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ABOUT COVER

Peer Reviewer of *World Journal of Clinical Infectious Diseases*, Liuhua Wang, MD, Associate Chief Physician, Department of General Surgery, Northern Jiangsu Province Hospital, Clinical Medical College, Yangzhou University, 98 Nantong West Road, Yangzhou City, Jiangsu Province 225001, China. 18051062945@yzu.edu.cn

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MINIREVIEWS

Monkeypox in humans: Transmission, pathophysiology, diagnosis, treatment, prevention, and all recent updates

Taral Parikh, Ashish Goti, Kanica Yashi, Nilesh Dankhara, Sandhya Kadam, Ramesh Dihora, Kapil Paiwal, Narendrasinh Parmar

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Taral Parikh, Department of Pediatrics, Hamilton Health Center, Harrisburg, PA 17104, United States

Ashish Goti, Department of Pediatric, Tulane Medical Center, New Orleans, LA 70112, United States

Kanica Yashi, Adult Medicine, Bassett Medical Center, Cooperstown, NY 13326, United States

Nilesh Dankhara, Department of Pediatric and Neonatology, University of Mississippi Medical Center, Jackson, MS 39216, United States

Sandhya Kadam, Department of Pediatric, Family Healthcare Network, Visalia, CA 93277, United States

Ramesh Dihora, Department of Pediatric, Nice Children Hospital, Surat 395003, India

Kapil Paiwal, Oral Maxillofacial Surgeon, Daswani Dental College and Research Center, Kota 324005, India

Narendrasinh Parmar, Department of Pediatrics, Brookdale University Hospital Medical Center, Brooklyn, NY 11212, United States

Corresponding author: Taral Parikh, MD, Doctor, Department of Pediatrics, Hamilton Health Center, 110 s 17th Street, Harrisburg, PA 17104, United States. parikhtaral@yahoo.com

Abstract

The Centers for Disease Control and Prevention (CDC) is monitoring an epidemic of monkeypox infection in the United States. The outbreak is now global and more than 6900 cases have already been reported. There are 83 confirmed cases among children and adolescents, as shown in the report published on November 3, 2022, in the USA. However, monkeypox in pediatric patients is still infrequent (< 0.3% of total cases). Among cases in the United States, 16 cases were in children < 5 years, 12 in the age group 5-12 years, and 55 cases in adolescents 13-17 years old. In the adolescent age group, 89% were male. For children < 12 years of age, close physical contact with an adult household with monkeypox was the primary exposure, but for adolescents, male-to-male sexual contact was found more frequently. The CDC advised United States healthcare providers to remain vigilant for patients with a rash resembling monkeypox, even if there is no history

of travel to a country with high risk. This article summarizes the history and epidemiology of monkeypox with a specific emphasis on clinical features and management in pediatric patients.

Key Words: Pediatric monkeypox; Smallpox; Monkeypox case definition; JYNNEOS vaccine; ACAM2000

Core Tip: This article describes current updates on the clinical features and management of pediatric monkeypox infection.

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INTRODUCTION

The monkeypox virus is an orthopoxvirus that causes monkeypox. Orthpoxviruses that infect humans range from lethal small poxviruses to highly contagious but benign molluscum contagiosum viruses[1]. Monkeypox has always been found in West and Central Africa. However, in May 2022, the United States and other countries reported cases of monkeypox, even though there was not previously documented monkeypox transmission[2]. There are two distinct monkeypox virus classes: The Congo basin clade, mainly in central Africa, and the West Africa clade[3]. The Congo basin clade is known to cause disease with a severe impact and causes more morbidity and mortality. Human-to-human transmission has also been reported more frequently with the Congo basin clade.

Monkeypox in non-human primates

The monkeypox virus was first discovered in 1958 from a monkey in Copenhagen, Denmark, at the Staten's Serum Institute - and that is how it got its name[4]; monkeypox virus-hosts also include dormice, pouched rats, rope squirrels, and tree squirrels. Like many other zoonoses, Pox virus is known to be transmitted accidentally to a human when dealing with infected animals.

Monkeypox in humans

The Dominican Republic (DR) of the Congo noted the first known human case of monkeypox in 1970. Six unvaccinated people from the DR of Congo, Liberia, and Sierra Leone presented with an illness similar to smallpox on clinical presentation[5]. The DR Congo reported the first pediatric case in a 9-month-old infant. Four other children from Bouduo and Liberia aged 4 to 9 years were also affected. Three children close to these cases also developed a rash in the following days, indicating possible exposure. There was also the case of the 24-year-old male reported in Sierra Leone who was reported to have removed the stomach and intestine from a red monkey, and after 3-4 wk, he felt ill. No one died of monkeypox.

In the United States, monkeypox cases were first reported in 2003[6]. Seventy-one people were infected by Gambian pouched rats and prairie dogs, when they received a shipment of these infected animals as pets. The Centers for Disease Control and Prevention (CDC) and Wisconsin Research Department mentioned this outbreak in which patients presented with febrile illness with vesiculopustular eruption between May and June 2003. The five male and six female patients were aged between 3 and 43 years. The possible epidemiology, clinical, and laboratory investigations in this outbreak were also summarized. Contact with ill pet prairie dogs exposed to sick rodents from West Africa and Ghana was identified in all these patients. The illness started with a fever with or without chills, skin rash, and excessive sweating. All patients reported papular skin rash and headache; many reported fevers, chills, sweating, or persistent cough, and approximately half of the patients had lymphadenopathy. The characteristic rash started as a papule followed by a vesiculopustular lesion surrounded by erythema. Lesions finally resolved with serous fluid and a hemorrhagic crust with a mean duration of 12 d (3-25 d). All cases had a mild disease course, and only four were hospitalized, but recovered quickly. This was the first time monkeypox was identified among humans in the Western world. Only five adults were vaccinated against smallpox, while others were too young to receive the vaccine.

An outbreak of human monkeypox occurred in Nigeria in 2017[7]. There were 38 suspected cases, of which 18 received laboratory confirmation, three cases were probable, and 17 did not meet the case definition. Most of the confirmed cases were male adults. There was an association with varicella, syphilis, and human immunodeficiency virus (HIV) in two confirmed cases, and one healthcare worker had a nosocomial infection.

In September 2018, the United Kingdom reported monkeypox transmission from a patient to a healthcare worker[8]. The possible source of infection was contaminated bedding. The hospital undertook all possible infection control measures to control the outbreak. Four of the 134 possible cases exposed became ill, but the clinical course was mild.

Transmission

Monkeypox infection resembles smallpox, and the illness may be initially diagnosed as smallpox as both illnesses share similar clinical features[9]. Monkeypox was identified after the eradication of smallpox. Monkeypox is a zoonosis, although human-to-human transmission can occur. Monkeypox can spread due to close or skin-to-skin contact. Direct contact with monkeypox rash and contact with the patient's saliva, upper respiratory secretions, and areas around the anus, rectum, or vagina can lead to infection. It is not as contagious as smallpox among humans. Although monkeys and other primates are the primary reservoirs, other animals, such as squirrels and other rodents, can also be reservoir hosts for this virus. Pox virus deoxyribonucleic acid (DNA) has been identified in anal and urethral swabs from persons who neither demonstrated clinical signs nor reported symptoms of illness at the time of specimen collection. Few cases remained asymptomatic despite having known or possible sexual exposure to infected personnel[10].

How monkeypox relates to smallpox

In 1980 smallpox was declared eradicated worldwide, and the last reported case was in 1977. However, Huang *et al*[11] reported that it had been over 40 years since all countries stopped administering the smallpox vaccine. Previous history of vaccination against smallpox can provide some protection against monkeypox, but it is uncertain how long this protection lasts. In the 2003 monkeypox outbreak and 2022 outbreak, multiple infected patients with monkeypox had a history of smallpox vaccination in past decades[12].

Pathophysiology

The monkeypox virus enters the body *via* routes such as the oropharynx, nasopharynx, or intradermal and replicates at the inoculation site, then spreads to local lymph nodes[13], followed by viremia and infection of organs. The incubation period typically ranges from 7 to 14 d, with a maximum of 21 d. Symptoms start with fever and lymphadenopathy 1-2 d before developing skin lesions. In the 2022 outbreak, it was noted that monkeypox spread from when symptoms appeared to the phase where the rash had healed completely, and a new layer of skin had formed[14].

Case definition and clinical features

Below is the Case definition by the CDC and European Centre for Disease Prevention and Control guidance[14,15] (Table 1).

Exclusion criteria

Another diagnosis is made or an individual with suspected monkeypox does not develop clinical symptoms or a rash within five days or suspicious clinical specimens fail to demonstrate orthopoxvirus infection or antibodies against the infection.

Clinical features

Monkeypox rash begins with macules followed by papules, vesicles, and pustules. Pustules are characteristically deep-seated, firm, and well-circumscribed. These lesions can progress to become umbilicated or confluent but ultimately progress to scabs[16]. The rash can also spread to other parts of the body. Lesions on a distinct body part are at the same stage in classic monkeypox.

Classic symptomatology during monkeypox infection includes fever with chills, malaise, sore throat, and lymphadenopathy, followed by a characteristic rash. However, in the 2022 outbreak, some patients developed perianal and genital lesions but no fever or other systemic symptoms.

Monkeypox rash can mimic other common illnesses in clinical practice such as syphilis, herpes simplex virus and varicella zoster infection, chancroid, and molluscum contagiosum, and these illnesses can frequently be associated with monkeypox. Therefore, it is necessary that the clinician remains vigilant, especially with patients who present with the characteristic rash and men who practice sex with men (Table 2).

How long is monkeypox contagious?

As shown by Guarner *et al*[1], the infected person is not contagious during the incubation period. However, humans can be infectious as soon as symptoms begin until all scabs on the pox lesions fall off.

Diagnosis

When monkeypox is suspected in the United States; the clinician should contact the health department to determine the availability of testing, and lesions should be thoroughly swabbed and sent to testing laboratories. The monkeypox virus can be detected by an orthopoxviral polymerase chain reaction (PCR) test at a designated laboratory, and a positive PCR is enough for the diagnosis of monkeypox. When complex cases or positive laboratory results do not meet epidemiological criteria, the CDC should be consulted so that additional tests such as viral-specific or clade-specific PCR and blood testing can be conducted.

Complications

Reported complications are encephalitis, secondary skin infections, conjunctivitis, keratitis, and secondary pneumonia. During outbreaks in epidemic areas, mortality can be between 0% and 11%, affecting significantly young children[17]. Severe monkeypox infection is common in immunocompromised patients. Patients with HIV infection suffered more during the 2017 Nigeria outbreak than HIV-negative patients, with severe skin lesions and genital ulcers. However, no

Table 1 Case definition and clinical features

Suspect case	New-onset typical rash
	Fulfill one of the epidemiologic criteria and have a solid clinical possibility of monkeypox
Probable case	No other possible orthopoxviral exposure (*e.g.*, vaccination), and evidence of the presence of
	orthopoxviral DNA by PCR in the patient's sample
	Presence of orthopoxvirus using immunohistochemical or electron microscopy testing methods
	Positive anti-orthopoxviral IgM antibody after onset of rash for a duration of 4 to 56 d. Men who practice sex with men
Confirmed case	Evidence of monkeypox virus DNA detected by PCR in a patient specimen or detection of virus in clinical specimen culture
	Epidemiological criteria: Within three weeks of beginning the illness: Possible exposure to a person with a characteristic rash or who was diagnosed with monkeypox or a probable case, or following intimate exposure to individuals with monkeypox-like symptoms. Travel to a monkeypox endemic country outside the United States or a country with a monkeypox outbreak, or contact with a dead or live wild animal or pet from an endemic African region or a product obtained from such animals

DNA: Deoxyribonucleic acid; PCR: Polymerase chain reaction; IgM: Immunoglobulin M.

Table 2 Monkeypox symptoms and treatment options

Monkeypox symptoms	Treatment options
Monkeypox symptoms: Itchy, painful pimple/blister-like rash with several stages	Oral antihistamines, creams, and lotions such as calamine lotion. Keep the rash covered, do not scratch, soak in a warm bath, use oatmeal
Fever, chills, lymph node swelling, body ache, URI symptoms	Symptomatic pain medications
Severe disease involving eyes, mouth, throat, genitals and anus	Antiviral tecovirimat

URI: Upper respiratory infection.

deaths were reported. Between September 2017 and June 2022, Nigeria reported 257 confirmed cases, with nine deaths; of the nine patients who died, five were immunocompromised[18]. Disfiguring scars and corneal damage can be frequent significant sequelae. It was noted that vaccinated patients experienced fewer complications, and the secondary case rate in such households was lower[19]. As shown by Mbala *et al*[20], pregnant patients had more complications, including preterm delivery, fetal death, or congenital diseases. An observational study was performed at the Hospital in Kole between 2007 and 2011, which showed that of four pregnant women with monkeypox, who were included in the study, one had a full-term, healthy baby, two experienced a stillbirth in the first trimester, and the remaining patient experienced fetal death.

Precautions

Monkeypox spreads from human to human *via* exposure to the rash, close contact, or articles contaminated with contagious inflammation or body secretions[21]. Standard care is required for all suspected monkeypox patients. People with monkeypox who are not hospitalized require isolation at home. For confirmed monkeypox, isolation must continue until the rash has healed, the scabs have fallen off, and skin is intact.

Treatment

As shown by Rizk *et al*[22], monkeypox does not require treatment in all patients. Immunocompromised patients, children under eight years of age, pregnant or breastfeeding women, and those with eczema or exfoliative skin lesions are considered high risk. Also, patients with severe complications or rashes involving the eyes, mouth, and private areas may qualify for treatment.

Unfortunately, there are no treatment protocols for pediatric patients with monkeypox; however, local public health officials can help with CDC consultation to initiate antiviral therapy.

Tecovirimat was developed to treat smallpox, which can be used for monkeypox and is currently the first-line treatment for children. An oral dose in children of more than 13 kg is possible, which can be taken as a capsule, or the capsule's content can be mixed with food. In children less than 13 kg, the intravenous formulation can be considered depending on clinical status. Monitoring renal function is recommended, especially in children under two years of age.

The CDC is also developing a protocol for intravenous immunoglobulin in patients with monkeypox, but its effectiveness has not been established.

Brincidofovir was Food and Drug Administration (FDA) approved for smallpox treatment, and cidofovir was FDA-approved for cytomegalovirus retinitis in acquired immunodeficiency syndrome in the pediatric population. However,

there is still a lack of data on the effectiveness of brincidofoir and cidofovir in treating pediatric monkeypox.

Post-exposure prophylaxis

The CDC is conducting studies to determine how long immunity lasts after vaccination. They are looking at specimen samples from infected patients to determine whether the virus has changed. The CDC works closely with local and state partners to determine how the virus spreads among monkeypox patients. Studies have been carried out to assess how many patients were vaccinated, if they were fully vaccinated, and when they were vaccinated. Close monitoring of those newly diagnosed with monkeypox after vaccination is ongoing.

Two vaccines can be given to people who have been in contact with a monkeypox patient[23]. Data on post-exposure prophylaxis (PEP) in children are limited. JYNNEOS is the only vaccine that can be used in pediatrics. The decision to vaccinate must be made according to the level of risk in terms of the patient's exposure and health conditions. While vaccination is preferred in most cases, immunoglobulin may be considered in an infant less than six months of age. There is the possibility of using anti-viral medication after consultation with the appropriate CDC facility for PEP.

JYNNEOS

This vaccine has not been extensively studied in pediatrics for monkeypox; it contains non-replicating vaccine virus. This vaccine has been used in pediatrics for illnesses such as tuberculosis, Ebola, and measles without major side effects. In 2018-2019, this vaccine was used in the United Kingdom in pediatrics following monkeypox exposure without any major side effects. In the current outbreak, JYNNOS is available for children and adolescents under 18 years of age, who are classified as having high-risk exposure according to the CDC[24]. The dose is 0.5 mL for each subcutaneous injection with a two-dose series, and ideally, the first dose should be given within 96 h post-exposure[24].

ACAM2000

As shown by Singhal *et al*[25], this vaccine contains replicating viruses associated with side effects such as uncontrolled viral replication and eczema vaccinatum. It is not a preferred vaccine for pediatrics and should only be considered if JYNNEOS is unavailable or contraindicated.

Immunoglobulin: Immunoglobulin is approved under the emergency authorization for the prevention of monkeypox and is preferred for infants less than six months old with high-risk exposure[26].

CONCLUSION

Monkeypox virus is a very contagious orthopoxvirus currently causing a global outbreak, and primarily affecting men who have sex with men. After discontinuing the smallpox vaccine, population immunity decreased and led to an increase in monkeypox cases. Furthermore, the increased number of cases outside Africa demonstrates the global spread of the disease. Obtaining control over this infection requires doctors, hospitals, and health care officials to work together and define appropriate diagnostic testing, contact tracing, and availability of medical care to the affected patient. It is very important that pediatric physicians should be aware of the clinical course and possible outcomes in pediatric patients. Monkeypox seems scary, but it is still a sporadic disease, especially in pediatrics. However, it is always good to be aware of health risks.

FOOTNOTES

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ORCID number: Taral Parikh 0000-0002-9019-6363; Narendrasinh Parmar 0000-0002-6442-4588.

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Retrospective Study

Analysis of clinical characteristics and risk factors between elderly patients with severe and nonsevere Omicron variant infection

Xiao-Qin Liu, Guan-Zhu Lu, Dong-Lin Yin, Yao-Yue Kang, Yuan-Yuan Zhou, Yu-Huan Wang, Jie Xu

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Xiao-Qin Liu, Guan-Zhu Lu, Dong-Lin Yin, Yao-Yue Kang, Yuan-Yuan Zhou, Yu-Huan Wang, Jie Xu, Department of Infectious Disease, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200011, China

Corresponding author: Jie Xu, MD, Chief Physician, Department of Infectious Disease, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, No. 639 Manufacturing Bureau Road, Huangpu District, Shanghai 200011, China. xujie@shsmu.edu.cn

Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to millions of confirmed cases and deaths worldwide. Elderly patients are at high risk of developing and dying from COVID-19 due to advanced age, decreased immune function, intense inflammatory response, and comorbidities. Shanghai has experienced a wave of infection with Omicron, a new variant of SARS-CoV-2, since March 2022. There is a pressing need to identify clinical features and risk factors for disease progression among elderly patients with Omicron infection to provide solid evidence for clinical policy-makers, public health officials, researchers, and the general public.

AIM

To investigate clinical characteristic differences and risk factors between elderly patients with severe and nonsevere Omicron SARS-CoV-2 variant infection.

METHODS

A total of 328 elderly patients with COVID-19 admitted to the Ninth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine from April 2022 to June 2022 were enrolled and divided into a severe group (82 patients) and a nonsevere group (246 patients) according to the diagnosis and treatment protocol of COVID-19 (version 7). The clinical data and laboratory results of both groups were collected and compared. A chi-square test, *t* test, Mann-Whitney U test, hierarchical log-rank test, univariate and multivariate logistic regression, and hierarchical analyses were used to determine significant differences.

RESULTS

The severe group was older (84 *vs* 74 years, $P < 0.001$), included more males (57.3% *vs* 43.9%, $P = 0.037$), had a lower vaccination rate ($P < 0.001$), and had a

higher proportion of comorbidities, including chronic respiratory disease (P = 0.001), cerebral infarction (P < 0.001), chronic kidney disease (P = 0.002), and neurodegenerative disease (P < 0.001), than the nonsevere group. In addition, severe disease patients had a higher inflammatory index (P < 0.001), greater need for symptomatic treatment (P < 0.001), longer hospital stay (P = 0.011), extended viral shedding time (P = 0.014), and higher mortality than nonsevere disease patients (P < 0.001). No difference was observed in the application of Paxlovid in the severe and nonsevere groups (P = 0.817). Oxygen saturation, cerebral infarction, and D-dimer were predictive factors for developing severe disease in patients with COVID-19, with D-dimer having an excellent role (area under the curve: 90.1%, 95%CI: 86.1-94.0%). In addition, D-dimer was a risk factor for developing severe COVID-19 according to multivariate stratified analysis.

CONCLUSION

The clinical course of severe COVID-19 is complex, with a higher need for symptomatic treatment. D-dimer is a suitable biomarker for identifying patients at risk for developing severe COVID-19.

Key Words: Coronavirus disease 2019; Omicron; Severe infection; Elderly patients; Clinical features; Risk factor

Core Tip: Since March 2022, the Omicron wave has affected Shanghai, China. Many elderly patients with severe and nonsevere Omicron severe acute respiratory syndrome coronavirus 2 variant infections have been admitted to our hospital. These patients have a precise diagnosis, complete examination, and clear treatment results. After China adjusts its coronavirus prevention and control policies in 2023, findings such as those in this article will no longer be available.

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INTRODUCTION

Currently, coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to millions of confirmed cases and deaths around the world. As of 6:32 pm Central European time, September 27, 2023, there were 770875433 confirmed cases of COVID-19 globally, including 6959316 deaths, reported to the WHO[1].

SARS-CoV-2 not only affects the respiratory tract, causing pneumonia, but it can also affect the gastrointestinal tract, nervous system, and cardiovascular system[2,3]. The severity of symptoms in COVID-19 patients varies from asymptomatic to life-threatening[4]. Among all age groups, elderly patients, defined as 60 years of age or older, are at higher risk of developing and dying from COVID-19[5,6]. In a multicentre study in the Netherlands, the in-hospital mortality of older hospitalized patients with COVID-19 was 38%[7]. From the perspective of epidemic transmission, many older people with disabilities and severe cardiovascular and neurological diseases live together in close contact in long-term care centres, which facilitates transmission of the virus and leads to infection as well as progression of severe COVID-19 in the elderly[8,9]. Based on analysis of global COVID-19 data, it was concluded that the causes of severe illness in elderly infected patients are closely related to their advanced age, decreased immune function, intense inflammatory response in the body, and comorbidities. In previous studies, hypertension, atrial fibrillation, type 2 diabetes, chronic respiratory disease, dementia, and depression were associated with hospitalization rates and mortality in elderly patients with COVID-19[10-12].

Previous studies have shown that excessive inflammation, cytokine storms, and coagulopathy are important pathological mechanisms of COVID-19[13,14]. The neutrophil-to-lymphocyte ratio (NLR) reflects the systemic inflammatory response and level of neutrophil-to-lymphocyte activation. The systemic inflammatory response index (SIRI) may also reflect the host's immune and inflammatory balance[15]. Additionally, white blood cell count, neutrophil percentage, C-reactive protein (CRP), procalcitonin (PCT), D-dimer, and lactate are closely related to the severity and mortality of COVID-19[16-19].

Shanghai has experienced a wave of infection with Omicron, a new variant of SARS-CoV-2, since March 2022. The Omicron variant, which was first identified in Botswana and South Africa in November 2021, accounted for 41% of all strains by August 20, 2022[20]. Omicron has several subvariants, including BA.1, BA.2, BA.3, BA.4, and BA.5, all of which have a high transmission rate and significant antibody avoidance, posing a great threat to the prevention and control of COVID-19[21-23]. This study retrospectively analysed the baseline clinical features and risk factors of older patients with severe and nonsevere Omicron infection to provide solid evidence for clinical policy-makers, public health officials, researchers, and the general public, to help to identify high-risk groups, and to promote appropriate remediation.

MATERIALS AND METHODS

Subjects

Clinical data for 328 elderly patients diagnosed with COVID-19 and admitted to the Ninth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine from April 2022 to June 2022 were collected during hospitalization. Confirmed diagnosis of COVID-19 was based on positive results for a nasopharyngeal swab sample tested by real-time reverse transcription polymerase chain reaction using a SARS-CoV-2 ZC-HX-201-2 kit (Biogerm, Shanghai, China). Elderly patients were defined as those diagnosed at age 60 years or older[6]. The discharge criteria for patients were as follows: (1) Body temperature returned to normal for more than 3 d; (2) respiratory symptoms improved obviously; (3) pulmonary imaging showed obvious absorption of inflammation; and (4) nucleic acid tests were negative twice consecutively (sampling interval of at least 24 h)[24].

In this study, 15 people died, comprising 0 nonsevere disease patients and 15 severe disease patients, and the direct cause of death was comorbidity. This study was approved by the Ethics Committee of the Ninth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (Ethics Approval No: SH9H-2022-T139-1).

Methods

Baseline data, vaccination status, onset time, onset symptoms, viral shedding time, comorbidities, laboratory data, therapeutic drugs, length of hospitalization, and survival for the 328 elderly patients with COVID-19 were collected. Laboratory tests included routine blood tests, CRP, PCT, coagulation function, liver function, cytokines, lactic acid, and other indicators. According to the discharge diagnosis and clinical data during hospitalization, the study cohort was divided into mild, general, severe, and critical severe types according to the clinical classification criteria of the novel coronavirus pneumonia diagnosis and treatment protocol (trial version 7)[24]: (1) Mild type: Fever and cough, nasal stuffiness, and other respiratory tract clinical symptoms are mild; no imaging manifestations of pneumonia; (2) general type: with the above clinical manifestations and imaging manifestations of pneumonia; (3) severe: Conformed to any of the following articles, including shortness of breath, respiratory frequency acuity 30 times/min; oxygen saturation 93% or less in the resting state; arterial blood oxygen partial pressure ≤ 300 mmHg or less oxygen concentration (1 mmHg = 0.133 kPa); and progressively worsening clinical symptoms and lung imaging showing lesions that progressed significantly more than 50% within 24-48 h; and (4) critical severe: Cases meeting any of the following criteria: respiratory failure and requiring mechanical ventilation; shock; with other organ failure requiring intensive care unit care.

Among the 328 elderly patients in this study, mild and general types were included in the nonsevere group (246 cases in total), whereas severe and critical severe types were included in the severe group (82 cases in total). The baseline data at admission, differences in mortality risk, and risk factors for developing severe disease among the patients in the severe and nonsevere groups were analysed retrospectively to verify the ability and clinical significance of using laboratory indicators to identify severe infection.

Statistical method

SPSS Software 25.0 (SPSS Inc., Chicago, United States) was used for statistical analysis. Measurement data with skewed distribution are represented by the median (interquartile range), while measurement data with normal distribution or approximate normal distribution are represented by the mean ± SD. The chi-square test or Fisher exact probability test and *t* test and the Mann-Whitney U test were used for comparisons between groups. Count data are expressed as the number of cases (percentage). A risk accumulation curve was determined using a stratified log-rank test and univariate and multivariate analyses with logistic regression. A receiver operating characteristic curve (ROC) was used to analyse and calculate the area under the curve (AUC). The optimal critical value of D-dimer and the corresponding sensitivity and specificity were calculated. The layered analysis was drawn by GraphPad 8.0 (GraphPad Software, San Diego, CA, United States). All tests were bilateral. A $P < 0.05$ was considered statistically significant.

RESULTS

Comparison of general data between severe and nonsevere COVID-19 patients

Among the 328 patients with COVID-19, 155 were males and 173 females, with a median age of 77 (68, 86) years. The severe infection group was older than the nonsevere infection group (84 *vs* 74 years, $P < 0.001$), included more males (57.3% *vs* 43.9%, $P = 0.037$), and had lower vaccination rates ($P < 0.001$). In terms of comorbidities, severe disease patients had higher rates of chronic respiratory disease ($P = 0.001$), cerebral infarction ($P < 0.001$), chronic kidney disease ($P = 0.002$), and neurodegenerative disease ($P < 0.001$) than nonsevere disease patients, and the difference was statistically significant. In terms of symptoms, the severe group included more patients with fever ($P < 0.001$), cough ($P < 0.001$), nasal stuffiness ($P = 0.026$), and other symptoms (including impaired smell, poor appetite, and nausea) than the nonsevere group ($P < 0.001$). In terms of disease severity, the inflammatory indicators SIRI, NLR, tumor necrosis factor-α, interleukin (IL)-10, IL-1, PCT, CRP, white blood cell, neutrophil percentage, lactic acid, and D-dimer in severe disease patients were significantly higher than those in nonsevere disease patients ($P < 0.001$). The glomerular filtration rate in severe disease patients was lower than that in nonsevere disease patients, and the difference was statistically significant ($P = 0.039$). Severe disease patients had significantly higher demands for respiratory support, glucocorticoids, anticoagulation (low molecular weight heparin or ordinary heparin), and antibiotics than nonsevere disease patients ($P < 0.001$). Application of Lianhua Qingwen granules in patients with severe COVID-19 was significantly lower than that in patients with

nonsevere COVID-19 (P = 0.007). There was no difference in the application of Paxlovid between the severe and nonsevere groups (P = 0.817). The length of hospitalization (P = 0.011) and virus shedding time (P = 0.014) in severe disease patients were higher than those in nonsevere disease patients, and the difference was statistically significant. In terms of clinical outcome, the number of deaths was 15, among which the mortality rate of nonsevere disease patients was 0% and that of severe disease patients was 18.29%. Thus, the mortality rate of severe disease patients was significantly higher than that of nonsevere disease patients (P < 0.001) (Table 1).

In this study, the viral shedding times of severe and nonsevere COVID-19 patients were 10.95 ± 7.74 and 8.65 ± 4.87 d, respectively. During the viral shedding period, a total of 15 patients died, all of whom had severe COVID-19. The cumulative incidence of death risk during viral shedding was higher in severe disease patients than in nonsevere disease patients (log-rank test = 36.286, P < 0.001) (Figure 1).

Univariate and multivariate analyses of the development of severe disease in elderly patients with COVID-19

Univariate and multivariate logistic regressions were used to analyse risk factors for developing severe infection in COVID-19 patients (Table 2). In univariate regression analysis, only oxygen saturation [Odds ratio (OR) = 0.513, 95%CI: 0.369-0.714; P < 0.001] was a risk factor for developing severe COVID-19. In multivariate logistic regression analysis, oxygen saturation (OR = 0.573, 95%CI: 0.451-0.728; P < 0.001), cerebral infarction (OR = 4.26, 95%CI: 1.012-17.937; P = 0.048), and D-dimer (OR = 1.394, 95%CI: 1.000-1.944; P = 0.05) were predictors of severe infection.

ROC curve analysis of elderly patients with severe COVID-19

A ROC curve was used to analyse and calculate the AUC of neutrophil percentage, CRP, D-dimer, NLR, SIRI, lactic acid, white blood cell count, and PCT indicators to assess the ability of each indicator to identify severe infection in elderly patients with COVID-19. Among them, the AUC of neutrophil percentage was 0.895, that of CRP 0.900, that of NLR 0.883, that of SIRI 0.854, that of lactic acid 0.764, that of white blood cell count 0.775, and that of PCT 0.871. The AUC of D-dimer was 0.901 (P < 0.001). When the threshold was 1.020 mg/L, the AUC was 90.1% (95%CI: 86.1%-94.0%). The sensitivity and specificity of D-dimer to identify severe disease in elderly patients with COVID-19 were 85.5% and 81.7%, respectively (Figure 2).

Multivariate stratified analysis of D-dimer levels in elderly patients with COVID-19

Figure 3 shows multivariate stratified analysis of D-dimer levels in elderly patients with COVID-19. Overall, D-dimer was a risk factor for the development of severe disease in elderly patients with COVID-19 (OR = 1.839, P < 0.001). In further variable stratification analysis, D-dimer remained a risk factor for the development of severe COVID-19, including in female patients (OR = 1.621, P < 0.001), male patients (OR = 2.288, P < 0.001), patients younger than the median age of 77 years (OR = 2.506, P < 0.001), patients older or equal to 77 years old (OR = 1.583, P < 0.001), patients not vaccinated against COVID-19 (OR = 1.702, P < 0.001), patients not vaccinated against COVID-19 (OR = 3.148, P = 0.006), patients without chronic respiratory disease (OR = 1.771, P < 0.001), patients with chronic respiratory disease (OR = 11.525, P = 0.006), patients without hypertension (OR = 1.621, P < 0.001), patients with hypertension (OR = 1.621, P < 0.001), patients without diabetes mellitus (OR = 1.754, P < 0.001), patients with diabetes mellitus (OR = 3.270, P = 0.002), patients without coronary heart disease (OR = 1.856, P < 0.001), patients with coronary heart disease (OR = 1.793, P = 0.009), patients without cerebral infarction (OR = 1.746, P < 0.001), patients with cerebral infarction (OR = 6.158, P = 0.002), patients without chronic kidney disease (OR = 1.811, P < 0.001), patients without immune system disease (OR = 1.886, P < 0.001), patients without neoplastic disease (OR = 1.802, P < 0.001), patients with neoplastic disease (OR = 3.161, P = 0.030), patients without neurodegenerative disease (OR = 1.765, P < 0.001), patients without other comorbidities (OR = 2.329, P < 0.001), patients with other comorbidities (OR = 1.492, P < 0.001), patients without Paxlovid (OR = 2.176, P < 0.001), patients with Paxlovid (OR = 1.739, P < 0.001), patients given Lianhua Qingwen granules (OR = 1.834, P < 0.001), and patients not given Lianhua Qingwen granules (OR = 1.835, P < 0.001).

In addition, in stratified analysis for chronic kidney disease (OR = 1.621, P = 0.067) and neurodegenerative disease (OR = 4.068, P = 0.075), although it did not achieve statistical significance, the OR of D-dimer was still greater than 1.0. In patients with immune system diseases (OR = 0.847, P = 0.753), the OR of D-dimer was less than 1.0, but there was no statistical significance.

DISCUSSION

Pneumonia is often regarded as a terminal event that complicates long-term diseases, such as dementia, cardiovascular disease, and cancer, in the elderly[25], SARS-CoV-2 mainly causes pulmonary interstitial pneumonia changes, typical bilateral patchy ground glass shadows, and peripheral consolidation. Compared with other age groups, the elderly seem to be more susceptible to COVID-19, and severe disease is an important reason for the high mortality rate and intensive care unit hospitalization rate of elderly patients with COVID-19[26,27]. In previous reports, the case fatality rate of elderly patients with COVID-19 ranged from 8.0% to 37.5%, increasing with age[26,28,29]. In addition, the population characteristics include a higher male proportion, intense inflammatory response in the body, prolonged viral shedding time, and prolonged hospital stay[26,30].

This study found that elderly patients with severe COVID-19 were older and comprised a higher proportion of males than nonsevere COVID-19 patients. The inflammatory reaction in severe disease patients was more intense than that in nonsevere disease patients. In addition, levels of lactic acid and D-dimer in severe disease patients were significantly higher than those in nonsevere disease patients, and the estimated glomerular filtration rate was lower. The length of

Table 1 Comparison of clinical data between the severe and non-severe groups of elderly patients with coronavirus disease 2019

Variables	Total (*n* = 328)	Non-severe (*n* = 246)	Severe (*n* = 82)	*P* value
Age (yr)	77.0 (68.0, 86.0)	74.0 (64.0, 84.0)	84.0 (75.0, 89.0)	< 0.001
Male sex	155 (47.4)	108 (43.9)	47 (57.3)	0.037
Vaccinations (times)	0 (0, 0)	0 (0, 2)	0 (0, 0)	< 0.001
Comorbidities				
Chronic respiratory disease	37 (11.2)	20 (7.8)	17 (20.7)	0.001
Hypertension	185 (56.4)	135 (54.8)	50 (61.0)	0.332
Diabetes mellitus	65 (19.9)	44 (17.8)	21 (25.6)	0.129
Coronary heart disease	56 (17.0)	40 (16.1)	16 (19.5)	0.478
Cerebral infarction	64 (19.6)	34 (13.5)	30 (36.6)	< 0.001
Chronic kidney disease	16 (4.8)	7 (2.6)	9 (11.0)	0.002
Immune system disease	6 (1.9)	5 (2.2)	1 (1.2)	0.589
Neoplastic disease	31 (9.6)	23 (9.6)	8 (9.8)	0.96
Neurodegenerative diseases	23 (7.1)	8 (3.0)	15 (18.3)	< 0.001
Other comorbidities	99 (30.1)	69 (27.8)	30 (36.6)	0.138
Symptoms				
Fever	61 (18.6)	33 (13.0)	28 (34.1)	< 0.001
Pharyngodynia	58 (17.6)	41 (16.5)	17 (20.7)	0.39
Cough	149 (45.5)	98 (39.6)	51 (62.2)	< 0.001
Nasal stuffiness	31 (9.6)	18 (7.4)	13 (15.8)	0.026
Diarrhea	3 (1.0)	1 (0.4)	2 (2.4)	0.11
Other symptoms	21 (6.4)	9 (3.5)	12 (14.6)	< 0.001
Laboratory data				
D-dimers (mg/ml)	0.66 (0.30, 1.85)	0.42 (0.21, 0.82)	3.19 (1.33, 7.32)	< 0.001
eGFR (ml/min/1.73 m^2)	76.63 ± 23.62	78.59 ± 20.82	71.09 ± 29.47	0.039
TNF-α (pg/ml)	9.78 (7.47, 12.60)	8.85 (7.12, 11.10)	12.37 (10.90, 18.80)	< 0.001
IL-10 (pg/ml)	5.00 (5.00, 5.82)	5.00 (5.00, 5.00)	6.47 (5.24, 8.99)	< 0.001
IL-1β (pg/ml)	5.00 (5.00, 5.55)	5.00 (5.00, 5.00)	5.55 (5.00, 7.17)	< 0.001
PCT (ng/ml)	1.58 ± 6.76	0.14 ± 0.57	5.66 ± 12.31	< 0.001
CRP (mg/L)	23.41 ± 38.25	9.83 ± 21.20	61.96 ± 48.30	< 0.001
WBC (10^9/L)	6.82 ± 3.29	5.92 ± 1.93	9.36 ± 4.72	< 0.001
Neutrophil percentage	69.80 ± 14.30	64.44 ± 11.38	85.02 ± 10.22	< 0.001
Lactic acid (mmol/L)	1.80 (1.37, 2.30)	1.64 (1.25, 2.00)	2.47 (1.81, 3.20)	< 0.001
SIRI	3.45 ± 5.08	1.71 ± 1.93	8.36 ± 7.48	< 0.001
NLR	5.27 ± 5.58	3.19 ± 3.05	11.17 ± 6.79	< 0.001
Oxygen saturation	96.13 (93.00, 97.13)	96.60 (95.98, 97.73)	91.00 (89.00, 92.90)	< 0.001
Treatment				
Respiratory support	108 (33.01)	29 (10.44)	79 (96.34)	< 0.001
Paxlovid	196 (59.62)	148 (60.00)	48 (58.54)	0.817
Glucocorticoids	78 (23.72)	24 (8.70)	54 (65.85)	< 0.001
Anticoagulation (low molecular weight heparin or regular heparin)	98 (29.81)	42 (16.09)	56 (68.29)	< 0.001

Lianhua Qingwen Granule	212 (64.74)	169 (69.13)	43 (52.44)	0.007
Antibiotics	113 (34.30)	46 (17.39)	67 (81.71)	< 0.001
Length of hospital stays (d)	8 (5, 11)	7 (5, 10)	8 (5, 14)	0.011
Viral shedding time (d)	9.25 ± 5.84	8.65 ± 4.87	10.95 ± 7.74	0.014
Death	15 (4.57)	0 (0.00)	15 (18.29)	< 0.001

Data are expressed as median (interquartile range), mean ± SD deviation, or number (percentage). eGFR: Estimated glomerular filtration rate; TNF: Tumor necrosis factor; IL: Interleukin; PCT: Procalcitonin; CRP: C-reactive protein; WBC: White blood cell; SIRI: Systemic inflammatory response index; NLR: Neutrophil to lymphocyte ratio.

Table 2 Univariate and multivariate analysis of the development of severe infection in elderly patients with coronavirus disease 2019

Variables	Univariate analysis OR (95%CI)	*P* value	Multivariate analysis OR (95%CI)	*P* value
Age	1.084 (0.978, 1.202)	0.126	-	-
Sex	0.575 (0.1, 3.322)	0.536	-	-
Vaccinations	0.636 (0.039, 10.385)	0.751	-	-
Chronic respiratory disease	0.559 (0.025, 12.453)	0.713	-	-
Diabetes mellitus	7.76 (0.446, 134.92)	0.16	-	-
Hypertension	3.267 (0.365, 29.275)	0.29	-	-
Coronary heart disease	0.142 (0.01, 1.926)	0.142	-	-
Cerebral infarction	7.757 (0.704, 85.443)	0.094	4.26 (1.012, 17.937)	0.048
Chronic kidney disease	0.057 (0.001, 4.578)	0.2	-	-
Neurodegenerative diseases	19.385 (0.149, 2527.003)	0.233	-	-
Neoplastic disease	0.527 (0.022, 12.846)	0.695	-	-
Immune system disease	0 (0, 203.169)	0.213	-	-
WBC	1.096 (0.669, 1.794)	0.716	-	-
Neutrophil percentage	1.125 (0.95, 1.331)	0.172	-	-
eGFR	1.044 (0.966, 1.128)	0.281	-	-
NLR	1.017 (0.636, 1.626)	0.943	-	-
SIRI	1.003 (0.534, 1.883)	0.993	-	-
CRP	1.023 (0.984, 1.063)	0.251	-	-
PCT	1.552 (0.67, 3.598)	0.305	-	-
Oxygen saturation	0.513 (0.369, 0.714)	0.000	0.573 (0.451, 0.728)	0.000
Lactic acid	0.768 (0.269, 2.194)	0.622	-	-
D-dimers	1.156 (0.754, 1.772)	0.507	1.394 (1, 1.944)	0.05
Viral shedding time	1.066 (0.892, 1.274)	0.484	-	-
Lianhua Qingwen Granule	0.486 (0.055, 4.302)	0.517	-	-
Paxlovid	2.505 (0.19, 33.049)	0.485	-	-

Bold letters represent significant predictors of the development of severe infection in elderly patients with coronavirus disease 2019. OR: Odds ratio; CI: Confidence interval; eGFR: Estimated glomerular filtration rate; NLR: Neutrophil to lymphocyte ratio; SIRI: Systemic inflammatory response index; CRP: C-reactive protein; PCT: Procalcitonin; WBC: White blood cell.

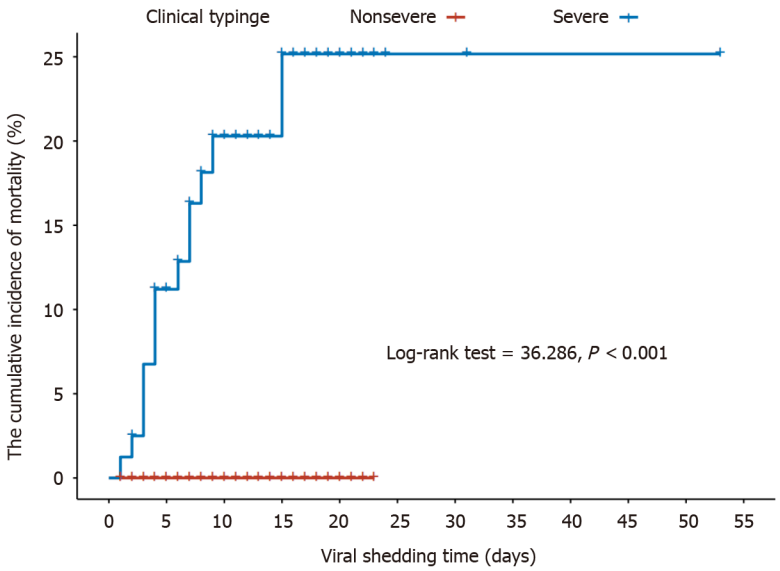

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Figure 1 The cumulative incidence of mortality in elderly patients with severe and non-severe coronavirus disease 2019 during viral shedding time.

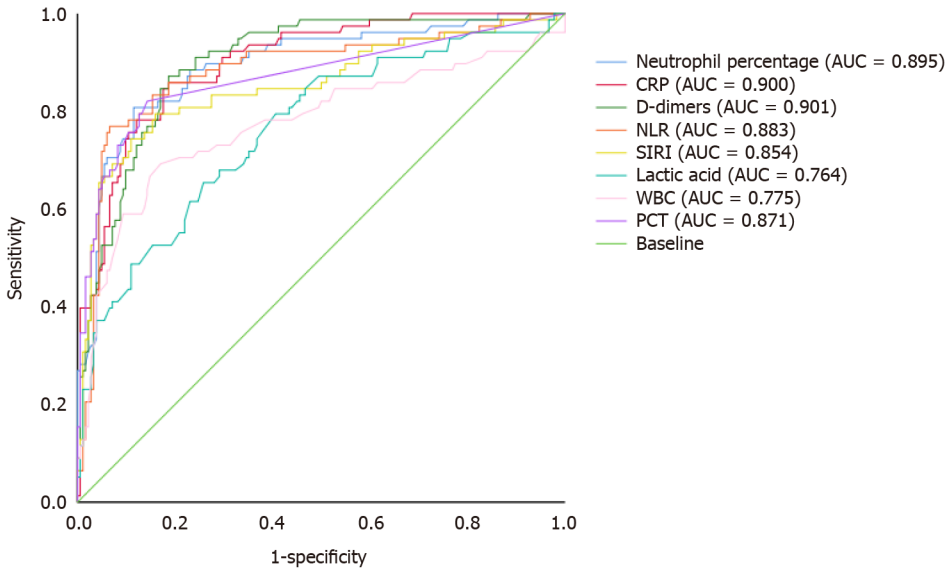

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Figure 2 Receiver operating characteristic curves in elderly patients with severe coronavirus disease 2019. CRP: C-reactive protein; NLR: Neutrophil to lymphocyte ratio; SIRI: Systemic inflammatory response index; WBC: White blood cell; PCT: Procalcitonin; AUC: Area under the curve.

hospitalization and viral shedding time of severe disease patients were longer than those of nonsevere disease patients. In this study, the severe infection group had lower vaccination rates than the nonsevere infection group; however, the vaccination status was not significant in univariate and multivariate analyses of the development of severe disease in elderly patients with COVID-19. This suggests that vaccination status is associated with a significantly lower risk of hospitalization for COVID-19 but is not associated with the development of severe COVID-19 in elderly patients, which was similar to a previous observational study[31]. Regarding the management and treatment of COVID-19 in this study, no difference was observed in the application of Paxlovid in the severe and nonsevere groups, suggesting that Paxlovid did not benefit patients in terms of avoiding the development of severe COVID-19 in this study. On the other hand, the need for respiratory support, glucocorticoids, anticoagulation (low molecular weight heparin or ordinary heparin), and antibiotic therapy was significantly higher in severe disease patients than in nonsevere disease patients. This is consistent with current research showing that COVID-19, similar to other community-acquired pneumonia, is considered to be a late-stage event that complicates long-term disease[26]. To personalize clinical management of COVID-19, researchers are also reflecting on better therapeutic strategies, including early adoption of non-steroidal anti-inflammatory drugs[32], application of broad-spectrum antimicrobials[33], and a personalized risk-benefit ratio for glucocorticoid use[34]. In terms of clinical outcome, 15 people died in this study; the mortality rate of nonsevere disease patients was 0%, and that of

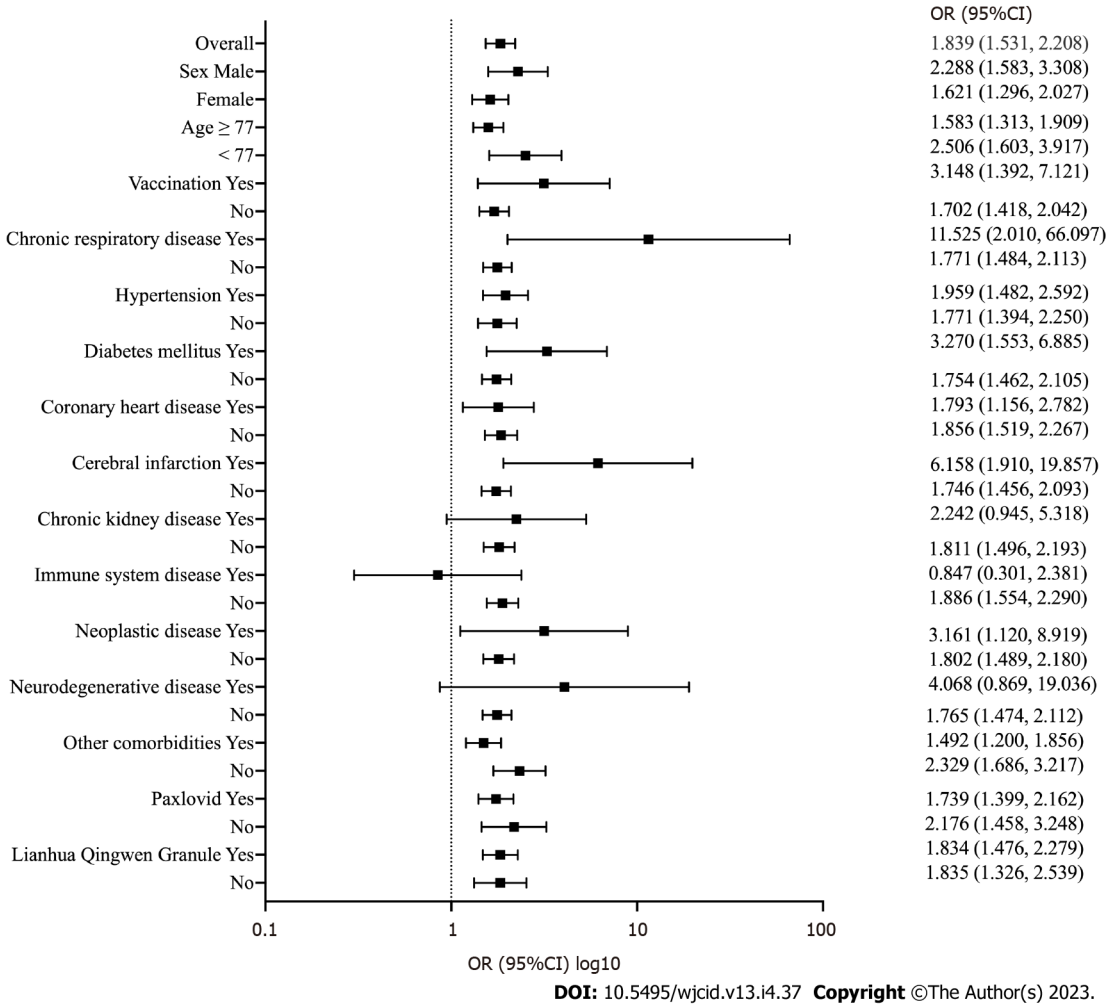

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Figure 3 Multivariate stratified analysis of D-dimer levels in elderly patients with coronavirus disease 2019. OR: Odds ratio; CI: Confidence interval.

severe disease patients was 18.29%. Hence, the mortality rate of severe disease patients was significantly higher than that of nonsevere disease patients, which was also consistent with previous literature reports[26,30].

In addition to age, the presence and quantity of comorbidities are considered to be key factors in predicting the death of elderly patients. However, the significance of specific comorbidities, such as hypertension, coronary heart disease, and respiratory diseases, in the development of severe COVID-19 in elderly patients varied in previous research[35-38]. The results of this study also showed that the proportions of chronic respiratory diseases, cerebral infarction, chronic renal diseases, and neurodegenerative diseases were higher in severe disease patients than in nonsevere disease patients. Further analysis of the predictive factors of severe disease in elderly patients showed that among all comorbidities, cerebral infarction was the only risk factor for the development of severe disease in elderly patients with COVID-19 in this study.

In addition, studies have found that elderly patients from long-term care centres seem to have a higher rate of severe illness and fatality on admission than elderly patients from family care situations[26]. Indeed, staying in a long-term care centre is a strong risk factor for COVID-19 diagnosis and all-cause mortality[39]. Studies have suggested that this may be related to the fact that elderly COVID-19 patients living in long-term care centres usually have more comorbidities, are physically weaker, and are more susceptible to infection when in a closed environment[26]. In this study, cerebral infarction was a risk factor for severe COVID-19 in elderly patients. This can be explained by the fact that elderly people with cerebral infarction may need to stay in bed for a longer period and need increased daily nursing care. As a result, early identification of COVID-19 tends to be missed in this group of people, and they tend to receive insufficient nursing care after developing COVID-19, leading to severe infection in these patients. Therefore, the results of this study showed that elderly COVID-19 patients with cerebral infarction may be the most vulnerable group of elderly COVID-19 patients during the current wave of Omicron infection in Shanghai.

In previous studies, plasma D-dimer levels were directly related to the development of pulmonary embolism and vascular thrombosis complications during COVID-19 and correlated highly with adverse outcomes[40,41]. In this study, D-dimer was also a risk factor for the development of severe COVID-19 in elderly patients, which is consistent with previous literature reports[42]. In previous studies, NLR, CRP, and neutrophil percentage were demonstrated to be predictors of severe diseases, showing good recognition ability for severe COVID-19[17,37,43]. In this study, it was found that compared with white blood cell count, neutrophil percentage, CRP, PCT, NLR, SIRI, and lactic acid, the ROC curve

of D-dimer yielded the largest AUC, with good sensitivity and specificity and an outstanding ability to identify severe COVID-19. In multivariate stratified analysis, D-dimer was a risk factor for the development of severe COVID-19 in elderly patients both at the overall level and stratified by sex, age, vaccination, chronic respiratory disease, hypertension, diabetes mellitus, coronary heart disease, cerebral infarction, chronic kidney disease, immune system disease, neoplastic disease, neurodegenerative disease, other comorbidities, use of Paxlovid, and use of Lianhua Qingwen granules. This confirms the important role of D-dimer in the course and outcome of COVID-19 in elderly patients.

This study has at least two limitations. First, the sample size was small, especially regarding the number of patients in the severe disease group. This may be related to the relatively reduced pathogenicity of the Omicron subtype in the current wave of COVID-19 and the protective effect of the vaccine in reducing the risk of hospitalization for COVID-19, which is a result of active participation in receiving the vaccine in Shanghai. Second, this study was a single-center study, and the patients were limited to those diagnosed with COVID-19 and admitted to the Ninth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine from April 2022 to June 2022. Because the outbreak is evolving rapidly around the world, follow-up studies with more patients are needed to improve the statistical power of these findings.

CONCLUSION

In conclusion, the results of this study suggest that COVID-19 complicates long-term illness in elderly patients. There are considerable differences in disease severity and adverse clinical outcomes between severe and nonsevere cases in older patients with COVID-19. Elderly people are vulnerable to severe illness and death due to their age and comorbidities, especially elderly patients with preexisting cerebral infarction. D-dimer is a risk factor for severe COVID-19 in elderly patients and has a good recognition function for severe disease. Therefore, a comprehensive assessment of the comorbidities of older patients with COVID-19 may help to establish risk stratification for admission of COVID-19 patients, and dynamic monitoring of D-dimer levels can provide valuable information for planning appropriate interventions at the health assistance level.

ARTICLE HIGHLIGHTS

Research background

Elderly patients are at higher risk of contracting and dying from coronavirus disease 2019 (COVID-19) due to advanced age, decreased immune function, intense inflammatory response, and comorbidities. Omicron, a new variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has a high transmission rate and significant antibody avoidance, posing a great threat to the prevention and control of COVID-19.

Research motivation

Previous studies have evaluated risk factors for severity or death among elderly people with COVID-19, though analyses of Omicron infection risk and protective factors among elderly people are relatively few.

Research objectives

To identify clinical features and risk factors for disease progression among elderly patients with Omicron infection to provide solid evidence for clinical policy-makers, public health officials, researchers, and the general public.

Research methods

A chi-square test, *t* test, Mann-Whitney U test, hierarchical log-rank test, univariate and multivariate logistic regression analyses, and hierarchical analyses were used to determine significant differences between elderly patients with severe and nonsevere Omicron SARS-CoV-2 variant infection.

Research results

The clinical course of severe disease patients is more complex, as both the need for symptomatic treatment and the risk of death are higher than those of nonsevere disease patients. Oxygen saturation, cerebral infarction, and D-dimer are risk factors for developing severe COVID-19. D-dimer also showed a suitable role in identifying severe infection.

Research conclusions

Elderly people are vulnerable to severe illness and death due to their age and comorbidities, especially elderly patients with preexisting cerebral infarction. D-dimer is a risk factor for severe COVID-19 in elderly patients and has a good recognition function for severe disease.

Research perspectives

A comprehensive assessment of the comorbidities of older patients with COVID-19 may help to establish risk stratification for admission of COVID-19 patients, and dynamic monitoring of D-dimer levels can provide valuable information for planning appropriate interventions at the health assistance level.

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FOOTNOTES

Author contributions: Liu XQ designed the research study, analysed the data, and wrote the manuscript; Lu GZ, Yin DL, Kang YY, Zhou YY, and Wang YH collected and analysed the data; Xu J designed the research study and reviewed and revised the paper.

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ORCID number: Xiao-Qin Liu https://orcid.org/0000-0002-3646-4427; Jie Xu https://orcid.org/0000-0002-9179-0049.

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