Pulm Ther (2023) 9:377–394
https://doi.org/10.1007/s41030-023-00231-1

ORIGINAL RESEARCH

Predictive Factors of Mortality in Patients with Severe COVID-19 Treated in the Intensive Care Unit: A Single-Center Study in Vietnam

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Received: April 13, 2023 / Accepted: June 12, 2023 / Published online: July 7, 2023

ABSTRACT

Introduction: The fourth outbreak of COVID-19 with the delta variant in Vietnam was very fierce due to the limited availability of vaccines and the lack of healthcare resources. During that period, the high mortality of patients with severe and critical COVID-19 caused many concerns for the health system, especially the intensive care units. This study aimed to analyze the predictive factors of death and survival in patients with severe and critical COVID-19.

Methods: We conducted a cross-sectional and descriptive study on 151 patients with severe and critical COVID-19 hospitalized in the Intensive Care Unit of Binh Duong General Hospital.

Results: Common clinical symptoms of severe and critical COVID-19 included shortness of breath (97.4%), fatigue (89.4%), cough (76.8%),

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chest pain (47.7%), loss of smell (48.3%), loss of taste (39.1%), and headache (21.2%). The abnormal biochemical features were leukopenia (2.1%), anemia, thrombocytopenia (18%), hypoxia with low PaO_2 (34.6%), hypocapnia with reduced $PaCO_2$ (29.6%), and blood acidosis (18.4%). Common complications during hospitalization were septic shock (15.2%), cardiogenic shock (5.3%), and embolism (2.6%). The predictive factors of death were being female, age > 65 years, cardiovascular comorbidity, thrombocytopenia (< 137.10^9/l), and hypoxia at inclusion or after the first week or blood acidosis (pH < 7.28). The use of a high dose of corticosteroids reduced the mortality during the first 3 weeks of hospitalization but significantly increased risk of death after 3 and 4 weeks.

Conclusions: Common clinical symptoms, laboratory features, and death-related complications of critical and severe COVID-19 patients were found in Vietnamese patients during the fourth wave of the COVID-19 pandemic. The results of this study provide new insight into the predictive factors of mortality for patients with severe and critical COVID-19.

Keywords: COVID-19; SARS-CoV-2; Delta variant; Severe and critical COVID-19; Predictive factor; Binh Duong Province

Key Summary Points

Why carry out the study?

The delta variant is responsible for significant outbreaks of COVID-19 around the world, with its ability to spread rapidly, cause severe illness, and reduce vaccine effectiveness, making them more deadly.

Data of severe–critical patients with COVID-19 are very useful for better understanding the symptoms, characteristics, and mortality risks of the disease.

Study on predictive factors of mortality and survival may help to identify the effectiveness of conventional treatment in patients with severe and critical COVID-19.

What was learned from the study?

Severe–critical COVID-19 patients with age > 65 years or cardiovascular comorbidity, had thrombocytopenia, comorbidity of cardiovascular diseases, and low PaO_2 or pH < 7.28 might have a high risk of death during hospitalization.

Use of high-dose corticosteroids could reduce mortality during the first 3 weeks of hospitalization but could significantly increase the risk of death afterwards.

INTRODUCTION

COVID-19, a disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has emerged as a global pandemic with severe consequences and has placed tremendous pressure on healthcare systems in numerous countries worldwide,, especially in emerging countries [1, 2]. According to Worldometers statistics, the SARS-CoV-2 virus infected more than 290 million people, with 5.4 million deaths globally by the end of 2021 [3]. The continuous emergence of new strains of the SARS-CoV-2 virus has posed crucial challenges for healthcare systems in terms of disease prevention and treatment. Delta variant, or B.1.167.2, first detected in India in December 2020, was considered the deadliest variant with more infectious and virulent, and it can reduce the vaccine's effectiveness [4–7]. Studies have shown that the delta variant is associated with being two times more contagious and more likely to cause severe illness compared to older strains. Specifically, it is 60% more transmissible than the alpha variant and has a shorter incubation period, around 2–3 days [8–11].

In addition, people infected with the delta strain had a nasal viral load 1000 times higher than those infected with the original strain

[12, 13]. Even the viral load in an unvaccinated person is equivalent to that of a fully vaccinated person when infected with this strain [14, 15], or in some cases, asymptomatic infected people have a higher viral load than hospitalized patients and become a mobile source of infection in the community [16]. As a result, the delta variant quickly became popular in most countries worldwide, and the dominant variant overwhelmed all other strains globally. The lethality of the delta variant was also confirmed by increased risk of hospitalization (120%) and intensive care unit (ICU) admission (287%), and 137% higher risk of death compared with the original variant [13, 17].

People with COVID-19 with the delta variant have a nonspecific clinical presentation or have symptoms ranging from mild fever, fatigue, cough, and shortness of breath [18, 19] to severe cases such as lower respiratory tract infections, pneumonia, and some cases progressed to severe acute respiratory distress syndrome (ARDS), or multi-organ failure leading to death [20, 21]. High mortality rates have been reported in Latin America and Europe, ranging from 13.9% to 21.0% in hospitalized patients, particularly in severe and critical cases [22–24] and up to 25% in elderly patients [25]. Therefore, it is crucial to have an appropriate approach to patients with early symptoms of severe COVID-19 for helping to classify correctly the disease severity to reduce the healthcare burden and to choose the correct treatment [26].

The delta variant of SARS-CoV-2 virus has caused the COVID-19 pandemic to re-emerge, creating a new wave of infection that can increase patients' severity and mortality risk. During the fourth wave of COVID-19 pandemic, the delta variant gave the healthcare burden in many countries worldwide. Thus, Vietnam had no exception, with the fourth wave started at the end of April 2021 [27]. According to a survey study in 23 countries on COVID-19 prevention policies in May 2020, Vietnam has a satisfaction level of people up to 77%, just behind China [28]. Indeed, Vietnam has been considered one of the most effective response countries to the COVID-19 pandemic. In the more than 15 months since the pandemic began in January 2020, the total number of officially recorded COVID-19 infections in Vietnam has been less than 3000 cases and 35 deaths out of a population of ~ 100 million. However, when delta variant arrived, the number of new cases increased to thousands of patients per day in July 2021 and continuously set new peaks. The highest record was set on August 8, 2021, with 9684 cases/day and 220,000 total infections, with 3757 deaths in Vietnam [29, 30].

However, during the fourth wave of the pandemic in Vietnam, some clinical studies on patients with severe–critical COVID-19 were also conducted, but the results have been limited and unpublished. Thus, the present study aimed to describe the clinical and laboratory characteristics and predictive factors of mortality in patients with severe and critical COVID-19 in Vietnam during the fourth wave of the COVID-19 pandemic.

METHODS

Study Design and Data Sources

Our study was a cross-sectional descriptive study, in compliance with STROBE guidelines (strengthening the reporting of observational studies in epidemiology) for cross-sectional studies [31] in 151 patients with severe and critical COVID-19 at the intensive care unit (ICU) of Binh Duong General Hospital from September 2021 to March 2022. The ICU of Binh Duong General Hospital was one of the facilities to collect and treat patients with severe and critical COVID-19 in the southern pandemic center of Vietnam.

This study was approved by the Ethics Committee of Binh Duong General Hospital (HDDD-BVDK BINH DUONG 09.2021). Written informed consent was obtained from the participants or their families for the study and publication. The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

The present study was conducted as a descriptive study and did not involve the use of a protocol or randomized control trial (RCT). The written consent of study subjects related to the data analysis and publication was obtained

for each patient (survival) or their families (dead patients).

The study recruited all COVID-19 patients who met the inclusion criteria from September 2021 to March 2022, resulting in a sample size for analysis.

Data Collection

Patients' data, including demographic information, clinical symptoms, laboratory results, and treatments were collected from medical records for analysis. The data were taken from the medical records related to the standard care.

Inclusion Criteria

Patients > 18 years old with a positive real-time (RT)-polymerase chain reaction (PCR) test result for SARS-CoV-2 were classified as severe and critical according to the Ministry of Health of Vietnamese guidelines.

Severity Level

- Respiratory signs of pneumonia accompanied by breathing rate > 25 breaths/minute; severe shortness of breath, contraction of accessory respiratory muscles; $SpO_2 < 94\%$ when breathing room air.
- Circulation, heart rate can be fast or slow, and normal blood pressure or increased.
- Neurologically, the patient may be restless or lethargic and tired. Chest X-ray and computed tomography of the chest: there are lesions, and lesions are more than 50%. Ultrasound shows many B waves and arterial blood gas: PaO_2/FiO_2 about 200–300.

Critical Level

- Respiration with manifestations of tachypnea > 30 breaths/minute or < 10 breaths/minute, signs of severe respiratory failure, labored breathing, abnormal breathing, or need for respiratory support with high-flow nasal cannula (HFNC), mechanical ventilation. The patient's consciousness is reduced or comatose.
- Circulation, the patient's heart rate may be fast or slow, blood pressure drops, urine is less, or anuria. Chest X-ray results and chest computed tomography showed lesions over 50%. Ultrasound image shows many B waves and arterial blood gases: $PaO_2/FiO_2 < 200$, respiratory acidosis, blood lactate > 2 mmol/l.

Exclusion Criteria

Patients under 18 years old, patients without COVID-19, patients with a positive RT-PCR test result for SARS-CoV-2, and which are not classified as severe/critical according to the guidelines of Vietnam's Ministry of Health.

Statistical Analysis

Categorical variables were given as percentages and frequencies; the continuous variables were determined by using mean ± standard deviation (SD). Data were analyzed by using SPSS 26 software (SPSS Inc., Chicago, IL, USA). The descriptive statistics, comparison test, and univariate regression analysis were used to describe the clinical and laboratory characteristics. Receiver operating characteristic (ROC) curve analysis was used to predict prognostic factors for the death of patients.

The relative risks (RR) of mortality related to anthropometry, comorbidities, and blood gases were analyzed in all study patients. The ROC curve was used to calculate the sensitivity and specificity of predicting value of the probability of death and survival. A Kaplan–Meier curve was used to evaluate survival during hospitalization. A p value < 0.05 was considered statistically significant.

RESULTS

General Characteristics of the Study Patients with Severe and Critical COVID-19

Clinical Characteristics of Study Patients

In the present study, there were 151 patients with the main characteristics described in Table 1. There were 55 male (36.4%) and 96 female (63.6%) and 71 patients under 50 years old (47%) vs. 80 patients over 50 years old (53%). The mean age of the study patients was

Table 1 Demographics and clinical characteristics of study patients

Clinical parameters	*N* = 151	%	Mean ± SD
Age (years)	–	–	53.7 ± 17.7
< 50 years	71	47	34.8 ± 14.9
≥ 50 years	80	53	67.6 ± 11.0
Sex	151	100.0	
Male	55	36.4	–
Female	96	63.6	–
Comorbidities	138	91.4	
Respiratory diseases	11	7.3	–
Hypertension	54	35.8	–
Cardiovascular diseases	21	13.9	–
Endocrinological diseases	50	33.1	–
Psychological disorders	2	1.3	–
Symptoms			
Fever	30	19.9	–
Cough	116	76.8	–
Chest pain	72	47.7	–
Shortness of breath	147	97.4	–
Anosmia	73	48.3	–
Ageusia	59	39.1	–
Headache	32	21.2	–
Sore throat	42	27.8	–
Tired	135	89.4	–
Treatments	151	100.0	–
Corticosteroids	148	98.0	–
Dexamethasone 6 mg/day*	111	73.5	–
Dexamethasone > 6-12 mg/day**	12	7.9	–
Dexamethasone > 12-20 mg/day***	25	16.6	–
Remdesivir	37	24.5	–
Ivermectin	4	2.6	–
Enoxaparin	149	98.7	–
Vasopressin	76	50.3	–
Others	2	1.4	–
Complications	35	23.1	–

Table 1 continued

Clinical parameters	*N* = 151	%	Mean ± SD
Septic shock	23	15.2	–
Thromboembolism	4	2.6	–
Cardiogenic shock	8	5.3	–
Hospitalized duration in ICU	151	100.0	10.8 ± 5.3
< 7 days	4	2.6	3.4 ± 1.7
7–14 days	56	37.1	11.2 ± 1.9
15–21 days	47	31.1	17.8 ± 2.6
≥ 22 days	44	29.2	26.5 ± 2.1

*or 1-2 mg/kg of methylprednisolone; ** > 2-3 mg/kg of methylprednisolone; ≥ 4 mg/kg of methylprednisolone

53.67 ± 17.7 years. The patients with comorbidities included 11 patients with chronic respiratory diseases (7.3%), 54 patients with hypertension (35.8%), 21 patients had cardiovascular diseases (13.9%), 50 patients with the comorbidity related to endocrinological disease (33.1%), and two patients with mental illness (1.3%, Table 1). Regarding common symptoms of COVID-19, the results showed that more than 40% of patients had typical symptoms of this disease such as cough, shortness of breath, chest pain, loss of smell and/or taste, and fatigue (Table 1).

The included patients were treated with enoxaparin (98.7%), vasopressors (50.3%), and remdesivir (24.5%; Table 1). Most patients were treated with dexamethasone 6 mg/day, accounting for 73.5%. During treatment, 23 patients (15.2%) had the complications with septic shock, four patients (2.6%) with thromboembolic complications, and eight patients (5.3%) had the complications of cardiogenic shock (Table 1).

Biological Characteristics of Study Patients

The laboratory testing results of patients with severe and critical COVID-19 in the present study are presented in Table 2. The results show that there were 2.1% patients with leukopenia, mainly with lymphocytopenia (14.9%) and 18.0% patients with thrombocytopenia. The arterial blood gas revealed that 34.6% patients with decreased PaO_2, 29.6% with low $PaCO_2$, and 18.4% with low pH. The mean values of biochemical parameters are presented in Table 2. The levels of CRP, fibrinogen, LDH, and lactate were significantly increased in study patients; the mean values of urea, creatinine, AST, and ALT were also higher than the normal limits (Table 2).

Clinical and Biological Characteristics of Survival Patients vs. Dead Patients

The results showed that there was a significant difference in the mean age of death patients with severe–critical COVID-19 compared to survival patients (57.8 ± 16.5 vs. 46.5 ± 17.4; $p < 0.001$; Table 3); death patients were mainly female (69.1%). Among the study patients, the percentage of comorbidity with cardiovascular diseases was higher in those who died compared to the patients who survived (19.6 vs. 3.7%; $p = 0.007$; Table 3). In comparison to survival patients, death patients were mainly treated with dexamethasone of 6 mg/day or equivalent with 1-2 mg/kg of methylprednisolone (84.6 vs. 53.7%; $p < 0.001$; Table 3). Survival patients had a higher percentage of remdesivir treatment, lower percentage of vasopressin use, and had no complications related to septic shock or cardiac shock during hospitalization (37.0 vs.

Table 2 Biological characteristics of study patients

Laboratory parameters	Normal range	Mean ± SD	Min–Max
Arterial blood gases			
PaO_2, mmHg	80.0–100.0	75.5 ± 26.9	30.0–170.0
$PaCO_2$, mmHg	35.0–45.0	46.2 ± 15.6	23.0–115.0
pH	7.35–7.45	7.34 ± 0.14	6.83–7.58
HCO_3^-, mEq/	18.0–23.0	24.7 ± 5.6	7.8–37.8
$AaDO_2$, mmHg	5–20	406 ± 143	53–624
Biochemical parameters			
CRP, mg/dl	< 1.0	8.7 ± 8.3	0.05–9.2
Fibrinogen, g/l	1.5–4.0	5.6 ± 1.5	1.9–10.7
LDH, U/l	< 247	2436 ± 1697	72–18,154
Lactate, mmol/l	0.5–2.2	3.5 ± 4.1	1.0–20.6
PCT, ng/ml	< 0.5	2.7 ± 6.9	0.1–37.9
Urea, mmol/l	2.8–7.2	8.2 ± 6.5	1.6–53.9
Creatinine, µmol/l	72–127	85 ± 56	42–504
AST, U/l	0–50	125 ± 45	17–498
ALT, U/l	0–50	108 ± 29	11–289
Blood test			
White blood cells, 10^9/l	4.0–11.0	12.4 ± 6.3	6.9–34.2
Neutrophils, 109/l	1.8–8.2	11.5 ± 5.6	12.5–30.2
Lymphocytes,10^9/l	0.80–4.90	0.85 ± 0.91	0.34–0.92
Red blood cells, 10^{12}/l	3.8–6.3	4.1 ± 0.6	1.3–5.8
Hemoglobin, g/dl	12.0–18.0	11.8 ± 2.1	4.5–16.0
Hematocrit, %	37.0–52.0	38.6 ± 22.3	14.7–58.5
Platelets, 10^9/l	140–500	265 ± 150	26–450

17.5% and $p = 0.007$; 1.9 vs. 77.3% and $p < 0.001$; 0.0 vs. 13.4% and $p = 0.005$; 0.0 vs. 8.2% and $p = 0.015$, respectively; Table 3).

The study results demonstrated that dead patients had a lower level of PaO_2 and pH than surviving patients (Table 3). The results of biochemical parameters showed that there were only significant differences between death and survival patients for lactate dehydrogenase (LDH) and urea ($p < 0.001$ and $p = 0.042$, respectively; Table 3). Platelet count of death patients was significantly lower than survival patients (309.4 vs. 125.9 [10^9/l]; $p = 0.002$; Table 3).

Table 3 Clinical and biological characteristics of surviving patients vs. dead patients

Clinical–laboratory parameters	Survival (N = 54)	Death (N = 97)	P
Age, mean ± SD (years)	46.5 ± 17.4	57.8 ± 16.5	< 0.001
Sex			
Male, %	53.7	30.9	0.002
Female, %	46.3	69.1	0.010
Comorbidities			
Respiratory diseases, %	5.6	8.2	0.545
Hypertension, %	25.9	41.2	0.061
Cardiovascular diseases, %	3.7	19.6	0.007
Endocrinological diseases, %	24.1	38.1	0.079
Psychological disorders, %	1.9	1.0	0.675
Treatments			
Corticosteroids			
Dexamethasone 6 mg/day*, %	53.7	84.6	< 0.001
Dexamethasone > 6-12 mg/day**, %	13.0	8.2	0.176
Dexamethasone > 12-20 mg/day***, %	33.3	7.2	< 0.001
Remdesivir, %	37.0	17.5	0.007
Ivermectin, %	3.7	2.1	0.550
Enoxaparin, %	98.1	99.0	0.675
Vasopressin, %	1.9	77.3	< 0.001
Complications			
Septic shock, %	0.0	13.4	0.005
Thromboembolism, %	0.0	4.1	0.065
Cardiac shock, %	0.0	8.2	0.015
Laboratory features			
Arterial blood gases			
PaO_2, mean ± SD (mmHg)	85.3 ± 29.0	71.0 ± 24.4	0.003
$PaCO_2$, mean ± SD (mmHg)	42.9 ± 8.7	47.9 ± 18.2	0.074
pH, mean ± SD	7.4 ± 0.1	7.3 ± 0.2	0.003
HCO_3^-, mean ± SD (mEq/l)	25.7 ± 3.8	24.2 ± 6.4	0.133
$AaDO_2$, mean ± SD (mmHg)	385.6 ± 143.9	418.9 ± 135.7	0.246
Biochemical parameters			
CRP, mean ± SD (mg/dl)	6.0 ± 4.2	15.7 ± 11.4	0.361
Fibrinogen, mean ± SD (g/l)	5.5 ± 1.1	5.8 ± 1.8	0.446

Table 3 continued

Clinical–laboratory parameters	Survival (N = 54)	Death (N = 97)	P
LDH, mean ± SD (U/l)	557.1 ± 133.8	3996.6 ± 2259.4	< 0.001
Lactate, mean ± SD (mmol/l)	6.9 ± 3.4	3.4 ± 13.0	0.472
PCT, mean ± SD (ng/mL)	0.3 ± 0.3	2.5 ± 5.0	0.095
Urea, mean ± SD (mmol/l)	6.6 ± 3.5	8.5 ± 5.8	0.042
Creatinine, mean ± SD (µmol/l)	80.2 ± 43.3	88.6 ± 62.3	0.411
AST, mean ± SD (U/l)	111.3 ± 77.7	567.0 ± 155.1	0.353
ALT, mean ± SD (U/l)	179.7 ± 95.3	342.8 ± 116.9	0.687
Blood test			
White blood cells, mean ± SD (10^9/l)	11,694 ± 4081	14,021 ± 6247	0.020
Neutrophils, mean ± SD (10^9/l)	10,035 ± 4049	12,627 ± 5934	0.007
Lymphocytes, mean ± SD (10^9/l)	1066 ± 1339	731 ± 564	0.039
Red blood cells, mean ± SD (10^{12}/l)	4.3 ± 0.6	4.1 ± 0.7	0.209
Hemoglobin, mean ± SD (g/dl)	12.0 ± 2.2	11.8 ± 2.0	0.558
Hematocrit, mean ± SD (%)	36.7 ± 6.5	39.8 ± 27.3	0.439
Platelets, mean ± SD (10^9/l)	309.4 ± 125.9	234.6 ± 137.0	0.002

*or 1–2 mg/kg of methylprednisolone; ** > 2–3 mg/kg of methylprednisolone; ≥ 4 mg/kg of methylprednisolone

Relative Risk of Mortality in Study Patients

The univariate regression analysis for the relative risk of mortality in study patients was presented in Table 4 and Fig. 1. The results showed that age > 65 years and comorbidity with cardiovascular disease were significantly associated with relative risk (RR) of mortality (RR = 4.140 and p = 0.001; RR = 6.333 and p = 0.007, respectively; Table 4 and Fig. 1). The treatment with dexamethasone of 12–20 mg/day (or methylprednisolone with ≥ 4 mg/kg/day) had a very low relative risk of death (RR = 0.137 and $p < 0.001$). At inclusion (admission), study patients with PaO_2 < 63 mmHg, pH < 7.28 and thrombocytopenia (< 137.10^9/l) had high relative risks of death (RR = 3.3293 and p = 0.004; RR = 8.138 and p = 0.001; RR = 7.779 and p = 0.002, respectively; Table 4 and Fig. 1). These parameters were still related to high relative risk of mortality when they continued to reduce after 1 week of treatment (Table 4 and Fig. 1).

Predicting value for the probability of survival and death

The ROC curve (Fig. 2A, B) demonstrated the predictors of survival with the cut-off of PaO_2 and pH in patients with severe and critical COVID-19. The sensitivity and specificity of the cut-off of PaO_2 and $PaCO_2$ were very low for predicting the probability of survival (Fig. 2A, B). However, the ROC curves in Fig. 3A showed the cut-off of age older > 50 years was related to the moderate sensitivity and specificity of death. The cut-off of $PaCO_2$ with 57.5 mmHg in severe–critical COVID-19 patients was associated with very high specificity of mortality in these patients (Fig. 3B).

Table 4 Relative risk of mortality in study patients

Clinical–Laboratory parameters	Relative risk	95%CI	*P*
Sex			
Female	1.925	0.958–3.866	0.061
Age > 65 years	4.140	1.634–10.493	0.001
Comorbidities			
Respiratory diseases	1.528	0.386–6.056	0.543
Hypertension	2.005	0.955–4.210	0.061
Cardiovascular diseases	6.333	1.356–29.585	0.007
Endocrinological diseases	1.945	0.913–4.145	0.079
Treatments			
Dexamethasone 12-20 mg/day	0.137	0.048–0.393	< 0.001
(or methylprednisolone ≥ 4 mg/kg/day)			
Arterial blood gases and biology			
At inclusion			
PaO_2 < 63 mmHg (with oxygen support)	3.293	1.382–7.847	0.004
$PaCO_2$ < 31.5 mmHg	0.860	0.264–2.804	0.802
pH < 7.28	8.138	1.715–38.623	0.001
Platelets < 137.10^9/l	7.779	1.648–36.722	0.002
Day 7 after initial treatment in ICU			
PaO_2 < 59 mmHg	4.133	1.394–12.354	0.005
$PaCO_2$ < 30.5 mmHg	0.691	0.109–4.361	0.692
pH < 7.22	0.385	0.139–0.608	0.002
Platelets < 103.10^9/l	7.655	0.901–65.068	0.028

Kaplan–Meier curve of survival patients

The Kaplan–Meier curves (Fig. 4A, B, C and D) showed the survival rate of patients with severe and critical COVID-19 at admission and the effectiveness of corticosteroid therapy. The survival rate of patients with predictive factors of death related to PaO_2 < 63 mmHg, pH < 7.28, and platelet count < 137.10^9/l was significantly and sharply decreased in the first 3 weeks of treatment and consecutively more stable after 3 weeks (Fig. 4A, B, and C).

The treatment with dexamethasone > 6 mg/day (or methylprednisolone > 2 mg/kg/day) was significantly associated with better survival than the dose ≤ 6 mg/day of dexamethasone (or ≤ 2 mg/kg/day of methylprednisolone) during the first 3 weeks (Fig. 4D). The results also showed that the treatment with a high dose of corticosteroids (12–20 mg/day of dexamethasone or ≥ 4 mg/kg/day of methylprednisolone) was related to low probability of survival after 3 weeks (Fig. 4D). However, the lower dose of corticosteroids (6-12 mg/day of dexamethasone or > 2-3 mg/kg/day of

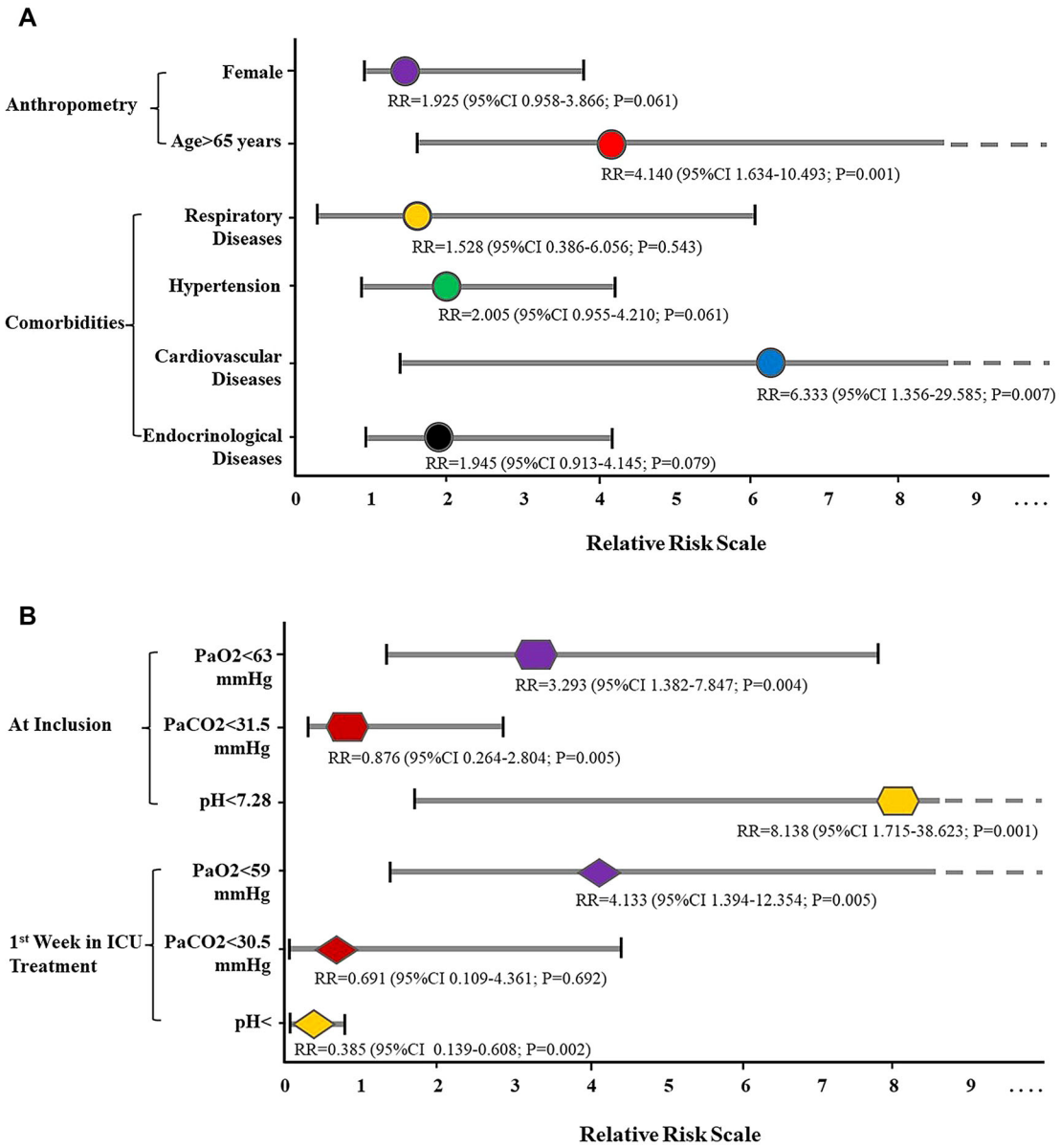

Fig. 1 **A** Relative risk of mortality related to anthropometry and comorbidities in study patients. **B** Relative risk of mortality related to arterial blood gases in study patients

methylprednisolone) had low probability of survival after 4 weeks (Fig. 4D).

DISCUSSION

COVID-19 is a highly dangerous infectious disease with significant morbidity and mortality rates globally. Therefore, it is crucial to comprehend the disease's characteristics and severity to facilitate informed decision-making in selecting appropriate care and enhancing treatment effectiveness. These measures are essential for reducing mortality rates and alleviating the burden on healthcare systems. Like other viral respiratory pathogens, without vaccination, COVID-19 presents in most cases with a rapidly progressive course of common

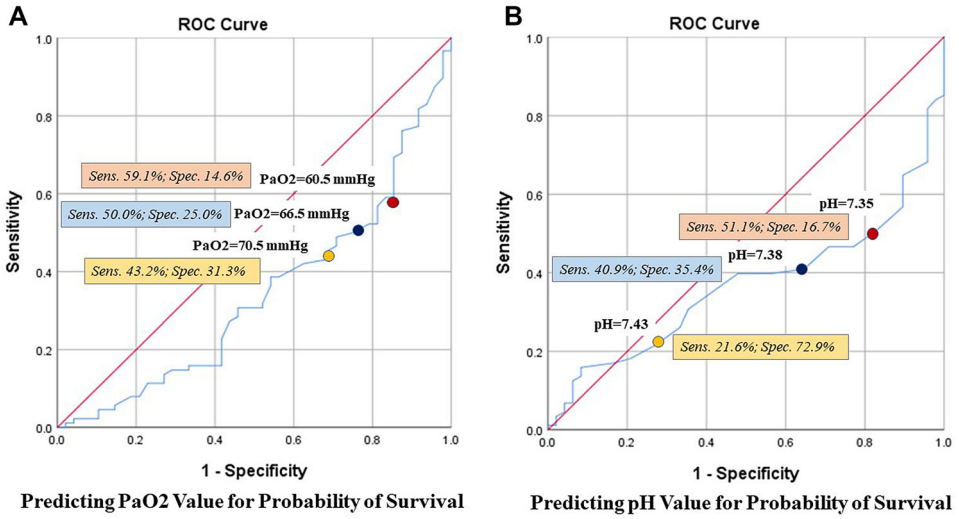

Fig. 2 Predicting value of the probability of survival

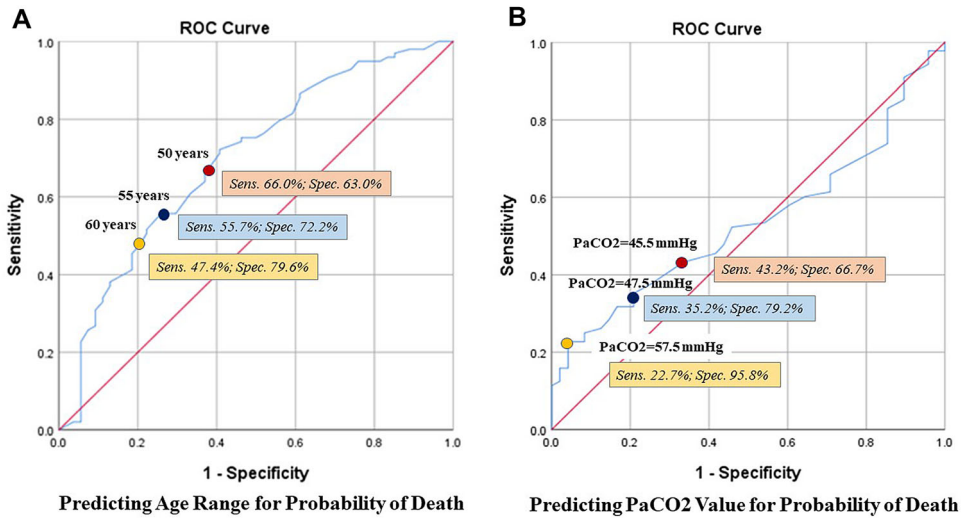

Fig. 3 Predicting value of the probability of death

symptoms such as fever, cough, and shortness of breath to ARDS. In the present study (Table 1), the clinical symptoms of patients with severe and critical COVID-19 were dyspnea (97.4%), fatigue (89.4%), and cough (76.8%). Some other extra-respiratory symptoms in these patients were also recognized, including a loss of smell (48.3%), loss of taste (39.1%), and headaches (21.2%). These symptoms are common in both alpha and delta variants of SARS-CoV-2 but more severe with the delta variant. Our results are also consistent with the clinical manifestations reported in a meta-analysis of 55 studies within 10,014 severe COVID-19 patients who had fever, cough, fatigue, anorexia, dyspnea, chest tightness, hemoptysis, diarrhea, and abdominal pain [19]. The study conducted by Wang et al. in the clinical characteristics of 138 COVID-19 patients in Wuhan, China, showed similar results. However, in Wang's study, the onset of symptoms was fever (98.6%), followed by fatigue and dry cough (69.6 and 59.4%, respectively) [18]. Another study published by Shang et al. [26] demonstrated the symptoms of

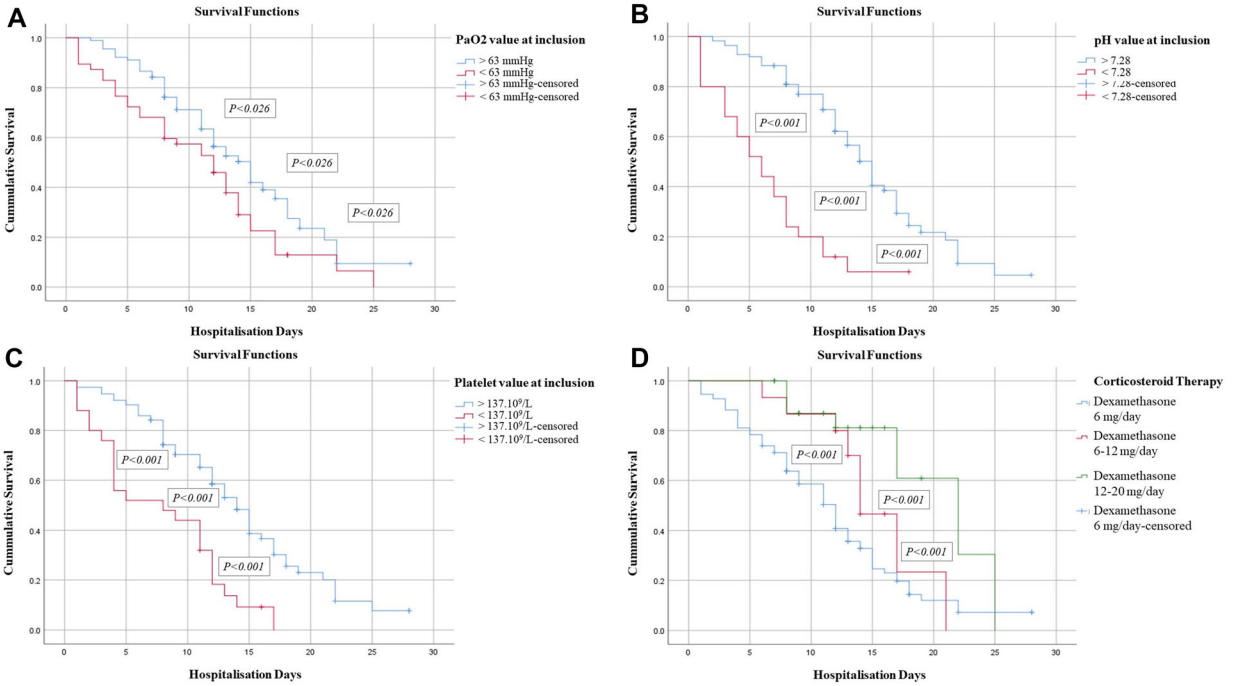

Fig. 4 Predicting value of the probability of survival

severe COVID-19 included fever (81.7%), cough (65.4%), dyspnea (51.5%), fatigue (38.3%), and expectoration (35.1%). Thus, the frequency of dyspnea, fatigue, and cough in our study was significantly higher than in previous studies. This difference might be due to the patient's initial severity on admission or the degree of response during treatment with different variants of the SARS-CoV-2 [26]. Dyspnea, or shortness of breath, fatigue, and cough has consistently been reported as common symptoms in severe and critical COVID-19 cases. While the exact rate may vary due to factors such as study design, population characteristics, and geographic location, it is generally recognized as a prominent symptom in severe cases.

The present study showed that there were some laboratory abnormalities such as leukopenia with mainly lymphocytopenia, anemia, thrombocytopenia, and abnormal arterial blood gas related to hypoxia, hypercapnia, and acidosis (Table 2). Thus, these laboratory characteristics might help clinicians in identifying COVID-19 patients with severe–critical illness in early stage, because most patients with severe and critical COVID-19 might present with rapid progression to multi-organ dysfunction. The present study also revealed that in comparison to survival COVID-19 patients, the common complications of dead patients were septic shock, cardiogenic shock, and embolism (Table 1). These complications might be related to nosocomial infections, cardiomyopathy, and coagulation compromised due to SARS-CoV-2 infection [32, 33]. Also, it has been found that stool and urine samples of COVID-19 patients were positive for SARS-CoV-2 nucleic acid and angiotensin-converting enzyme 2 (ACE2) expression in small intestinal epithelial cells and biliary and pancreatic cells, suggesting SARS-CoV-2 infection can cause multi-organ damage in COVID-19 patients [34–36].

In the present study, the patients with severe and critical COVID-19 were mainly treated with enoxaparin, vasopressors, and remdesivir (Table 1). However, remdesivir was not recommended for severe COVID-19 patients due to conflicting reports on its efficacy for improving clinical status, reducing the duration of mechanical ventilation, as well as morbidity and mortality for these patients [18, 37, 38]. The

use of corticosteroids with different doses, including dexamethasone with doses of 6 mg/day (73.5%), 6–12 mg/day (7.9%), and 12–20 mg/day (16.6%) was also demonstrated in the present study. While the treatment with a high dose of corticosteroids (12–20 mg/day of dexamethasone or ≥ 4 mg/kg/day of methylprednisolone) was associated with a low survival after 3 weeks, the treatment with the dose of dexamethasone of 6-12 mg/day (or > 2-3 mg/kg/day of methylprednisolone) had a low probability of survival after 4 weeks in comparison to the dose of dexamethasone of 6 mg/day (Fig. 4D). Interestingly, the treatment with dexamethasone > 6 mg/day (or methylprednisolone > 2 mg/kg/day) was significantly associated with better survival than the conventional dose of dexamethasone (6 mg/day or equivalent dose of methylprednisolone) during first 3 weeks (Fig. 4D). This result was consistent with the recommendations which suggest that low-dose and short-term treatment of dexamethasone may be used for symptomatic treatment of patients with severe and critical COVID-19 [37, 39, 40]. In fact, the efficacy of dexamethasone 6 mg/day used for 10 consecutive days to reduce hospital stay and mortality in COVID-19 patients who required oxygen or invasive mechanical ventilation has been demonstrated previously [41–43]. However, it has also been reported that the abuse of dexamethasone or methylprednisolone with high doses might increase the patient mortality and slow down the clearance of viral RNA in severe COVID-19 patients [44, 45]. Thus, the identification of predictive mortality and survival factors is critical in choosing the appropriate treatment regimen in patients with severe and critical COVID-19.

The results of our study clearly demonstrated that deceased patients were older and predominantly female. Additionally, they exhibited a higher prevalence of cardiovascular diseases, elevated levels of LDH and urea, lower levels of PaO_2 and pH, as well as lower platelet counts compared to the patients who survived (Tables 3 and 4). Inversely, the surviving patients had a higher percentage of remdesivir treatment, a lower percentage of vasopressin use, and had no complications related to septic shock or cardiac shock during hospitalization (Table 3). However, the results of our study demonstrated that the sensitivity and specificity of the cut-off of age, PaO_2 or $PaCO_2$, and pH was not relevant for predicting the probability of mortality and survival (Fig. 2A, B). Previous studies have suggested that age, low oxygen saturation, and co-morbid chronic diseases were also risk factors for the increased prevalence of mortality in COVID-19 patients [46–48]. By univariate regression analysis, the present study also indicated that age > 65 years, history of cardiovascular disease, thrombocytopenia ($< 137.10^9$/l), hypoxia ($PaO_2 < 63$ mmHg), or acidosis (pH < 7.28) were the relative risks of mortality in patients with severe–critical COVID-19 (Table 4). This result was also confirmed by analyzing the mortality and survival of study patients via Kaplan–Meier curves (Fig. 4A, B, and C). Recently, Lavrentieva et al. have reported that the survival rates inside the ICU for the four main COVID-19 variants are 54.9, 50.3, 39.7, and 50% for the alpha, beta, delta, and omicron variants, respectively [49]. These authors also demonstrated the parameters that have been independently associated with ICU survival are SOFA (Sequential Organ Failure Assessment)–day 1, remdesivir use, AKI (acute kidney injury), sepsis, enteral insufficiency, duration of ICU stay and white blood cells. Our previous reports also revealed the severity of patients hospitalized in ICU who needed to have the optimal treatment with mechanical ventilation or therapeutic plasma exchange were related to AKI, pregnancy, and acute neurological complications [50–53].

Finally, the present study has some main limitations, as described in the following order: a small number of study subjects; patients were included only for a descriptive study without a control group; the choice of low to high corticosteroid doses was dependent on the physicians' decisions. However, this study does give some relevant information, which elucidates the predictive factors of mortality and survival for severe–critical COVID-19 patients and provides the primary data for clinicians to classify COVID-19 patients on admission and have appropriate treatment.

CONCLUSIONS

Common clinical symptoms, laboratory features, and death-related complications of critical-severe COVID-19 patients were found in Vietnamese patients during the fourth wave of the COVID-19 pandemic. This population might have some clinical characteristics and predictive factors of high risk of death and survival for those with severe and critical COVID-19. Thus, the present study suggests that during the fourth wave of the COVID-19 pandemic, the patients with severe and critical COVID-19 who were older or had the medical history of cardiovascular disease or treatment with high dose of corticosteroids, might increase the rate of mortality during hospitalization. In addition, some laboratory features such as thrombocytopenia at admission, significant hypoxia, or blood acidosis under optimal treatment in patients with severe and critical COVID-19 might also be considered as the relevant predictive factors of mortality. Therefore, these findings may provide valuable insights into developing effective treatment regimens and prognostic indicators for the survival of patients with severe and critical COVID-19.

ACKNOWLEDGEMENTS

Funding. This study was funded by the Sciences and Technology Department of Binh Duong province (No. 1539/QD-UBND.28.6.2022). The Rapid Service Fee was funded by the authors.

Author Contributions. The literature search was performed by Sy Duong-Quy, Duc Huynh-Truong-Anh, Tien Nguyen-Quang, Thanh Nguyen-Thi-Kim, Thuy Tran-Ngoc-Anh, Nam Nguyen-Van-Hoai, Mai Do-Thi-Thu, Tram Tang-Thi-Thu, Anh Nguyen-Tuan, and Toi Nguyen-Van with significant contributions from Quan Nguyen-Hoang, Phung Hoang-Phi-Tuyet, Vinh Nguyen-Nhu, Hieu Nguyen-Lan, Sy Dinh-Ngoc, Dung Truong-Viet, and Thai Nguyen-Duy. Data collection was done by Sy Duong-Quy, Duc Huynh-Truong-Anh, Tien Nguyen-Quang, Thanh Nguyen-Thi-Kim, Thanh Nguyen-Chi, Thuy Tran-Ngoc-Anh, Nam Nguyen-Van-Hoai, and Mai Do-Thi-Thu. All authors contributed equally to the analysis and interpretation of data of the case report. Sy Duong-Quy, Duc Huynh-Truong-Anh, Tien Nguyen-Quang, Thanh Nguyen-Thi-Kim, Thuy Tran-Ngoc-Anh, Nam Nguyen-Van-Hoai, Mai Do-Thi-Thu, Tram Tang-Thi-Thu, Anh Nguyen-Tuan, Toi Nguyen-Van, and Thai Nguyen-Duy drafted the manuscript, with significant contributions from Quan Nguyen-Hoang, Vinh Nguyen-Nhu, Phung Hoang-Phi-Tuyet, Hieu Nguyen-Lan, Sy Dinh-Ngoc, and Dung Truong-Viet.

Disclosures. Sy Duong-Quy, Duc Hunyh-Truong-Anh, Tien Nguyen-Quang, Thanh Nguyen-Thi-Kim, Thuy Tran-Ngoc-Anh, Nam Nguyen-Van-Hoai, Mai Do-Thi-Thu, Tram Tang-Thi-Thu, Anh Nguyen-Tuan, and Toi Nguyen-Van, Phung Hoang-Phi-Tuyet, Quan Nguyen-Hoang, Vinh Nguyen-Nhu, Hieu Nguyen-Ian, Chuong Nguyen-Hong, Sy Dinh, Ngoc, Thai Nguyen-Duy and Dung Truong-Viet have nothing to disclose.

Compliance with Ethics Guidelines. This study was approved by the Ethics Committee of Binh Duong General Hospital (HDDD-BVDK BINH DUONG 09.2021). Written informed consent was obtained from the participants or their family for the study and publication.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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