BMC Infectious Diseases

RESEARCH

Open Access

Viral sepsis-induced mortality of older patients infected by the Omicron subvariant BA.5 of SARS-CoV-2: a retrospective study

Yu Zhang[1†], Jiaxin Li[2†], Chenglei Su[2], Xianliang Yan[2,3], Jianguo Zhang[1*] and Zhimin Tao[1,4*]

Abstract

Background The infection by the Omicron variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) among the older population induced viral sepsis and put them at high risk of severity and mortality.

Methods We retrospectively investigated 268 patients infected with the Omicron variant of SARS-CoV-2 and hospitalized in two tertiary medical centers in Jiangsu Province, China, from December 2022 to January 2023, who met the Sepsis- 3 criteria. Patients were divided into the survivor ($n = 111$) and non-survivor ($n = 157$) groups, and their baseline clinical characteristics, including their demographic information, medical history, clinical manifestation, laboratory test results, arterial blood gas profiles and computed tomography (CT) patterns, were compared between the two groups to evaluate the risk factors for in-hospital death caused by viral sepsis.

Results The median age of the patients hospitalized was 78.5 (IQR: 71.3–84.8), and 69.0% of them were male. 45.9% of the patients were aged ≥ 80 years. From illness onset to hospitalization the median length of time was 7 days, while the duration of hospitalization was 10.0 days (IQR: 6.0–20.8) and the stay in the intensive care unit (ICU) was 7.0 days (IQR: 4.0–14.0). The median cycle threshold (Ct) values for *ORF1ab* and *N* gene amplification were 30.3 and 29.2, respectively. Hypertension, diabetes, and cardiovascular diseases prevailed in the patients' comorbidity list. After laboratory parameters, arterial blood gas exchange profiles, and radiological patterns were examined, a substantial impact of multiple organ dysfunctions induced by Omicron subvariant BA.5 infection was observed in both groups. As a result, the Sequential Organ Failure Assessment (SOFA) score was significantly factorial in the in-hospital mortality of older patients with COVID-19 (a fatality rate of 58.6%), consistent with determinants in death from non-viral sepsis.

Conclusion With the Omicron subvariants having lower pathogenicity but higher transmissibility compared to pre-Omicron variant of concern (VOC), the older population remains the most vulnerable to COVID-19 infection, which could lead to sepsis and septic shock, highlighting the importance of timely booster vaccinations.

Keywords Viral sepsis, Geriatric patient, SARS-CoV-2, Omicron subvariant, COVID-19

[†]Yu Zhang and Jiaxin Li contributed equally to this work.

*Correspondence:
Jianguo Zhang
1000011431@ujs.edu.cn
Zhimin Tao
jsutao@ujs.edu.cn
Full list of author information is available at the end of the article

Introduction

Geriatric risks related to the coronavirus disease 2019 (COVID-19) have been recognized since the onset of the pandemic, as infections by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in older adults are often associated with poor prognoses due to the age-related changes in the immune system [1]. Compared to younger adults, older patients with COVID-19 were at higher risks for viral infection, and once infected, they tended to experience worse clinical outcomes [2–4]. In addition to immunosenescence, the presence of hyper-inflammatory conditions in older patients with at least one comorbidity may lead to more rapid disease progression after infection [3, 4].

SARS-CoV-2 has undergone constant mutations through the pandemic, resulting in the emergence of numerous variants. Among them, five variants (i.e., Alpha, Beta, Gamma, Delta, and Omicron) have been classified as Variants of Concern (VOCs) due to their elevated capacities of transmission and immune evasion [5]. Following a shift in COVID-19 containing policy in China on December 7, 2022, an outbreak of SARS-CoV-2 infection occurred. Within the next month, it was reported that 82.4% of the Chinese population had been infected, where the dominant strains were the Omicron subvariants BA.5.2, BF.7, and their descendants at that time [6–8]. Both BA.5.2 and BF.7 (i.e., BA.5.2.1.7) belong to the BA.5 sublineage with higher transmissibility and shorter incubation time than the Delta variant or the prior Omicron subvariant BA.2 [9–11]. The pooled time-varying reproduction number for this Omicron subvariant infection cross China was estimated to be 4.7 [12]. Although the animal studies have suggested BA.5 may possess higher pathogenicity than BA.2, clinical research has revealed similar hospitalization odds and disease severity among infected individuals by these different Omicron subvariants, and persistently lower severity compared to that caused by the Delta variant [13–15].

During the early waves of SARS-CoV-2 infection, a significant proportion (77.9%) of patients with COVID-19 in the ICU met the criteria for sepsis, among which the prevalent organ dysfunction (87.5%) was acute respiratory distress syndrome (ARDS) [16]. After the Omicron BA.5.2/BF7 infection swept through China, over 20% of hospitalized patients with SARS-CoV-2 had bacterial coinfections, and 30% of those with bacterial coinfection developed severe cases [17]. Therefore, severe patients with COVID-19, whether suffering from viral infection or secondary bacterial infection, often display characteristics of sepsis that present systemic inflammation, particularly among older individuals.

In this study we investigate the clinical characteristics and outcomes of critically ill older patients with COVID-19 and sepsis who were hospitalized during the Omicron subvariant BA.5 wave in China from December 2022 to January 2023. With an aim to illustrate the risk factors associated with the in-hospital death among older patients caused by sepsis, we strive for the key implications for the geriatric risks posed by the ongoing and future threats of COVID-19.

Methods

Patient information

The retrospective study included critically ill older patients (≥ 60 years old) who were admitted into the ICUs at Affiliated Hospital of Jiangsu University (AHJU) in Zhenjiang city, and Affiliated Hospital of Xuzhou Medical University (AHXMU), both in Jiangsu Province, China, from December 7, 2022 to January 31, 2023. They were confirmed with SARS-CoV-2 infections by following procedures reported [18]. Given medical emergency at the time, all geriatric patients included in our study were either directly admitted into the ICU due to their critical conditions upon hospital visits or transferred to the ICU after their hospital admissions due to rapid deterioration. Patient selection and exclusion criteria were illustrated in Fig. 1. Based on their outcomes, they were retrospectively divided into the survivor group ($n = 111$) and non-survivor group ($n = 157$). The study was conducted in accordance with the Declaration of Helsinki and approved by the Research Ethics Commission of AHJU and AHXMU, respectively. Patient information remained anonymous,

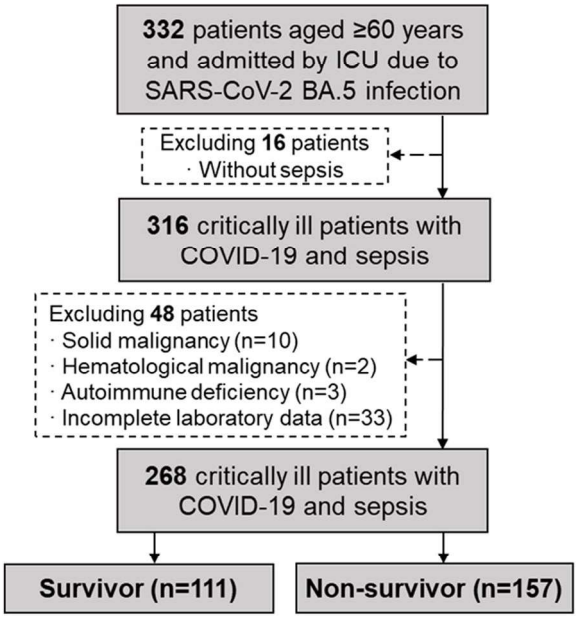

Fig. 1 The flowchart illustrates the patient selection and exclusion criteria

and informed consents were obtained from the patient or next of kin over the phone.

Procedure

Patients infected by the Omicron variant of SARS-CoV-2 were hospitalized and treated as reported [18]. Demographic data, medical history, clinical characteristics, arterial blood gas exchange profiles, and CT scans of patients with COVID-19 were obtained. The confirmed patients were treated with antiviral drugs, including nirmatrelvir/ritonavir, azvudine, and corticosteroids. Antibiotics were prescribed when bacterial co-infection was suspected or confirmed. Patients were evaluated for SOFA scores upon ICU admission and those who met the criteria of Sepsis-3 were diagnosed as sepsis [19]. Briefly, organ dysfunction in patients with sepsis can be quantitatively assessed as SOFA score ≥ 2; moreover, with persistent hypotension after fluid resuscitation that requires vasopressors to maintain MAP > 65 mmHg, patients having serum lactate level > 2 mmol/L can be diagnosed as septic shock. Patients can also be promptly identified at the bedside using quick SOFA criteria, including respiratory rate ≥ 22/min, altered mental status, and systolic blood pressure ≤ 100 mmHg [19]. The survival status of a patient was determined at the time of hospital discharge.

Statistical analysis

Data were summarized as median and interquartile range (IQR) values for continuous variables, and frequencies for categorical variables. For comparisons between the two groups, Mann–Whitney U test was used for continuous variables. Categorical variables were examined by χ^2 test, or Fisher exact text was used when data were limited. All calculated p values were two-sided, and p values < 0.05 were considered statistically significant. The selected variables according to their clinical relevance and statistical significance in univariate analysis ($p < 0.05$) were further assessed by multivariable logistic regression to explore the independent risk factors for in-hospital mortality when the lower values of selected variables were chosen as the reference group. All statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL).

Results

Baseline characteristics of older patients infected by the Omicron subvariant BA.5 of SARS-CoV-2

In this study 268 older patients infected by the Omicron variant of SARS-CoV-2 were hospitalized at two medical centers in Jiangsu Province, China, during December 2022-January 2023. Among these patients, 199 patients (74.3%) were admitted directly to ICUs upon hospitalization, while the remaining 69 patients (25.7%) had the median time of 6.0 days (IQR: 3.0–11.5) from hospitalization to ICU admission. For all the patients included, their median age was 78.5 years (IQR: 71.3–84.8), and 45.9% of them were aged 80 years or higher (Table 1). Additionally, 69.0% of the patients were male, and 13.8% had a history of smoking. The median time from illness onset to hospitalization was 7.0 days (IQR: 3.0–10.0). Their median durations of hospital and ICU stays were 10.0 days (IQR: 6.0–20.8) and 7.0 days (IQR: 4.0–14.0), respectively. Compared to the survivor group, the non-survivor group showed statistically similar age, but much shorter length of hospital or ICU stays.

At the time of hospital admission, all patients were tested for SARS-CoV-2 viral loads, and no statistically significant differences were found between the survivor and non-survivor groups based on the Ct values for *ORF1ab* or *N* gene amplification, respectively. The clinical presentations of survivors and non-survivors were comparable, with similar incidences of symptoms such as fever, cough, dyspnea, expectoration, and chest distress, etc. Notably, 34.3% of the patients presented with disorder of consciousness. Hypertension, diabetes, and cardiovascular diseases were the most common comorbidities, followed by cerebral infarction, chronic obstructive pulmonary disease (COPD), and cerebral hemorrhage. Furthermore, there were no statistically significant differences in the proportions of patients with none, one, or two comorbidities and more (i.e., multimorbidity) between the survivor and non-survivor groups.

Laboratory parameters of older patients infected by the Omicron subvariant BA.5 of SARS-CoV-2

Laboratory analyses revealed that the viral impact on the patients' blood profiles was notable (Table 2). Both survivor and non-survivor groups showed similar abnormalities in major blood cell counts, including leukocytosis, neutrophilia, monocytosis, anemia, and thrombocytopenia; however, lymphocytopenia was more pronounced in the non-survivor group. Coagulopathy was also comparable between the two groups, shown by prolonged prothrombin time and activated partial thromboplastin time (aPTT), along with elevated fibrinogen level. Markedly, the non-survivor group demonstrated a much higher D-dimer level than the survivor group.

Results from the blood biochemical tests reflected the organ dysfunctions in patients infected by the Omicron subvariant BA.5 of SARS-CoV-2. While many biochemical indicators did not differ significantly between the survivor and non-survivor groups, the latter group exhibited heightened levels of several parameters that included alanine transaminase (ALT), aspartate transferase (AST), blood urea nitrogen (BUN), creatinine, LDH (lactate dehydrogenase), and CRP (c-reactive protein). Both

Table 1 Demographic information, immunization record, comorbidity or multimorbidity, and clinical sign of the patients infected by the Omicron subvariant BA.5 in Jiangsu Province, China during December 2022-January 2023 were compared between the survivor and non-survivor groups. Data were summarized as median and IQR values for continuous variables, and frequencies for categorical variables

	Total ($n = 268$)	Survival ($n = 111$)	Non-survivor ($n = 157$)	*p* value
Age	78.5 (71.3–84.8)	78.0 (70.0–84.0)	79.0 (72.5–85.0)	0.063
Patients aged ≥ 80 years	123 (45.9%)	45 (40.5%)	78 (49.7%)	0.139
Gender, female N (%)	83 (31.0%)	37 (33.3%)	46 (29.3%)	0.482
Patients with smoking history	37 (13.8%)	14 (12.6%)	23 (14.6%)	0.634
Onset to hospitalization, day	7.0 (3.0–10.0)	5.0 (3.0–10.0)	7.0 (3.0–10.0)	0.182
Hospital day, day	10.0 (6.0–20.8)	13.0 (6.0–24.0)	9.0 (5.0–15.5)	*0.004*
ICU stay, day	7.0 (4.0–14.0)	9.0 (5.0–20.0)	6.0 (3.0–12.5)	*0.003*
Ct (*ORF1ab*)	30.3 (26.7–34.3)	31.1 (26.9–34.6)	29.8 (26.1–34.3)	0.718
Ct (*N*)	29.2 (25.7–33.0)	29.7 (26.4–32.8)	29.0 (25.7–33.1)	0.921
Symptom				
Fever	183 (68.3%)	71 (64.0%)	112 (71.3%)	0.201
Cough	168 (62.7%)	65 (58.6%)	103 (65.6%)	0.240
Dyspnea	167 (62.3%)	63 (56.8%)	104 (66.2%)	0.114
Expectoration	159 (59.3%)	63 (56.8%)	96 (61.1%)	0.471
Chest distress	111 (41.4%)	42 (37.8%)	69 (43.9%)	0.317
Disorder of consciousness	92 (34.3%)	37 (33.3%)	55 (35.0%)	0.773
Fatigue	58 (21.6%)	29 (26.1%)	29 (18.5%)	0.134
Underlying chronic disease				
Hypertension	155 (57.8%)	70 (63.1%)	85 (54.1%)	0.145
Diabetes	89 (33.2%)	36 (32.4%)	53 (33.8%)	0.820
Cardiovascular diseases	77 (28.7%)	32 (28.8%)	45 (28.7%)	0.976
Cerebral infarction	62 (23.1%)	20 (18.0%)	42 (26.8%)	0.095
COPD	26 (9.7%)	7 (6.3%)	19 (12.1%)	0.114
Cerebral hemorrhage	13 (4.9%)	3 (2.7%)	10 (6.4%)	0.169
Number of comorbidities				
0	58 (21.6%)	26 (23.4%)	32 (20.4%)	0.551
1	73 (27.2%)	31 (27.9%)	42 (26.8%)	0.831
2	84 (31.3%)	32 (28.8%)	52 (33.1%)	0.456
> 2	53 (19.8%)	22 (19.8%)	31 (19.7%)	0.998

groups showed unusually high values for LDH, CRP, and glucose.

ICU panel of older patients infected by the Omicron subvariant BA.5 of SARS-CoV-2

After hospitalization, all patients demonstrated deleterious development rapidly, and they were transferred to ICU for critical care, where the SOFA and Glasgow Coma Scale (GCS) scores were estimated. Compared to the survival group, the non-survival group had significantly higher SOFA and lower GCS scores (Table 3). Although mean arterial pressures (MAPs) were comparable between the two groups, the non-survival group displayed a much higher lactate level and a much greater portion of patients with septic shock.

Upon transfer to ICU, arterial blood gas profiles were examined (Table 3). Compared to the survivor group, the non-survivor group demonstrated similar pH levels and partial pressure of carbon dioxide ($PaCO_2$), but much lower partial pressure of oxygen (PaO_2) and oxygen saturation (SO_2). Simultaneously, the non-survivor group required a considerably higher fraction of inspired oxygen (FiO_2). In analyzing the PaO_2/FiO_2 (P/F) ratio that defines severity of ARDS, the proportions of patients with none (P/F > 300 mmHg), mild (200 mmHg < P/F ≤ 300 mmHg), moderate (100 mmHg < P/F ≤ 200 mmHg) and severe ARDS (P/F ≤ 100 mmHg) were 21.3%, 28.4%, 28.7%, and 21.6%, respectively. The median P/F ratio was significantly lower in the non-survivor group than in the survivor group.

Table 2 Baseline characteristics of patients infected by the Omicron subvariant BA.5 of SARS-CoV-2. Hematological profiles, including blood cell counts, biochemical parameters and coagulation indicators were compared between the survivor and non-survivor groups. Data were summarized as median and IQR values for continuous variables

	Normal range	Total ($n=268$)	Survival ($n=111$)	Non-survivor ($n=157$)	*p* value
Blood cell count					
White blood cells, $\times 10^9$/L	3.5–9.5	9.4 (6.1–12.7)	9.4 (6.0–12.5)	9.4 (6.1–12.8)	0.531
Neutrophils, $\times 10^9$/L	1.8–6.3	8.1 (5.1–11.4)	8.0 (4.5–11.3)	8.2 (5.2–11.7)	0.486
Lymphocytes, $\times 10^9$/L	1.1–3.2	0.6 (0.4–0.8)	0.6 (0.4–0.9)	0.5 (0.4–0.8)	*0.006*
Monocytes, $\times 10^9$/L	0.1–0.6	0.4 (0.3–0.7)	0.4 (0.3–0.7)	0.4 (0.2–0.7)	0.537
Red blood cells, $\times 10^{12}$/L	4.3–5.8	4.0 (3.4–4.4)	4.0 (3.5–4.5)	3.9 (3.3–4.3)	0.373
Hemoglobin, g/L	130–175	121.0 (103.3–133.8)	122.0 (108.0–136.0)	120.0 (99.5–131.0)	0.358
Hematocrit, %	40–50	36.9 (32.0–41.5)	36.9 (33.5–42.1)	36.5 (31.5–41.1)	0.497
MCV, fL	82–100	93.4 (89.9–97.3)	92.9 (89.4–96.5)	93.4 (90.4–97.7)	0.257
MCH, pg	27–34	30.4 (29.2–31.6)	30.3 (29.3–31.4)	30.5 (29.2–32.1)	0.489
MCHC, g/L	316–354	325.0 (313.3–337.0)	325.0 (314.0–337.0)	325.0 (313.0–337.0)	0.657
RDW, %	11.5–17.8	13.2 (12.8–14.2)	13.1 (12.6–14.0)	13.4 (12.9–14.3)	*0.030*
Platelets, $\times 10^9$/L	125–350	153.0 (113.3–221.5)	165.0 (121.0–224.0)	149.0 (109.0–214.0)	0.129
MPV, fL	7.4–12.5	10.7 (9.8–11.8)	10.7 (9.8–11.7)	10.7 (9.8–11.8)	0.720
PDW, %	9–17	16.0 (12.4–16.6)	15.4 (11.7–16.5)	16.1 (13.0–16.7)	*0.021*
Coagulation function					
Prothrombin time, s	9–13	12.4 (11.4–13.7)	12.2 (11.3–13.2)	12.5 (11.5–13.9)	0.058
INR	0.8–1.2	1.1 (1.0–1.2)	1.1 (1.0–1.2)	1.1 (1.0–1.2)	*0.024*
aPTT, s	23.3–32.5	31.6 (27.9–35.8)	31.5 (28.6–35.8)	31.7 (27.3–35.9)	0.786
Thrombin time, s	14–21	15.6 (14.4–17.3)	15.6 (14.4–17.4)	15.6 (14.5–17.3)	0.876
Fibrinogen, g/L	2–4	4.4 (3.2–5.5)	4.3 (3.2–5.1)	4.4 (3.2–5.6)	0.419
D-dimer, mg/L	< 0.55	2.4 (1.1–7.9)	1.7 (0.8–7.3)	2.6 (1.3–8.6)	*0.005*
Biochemical indicators					
Total bilirubin, mmol/L	3–22	11.0 (7.1–17.0)	11.4 (7.7–18.3)	10.9 (6.6–16.1)	0.284
Direct bilirubin, mmol/L	0–5	4.7 (3.0–7.8)	4.5 (3.1–8.5)	4.9 (2.9–7.7)	0.737
Indirect bilirubin, mmol/L	0–19	5.9 (3.4–9.0)	6.5 (3.8–10.3)	5.7 (3.3–8.3)	0.109
ALT, U/L	9–50	25.0 (16.2–43.0)	23.0 (14.0–37.0)	28.0 (17.2–48.0)	*0.035*
AST, U/L	15–40	37.5 (25.0–63.8)	34.5 (25.0–51.9)	42.0 (25.4–68.3)	*0.021*
ALP, U/L	32–126	78.5 (61.3–102.0)	76.0 (59.0–98.0)	80.5 (64.0–111.5)	0.148
GGT, U/L	12–73	31.5 (18.3–59.3)	28.0 (17.0–57.0)	33.0 (20.0–62.5)	0.123
Total protein, g/L	65–85	59.1 (54.8–65.8)	58.6 (54.5–65.5)	59.6 (54.9–65.9)	0.512
Albumin, g/L	40–55	31.8 (28.4–35.2)	32.3 (29.1–35.2)	31.0 (27.7–35.3)	0.070
Globulin, g/L	20–40	27.6 (23.9–31.5)	26.5 (23.1–30.8)	28.5 (24.9–32.1)	*0.014*
BUN, mmol/L	2.86–8.20	9.6 (6.0–16.2)	8.1 (4.9–14.2)	10.6 (7.2–17.2)	*0.001*
Creatinine, mmol/L	31.7–133	81.9 (57.3–147.8)	65.6 (53.0–101.9)	93.9 (62.0–162.1)	*0.002*
Glucose, mmol/L	3.89–6.11	8.3 (6.6–11.3)	8.2 (6.5–10.7)	8.3 (6.7–12.0)	0.446
LDH, U/L	80–285	320.0 (236.0–473.3)	296.0 (212.0–402.0)	357.0 (261.5–519.5)	*0.001*
CRP, mg/L	0–10	94.8 (46.5–150.3)	79.8 (39.3–144.2)	102.3 (59.7–154.7)	*0.028*
Potassium, mmol/L	3.5–5.3	3.9 (3.5–4.4)	3.8 (3.4–4.2)	4.0 (3.6–4.5)	*0.003*
Sodium, mmol/L	137–147	139.1 (135.1–143.0)	139.0 (135.0–142.9)	139.4 (135.4–143.0)	0.513
Total calcium, mmol/L	2.08–2.60	2.0 (1.8–2.1)	2.0 (1.8–2.1)	2.0 (1.7–2.1)	0.908

Abbreaviation: MCV mean corpuscular volume, *MCH* mean corpuscular hemoglobin, *MCHC* mean corpuscular hemoglobin concentration, *RDW* red blood cell distribution width, *MPV* mean platelet volume, *PDW* platelet distribution width, *INR* international normalization ratio, *aPTT* activated partial thromboplastin time, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *ALP* alkaline phosphatase, *GGT* γ-glutamyl transferase, *BUN* blood urea nitrogen, *LDH* lactate dehydrogenase, *CRP* c-reactive protein

Table 3 Upon ICU admission sepsis evaluations and arterial blood gas profiles for all patients infected by the Omicron subvariant BA.5 of SARS-CoV-2, with a comparison between the survivor and non-survivor groups. Data were summarized as median and IQR values for continuous variables, and frequencies for categorical variables

	Normal range	Total ($n = 268$)	Survival ($n = 111$)	Non-survivor ($n = 157$)	*p* value
Sepsis evaluation					
GCS score		12.0 (9.0–14.0)	13.0 (11.0–15.0)	11.0 (6.0–12.0)	*< 0.001*
SOFA score		7.0 (5.0–10.0)	5.0 (3.0–7.0)	9.0 (7.0–11.0)	*< 0.001*
MAP, mmHg		95.5 (84.3–105.8)	95.0 (87.0–104.0)	96.0 (81.0–108.0)	0.966
Lactate, mmol/L		1.9 (1.4–2.6)	1.7 (1.3–2.0)	2.2 (1.5–3.1)	*< 0.001*
Septic shock		28 (10.4%)	4 (3.6%)	24 (15.3%)	*0.002*
Arterial blood gas profiles					
pH	7.35–7.45	7.4 (7.3–7.5)	7.4 (7.4–7.5)	7.4 (7.3–7.5)	0.448
$PaCO_2$, mmHg	35–45	36.0 (31.0–42.2)	35.3 (31.5–42.2)	36.0 (31.0–42.3)	0.931
PaO_2, mmHg	80–100	78.1 (60.4–101.0)	86.9 (67.3–107.0)	71.5 (57.6–98.3)	*0.002*
SO_2, %	95–100	96.0 (92.1–98.2)	97.6 (94.5–98.8)	95.0 (91.0–97.7)	*< 0.001*
FiO_2		0.4 (0.3–0.6)	0.4 (0.2–0.5)	0.5 (0.4–0.8)	*< 0.001*
PaO_2/FiO_2, mmHg	> 300	195.5 (115.0–277.2)	238.0 (179.0–368.0)	151.0 (90.8–241.4)	*< 0.001*

Abbreviations: MAP mean arterial pressure, *$PaCO_2$* partial pressure of carbon dioxide, *PaO_2* partial pressure of oxygen, *SO_2* oxygen saturation, *FiO_2* fraction of inspired oxygen, *PaO_2/FiO_2* oxygenation index

Table 4 Variables ($p < 0.05$) with clinical relevance were performed using multivariable logistic regression analysis to explore the independent risk factors associated with the in-hospital death of patients infected with the Omicron subvariant BA.5

Variables	Adjusted odds ratio (OR)	*p* value	95% Confidence interval (CI)
Lymphocytes, $\times 10^9$/L	0.869	0.628	0.491–1.535
D-dimer, mg/L	1.020	0.396	0.974–1.068
AST, U/L	1.000	0.427	0.999–1.001
BUN, mmol/L	0.993	0.341	0.979–1.007
LDH, U/L	1.000	0.959	0.999–1.001
CRP, mg/L	1.002	0.371	0.998–1.006
SOFA score	1.456	*< 0.001*	1.301–1.631
Lactate, mmol/L	1.000	0.997	0.866–1.155
SO_2, %	0.980	0.253	0.946–1.015

Multivariable logistic regression analysis was conducted, including all variables with $p < 0.05$ from the univariate analysis. The results, shown in Table 4, indicated that the SOFA score (OR = 1.456, 95% CI = 1.301–1.631, $p < 0.001$) is an independent risk factor for in-hospital mortality among older patients infected by the Omicron subvariant BA.5 of SARS-CoV-2, despite comparable baseline characteristics between the two groups.

CT features of older patients infected by the Omicron subvariant BA.5 of SARS-CoV-2

Upon hospitalization, the CT scans of 256 patients, including 110 in the survival group and 146 in the non-survival group, were obtained and thoroughly examined (Table 5). Examples that showed the typical pathological changes in their lungs were displayed in Fig. 2. The proportion of patients with characteristic CT patterns in each group was calculated and compared between the two groups. As a result, there were high incidences of featured pathological events in the patients' lungs infected by the Omicron subvariant BA.5 of SARS-CoV-2, such as ground glass opacity (GGO), linear opacity, and pleural effusion, showing predominant bilateral involvement and peripheral + central distribution. There were no statistically significant differences in characteristic CT patterns examined between the survivor and non-survivor groups, except that the non-survivor group demonstrated higher incidences of GGO + consolidation and air bronchogram, but a lower incidence of GGO alone.

Discussion

Our retrospective study examined the clinical manifestation of 268 critically ill older patients (≥ 60 years old) infected with the Omicron subvariant BA.5 of SARS-CoV-2, all of whom met the criteria for Sepsis- 3. We found a high fatality rate of 58.6% among these patients with severe COVID-19 and induced sepsis. We divided the patients into survivors and non-survivors and compared their baseline characteristics and laboratory

Table 5 Radiological features of patients infected by the Omicron subvariant BA.5 of SARS-CoV-2 were divided into two subgroups as indicated and compared

	Total ($n = 256$)	Survival ($n = 110$)	Non-survivor ($n = 146$)	*p* value
Lung involvement				
Unilateral	2 (0.8%)	1 (0.9%)	1 (0.7%)	1.000
Bilateral	254 (99.2%)	109 (99.1%)	145 (99.3%)	1.000
Predominant distribution				
Central	1 (0.4%)	1 (0.9%)	0 (0.0%)	0.430
Peripheral	46 (18.0%)	27 (24.5%)	19 (13.0%)	*0.017*
Central + Peripheral	209 (81.6%)	82 (74.5%)	127 (87.0%)	*0.011*
Characteristic pattern				
Ground glass opacity (GGO)	149 (58.2%)	73 (66.4%)	76 (52.1%)	*0.022*
Consolidation	1 (0.4%)	1 (0.9%)	0 (0.0%)	0.430
GGO + Consolidation	94 (36.7%)	31 (28.2%)	63 (43.2%)	*0.014*
Crazy paving pattern	83 (32.4%)	32 (29.1%)	51 (34.9%)	0.323
Linear opacities	201 (78.5%)	85 (77.3%)	116 (79.5%)	0.674
Rounded opacities	1 (0.4%)	1 (0.9%)	0 (0.0%)	0.430
Halo sign	5 (2.0%)	3 (2.7%)	2 (1.4%)	0.748
Nodules	89 (34.8%)	32 (29.1%)	57 (39.0%)	0.098
Tree-in-bud sign	37 (14.5%)	17 (15.5%)	20 (13.7%)	0.692
Air bronchogram	88 (34.4%)	28 (25.5%)	60 (41.1%)	*0.009*
Interlobular septal thickening	91 (35.5%)	36 (32.7%)	55 (37.7%)	0.413
Bronchiolar wall thickening	21 (8.2%)	5 (4.5%)	16 (11.0%)	0.064
Pleural effusion	144 (56.3%)	63 (57.3%)	81 (55.5%)	0.775
Pericardial effusion	38 (14.8%)	14 (12.7%)	24 (16.4%)	0.408

(Central + Peripheral) depicts the distribution of lesions in the central and peripheral regions of lungs. (GGO + Consolidation) means both patterns of GGO and consolidation displayed in the CT graph of patient

Abbreviation: GGO ground-glass opacity

parameters to identify risk factors associated with in-hospital mortality, so underlining the geriatric risks linked to Omicron subvariant BA.5 infection. Factors comprised of lymphocytopenia, elevated coagulopathy or protein abnormality (D-dimer, AST, BUN, creatinine, LDH, and CRP), heightened SOFA score, lowered GCS score, and increased barriers in arterial blood gas exchange (increased lactate level and decreased SO_2 and PaO_2/FiO_2), all putting older patients at high risk for mortality. Among these, the SOFA score was determined as the critical independent factor associated with mortality in older patients with COVID-19.

During the earlier Omicron BA.2 outbreak in Shanghai, China from March to May 2022, the COVID-19 patients aged 60 years and above with a higher burden of comorbidities showed higher inflammation responses and viral loads, accounting for the worse clinical outcomes [20]. For infections by the Omicron BF.7 subvariant, the duration when the Ct value for viral gene amplification remained below 35 was lengthier in older patients, indicative of longer viral shedding [21]. Moreover, the clinical characteristics of patients with COVID-19 during a regional BA.5 Omicron wave indicated that advanced age constitutes a significant and independent risk factor for disease severity and mortality, probably due to elevated inflammatory levels [22]. Consistently, for patients with sepsis, age per se was an independent predictor of mortality [19]. As of February 7, 2023, approximately 82.4% of the Chinese population had been infected during this Omicron wave in China [23]. Among them, 90% of COVID-19 related deaths were occurring in individuals aged ≥65 years, and more than half of these deaths were among individuals ≥80 years [24]. Simultaneously, as of August 10, 2022, the rates of full (85.6%) and booster (67.8%) vaccination in older adults in China were lower than those in other countries, such as Japan (92.4%, 90.3%), Germany (91.2%, 85.9%) and the United States (92.1%, 70.7%) [25].

Compared to pre-Omicron and other Omicron lineages (e.g., BA.1, BA.2), BA.5 exhibited a heightened ability of immune escape from previous infection or booster vaccination due to multiple novel mutations. For instance, given their essential role in antibody recognition, R346 and F486 substitutions in the spike protein increase the neutralization resistance to sera produced by booster mRNA vaccine or prior Omicron infection [26]. In

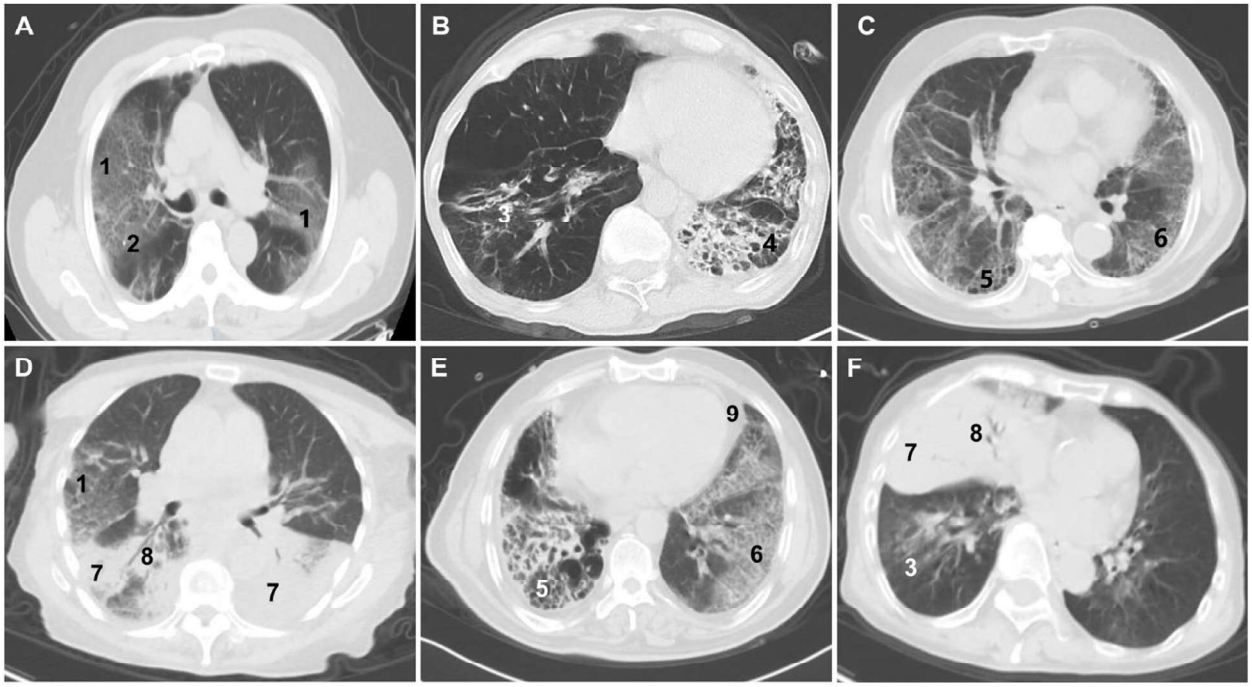

Fig. 2 Representative CT images of patients infected by the Omicron subvariant BA.5 of SARS-CoV-2 taken upon hospital admission, from the survivor (**A**-**C**) and the non-survivor (**D**-**F**) group, respectively. Numbers in each image indicate the pathological findings in the lesion. 1 = GGO; 2 = nodules; 3 = linear opacities; 4 = bronchiolar wall thickening; 5 = interlobular septal thickening; 6 = crazy paving pattern; 7 = consolidation; 8 = air bronchogram; 9 = pericardial effusion

particular, R346 T mutation in BF.7 promotes its capacity to evade the therapeutical neutralization of monoclonal antibodies [27]. As a result, the third dose of inactivated vaccine, albeit it showed substantial protection, had < 50% effectiveness against the BA.5 Omicron infection in China within three months post booster vaccination, and this effectiveness declined significantly thereafter [23, 28]. Similar reductions in vaccine effectiveness were also observed when an additional dose of the mRNA vaccine was administered during periods dominated by successive Omicron sublineages [29, 30]. Even though prior vaccination did not confer a sustained and long-lasting protection, a third or fourth dose of COVID-19 vaccines significantly lowered the risk of hospital admission and death, especially among older adults [31, 32]. To gain the optimized immunity, especially in the older population, a heterologous type of booster vaccine and a 4–5-month interval between the full and booster doses have been recommended [33, 34]. In addition, a variant-adapted booster vaccination should be developed to effectively restore the protection against the evolving SARS-CoV-2 [29].

Compared to prior Omicron subvariants, the Omicron BA.5 exhibited comparable fusogenicity, infectivity, and pathogenicity, leading to similar clinical severity and organ injury [14, 35, 36]. Moreover, the BA.5 infection tended to present with generalized symptoms rather than primarily respiratory symptoms and become low with pneumonia risk [22, 37]. Compared to prior BA.2, BA.5 had higher asymptomatic infection and faster viral clearance, although it produced lower antibody levels more slowly [38, 39]. Yet, it still poses a significant threat to high-risk groups that include seniors. CT imaging in our study indicated that the pathological lesions were frequently localized with bilateral lung involvement. Additionally, the proportions of patients with linear opacity, GGO, and pleural effusion were more than half. This suggests that a substantial number of infections among older patients are occurring in the lower respiratory tract, causing damage to deep lungs. Consistently, initial CT manifestations upon hospital admission, including GGO + consolidation and air bronchogram, are prognostic of in-hospital death for older patients with COVID-19. This is aligned with previous reports [40, 41].

Leukocytosis, neutrophilia, lymphocytopenia, monocytosis, and anemia were found common in older patients with COVID-19, showing a sign of dysregulated immunity because of viral infection and likely bacterial co-infection. Those results are mirrored by previous studies on the hematological abnormalities in the general population induced by SARS-CoV-2 infection [2, 42–44]. In addition, increased levels of D-dimer, LDH, CRP,

creatinine and lactate were predictive of the COVID-19 mortality in older patients, in agreement with previous reports [45–47]. In fact, both blood LDH and lactate levels have been suggested as prognostic biomarkers for mortality of patients with serious inflammatory diseases, including sepsis and ARDS [48, 49]. Those results were in line with our findings here, where the LDH and lactate levels and the SOFA score were closely associated with mortality of patients suffering from SARS-CoV-2 infection-induced sepsis. Among them, the SOFA score was key determinant of mortality among older patients with COVID-19.

Our study has several limitations. First, this is a retrospective and bicenter study. The patient number is relatively small, and the lack of sufficient and complete data limits the validation of regression analysis. For example, the missing information of viral or bacterial co-infection in patients made impossible assessment on its contribution in patients' severity and mortality. Second, in the patient groups we studied, IgG/IgM antibody production due to either infection or/and immunization was not tested. The ability to produce robust antibody and the titer of antibody levels, if available, would have been prognostic indicators in older patients. Third, this study contains no continuous dataset during hospitalization, such as the SOFA scores or serum cytokine levels over time, which may otherwise render a better understanding towards the disease profile of viral sepsis in patients with COVID-19.

Conclusion

During the Omicron wave in China from December 2022 to January 2023, a staggering fatality rate of 58.6% was observed among geriatric patients infected with the Omicron sublineage BA.5 of SARS-CoV-2 and compounded by viral infection-induced sepsis. Under this circumstance the SOFA score was concluded as a critical independent risk factor for in-hospital mortality. Although this strain displayed reduced pathogenicity and elevated transmissibility compared to pre-Omicron variant or prior Omicron subvariant, the ongoing circulation of SARS-CoV-2 variants continued to threaten the older population with the risk of sepsis or septic shock, highlighting the pressing need for timely booster vaccinations.

Abbreviations

AHJU	Affiliated Hospital of Jiangsu University
AHXMU	Affiliated Hospital of Xuzhou Medical University
ALT	Alanine Transaminase
aPTT	Activated Partial Thromboplastin Time
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate Transferase
BUN	Blood Urea Nitrogen
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CRP	C-Reactive Protein
Ct	Cycle Threshold
CT	Computed Tomography
FiO_2	Fraction of Inspired Oxygen
GCS	Glasgow Coma Scale
GGO	Ground Glass Opacity
ICU	Intensive Care Unit
IQR	Interquartile Range
LDH	Lactate Dehydrogenase
MAPs	Mean Arterial Pressures
$PaCO_2$	Partial Pressure of Carbon Dioxide
PaO_2	Partial Pressure of Oxygen
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SOFA	Sequential Organ Failure Assessment
SO_2	Oxygen Saturation
VOC	Variant of Concern

Acknowledgements

We thank Jiangsu University and Xuzhou Medical University for financial support.

Authors' contributions

JZ and ZT conceived the idea and designed the study. YZ, JL, CS, XY, and ZT contributed to the data processing and table/figure preparation. YZ, JL, JZ, and ZT contributed to the statistical analysis. All authors contributed to the manuscript writing and approved the manuscript submission.

Funding

This study was supported by Jiangsu Provincial Science and Technology Development Plan for Traditional Chinese Medicine (MS2022148).

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding authors (JZ/ZT) on request.

Declarations

Ethics approval and consent to participate

The study was approved by the Research Ethics Commission of AHJU and AHXMU, respectively. Patient information remained anonymous, and informed consents were obtained from the patient or next of kin via phone.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Emergency Medicine, Affiliated Hospital of Jiangsu University, Zhenjiang, Jiangsu 212001, China. [2]Department of Emergency Medicine, Affiliated Hospital of Xuzhou Medical University, Xuzhou, Jiangsu 221000, China. [3]Department of Emergency Medicine, Suining People's Hospital, Suining, Jiangsu 221200, China. [4]Department of Laboratory Medicine, Jiangsu Province Key Laboratory of Medical Science and Laboratory Medicine, School of Medicine, Jiangsu University, Zhenjiang, Jiangsu 212013, China.

Received: 19 August 2024 Accepted: 2 April 2025
Published online: 22 April 2025

References

1. Singhal S, Kumar P, Singh S, Saha S, Dey AB. Clinical features and outcomes of COVID-19 in older adults: a systematic review and meta-analysis. BMC Geriatr. 2021;21(1):321.
2. Zhang J, Chen N, Zhao D, Zhang J, Hu Z, Tao Z. Clinical characteristics of COVID-19 patients infected by the Omicron variant of SARS-CoV-2. Front Med. 2022;9:9.

3. Zhang J, Zhang J, Tao Z. Effect of comorbid diabetes on clinical characteristics of COVID-19 patients infected by the wild-type or delta variant of SARS-CoV-2. Front Endocrinol. 2022;13:861443.
4. Zhang J, Zhang J, Tao Z. Effect of hypertension comorbidity on clinical characteristics of COVID-19 patients infected by the wild-type, the delta or omicron variant SARS-CoV-2. RCM. 2022;23(12):395.
5. Carabelli AM, Peacock TP, Thorne LG, Harvey WT, Hughes J, de Silva TI, Peacock SJ, Barclay WS, de Silva TI, Towers GJ, et al. SARS-CoV-2 variant biology: immune escape, transmission and fitness. Nat Rev Microbiol. 2023;21(3):162–77.
6. Sun Y, Wang M, Lin W, Dong W, Xu J. Evolutionary analysis of Omicron variant BF.7 and BA.5.2 pandemic in China. J Biosaf Biosecur. 2023;5(1):14–20.
7. Wang S, Niu P, Su Q, He X, Tang J, Wang J, Feng Y, Chen C, Zhao X, Chen Z, et al. Genomic surveillance for SARS-CoV-2 - China, September 26, 2022 to January 29, 2023. China CDC Wkly. 2023;5(7):143–51.
8. Fu D, He G, Li H, Tan H, Ji X, Lin Z, Hu J, Liu T, Xiao J, Liang X, et al. Effectiveness of COVID-19 vaccination against SARS-CoV-2 Omicron variant infection and symptoms — China, December 2022–February 2023. China CDC Wkly. 2023;5(17):369-73.
9. Ogata T, Tanaka H. SARS-CoV-2 incubation period during the omicron BA.5–dominant period in Japan. Emerg Infect Dis J. 2023;29(3):595.
10. Leung K, Lau EHY, Wong CKH, Leung GM, Wu JT. Estimating the transmission dynamics of SARS-CoV-2 Omicron BF.7 in Beijing after adjustment of the zero-COVID policy in November–December 2022. Nat Med. 2023;29(3):579–82.
11. Wang S, Zhang F, Wang Z, Du Z, Gao C. Reproduction numbers of SARS-CoV-2 Omicron subvariants. J Travel Med. 2022;29(8):taac108.
12. Bai Y, Shao Z, Zhang X, Chen R, Wang L, Ali ST, Chen T, Lau EHY, Jin DY, Du Z. Reproduction number of SARS-CoV-2 Omicron variants, China, December 2022–January 2023. J Travel Med. 2023;30(5):taad049.
13. Kimura I, Yamasoba D, Tamura T, Nao N, Suzuki T, Oda Y, Mitoma S, Ito J, Nasser H, Zahradnik J, et al. Virological characteristics of the SARS-CoV-2 Omicron BA.2 subvariants, including BA.4 and BA.5. Cell. 2022;185(21):3992-4007.e3916.
14. Wolter N, Jassat W, Walaza S, Welch R, Moultrie H, Groome MJ, Amoako DG, Everatt J, Bhiman JN, Scheepers C, et al. Clinical severity of SARS-CoV-2 Omicron BA.4 and BA.5 lineages compared to BA.1 and Delta in South Africa. Nat Commun. 2022;13(1):5860.
15. Lewnard JA, Hong V, Kim JS, Shaw SF, Lewin B, Takhar H, Tartof SY. Association of SARS-CoV-2 BA.4/BA.5 Omicron lineages with immune escape and clinical outcome. Nat Commun. 2023;14(1):1407.
16. Karakike E, Giamarellos-Bourboulis EJ, Kyprianou M, Fleischmann-Struzek C, Pletz MW, Netea MG, Reinhart K, Kyriazopoulou E. Coronavirus Disease 2019 as cause of viral sepsis: a systematic review and meta-analysis. Crit Care Med. 2021;49(12):2042–57.
17. Fan H, Zhou L, Lv J, Yang S, Chen G, Liu X, Han C, Tan X, Qian S, Wu Z, et al. Bacterial coinfections contribute to severe COVID-19 in winter. Cell Res. 2023;33(7):562–4.
18. RbNH C. National Administration of Traditional Chinese Medicine on March 15: diagnosis and treatment protocol for COVID-19 patients (Trial Version 9). Health Care Sci. 2022;1(1):14–28.
19. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche J-D, Coopersmith CM, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):801–10.
20. Lu G, Zhang Y, Zhang H, Ai J, He L, Yuan X, Bao S, Chen X, Wang H, Cai J, et al. Geriatric risk and protective factors for serious COVID-19 outcomes among older adults in Shanghai Omicron wave. Emerg Microbes Infect. 2022;11(1):2045–54.
21. Zhang Q, Feng Z, Hao Y, Wei L, Wang A, Han Z, Tian M, Sun S, Li X, Xue T, et al. Dynamic changes of ORF1ab and N gene Ct values in COVID-19 Omicron inpatients of different age groups - Beijing Municipality, China, November-December 2022. China CDC Wkly. 2023;5(8):180–3.
22. Salehi M, Salami Khaneshan A, Farahani AS, Doomanlu M, Arabzadeh M, Sobati A, Farhadi K, Fattahi R, Mohammadnejad E, Abdoli A, et al. Characteristics and outcomes of COVID-19 patients during the BA.5 omicron wave in Tehran, Iran: a prospective observational study. BMC Infect Dis. 2023;23(1):237.
23. Fu D, He G, Li H, Tan H, Ji X, Lin Z, Hu J, Liu T, Xiao J, Liang X, et al. Effectiveness of COVID-19 vaccination against SARS-CoV-2 omicron variant infection and symptoms - China, December 2022-February 2023. China CDC Wkly. 2023;5(17):369–73.
24. Su B, Luo Y, Tian Y, Chen C, Zheng X. Confronting COVID-19 and prioritizing aging population. China CDC Wkly. 2023;5(10):229–33.
25. Zang S, Zhang X, Qu Z, Chen X, Hou Z. Promote COVID-19 vaccination for older adults in China. China CDC Wkly. 2022;4(37):832–4.
26. Qu P, Evans JP, Faraone JN, Zheng YM, Carlin C, Anghelina M, Stevens P, Fernandez S, Jones D, Lozanski G, et al. Enhanced neutralization resistance of SARS-CoV-2 Omicron subvariants BQ.1, BQ.1.1, BA.4.6, BF.7, and BA.2.75.2. Cell Host Microbe. 2023;31(1):9-17.e13.
27. Arora P, Zhang L, Nehlmeier I, Kempf A, Cossmann A, Dopfer-Jablonka A, Schulz SR, Jäck H-M, Behrens GMN, Pöhlmann S, et al. The effect of cilgavimab and neutralisation by vaccine-induced antibodies in emerging SARS-CoV-2 BA.4 and BA.5 sublineages. Lancet Infect Dis. 2022;22(12):1665–6.
28. Wang K, Guo Z, Zeng T, Sun S, Lu Y, Wang J, Li S, Luan Z, Li H, Zhang J, et al. Transmission characteristics and inactivated vaccine effectiveness against transmission of SARS-CoV-2 Omicron BA.5 variants in Urumqi, China. JAMA Network Open. 2023;6(3):e235755–e235755.
29. Lee N, Nguyen L, Austin PC, Brown KA, Grewal R, Buchan SA, Nasreen S, Gubbay J, Schwartz KL, Tadrous M, et al. Protection conferred by COVID-19 vaccination, prior SARS-CoV-2 infection, or hybrid immunity against Omicron-associated severe outcomes among community-dwelling adults. Clin Infect Dis. 2024;78(5):1372–82.
30. Laniece Delaunay C, Mazagatos C, Martínez-Baz I, Túri G, Goerlitz L, Domegan L, Meijer A, Rodrigues AP, Sève N, Ilic M, et al. COVID-19 vaccine effectiveness in autumn and winter 2022 to 2023 among older Europeans. JAMA Netw Open. 2024;7(7):e2419258.
31. Andersson NW, Thiesson EM, Baum U, Pihlström N, Starrfelt J, Faksová K, Poukka E, Lund LC, Hansen CH, Aakjær M, et al. Comparative effectiveness of heterologous third dose vaccine schedules against severe covid-19 during omicron predominance in Nordic countries: population based cohort analyses. BMJ. 2023;382: e074325.
32. Andersson NW, Thiesson EM, Baum U, Pihlström N, Starrfelt J, Faksová K, Poukka E, Meijerink H, Ljung R, Hviid A. Comparative effectiveness of bivalent BA.4–5 and BA.1 mRNA booster vaccines among adults aged ≥50 years in Nordic countries: nationwide cohort study. BMJ. 2023;382:e075286.
33. Yang H, Meng X, Zhuang T, Wang C, Yang Z, Zhu T, Li M, Zheng Y, Wu Q, Hu Y, et al. Immunogenicity and safety of homologous booster doses of CoronaVac COVID-19 vaccine in elderly individuals aged 60 years and older: a dosing interval study - Yunnan Province, China, 2021–2022. China CDC Wkly. 2023;5(6):125–30.
34. Chen X, Bai X, Chen X, Zheng N, Yang J, Zhang J, Yu H. Modeling the prediction on the efficacy of a homologous third dose of CoronaVac against SARS-CoV-2 Omicron BA.1, BA.2, BA.2.12.1, and BA.4/5 - China, 2020-2021. China CDC Wkly. 2023;5(5):103–7.
35. Wang X-J, Yao L, Zhang H-Y, Zhu K-L, Zhao J, Zhan B-D, Li Y-K, He X-J, Huang C, Wang Z-Y, et al. Neutralization sensitivity, fusogenicity, and infectivity of Omicron subvariants. Genome Medicine. 2022;14(1):146.
36. Deng H, Mai Y, Liu H, Guan J. Clinical characteristics of liver injury in SARS-CoV-2 Omicron variant- and Omicron subvariant-infected patients. Ann Hepatol. 2023;28(1):100763.
37. Hirama R, Takeda K, Sakao S, Kasai H, Miyata S, Shikano K, Naito A, Abe M, Kawasaki T, Shigeta A, et al. A comparison of clinical presentations in coronavirus disease 2019 caused by different omicron variants in Japan: a retrospective study. Internal Med. 2023;62(16):2321–8.
38. Guo L, Liu X, Gu Y, Jiang J, Yang Z, Lv Q, Guo D, Yang Y, Lu H, Yuan J: Distinct and relatively mild clinical characteristics of SARS-CoV-2 BA.5 infections against BA.2. Signal Transduct Target Ther. 2023;8(1):171.
39. Kang S-W, Park H, Kim JY, Lim SY, Lee S, Bae J-Y, Kim J, Chang E, Bae S, Jung J, et al. Comparison of the clinical and virological characteristics of SARS-CoV-2 Omicron BA.1/BA.2 and omicron BA.5 variants: A prospective cohort study. Journal of Infection. 2023;86(5):e148–51.
40. Li Y, Yang Z, Ai T, Wu S, Xia L. Association of "initial CT" findings with mortality in older patients with coronavirus disease 2019 (COVID-19). Eur Radiol. 2020;30(11):6186–93.
41. Wang C, Shi B, Wei C, Ding H, Gu J, Dong J. Initial CT features and dynamic evolution of early-stage patients with COVID-19. Radiology of Infectious Diseases. 2020;7(4):195–203.

42. Liu X, Zhang R, He G. Hematological findings in coronavirus disease 2019: indications of progression of disease. Ann Hematol. 2020;99(7):1421–8.
43. Zhang J, Ding D, Huang X, Zhang J, Chen D, Fu P, Shi Y, Xu W, Tao Z. Differentiation of COVID-19 from seasonal influenza: A multicenter comparative study. J Med Virol. 2021;93(3):1512–9.
44. Zhang J, Huang X, Ding D, Tao Z. Platelet-driven coagulopathy in COVID-19 patients: in comparison to seasonal influenza cases. Exp Hematol Oncol. 2021;10(1):34.
45. Zhang J, Huang X, Tao Z. Correlation of clinical characteristics between patients with seasonal influenza and patients infected by the wild type or delta variant of SARS-CoV-2. Front Public Health. 2022;10:981233.
46. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, Li J, Yao Y, Ge S, Xu G. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int. 2020;97(5):829–38.
47. Ulugerger Avci G, Bektan Kanat B, Suzan V, Can G, Korkmazer B, Karaali R, Tabak F, Borekci S, Aygun G, Yavuzer H, et al. Clinical outcomes of geriatric patients with COVID-19: review of one-year data. Aging Clin Exp Res. 2022;34(2):465–74.
48. Gupta GS. The lactate and the lactate dehydrogenase in inflammatory diseases and major risk factors in COVID-19 patients. Inflammation. 2022;45(6):2091–123.
49. Lu J, Wei Z, Jiang H, Cheng L, Chen Q, Chen M, Yan J, Sun Z. Lactate dehydrogenase is associated with 28-day mortality in patients with sepsis: a retrospective observational study. J Surg Res. 2018;228:314–21.

Publisher's Note