**0.022**
	Albumin, g/dl	3.3 (1.8-4.3)	3.5 ± 0.4	3.1 ± 0.5	**<0.001**
	Aspartate transaminase, u/l	34 (9-1190)	26 (9-296)	39 (14-1190)	**<0.001**
	Alanine transaminase, u/l	23 (2-1100)	20 (2-473)	25 (6-1100)	**0.004**
	D-dimer, ng/ml	718.5 (150-53286)	469 (150-3946)	1123 (150-53286)	**<0.001**
	Troponin, ng/ml	0.014 (0.002-12.769)	0.006 (0.002-12.769)	0.059 (0.002-1.969)	**<0.001**
	Ferritin ng/ml	411.7 (11.7-1661.3)	262.9 (11.7-1650)	625.5 (24.5-1661.3)	**<0.001**
	Haemoglobin, g/dl	11.3 ± 1.9	11.4 ± 1.9	11.2 ± 2	0.205
	Leukocyte, $x10^3/\mu l$	11200 (2800-45900)	9600 (2800-39300)	13400 (3400-45900)	**<0.001**
	Lymphocyte, $x10^3/\mu l$	980 (110-4040)	1120 (310-3380)	810 (110-4040)	**0.003**
	C-reactive protein (CRP), mg/dl	184.7 (30.5-414.2)	151.9 ± 719	220.5 ± 81.8	**<0.001**
	CRP/Albumin ratio	54.5 (7.8-170.3)	40 (7.8-126.8)	68 (9.1-170.3)	**<0.001**
Medications, n (%)					
	Acetylsalyclic acid	96 (48.5)	48 (46.6)	48 (50.5)	0.581
	Clopidogrel	26 (13.1)	11 (11.6)	15 (14.6)	0.535
	ACE-I / ARB	126 (63.6)	68 (71.6)	58 (56.3)	**0.026**
	Beta-blocker	59 (29.8)	26 (27.4)	33 (32.0)	0.473
	Dihidro-Calcium canal blockers	78 (39.4)	30 (31.6)	48 (46.6)	**0.031**
	Non-Dihidro-Calcium canal blockers	8 (4.0)	4 (4.2)	4 (3.9)	1.000
	Aldosterone antagonists	16 (8.1)	7 (7.4)	9 (8.7)	0.724
	Statin	20 (10.1)	12 (12.6)	8 (7.8)	0.256
	Hydroxychloroquine	192 (97.0)	93 (97.9)	99 (96.1)	0.684
	Azithromycin	131 (66.2)	61 (64.2)	70 (68.0)	0.577
	Favipiravir	117 (59.1)	49 (51.6)	68 (66.0)	**0.039**
	Immunosuppressive agent or steroid	77 (38.9)	30 (31.6)	47 (45.6)	**0.043**

Data are presented as the mean ± standard deviation or median (minimum-maximum) for continuous variables and as counts (%) for categorical variables.

HFrEF, heart failure with reduced ejection fraction; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; TIA, transient ischemic attack, ACE-i: Angiotensin-Converting Enzyme Inhibitor, ARB: Angiotensin Receptor Blocker

Statistically significant p values are shown in bold

Univariate associations between the baseline clinical characteristics and mortality are shown in Table 2. Mortality was higher in patients with hypertension aged > 81 years, with a median survival time of 10 days. On the other hand, it was determined that gender did not significantly affect survival. It was observed that 54.38% of the deaths in men and 58.69% in women occurred during the first 10 days of ICU follow-up. Furthermore, shortness of breath is associated with mortality, whereas cough is associated with survival. Interestingly, diabetes mellitus was associated with half-decreased mortality risk (hazard ratio (HR), 0.49; 95%CI, 0.33–0.74, p = 0.002). On the other hand, mortality was found to be 2.38 times higher in the presence of renal failure (p < 0.001). However, dialysis had no significant effect on the mortality rate.

The cut-off values of the laboratory parameters are listed in Figure 2. The best power to predict mortality was found for the serum CRP/albumin ratio, with an AUC of 0.77, followed by aspartate transaminase, troponin, C-reactive protein, and the other laboratory parameters. In the univariate analysis, the HRs for death during hospitalization was significantly higher for patients with concentrations of all evaluated tests, except for albumin and lymphocytes above the selected cut-offs (Table 2).

In the multivariate analysis, Shortness of breath (HR: 1.65, 95% CI: 1.04–2.61, p: 0.034), CRP/albumin ratio (>51.32) (HR: 1.83, 95% CI: 1.12–2.97, p: 0.015), serum creatinine (>1.62 mg/dl) (HR: 2.04, 95% CI: 1.13–3.33, p: 0.001), aspartate transaminase (>34 u/l) (HR: 1.99, 95% CI: 1.28–3.09, p: 0.002), D-dimer (>781 ng/ml) (HR: 1.59, 95% CI: 1.04–2.43, p: 0.031), leukocyte (>12,000 x10^3/µl) (HR: 1.68, 95% CI: 1.09–2.59, p: 0.018) and lymphocte, (≤660´ 10^3/µl) (HR: 1.76, 95% CI: 1.17–2.63, p: 0.006) were independent predictors for mortality in elderly hypertensive patients (Table 3).

DISCUSSION

COVID-19 patients over 65 are more likely to die (7, 8). Comorbidities can also significantly affect the prognosis of COVID-19. Hypertension plays a special role. Hypertension has also been reported in several studies and is a common underlying condition (9, 10). A meta-analysis by Tian et al. observed that hypertension increased the probability of death from COVID-19 by more than 2.5 times (11). Although there are data from many subgroups of COVID patients, we aimed to reveal the predictors of mortality in hypertensive patients aged ≥ 65 years who were followed up in the ICU. This retrospective cohort study identified several risk factors for death in elderly hypertensive adults hospitalized with COVID-19. In our study, 62.78% of the patients in the ICU were aged ≥ 65 years, and hypertension was present in 64.49% of the patients. A higher median age may explain our study's higher prevalence of hypertension. The fact that the cohort was composed of ICU patients is also a contributing factor. Although the number of male patients was significantly higher in the non-survivor group, we did not observe any significant association between mortality and sex.

The most common presenting symptom in the deceased patients was shortness of breath, an independent predictor of mortality in our study. Ghweil et al. reported a significant positive association between shortness of breath and COVID-19 progression to severe illness and death (12). Additionally, a meta-analysis reported similar findings and recommended dyspnea rather than fever as an indicator of poor outcomes in COVID-19 patients (13). The presence of shortness of breath at presentation may indicate extensive pulmonary involvement. The fact that cough has been observed less frequently in deceased patients and is associated with survival supports the speculation that a lack of a cough reflex may promote worse infection in elderly patients (14).

In our study, histories of renal failure and serum creatinine levels were significantly higher in patients who died than in those who survived. Such patients are known to have a proinflammatory state with functional defects in innate and adaptive immune cell populations and are at a higher risk of upper respiratory tract infection and pneumonia (15). In contrast, serum creatinine level at a cut-off of 1.62 mg/dl was an independent predictor of mortality. Furthermore, the risk of death doubled in patients with a serum creatinine value > 1.62 mg/dl. These data suggest that the kidneys may be a potential target in patients with COVID-19 (16). The novel coronavirus uses angiotensin-converting enzyme 2 (ACE2) as its cell-entry receptor. Recent RNA sequencing data of human tissues have shown that ACE2 expression in the kidney is approximately 100-fold higher than in the lungs (17). Therefore, deterioration in renal function may be caused by the entry of coronaviruses into kidney cells via an ACE2-dependent pathway. Renal involvement due to hypertension can cause this process to enter a vicious circle.

In the present study, serum levels of both ALT and AST were significantly higher, and serum levels of albumin were significantly lower in non-surviving patients. Additionally, we reported that elevated serum ALT and AST levels and low serum albumin levels were significantly associated with mortality. Still, only the AST level (>34 u/l) was an independent predictor of mortality. There is a strong and reasonable relationship between abnormal liver biochemistry and SARS-CoV-2 infection severity (18). It is unclear whether a liver injury results directly from a viral infection, due to potentially hepatotoxic drugs, or as a part of multi-organ dysfunction in COVID-19. Unlike ALT, AST can be released from the cardiac and body muscles and the liver. The fact that AST level is an independent predictor of mortality suggests that it may also reflect muscle and heart attitudes. Bloom et al. noted that an AST-dominant aminotransferase elevation is common in COVID-19, reflecting disease severity and appears to reflect true hepatic injury. Additionally, they found that AST levels correlated with markers of muscle injury, including lactate dehydrogenase and creatine kinase (19).

The CRP/albumin ratio is a newly defined, simple, useful, and inexpensive systemic inflammatory marker that combines the CRP and albumin levels. Several previous studies have demonstrated the prognostic value of CAR in COVID-19 patients (20, 21). We found that the 51.32 cut-off CRP/albumin ratio was an independent prognostic biomarker of mortality in our study population. Similar to our study, Güney et al. reported that CRP/albumin was significantly elevated compared to that in the non-severe group and that CRP/albumin was an independent risk factor for COVID-19 mortality (20). When the patients were divided into three groups according to their CRP/albumin levels from low to high, they found that the mortality in the highest group was 12.6 times higher than that in the lowest group. Our study found that mortality was 1.83 times higher, and the median survival time was 3 times less in patients with a CRP/albumin level above 51.32.

Abnormal D-dimer levels are thought to indicate hypercoagulation rather than consumptive coagulopathy. Hyperfibrinogenemia has been suggested to lead to fibrin polymerization, thrombus formation, and complications or adverse outcomes (22). Several studies have demonstrated the role of D-dimer as an effective predictor of COVID-19 mortality. Various thresholds for D-dimer values have been proposed, with most values ranging between 1000 and 2500 ng/mL (23, 24). However, we observed higher sensitivity and specificity at values below 1000 ng/mL, and the Youden index was maximum at 781 ng/mL. This study found that D-dimer levels of > 781 ng/mL were independently associated with fatal COVID-19 outcomes.

A wide range of hematologic parameter abnormalities have been reported with different disease severities, but marked changes were more com-

Tablo 2. Univariate association of baseline clinical characteristics and laboratory parameters to mortality in elder hypertensive COVID-19 patients

		Mortality n, (%)	Median Survival (days)	Hazard ratio	%95 CI	p-value (log rank)
Age, years	≤81 (n:151)	68 (45%)	19	2.13	1.31-3.48	<0.001
	>81 (n:47)	35 (74.5%)	10			
Gender	Male (n:94)	57 (60.6%)	13	0.74	0.50-1.10	0.127
	Female (n:104)	46 (44.2%)	19			
Body mass index, kg/m2	>27.92 (n:61)	23 (37.7%)	19	1.48	0.97-2.26	0.082
	≤27.92 (n:137)	80 (58.4%)	14			
Symptoms at admission						
Cough	Absent (n:139)	79 (56.8%)	13	0.52	0.35-0.79	0.004
	Present (n:59)	24 (40.7%)	20			
Shortness of breath	Absent (n:74)	28 (37.8%)	20	1.79	1.20-2.65	0.005
	Present (n:124)	75 (60.5%)	13			
Diarrhoea	Absent (n:181)	98 (54.1%)	15	0.55	0.27-1.10	0.175
	Present (n:17)	5 (29.4%)	-			
Fatigue, tiredness	Absent (n:183)	99 (54.1%)	15	0.42	0.21-0.83	0.071
	Present (n:15)	4 (26.6%)	-			
Comorbidities						
Diabetes Mellitus	Absent (n:137)	82 (59.8%)	14	0.49	0.33-0.74	0.002
	Present (n:61)	21 (34.4%)	26			
Renal failure	Absent (n:135)	60 (44.4%)	19	2.38	1.50-3.77	<0.001
	Present (n:63)	43 (68.2%)	9			
Dialysis	Absent (n:178)	89 (50%)	15	1.62	0.82-3.20	0.080
	Present (n:20)	14 (70%)	9			
Malignancy	Absent (n:187)	96 (51.3%)	16	1.92	0.68-5.38	0.079
	Present (n:11)	7 (63.6%)	11			
Coronary Artery Disease	Absent (n:152)	76 (50%)	17	1.40	0.86-2.27	0.116
	Present (n:46)	27 (58.7%)	12			

Laboratory parameters						
Urea, mg/dl	≤67 (n:105)	38 (36.2%)	21	2.56	1.72-3.80	<0.001
	>67 (n:93)	65 (69.9%)	11			
Serum creatinine, mg/dl	≤1.62 (n:139)	59 (42.4%)	19	2.84	1.76-4.57	<0.001
	>1.62 (n:59)	44 (74.5%)	8			
Serum potassium, mmol/l	≤5.1 (n:181)	88 (48.6%)	19	3.75	1.45-9.68	<0.001
	>5.1 (n:17)	15 (88.2%)	7			
Uric acid, mg/dl	≤5.6 (n:85)	36 (42.3%)	20	1.75	1.19-2.58	<0.005
	>5.6 (n:113)	67 (59.3%)	12			
Albumin, g/dl	≤3.2 (n:90)	63 (70%)	12	1.96	1.33-2.90	<0.001
	>3.2 (n:108)	40 (37%)	19			
Aspartate transaminase, u/l	≤34 (n:103)	33 (32%)	25	2.46	1.67-3.62	<0.001
	>34 (n:95)	70 (73.7%)	11			
Alanine transaminase, u/l	≤15 (n:58)	20 (34.5%)	26	1.66	1.08-2.54	0.033
	>15 (n:140)	83 (59.3%)	14			
D-dimer, ng/ml	≤781 (n:112)	40 (35.7%)	25	2.45	1.65-3.65	<0.001
	>781 (n:86)	63 (73.2%)	11			
Troponin, ng/ml	≤0.008 (n:78)	21 (26.7%)	26	2.49	1.68-3.70	<0.001
	>0.008 (n:120)	82 (68.3%)	12			
Ferritin ng/ml	≤496 (n:109)	38 (34.9%)	21	2.10	1.43-3.10	<0.001
	>496 (n:89)	65 (73%)	12			
Leukocyte, $x10^3/\mu l$	≤12,000 (n:108)	38 (35.2%)	26	2.30	1.55-3.40	<0.001
	>12,000 (n:90)	65 (72.2%)	11			
Lymphocyte, $x10^3/\mu l$	≤660 (n:58)	41 (70.7%)	11	1.82	1.18-2.83	<0.005
	>660 (n:140)	62 (44.3%)	19			
C-reactive protein (CRP), mg/dl	≤185.2 (n:100)	33 (33%)	25	2.62	1.78-3.82	<0.001
	>185.2 (n:98)	70 (71.4%)	11			
CRP/Albumin ratio	≤51.32 (n:88)	25 (28.4%)	33	2.93	1.9-4.32	<0.001
	>51.32 (110)	78 (70.1%)	11			

Only variables with p values of ≤0.20 are presented in the table

CI: confidence ınterval

Table 3. Cox regression analysis (backwards stepwise model) summarizing significant independent prognostic factors for mortality in elder hypertensive COVID-19 patients

Variable	Hazard Ratio	95% CI	p-value
Shortness of breath	1.65	1.04-2.61	0.034
CRP/Albumin ratio, (>51.32)	1.83	1.12-2.97	0.015
Serum creatinine, (>1.62 mg/dl)	2.04	1.33-3.13	0.001
Aspartate transaminase, (>34 u/l)	1.99	1.28-3.09	0.002
D-Dimer, (>781 ng/ml)	1.59	1.04-2.43	0.031
Leukocyte, (>12,000 x10^3/µl)	1.68	1.09-2.59	0.018
Lymphocte, (≤660 x10^3/µl)	1.76	1.17-2.63	0.006

CRP: C-reactive protein

Figure 1. Receiver operator characteristics curves to obtain cut-off values for parameters used in the multivariate analysis. (A) CRP/Albumin ratio, (B) Serum creatinine, (C) Aspartate transaminase, (D) D-dimer, (E) Leukocyte, (F) Lymphocyte

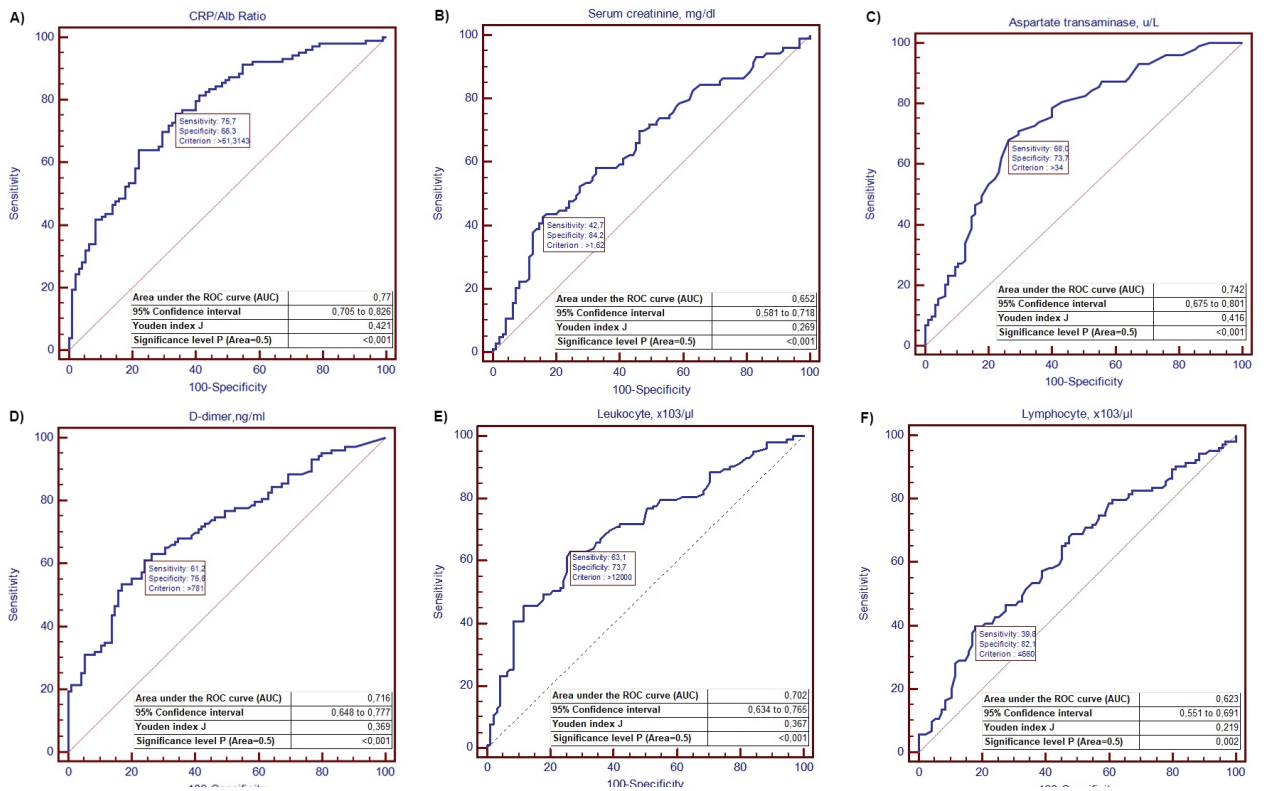
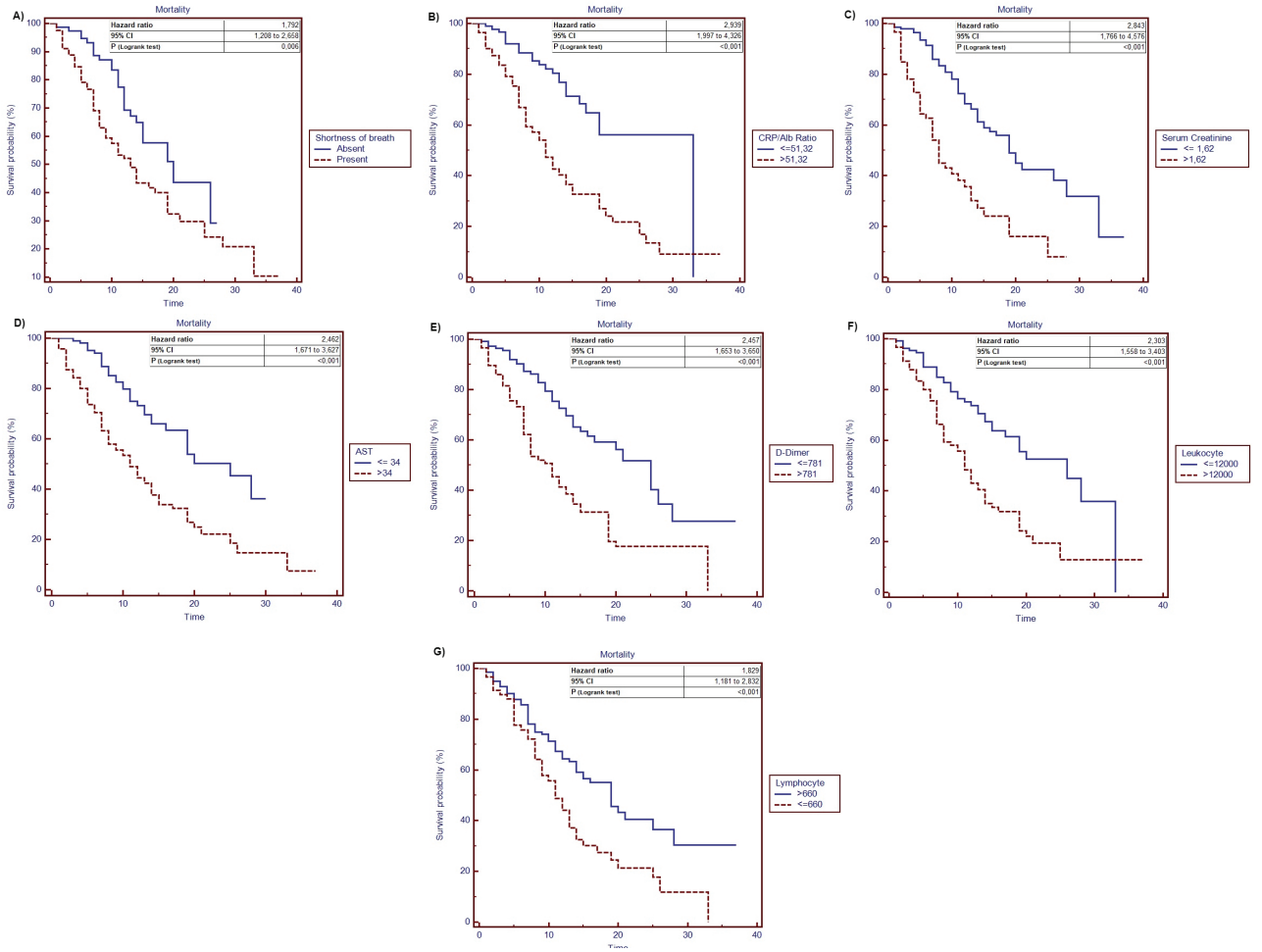


Figure 2. Kaplan–Meier survival curves for mortality from the time of intensive care unit admission. (A) Shortness of breath, (B) CRP/Albumin ratio (>51.32), (C) Serum creatinine (>1.62 mg/dl), (D) Aspartate transaminase (>34 u/l), (E) D-Dimer (>781 ng/ml, (F) Leukocyte (>12,000 x10^3/µl), (G) Lymphocte, (≤660 x10^3/µl). The timeline is expressed in days.



monly seen in samples from severe and critically ill patients. Our study observed that patients who died had significantly higher leukocyte and lymphocyte levels than survivors. Patients with severe and fatal disease have been shown to have significantly higher leukocyte and lower lymphocyte counts than non-serious diseases or survivors (25). We determined leukocyte levels > 12,000 x 10^3/µl as an independent predictor of mortality. Very low lymphocyte count (≤ 660 x 10^3/µl) was an independent predictor. The decrease in lymphocyte count is best explained by the role of both CD4 and CD8 T lymphocytes in eliminating virus-infected cells, and this is consistent with low lymphocyte counts being associated with poor case outcomes.

Limitations

Our study has some limitations. First, the data were collected from a single pandemic hospital and

cannot be generalized to all other regions. Second, due to the retrospective study design, the impact of selection bias cannot be completely ruled out. Third, not all laboratory tests were performed on all patients (lactate dehydrogenase, interleukin-6, and serum ferritin). Therefore, their role in predicting in-hospital mortality may have been underestimated. However, these limitations did not affect the reliability of the overall results. Finally, the data in this study permits a short-term assessment of the clinical outcomes of elderly hypertensive patients hospitalized in the intensive care unit. However, long-term prospective studies are needed, including patients who are followed-up and treated in the ward or as outpatients.

CONCLUSIONS

In the current study, hypertensive patients aged ≥ 65 years hospitalized for COVID-19 had high in-hospital mortality rates. The results of this study suggest that shortness of breath levels and some laboratory parameters may represent invaluable aids in identifying patients with a higher risk of mortality. In addition, these parameters can serve as a guide for clinicians in the early identification and management of at-risk patients.

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REFERENCES

1. Xu J, Yang X, Yang L, et al. Clinical course and predictors of 60-day mortality in 239 critically ill patients with COVID-19: a multicenter retrospective study from Wuhan, China. Critical care (London, England). 2020;24(1):394. (PMID: 32631393).
2. 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. The Lancet Respiratory medicine. 2020;8(5):475-81. (PMID: 32105632).
3. Iaccarino G, Grassi G, Borghi C, Ferri C, Salvetti M, Volpe M. Age and Multimorbidity Predict Death Among COVID-19 Patients: Results of the SARS-RAS Study of the Italian Society of Hypertension. Hypertension (Dallas, Tex : 1979). 2020;76(2):366-72. (PMID: 32564693).
4. Semenzato L, Botton J, Drouin J, et al. Chronic diseases, health conditions and risk of COVID-19-related hospitalization and in-hospital mortality during the first wave of the epidemic in France: a cohort study of 66 million people. The Lancet regional health Europe. 2021;8:100158. (PMID: 34308411).
5. Thakur B, Dubey P, Benitez J, et al. A systematic review and meta-analysis of geographic differences in comorbidities and associated severity and mortality among individuals with COVID-19. Scientific reports. 2021;11(1):8562. (PMID: 33879826).
6. Gao C, Cai Y, Zhang K, et al. Association of hypertension and antihypertensive treatment with COVID-19 mortality: a retrospective observational study. Eur Heart J. 2020;41(22):2058-66. (PMID: 32498076).
7. Zheng Z, Peng F, Xu B, et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. The Journal of infection. 2020;81(2):e16-e25. (PMID: 32335169).
8. Le Borgne P, Dellenbach Q, Alame K, et al. The Impact of Age on In-Hospital Mortality in Critically Ill COVID-19 Patients: A Retrospective and Multicenter Study. Diagnostics (Basel, Switzerland). 2022;12(3). (PMID: 35328219).
9. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel medicine and infectious disease. 2020;34:101623. (PMID: 32179124).
10. Hu Y, Sun J, Dai Z, et al. Prevalence and severity of corona virus disease 2019 (COVID-19): A systematic review and meta-analysis. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology. 2020;127:104371. (PMID: 32315817).
11. Tian W, Jiang W, Yao J, et al. Predictors of mortality in hospitalized COVID-19 patients: A systematic review and meta-analysis. Journal of medical virology. 2020;92(10):1875-83. (PMID: 32441789).

12. Ghweil AA, Hassan MH, Khodeary A, et al. Characteristics, Outcomes and Indicators of Severity for COVID-19 Among Sample of ESNA Quarantine Hospital's Patients, Egypt: A Retrospective Study. Infection and drug resistance. 2020;13:2375-83. (PMID: 32765012).

13. Shi L, Wang Y, Wang Y, Duan G, Yang H. Dyspnea rather than fever is a risk factor for predicting mortality in patients with COVID-19. The Journal of infection. 2020;81(4):647-79. (PMID: 32417316).

14. Chinnadurai R, Ogedengbe O, Agarwal P, et al. Older age and frailty are the chief predictors of mortality in COVID-19 patients admitted to an acute medical unit in a secondary care setting- a cohort study. BMC geriatrics. 2020;20(1):409. (PMID: 33066750).

15. Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney international. 2020;97(5):829-38. (PMID: 32247631).

16. Sun J, Zhu A, Li H, et al. Isolation of infectious SARS-CoV-2 from urine of a COVID-19 patient. Emerging microbes & infections. 2020;9(1):991-3. (PMID: 32342724).

17. Li Z, Wu M, Yao J, et al. Caution on Kidney Dysfunctions of COVID-19 Patients. 2020:2020.02.08.20021212. (PMID: 35255789).

18. Zhu C, Sun B, Zhang X, Zhang B. Research Progress of Genetic Structure, Pathogenic Mechanism, Clinical Characteristics, and Potential Treatments of Coronavirus Disease 2019. Front Pharmacol. 2020 Aug 27;11:1327. (PMID: 32973534)

19. Bloom PP, Meyerowitz EA, Reinus Z, et al. Liver Biochemistries in Hospitalized Patients With COVID-19. Hepatology (Baltimore, Md). 2021;73(3):890-900. (PMID: 32415860).

20. Güney B, Taştan Y, Doğantekin B, et al. Predictive Value of CAR for In-Hospital Mortality in Patients with COVID-19 Pneumonia: A Retrospective Cohort Study. Archives of medical research. 2021;52(5):554-60. (PMID: 33593616).

21. Karakoyun I, Colak A, Turken M, et al. Diagnostic utility of C-reactive protein to albumin ratio as an early warning sign in hospitalized severe COVID-19 patients. International immunopharmacology. 2021;91:107285. (PMID: 33348293).

22. Spiezia L, Boscolo A, Poletto F, et al. COVID-19-Related Severe Hypercoagulability in Patients Admitted to Intensive Care Unit for Acute Respiratory Failure. Thrombosis and haemostasis. 2020;120(6):998-1000. (PMID: 32316063).

23. 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. Journal of intensive care. 2020;8:49. (PMID: 32665858).

24. Poudel A, Poudel Y, Adhikari A, et al. D-dimer as a biomarker for assessment of COVID-19 prognosis: D-dimer levels on admission and its role in predicting disease outcome in hospitalized patients with COVID-19. PloS one. 2021;16(8):e0256744. (PMID: 34437642).

25. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clinical chemistry and laboratory medicine. 2020;58(7):1021-8. (PMID: 32286245).