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Age differences in clinical features and outcomes in patients with COVID-19, Jiangsu, China: a retrospective, multicentre cohort study

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ABSTRACT

Objectives To determine the age-specific clinical presentations and incidence of adverse outcomes among patients with COVID-19 in Jiangsu, China.

Design and setting Retrospective, multicentre cohort study performed at 24 hospitals in Jiangsu, China.

Participants 625 patients with COVID-19 enrolled between 10 January and 15 March 2020.

Results Of the 625 patients (median age, 46 years; 329 (52.6%) men), 37 (5.9%) were children (18 years or younger), 261 (41.8%) young adults (19–44 years), 248 (39.7%) middle-aged adults (45–64 years) and 79 (12.6%) elderly adults (65 years or older). The incidence of hypertension, coronary heart disease, chronic obstructive pulmonary disease and diabetes comorbidities increased with age (trend test, p<0.0001, p=0.0003, p<0.0001 and p<0.0001, respectively). Fever, cough and shortness of breath occurred more commonly among older patients, especially the elderly, compared with children (χ^2 test, p=0.0008, 0.0146 and 0.0282, respectively). The quadrant score and pulmonary opacity score increased with age (trend test, both p<0.0001). Older patients had many significantly different laboratory parameters from younger patients. Elderly patients had the highest proportion of severe or critically-ill cases (33.0%, χ^2 test p<0.0001), intensive care unit use (35.4%, χ^2 test p<0.0001), respiratory failure (31.6%, χ^2 test p<0.0001) and the longest hospital stay (median 21 days, Kruskal–Wallis test p<0.0001).

Conclusions Elderly (≥65 years) patients with COVID-19 had the highest risk of severe or critical illness, intensive care use, respiratory failure and the longest hospital stay, which may be due partly to their having a higher incidence of comorbidities and poor immune responses to COVID-19.

Strengths and limitations of this study

► This cohort consists of almost all COVID-19 patients in Jiangsu province, with a population of over 80 million. Findings are, therefore, representative of the hospitalised patient population in the whole province. They are inclusive across the range of disease severity, so are subject to less selection bias.

► The study includes imported and local cases with different types of exposure.

► This is an observational exploratory study and our results may thus be subject to possible confounding factors and false-positive error.

INTRODUCTION

COVID-19 infection causes a wide spectrum of disease, which may lead to respiratory failure and organ failure, leading to death. Most of the available studies prior to the COVID-19 pandemic found that people of all ages are susceptible to SARS-CoV-2 infection but noted higher positivity rates in real-time reverse transcriptase-PCR (RT-PCR) assays and hospitalisation burden in older people.[1–3] Similar to SARS, deaths and adverse clinical outcomes have been found to be more common in the elderly with known comorbidities for patients with COVID-19.[4–6] Evidence suggests that asymptomatic carriers were more common among middle-aged people in close contact with infected family members.[7] One study found that elderly patients with COVID-19 had some different clinical features compared with younger patients.[8] Because age is a host factor that leads to a higher risk of severe COVID-19 and worse prognosis, it is important to better understand age-related susceptibility and pathology. However, published data on age differences in clinical features and clinical outcomes associated with COVID-19 remain scarce. This study aimed to investigate differences in clinical characteristics, disease severity and clinical outcome burden in different age groups of patients with COVID-19.

METHODS
Study design and participants

This retrospective cohort study included all patients who met the study's inclusion and

exclusion criteria. The inclusion criterion was up to 15 March 2020, all patients diagnosed with COVID-19 in Jiangsu province according to the 'Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7)' released by the National Health Commission and National Administration of Traditional Chinese Medicine of China.[9] The only exclusion criterion was any patient with no available medical records. A standard criterion was set for discharge: a patient's body temperature must be normal for more than 3 days, symptoms were resolved (if there were symptoms) and RT-PCR assays (throat swab samples, with at least 1 day sampling interval) showed two consecutive negative results.

Data collection and definition of variables

Epidemiological, clinical, laboratory and radiologic parameters on admission; disease severity (asymptomatic, mild, moderate, severe and critically ill) and clinical outcomes data were extracted from medical records. A clustered onset was defined as the occurrence of two or more confirmed COVID-19 cases in the same cluster/group within 14 days, such as family, community, hospital, working place or public place. A clustered onset could occur from interpersonal transmission via close contact with, or joint exposure to, a confirmed COVID-19 case. Other cases not meeting the conditions of a clustered onset were classified as 'single onset'. Disease severity was assessed at days 1, 2, 3, 4, 5, 6, 7 and 14 after admission, except for those who were discharged, and the highest degree of disease severity during the 14-day follow-up was selected for analysis. Data on mortality and other clinical outcomes were available until 15 March 2020. Asymptomatic infection was defined as the absence of clinical symptoms but with a positive nucleic acid test result. Mild disease was defined as having mild clinical symptoms and the absence of imaging manifestations of pneumonia in CT scans. Moderate disease was defined as the presence of fever, respiratory tract symptoms or other symptoms, and imaging manifestations of pneumonia. Severe disease was defined as the presence of at least one of the following conditions: respiratory distress, respiratory rate $\geq$30 breaths/min; oxygen saturation in resting state (SpO_2) $\leq$93%; or arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen $\leq$300 mm Hg (1 mm Hg=0.133 kPa). Critically ill was defined as having respiratory failure requiring mechanical ventilation, shock or combined organ failure requiring intensive care unit (ICU) monitoring and treatment. We categorised the population into four age groups: children (18 years or younger), young adults (19–44 years), middle-aged adults (45–64 years) and elderly adults (65 years or older).

All of the patients in Jiangsu had a high-resolution CT thorax examination to identify lung lesions. CT images were assessed visually by two radiologists who had more than 5 years of working experience in chest imaging. The radiologists were blinded to the patients' characteristics. Quadrant scores were the sum of the number of quadrants containing pulmonary opacities extending from the proximal to the distal end of the chest, with a score ranging from 0 to 4. For pulmonary opacity, bilateral lungs were scored manually and assigned an estimated percentage of pulmonary opacity relative to the whole lung, rounded to the nearest 5%.

Statistical analysis

Normally distributed variables were summarised using mean (SD) by group and compared using analysis of variance tests, while skewed distributed variables were summarised using median (IQR) by group and compared using Kruskal-Wallis tests. Categorical variables were summarised using frequency and percentage and compared using χ^2/Fisher exact test. To assess the linear trend effect of age on demographic and clinical variables, generalised linear models were employed with age (in years) as the only predictor. Normal distribution and identity link function were used for continuous variables, whereas binomial distribution and logit link function were used for binary variables. Analyses were performed using SAS V.9.4 (SAS Institute) and a two-sided p<0.05 was considered statistically significant.

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

RESULTS

Of the 721 suspected cases with possible COVID-19 during the study period, 631 patients were found to be RT-PCR positive for COVID-19. Only 625 patients were included in the study with complete data (figure 1). The median age was 46 years (IQR, 32–57; range, 0.75–96 years) and 329 (52.6%) were men (table 1). Thirty-seven (5.9%) were children, 261 (41.8%) young adults of 19–44 years, 248 (39.7%) middle-aged of 45–64 years and 79 (12.6%) elderly of 65 years or older.

There was no significant difference in the proportion of men and women in each age group (table 1). The disease onset was clustered among a significantly higher proportion of young patients aged 18 years and below compared with older patients (aged 18 years and younger, young adult, middle-aged and elderly patients: 78.4%, 43.3%, 52.8% and 53.2%, respectively, p=0.0005). The comorbidities incidence of hypertension, coronary heart disease, chronic obstructive pulmonary disease and diabetes increased with age (trend test, p<0.0001, p=0.0003, p<0.0001 and p<0.0001, respectively). Fever, cough and shortness of breath occurred significantly more commonly among young adult, middle-aged and elderly patients compared with children (67.8%, 68.5%, 65.8% vs 35.1%, p=0.0008; 57.9%, 56%, 54.4% vs 29.7%, p=0.0146; 1.9%, 3.2%, 8.9% vs 0%, p=0.0282, respectively). The frequencies of these symptoms were similar among different age groups of adults except for shortness of breath which was dramatically more common (8.9%)
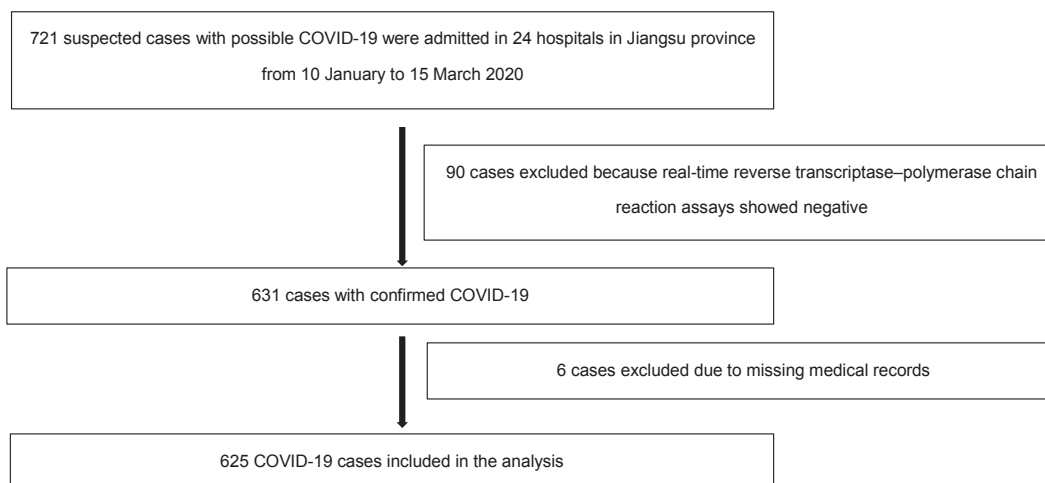
Figure 1 Study flow diagram.

in elderly adult patients aged 65 years or older. Compared with children and young adult patients, the incidence of smoking and drinking alcohol was significantly (twice the rate) higher among middle-aged and elderly patients. Three vital sign parameters on admission: systolic blood pressure (SBP) (mm Hg), diastolic blood pressure (DBP) (mm Hg) and SpO_2 (%), changed linearly with age (trend tests, all p<0.0001). The quadrant score and pulmonary opacity score increased with age (trend tests, both p<0.0001).

Significant differences were observed in some laboratory test results (table 2). Older patients tended to have lower PaO_2 (mm Hg) and partial pressure of carbon dioxide (mm Hg) in blood gas analysis. In blood tests, they had lower white blood cell count (10^9/L), lymphocyte count (10^9/L), haemoglobin level (g/L) and platelet count (10^9/L). In organ function tests, these patients had higher levels of alanine aminotransferase (U/L) and creatinine (µmol/L) and lower albumin levels (g/L). In inflammatory factor tests they had higher levels of C-reactive protein (mg/L); and in coagulation function tests shorter activated partial thromboplastin time (s) and higher levels of fibrinogen (g/L) and D-dimer (mg/L).

The proportion of patients who received supportive treatment and antiviral and antibiotic therapy increased significantly with patients' age, except for the very rare procedure of continuous renal replacement therapy and extracorporeal membrane oxygenation treatment and the very common use of interferon among different age groups (online supplemental table S1).

The proportion of patients with severe or critical illness was 33% among elderly patients, compared with 13% among middle-aged patients, 2.3% among young adult patients and 0% among children (p<0.0001) (table 3).

By the end of the study, none of the patients had died and all 625 patients had been discharged. The ICU rate (trend test, p<0.0001), respiratory failure rate (trend test, p<0.0001) and length of hospital stays (trend test, p<0.0001) increased with age (table 4). The proportion of patients requiring ICU care (p<0.0001) and developing respiratory failure (p<0.0001) among elderly patients was 35.4% and 31.6%, respectively, compared with 14.5% and 12.5% among middle-aged patients, 2.3% and 1.9% among young adult patients and none among children, respectively. Elderly patients also had longer hospital stays (median (IQR), 21.0 (14.0–26.0) days) than all other age groups (15.0 (11.0–21.0) for children, 14.0 (11.0–19.0) for young adults and 17.0 (13.0–22.0) for middle-aged adults, p<0.0001).

DISCUSSION

To our knowledge, this is the largest cohort of 625 patients followed to date, to assess age differences in clinical features and clinical outcomes associated with COVID-19. We observed that the majority (~80%) of COVID-19 cases were among young adult patients of 19–44 years and middle-aged patients of 45–64 years, with the remainder of patients comprising children of 18 years or under (5.9%) and elderly patients of 65 years or over (12.6%). This is consistent with a previous study from Korea which reported 6.3% of cases with COVID-19 were children under 19 years old, a study which had tested the broadest and hence the most representative population during this study period.[10]

Our study showed that compared with adults, children were more likely to get infected through cluster

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Table 1 Demographic and clinical characteristics of patients with COVID-19 at admission by age group

| Category | Characteristics* | All (N=625) | Age group | | | | P value† | P value‡ |
			Children (≤18 years) (N=37)	Young adulthood (19–44 years) (N=261)	Middle adulthood (45–64 years) (N=248)	Elderly (≥65 years) (N=79)		
Demographic, n(%)	Male	329 (52.6%)	23 (62.2%)	137 (52.5%)	132 (53.2%)	37 (46.8%)	0.4844	0.7235
Exposure type, n(%)	Imported cases	219 (35.0%)	10 (27.0%)	98 (37.5%)	88 (35.5%)	23 (29.1%)	0.3908	0.5508
	Local cases	406 (65.0%)	27 (73.0%)	163 (62.5%)	160 (64.5%)	56 (70.9%)		
Types of disease onset, n(%)	Single onset	310 (49.6%)	8 (21.6%)	148 (56.7%)	117 (47.2%)	37 (46.8%)	0.0005	0.5335
	Clustered onset	315 (50.4%)	29 (78.4%)	113 (43.3%)	131 (52.8%)	42 (53.2%)		
Initial symptoms, n(%)	Fever	412 (65.9%)	13 (35.1%)	177 (67.8%)	170 (68.5%)	52 (65.8%)	0.0008	0.0341
	Cough	344 (55.0%)	11 (29.7%)	151 (57.9%)	139 (56.0%)	43 (54.4%)	0.0146	0.3678
	Sputum	166 (26.6%)	3 (8.1%)	70 (26.8%)	68 (27.4%)	25 (31.6%)	0.0548	0.2217
	Shortness of breath	20 (3.2%)	0 (0.0%)	5 (1.9%)	8 (3.2%)	7 (8.9%)	0.0282	0.0016
Medical history, n(%)	Hypertension	91 (14.6%)	0 (0.0%)	11 (4.2%)	49 (19.8%)	31 (39.2%)	<0.0001	<0.0001
	Coronary heart disease	13 (2.1%)	0 (0.0%)	1 (0.4%)	5 (2.0%)	7 (8.9%)	0.0006	0.0003
	Chronic obstructive pulmonary disease	9 (1.4%)	0 (0.0%)	0 (0.0%)	3 (1.2%)	6 (7.6%)	0.0003	<0.0001
	Diabetes	40 (6.4%)	1 (2.7%)	4 (1.5%)	21 (8.5%)	14 (17.7%)	<0.0001	<0.0001
	Current smoker	38 (6.1%)	0 (0.0%)	8 (3.1%)	25 (10.1%)	5 (6.3%)	0.0035	0.0034
	Drinking alcohol	33 (5.3%)	1 (2.7%)	6 (2.3%)	20 (8.1%)	6 (7.6%)	0.0137	0.0032
Vital signs, mean (SD)	Temperature (°C)	37.05 (0.73)	36.86 (0.44)	37.03 (0.69)	37.09 (0.81)	37.07 (0.73)	0.3558	0.2324
	HR (bpm)	87.17 (13.46)	91.43 (17.84)	86.90 (13.01)	86.92 (12.77)	86.84 (14.62)	0.2672	0.2721
	SBP (mmHg)	128.83 (15.66)	120.11 (16.17)	123.14 (12.37)	132.85 (13.94)	139.06 (20.38)	<0.0001	<0.0001
	DBP (mmHg)	81.47 (10.51)	72.41 (11.24)	80.87 (9.98)	83.60 (10.30)	80.99 (10.16)	<0.0001	<0.0001
	Respiratory rate (breath per min)	19.08 (2.56)	19.86 (3.15)	18.74 (1.99)	19.38 (3.00)	18.92 (2.21)	0.0086	0.8381
	SpO₂ (%)	97.68 (1.99)	98.05 (1.05)	98.03 (1.24)	97.58 (1.92)	96.65 (3.57)	<0.0001	<0.0001
CT image, N,median (IQR)	Quadrant score (0–4)	496,2.0 (1.0–4.0)	27,0.0 (0.0–1.0)	205,2.0 (1.0–3.0)	196,3.0 (2.0–4.0)	68,3.0 (2.0–4.0)	<0.0001	<0.0001
	Pulmonary opacity (%)	496,20.0 (5.0–40.0)	27,0.0 (0.0–5.0)	205,15.0 (5.0–30.0)	196,30.0 (12.5–45.0)	68,27.5 (10.0–50.0)	<0.0001	<0.0001

*Missing data only occurred to two CT parameters.
†P value from testing differences in proportions or means or distributions among different age groups.
‡P value from trend test of linear age effect in generalised linear model in which age (year) was included as the only predictor.
DBP, diastolic blood pressure ; HR, heart rate; SBP, systolic blood pressure; SpO₂, oxygen saturation in resting state.

Table 2 Laboratory parameters of patients with COVID-19 at admission by age group

Category	Parameters	All (N=625)	Age group, N, median(IQR)				P value*	P value†
			Children (≤18years) (N=37)	Young adulthood (19–44years) (N=261)	Middle adulthood (45–64 years) (N=248)	Elderly (≥65years) (N=79)		
Blood gas analysis	pH	252,7.4 (7.4–7.4)	9,7.4 (7.4–7.4)	92,7.4 (7.4–7.4)	117,7.4 (7.4–7.5)	34,7.4 (7.4–7.5)	0.0213	0.0007
	PaO₂ (mmHg)	252,94.0 (78.0–110.0)	9,94.0 (86.7–113.0)	92,102.0(87.0–124.5)	117,89.0 (76.2–106.0)	34,81.7 (74.0–101.0)	0.0002	0.0009
	PaCO₂ (mmHg)	252,39.0 (36.0–42.0)	9,45.0 (42.0–49.0)	92,39.5 (37.2–42.0)	117,39.0 (35.6–42.0)	34,37.2 (34.6–42.0)	0.0016	0.0087
	Lactate (mmol/L)	260,2.1 (1.3–2.8)	17,2.3 (1.5–3.1)	98,2.1 (1.3–2.8)	106,1.9 (1.3–2.8)	39,2.3 (1.3–3.1)	0.5056	0.5554
Blood test	WBC (10⁹/L)	513,4.9 (3.9–6.2)	33,6.0 (4.8–7.2)	213,4.9 (3.9–6.1)	205,4.8 (3.8–6.1)	62,4.6 (3.9–6.4)	0.0119	0.1275
	Neutrophil (10⁹/L)	507,3.0 (2.2–4.0)	33,3.2 (2.0–4.6)	210,2.8 (2.1–3.9)	203,3.1 (2.2–4.1)	61,3.4 (2.4–4.3)	0.4466	0.2909
	Lymphocyte (10⁹/L)	505,1.3 (0.9–1.7)	33,1.8 (1.5–2.5)	209,1.4 (1.0–1.9)	202,1.1 (0.9–1.6)	61,1.0 (0.7–1.3)	<0.0001	<0.0001
	Haemoglobin (g/L)	510,137.0(124.0–150.0)	33,138.0(126.0–148.0)	212,139.5(123.0–154.0)	204,136.5(125.0–148.0)	61,129.0(121.0–140.0)	0.025	0.005
	Platelet (10⁹/L)	494,183.5(151.0–219.0)	33,236.0(192.0–298.0)	203,197.0(161.0–228.0)	198,171.5(143.0–206.0)	60,152.0(125.0–186.5)	<0.0001	<0.0001
Organ function	Alanine aminotransferase (U/L)	425,25.0 (16.5–38.0)	33,19.0 (16.0–30.0)	169,25.0 (16.0–39.3)	170,26.8 (19.0–42.0)	53,22.0 (15.0–33.0)	0.0499	0.3126
	Albumin (g/L)	480,41.4 (38.0–45.1)	33,45.0 (40.1–47.9)	194,42.1 (38.0–46.6)	193,41.5 (38.0–44.4)	60,38.9 (35.4–43.1)	0.0001	<0.0001
	Total bilirubin (umol/L)	465,9.8 (6.0–14.7)	33,7.7 (5.0–10.8)	186,9.8 (6.1–14.8)	188,10.0 (6.3–14.9)	58,10.4 (6.6–15.3)	0.1141	0.3401
	Creatinine (umol/L)	476,63.9 (51.0–79.0)	32,54.5 (36.0–61.0)	193,64.0 (51.3–78.0)	191,64.0 (51.0–80.0)	60,67.0 (56.0–85.1)	0.0003	0.0004
Inflammatory factors	C-reactive protein (mg/L)	474,10.0 (2.7–22.6)	30,5.1 (1.2–10.0)	193,9.6 (2.0–16.2)	189,10.0 (4.4–26.3)	62,16.8 (5.0–51.1)	<0.0001	<0.0001
	Procalcitonin (ng/mL)	408,0.0 (0.0–0.2)	28,0.0 (0.0–0.2)	170,0.0 (0.0–0.1)	157,0.1 (0.0–0.2)	53,0.0 (0.0–0.2)	0.8557	0.098
Coagulation function test	Activated partial thromboplastin time (s)	513,32.2 (28.0–37.2)	31,37.2 (30.1–41.8)	217,32.2 (27.9–36.5)	203,31.8 (28.0–36.6)	62,33.0 (27.9–38.1)	0.0448	0.274
	Fibrinogen (g/L)	496,3.5 (2.7–4.2)	30,2.6 (2.2–2.9)	209,3.3 (2.6–4.1)	198,3.8 (3.0–4.4)	59,3.7 (2.6–4.8)	<0.0001	<0.0001
	D-dimer (mg/L)	475,0.2 (0.1–0.4)	30,0.2 (0.1–0.3)	191,0.2 (0.1–0.3)	195,0.2 (0.1–0.4)	59,0.4 (0.2–0.7)	0.0016	0.0049

*P value from Kruskal-Wallis test of differences in distributions among different age groups.
†P value from trend test of linear age effect in generalised linear model in which age (year) was included as the only predictor.
PaCO₂, partial pressure of carbon dioxide; PaO₂, arterial partial pressure of oxygen.

Table 3 Highest degree of disease severity of patients with COVID-19 during hospital stay by age group

Highest degree of disease severity	All (N=625)	Age group, n(%)				P value
		Children (≤18 years) (N=37)	Young adulthood (19–44 years) (N=261)	Middle adulthood (45–64 years) (N=248)	Elderly (≥65 years) (N=79)	
Asymptomatic	24 (3.8%)	8 (21.6%)	5 (1.9%)	7 (2.8%)	4 (5.1%)	<0.0001
Mild	34 (5.4%)	11 (29.7%)	18 (6.9%)	4 (1.6%)	1 (1.3%)	
Moderate	503 (80.5%)	18 (48.6%)	232 (88.9%)	205 (82.7%)	48 (60.8%)	
Severe	30 (4.8%)	0 (0.0%)	4 (1.5%)	16 (6.5%)	10 (12.7%)	
Critically ill	34 (5.4%)	0 (0.0%)	2 (0.8%)	16 (6.5%)	16 (20.3%)	

gatherings. A previous study reported that COVID-19 in children was mainly caused by family transmission.[11]

Our study in Jiangsu, found that all patients were discharged with no deaths. Elderly patients were more than twice as likely to have a severe or critical illness compared with middle-aged patients, while a smaller proportion of young adult patients had severe symptoms, and child patients exhibited none. The ICU use and respiratory failure rate, and length of hospital stay increased with age. Many case studies have shown that older patients are refractory (not yielding to treatment or not significantly improved after treatment) and likely to be at higher risk of more severe disease including acute respiratory distress syndrome (ARDS), respiratory failure and death,[12–19] while younger patients are more likely to have a mild or moderate type of COVID-19.[11 20 21] This is similar to SARS characteristics that, compared with adults and adolescents, the disease appears to be less severe in younger children.[6]

We found that initial symptoms including fever, cough and shortness of breath occurred more frequently among adults compared with child patients and especially shortness of breath was dramatically more common in elderly adult patients aged 65 years or older. This is consistent with the previous study showing that the older group (≥60 years) had a higher rate of shortness of breath than the younger group (<60 years).[22] However, another study showed that only sore throat showed a significant difference between age groups but fever, cough, sputum and diarrhoea did not show differences, probably due to the small sample size.[21] Another study which evaluated age difference only found four patients in total with symptoms of chest tightness or difficulty of breathing; however, the sample size (56 patients) was too small to draw any conclusions.[8] Such symptoms may be the early signs of more severe illness and poorer outcomes in older patients. The frequency of these symptoms among adult patients in different age groups was similar except for shortness of breath, which was dramatically more common in elderly patients than younger adult groups in our study. This is different from the characteristics of influenza, where the initial clinical manifestations of frail elderly patients are usually subtle compared with young patients.[23 24] In our study, the difference in vital signs of

SBP and DBP on admission for different age groups were statistically significant (increasing with age) but may not be clinically significant.

Our study showed that the age differences in clinical outcomes may also have partially resulted from the increased incidence of comorbidities with age, including hypertension, coronary heart disease, chronic obstructive pulmonary disease and diabetes. This may have increased susceptibility to the virus infection; such comorbidities are identified as risk factors of more severe disease including respiratory failure and death in patients with COVID-19.[13 17–19 25] Other explanations about why older people suffer poorer outcomes may be due to the higher prevalence of smoking and alcohol drinking in older patients with COVID-19 in Jiangsu. A history of smoking has been identified as a factor contributing to the progression of COVID-19 pneumonia.[26]

Our study demonstrated that the quadrant score and pulmonary opacity score increased with age, suggesting more severe abnormal imaging manifestation on admission among these older patients. This is consistent with the finding that the proportion of multiple lobe involvement in older patients was higher than in younger cases.[8] Previous reports have also found some imaging differences by age groups; for example, primarily elderly patients were reported to have atypical imaging findings of consolidative opacities superimposed on ground-glass opacification,[27] while paediatric patients showed more modest pulmonary involvement and less commonly reported consolidation complicated peripheral halo signs, compared with adults.[28–30]

Abnormal values in laboratory parameters in older patients may also be an early sign of, and a contribution to, severe illness and poor outcomes. This is consistent with previous studies showing the level of lymphocytes and albumin in the older cases was significantly lower and the level of C-reactive protein was higher than in the younger patients.[8 21] Studies showed that albumin and C-reactive protein were associated with the progression of COVID-19 pneumonia,[26] greater D-dimer on admission increased risk of in-hospital death,[14] and organ and coagulation dysfunction (eg, higher D-dimer) contributed to the development of ARDS and progression from ARDS to death.[16]

Table 4 Clinical outcome of patients with COVID-19 by age group

Clinical outcome	Age group, n (%) or median (IQR)					P value*	P value†
	All (N=625)	Children (≤18 years) (N=37)	Young adulthood (19–44 years) (N=261)	Middle adulthood (45–64 years) (N=248)	Elderly (≥65 years) (N=79)		
Intensive care unit	70 (11.2)	0 (0.0)	6 (2.3)	36 (14.5)	28 (35.4)	<0.0001	<0.0001
Shock	2 (0.3)	0 (0.0)	0 (0.0)	1 (0.4)	1 (1.3)	0.3581	0.0672
Respiratory failure	61 (9.8)	0 (0.0)	5 (1.9)	31 (12.5)	25 (31.6)	<0.0001	<0.0001
Renal failure	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.5)	0.0031	0.0266
Hospital stay (day)	16.0 (12.0–22.0)	15.0 (11.0–21.0)	14.0 (11.0–19.0)	17.0 (13.0–22.0)	21.0 (14.0–26.0)	<0.0001	<0.0001

*P value from testing differences in proportions or distributions among different age groups.
†P value from trend test of linear age effect in generalised linear model in which age (year) was included as the only predictor.
‡

Our study indicated that lymphopenia (normal range: $(0.3–3.0)\times10^9/L$) was shown in all age groups, but white blood cell and lymphocytes counts were lower in older patients, indicating that live SARS-COV-2 virus stimulated poorer responses in older patients. The mechanism in old patients with a severe COVID-19 illness may be that older patients have a diminished immune response to the novel SARS-COV-2 virus, which is a defence mechanism against respiratory viruses and contributes to virus clearance. The thymic involution in older patients causes an age-related reduction of T cell repertoire diversity and defects in CD4+ and CD8+ T cell function and hence significantly reduces immune function (known as immunosenescence).[31 32] Immunosenescence makes many viral infections worse in older patients.[33] But further research is necessary to investigate whether age differences in disease severity and outcomes of COVID-19 result from ageing of the immune system and reduced responsiveness. This is because some respiratory viruses could escape antiviral mechanisms and immune responses.[34] For example, a study of H1N1pdm (respiratory viruses) on ferrets found no significant difference in viral clearance between young and adult subjects.[35] However, studies found that the pulmonary pathology improved earlier in young ferrets, regulatory interleukin-10 (which is mainly produced by monocytes and lymphocytes) and interferon responses were more robust in young ferrets.[35–37] Also, H1N1pdm infection triggered the formation of lung structures that resembled inducible bronchus-associated lymphoid tissues in young ferrets which contributes to pulmonary immune responses and were not seen in the adult ferrets with severe disease.[35–37] Some other studies demonstrated aged ferrets infected with influenza viruses had reduced antibody production and delayed peripheral blood T-cell responses compared with adult counterparts.[31 32 38] Another study reported that, except for immunosenescence in older people, age-related increases in levels of phospholipase could also result in a delay of immune response and poor outcomes after SARS-CoV infection.[33] Overall, research focused on innate immune-related mechanisms and viral clearance in patients with COVID-19 of different age groups may help determine the underlying mechanisms of disease severity.

Some other reasonable mechanisms of mild presentation in children include qualitatively different response to SARS-CoV-2, or different expression of ACE2 receptors required for SARS-CoV-2 infection, or different virus-to-virus interaction and competition from other viruses limiting SARS-CoV-2 growth.[10]

A larger proportion of older patients in this study received supportive treatment and antiviral and antibiotic therapies which was due in part to the increasing proportion of severe or critical illness in older adults. Previous studies similarly showed that treatment was statistically different by age group.[8 21]

We believe that the findings from this study are generalisable to populations in similar settings (eg, outside the initial pandemic centre) for two reasons: (1) we

included nearly all patients in Jiangsu province, China; (2) the study population consisted of cases confirmed by laboratory tests including those who were screened from suspected cases who had been to the pandemic centre (Wuhan), or had contact with people who had been to Wuhan or who had a confirmed diagnoses of COVID-19.

Our study has several limitations. First, the relatively short follow-up time and a very small proportion of patients who remained in hospital after the 14-day follow-up period may have resulted in incomplete estimates for disease severity. This would limit our interpretation of age differences in the burden associated with COVID-19. However, this impact is minor and may not strongly affect the study results because we included analyses of clinical outcomes at the end of the study. Second, we were unable to perform multiple regression analysis to control for possible bias in the observed age impact on clinical features and outcomes. As a result, the observed age differences may still be subject to possible confounding factors. Third, this is an observational and exploratory analysis in which many statistical tests have been performed. As a result, there may be some false-positive results.

CONCLUSIONS

Older patients outside the pandemic centre of Wuhan, China, tended to have relatively more severe clinical infections and poorer clinical outcomes associated with COVID-19 compared with younger patients. Elderly patients aged 65 and older were at a much higher risk of developing severe or critical illness than other age groups. The ICU and respiratory failure rate, and length of hospital stay increased with age. Older patients had worse clinical outcomes, in part due to comorbidities in older people, and higher rates of smoking and drinking habits, and immune, organ and coagulation dysfunction on admission. In studying the pathogenesis and developing management strategies of COVID-19, age is confirmed as a critical factor in the severity of infection.

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