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# Clinical features and forecast indexes of the disease severity of SARS-CoV-2: a retrospective cohort study comparing the wild-type strain and the Delta VOC

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## Abstract

**Background:** A novel variant of SARS-CoV-2, the Delta variant of concern (VOC), on disease severity is very unclear. In this retrospective study, we compared the clinical characteristics and the outcomes of patients infected with the Delta VOC and with wild-type strains during the local outbreak in Xi'an and Wuhan, China.

**Methods:** The clinical information pertaining to the 2927 cases (between February 10 and March 8, 2020) infected with wild-type strains and the 993 cases (between December 22, 2021and February 17, 2022) infected with the Delta VOC were extracted. The clinical characteristics and outcomes were compared the cohort of wild-type infection with the cohort of Delta VOC.

**Results:** Among patients younger than 18 years old, the proportion of patients infected with the Delta VOC was significantly higher than that of patients infected with wild-type strains (12.2% vs. 0.3%). In cases with mild and moderate illness, the proportion of patients was higher in the Delta VOC group than that in the wild-type strain (40.9% and 56.6% vs. 0.70% and 3.10%). However, in severe and critical patients, the proportion of patients was significantly less in the Delta VOC group than that in the wild-type strain (1.6% and 0.9% vs. 24.2% and 72.0%). In cases with severe or critical illness, and in the Delta VOC cohort or the wild-type cohort, the prognosis of patients with lymphocytes blood levels that gradually rising is good after treatment, while the prognosis of patients with lymphocytes blood levels that remain low is poor and even death(p<0.001). The Cox regression analysis revealed that the infection with the lineage of the wide-type strain had a higher risk than the Delta VOC in deteriorating to critical illness (hazards ratio 2.54[95%CI 1.279-5.026]; p = 0.008).

**Conclusions:** Infection with the Delta VOC is characterized by younger patients, milder illness, and decreased risk of disease prognosis compared with the SARS-CoV-2 wild-type lineage; lymphopenia is an effective predictor of deterioration in patients with Delta VOC and wild-type strains, calling for clinicians to understand of characteristics of them, and to guide clinical decision-making.


## 1. Introduction

Since the onset of the wild-type strain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019, which causes coronavirus disease 2019 (COVID-19), there have been several globally circulating multiple new variants of concern (VOC). To date, there have been five main lineages that are identified as the VOC by the World Health Organization (WHO), such as B.1.1.7 (Alpha)[1], B.1.351 (Beta) [2], P.1 (Gamma)[3], B.1.617.2 (Delta)[4], and B.1.1.529(Omicron)[5]. The variants associated with increased transmissibility[6]. The Delta VOC first reported in India in December 2020 and was fast becoming the dominant strain in many countries and regions[7]. Currently, some studies have shown that the Delta VOC have increased by 97% compared with the wild-type strain and children aged 5–9 years were more susceptible to viral infection[6, 8, 9] However, clinical features of patients infected with Delta VOC, the impact of the disease severity, forecast indexes of the poor prognosis and the difference with other SARS-CoV-2 strains remain very unclear and need further investigation.

In December 2021, the Delta VOC had led to a new wave of outbreak in Xi'an, Shaanxi Province. The local outbreak in Xi'an, mainly transferred to Xi'an chest hospital, the official designated hospital to manage the SARS-CoV-2 patients, comprised 998 locally transmitted cases (993 cases infected with Delta VOC strain and 5 cases of Omicron strain) during the study period. All patients were confirmed infected with the same strain of Delta VOC and Omicron VOC by next-generation sequencing. In addition, I also was lucky enough to go to the Wuhan Huoshenshan Hospital, only one of official designated hospitals, to treat COVID-19 with the wild-type strain in 2020. Therefore, our study provided an incredible opportunity to explore their difference in impact factors of the disease severity, forecast indexes of the poor prognosis and clinical characteristics.

## 2. Materials And Methods

### 2.1 Patients' involvement and data collection

All hospitalized patients (n=3925), diagnosed with COVID-19 based on regions with prevalent epidemic and positive nucleic acid detection results, with or without their clinical symptoms (fever or respiratory symptoms) and typical changes in chest radiology, were involved in this study. Among them, 2927 cases (admission date from February 10 to March 8, 2020) were from Huoshenshan Hospital of Wuhan, Huoshenshan Hospital of Wuhan was a new hospital for hospitalizing patients with COVID-19 after completion on February 2, 2020, and 998 cases (admission date From December 22, 2021, to February 17, 2022) were from in Xi'an Chest Hospital (Fig. 1). The epidemiologic characteristics, clinical characteristics, laboratory finding, and imaging features were collected. All patients involved in this study were living in Wuhan and Xi'an during the outbreak period of COVID-19. Patients in Xi'an were the local residents and epidemiologically confirmed to be linked to delta strain and omicron strain. Meanwhile, a wild-type strain cohort from the Huoshenshan hospital two years ago was also included for comparison (Fig. 3). The wild-type strain cohort consisted of all the cases with complete medical records from February to March 2020, the first wave of the pandemic in China.

All patients were confirmed by the local Centers for Disease Control and transferred to Huoshenshan hospital and Xi'an Chest Hospital, the official designated hospital to manage the COVID-19 in Wuhan and Xi'an. Referring to guidelines issued by Chinese National Health Commission (Trial Version 7&8). Severe COVID-19 was designated when the patients had one of the following criteria: (a) respiratory distress with respiratory frequency ≥30/min; (b) pulse oximeter oxygen saturation ≤93% at rest; and (c) oxygenation index (artery partial pressure of oxygen/inspired oxygen fraction, $PaO_2/FiO_2$) ≤300 mm Hg. Critical COVID-19 was designated when the patients had one of the following criteria: (a) respiratory failure with mechanical ventilation; (b) shock; and (c) combination with other organ failure; requirement of Intensive Care Unit (ICU) for monitoring and treatment.

### 2.2 Laboratory testing

Blood testing for all patients was performed by the clinical laboratory of Huoshenshan Hospital of Wuhan and Xi'an Chest Hospital. Medical laboratory results in this study, including the numbers of leukocytes, lymphocytes, C-reaction protein (CRP), D-dimer, alanine aminotransferase (ALT), and blood urea nitrogen (BUN), were collected for each severe and critical patient. Laboratory findings were derived from the electronic medical charts. The data were extracted by two independent clinicians into the electronic database. Any major dispute was resolved by consultation with a third reviewer.

### 2.3 Statistical analysis

Categorical variables were described as a number (%), and continuous variables were expressed as interquartile range (IQR). Comparisons of continuous variables were performed with Mann-Whitney U test for non-normally distributed data. To compare continuous variables for the data of different patient groups, the Kruskal-Wallis H(K) test were used appropriately. Categorical variables were compared using $\chi^2$ test, as appropriate. Statistical analyses were processed by the statistic package deal SPSS 23.0. Variables, survival analysis were processed by GraphPad Prism version 5.00 software. All graphs were generated and plotted using GraphPad Prism version 5.00 software (GraphPad Software Inc). P values of less than 0.05 were considered statistically significant.

### 2.4 Ethical approval

The study was approved by the Ethics Committee for Scientific research of Xi'an Chest Hospital (No. S2022-0010).

### 2.5 Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit for publication.

## 3. Results

### 3.1 Demographics and clinical characteristics

#### 3.1.1 Strain and age distribution characteristics in the two waves of pandemic

These data show that 99.5% of the outbreaks in Xi'an from 2021 to 2022 were Delta strain and 5% were Omicron strain (Fig 3, A). Among the 99.5% delta strains, 87.3% were patients over 18 years old, while 12.2% were patients under 18 years old (Fig 3, B). However, the outbreaks in Wuhan from 2019 to 2020 were wild-type strain (WT strain), of which 99.7% were patients over the age of 18, while only 0.3% were patients under the age of 18 (Fig3, C).

#### 3.1.2 Clinical analysis of 5 patients with Omicron strain

There were only 5 cases of Omicron strain in the epidemic in Xi'an. They have flown or been to the airport in the previous 14 days (Table 2). 20% (1/5) of patients were aged 60 years or greater, 60% (3/5) were female, and none had comorbidity. Five cases completed full vaccination. Among them, 20% (1/5) were asymptomatic cases, 40% (2/5) were mild cases, 40% (2/5) were moderate cases. The most common symptoms within three days on admission was cough and sore throat (respectively, 40%), followed by fever, sputum, and shortness of breath (respectively, 20%). 60%（3/5） of the patients had chest CT changes, such as consolidation, reticulations or ground glass opacity. The first nucleic acid test of all patients was positive almost at the same time, and they all produced antibodies. The hospital stay was 15-34 days.

#### 3.1.3 Clinical typing characteristics in the two waves of pandemic.

Most of the outbreaks in Xi'an from 2021 to 2022 were mild and moderate (40.9% and 56.6%, respectively), of while severe and critical are very rare (1.6% and 0.9%, respectively) (Fig. 4 A). As of the time of data statistics, 0.3% of the critically ill patients were recovered, while 0.6% relied on life-support machine (Fig. 4B). Most of the outbreaks in Wuhan from 2019 to 2020 were severe and moderate (24.2% and 72.0%, respectively), of while mild and critical are less (0.70% and 3.10%, respectively) (Fig. 4C). In critically ill patients, 1.3% of the patients were recovered, while 1.80% were died (Fig. 4D). Compared with the epidemic in Wuhan two years ago, the epidemic in Xi'an is dominated by mild and moderate types, while there are few severe and critical cases (Fig. 4E).

The relationship between age and clinical classification was further analyzed. Among the COVID-19 over 18 years old, the cases were mainly WT strain and delta strain cases of moderate, while mild and severe was less (Fig 3, DE). Moreover, the age of the WT strain cases was 50-60 years, while the age of the Delta strain cases was mainly 30-49 years old in the novel coronavirus pneumonia patients (Table 1). Among the COVID-19 under 18 years old, the cases were mainly delta strain cases of mild and moderate, while wild type was very rare (Fig 3, FG) and no severe or critical cases, regardless of infection with the wild-type strain or Delta VOC.

#### 3.1.4 Gender and comorbidity characteristics in the two waves of pandemic.

Patients infected with the Delta VOC and those infected with the wild-type strain shared similar distribution of gender. Among patients older than 18 years, there was no gender difference between the two cohorts, regardless of the severity of the disease. Compared with patients in delta strain group, the basic diseases, such as hypertension, diabetes mellitus, chronic respiratory diseases, coronary heart disease, chronic liver disease, tuberculosis, malignant tumor and so on, were significantly different in patients with moderate type in the wild-type cohort (P0.001), but there was no significant difference in other types (Table 1). Among them, the proportion of diabetic patients in the former group was significantly lower than that in the latter group (2.4% vs 19.1%; $p < 0.001$).

#### 3.1.5 Clinical symptoms and radiological findings

Main clinical symptoms of mild, moderate, and severe cases at the onset of illness are shown in Table 3. The most common symptoms were fever, cough, chest tightness/dyspnea, muscle aches and fatigue. Compared with patients with Delta strain, the proportion of muscle aches and fatigue in patients with WT strain increased significantly in all three types (P□0.05). Of course, fever, cough and Chest tightness/dyspnea are very high in the two cohort.

Radiologic findings were derived from the electronic medical charts. Chest CT was the primary source of radiologic assessment and was performed within three days of admission, and abnormalities in chest CT images were detected in all patients. Of the 3129 patients, 1666(73.5%) WT strain patients and 521(60.4%) delta patients had multiple ground glass in both lungs, while the patchy shadows and consolidation are less. Further analysis revealed that the proportion of consolidation in the Delta VOC cohort was significantly more than that in the wild-type cohort (11.5% vs 1.7%; p < 0.001) (Table 3).

### 3.1.6 Laboratory findings

Patients with severe and critical illness are our focus. Therefore, the blood tests of the patients during their hospitalization were collected at admission, 25%, 50%, 75% and discharge (Fig. 2). The results showed that there were differences in lymphocytes, CRP, and ALT at many time points in the two cohorts (Table 4-5; Fig. 5BCE). Compared with cases infected with the wild-type strain, the CRP and ALT of patients with infection delta VOC were significantly higher (Fig. 5CE; p□0.05), while their lymphocytes were similar (Fig. 5B; p□0.05), and the CRP and lymphocytes of these two cohorts gradually returned to normal after treatment (Fig. 5BC; p□0.05), among the severe cases. However, no differences in leukocytes, D-Dimer and BUN were found between the two cohorts in the severe patients (Fig. 5ADF; p□0.05)). In the next analysis, patients infected with the delta VOC showed significant difference in leukocytes, lymphocytes, CRP, D-Dimer, and BUN among the critical cases when compared with them of patients infected with the wild-type strain. Compared with recovered patients infected with the wild-type strain and delta VOC, the leukocytes, D-Dimer and BUN of dead patients with the wild-type strain and machine supported patients with infection delta VOC were significantly higher (Fig. 6ADF; p□0.001), while their lymphocytes have been at a relatively low level (Fig. 6B; p□0.001), and they have not recovered returned to normal after treatment. Further analysis revealed that leukocytes, CRP, D-Dimer and BUN of dead patients with the wild-type strain were very high (Fig. 6ACD; p□0.001), while ALT was no significant difference, in these four groups (Table 4-5; Fig. 6E; p□0.05).

### 3.2 The risk factors for disease progression and outcomes

The univariate Cox regression analysis revealed that the strain, comorbidity (including chronic respiratory disease, hypertension) and symptoms (including cough) were associated with the deterioration to critical illness (p < 0.05). Multivariate Cox regression analysis indicated that delta VOC infection (HR 2.54[95%CI 1.279-5.026]) and chronic respiratory disease (HR 1.97[95%CI 1.15-3.38]) were the independent risk factors associated with the deterioration to critical illness (p < 0.05; Table 6). The Cox regression survival plots for the time from symptom onset to critical status categorized by chronic respiratory disease and virus lineage (Delta VOC vs wild-type strain) in the two cohorts were shown in Fig. 7A and B.

## 4. Discussion

This was a retrospective cohort study which has thoroughly described the clinical distribution characteristics (including age, gender, comorbidities, symptoms,and clinical typing), the laboratory finding, the imaging features, the variants of concern in the two waves of pandemic. Compared with a wild-type cohort admitted to the Huoshenshan Hospital of Wuhan more than 2 years ago, infection with the Delta VOC admitted to the Xi'an Chest Hospital was associated with younger patients, milder illness, shorter incubation period. Different VOCs was proven as an independent risk factor of illness severity.

Compared with patients with the wild-type strain, a greater proportion of cases aged < 18 years with the delta variant were found (12.2% vs 0.3%; p < 0.01). This was in line with the recent study in Guangzhou which found a larger proportion of the young patients infected with the Delta VOC compared with the wild-type strain cases (16% vs 3%; p < 0.01)[10]. Sheikh, a et al show that the Delta VOC in Scotland was found mainly in younger groups[9]. The similar trend was also reported in London, UK[11] and Ontario, Canada[12]. However, no difference in the proportion of infected cases aged□30 years was found between the Delta VOC cohort and the wide-type cohort. Subsequently, in further subgroup analysis, the young individuals aged < 18 years are almost all the mild and moderate in the Delta VOC cohort, but rarely in the wide-type cohort. The difference indicated that the young patients were more susceptible to the infection with the Delta VOC. The susceptibility to the Delta VOC infection in the young patients has been associated with higher viral loads and a lower minimal infective dose and rapid transmission of the Delta compared to the WT[10, 13], and a wide social activity of young people. In addition, among patients aged ≥18 years(especially those over 50-60 years), the clinical outcomes were significantly different in the infection of the Delta VOC and the wild-type strain. Patients infected with the Delta VOC had a few severe and critical cases, while patients infected with the wild-type strain had relatively more severe and critical cases (table 1, 4 &5). Elderly patients in the wild-type cohort have an increased risk in deteriorating to critical illness, because of not well known to COVID-19 and no delay in visiting more than 2 years ago, also no vaccines against the SARS-CoV-2, compared with those in the Delta VOC cohort now[14]. Clinical trials studies have demonstrated vaccine efficacy against VOC[15-18]. Detailed epidemiologic investigation of vaccine effectiveness against VOCs was beyond the scope of this study.

Similar distribution of gender was found in the infection of the Delta VOC and the wild-type strain. Compared with patients in the Delta VOC cohort, diabetic patients were significantly higher in the wild-type cohort (2.4% vs 19.1%; p < 0.001). Consistent with previous findings[10, 19, 20], fever and cough were two salient symptoms among patients infected with the Delta strain and the wild-type strain, suggesting the need to integrate prevalent epidemic, nucleic acid detection results, and symptom screening in identifying the cases in community settings. Other symptoms including muscle aches and fatigue in the Delta VOC cohort were less frequent, compared with the wide-type strain infection. Moreover, our data showed that multiple ground glass in both lungs in chest CT images has a relatively high proportion in all patients, while the Delta VOC cohort had more consolidation, compared with the wide-type cohort (11.5% vs 1.7%; p < 0.001) (Table 3). The significance of these diabetic, symptom, and CT images differences is admitted for clinical evaluation.

Patients with severe and critical illness are another focus of our great attention, so leukocytes, lymphocytes, CRP, D-Dimer, ALT, and BUN of them were further dynamic observed. Our data showed that the prognosis of patients with lymphocytes blood levels that gradually rising is good after treatment, while the

prognosis of patients with lymphocytes blood levels that remain low is poor and even death, in cases with severe or critical illness, and in the Delta VOC cohort or the wild-type cohort, (p 0.001).This is consistent with our previous findings[20]. Lymphopenia was considered to be the predictors for deterioration[10, 21, 22]. It is worth noting that the differences of leukocytes, CRP, D-Dimer, BUN, and ALT were obvious in critically ill cases without recovery with the Delta VOC cohort, compared with the wild-type strain. This might be associated with a stronger viral virulence in patients with wild-type strain, which warrants a further investigation of the cytokine storm induced by virus invasion[23] .

The Cox regression analysis for the virus lineage to disease progression found that the infection with the lineage of the wide-type strain had a higher risk than the Delta VOC in deteriorating to critical illness. A recent study conducted in Scotland demonstrated that an association between VOCs and clinical severity is concerning[9]. Therefore, infection with wide-type strain indicated a possibility of more severe clinical status and poorer outcome, which called for a more elaborate research program for a larger sample.

There are several limitations to this study. First, considering that the cohort infected with the Delta VOC was included from a local epidemic, which was quickly controlled within about one month, the sample size was still relatively small, there were few patients who need to supplemental oxygen or ICU admission, and there were also fewer deaths. Smaller but statistically significant differences in clinical features with VOCs could have been missed due to the small sample size. Larger cohort studies to compare different VOCs should be conducted. Second, as this was a retrospective study, the lack of a randomized control group, so we cannot draw definitive conclusions. However, comparing the clinical features of wild-type strain and the Delta VOC would be valuable in driving the progression of COVID-19. Third, because the Delta VOC cohort and the wild-type strain were included in the two hospitals, and the interval is more than 2 years, initial blood samples were also not processed in a centralized same laboratory; therefore, there are some differences in inspection methods and results. However, the clinical testing protocol in China is conducted in a standardized manner, and any possible intraassay variability would have been distributed equally across the entire cohort. Despite this, the present results are in line with the previously study of different VOCs in COVID-19[8, 10], and in a previously little research continuous dynamic monitoring blood test of severe and critical patients. Therefore, we believe that the study here is meaningful. In addition, more detailed patient information, larger sample size, particularly regarding clinical data of severe and critical, was very necessary at the time of analysis. Greater efforts should be made to solve these problems in the future research.

## Conclusions

In this retrospective study, we found younger patients, milder illness, and decreased risk of disease prognosis of Delta VOC, compared with the SARS-CoV-2 wild-type lineage; lymphopenia is an effective predictor of deterioration in patients with delta VOC and wild-type strains. These data provide insights to the understanding of characteristics of the Delta VOC, which is helpful for clinicians identify patients with a poor prognosis and may be useful for guiding clinical decision-making, to combat this rapidly spreading global pandemic.

## Abbreviations

VOC = variant of concern, COVID-19 = coronavirus disease-2019, CT = computed tomography, ICU = Intensive Care Unit, CRP = C-reaction protein, ALT = alanine aminotransferase, BUN = blood urea nitrogen, IQR = interquartile range, CI = confidence interval, HR = hazards ratio, $PaO_2/FiO_2$ = artery partial pressure of oxygen/ inspired oxygen fraction, WT = wild-type, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, WHO = World Health Organization.

## Declarations


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### Authors' contributions

Wen-hao Zheng and Tian-tian Ma mainly collect and sort out data Hong-jun Zhang and Yue-e Chen wrote the main manuscript text, Fen-qing Shang and Yan-wei Chen prepared figures 1-3, Rui-xuan Wang and Xiu-cheng Zhang prepared figures 4-5, Wen-jie Li and Xing Gu prepared tables 1-2. All authors reviewed the manuscript.


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### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon individual specific and reasonable request.

### Ethics approval and consent to participate

The study was approved by the Ethics Committee for Scientific research of Xi'an Chest Hospital (No. S2022-0010). Written informed consent was obtained from all the patients or their trusted persons.

### Consent for publication

Not applicable.

**Competing interests**

No conflict of interest exits in the submission of this manuscript, and manuscript is approved by all authors for publication.

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## References

1. Volz E, Mishra S, Chand M, Barrett JC, Johnson R, Geidelberg L, Hinsley WR, Laydon DJ, Dabrera G, O'Toole A *et al*: **Assessing transmissibility of SARS-CoV-2 lineage B.1.1.7 in England**. Nature 2021, **593**(7858):266–269.
2. Tegally H, Wilkinson E, Giovanetti M, Iranzadeh A, Fonseca V, Giandhari J, Doolabh D, Pillay S, San EJ, Msomi N *et al*: **Detection of a SARS-CoV-2 variant of concern in South Africa**. Nature 2021, **592**(7854):438–443.
3. Faria NR, Mellan TA, Whittaker C, Claro IM, Candido DDS, Mishra S, Crispim MAE, Sales FCS, Hawryluk I, McCrone JT *et al*: **Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil**. Science 2021, **372**(6544):815–821.
4. Vaidyanathan G: **Coronavirus variants are spreading in India - what scientists know so far**. Nature 2021, **593**(7859):321–322.
5. Shuai H, Chan JF, Hu B, Chai Y, Yuen TT, Yin F, Huang X, Yoon C, Hu JC, Liu H *et al*: **Attenuated replication and pathogenicity of SARS-CoV-2 B.1.1.529 Omicron**. Nature 2022, **603**(7902):693–699.
6. Campbell F, Archer B, Laurenson-Schafer H, Jinnai Y, Konings F, Batra N, Pavlin B, Vandemaele K, Van Kerkhove MD, Jombart T *et al*: **Increased transmissibility and global spread of SARS-CoV-2 variants of concern as at June 2021**. Euro Surveill 2021, **26**(24).
7. Aleem A, Akbar Samad AB, Slenker AK: **Emerging Variants of SARS-CoV-2 And Novel Therapeutics Against Coronavirus** (**COVID-19**). In: *StatPearls*. Treasure Island (FL); 2022.
8. Ong SWX, Chiew CJ, Ang LW, Mak TM, Cui L, Toh M, Lim YD, Lee PH, Lee TH, Chia PY *et al*: **Clinical and virological features of SARS-CoV-2 variants of concern**: **a retrospective cohort study comparing B.1.1.7** (**Alpha**), **B.1.315** (**Beta**), **and B.1.617.2** (**Delta**). *Clin Infect Dis* 2021.
9. Sheikh A, McMenamin J, Taylor B, Robertson C, Public Health S, the EIIC: **SARS-CoV-2 Delta VOC in Scotland**: **demographics**, **risk of hospital admission**, **and vaccine effectiveness**. *Lancet (London, England)* 2021, **397**(10293):2461–2462.
10. Wang Y, Chen R, Hu F, Lan Y, Yang Z, Zhan C, Shi J, Deng X, Jiang M, Zhong S *et al*: **Transmission**, **viral kinetics and clinical characteristics of the emergent SARS-CoV-2 Delta VOC in Guangzhou**, **China**. *EClinicalMedicine* 2021, **40**:101129.
11. Frampton D, Rampling T, Cross A, Bailey H, Heaney J, Byott M, Scott R, Sconza R, Price J, Margaritis M *et al*: **Genomic characteristics and clinical effect of the emergent SARS-CoV-2 B.1.1.7 lineage in London, UK: a whole-genome sequencing and hospital-based cohort study**. The Lancet Infectious diseases 2021, **21**(9):1246–1256.
12. Fisman DN, Tuite AR: **Evaluation of the relative virulence of novel SARS-CoV-2 variants**: **a retrospective cohort study in Ontario**, **Canada**. *CMAJ: Canadian Medical Association journal = journal de l'Association medicale canadienne* 2021, **193**(42):E1619-E1625.
13. Riediker M, Briceno-Ayala L, Ichihara G, Albani D, Poffet D, Tsai DH, Iff S, Monn C: **Higher viral load and infectivity increase risk of aerosol transmission for Delta and Omicron variants of SARS-CoV-2**. Swiss medical weekly 2022, **152**:w30133.
14. Wang F, An Z, Rodewald L, Wu D, Tang L, Zheng H, Liu Q, Gao GF, Yin Z: **Guangdong's Study of the Effectiveness of China's Inactivated Vaccines Against the SARS-CoV-2 B.1.617.2 (Delta) Variant**. China CDC Wkly 2021, **3**(34):728–730.
15. Abu-Raddad LJ, Chemaitelly H, Butt AA, National Study Group for C-V: **Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants**. N Engl J Med 2021, **385**(2):187–189.
16. Shinde V, Bhikha S, Hoosain Z, Archary M, Bhorat Q, Fairlie L, Lalloo U, Masilela MSL, Moodley D, Hanley S *et al*: **Efficacy of NVX-CoV2373 Covid-19 Vaccine against the B.1.351 Variant**. N Engl J Med 2021, **384**(20):1899–1909.
17. Lopez Bernal J, Andrews N, Gower C, Robertson C, Stowe J, Tessier E, Simmons R, Cottrell S, Roberts R, O'Doherty M *et al*: **Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms**, **hospital admissions**, **and mortality in older adults in England**: **test negative case-control study**. *BMJ (Clinical research ed)* 2021, **373**:n1088.
18. Lopez Bernal J, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, Stowe J, Tessier E, Groves N, Dabrera G *et al*: **Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant**. N Engl J Med 2021, **385**(7):585–594.
19. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC *et al*: **Clinical Characteristics of Coronavirus Disease 2019 in China**. N Engl J Med 2020, **382**(18):1708–1720.

20. Zhang HJ, Qi GQ, Gu X, Zhang XY, Fang YF, Jiang H, Zhao YJ: **Lymphocyte blood levels that remain low can predict the death of patients with COVID-19**. Medicine (Baltimore) 2021, **100**(28):e26503.
21. Liang W, Liang H, Ou L, Chen B, Chen A, Li C, Li Y, Guan W, Sang L, Lu J *et al*: **Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19**. JAMA Intern Med 2020, **180**(8):1081–1089.
22. Long L, Zeng X, Zhang X, Xiao W, Guo E, Zhan W, Yang X, Li C, Wu C, Xu T *et al*: **Short-term outcomes of COVID-19 and risk factors for progression**. Eur Respir J 2020, **55**(5).
23. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y *et al*: **Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China**. *JAMA* 2020.

## Tables 1-2

TABLE1 Demographics and baseline characteristics of COVID-19 patients over 18 years old with different strains.

| | Total(n=3129) | | | | Mild(n=325) | | | | Moderate(n=2643) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | WT strain | Delta strain | | | WT strain | Delta strain | | | WT strain | Delta strain | | |
| | n=2267 | n=862 | *x* value | *P* value | (n=18) | (n=307) | *x* value | *P* value | (n=2104) | (n=539) | *x* value | *P* value |
| Age—mean (range) | 57.0(24-97) | 40.5(18-87) | | | 46.2(25-75) | 36.1(18-78) | | | 56.4(18-97) | 42.4(18-87) | | |
| Age-groups-No. (%) | | | | | | | | | | | | |
| 18-30y | 103(4.5) | 218(25.3) | 614.619 | 0.001 | 3(16.7) | 115(37.5) | 11.707 | 0.008 | 99(4.7) | 103(19.1) | 318.295 | 0.001 |
| 31-49y | 526(23.2) | 413(47.9) | | | 7(38.9) | 145(47.2) | | | 512(24.3) | 264(49.0) | | |
| 50-69y | 1237(54.6) | 203(23.5) | | | 7(38.9) | 44(14.3) | | | 1146(54.5) | 155(28.6) | | |
| ≥70y | 401(17.7) | 28(3.2) | | | 1(5.5) | 3(1.0) | | | 347(16.5) | 17(3.3) | | |
| Sex-No. (%) | | | | | | | | | | | | |
| Female | 1141(50.3) | 392(45.5) | 5.891 | 0.015 | 9(50.0) | 130(42.3) | 0.407 | 0.523 | 1068(50.8) | 254(47.1) | 2.269 | 0.132 |
| Male | 1126(49.7) | 470(54.5) | | | 9(50.0) | 177(57.7) | | | 1036(49.2) | 285(52.9) | | |
| Comorbidity-No. (%) | | | | | | | | | | | | |
| Hypertension | 258(11.4) | 72(8.4) | 103.355 | 0.001 | 3(16.7) | 16(5.2) | 0.711 | 0.701 | 193(9.2) | 50(9.3) | 99.719 | 0.001 |
| Diabetes mellitus | 430(19.0) | 21(2.4) | | | 1(5.6) | 7(2.3) | | | 401(19.1) | 13(2.4) | | |
| Chronic respiratory diseases | 58(2.6) | 8(0.9) | | | 0 | 0 | | | 44(2.1) | 6(1.1) | | |
| Coronary heart disease | 106(4.7) | 8(0.9) | | | 1(5.6) | 2(0.7) | | | 85(4.0) | 6(1.1) | | |
| Chronic kidney disease | 33(1.5) | 3(0.3) | | | 0 | 2(0.7) | | | 33(1.6) | 1(0.2) | | |
| Chronic liver disease | 65(2.9) | 15(1.7) | | | 0 | 6(2.0) | | | 59(2.8) | 8(1.5) | | |
| Tuberculosis | 5(0.2) | 11(1.3) | | | 0 | 1(0.3) | | | 5(0.2) | 9(1.7) | | |
| Malignant tumor | 26(1.1) | 6(0.7) | | | 0 | 0 | | | 25(1.2) | 6(1.1) | | |

*1.Abbreviations: WT strain, wild-type strain. 2. Items with '0' are not included in statistical analysis.3.Since there are only 9 critical patients with Delta strain, s*

(continue)

| | Total(n=3129) | | | | Mild(n=325) | | | | Moderate(n=2643) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | WT strain | Delta strain | | | WT strain | Delta strain | | | WT strain | Delta strain | | |
| | n=2267 | n=862 | *x* value | *P* value | (n=18) | (n=307) | *x* value | *P* value | (n=2104) | (n=539) | *x* value | *P* valu |
| Signs and symptoms—No./total No. (%) | | | | | | | | | | | | |
| Fever | 1467(64.7) | 370(42.9) | 304.77 | 0.001 | 5(27.8) | 84(27.4) | 14.393 | 0.006 | 1350(64.2) | 272(50.5) | 220.177 | 0.00 |
| Cough | 1367(60.0) | 508(58.9) | | | 7(38.9) | 133(43.3) | | | 1233(58.6) | 361(67.0) | | |
| Chest tightness/dyspnea | 906(40.0) | 109(12.6) | | | 1(5.6) | 15(4.9) | | | 807(38.4) | 78(14.5) | | |
| Muscle aches | 483(21.3) | 23(2.7) | | | 2(11.1) | 4(1.3) | | | 425(20.2) | 18(3.3) | | |
| Fatigue | 1037(45.7) | 81(9.4) | | | 5(27.8) | 21(6.8) | | | 943(44.8) | 57(10.6) | | |
| Chest CT images—No./total No. (%) | | | | | | | | | | | | |
| Patchy shadows | 158(7.0) | 79(9.2) | 155.04 | 0.001 | 2(11.1) | 13(4.2) | 3.381 | 0.184 | 127(6.0) | 64(11.9) | 66.051 | 0.00 |
| Ground glass opacity | 1666(73.5) | 521(60.4) | | | 5(27.8) | 74(24.1) | | | 1558(74.0) | 433(80.3) | | |
| Consolidation | 39(1.7) | 99(11.5) | | | 1(5.6) | 54(17.6) | | | 30(1.4) | 44(8.2) | | |

**Since there are only 9 critical patients with Delta strain, such patients are not included in this table.*

Table2 Univariate and Multivariate Cox regression analysis of the risk factors for deterioration to critical status in patients with COVID-19.

| Variables | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | HR (95% CI) | p value | HR (95% CI) | p value |
| Lineage | | | | |
| Wild-type | Ref. | - | Ref. | - |
| Delta | 0.27 (0.10-0.71) | 0.008 | 2.54 (1.279-5.026) | 0.008 |
| Age | | | | |
| 60 | Ref. | - | - | - |
| =60 | 0.73 (0.42-1.27) | 0.268 | | |
| Sex | | | | |
| Female | Ref. | - | - | - |
| Male | 1.37 (0.75-2.51) | 0.309 | | |
| Comorbidities | | | | |
| Chronic respiratory disease | | | | |
| No | Ref. | - | Ref. | - |
| Yes | 0.38 (0.21-0.70) | 0.002 | 1.97 (1.15-3.38) | 0.014 |
| Chronic heart disease | | | | |
| No | Ref. | - | - | - |
| Yes | 0.73 (0.37-1.46) | 0.376 | | |
| Hypertension | | | | |
| No | Ref. | - | - | - |
| Yes | 2.63 (1.53-4.45) | 0.0003 | | |
| Diabetes | | | | |
| No | Ref. | - | - | - |
| Yes | 1.23 (0.66-2.31) | 0.513 | | |
| Symptoms | | | | |
| Fever | | | | |
| No | Ref. | - | - | - |
| Yes | 1.07 (0.62-1.84) | 0.823 | | |
| Cough | | | | |
| No | Ref. | - | - | - |
| Yes | 2.03 (1.09-3.81) | 0.026 | | |
| Chest tightness/dyspnea | | | | |
| No | Ref. | - | - | - |
| Yes | 0.84 (0.50-1.41) | 0.498 | | |

HR, hazard ratio; CI, confidence interval.

## Tables 3-6

Tables 3-6 are not available with this version.

## Figures

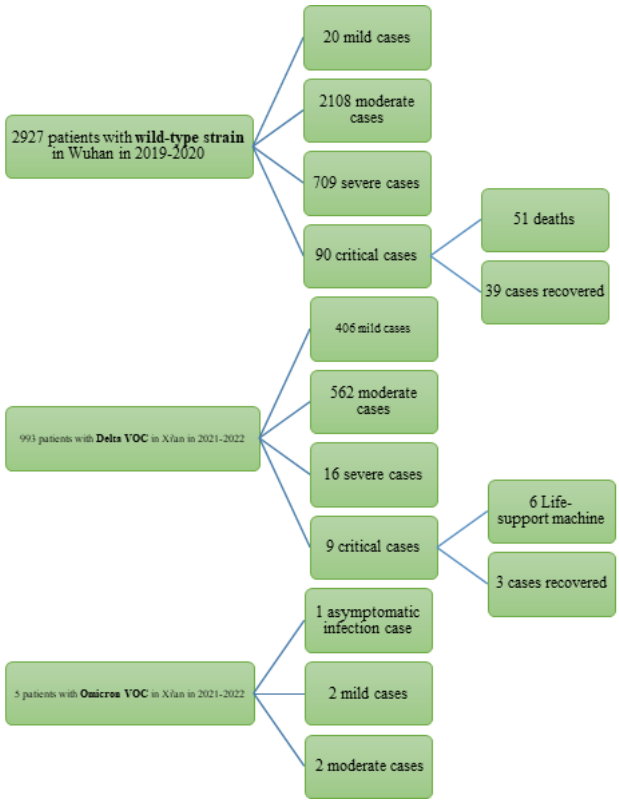


**Figure 1**

Flowchart of study sample selection.

A total of 3925 patients diagnosed with COVID-19 were included in this study, with 2927 patients with wild-type strain in Wuhan in 2019-2020[20 patients categorized as mild cases; 2108 moderate patients; 709 severe cases, and 90 critical cases (39 recovered cases, 51 deaths)]; 993 patients with Delta VOC in Xi'an in 2021-2022[406 patients categorized as mild cases; 562 moderate patients; 16 severe cases, and 9 critical cases (3 recovered cases, life-support machine)]; 5 patients with Omicron VOC in Xi'an in 2021-2022.

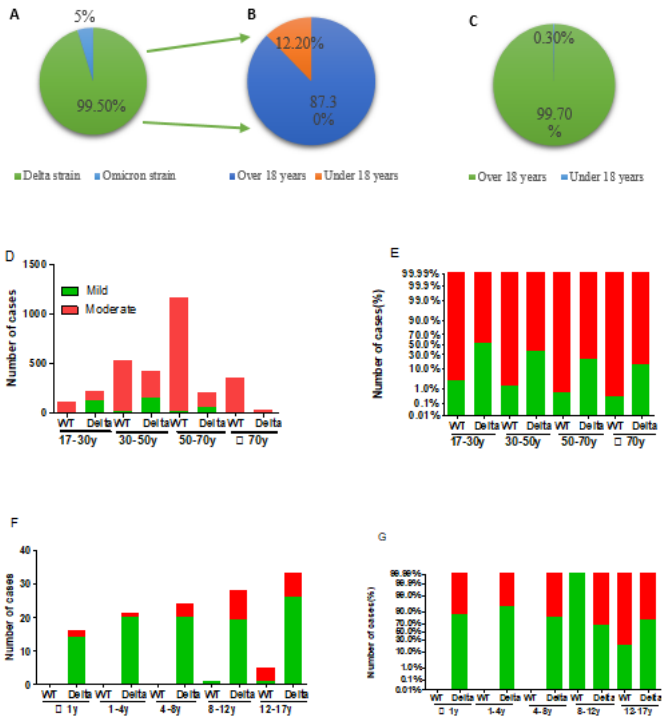


**Figure 2**

Time points of blood routine collection during hospitalization.

We divided the length of hospitalization into five time points, namely admission, 25%, 50%, 75% and discharge, according to the principle of interquartile distance.

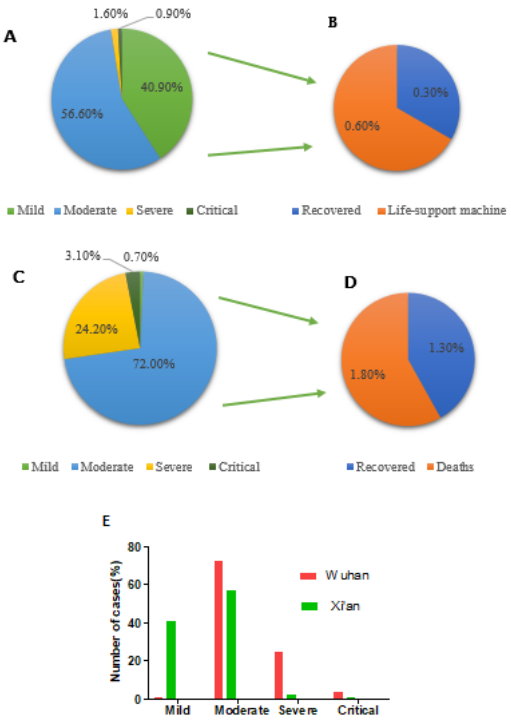


**Figure 3**

Strain and age distribution characteristics in the two waves of pandemic.

99.5% of the outbreaks in Xi'an from 2021 to 2022 were delta strain and 5% were Omicron strain (A). Among the 99.5% delta strains, 87.3% were patients over 18 years old, while 12.2% were patients under 18 years old (B). The outbreaks in Wuhan from 2019 to 2020 were WT strain, of which 99.7% were patients over the age of 18, while only 0.3% were patients under the age of 18 (C). Among the COVID-19 over 18 years old, the cases were mainly WT strain and delta strain cases of moderate, while wild type was less (D, E). Among the COVID-19 under 18 years old, the cases were mainly delta strain cases of mild and moderate, while wild type was very rare (F, G).

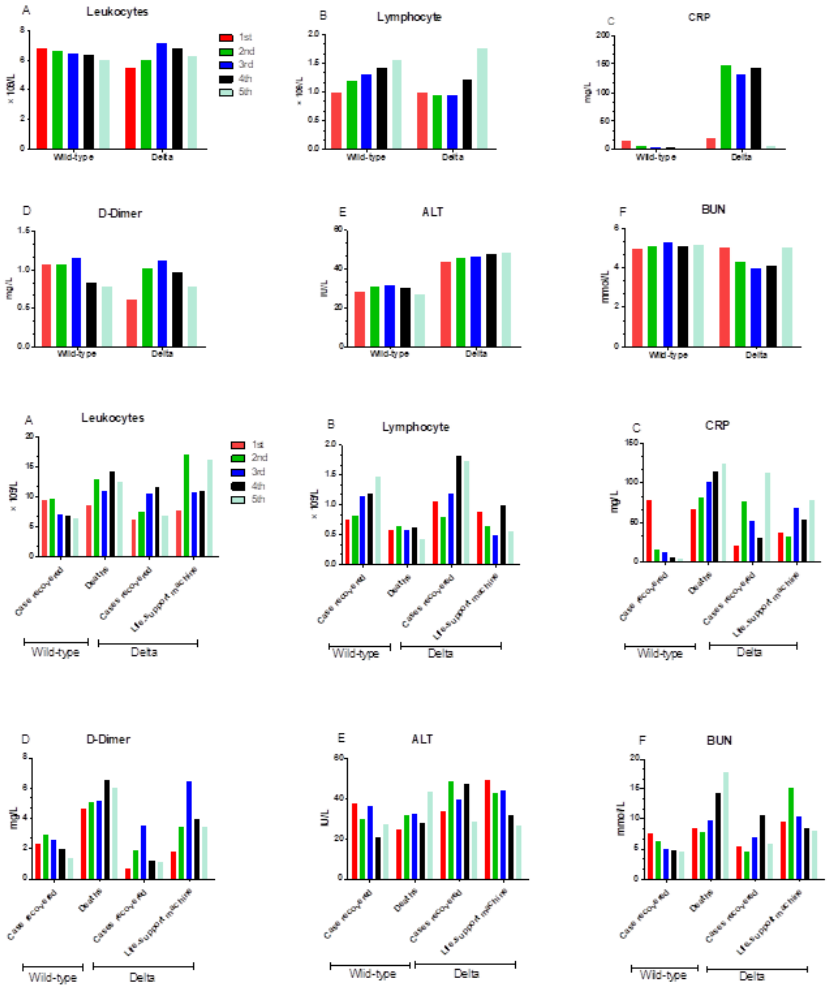


Figure 4

Clinical typing characteristics in the two waves of pandemic.

Most of the outbreaks in Xi'an from 2021 to 2022 were mild and moderate (40.9% and 56.6%, respectively), of while severe and critical are very rare (1.6% and 0.9%, respectively) (A). As of the time of data statistics, 0.3% of the critically ill patients were recovered, while 0.6% relied on life-support machine (B). Most of the outbreaks in Wuhan from 2019 to 2020 were severe and moderate (24.2% and 72.0%, respectively), of while mild and critical are less (0.70% and 3.10%, respectively) (C). In critically ill patients, 1.3% of the patients were recovered, while 1.80% were died (D). Comparison of the proportion of four clinical types of patients in two hospitals (E).

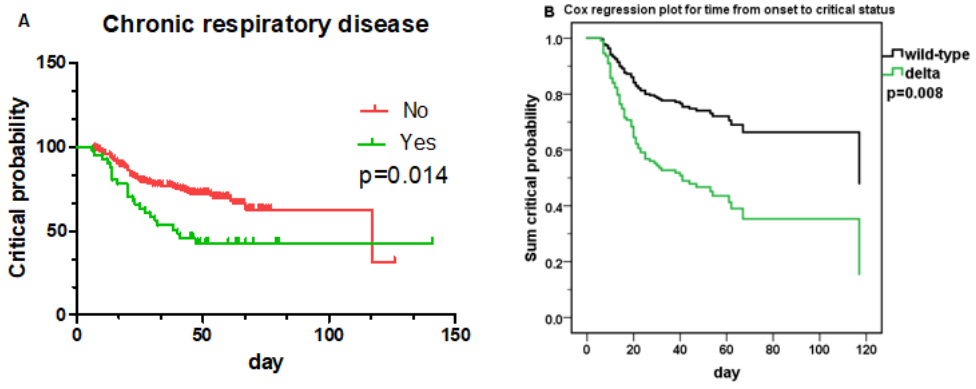


Figure 5

Dynamic changes of blood test in severe patients with COVID-19.

Compared with cases infected with the wild-type strain, the CRP and ALT of patients with infection delta VOC were significantly higher (CE, p0.05), while their lymphocytes were similar (B, p0.05), and the CRP and lymphocytes of these two cohorts gradually returned to normal after treatment (BC, p0.05), among the severe cases. However, no differences in leukocytes, D-Dimer and BUN were found between the two cohorts in the severe patients (ADF, p0.05).

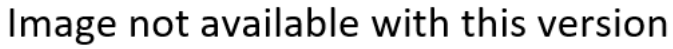


**Figure 6**

Dynamic changes of blood test in critical patients with COVID-19.

Compared with recovered patients infected with the wild-type strain and Delta VOC, the leukocytes, D-Dimer and BUN of dead patients with the wild-type strain and machine supported patients with infection Delta VOC were significantly higher (ADF; p0.001), while their lymphocytes have been at a relatively low level(B; p0.001). Further analysis revealed that leukocytes, CRP, D-Dimer and BUN of dead patients with the wild-type strain were very high (ACD; p0.001), while ALT was no significant difference, in these four groups (E; p0.05).

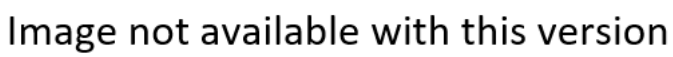


**Figure 7**

Cox Regression plots for the prognostic factors.

The Cox regression survival plots for the time from symptom onset to critical status categorized by chronic respiratory disease (No vs Yes) (A; p0.014) and virus lineage (Delta VOC vs wild-type strain) (B; p0.008) in the two cohorts.