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Cardiovascular drugs and analysis of potential risk factors associated with mortality in severe coronavirus disease 2019 patients

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SUMMARY

OBJECTIVES: Cardiovascular diseases are also considered to increase the risk of death in COVID-19 patients. However, real-world data concerning the risk factors for death in patients with severe COVID-19 still remain vague. This study aimed to identify the potential risk factors associated with mortality in severe COVID-19 patients.

METHODS: All consecutive patients admitted to the intensive care unit (ICU) of our institute for COVID-19 for severe COVID-19 pneumonia from April 1, 2020 to July 20, 2020 were included in the analysis. Patient characteristics, including complete medical history and comorbid diseases, blood test results during admission and on day 7, and clinical characteristics were compared between survivors and nonsurvivors.

RESULTS: There was no significant difference between survivors and nonsurvivors regarding age, gender, and preexisting cardiovascular diseases. Moreover, the rate of the medications including angiotensin-converting enzyme (ACE) inhibitor and angiotensin receptor blockers did not differ between survivors and nonsurvivors. The peak C-reactive protein (CRP), procalcitonin, fibrinogen, and D-dimer levels and the rate for chronic renal failure were significantly higher in nonsurvivors compared with survivors. Intubated patients had a higher risk of death than the others had.

CONCLUSIONS: This study failed to demonstrate a significant difference in preexisting cardiovascular diseases and cardiovascular medications between survivors and nonsurvivors who were admitted to ICU for severe COVID-19. Our findings indicate that the presence of chronic renal failure, a high peak ferritin concentration, and the need for invasive mechanical ventilation appear predictive for mortality. We propose that these risk factors should be taken into account in defining the risk status of severe COVID-19 patients admitted to the ICU.

KEYWORDS: COVID-19. Cardiovascular drugs. Potential risk factors. Renal failure. Intubation.

INTRODUCTION

A few cases of acute respiratory distress syndrome (ARDS) accompanying pneumonia with unknown etiology have been observed in Wuhan, China in late 2019[1]. Although the course of the disease was favorable in some of the cases, noninvasive and invasive mechanical ventilations were required in serious cases in whom fever and fatigue were the predominant symptoms[2]. A novel coronavirus, named 2019-nCoV by the World Health Organization (WHO), was identified in the throat swab samples of subjects[3]. After the rapid spread of the confirmed cases, it was defined as the outbreak by the WHO. Then, the International Committee on Taxonomy of Viruses decided to rename the virus as the SARS-CoV-2[4]. Since around October 3, 2020, it has been recorded that more than 35 million people were infected and 1 million deaths were recorded worldwide due to COVID-19[5]. The lung is the main target organ for COVID-19 and causes pneumonia; however, novel data indicate that COVID-19 is a systemic disease, which presents with gastrointestinal and neurological disorders, renal failure, and some cardiologic and pulmonary problems[6]. Certain populations including immunocompromised individuals, those with pulmonary disease, diabetes, and being above 65 years are regarded as the higher risk group during COVID-19[7]. Cardiovascular diseases are also considered to raise the mortality risk in COVID-19 cases[8]. However, real-world data about the risk factors for mortality in COVID-19 still remain unproved.

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In this study, we aimed to find out the possible risk factors related to mortality and the impact of preexisting cardiovascular diseases and medications on mortality in hospitalized COVID-19 cases.

METHODS

This cohort study was comprised of the patients admitted to the intensive care unit (ICU) for severe COVID-19 pneumonia from April 1, 2020 to July 20, 2020, who were included in retrospective analysis. Demographic and clinical characteristics, comorbid diseases, and daily blood test results were recorded. COVID-19 was diagnosed with the polymerase chain reaction (PCR) test in patients presenting with flu-like symptoms. All patients signed informed consent. The local ethical committee approved the study, and necessary procedures were followed up.

Severe COVID-19 pneumonia was defined as $SatO_2$<90% or PaO_2<70 mmHg, PaO_2<70 mmHg despite 5 L/min nasal O_2 supplementation, a respiratory rate>30/min, the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2)<300, lactate>4 mmol/L or lung infiltrates>50%. Patients were treated with favipiravir 1600 mg twice daily on the 1st day of treatment and 600 mg twice daily for 4 days, azithromycin 250 mg once daily following a 500-mg loading dose, a prophylactic dose of low-molecular-weight heparin based on the patient's weight, and corticosteroids (dexamethasone and methylprednisolone) based on the patient's symptoms. Patients admitted to ICU were also treated similarly. The hospital digital database was used for the patients' records. The study group was divided into two groups based on the survival status, namely, survivors and nonsurvivors.

Statistical analysis

Data were recorded and analyzed using SPSS version 21 (SPSS Inc., Chicago, IL, USA). p<0.05 was accepted as the statistically significant level. Normality was tested using Q-Q plots. Mean±standard deviation (SD) or median (1st–3rd quartile) were used to express continuous data according to the normality level. Normally distributed data were compared using t-test, while nonnormally distributed data were analyzed using the Mann–Whitney U-test. The chi-square test was used for the categorical data comparison. Paired continuous variables were compared using the analysis of variance (ANOVA) and Wilcoxon signed-rank test.

RESULTS

A total of 200 COVID-19 patients were admitted to ICU in a defined time period for this study [median age 68 (56.5–76) years, 55.5% male]. Notably, 97 of them were discharged, while 103 of them died during hospitalization. Nonsurvivors were older [70 (59–78) years vs. 66 (53–74), years, p=0.008] and had a higher rate for chronic renal failure compared with survivors (39.81% vs. 15.46%, p<0.001). Both groups were similar with respect to gender, age, and preexisting other diseases. Moreover, the rate of the medications used for comorbid diseases was also similar for both groups (Figure 1A). However, the intubation rate was found to be greater in nonsurvivors compared with survivors (Figure 1B).

The comparison and distribution of measurements of the patients are summarized in Table 1. A significant increase was observed in the leukocyte count (p=0.001), procalcitonin (p<0.001), aPTT (p=0.029), fibrinogen (p=0.007), AST and ALT (p<0.001), mean platelet volume (p<0.001), and ferritin concentration (p=0.001) and in glomerular filtration rate (p=0.001) from baseline to day 7 of COVID-19 among non-survivors. In contrast, lymphocyte (p=0.015), monocyte count (p = 0.009) and albumin concentration (p < 0.001) decreased significantly from baseline to day 7 of COVID-19 among nonsurvivors.

To evaluate the independently related factors with mortality, we conducted multiple logistic regression analysis (Table 2). We detected that patients who needed intubation had a 232.669-fold higher risk of mortality compared with patients without intubation [odds ratio (OR): 232.669, 95% confidence interval (CI): 50.198–1078.429, and p<0.001)]. The renal failure increased the risk of mortality 3.524-fold (OR: 3.524, 95%CI: 1.133–10.956, and p=0.030). Moreover, we also noticed that higher ferritin rates (p=0.035) are associated with an elevated risk of mortality (Figure 1C and D).

DISCUSSION

This study shows that the rate of concomitant cardiovascular disease and medications used for preexisting cardiovascular disorders do not differ between survivors and nonsurvivors from severe COVID-19. However, chronic renal failure is more prevalent among nonsurvivors relative to survivors. Our findings indicate that presence of chronic renal failure, a high peak ferritin concentration, and the need for invasive mechanical ventilation appear predictive for mortality.

The mortality from COVID-19 is continuing to rise globally. Identifying the factors associated with mortality, particularly in those with severe illness, is therefore critical to introduce advanced treatment options and to forecast who will need ICU admission. Early reports from China have revealed that age, elevation in inflammatory markers, and the presence

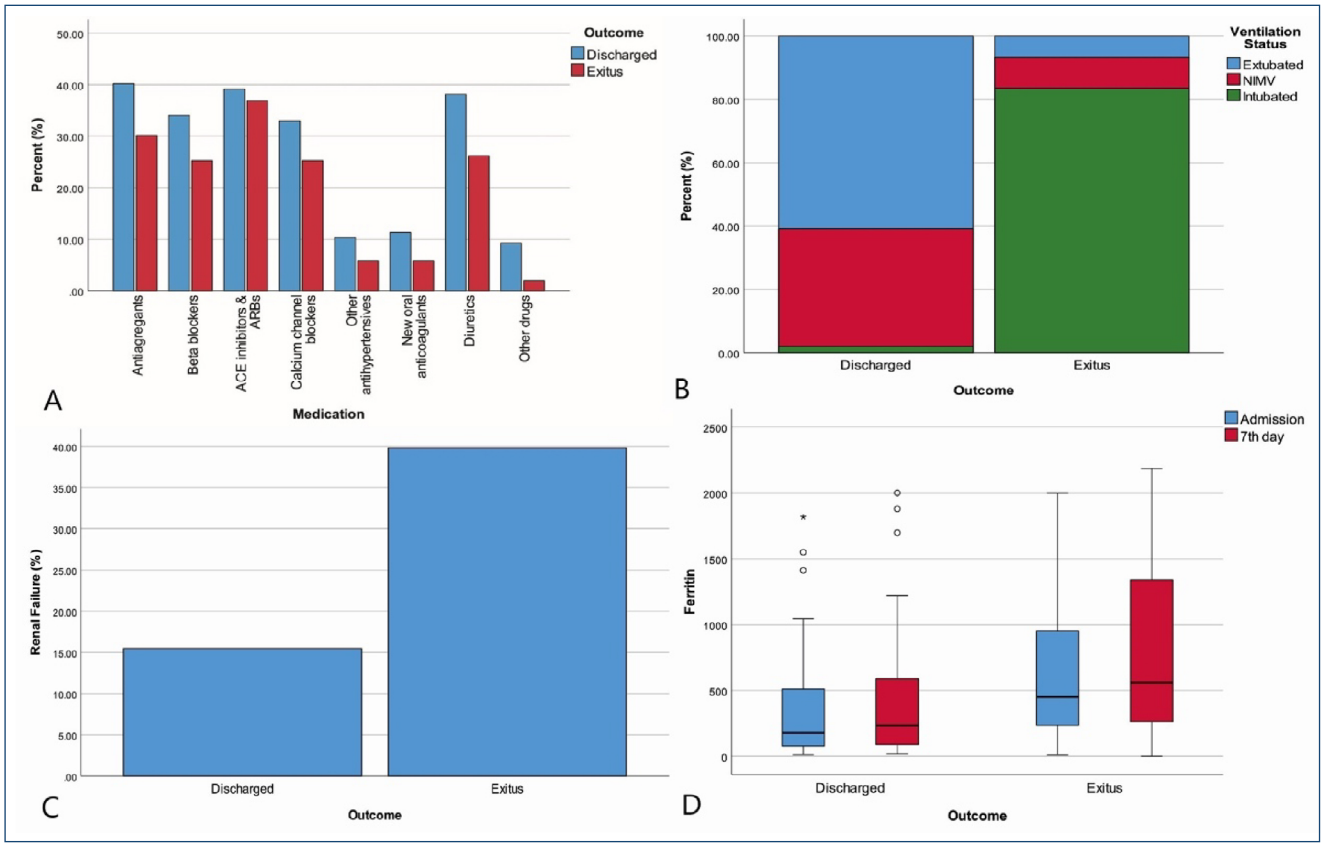

Figure 1. Results of **(A)** history of use of cardiovascular medications, **(B)** ventilation status, **(C)** renal failure percentages, and **(D)** ferritin values. * indicates that the p-value is statistically significant but close to each other.

Table 1. Summary of biochemical measurements during admission and on day 7.

	Outcome		Total	p (between variables)
	Discharged (n=97)	Exitus (n=103)		
WBC				
Admission	8.3 (6.2–12)	10.5 (7.2–15)	9.56 (6.45–13.45)	**0.012**
Day 7	8.3 (6–12)	13 (9.5–17)	10.6 (7.23–14.8)	**<0.001**
p (within variables)	0.575	**0.001**	**0.012**	
CRP				
Admission	44 (11.8–124.7)	93 (39–157)	73.5 (19.8–141.5)	**0.005**
Day 7	16 (7.8–68)	94 (34–154)	50 (10.83–112)	**<0.001**
p (within variables)	**<0.001**	0.745	**0.002**	
Procalcitonin				
Admission	0.19 (0.09–0.79)	0.60 (0.19–2.00)	0.30 (0.12–1.30)	**<0.001**
Day 7	0.12 (0.05–0.45)	1.90 (0.50–5.30)	0.49 (0.09–2.20)	**<0.001**
p (within variables)	**<0.001**	**<0.001**	0.053	
PT				
Admission	72.53±18.67	71.77±18.92	72.14±18.76	0.776
Day 7	75.90±17.23	67.13±18.64	71.38±18.45	**0.001**
p (within variables)	0.066	**0.009**	0.618	

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Table 1. Continuation.

	Outcome		Total	p (between variables)
	Discharged (n=97)	Exitus (n=103)		
aPTT				
Admission	31 (27–35)	29 (24.6–34)	30 (26–35)	0.149
Day 7	30 (26–35)	31 (28–37)	30 (27–35.5)	0.111
p (within variables)	0.335	**0.029**	0.346	
INR				
Admission	1.10 (1.00–1.23)	1.10 (1.00–1.30)	1.10 (1.00–1.30)	0.343
Day 7	1.09 (1.00–1.20)	1.20 (1.00–1.40)	1.10 (1.00–1.30)	**0.003**
p (within variables)	0.074	0.133	0.858	
Fibrinogen				
Admission	381.89±142.44	458.81±146.93	421.50±149.46	**<0.001**
Day 7	377.31±139.45	488.58±160.81	434.61±160.45	**<0.001**
p (within variables)	0.687	**0.007**	0.112	
D-Dimer				
Admission	413 (178–723)	1155 (598–6765)	673 (339.5–2196)	**<0.001**
Day 7	410 (188–996)	1723 (650–4580)	850.5 (336.5–2373.5)	**<0.001**
p (within variables)	0.363	0.704	0.503	
Fasting blood glucose				
Admission	135 (106.9–174)	164 (118–225)	148.5 (114.5–205.5)	**0.024**
Day 7	124 (101–176)	169 (115–271)	145 (105–225)	**0.002**
p (within variables)	0.385	0.327	0.910	
AST				
Admission	27 (18–41)	36 (22–61)	29.5 (20.35–49.5)	**0.008**
Day 7	22 (17–33)	61 (32–150)	33 (19–79)	**<0.001**
p (within variables)	0.091	**<0.001**	**0.012**	
ALT				
Admission	21 (14–40)	23 (13–40)	22 (13.5–40)	0.487
Day 7	24 (17–35)	43 (21–80)	30 (19–56.25)	**<0.001**
p (within variables)	0.117	**<0.001**	**<0.001**	
CK				
Admission	90 (57–202)	147 (55–330)	107.5 (56–242.5)	**0.014**
Day 7	51 (34–109)	185 (66–433)	93 (41.5–287)	**<0.001**
p (within variables)	**<0.001**	0.154	0.233	
CK-MB				
Admission	29 (19–47)	39 (25–65)	34 (21–58)	**<0.001**
Day 7	24 (15–35)	40 (25–70)	32.9 (19.5–53.5)	**<0.001**
p (within variables)	0.086	0.831	0.198	
Troponin				
Admission	0.1 (0.1–0.1)	0.1 (0.1–0.32)	0.1 (0.1–0.16)	0.059
Day 7	0.1 (0.1–0.1)	0.1 (0.1–1.5)	0.1 (0.1–0.43)	**<0.001**
p (within variables)	**0.025**	0.662	0.483	

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Table 1. Continuation.

	Outcome		Total	p (between variables)
	Discharged (n=97)	Exitus (n=103)		
GFR				
Admission	75 (41–94)	53 (38–77)	62 (39–87.25)	**0.003**
Day 7	77 (51–102)	44 (17–71)	60 (29.5–89.5)	**<0.001**
p (within variables)	**0.002**	**0.001**	0.621	
Lymphocyte				
Admission	9.8 (5.7–20)	6.7 (3.2–12.6)	7.75 (4.4–16.25)	**0.001**
Day 7	12 (6.6–20)	5.5 (3.4–9.6)	7.95 (4.2–14.95)	**<0.001**
p (within variables)	0.313	**0.015**	0.298	
Monocyte				
Admission	5.2 (3.7–7.1)	4.2 (2–6)	4.8 (2.85–6.4)	**0.004**
Day 7	5.9 (4–7.1)	2.8 (2–5.2)	4.4 (2.55–6.4)	**<0.001**
p (within variables)	0.613	**0.009**	0.149	
MPV				
Admission	10.38±1.25	9.80±1.10	10.08±1.21	**0.001**
Day 7	9.47±1.11	11.50±1.65	10.52±1.74	**<0.001**
p (within variables)	**<0.001**	**<0.001**	**<0.001**	
Ferritin				
Admission	178 (76–510)	450 (235–963)	342 (107.5–713.5)	**<0.001**
Day 7	235 (88–588)	560 (257–1353)	365.5 (131–880.5)	**<0.001**
p (within variables)	**0.004**	**0.001**	**<0.001**	
Albumin				
Admission	3.44±0.44	3.35±0.36	3.39±0.41	0.102
Day 7	3.27±0.46	2.45±0.38	2.85±0.59	**<0.001**
p (within variables)	**<0.001**	**<0.001**	**<0.001**	

Data are given as mean±standard deviation or median (1st–3rd quartile) according to the normality of distribution. Bold values denote statistical significance at p<0.05.

Table 2. Significant risk factors of the death and multiple logistic regression analysis.

	β	Standard error	Wald	p	Exp (β)	95% Confidence interval for Exp (β)	
Renal failure	1.260	0.579	4.737	0.030	3.524	1.133	10.956
Intubated	5.450	0.782	48.504	<0.001	232.669	50.198	1078.429
Ferritin	0.001	0.001	4.435	0.035	1.001	1.000	1.002
Constant	-2.571	0.449	32.787	<0.001	0.076		

Dependent variable: outcome (Exitus); Nagelkerke R^2=0.768.

of underlying diseases or secondary infection were predictive for fatal outcome[9]. Several reviews and meta-analysis investigating the risk factors for mortality have been published recently. Subjects with concomitant cardiometabolic disease and those presenting with acute inflammation and end-organ damage have been shown to have a higher risk of death from COVID-19[10]. In-hospital mortality due to COVID-19 was reported to be 4.85 fold increased in patients with cardiovascular disorders, particularly in those with elevated troponin levels[11]. A recent prospective cohort study has reported that

the presence of cardiovascular or cerebrovascular diseases, age of ³65 years, and cardiac troponin I higher than 0.05 ng/mL were correlated with high mortality rate in COVD-19 patients[12]. Elevated neutrophil-to-lymphocyte ratio, D-dimer, C-reactive protein (CRP), aspartate aminotransferase, and reduced albumin concentration and glomerular filtration rate were also found to be related to a bad outcome in COVID-19 patients[13]. The meta-analysis that included 21 papers including 3,377 patients has reported that compared with nonserious diseases and survivors, subjects with severe and terminal diseases had significantly higher leukocyte, ferritin, and lymphopenia counts. Unlike the group of survivors, heart attack, surrogate markers of inflammation, liver and kidney functions, and coagulopathy have been observed to be elevated in nonsurvivors[14].

In this study, we indicated that there is no impact of comorbid cardiovascular diseases on mortality in severe COVID-19. This is somewhat challenging with the results of previous data. We speculate that the severity of the preexisting cardiovascular disease has a higher impact on mortality than the sole presence of concomitant cardiovascular disease in COVID-19. In other words, subjects with severe left ventricular dysfunction might have poorer outcomes from COVID-19 than those with mild left ventricular systolic dysfunction, although both are classified as heart failure. In addition, subjects with severe multivessel coronary artery disease might have a higher mortality from COVID-19 than those with single-vessel coronary artery disease, although both are defined as atherosclerotic cardiovascular disease. From this point of view, we considered that clinicians should take the severity of preexisting cardiovascular disorders into account to address the underlying disease as a significant predictor of mortality from COVID-19.

Findings of this study have also shown that the use of preexisting medications, including calcium channel blockers, antiaggregant, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers, beta-blockers, and oral anticoagulant agents used for comorbid disease, was similar between survivors and nonsurvivors. This finding supports previous evidence indicating that ACE inhibitors and angiotensin receptor blockers have no significant impact on mortality in COVID-19[15,16]. We consider that ACE inhibitors and angiotensin receptor blockers should be continued even in severe COVID-19 patients since treatment with these agents appears safe.

This study has also demonstrated that CRP, procalcitonin, and fibrinogen, which are surrogates of inflammatory state, and D-dimer level, which is the indicator of a prothrombotic state, have been found elevated in the group of nonsurvivors related to the other group from severe COVID-19. These results are compatible with the data gathered from the previous studies[17]. The recent information indicates that acquired, endothelial interaction-mediated prothrombotic coagulopathy had a role in worsening clinical course[18]. Accordingly, elevated D-dimer levels found among nonsurvivors in our research can be explained by the existence of a prothrombotic environment secondary to serious COVID-19.

Logistic regression analyses showed that intubation and high ferritin concentration were independent predictors for mortality in severe COID-19 patients. Patients requiring intubation and mechanical ventilation have been noted to have advanced pulmonary involvement; thus, these patients are at high risk for mortality[19]. The increase in ferritin concentrations among no-survivors is probably associated with the hyperinflammation-cytokine storm which leads to fatal multi-organ failure[20]. We also found that chronic kidney disease was an independent indicator for death in COVID-19. The early data regarding the role of renal failure on mortality in COVID-19 support our finding. Cheng et al[21]. have reported that the prevalence of kidney disease on admission was correlated with in-hospital death rates in COVID-19[21].

Accordingly, we consider that subjects with severe COVID-19, increased CRP, procalcitonin, fibrinogen, D-dimer levels, and chronic renal disease are at greater risk for mortality. Thus, these subjects might be candidates for corticosteroids and IL-6 antagonists, which have been shown to improve survival in critically ill COVID-19 patients.

The major limitation of this research is the comparatively limited sample size. The other one is also the absence of details about the level of cardiovascular comorbidity. We did not investigate the duration of disease, functionality levels, and other parameters which could be the important factors for the prognosis of cardiovascular patients.

CONCLUSIONS

This study failed to demonstrate the significant difference in preexisting cardiovascular diseases and cardiovascular drugs between survivor and nonsurvivor patients who were admitted to ICU for severe COVID-19. However, CRP, ferritin, procalcitonin, fibrinogen, and D-dimer levels in nonsurvivors were higher than that of survivors indicating that the hyperinflammation and prothrombotic state may have a role on poor outcomes in COVID-19 patients. Our findings indicate that presence of chronic renal failure, a high peak ferritin concentration, and the need for invasive mechanical ventilation appear predictive for

mortality. We propose that these risk factors should be taken into account in defining the risk status of severe COVID-19 patients admitted to the ICU.

ETHICAL APPROVAL

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethics for the study were obtained from the Van Training and Research Hospital (dated: 08/07/2020 decision number: 2020/13). Informed consent was obtained from all individual participants included in this study.

AUTHORS' CONTRIBUTIONS

RDA, NA: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Writing – original draft, Writing – review & editing. **AŞ, TA:** Project administration, Resources, Software, Supervision. **ZD, MÖ:** Data curation, Validation, Visualization, Writing – review & editing.

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