Twenty-eight–day mortality among patients with severe or critical COVID-19 in Hong Kong during the early stages of the pandemic

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ABSTRACT

Introduction: In 2020, patients with critical coronavirus disease 2019 (COVID-19) had a 28-day mortality rate of 30% to 50% worldwide; outcomes among such patients in Hong Kong were unknown. This study investigated 28-day mortality and corresponding risk factors among patients with severe or critical COVID-19 in Hong Kong.

Methods: This retrospective cohort study included adult patients with severe or critical COVID-19 who were admitted to three public hospitals in Hong Kong from 22 January to 30 September 2020. Demographics, comorbidities, symptoms, treatment, and outcomes were examined.

Results: Among 125 patients with severe or critical COVID-19, 15 (12.0%) died within 28 days. Overall, the median patient age was 64 years; 48.0% and 54.4% of patients had hypertension and obesity, respectively. Respiratory samples were confirmed severe acute respiratory syndrome coronavirus 2 RNA–positive after a median of 3 days. The most common presenting symptom was fever (80.0% of patients); 45.6% and 32.8% of patients received care in intensive care unit and required mechanical ventilation, respectively. In logistic regression analysis comparing 28-day survivors and non-survivors, factors associated with greater 28-day mortality were older age (odds ratio [OR] per 1-year increase in age=1.12, 95% confidence interval [CI]=1.04-1.21; P=0.002), history of stroke (OR=15.96, 95% CI=1.65-154.66; P=0.017), use of renal replacement therapy (OR=15.32, 95% CI=2.67-87.83; P=0.002), and shorter duration of lopinavir-ritonavir treatment (OR per 1-day increase=0.82, 95% CI=0.68-0.98; P=0.034).

Conclusion: The 28-day mortality rate among patients with severe or critical COVID-19 in Hong Kong was 12.0%. Older age, history of stroke, use of renal replacement therapy, and shorter duration of lopinavir-ritonavir treatment were independent predictors of 28-day mortality.

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New knowledge added by this study

- The 28-day mortality rate among patients with severe or critical coronavirus disease 2019 (COVID-19) was lower in this study than in other studies.
- Older age, history of stroke, use of acute renal replacement therapy, and shorter duration of lopinavir-ritonavir were independent predictors of 28-day mortality among patients with severe or critical COVID-19.

Implications for clinical practice or policy

- The risk of COVID-19-related mortality is greater among patients who are older, have a history of stroke, require acute renal replacement therapy, and have a shorter course of lopinavir-ritonavir.
- Future studies with larger sample sizes, focused on viral and host factors such as spike gene mutations and interferon-1 immunity status, may help optimise prognosis prediction.

Introduction

Because of its close geographical proximity to mainland China, Hong Kong was one of the first regions outside of the Mainland to be affected by the severe acute respiratory syndrome (SARS) and coronavirus disease 2019 (COVID-19) epidemics.[1] Since 2020, Hong Kong experienced an initial epidemic wave of imported COVID-19 cases and spillover effects, as well as subsequent epidemic waves of imported COVID-19 cases and associated local transmission.

The COVID-19 epidemic has resulted in

新型冠狀病毒疫情初期香港新冠嚴重及危重患者的28天死亡率

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簡介：2020年全球新型冠狀病毒的危重患者的28天死亡率為30%至50%，但鮮有關於香港病患者的研究。本研究旨在找出香港新型冠狀病毒的嚴重及危重患者的28天死亡率及相關風險因素。

方法：這項回顧性隊列研究納入2020年1月22日至9月30日在三間香港公立醫院留醫的新型冠狀病毒的嚴重及危重成年患者，分析他們的人口統計資料、合併症、症狀、治療及結果。

結果：125名患者患有嚴重或危重新型冠狀病毒感染，15人（12.0%）於28天內死亡。患者年齡中為數為64歲；48.0%有高血壓，54.4%為肥胖。呼吸道分泌樣本在中位數3天後確定為嚴重急性呼吸綜合症冠狀病毒2型核糖核酸陽性。最常見的發病症狀是發燒（80.0%患者）；45.6%患者曾需要深切治療部護理，32.8%用到呼吸機。比較28天存活者及去世者的邏輯迴歸分析顯示，年齡較大（每增加一歲的勝算比=1.12，95%置信區間=1.04-1.21；P=0.002）、曾經中風（勝算比=15.96，95%置信區間=1.65-154.66；P=0.017）、需要腎臟替換治療（勝算比=15.32，95%置信區間=2.67-87.83；P=0.002）及接受較短的洛匹那韋—利托那韋療程（每多一天的勝算比=0.82，95%置信區間=0.68-0.98；P=0.034）會增加28天死亡的風險。

結論：香港新型冠狀病毒的嚴重及危重患者的28天死亡率為12.0%。年紀較大、中風史、使用腎臟替換治療及洛匹那韋—利托那韋治療時間較短是28天死亡率的獨立預測因素。

millions of deaths worldwide. By late 2020, there had been multiple country-level analyses in other regions; however, there were limited data concerning outcomes among patients with severe or critical COVID-19 in Hong Kong.[2] This study analysed 28-day mortality in these patients and explored risk factors for mortality among them during the first several months of the COVID-19 pandemic.

Methods

Study design and data collection

This retrospective multi-centre cohort study included all adult patients aged ≥18 years with severe or critical COVID-19 who were admitted to the medical wards or intensive care units (ICUs) of three public acute hospitals in Hong Kong from 22 January to 30 September 2020. The three hospitals were Pamela Youde Nethersole Eastern Hospital, Princess Margaret Hospital, and Ruttonjee and Tang Shiu Kin Hospitals.

Patients were diagnosed with COVID-19 if their respiratory samples contained severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA, according to reverse transcription polymerase chain reaction (RT-PCR) analysis. Respiratory samples included nasopharyngeal aspirate, nasopharyngeal swab, nasopharyngeal aspirate or swab paired with throat swab, or deep throat saliva. Coronavirus disease 2019 grade was considered mild, severe, or critical, in accordance with the guidelines of the Chinese Center for Disease Control and Prevention.[3] Severe COVID-19 was characterised by dyspnoea, respiratory rate of ≥30 breaths/minute, blood oxygen saturation <94%, ratio of arterial oxygen partial pressure to fractional inspired oxygen (P/F ratio) <300, and/or a 50% increase in lung infiltrates within 2 days.[3] Critical COVID-19 was characterised by respiratory failure, septic shock, and/or multiple organ dysfunction or failure.[3]

Hong Kong experienced three epidemic waves during the study period.[4] The first epidemic wave, from mid-January to early March 2020, occurred after travellers from mainland China arrived in Hong Kong during the Chinese New Year. The second epidemic wave occurred when Hong Kong residents returned from overseas during the Easter Holiday, from mid-March to May 2020. The third epidemic wave extended from early July until late September 2020; disease transmission may have originated among commercial airline crews.[4] Cases were classified as imported or local by the Centre for Health Protection within the Department of Health. Medical comorbidities were defined according to the International Classification of Diseases, Tenth Revision. Comorbidities were selected based on the STOP-COVID (Study of the Treatment and Outcomes in Critically Ill Patients With COVID-19) in the US, which analysed critical COVID-19 cases at 65 ICUs.[5]

All medical records and data from the Clinical Management System of Hospital Authority and Clinical Information System (IntelliVue Clinical Information Portfolio; Philips Medical, Amsterdam, Netherlands) used by the ICUs were retrospectively reviewed. Upper respiratory tract infection (URI)–related symptoms included cough, rhinorrhoea, and sore throat. For patients admitted to the ICU, disease grade on admission was determined using the APACHE IV (Acute Physiology and Chronic Health Evaluation IV) score and the SOFA (Sequential Organ Failure Assessment) score. For patients requiring mechanical ventilatory support, disease grade was determined by the P/F ratio on the day of intubation. Blood test parameters included minimum lymphocyte count, maximum C-reactive protein level, maximum lactate dehydrogenase (LDH) level, and maximum alanine aminotransferase level. Clinical outcome data included the use of oxygen supplementation, mechanical ventilation, vasopressor or inotrope, renal replacement therapy (RRT), extracorporeal membrane oxygenation, and cardiopulmonary resuscitation, as well as mortality and length of stay in the ICU and hospital. Patients were followed up until death or 31 March 2021, whichever occurred earlier.

The primary outcome was 28-day mortality. Secondary outcomes included length of stay and mortality in the ICU and hospital, duration of oxygen supplementation and mechanical ventilatory support, and time to viral clearance or time to development of antibodies against SARS-CoV-2. Viral clearance was defined as the collection of two consecutive respiratory samples at least 24 hours apart that were both SARS-CoV-2–negative, according to RT-PCR analysis. Cycle threshold (Ct) value indicated the number of RT-PCR cycles required to amplify the viral RNA to a detectable level; this value was inversely related to viral load.[6] Minimum Ct values were recorded to determine maximum viral load. Each patient's blood was collected and qualitatively tested for antibodies against SARS-CoV-2 (ie, antibodies to SARS-CoV-2 nucleoprotein) using the Abbott SARS-CoV-2 Immunoglobulin G assay. Patients were generally released from isolation when they met the requirement for viral clearance or when they displayed serum antibodies, in accordance with recommendations from the Scientific Committee on Emerging and Zoonotic Diseases under the Centre for Health Protection within the Department of Health.[7]

Statistical analysis

The clinical characteristics and outcomes of patients with severe or critical COVID-19 were compared between 28-day survivors and non-survivors. Subgroup analysis was performed among patients who received ICU care between 28-day survivors and non-survivors; it was also performed among patients whose laboratory reports provided information regarding viral load (ie, Ct values) in respiratory samples. The frequencies of these characteristics and outcomes were expressed as medians ± interquartile ranges (IQRs) or as numbers of patients and corresponding percentages.

Based on the population of patients with COVID-19 (n=5080) in Hong Kong on 29 September 2020, where 351 patients had ever displayed serious or critical disease, the prevalence of outcome factors in this patient population was 6.9%. Using a confidence limit of 5% and a design effect of 2, the sample sizes required to achieve statistical powers of 80% and 90% were 84 patients and 138 patients, respectively.

For univariate analyses, the Pearson Chi squared test or Fisher's exact test was used to compare categorical variables; the Mann-Whitney *U* test was used to compare continuous variables. Variables with a P value of <0.1 in univariate analyses were included in subsequent multivariable analyses. Independent predictors of 28-day mortality were assessed by logistic regression analysis using a forward stepwise approach. Considering the potential for unstable or extreme estimates because of the small sample sizes in subgroup analyses, logistic regression was not performed. All statistical analyses were performed using SPSS (Windows version 23.0; IBM Corp, Armonk [NY], US).

Results

Study population

From 22 January to 30 September 2020, 1312 adult patients with COVID-19 were admitted to Princess Margaret Hospital, Pamela Youde Nethersole Eastern Hospital, and Ruttonjee and Tang Shiu Kin Hospitals. In total, 125 patients had severe or critical COVID-19.

Baseline characteristics

The median age was 64 years (IQR=57-75); 69.6% of the patients were men and 93.6% were Chinese (Table 1). In total, 68.8% of the patients were admitted in the third epidemic wave and 86.4% acquired COVID-19 in Hong Kong. Almost half of the patients had hypertension or obesity (48.0% and 54.4%, respectively); 27.2% of patients had diabetes mellitus, and 21.6% had ever smoked. The median duration of symptoms before respiratory samples were confirmed SARS-CoV-2–positive was 3 days. The most common presenting symptom was fever (80.0%), followed by URI-related symptoms (64.8%). Overall, 5.6% of the patients were asymptomatic before their positive test result.

Interventions

As shown in Table 1, 60% to 80% of patients received lopinavir-ritonavir, ribavirin, interferon beta-1b, or corticosteroids. Nearly half of the patients (48.8%) received anticoagulation treatment; <20% received remdesivir, tocilizumab, or convalescent plasma. More than 80% of the patients received antibiotics during hospitalisation. In total, 45.6% of the patients received ICU care. One patient received non-invasive ventilation, 41 patients (32.8%) received mechanical ventilation, and 11 patients (8.8%) received prone ventilation. Only one patient required extracorporeal membrane oxygenation. Approximately one-fourth of the patients required vasopressor support; 14 patients (11.2%) received acute RRT.

Outcomes

Fifteen patients (12%) died within 28 days (Table 1). Four additional patients died during hospitalisation; thus, the overall hospital mortality rate among patients with severe or critical COVID-19 was 15.2%. The median hospital length of stay was 21.8 days (IQR=15-31.8) and the median duration of oxygen supplementation was 7 days (IQR=4-12.5).

TABLE 1. Characteristics and outcomes of patients with severe or critical coronavirus disease 2019 in Hong Kong*

	Total (n=125)	28-Day survivors (n=110)	28-Day non-survivors (n=15)	P value
Age, y	64 (57-75)	62 (56-71.3)	84 (71-86)	<0.001
Male sex	87 (69.6%)	75 (68.2%)	12 (80.0%)	0.550
Ethnicity				
Chinese	117 (93.6%)	102 (92.7%)	15 (100%)	0.761
White	6 (4.8%)	6 (5.5%)	0	
Southeast Asian	2 (1.6%)	2 (1.8%)	0	
Wave				
1st	17 (13.6%)	14 (12.7%)	3 (20.0%)	0.148
2nd	22 (17.6%)	22 (20.0%)	0	
3rd	86 (68.8%)	74 (67.3%)	12 (80.0%)	
Local/imported infection				
Local	108 (86.4%)	95 (86.4%)	13 (86.7%)	1
Acute hospital				
PMH	60 (48.0%)	55 (50.0%)	5 (33.3%)	0.408
PYNEH	55 (44.0%)	46 (41.8%)	9 (60.0%)	
RTSKH	10 (8.0%)	9 (8.2%)	1 (6.7%)	
Comorbidities				
Ever-smoker	27 (21.6%)	21 (19.1%)	6 (40.0%)	0.071
Chronic lung disease	6 (4.8%)	5 (4.5%)	1 (6.7%)	0.543
Hypertension	60 (48.0%)	50 (45.5%)	10 (66.7%)	0.102
Diabetes mellitus	34 (27.2%)	28 (25.5%)	6 (40.0%)	0.188
Obesity	68 (54.4%)	63 (57.3%)	5 (33.3%)	0.071
Ischaemic heart disease	10 (8.0%)	6 (5.5%)	4 (26.7%)	0.019
Stroke	9 (7.2%)	5 (4.5%)	4 (26.7%)	0.012
Chronic renal failure	3 (2.4%)	3 (2.7%)	0	0.679
Cirrhosis	1 (0.8%)	1 (0.9%)	0	0.880
Malignancy	6 (4.8%)	6 (5.5%)	0	0.457
Immunocompromised	5 (4.0%)	4 (3.6%)	1 (6.7%)	0.478
Duration of symptoms before positive test, d	3 (1-5)	3 (1-6)	1 (1-2)	0.014
Symptoms before positive test				
Fever	100 (80.0%)	89 (80.9%)	11 (73.3%)	0.498
URI-related	81 (64.8%)	76 (69.1%)	5 (33.3%)	0.010
Dyspnoea	30 (24.0%)	26 (23.6%)	4 (26.7%)	0.755
Diarrhoea	11 (8.8%)	10 (9.1%)	1 (6.7%)	1
Asymptomatic	7 (5.6%)	5 (4.5%)	2 (13.3%)	0.198
Laboratory findings				
Minimum lymphocyte count, × 10^9/L	0.5 (0.32-0.7)	0.5 (0.35-0.7)	0.4 (0.18-0.55)	0.127
Maximum CRP level, mg/L	111 (67.8-193)	103 (63.6-153.5)	209 (82-248)	0.031
Maximum LDH level, U/L	427 (345-536.25)	423 (346.5-501.5)	646.5 (337.5-1251)	0.095
Maximum ALT level, U/L	101 (54-171)	102.5 (54.3-158.5)	101 (51-356)	0.761

Abbreviations: ALT = alanine aminotransferase; CPR = cardiopulmonary resuscitation; CRP = C-reactive protein; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; LDH = lactate dehydrogenase; PMH = Princess Margaret Hospital; PYNEH = Pamela Youde Nethersole Eastern Hospital; RTSKH = Ruttonjee and Tang Shiu Kin Hospitals; URI = upper respiratory tract infection

* Data are shown as No. (%) or mean ± interquartile range, unless otherwise specified

TABLE 1. (cont'd)

	Total (n=125)	28-Day survivors (n=110)	28-Day non-survivors (n=15)	P value
Medical treatment				
Antivirals				
Lopinavir-ritonavir				
Use	91 (72.8%)	83 (75.5%)	8 (53.3%)	0.117
Duration, d	5 (0-10)	6 (0.75-11)	1 (0-2)	0.007
Ribavirin				
Use	78 (62.4%)	70 (63.6%)	8 (53.3%)	0.782
Duration, d	6 (0-10)	6 (0-11)	4 (0-8)	0.582
Interferon beta-1b				
Use	99 (79.2%)	87 (79.1%)	12 (80.0%)	1
No. of 8-μg doses	4 (1-10)	4 (1-10)	6 (1-10)	0.985
Remdesivir				
Use	20 (16.0%)	17 (15.5%)	3 (20.0%)	0.707
Duration, d	0 (0-0)	0 (0-0)	0 (0-0)	0.747
Anticoagulation				
Use	61 (48.8%)	52 (47.3%)	9 (60.0%)	0.416
Duration, d	0 (0-10.5)	0 (0-11.3)	4 (0-10)	0.941
Corticosteroids				
Use	95 (76.0%)	84 (76.4%)	11 (73.3%)	0.755
Duration, d	6 (1-9)	6 (1-9)	4 (0-8)	0.297
Tocilizumab	18 (14.4%)	15 (13.6%)	3 (20.0%)	0.453
Convalescent plasma	6 (4.8%)	6 (5.5%)	0	1
Other antibacterial agents	103 (82.4%)	88 (80.0%)	15 (100%)	0.071
Duration of oxygen supplementation, d	7 (4-12.5)	7 (4-13)	6.8 (1-10)	0.111
Hospital stay				
Length of stay, d	21.8 (15-31.8)	23.7 (16.7-36.1)	8.5 (3.8-15)	
Discharged by day 28	69 (55.2%)			
Received ICU care	57 (45.6%)	48 (43.6%)	9 (60.0%)	0.179
Hypoxaemia interventions				
High-flow nasal cannula	6 (4.8%)	5 (4.5%)	1 (6.7%)	0.543
Non-invasive ventilation	1 (0.8%)	0	1 (6.7%)	0.120
Prone ventilation	11 (8.8%)	9 (8.2%)	2 (13.3%)	0.621
Mechanical ventilation	41 (32.8%)	31 (28.2%)	10 (66.7%)	0.006
Inhaled nitric oxide	0			
Tracheostomy	7 (5.6%)	7 (6.4%)	0	0.597
Chest drain insertion	5 (4.0%)	4 (3.6%)	1 (6.7%)	0.478
Acute renal replacement therapy	14 (11.2%)	8 (7.3%)	6 (40.0%)	0.002
Vasopressor use	31 (24.8%)	21 (19.1%)	10 (66.7%)	<0.001
CPR	3 (2.4%)	1 (0.9%)	2 (13.3%)	0.038
ECMO	1 (0.8%)	1 (0.9%)	0	1

Comparison between 28-day survivors and non-survivors

Twenty-eight–day non-survivors were older than 28-day survivors (84 years [IQR=71-86] vs 62 years [IQR=56-71.3]; P<0.001) and more frequently had a history of ischaemic heart disease (26.7% vs 5.5%; P=0.019) or stroke (26.7% vs 4.5%; P=0.012). Moreover, non-survivors had a shorter duration of symptoms before RT-PCR confirmation of SARS-CoV-2 positivity in respiratory samples (1 day [IQR=1-2] vs 3 days [IQR=1-6]; P=0.014); fewer non-survivors displayed URI-related symptoms (33.3% vs 69.1%; P=0.010). Non-survivors had a higher maximum C-reactive protein level (209 mg/L [IQR=82-248] vs 103 mg/L [IQR=63.6-153.5]; P=0.031); they more frequently received mechanical ventilation (66.7% vs 28.2%; P=0.006), acute RRT (40.0% vs 7.3%; P=0.002), and vasopressor support (66.7% vs 19.1%; P<0.001). Finally, non-survivors received a shorter duration of lopinavir-ritonavir treatment (1 day [IQR=0-2] vs 6 days [IQR=0.75-11]; P=0.007) [Table 1].

Independent predictors of 28-day mortality

Logistic regression analysis revealed that age (odds ratio [OR] per 1-year increase in age=1.12, 95% confidence interval [CI]=1.04-1.21; P=0.002), history of stroke (OR=15.96, 95% CI=1.65-154.66; P=0.017), use of acute RRT (OR=15.32, 95% CI=2.67-87.83; P=0.002), and lopinavir-ritonavir duration (OR per 1-day increase=0.82, 95% CI=0.68-0.98; P=0.034) were independent predictors of 28-day mortality (Table 2).

Subgroup analysis of intensive care unit patients

Comparison between 28-day survivors and non-survivors

Among the 57 patients admitted to the ICU, nine died; the ICU mortality rate was 15.8% (Table 3). The median ICU length of stay was 9.6 days (IQR=4.6-14.9). Univariate analysis demonstrated that 28-day non-survivors were older; more frequently had a history of ischaemic heart disease or stroke; had a shorter duration of symptoms; less frequently presented with URI-related symptoms; more frequently received mechanical ventilation, acute RRT, and vasopressor support; and received a shorter course of lopinavir-ritonavir treatment. Other significant differences between non-survivors and survivors were the minimum lymphocyte count (0.32×10^9/L [IQR=0.17-0.4] vs 0.4×10^9/L [IQR=0.3-0.6]; P=0.042), maximum LDH level (706 U/L [IQR=492.2-5255.5] vs 474.5 U/L [IQR=406.3-616]; P=0.043), anticoagulation duration (8 days [IQR=3-10] vs 12.5 days [IQR=7.5-26.8]; P=0.045), APACHE IV score upon ICU admission (83 [IQR=64.5-98] vs 54.5 [IQR=46-61.8]; P<0.001), and SOFA score upon ICU admission (10 [IQR=5.5-13] vs 4 [IQR=3-5.8]; P=0.001).

P/F ratio and duration of ventilation

The median P/F ratio on the day of intubation was 94.1 (IQR=81.9-117.7) for patients with COVID-19 requiring mechanical ventilation, and the median duration of ventilation for all ICU patients with COVID-19 was 8.5 days (IQR=5-18); these values were similar between survivors and non-survivors (Table 3).

Subgroup analysis of cycle threshold values

As shown in Table 4, 28-day non-survivors were older and more frequently had a history of ischaemic heart disease or stroke; fewer of them had URI-related symptoms (36.4% vs 68.8%; P=0.010). Non-survivors more frequently received mechanical ventilation (81.8% vs 29.9%; P=0.001), acute RRT (45.5% vs 7.8%; P=0.004), and vasopressor support (81.8% vs 23.4%; P<0.001); they received a shorter course of lopinavir-ritonavir treatment (1 day [IQR=0-2] vs 6 days [IQR=0.75-11]; P=0.010). Additionally, non-survivors had a lower minimum lymphocyte count (0.37×10^9/L [IQR=0.16-0.4] vs 0.49×10^9/L [IQR=0.3-0.7], P=0.041) and lower minimum Ct value (15.1 [IQR=12.6-18.5] vs 19 [IQR=16.4-22.9]; P=0.004).

Other viral parameters

Among the 125 patients with severe or critical COVID-19, 38 underwent regular monitoring of viral load via RT-PCR analysis of respiratory samples for SARS-CoV-2 RNA; viral clearance was achieved within a median of 26 days (IQR=19-35). Among the 79 patients with access to antibody testing, a median of 14 days (IQR=10-18) was elapsed between the first positive RT-PCR result and the emergence of antibodies against SARS-CoV-2.

TABLE 2. Independent predictors of 28-day mortality according to logistic regression analysis

	Odds ratio	95% Confidence interval	P value
Age	1.12	1.04-1.21	0.002
Comorbidity: stroke	15.96	1.65-154.66	0.017
Acute renal replacement therapy	15.32	2.67-87.83	0.002
Lopinavir-ritonavir duration	0.82	0.68-0.98	0.034

TABLE 3. Clinical characteristics and outcomes among patients who received care in intensive care unit compared between 28-day survivors and non-survivors*

	Total (n=57)	28-Day survivors (n=48)	28-Day non-survivors (n=9)	P value
Age, y	66 (59.5-79.5)	64 (57-71.8)	80 (70.5-85)	0.002
Male sex	41 (71.9%)	33 (68.8%)	8 (88.9%)	0.420
Ethnicity				0.743
Chinese	54 (94.7%)	45 (93.8%)	9 (100%)	
White	2 (3.5%)	2 (4.2%)	0	
Southeast Asian	1 (1.8%)	1 (2.1%)	0	
Wave				0.298
1st	7 (12.3%)	6 (12.5%)	1 (11.1%)	
2nd	10 (17.5%)	10 (20.8%)	0	
3rd	40 (70.2%)	32 (66.7%)	8 (88.9%)	
Local/imported infection				1
Local	50 (87.7%)	42 (87.5%)	8 (88.9%)	
Acute hospital				0.410
PMH	24 (42.1%)	22 (45.8%)	2 (22.2%)	
PYNEH	29 (50.9%)	23 (47.9%)	6 (66.7%)	
RTSKH	4 (7.0%)	3 (6.3%)	1 (11.1%)	
Comorbidities				
Ever-smoker	14 (24.6%)	9 (18.8%)	5 (55.6%)	0.032
Chronic lung disease	2 (3.5%)	2 (4.2%)	0	1
Hypertension	31 (54.4%)	25 (52.1%)	6 (66.7%)	0.488
Diabetes mellitus	21 (36.8%)	16 (33.3%)	5 (55.6%)	0.266
Obesity	34 (59.6%)	31 (64.6%)	3 (33.3%)	0.137
Ischaemic heart disease	6 (10.5%)	3 (6.3%)	3 (33.3%)	0.044
Stroke	2 (3.5%)	0	2 (22.2%)	0.023
Chronic renal failure	2 (3.5%)	2 (4.2%)	0	1
Cirrhosis	0			
Malignancy	1 (1.8%)	1 (2.1%)	0	1
Immunocompromised	2 (3.5%)	1 (2.1%)	1 (11.1%)	0.293
Duration of symptoms before positive test, d	3 (1-7)	3 (2-7.8)	1 (1-4)	0.082
Symptoms before positive test				
Fever	47 (82.5%)	39 (81.3%)	8 (88.9%)	1
URI-related	42 (73.7%)	39 (81.3%)	3 (33.3%)	0.007
Dyspnoea	15 (26.3%)	13 (27.1%)	2 (22.2%)	1
Diarrhoea	5 (8.8%)	4 (8.3%)	1 (11.1%)	1
Asymptomatic	1 (1.8%)	1 (2.1%)	0	1
Laboratory findings				
Minimum lymphocyte count, × 10^9/L	0.4 (0.3-0.57)	0.4 (0.3-0.6)	0.32 (0.17-0.4)	0.042
Maximum CRP level, mg/L	145 (87.7-232)	143 (87.5-229.8)	214 (99.5-295)	0.518
Maximum LDH level, U/L	502 (406.5-661.5)	474.5 (406.3-616)	706 (492.2-5255.5)	0.043
Maximum ALT level, U/L	111 (61-217.5)	110 (76.3-186.8)	171 (53-2120.5)	0.431

Abbreviations: ALT = alanine aminotransferase; APACHE IV = Acute Physiology and Chronic Health Evaluation IV; CPR = cardiopulmonary resuscitation; CRP = C-reactive protein; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; LDH = lactate dehydrogenase; PMH = Princess Margaret Hospital; PYNEH = Pamela Youde Nethersole Eastern Hospital; RTSKH = Ruttonjee and Tang Shiu Kin Hospitals; SOFA = Sequential Organ Failure Assessment; URI = upper respiratory tract infection

* Data are shown as No. (%) or mean ± interquartile range, unless otherwise specified

TABLE 3. (cont'd)

	Total (n=57)	28-Day survivors (n=48)	28-Day non-survivors (n=9)	P value
Medical treatment				
Antivirals				
Lopinavir-ritonavir				
Use	43 (75.4%)	38 (79.2%)	5 (55.6%)	0.202
Duration, d	3 (0.5-9.5)	5 (1-10)	1 (0-3.5)	0.017
Ribavirin				
Use	40 (70.2%)	34 (70.8%)	6 (66.7%)	1
Duration, d	7 (0-10)	7 (0-10)	7 (0-8)	0.859
Interferon beta-1b				
Use	46 (80.7%)	39 (81.3%)	7 (77.8%)	1
No. of 8-μg doses	5 (1-12)	4 (1-12)	6 (0.5-11)	0.869
Remdesivir				
Use	17 (29.8%)	14 (29.2%)	3 (33.3%)	1
Duration, d	0 (0-5)	0 (0-5)	0 (0-3.5)	0.978
Anticoagulation				
Use	49 (86.0%)	41 (85.4%)	8 (88.9%)	1
Duration, d	11 (7-22)	12.5 (7.5-26.8)	8 (3-10)	0.045
Corticosteroids				
Use	49 (86.0%)	41 (85.4%)	8 (88.9%)	1
Duration, d	8 (3-9)	8 (3-9)	6 (1-9)	0.581
Tocilizumab	17 (29.8%)	14 (29.2%)	3 (33.3%)	1
Convalescent plasma	4 (7.0%)	4 (8.3%)	0	1
Other antibacterial agents	55 (96.5%)	46 (95.8%)	9 (100%)	1
Duration of oxygen supplementation, d	12 (7-27.5)	12 (7.3-28.8)	9.7 (3.9-12.4)	
Hospital stay				0.421
Length of stay, d	27.2 (17.3-51)	29.8 (23-60.3)	9.9 (4.3-15.9)	
Discharged by day 28	21 (36.8%)			
ICU length of stay, d	9.6 (4.6-14.9)	9.72 (4.4-21.6)	9.5 (4-11.5)	
APACHE IV score upon ICU admission	56 (49-69)	54.5 (46-61.8)	83 (64.5-98)	<0.001
SOFA score upon ICU admission	4 (3-7.5)	4 (3-5.8)	10 (5.5-13)	0.001
Hypoxaemia interventions				
High-flow nasal cannula	6 (10.5%)	5 (10.4%)	1 (11.1%)	1
Non-invasive ventilation	0			
Prone ventilation	11 (19.3%)	9 (18.8%)	2 (22.2%)	1
Mechanical ventilation	40 (70.2%)	31 (64.6%)	9 (100%)	0.046
Ventilator duration, d	8.5 (5-18)	9 (5-22)	8 (3-9.5)	
P/F ratio	94.1 (81.9-117.7)	91.2 (79.7-111.1)	115.7 (87.8-125.6)	
Inhaled nitric oxide	0			
Tracheostomy	7 (12.3%)	7 (14.6%)	0	0.582
Chest drain insertion	5 (8.8%)	4 (8.3%)	1 (11.1%)	1
Acute renal replacement therapy	14 (24.6%)	8 (16.7%)	6 (66.7%)	0.004
Vasopressor use	29 (50.9%)	21 (43.8%)	8 (88.9%)	0.025
CPR	2 (3.5%)	1 (2.1%)	1 (11.1%)	0.293
ECMO	1 (1.8%)	1 (2.1%)	0	1

TABLE 4. Clinical characteristics and outcomes among patients with available cycle threshold values compared between 28-day survivors and non-survivors*

	Total (n=88)	28-Day survivors (n=77)	28-Day non-survivors (n=11)	P value
Age, y	65 (57-75.8)	64 (56.5-71.5)	85 (71-86)	<0.001
Male sex	62 (70.5%)	53 (68.8%)	9 (81.8%)	0.496
Ethnicity				
Chinese	84 (95.5%)	73 (94.8%)	11 (100%)	0.741
White	2 (2.3%)	2 (2.6%)	0	
Southeast Asian	2 (2.3%)	2 (2.6%)	0	
Wave				
1st	0	0	0	0.588
2nd	8 (9.1%)	8 (10.4%)	0	
3rd	80 (90.9%)	69 (89.6%)	11 (100%)	
Local/imported infection				
Local	83 (94.3%)	72 (93.5%)	11 (100%)	1
Acute hospital				
PMH	41 (46.6%)	38 (49.4%)	3 (27.3%)	0.379
PYNEH	40 (45.5%)	33 (42.9%)	7 (63.6%)	
RTSKH	7 (8.0%)	6 (7.8%)	1 (9.1%)	
Comorbidities				
Ever-smoker	20 (22.7%)	15 (19.5%)	5 (45.5%)	0.116
Chronic lung disease	2 (2.3%)	1 (1.3%)	1 (9.1%)	0.236
Hypertension	47 (53.4%)	40 (51.9%)	7 (63.6%)	0.533
Diabetes mellitus	25 (28.4%)	21 (27.3%)	4 (36.4%)	0.500
Obesity	50 (56.8%)	47 (61.0%)	3 (27.3%)	0.050
Ischaemic heart disease	9 (10.2%)	5 (6.5%)	4 (36.4%)	0.024
Stroke	6 (6.8%)	3 (3.9%)	3 (27.3%)	0.012
Chronic renal failure	3 (3.4%)	3 (3.9%)	0	1
Cirrhosis	1 (1.1%)	1 (1.3%)	0	1
Malignancy	4 (4.5%)	4 (5.2%)	0	1
Immunocompromised	4 (4.5%)	3 (3.9%)	1 (9.1%)	0.420
Duration of symptoms before positive test, d	2 (1-4)	2 (1-5)	1 (1-2)	0.055
Symptoms before positive test				
Fever	71 (80.7%)	62 (80.5%)	9 (81.8%)	0.498
URI-related	57 (64.8%)	53 (68.8%)	4 (36.4%)	0.010
Dyspnoea	17 (19.3%)	14 (18.2%)	3 (27.3%)	0.755
Diarrhoea	10 (11.4%)	9 (11.7%)	1 (9.1%)	1
Asymptomatic	5 (5.7%)	4 (5.2%)	1 (9.1%)	0.198
Ct value	18.8 (16.2-22)	19 (16.4-22.9)	15.1 (12.6-18.5)	0.004
Laboratory findings				
Minimum lymphocyte count, × 10^9/L	0.42 (0.3-0.66)	0.49 (0.3-0.7)	0.37 (0.16-0.4)	0.041
Maximum CRP level, mg/L	105.5 (70.6-186.3)	101 (65-151)	200 (82-228)	0.108
Maximum LDH level, U/L	421 (348.5-530)	413 (349-501)	635 (341-1185)	0.106
Maximum ALT level, U/L	109 (51.5-174.8)	109 (51.5-168.5)	62 (51-1670)	0.781

Abbreviations: ALT = alanine aminotransferase; CPR = cardiopulmonary resuscitation; CRP = C-reactive protein; Ct = cycle threshold; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; LDH = lactate dehydrogenase; PMH = Princess Margaret Hospital; PYNEH = Pamela Youde Nethersole Eastern Hospital; RTSKH = Ruttonjee and Tang Shiu Kin Hospitals; URI = upper respiratory tract infection

* Data are shown as No. (%) or mean ± interquartile range, unless otherwise specified

TABLE 4. (cont'd)

	Total (n=88)	28-Day survivors (n=77)	28-Day non-survivors (n=11)	P value
Medical treatment				
Antivirals				
Lopinavir-ritonavir				
Use	60 (68.2%)	55 (71.4%)	5 (45.5%)	0.097
Duration, d	3 (0-8)	6 (0.75-11)	1 (0-2)	0.010
Ribavirin				
Use	51 (58.0%)	44 (57.1%)	7 (63.6%)	0.755
Duration, d	4 (0-8)	6 (0-11)	4 (0-8)	0.823
Interferon beta-1b				
Use	82 (93.2%)	73 (94.8%)	9 (81.8%)	0.161
No. of 8-μg doses	6 (3-12)	4 (1-10)	6 (1-10)	0.591
Remdesivir				
Use	16 (18.2%)	13 (16.9%)	3 (27.3%)	0.413
Duration, d	0 (0-0)	0 (0-0)	0 (0-0)	0.492
Anticoagulation				
Use	51 (58.0%)	43 (55.8%)	8 (72.7%)	0.345
Duration, d	6 (0-11)	0 (0-11.3)	4 (0-10)	0.941
Corticosteroids				
Use	74 (84.1%)	66 (85.7%)	8 (72.7%)	0.372
Duration, d	7 (4-9)	8 (4-9)	6 (0-9)	0.216
Tocilizumab	17 (19.3%)	14 (18.2%)	3 (27.3%)	0.438
Convalescent plasma	5 (5.7%)	5 (6.5%)	0	1
Other antibacterial agents	69 (78.4%)	58 (75.3%)	11 (100%)	0.112
Duration of oxygen supplementation, d	8 (4-13)	8 (4.5-13)	9 (1-11.9)	0.321
Hospital stay				
Length of stay, d	23.8 (15-31.8)	23.6 (16.4-31.8)	9.9 (1.8-15)	
Discharged by day 28	51 (58.0%)			
Received ICU care	44 (50.0%)	36 (46.8%)	8 (72.7%)	0.196
Hypoxaemia interventions				
High-flow nasal cannula	2 (2.3%)	1 (1.3%)	1 (9.1%)	0.236
Non-invasive ventilation	0	0	0	0.120
Prone ventilation	10 (11.4%)	8 (10.4%)	2 (18.2%)	0.607
Mechanical ventilation	32 (36.4%)	23 (29.9%)	9 (81.8%)	0.001
Inhaled nitric oxide	0			
Tracheostomy	5 (5.7%)	5 (6.5%)	0	1
Chest drain insertion	4 (4.5%)	3 (3.9%)	1 (9.1%)	0.420
Acute renal replacement therapy	11 (12.5%)	6 (7.8%)	5 (45.5%)	0.004
Vasopressor use	27 (30.7%)	18 (23.4%)	9 (81.8%)	<0.001
CPR	2 (2.3%)	1 (1.3%)	1 (9.1%)	0.236
ECMO	1 (1.1%)	1 (1.3%)	0	1

Discussion

Outcomes compared with international data

In this cohort of Hong Kong patients with severe or critical COVID-19, the 28-day mortality rate was 12.0%; it was 15.8% among such patients who were admitted to the ICU. In 2020, higher mortality rates were observed among cohorts in the US (35.4% in the STOP-COVID cohort[5]), Italy (ICU and hospital mortality rates of 48.8% and 53.4%, respectively[8]), and China (28-day mortality of 38.7% among severely and critically ill patients[9]). Patient baseline characteristics were similar across the cohorts—the median age was 60 to 70 years and the most common comorbidity was hypertension (40%-50%).[5,8,9] The proportion of patients requiring mechanical ventilation varied across cohorts, ranging from 67% to 87% in the US[5] and Italian[8] cohorts, whereas it was 30% in the Chinese cohort.[9] Overall, 70.2% of patients in our ICU subgroup received mechanical ventilation, which is comparable with the percentages in the US[5] and Italy.[8] The P/F ratio in our cohort was similar to the ratio in the STOP-COVID (median, 94.1 vs 124),[5] reflecting moderate to severe hypoxaemia. Extracorporeal membrane oxygenation was required by <3% of patients in our cohort and the three comparison cohorts. In addition to patient factors, non-patient factors (eg, ICU bed availability and patient-to–hospital staff ratio) may affect quality of care and patient outcomes. Among hospitals of the Department of Veterans Affairs in the US, COVID-19 mortality was significantly greater when ICU demand exceeded 75%.[10] Hospitals in the US with fewer ICU beds and nurses per COVID-19 case also had greater mortality.[11] The relatively low prevalence, limited local transmission, and better ICU availability in Hong Kong may have contributed to the lower mortality rate observed in this study.

Independent predictors of 28-day mortality

In our cohort, older age, history of stroke, use of acute RRT, and shorter duration of lopinavir-ritonavir treatment were independent predictors of 28-day mortality. Across studies in 2020, older age was commonly identified as a risk factor for COVID-19 mortality.[5,8,9] A history of stroke was also identified as a significant risk factor for COVID-19 mortality in a large cohort study in China; higher neutrophil and interleukin-6 levels were observed in patients with a history of stroke, possibly because of a stronger inflammatory response to COVID-19.[12] In an American cohort, the hospital mortality rate was 50% among patients who developed acute kidney injury, and the highest mortality risk was present in patients requiring dialysis.[13] In 2020, the mechanism of acute kidney injury was speculated to involve direct viral invasion of renal tissue, considering post-mortem findings in China.[14] Such injury was closely related to respiratory failure; in another American cohort, the median time from mechanical ventilation to the initiation of acute RRT was 0.3 hour.[15]

A shorter duration of lopinavir-ritonavir was identified as a risk factor in our cohort. Lopinavir-ritonavir was originally a protease inhibitor for the treatment of human immunodeficiency virus infection.[16] In 2020, this repurposed drug was included in treatment recommendations in Hong Kong, where it effectively reduced viral load when used in combination with ribavirin and/or interferon beta-1b[16]; however, there was no difference in mortality between treatment and control groups as no patient died during the study.[16] Two Chinese cohorts did not show significant outcome differences when using lopinavir-ritonavir,[17] consistent with interim results from the World Health Organization Solidarity trial.[18] Lopinavir-ritonavir treatment has been associated with gastrointestinal upset and liver dysfunction. Our findings may differ from the results of other cohort studies because, in the present study, lopinavir-ritonavir treatment was not administered to patients with severe liver dysfunction or to those who were presumably unable to tolerate side-effects because of their illness. In contrast, up to 80% of the ICU patients in an American cohort received hydroxychloroquine and/or azithromycin,[5] despite doubtful efficacy and significant arrhythmia risk with QT prolongation.[19] The selection of antiviral treatment may partly explain the differences in mortality among cohorts.

Other risk factors based on univariate analysis

Regarding viral load, univariate analysis in our cohort showed that lower minimum Ct values were associated with greater 28-day mortality. In a study at Cornell in the US,[6] the SARS-CoV-2 viral load on admission independently predicted the risks of intubation and mortality. In a Brazilian cohort, Ct values of <25 were associated with greater mortality.[21] The implications of Ct values may become clearer if patients with mild disease are analysed together.

Lymphopenia on admission has been associated with worse outcomes in terms of ICU care requirement and mortality,[22] presumably because of the cytokine storm phenomenon and the infection of T cells by SARS-CoV-2,[19] which infection of T cells by SARS-CoV-2 was confirmed both in vitro and by flow cytometry and immunofluorescence studies.[20] In the present study, the minimum lymphocyte count was significantly lower among 28-day non-survivors in both subgroups. Multi-centre COVID-19 studies have shown that an elevated LDH level is associated with a six-fold increase in the likelihood of severe disease and a 16-fold increase in the likelihood of mortality.[24] In the present study, although univariate

analysis showed that the maximum LDH level was associated with greater 28-day mortality in the overall cohort, it was not an independent predictor in logistic regression; this finding may have been influenced by the sample size.

Strengths

To our knowledge, this large study was the first investigation in Hong Kong concerning the clinical characteristics and outcomes of patients with severe or critical COVID-19; it included three public acute hospitals and covered three waves of the COVID-19 pandemic in Hong Kong. This study also explored the impacts of viral parameters and treatment modalities on 28-day mortality.

Limitations

First, this retrospective study in Hong Kong may have been subject to confounding factors and selection bias. The results may not be generalisable to patients with COVID-19 worldwide. Second, this study lacked information concerning viral parameters (eg, specific SARS-CoV-2 strains or mutations). Third, although some studies showed that inborn errors in type 1 interferon immunity and autoantibodies to type 1 interferons were associated with critical COVID-19,[25,26] this study did not explore such factors because patient immunity data were unavailable. Fourth, the use of remdesivir was limited; most treatment courses were solely available to patients enrolled in studies by the pharmaceutical company concerned. Finally, other novel treatment options, including antivirals such as nirmatrelvir/ritonavir and molnupiravir, anti-inflammatory agents such as baricitinib and tocilizumab, and neutralising monoclonal antibodies against SARS-CoV-2, were not available or introduced during the study period. Fifth, the sample size of this study did not reach the statistical powers of 90% and may then not be of high enough power.

Conclusion

In this Hong Kong cohort, the 28-day mortality among patients with severe or critical COVID-19 was 12.0%. Age, history of stroke, use of RRT, and shorter course of lopinavir-ritonavir treatment were associated with greater 28-day mortality. In the future, larger studies with a focus on viral and host factors (eg, mutations in SARS-CoV-2 spike genes and interferon-1 immunity status) could improve prognosis prediction.

Author contributions

All authors contributed to the concept or design of the study, acquisition of data, analysis or interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Ethics approval

The study protocol was approved by the Hong Kong East Cluster Research Ethics Committee (Ref No.: HKECREC—2020-115) and the Kowloon West Cluster Research Ethics Committee (Ref No.: KW/EX-21-005 [155-05]). The requirement for written informed patient consent was waived by both Committees due to the retrospective nature of the research.

References

1. Wong SY, Kwok KO, Chan FK. What can countries learn from Hong Kong's response to the COVID-19 pandemic? CMAJ 2020;192:E511-5.
2. Ling L, So C, Shum HP, et al. Critically ill patients with COVID-19 in Hong Kong: a multicentre retrospective observational cohort study. Crit Care Resusc 2020;22:119-25.
3. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020;323:1239-42.
4. To KK, Chan WM, Ip JD, et al. Unique clusters of severe acute respiratory syndrome coronavirus 2 causing a large coronavirus disease 2019 outbreak in Hong Kong. Clin Infect Dis 2021;73:137-42.
5. Gupta S, Hayek SS, Wang W, et al. Factors associated with death in critically ill patients with coronavirus disease 2019 in the US. JAMA Intern Med 2020;180:1436-47.
6. Magleby R, Westblade LF, Trzebucki A, et al. Impact of severe acute respiratory syndrome coronavirus 2 viral load on risk of intubation and mortality among hospitalized patients with coronavirus disease 2019. Clin Infect Dis 2021;73:e4197-205.
7. Scientific Committee on Emerging and Zoonotic Diseases, Centre for Health Protection, Hong Kong SAR Government. Updated consensus recommendations on criteria for releasing confirmed COVID-19 patients from isolation (July 29, 2020). Available from: https://www.chp.gov.hk/files/pdf/updated_consensus_recommendations_on_criteria_for_releasing_confirmed_covid19_patients_from_isolation29july2020.pdf. Accessed 1 Oct 2020.

8. Grasselli G, Greco M, Zanella A, et al. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. JAMA Intern Med 2020;180:1345-55.
9. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475-81.
10. Bravata DM, Perkins AJ, Myers LJ, et al. Association of intensive care unit patient load and demand with mortality rates in US Department of Veterans Affairs hospitals during the COVID-19 pandemic. JAMA Netw Open 2021;4:e2034266.
11. Janke AT, Mei H, Rothenberg C, Becher RD, Lin Z, Venkatesh AK. Analysis of hospital resource availability and COVID-19 mortality across the United States. J Hosp Med 2021;16:211-4.
12. Qin C, Zhou L, Hu Z, et al. Clinical characteristics and outcomes of COVID-19 patients with a history of stroke in Wuhan, China. Stroke 2020;51:2219-23.
13. Chan L, Chaudhary K, Saha A, et al. AKI in hospitalized patients with COVID-19. J Am Soc Nephrol 2021;32:151-60.
14. Su H, Yang M, Wan C, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int 2020;98:219-27.
15. Hirsch JS, Ng JH, Ross DW, et al. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int 2020;98:209-18.
16. Hung IF, Lung KC, Tso EY, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet 2020;395:1695-704.
17. Wong CK, Wan EY, Luo S, et al. Clinical outcomes of different therapeutic options for COVID-19 in two Chinese case cohorts: a propensity-score analysis. EClinicalMedicine 2021;32:100743.
18. WHO Solidarity Trial Consortium; Pan H, Peto R, et al. Repurposed antiviral drugs for COVID-19—interim WHO solidarity trial results. N Engl J Med 2021;384:497-511.
19. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. JAMA 2020;323:1824-36.
20. Pontelli MC, Castro ÍA, Martins RB, et al. SARS-CoV-2 productively infects primary human immune system cells in vitro and in COVID-19 patients. J Mol Cell Biol 2022;14:mjac021.
21. Faíco-Filho KS, Passarelli VC, Bellei N. Is higher viral load in SARS-CoV-2 associated with death? Am J Trop Med Hyg 2020;103:2019-21.
22. Huang I, Pranata R. Lymphopenia in severe coronavirus disease-2019 (COVID-19): systematic review and meta-analysis. J Intensive Care 2020;8:36.
23. Tavakolpour S, Rakhshandehroo T, Wei EX, Rashidian M. Lymphopenia during the COVID-19 infection: what it shows and what can be learned. Immunol Lett 2020;225:31-2.
24. Henry BM, Aggarwal G, Wong J, et al. Lactate dehydrogenase levels predict coronavirus disease 2019 (COVID-19) severity and mortality: a pooled analysis. Am J Emerg Med 2020;38:1722-6.
25. Zhang Q, Bastard P, Liu Z, et al. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. Science 2020;370:eabd4570.
26. Bastard P, Rosen LB, Zhang Q, et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. Science 2020;370:eabd4585.