

RESEARCH ARTICLE



Real-world effectiveness of influenza vaccine against medical-attended influenza infection during 2023/24 season in Ili Kazakh Autonomous Prefecture, China: A test-negative, case-control study

Jia Mi^{a*}, Juping Wang^{b*}, Luping Chen^{a*}, Zihao Guo^{c,d*}, Hao Lei^e, Marc KC Chong^{c,d}, Jiangatai Talifu^b, Shengmei Yang^b, Kamuranni Luotebula^b, Maierhaba Ablikemu^b, Chunyu Ma^f, Wenli Lu^{f,g,h}, Zhaohui Luoⁱ, Chuanfa Liuⁱ, Shengzhi Sun^k, Jianghong Dai^a, Kai Wang^{a,l}, Kailu Wang^{c,d}, and Shi Zhao^{f,g,h}

^aSchool of Public Health, Xinjiang Medical University, Urumqi, China; ^bIli Kazakh Autonomous Prefecture Center for Disease Control and Prevention, Ili Kazakh Autonomous Prefecture, China; ^cCUHK SZRI, Shenzhen, China; ^dJC School of Public Health and Primary Care, Chinese University of Hong Kong, Hong Kong, China; ^eSchool of Public Health, Zhejiang University, Hangzhou, China; ^fSchool of Public Health, Tianjin Medical University, Tianjin, China; ^gTianjin Key Laboratory of Environment, Nutrition and Public Health, Tianjin Medical University, Tianjin, China; ^hMoE Key Laboratory of Prevention and Control of Major Diseases in the Population, Tianjin Medical University, Tianjin, China; ⁱThe Sixth Affiliated Hospital of Xinjiang Medical University, Urumqi, China; ^jDepartment of Medicine and Therapeutics, Chinese University of Hong Kong, Hong Kong, China; ^kSchool of Public Health, Capital Medical University, Beijing, China; ^lKey Laboratory of Special Environment and Health Research in Xinjiang, Xinjiang Medical University, Urumqi, China

ABSTRACT

In the post-COVID-19 pandemic era, influenza virus infections continuously lead to a global disease burden. Evaluating vaccine effectiveness against influenza infection is crucial to inform vaccine design and vaccination strategy. In this study, we recruited 1120 patients with influenza-like illness (ILI) who attended fever clinics of 4 sentinel hospitals in the Ili Kazakh Autonomous Prefecture, Xinjiang Uygur Autonomous Region, China, from January 1 to April 7, 2024. Using a test-negative design, we estimated influenza vaccine effectiveness (VE) of 54.7% (95% CrI: 23.7, 73.1) against medical-attended influenza infection, with 62.3% (95% CrI: 29.3, 79.8) against influenza A, and 51.2% (95% CrI: 28.7, 83.0) against influenza B. Despite the moderate VE estimated in this study, influenza vaccination remains the most important approach to prevent influenza at the community level.

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Introduction

Influenza is an acute respiratory infectious disease caused by influenza viruses, which pose a serious health risk to humans. Influenza viruses have variable antigenic properties and spread rapidly, causing seasonal epidemics every year, and outbreaks are easy to occur in places where people gather, such as schools, childcare institutions, and nursing homes. The population is generally susceptible to influenza viruses, and the hazards of influenza infection in high-risk groups, such as pregnant women, infants and young children, the elderly, and patients with chronic diseases are more serious.¹ Influenza has long imposed a heavy disease burden on humans, resulting in 290,000 to 650,000 respiratory deaths annually.²

The strict public health and social measures (PHSMs) in China against the COVID-19 pandemic, including lockdown, social distancing, and self-protective behavior (e.g., mask-wearing), led to a dramatic decrease in the spread of influenza viruses globally.³ In China, the “zero-COVID” policy was imposed at the early stage of the pandemic, led to an estimated 79.2% and 79.4% reduction in influenza activity in southern

and northern China, respectively.⁴ Although the consequences were favorable in the short term, the low level of viral transmission may have hampered individuals from developing immunity due to a lack of exposure, which may make the population more susceptible in the following influenza season. Since November 2022, the strict PHSMs have been gradually lifted, and a rapid growth of influenza incidence was seen in December 2022.⁵ The 2023/2024 influenza season, i.e., from October 2023 to March 2024, started earlier than the past year with a higher level of activity in general. As of April 4, 235 outbreaks had been detected in the current season.⁶

Influenza vaccination is the primary means of preventing influenza.⁷ Clinical trials and epidemiologic studies are commonly used to assess vaccine efficacy to determine the preventive effect of the vaccine in a population. Timely assessing the effectiveness of influenza vaccines could prompt the dissemination of relevant public health information in the current season and influence vaccination rates.⁸ In this study, we conducted a test-negative case-control study to evaluate the effectiveness of influenza vaccine (VE) against medically attended influenza infections in four sentinel hospitals across

CONTACT Kai Wang  wangkaimath@sina.com  School of Public Health, Xinjiang Medical University, Urumqi 830017, China; Kailu Wang  kailuwang@cuhk.edu.hk  CUHK SZRI, Shenzhen, China; Shi Zhao  zhaoshi.cmsa@gmail.com  School of Public Health, Tianjin Medical University, Tianjin 300070, China

*These authors contributed equally, and thus they were joint-first authors.

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three cities (Yining city, Kuitun city, and Khorghos city) in Ili, Xinjiang, China, from January 1 to April 7, 2024.

Methods

Study setting

From 2013 to 2020, the annual influenza season in Xinjiang usually started in October and ended in April, with influenza incidence peaked from December to January.⁹ In addition, Xinjiang has variable weather and more sandstorms in the spring, and this climatic condition may increase the risk of influenza virus transmission and invasion, making the spring also one of the high-incidence season of influenza.

Study design and data collection

Individual-level data of patients with influenza-like illnesses, including fever, runny nose, cough, and sore throat, were collected for 14 epidemiologic weeks between January 1 and April 7, 2024, who visited the outpatient clinics of four designated hospitals in Yining, Kuitun, and Horgos cities. Each week, 5 to 50 nasal or nasopharyngeal specimens were randomly selected from outpatients, and were sent for laboratory testing for the influenza virus. Individual information including sex, age, ethnicity, influenza vaccination status, and stratification of priority vaccination populations as recommended by the Chinese Center for Disease Control and Prevention (four categories: medical staff, vulnerable populations and employees of elderly care facilities, long-term care facilities, welfare homes, and other congregations, and populations in key locations and other influenza high-risk populations) were recorded by using standardized questionnaires. Individual data for minor patients were obtained from legal guardians.

Patients who received the influenza vaccine at least 14 days before the date of symptom onset were considered vaccinated, and patients who had never been vaccinated and those who were vaccinated within 14 days before the date of symptom onset were considered unvaccinated. We excluded children under half a year old since the vaccinated pregnant women only protect the newborns for up to 6 months by transferring antibodies against influenza.¹

Statistical analysis

Bayesian logistic regression models were used to estimate VE, with adjustment in the prior probability based on the crude odds ratio. Confounders including sex, interval between symptom onset and specimen collection (0–2, 3–4, 5–7, 7+ days), calendar date (adjusted as spline function), age group (0.5–3, 4–6, 7–17, 18–59, 60+ years), and body mass index (BMI) were considered in the model. VE for laboratory-confirmed influenza cases was calculated as $100\% \times (1 - \text{adjusted odds ratio})$.¹⁰ Uncertainty in model coefficients was quantified by constructing 95% credible interval (CrI) of the posterior samples.

All statistical analyses were performed in R (version 4.3.2) statistical software (R Foundation for Statistical Computing, Vienna, Austria).

Results

Between January 1 and April 7, 2024, a total of 1120 patients who visited the hospitals for influenza-like illness were identified. After excluding 26 neonates under 6 months of age, a total of 1094 patients were eligible for inclusion in the analysis. Of these, 87 patients (7.95%) were test-positive for influenza, with most of the confirmed cases (71 out of 87, 81.6%) infected by influenza B. Among test-positive cases, the median age was 12, with 47 (54.0%) males and 49 (56.3%) children or adolescents aged below 17 years. The majority of the confirmed influenza cases were underweight (39.1%), and only 7 (8.0%) cases were vaccinated, as opposed to 153 (15.2%) vaccinated patients in the control group who were test-negative (Table 1, Figure 1).

As shown in Figure 2, the incidence of influenza A gradually decreased from 4.2% to 1.2% from week 1 to 11, with no test-positives of influenza A in weeks 6, 7 and 10. The influenza B incidence rose since the first week (5.6%) and reached a peak in the fifth week (17.1%). Subsequently, the incidence declined until week 9, after which a small fluctuation was noted.

Overall, the estimated VE against medically attended influenza A or B infection was 54.7% (95% CrI: 23.7, 73.1), with a VE of 62.3% (95% CrI: 29.3, 79.8) for influenza A and 51.2% (95% CrI: 28.7, 83.0) for influenza B (Table 2). After stratifying the study participants by age (reference level: 60+ y), the adjusted VE was 63.1% (95% CrI: 33.2, 79.6) for the younger group (6 months to 6 y), which was similar for the young adult group (18–59 y) (60%; 95% CrI: 25.5, 79.8). A similar pattern was observed for the influenza B subgroup but not for influenza A, due to a limited number of observations.

Discussion

In this study, using outpatient data from four hospitals in Xinjiang, China, we assessed the influenza VE against medically attended influenza infection during the 2023/2024 winter influenza season. Our findings suggested an overall moderate VE against influenza infection, with a comparable level of VE against influenza A and B.

Our estimated overall VE of 54.7% in the current influenza season is consistent with the findings from a previous single-center test-negative case-control study conducted in Shihezi, Xinjiang, during the 2022/2023 winter influenza season (56.3%),¹¹ and is higher than a multicenter study conducted in Europe (27%).¹² For the current influenza season, studies related to the effectiveness of influenza vaccine have been conducted in various countries and regions. A modest VE against influenza A (22%) was found in a study performed in South Korea during the 2023/2024 influenza season.¹³ Moreover, a recent report showed that in 2023, the VE against hospitalizations for severe acute respiratory infections caused by any influenza virus in the Southern Hemisphere region was 51.9%.¹⁴ Our influenza VE estimates were comparable to the previous report of the influenza VE during past seasons provided by the United States center for disease control and prevention.¹⁵ In a study conducted during the early 2023/2024 influenza season in the United States, the VE against laboratory-confirmed influenza infection was estimated to be

Table 1. Demographic and clinical characteristics of test-positive and -negative patients for influenza virus.

Baseline characteristics	Test-positive patients			Test-negative patients, <i>n</i> (column %)
	Influenza A, <i>n</i> (column %)	Influenza B, <i>n</i> (column %)	Subtotal, (column %)	
Total	16 (100%)	71 (100%)	87 (100%)	1007 (100%)
Sex				
Male	10 (62.5%)	37 (52.1%)	47 (54.0%)	505 (50.1%)
Female	6 (37.5%)	34 (47.9%)	40 (46.0%)	502 (49.9%)
Age group				
0.5 - 3 yr	5 (31.3%)	8 (11.3%)	13 (14.9%)	140 (13.9%)
4 - 6 yr	3 (18.7%)	15 (21.1%)	18 (20.7%)	135 (13.4%)
7 - 17 yr	0 (0.0%)	18 (25.4%)	18 (20.7%)	352 (35.0%)
18 - 59 yr	5 (31.3%)	26 (36.6%)	31 (35.6%)	278 (27.6%)
60+ yr	3 (18.7%)	4 (5.6%)	7 (8.1%)	102 (10.1%)
Median age, yr [IQR]	13 (2.8, 34.5)	12 (5.0, 27.0)	12 (4.5, 28.0)	13 (6.0, 32.5)
Ethnicity				
Han	8 (50.0%)	42 (59.2%)	50 (57.5%)	608 (60.4%)
Uyghurs	6 (37.5%)	18 (25.4%)	24 (27.6%)	236 (23.4%)
Hui	1 (6.3%)	4 (5.6%)	5 (5.7%)	40 (4.0%)
Kazakh	1 (6.3%)	6 (8.5%)	7 (8.1%)	114 (11.3%)
Other ethnicities	0 (0.0%)	1 (1.4%)	1 (1.1%)	9 (0.9%)
BMI strata				
Underweight: < 18.5	6 (37.5%)	28 (39.4%)	34 (39.1%)	390 (38.6%)
Normal: 18.5 - 23.0	5 (31.3%)	23 (32.4%)	28 (32.2%)	383 (38.4%)
Overweight: 23.0 - 27.5	3 (18.7%)	18 (25.4%)	21 (24.1%)	187 (18.3%)
Obese: > 27.5	2 (12.5%)	2 (2.8%)	4 (4.6%)	47 (4.8%)
Median BMI [IQR]	21.3 (14.8, 23.8)	19.8 (16.7, 23.6)	20.0 (16.4, 23.6)	19.8 (16.9, 22.7)
Calendar month of ILI onset in 2024				
January	8 (50.0%)	45 (63.4%)	53 (60.9%)	331 (32.9%)
February	2 (12.5%)	15 (21.1%)	17 (19.5%)	276 (27.4%)
March	4 (25.0%)	11 (15.5%)	15 (17.2%)	316 (31.4%)
April	2 (12.5%)	0 (0.0%)	2 (2.3%)	84 (8.3%)
Time interval from ILI onset to specimen collection				
0 - 2 days	15 (93.7%)	57 (80.3%)	72 (82.8%)	781 (77.6%)
3 - 4 days	1 (6.3%)	9 (12.7%)	10 (11.5%)	138 (13.7%)
5 - 7 days	0 (0.0%)	4 (5.6%)	4 (4.6%)	58 (5.8%)
>7 days	0 (0.0%)	1 (1.4%)	1 (1.1%)	30 (3.0%)
Median time interval, days [IQR]	1 (0.0, 1.0)	1 (0.0, 2.0)	1 (0.0, 2.0)	1 (0.0, 2.0)
China CDC recommended priority vaccination groups based on self-report (% out of total)				
Medical personnel	0 (%)	1 (%)	1 (%)	18 (%)
Elderly aged 60+ yr	3 (%)	4 (%)	7 (%)	102 (%)
Children aged 0.5 to 5 yr	8 (%)	19 (%)	27 (%)	239 (%)
Patients with comorbidity	1 (%)	0 (%)	1 (%)	38 (%)
Staff or elderly of nursing home	0 (%)	0 (%)	0 (%)	9 (%)
Staff at school or kindergarten	2 (%)	7 (%)	9 (%)	153 (%)
Pregnant woman	0 (%)	0 (%)	0 (%)	0 (%)
Influenza vaccination status in the past 24 months				
Unvaccinated	15 (93.7%)	65 (91.5%)	80 (92.0%)	854 (84.8%)
Vaccinated	1 (6.3%)	6 (8.5%)	7 (8.0%)	153 (15.2%)

ILI: influenza-like illness.

45%, with a significantly higher VE against influenza A than influenza B.¹⁶ In our study, although the point VE estimates for influenza A were higher than that for influenza B, the wide credible interval may not lead to conclusive evidence. Another United States study conducted during a similar period suggested the estimated VE against both influenza A and B were generally higher for children and adolescents than for adults.¹⁷ Our VE estimates for influenza B support such findings. It should be noted that the participants in these studies were mostly infected by influenza A, whereas in our study setting, influenza B was the dominant strain, accounting for 81.61% of the total influenza test-positive cases. This study collected data from a multi-ethnic area, so the vaccine effectiveness results obtained are useful in guiding vaccination strategies.

Seasonal influenza vaccination remains the most effective public health strategy for preventing influenza illness and serious complications, and it provides modest protection in infants, children, adolescents, and adults, especially against laboratory-confirmed cases of influenza. In addition, influenza vaccination not only helps to protect vulnerable populations^{18–20} but also helps to promote the prevention and control benefits of other diseases,^{21,22} as well as contributing positively to health economics.^{23,24} According to the recommendations from the relevant authorities, all individuals aged 6 months and older who have no contraindications to vaccination should be vaccinated against influenza annually.^{25,26} In China, the annual national influenza vaccination coverage rate was significantly lower than that of other countries from 2020 to 2021, in

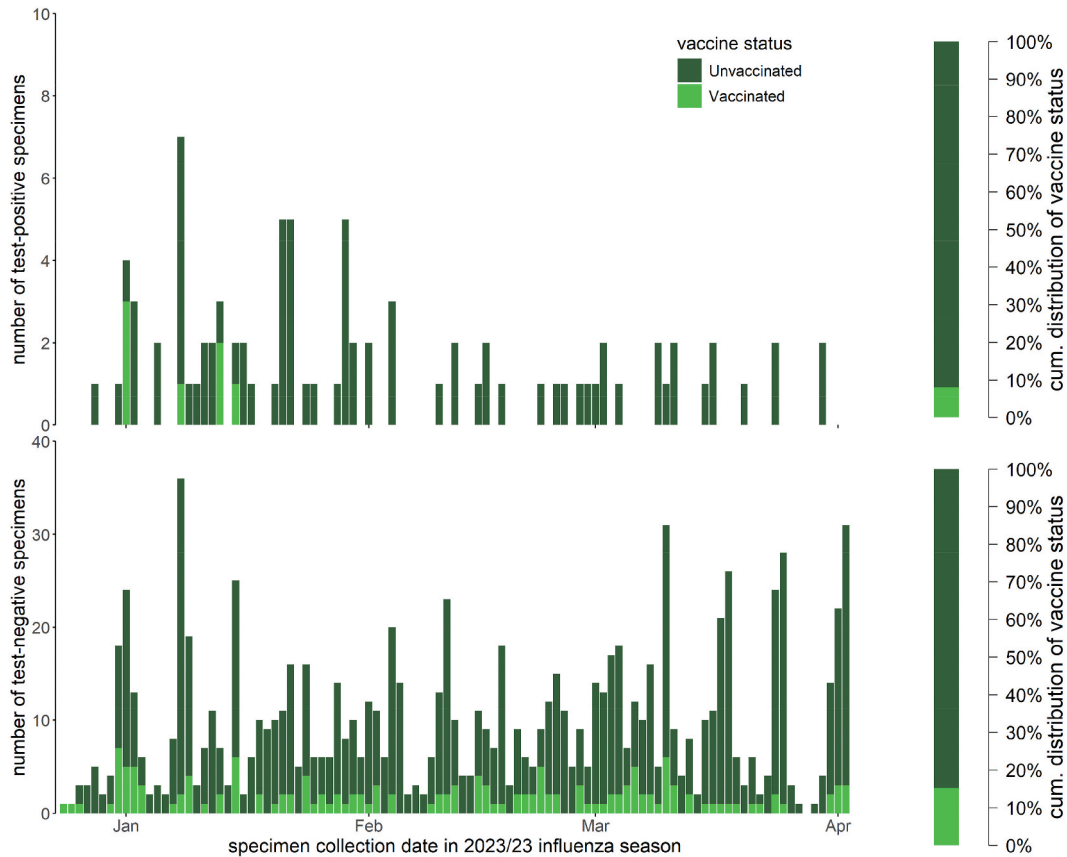


Figure 1. The daily number of patients with influenza-like illness reported in the four designated hospitals in Ili, Xinjiang, categorized by influenza vaccination status prior to influenza infection. The upper panel shows the temporal and cumulative distribution of vaccination status for influenza-positive cases; the lower panel shows the temporal and cumulative distribution of vaccination status for influenza-negative controls.

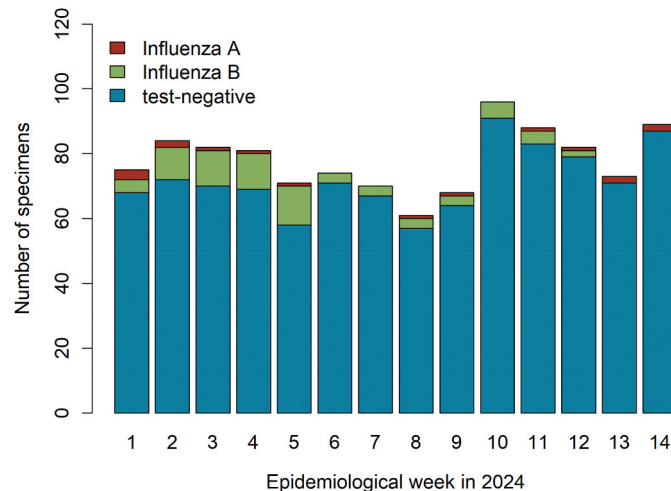


Figure 2. Weekly recruited individuals that were test-negative or test-positive for influenza virus in Ili Kazakh autonomous prefecture, Xinjiang uygur autonomous region, China ($n = 1094$).

a range of 2–3%,²⁷ compared to a global scale of 6.9%.²⁸ It is crucial for public health authorities to give priority to enhancing influenza vaccines and guaranteeing their widespread distribution, along with promoting and ensuring accessibility of vaccination campaigns to all population groups, particularly young and elderly groups.

This study has limitations. First, as the influenza subtypes cannot be determined during laboratory testing, we were unable to evaluate the VE against a specific subtype. The VE could be different across subtypes. Second, unobserved confounding factors may have biased our VE estimates. Third, the small sample size for influenza A cases

Table 2. Estimates of the effectiveness of influenza vaccines against influenza A and B, stratified by age.

	Test-positive patients		Test-negative patients		adjusted VE (95% CrI)
	subtotal	vaccinated (%)	subtotal	vaccinated (%)	
Any influenza virus infection					
Overall	87	7 (8.0%)	1007	153 (15.2%)	54.7% (23.7, 73.1)
Stratified by age groups					
0.5 - 6 yr	31	2 (6.5%)	275	48 (17.5%)	63.1% (33.2, 79.6)
7 - 17 yr	18	4 (22.2%)	352	75 (21.3%)	-23.0% (-56.0, 34.8)
18 - 59 yr	31	1 (3.2%)	278	21 (7.6%)	60.0% (25.5, 78.5)
60+ yr	7	0 (0.0%)	102	9 (8.8%)	100% (not estimated)
Influenza A virus infection					
Overall	16	1 (6.3%)	1007	153 (15.2%)	62.3% (29.3, 79.8)
Stratified by age groups					
0.5 - 6 yr	8	1 (12.5%)	275	48 (17.5%)	38.8% (-14.8, 67.4)
7 - 17 yr	0	0 (0.0%)	352	75 (21.3%)	100% (not estimated)
18 - 59 yr	5	0 (0.0%)	278	21 (7.6%)	100% (not estimated)
60+ yr	3	0 (0.0%)	102	9 (8.8%)	100% (not estimated)
Influenza B virus infection					
Overall	71	6 (8.5%)	1007	153 (15.2%)	51.2% (28.7, 83.0)
Stratified by age groups					
0.5 - 6 yr	23	1 (4.3%)	275	48 (17.5%)	80.0% (62.6, 89.2)
7 - 17 yr	18	4 (22.2%)	352	75 (21.3%)	-7.9% (-62.2, 38.4)
18 - 59 yr	26	1 (3.8%)	278	21 (7.6%)	50.2% (7.3, 73.2)
60+ yr	4	0 (0.0%)	102	9 (8.8%)	100% (not estimated)

and the overall low influenza infection test-positive rate led to a wide credible interval of VE estimates.

Conclusions

We found the effectiveness of influenza vaccine against medical-attended influenza illness at 54.7%, and against influenza A and B at 62.3% and 51.2%, respectively, during the 2023/24 influenza season. Despite the moderate VE estimated in this study, influenza vaccination remains the most important approach to prevent influenza at community level, and offers multiple public health benefits which were recommended by China CDC.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Notes on contributors

Prof. Kailu Wang obtained his PhD in Public Health from the Chinese University of Hong Kong, China, and is currently a research assistant professor in the same institution. His research covers a wide range of topics in health preference research, and long-term care services, with aims to improve health outcomes, and care experience.

Prof. Kai Wang received PhD degree in mathematics from Xinjiang University, China, in 2011. He is a professor of epidemiology and health

statistics in Xinjiang Medical University, China. His current research interests include mathematical biology, and bioinformatics.

Prof. Shi Zhao earned PhD in Public Health from the Chinese University of Hong Kong and is currently a professor of biostatistics in Tianjin Medical University, China. His research interests focus on emerging infectious disease epidemiology.

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Authors' contribution

Conceptualization: Shi Zhao, Juping Wang and Kai Wang. Methodology: Shi Zhao, Zihao Guo, and Kai Wang. Software: Jia Mi, Hao Lei and Luping Chen. Validation: Kailu Wang, Zihao Guo, Shi Zhao, and Kai Wang. Formal analysis: Juping Wang, Zihao Guo and Kai Wang. Investigation: Kailu Wang, and Kai Wang. Resources: Juping Wang, and Kai Wang. Data Curation: Jiangatai Talifu, Shengmei Yang, Kamuranni Luotebula and Maierhaba Ablikemu. Writing – Original Draft: All authors. Writing – Review and Editing: All authors. Visualization: Kai Wang. Supervision: Shi Zhao, and Kai Wang. Project Administration: Kai Wang. Funding acquisition: Kai Wang. All authors critically read the manuscript and gave final approval for publication.

Data sharing statement

The original database containing confidential patient information cannot be made publicly available. The anonymized data used in this study were available based on reasonable request to the corresponding authors.

Ethics approval

This study was reviewed and approved by the Ethics Committee of Xinjiang Medical University.

Consent of information collection

Individual verbal consent was obtained when collecting personal information and human samples by governmental health-care professionals in the field.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, writing of the manuscript, or the decision to submit for publication. All authors had full access to all the data in the study and were responsible for the decision to submit the manuscript for publication.

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