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Coronavirus Pandemic

Clinical characteristics and risk factors of non-mild outcomes in patients with Omicron variant COVID-19 in Shanghai, China

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Abstract

Introduction: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron variant rapidly appeared in Shanghai, China in early March 2022. Although a few studies have analyzed the risk factors of the severe type, identifying risk factors for non-mild COVID-19 outcomes (general/severe/critical type) which occur with radiographic evidence of pneumonia is lacking.

Methodology: The COVID-19 patients admitted to a district-level designated hospital from April 26 to May 21 were enrolled in this retrospective study. The clinical manifestations and laboratory examinations were analyzed. Logistic regression was employed to evaluate risk factors for non-mild outcomes.

Results: Of the 311 patients, 196 (63.0%) were mild and 115 (37.0%) were non-mild. Among them, 215 cases (69.1%) were unvaccinated. Male, ≥ 60 years age, and chronic kidney disease were risk factors of progressing to non-mild. Patients with more than two comorbidities were more likely to become non-mild, whereas two/booster doses vaccinated patients had a lower risk of developing to non-mild. The median negative conversion days (NCDs) were 12 days. Non-mild, > 2 comorbidities, delayed admission (> 3 days), and Paxlovid (Pfizer, Freiburg, Germany) treatment significantly lengthened the NCDs.

Conclusions: Our results call for special concern for full and booster vaccination of the elderly, which will effectively protect from progression of COVID-19 to non-mild state. In the meantime, symptomatic COVID-19 patients should be treated as soon as possible.

Key words: COVID-19; Omicron; vaccination; outcome; risk factor.

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Introduction

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was first reported in December 2019 [1,2]. The pandemic has been spreading globally for three years. As of 19 December 2022, more than 649 million confirmed cases and 6.6 million confirmed deaths have been reported according to the World Health Organization (WHO) statistics [3].

Since 31 December 2021, the fifth wave of COVID-19 hit Hong Kong. The SARS-CoV-2 variant in this wave was Omicron BA.2, which was more transmissible and less virulent than the previous variants. The majority of the infections have been asymptomatic and mild [4]. In early March 2022, COVID-19 rapidly appeared in the communities in Shanghai due to lapses in the management of a quarantine hotel. Shanghai immediately took strict public health measures, including large-scale nucleic acid and antigen tests, quarantine of infected cases in shelter hospitals and close contacts in hotels, and lockdown of districts with severe outbreak, and it was found that the pandemic control strategies reduced the number of people infected and provided early diagnosis and appropriate treatment for severe COVID-19 [5,6].

According to diagnosis and treatment guidelines on COVID-19 (the ninth trial version) issued by the National Health Commission of the People's Republic

of China and the National Administration of Traditional Chinese Medicine [7], the clinical types of confirmed cases include mild, general, severe and critical. The general, severe and critical types (denoted as non-mild) are accompanied with radiographic evidence of pneumonia. The general, severe, and critical cases, and cases with severe high-risk factors were transferred to designated hospitals for treatment. To date, there are lots of studies on the SARS-CoV-2 neutralizing antibody in vivo [8]. Although a few studies have analyzed risk factors of the severe type of COVID-19 [9-12], there are few data on risk factors of non-mild patients infected with the Omicron variant in designated hospitals. This study focuses on the retrospective analysis of the clinical manifestations, laboratory examinations and risk factors of non-mild outcomes in 311 COVID-19 patients admitted to a district-level designated hospital in Shanghai from April 26 to May 21, 2022. Our results call for special concern for full and booster vaccination of the elderly, which will effectively protect from progression to non-mild condition. In the meantime, symptomatic COVID-19 patients should be treated as soon as possible.

Methodology

Confirmed patients were divided into 4 types based on clinical severity according to the diagnosis and treatment guideline on COVID-19 (the ninth trial version) [7]: mild, general, severe and critical. The diagnostic criteria for mild patients were mild clinical symptoms and no signs of pneumonia on imaging. General patients were defined as those with fever and/or respiratory symptoms and radiographic evidence of pneumonia. Severe adult patients were those with any one of the following: (1) shortness of breath with respiratory rate (RR) ≥ 30 times/min; (2) oxygen saturation in the resting state ≤ 93% when inhaling air; (3) partial pressure of oxygen (PaO_2) / fraction of inspired oxygen (FiO_2) ≤ 300 mmHg; (4) progressive symptoms and pulmonary imaging showing that the lesion had obvious progression over 50% within 24-48 hours. Critical cases referred to patients who met any one of the following three criteria: (1) respiratory failure that requires mechanical ventilation; (2) shock; (3) other organ failure requiring intensive care unit monitoring and treatment.

Discharge criteria [7] included the following (1) normal body temperature > 3 days; (2) significant improvement of respiratory symptoms; (3) significant improvement of acute exudative lesions shown on lung imaging; (4) two consecutive nucleic acid negative results of respiratory tract samples (sampling interval at least 24 h).

Negative conversion days (NCDs) were denoted as the first day of the positive SARS-CoV-2 nucleic acid test to the date of the first negative test of the consecutive nucleic acid negative results.

Delay days were defined as the time interval from the initial date of the positive SARS-CoV-2 nucleic acid test to the date of admission to hospital.

Data sources and collection

The data were obtained from the electronic medical record system of Shidong Hospital in Yangpu district, Shanghai. Inclusion criteria were all adult patients (≥ 18 years old) with laboratory confirmed COVID-19 according to diagnosis and treatment guideline on COVID-19 (the ninth trial version) [7]. The throat or nose swab samples of patients had tested positive for SARS-CoV-2 nucleic acid by real time reverse transcription-polymerase chain reaction (RT-PCR). Exclusion criteria were patients with incomplete clinical data. Data included demographic characteristics, comorbidities, symptoms, laboratory examination results, clinical type, treatment, and prognosis. Laboratory examination data were collected within 48 hours of admission for patients with mild and general types, and within 48 hours of clinical confirmation of severe/critical symptoms for patients with severe/critical types. All data were collected under the guidance of a senior physician. In total, 311 patients with confirmed COVID-19 admitted to the hospital from April 26 to May 21, 2022 were included. The privacy of all patients was fully protected. Informed consent was waived because of the nature of the retrospective study and anonymous clinical data. This study was approved by the ethical committee of Shidong Hospital (2022-052-01).

Statistical analysis

Categorical variables were described by frequency and percentage, and continuous variables were described using median and interquartile range (IQR). We employed logistic regression to analyze risk factors for non-mild outcomes, and calculated odds ratio (OR) and 95% confidence interval (CI). The factors influencing viral clearance were evaluated using Cox regression, and hazard ratio (HR) and 95% CI were calculated [9]. The comparison between the groups was conducted using the Chi square test for categorical variables and Mann-Whitney test for continuous variables (non-normal distribution) [1]. All statistical analyses were performed using SPSS (Statistical

Package for the Social Sciences) version 23.0 (SPSS Inc.). The tests were two-sided, and $p < 0.05$ was considered statistically significant.

Results

Clinical characteristics of COVID-19 patients

Of the 311 patients, 196 (63.0%) were mild, 100 (32.2%) were general, and 15 (4.8%) were severe/critical. The median age was 76 years (IQR, 63-86; range, 20-101 years), and 139 (44.7%) were men. In terms of underlying comorbidities, 274 (88.1%) had 1 or more coexisting chronic diseases. Hypertension (186 [59.8%]), cardiovascular disease (94 [30.2%]), diabetes (60 [19.3%]), and cerebrovascular disease (58 [18.6%]) were the most common coexisting conditions. Regarding COVID-19 vaccination, 215 cases (69.1%) were unvaccinated, 3 cases (1.0%) received one dose, 38 cases (12.2%) received two doses, and 55 cases (17.7%) received booster vaccination (Table 1).

The most common symptoms at admission were expectoration (134 [43.1%]), fever (88 [28.3%]), dry cough (72 [23.2%]), sore throat (33 [10.6%]), and myalgia/fatigue (31 [10.0%]). Less common symptoms were nasal obstruction/rhinorrhoea, nausea/ vomiting and stomach ache/diarrhoea (Table 1).

As of 11 June 2022, 293 patients (94.2%) were discharged, and 14 patients (4.5%) were transferred to a higher level hospital. Among the transferred cases, 13

Table 1. Demographics and baseline characteristics of COVID-19 patients.

	No. (%)			
	All patients (n = 311)	**Mild group (n = 196)**	**General group (n = 100)**	**Severe or critical group (n = 15)**
Age range (years), median (IQR)	76 (63, 86)	69 (59, 82)	83 (74, 88)	87 (83, 89)
18-39	16 (5.1)	16 (8.2)	0 (0.0)	0 (0.0)
40-59	41 (13.2)	38 (19.4)	3 (3.0)	0 (0.0)
60-69	61 (19.6)	48 (24.5)	11 (11.0)	2 (13.3)
70-79	51 (16.4)	29 (14.8)	22 (22.0)	0 (0.0)
≥ 80	142 (45.7)	65 (33.2)	64 (64.0)	13 (86.7)
Gender				
Male	139 (44.7)	78 (39.8)	52 (52.0)	9 (60.0)
Comorbidities				
No comorbidity	37 (11.9)	33 (16.8)	4 (4.0)	0 (0.0)
1 comorbidity	83 (26.7)	61 (31.1)	22 (22.0)	0 (0.0)
2 comorbidities	86 (27.7)	52 (26.5)	32 (32.0)	2 (13.3)
≥ 3 comorbidities	105 (33.8)	50 (25.5)	42 (42.0)	13 (86.7)
Types of comorbidities				
Hypertension	186 (59.8)	113 (57.7)	66 (66.0)	7 (46.7)
Cardiovascular disease	94 (30.2)	53 (27.0)	30 (30.0)	11 (73.3)
Diabetes	60 (19.3)	32 (16.3)	24 (24.0)	4 (26.7)
Cerebrovascular disease	58 (18.6)	28 (14.3)	24 (24.0)	6 (40.0)
Respiratory system disease	39 (12.5)	18 (9.2)	15 (15.0)	6 (40.0)
Malignant tumor	27 (8.7)	14 (7.1)	12 (12.0)	1 (6.7)
Chronic kidney disease	28 (8.0)	8 (4.1)	12 (12.0)	5 (33.3)
Smoking	11 (3.5)	8 (4.1)	2 (2.0)	1 (6.7)
COVID-19 vaccination				
Unvaccinated	215 (69.1)	116 (59.2)	85 (85.0)	14 (93.3)
One dose	3 (1.0)	2 (1.0)	1 (1.0)	0 (0.0)
Two doses	38 (12.2)	29 (14.8)	8 (8.0)	1 (6.7)
Booster dose	55 (17.7)	49 (25.0)	6 (6.0)	0 (0.0)
Symptoms at admission				
Expectoration	134 (43.1)	81 (41.3)	43 (43.0)	10 (66.7)
Fever	88 (28.3)	58 (29.6)	25 (25.0)	5 (33.3)
Dry cough	72 (23.2)	51 (26.0)	20 (20.0)	1 (6.7)
Sore throat	33 (10.6)	20 (10.2)	13 (13.0)	0 (0.0)
Myalgia or fatigue	31 (10.0)	19 (9.7)	10 (10.0)	2 (13.3)
Nasal obstruction or rhinorrhoea	15 (4.8)	11 (5.6)	4 (4.0)	0 (0.0)
Nausea or vomiting	11 (3.5)	8 (4.1)	3 (3.0)	0 (0.0)
Stomach ache or diarrhoea	6 (1.9)	6 (3.1)	0 (0.0)	0 (0.0)
Antiviral drug treatment	148 (47.6)	82 (41.8)	55 (55.0)	11 (73.3)
Delay days, median (IQR)	3 (2, 6)	3 (2, 5)	4 (2, 7)	2 (1, 5)
Hospitalization days, median (IQR)	12 (9, 16)	12 (9, 15)	13 (9, 16)	9 (4, 13)
Negative conversion daysa, median (IQR)	12 (10, 16)	12 (9, 15)	13.5 (11.8, 18)	14 (11.8, 16.3)
Clinical outcome				
Discharge	293 (94.2)	193 (98.5)	96 (96.0)	4 (26.7)
Transfer to higher level hospitalb	14 (4.5)	3 (1.5)	3 (3.0)	8 (53.3)
Death	4 (1.3)	0 (0.0)	1 (1.0)	3 (20.0)

[a]The patients were transferred to higher level hospital or dead and there was lack of the information on negative conversion days. bOne mild patient was transferred to higher level hospital due to accompanying family members. COVID-19, Coronavirus disease 2019; IQR, interquartile range.

patients (4.2%) needed further treatment while one mild patient (0.3%) voluntarily accompanied her transferred family members (Table 1). Four patients (1.3%) died, including one general and three severe/critical patients. All were more than 80 years old with underlying diseases and had no COVID-19 vaccination history.

Risk factors of progressing to non-mild

Based on baseline characteristics, we analyzed the risk factors of progressing to non-mild. Using univariate analysis, we found that patients who were male, ≥ 60 years old, and had comorbidities such as cerebrovascular disease, respiratory disease and chronic kidney disease were more likely to progress to non-mild (Table 2).

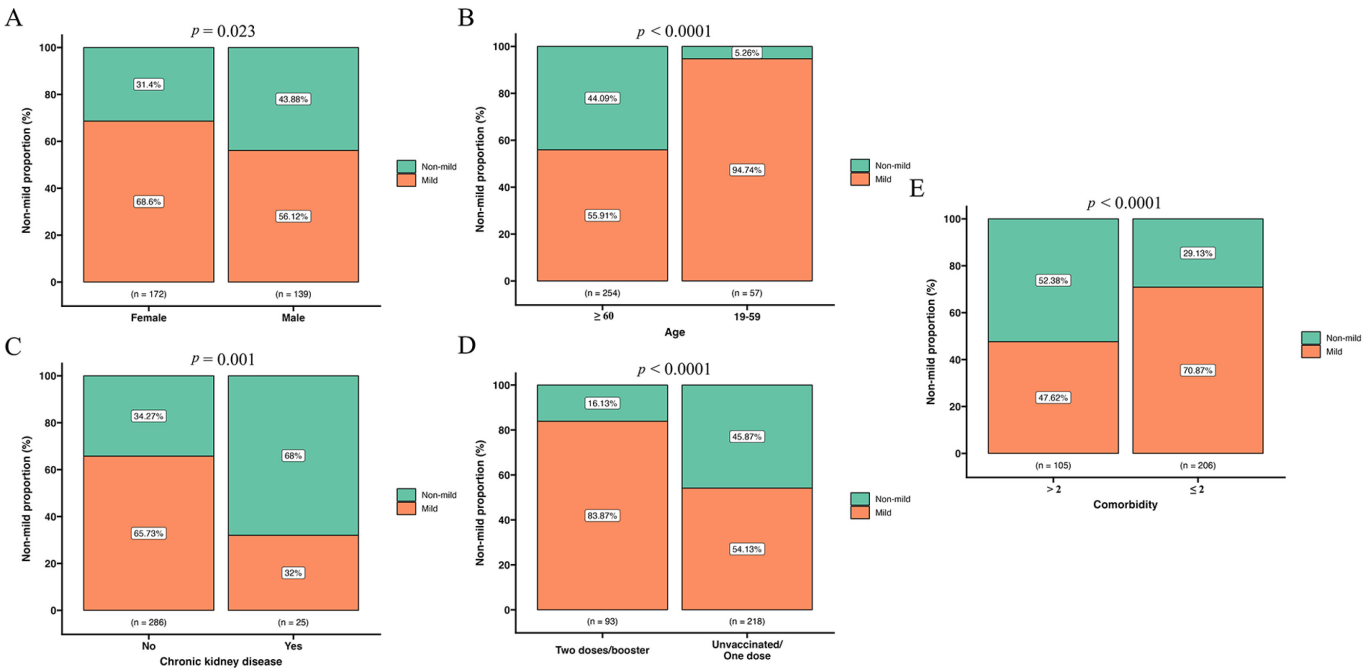
Using multivariate analysis, we determined that patients who were male, ≥ 60 years old, and had chronic kidney disease were more likely to become non-mild (adjusted OR = 2.17 [95% CI: 1.27-3.72], $p = 0.005$; adjusted OR = 10.77 [95% CI: 3.12-37.11], $p < 0.001$; adjusted OR = 2.96 [95% CI: 1.13-7.76], $p = 0.027$, respectively). Vaccinated patients with two/booster

Table 2. Risk factors of progressing to non-mild.

	Univariate		Multivariate	
	OR	**p**	**Adjusted OR**	**p**
Male	1.71 (1.07-2.72)	0.024	2.17 (1.27-3.72)	0.005
Age (years)				
19-59	1.00		1.00	
≥ 60	14.2 (4.32-46.61)	< 0.001	10.77 (3.12-37.11)	< 0.001
Comorbidity types				
Hypertension	1.28 (0.79-2.05)	0.312	0.69 (0.39-1.22)	0.207
Cardiovascular disease	1.49 (0.91-2.45)	0.111	0.98 (0.56-1.74)	0.955
Diabetes	1.65 (0.93-2.92)	0.085	1.66 (0.87-3.18)	0.126
Cerebrovascular disease	2.12 (1.19-3.77)	0.011	1.49 (0.79-2.79)	0.219
Respiratory disease	2.21 (1.12-4.35)	0.022	1.3 (0.60-2.79)	0.505
Malignant tumor	1.66 (0.75-3.66)	0.212	1.13 (0.46-2.73)	0.793
Chronic kidney disease	4.08 (1.70-9.78)	0.002	2.96 (1.13-7.76)	0.027
COVID-19 vaccination				
Unvaccinated/one dose	1.00		1.00	
Two/booster doses	0.23 (0.12-0.42)	< 0.001	0.35 (0.18-0.68)	0.002

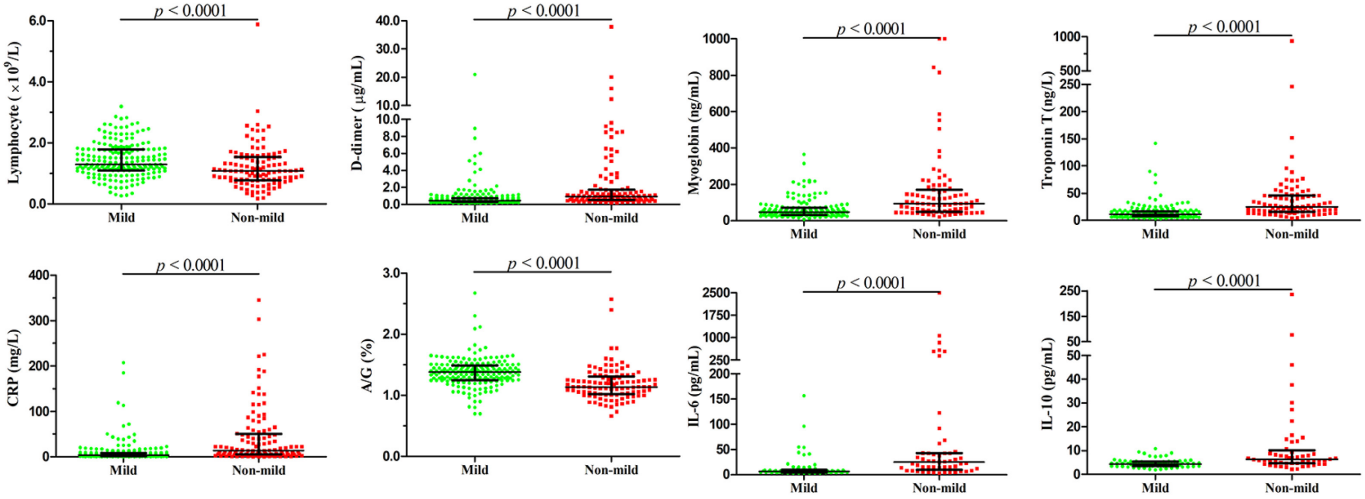
Age 19-59 years was used as the reference group for age. Unvaccinated/one dose was used as the reference group for COVID-19 vaccination. Covariates included gender, age, comorbidity types, and COVID-19 vaccination. Non-mild, included general, severe and critical types. OR, odds ratio. COVID-19, coronavirus disease 2019.

Figure 1. The proportion of non-mild type patients according to gender, age, chronic kidney disease, vaccination, and comorbidity numbers.



Non-mild, included general, severe and critical types.

Figure 2. Differential indicators from laboratory results between mild and non-mild patients.



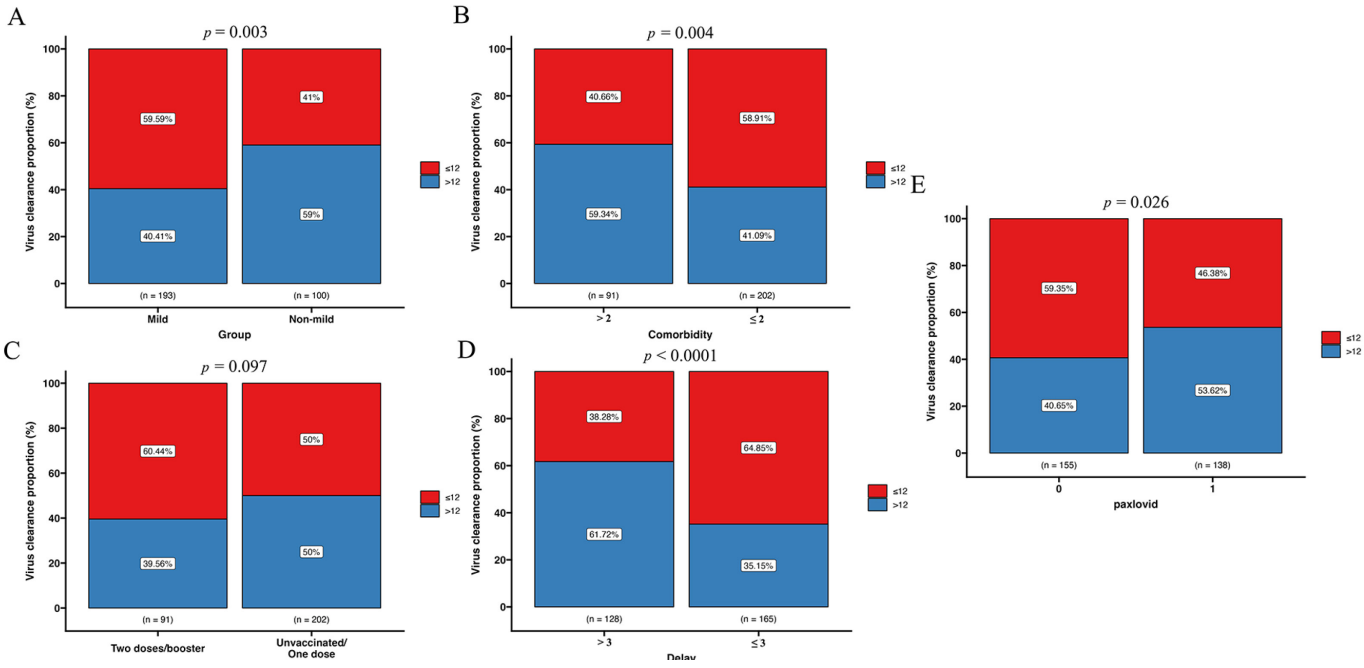
The indicators include lymphocyte count, A/G ratio, myoglobin, troponin T, D-dimer, and inflammatory markers (CRP, IL-6, and IL-10). Non-mild included general, severe and critical types.

doses had a lower risk with an adjusted OR of 0.35 (95% CI: 0.18-0.68, p = 0.002) (Table 2, Figure 1). Moreover, we also analyzed the risk according to numbers of comorbidities. The risk of the group with > 2 comorbidities was 1.87 times higher compared with those who had ≤ 2 comorbidities (95% CI: 1.11-3.16, p = 0. 019) (Figure 1, Supplementary Table 1).

Differential laboratory results between mild and non-mild patients

The results of the blood routine showed that 43 (13.8%), 105 (33.8%) and 43 (13.8%) patients had decreased leucocytes, lymphocytes and platelet counts, respectively. The blood biochemistry showed increased levels of myoglobin (111 [35.7%]), troponin T (125 [40.2%]) and creatinine (Cr) (67 [21.5%]), and decreased albumin/globulin (A/G) ratio (86 [27.7%]).

Figure 3. The proportion of negative conversion days ≤ 12 days and > 12 days according to clinical types, comorbidity numbers, vaccination, delay days, and Paxlovid use.



Non-mild included general, severe and critical types.

One hundred and ten (35.4%) patients had hyponatremia and 112 patients (36.0%) had hypokalemia. Levels of D-dimer in coagulation function test were increased in 174 patients (55.9%). In the case of infection-related biomarkers, there were 106 (34.1%), 130 (41.8%) and 159 (51.1%) patients with increased C-reactive protein (CRP), procalcitonin (PCT) and serum amyloid A (SAA), respectively. Additionally, increased levels of interleukin-6 (IL-6) and interleukin-10 (IL-10) were found in 91 (29.3%) and 60 (19.3%) patients, respectively (Supplementary Table 2).

There were numerous differences in laboratory results between the mild and the non-mild patients. The lymphocyte count and A/G ratio in the non-mild group were significantly lower than that in mild group ($p < 0.0001$). The myoglobin, troponin T, D-dimer, and inflammatory indicators (CRP, PCT, SAA, IL-6, and IL-10) in patients in the non-mild group were significantly higher than that in patients with mild type ($p < 0.0001$, Figure 2, Supplementary Table 2).

Influencing factors of virus clearance

Since 18 patients were transferred to a higher level hospital or were dead, we analyzed 293 patients with negative conversion days (NCDs). The median NCDs were 12 days (IQR: 10–16 days). The median duration of NCDs was 12 days for mild patients, 13.5 days for general patients, and 14 days for severe/critical patients (Table 1). Patients in the mild group, those with ≤ 2 group comorbidities, two doses/booster vaccine, and ≤ 3 delay days were more likely to clear the virus within 12 days (59.59% vs. 41.00%, $p = 0.003$; 58.91% vs. 40.66%, $p = 0.004$; 60.44% vs. 50.00%, $p = 0.097$; and 64.85% vs. 38.28%, $p < 0.0001$, respectively) (Figure 3).

The multivariate analysis showed that the NCDs were longer in the non-mild group than in the mild group (adjusted HR, 0.77 [95% CI: 0.59-1.01]; $p = 0.057$). The comorbidity > 2 group also lengthened the NCDs (adjusted HR, 0.67 [95% CI: 0.51-0.87]; $p = 0.003$). Moreover, the NCDs were also significantly associated with delayed admission of patients. Surprisingly, Paxlovid (Pfizer, Freiburg, Germany) lengthened the NCDs (adjusted HR, 0.56 [95% CI: 0.43-0.72]; $p < 0.001$) (Table 3).

Discussion

COVID-19 remains a global pandemic, and SARS-CoV-2 variants have aroused great concern. Recently, it was reported that the Omicron variant is still evolving continuously which can cause immune evasion and reinfection, and the spread of COVID-19 is still not controlled [13-17]. During the epidemic, the designated hospitals could effectively treat and control the source of infection. This retrospective study aimed to analyze the clinical characteristics and risk factors in COVID-19 patients admitted to designated hospitals, hoping to identify high-risk populations who need appropriate protective measures and timely clinical care.

In this study, the proportion of elderly patients was very high: 81.7% were ≥ 60 years old and 45.7% were ≥ 80 years old. The patients who were ≥ 60 years old were more than 10 times more likely to progress to non-mild. The prognosis of patients older than 60 years was worse, which indicated that clinicians should pay more

Table 3. Factors influencing negative conversion days.

	Univariate		Multivariate	
	HR	**p**	**Adjusted HR**	**p**
Male	1.08 (0.86-1.36)	0.528	0.91 (0.72-1.16)	0.465
Age (years)				
19-59	1.00		1.00	
≥ 60	0.60 (0.45-0.80)	0.001	0.81 (0.58-1.12)	0.209
Clinical types				
Mild	1.00		1.00	
Non-mild	0.59 (0.46-0.76)	< 0.001	0.77 (0.59-1.01)	0.057
Comorbidity numbers				
≤ 2	1.00		1.00	
> 2	0.68 (0.53-0.87)	0.003	0.67 (0.51-0.87)	0.003
COVID-19 vaccination				
Unvaccinated/one dose	1.00		1.00	
Two/booster doses	1.35 (1.05-1.73)	0.020	1.13 (0.86-1.50)	0.376
Delay days				
≤ 3	1.00		1.00	
> 3	0.91 (0.89-0.94)	< 0.001	0.88 (0.85-0.91)	< 0.001
Paxlovid	0.79 (0.63-1.00)	0.049	0.56 (0.43-0.72)	< 0.001

Age 19-59 years was used as the reference group for age. Mild was used as the reference group for clinical type. Comorbidities ≤ 2 was used as the reference group for comorbidity numbers. Unvaccinated/one dose was used as the reference group for COVID-19 vaccination. Covariates included gender, age, clinical type, comorbidity numbers, COVID-19 vaccination, delay days and Paxlovid use. Non-mild, included general, severe and critical types. HR: hazard ratio; COVID-19: coronavirus disease 2019.

attention to these patients [18]. We also found that male gender was more likely to get non-mild symptoms, and it was an independent risk factor. Moreover, there are reports that male COVID-19 patients are at a higher risk of death [19,20]. In addition, patients with more than two underlying comorbidities were more likely to develop non-mild symptoms, and chronic kidney disease is a risk factor for progressing to non-mild, which is consistent with previous studies [9,10,21].

Studies have shown that unvaccinated and non-fully vaccinated people, especially the elderly, are at higher risk of severe symptoms and death. During the fifth wave of COVID-19 in Hong Kong, China, 95.9% of the deaths occurred in people over 60 years old, 70.2% of whom were not vaccinated and 18.1% of whom were not fully vaccinated, and the relative mortality risk of unvaccinated and non-fully vaccinated people who were ≥ 60 years was 21.3 times and 2.3 times of fully vaccinated people ≥ 60 years, respectively [22]. In contrast to Singapore, the full vaccination coverage for total population in Hong Kong SAR, China was lower (76.15% vs. 92.00%; especially for people ≥ 70 years: 56.82% vs. 95.00%). Correspondingly, the case fatality ratio in Hong Kong SAR, China was higher than in Singapore (0.53% vs. 0.06%), especially for people ≥ 70 years (4.46% vs. 0.48%) [23]. As of 4 May 2022, only 25 out of 503 COVID-19 related deaths had received at least one dose of vaccine in Shanghai [5]. In our study, patients who had received two/booster doses of the vaccine had a lower risk of progressing to non-mild (adjusted OR = 0.35). Moreover, the patients who died were elderly and had not been vaccinated. Therefore, it is imperative to strengthen the vaccination of the elderly, especially those with more than two comorbidities.

Laboratory results showed that there were numerous differences between mild and non-mild patients. Lymphocyte counts significantly decreased with the increase of disease severity (Supplementary Figure 1), which is consistent with previous reports on immune changes in COVID-19 patients with different illness severities [9,24]. In addition, non-mild patients appeared to have a more obvious increase in D-dimer levels. A three to four-fold increase in D-dimer is closely associated with poor prognosis, and determination of D-dimer level at the early stage of COVID-19 disease contributes to timely clinical management of patients [25,26]. IL-6 was also significantly higher in patients with non-mild type, which was identified as a central role in cytokine storms associated with COVID-19 and helpful for predicting the prognosis [27,28]. Biochemical examination showed that troponin T and myoglobin levels were significantly higher with the increased severity of disease (Supplementary Figure 1). The increased inflammatory (for example CRP, PCT and interleukins) and prothrombotic (D-dimer) responses following SARS-CoV-2 infection can contribute to acute nonischemic myocardial injury and acute myocardial infarction with increases in cardiac troponin, which is related with adverse outcomes [29]. Measurement of troponin T and myoglobin has the potential to facilitate risk stratification in hospitalized COVID-19 patients [29,30].

The two doses/booster vaccination were more likely to shorten NCDs, which is consistent with a previous study on virus clearance time [9]. We also found that delayed admission of patients significantly lengthened NCDs, suggesting that general treatments should be started as soon as possible in symptomatic COVID-19 patients [31,32]. Some studies showed that Paxlovid (Pfizer, Freiburg, Germany) use could shorten the viral shedding time [9,33]. In contrast, our study indicated that Paxlovid as an independent influencing factor significantly lengthened NCDs, which could be partially interpreted as viral rebound after Paxlovid treatment [34-38].

Two limitations of this study are as follows: first, it is a single center retrospective study with limited sample size. Second, COVID-19 patients admitted to a district-level designated hospital are basically from a district with a relative elderly population.

Conclusions

Our study performed a retrospective analysis of the clinical manifestations, laboratory examinations and risk factors in COVID-19 patients admitted to a designated hospital in Shanghai in 2022. Our findings suggest that being male, ≥ 60 years old, and chronic kidney disease are risk factors of progressing to non-mild stage. Patients with > 2 comorbidities were more likely to become non-mild, whereas two/booster doses vaccinated patients had a lower risk of developing to non-mild stage. Our results call for special concern for full and booster vaccination of the elderly, which will effectively protect from progression to non-mild stage. In the meantime, symptomatic COVID-19 patients should be treated as soon as possible.

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Annex – Supplementary Items

Supplementary Table 1. Risk factors of progressing to non-mild according to comorbidity numbers.

	Univariate		Multivariate	
	OR	**p**	**Adjusted OR**	**p**
Male	1.71 (1.07-2.72)	0.024	2.00 (1.19-3.34)	0.008
Age (years)				
19-59	1.00		1.00	
≥ 60	14.2 (4.32-46.61)	< 0.001	9.93 (2.92-33.76)	< 0.001
Comorbidity numbers				
≤ 2	1.00		1.00	
> 2	2.68 (1.64-4.36)	< 0.001	1.87 (1.11-3.16)	0.019
COVID-19 vaccination				
Unvaccinated/one dose	1.00		1.00	
Two/booster doses	0.23 (0.12-0.42)	< 0.001	0.32 (0.16-0.61)	0.001

Age 19-59 years was used as the reference group for age. Comorbidities ≤ 2 was used as the reference group for comorbidity numbers. Unvaccinated/one dose was used as the reference group for COVID-19 vaccination. Covariates included gender, age, comorbidity numbers, and COVID-19 vaccination. Non-mild, included general, severe and critical types. OR: odds ratio; COVID-19: Coronavirus disease 2019.

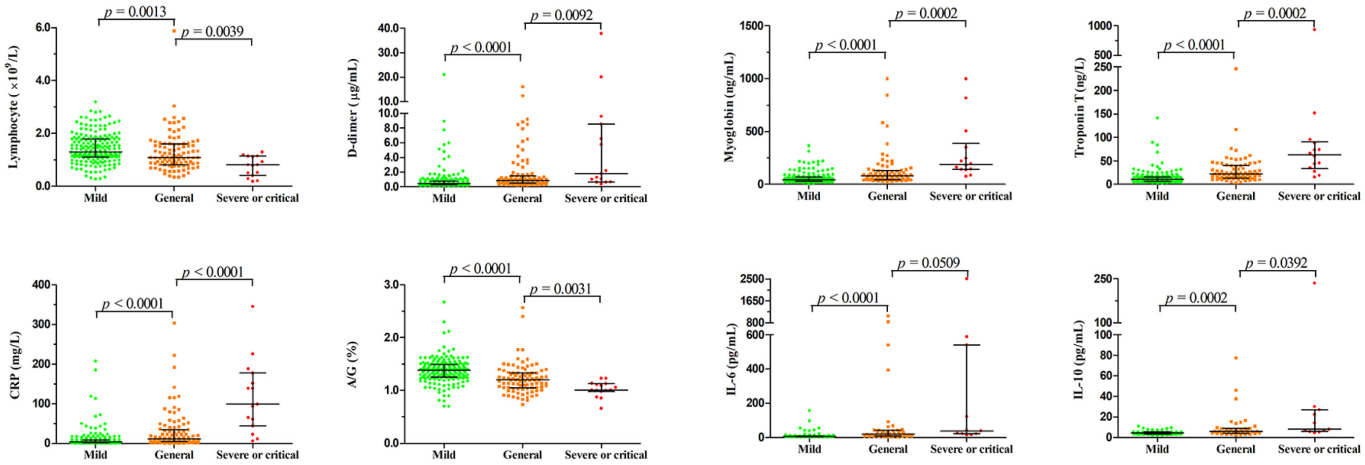
Supplementary Table 2. Laboratory results of COVID-19 patients.

	Mild group (n = 196)	**Non-mild group (n = 115)**	**p value**
Blood routine			
Leucocytes (× 109 per L; normal range 3.5-9.5)	4.8 (3.8, 6.0)	5.4 (3.9, 7.5)	0.027
Increased	7 (3.6)	17 (14.8)	
Decreased	28 (14.3)	15 (13.0)	
Neutrophils (× 109 per L; normal range 1.8-6.3)	2.7 (2.1, 3.8)	3.2 (2.2, 5.7)	0.002
Increased	8 (4.1)	23 (20.0)	
Decreased	31 (15.8)	20 (17.4)	
Lymphocytes (× 109 per L; normal range 1.1-3.2)	1.3 (1.1, 1.8)	1.1 (0.8, 1.5)	< 0.0001
Decreased	46 (23.5)	59 (51.3)	
Platelets (× 109 per L; normal range 125.0-350.0)	181.0 (147.0, 232.0)	182.0 (132.5, 232.0)	0.785
Decreased	23 (11.7)	20 (17.4)	
Blood biochemistry			
Alanine aminotransferase (U/L; normal range ≤ 35.0)	18.0 (14.0, 25.0)	17.0 (13.0, 25.0)	0.458
Increased	22 (11.2)	11 (9.6)	
Aspartate aminotransferase (U/L; normal range 14.0-36.0)	28.0 (23.0, 35.0)	30.0 (24.3, 39.0)	0.018
Increased	38 (19.4)	34 (29.6)	
A/G (%; normal range 1.2-2.5)	1.4 (1.3, 1.5)	1.1 (1.0, 1.3)	< 0.0001
Decreased	28 (14.3)	58 (50.4)	
Sodium (mmol/L; normal range 137-145)	138.6 (136.3, 140.8)	137.8 (133.7, 140.5)	0.118
Decreased	57 (29.1)	53 (46.1)	
Potassium (mmol/L; normal range 3.5-5.1)	3.6 (3.4, 3.9)	3.7 (3.3, 4.1)	0.350
Decreased	75 (38.3)	37 (32.2)	
Myoglobin (ng/mL; normal range 25-58)	46.7 (31.6, 71.2)	92.9 (48.8, 169.3)	< 0.0001
Increased	52 (26.5)	59 (51.3)	
Troponin T (ng/L; normal range 0-14)	10.7 (7.2, 16.6)	24.5 (15.7, 45.4)	< 0.0001
Increased	54 (27.6)	71 (61.7)	
Creatinine (μmol/L; normal range 46-92)	68.8 (56.5, 84.4)	74.5 (60.1, 102.4)	0.014
Increased	31 (15.8)	36 (31.3)	
Glucose (mmol/L; normal range 4.1-5.9)	5.6 (4.9, 6.7)	6.0 (5.1, 8.0)	0.023
Increased	81 (41.3)	56 (48.7)	
Decreased	5 (2.6)	3 (2.6)	
Coagulation function			
Activated partial thromboplastin time (s, normal range 20.0-40.0)	27.9 (26.3, 29.5)	29.6 (27.3, 32.0)	< 0.0001
Prothrombin time (s, normal range 9.0-13.0)	11.4 (10.9, 11.9)	11.7 (11.2-12.5)	0.0005
D-dimer (μg/mL; normal range 0.0-0.5)	0.4 (0.3, 0.7)	0.9 (0.5, 1.7)	< 0.0001
Increased	83 (42.3)	91 (79.1)	
Infection-related biomarkers			
C-reactive protein (mg/L; normal range 0.0-10.0)	3.7 (1.4, 8.7)	13.8 (5.4, 50.5)	< 0.0001

	Mild group (n = 196)	Non-mild group (n = 115)	p value
Increased	39 (19.9)	67 (58.3)	
Procalcitonin (ng/mL; normal range 0.0-0.046)	0.04 (0.03, 0.06)	0.07 (0.03, 0.20)	< 0.0001
Increased	70 (35.7)	60 (52.2)	
Serum Amyloid A (mg/L; normal range 0-10)	10.1 (3.7, 27.6)	72.3 (13.4, 248.8)	< 0.0001
Increased	84 (42.9)	75 (65.2)	
Interleukin-2 (pg/mL; normal range 0.0-5.71)	0.84 (0.72, 1.08)	1.02 (0.75, 1.37)	0.013
Interleukin-4 (pg/mL; normal range 0.0-2.8)	0.86 (0.64, 1.19)	1.15 (0.77, 1.71)	0.004
Interleukin-6 (pg/mL; normal range 0.0-5.3)	6.77 (4.39, 9.82	25.17 (9.81, 42.6)	< 0.0001
Increased	44 (22.4)	47 (40.9)	
Interleukin-10 (pg/mL; normal range 0.0-4.91)	4.28 (3.44, 5.31)	6.40 (4.60, 10.12)	< 0.0001
Increased	22 (11.2)	38 (33.0)	
TNF-α (pg/mL; normal range 0.0-2.31)	0.53 (0.29, 0.82)	0.66 (0.49, 1.12)	0.021
IFN-γ (pg/mL; normal range 0.0-7.42)	2.38 (1.69, 3.84)	2.72 (2.06, 4.55)	0.082
Interleukin-17A (pg/mL; normal range 0.0-20.6)	1.00 (0.00, 2.85)	2.58 (0.86, 7.21)	0.0008

Data are number (%) or median (IQR). Non-mild group includes general, severe, and critical patients. A/G, albumin/globulin. Increased means over the upper limit of the normal range and decreased means below the lower limit of the normal range.

Supplementary Figure 1. Differential indicators from laboratory results among mild, general, severe/critical patients.



The indicators include lymphocyte count, A/G ratio, myoglobin, troponin T, D-dimer, and inflammatory markers (CRP, IL-6, and IL-10).