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Analysis of clinical features and early warning indicators of death from severe fever with thrombocytopenia syndrome

Xiaowen Xu[1], Zhenlu Sun[1], Jingyu Liu, Jianjun Zhang, Tao Liu, Xiaodong Mu, Mei Jiang*

Yantai Center for Disease Control and Prevention, Yantai, Shandong, PR China

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ABSTRACT

Objective: To determine the clinical features of confirmed cases of severe fever with thrombocytopenia syndrome (SFTS) and to explore the early warning indicators of death from SFTS.
Methods: A retrospective case–control study was performed at a single medical institution in Yantai. A total of 20 SFTS patients who died (death group) during January 2014 to December 2015 and another 40 age- and sex-matched SFTS patients who survived (survivor group) were identified from the case records. The differences in demographic characteristics, clinical signs and symptoms, and laboratory parameters in the early stage of disease were compared between the two groups. Conditional logistic regression was used to identify the independent risk factors for mortality in SFTS patients.
Results: Univariate logistic regression analysis showed that a disturbance of consciousness, pulse–temperature deficit, neurological signs, hemorrhagic manifestations, pulmonary infection, decreased lymphocyte percentage, high lactate dehydrogenase and creatine kinase levels, increased serum creatinine, blood urea nitrogen, and C-reactive protein (CRP), hyponatremia, and prolonged activated partial thromboplastin time (APPT) and prothrombin time were associated with mortality. On multivariate logistic regression analysis, the independent predictors of death were neurological signs (odds ratio (OR) 31.247, 95% confidence interval (CI) 4.813–202.853), hemorrhagic manifestations (OR 20.251, 95% CI 2.056–199.443), disturbance of consciousness (OR 15.359, 95% CI 2.139–110.268), hyponatremia (OR 5.280, 95% CI 1.235–22.575), increased CRP (OR 2.641, 95% CI 1.090–6.396), increased serum creatinine (OR 6.776, 95% CI 1.047–43.840), and prolonged APTT (OR 6.018, 95% CI 1.450–24.975).
Conclusions: Neurological signs, hemorrhagic manifestations, disturbance of consciousness, hyponatremia, prolonged APTT, and increased CRP and serum creatinine are risk factors for death in SFTS.

Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is an infectious disease caused by the SFTS virus (SFTSV). First reported from China in 2010, it is characterized by high-grade fever with thrombocytopenia, systemic infection symptoms, multiple organ dysfunction, and a mortality rate of 12–30% (Yu et al., 2011; Zhao et al., 2012). The aim of this retrospective case–control study was to identify the early predictors of mortality in patients with SFTS.

Patients and methods

Study setting and patients

This retrospective case–control study was conducted at a medical institution in Yantai during the period January 2014 to December 2015. A total of 20 patients who died of SFTS (death group) and another 40 age- and sex-matched SFTS patients who survived (survivor group) were selected from the case records. Patients were eligible for inclusion if they had (1) a diagnosis of SFTS according to the criteria recommended in the Severe Fever with Thrombocytopenia Syndrome Prevention and Control Guidelines (2010 version) published by the Ministry of Health of the People's Republic of China (Ministry of Health of People's Republic of China, 2011), (2) no history of travel outside the country for 6 months prior to the onset of illness, (3) no history of inpatient treatment for any other disease in the preceding 6 months, and (4)

* Corresponding author at: Yantai Center for Disease Control and Prevention, 17 Fuhou Road, Yantai, Shandong 264003, PR China.
E-mail address: sunluyu1007@126.com (M. Jiang).
[1] Xiaowen Xu and Zhenlu Sun contributed equally to this work.

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had received a comprehensive physical examination and laboratory examinations after admission and all data were available.

Blood samples were tested by real-time polymerase chain reaction (RT-PCR) at the central laboratory of Yantai Center for Disease Control and Prevention (Gong et al., 2013). The sample was considered positive if the cycle threshold (Ct) value was ≤35, the curve was S-type, and there was a significant exponential growth phase. The sample was considered negative if the Ct value was >38 or was not detected. When the Ct value was between 35 and 38 the test was repeated. If the Ct value was still in the range of 35–38, but the curve was a standard S-type and there was a significant exponential growth phase, then the sample was considered positive, otherwise it was considered negative.

Methods

Demographic characteristics, clinical manifestations, and laboratory test results of the death group and the survivor group were compared retrospectively.

Statistical analysis

EpiData 3.0 software (The EpiData Association, Odense, Denmark) was used to establish the database. Data were entered into the database by two investigators and then compared. SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Single-variable logistic regression was performed to assess the relationship between demographic characteristics, clinical manifestations, and laboratory test results and death. The variables that were significant ($p \leq 0.05$) in the univariate analysis were analyzed by multivariate logistic stepwise regression analysis. For the data analysis, continuous variables were converted into categorical variables using the normal values or multiples of the normal values as the cut-off points. Normally distributed data were summarized as the mean ± standard deviation, and non-normally distributed data as the median with interquartile range (IQR). Differences between the death group and the survivor group were analyzed using the independent-samples *t*-test, the Wilcoxon signed-rank test, or the Chi-square test, as appropriate.

Results

General information

A total of 60 patients were included in the study: 20 patients in the death group and 40 in the survivor group. All patients were from Yantai and were admitted during May to October. The male to female ratio was 1:1.22, and the mean age was 65.82 ± 11.36 years. Most patients (83.33%) were 'farmers' by occupation. Deaths occurred during May to September, with 85% occurring during May to August. In the death group, the median time from disease onset to death was 9 days (range 8–11 days). In the survivor group, the median time from disease onset to discharge from hospital was 19 days (range 15–23 days). Mean age, median time from disease onset to hospital admission, underlying diseases, history of tick bite, and Ct values were comparable in the two groups (Table 1). Of the 20 patients in the death group, 13 died due to cardiorespiratory failure. The other seven patients discontinued treatment because they could not afford it. Of these seven patients, five had multiple organ failure and one had acute respiratory failure when they left hospital; the remaining one patient, a 78-year-old man, had thrombocytopenia and liver function derangement and was seriously ill, although he did not meet the criteria for multiple organ failure. All seven of these patients died shortly after discharge.

After admission to hospital, all patients received treatment according to the recommended guidelines (Ministry of Health of People's Republic of China, 2011). Ribavirin (0.5 g/day) was started in all cases and was stopped only after body temperature returned to normal. Treatment generally did not exceed 5–7 days. Plasma and platelet infusions were administered for serious bleeding or thrombocytopenic crises. In general, a single dose of platelets ($\geq 2.5 \times 10^{11}$/l) was injected when the platelet count was less than 30×10^9/l. The infusion was repeated if necessary the next day after a review of the patient's general condition and platelet count. When there was severe hemorrhage (such as severe gastrointestinal blood loss), red blood cells were transfused, along with plasma, to supplement the coagulation factors. If the neutrophil count was less than 1.0×10^9/l, a subcutaneous injection of 150 μg or 100 μg recombinant human granulocyte colony stimulating factor was administered. The dose was repeated if necessary after a review on the second day. Symptomatic treatments were provided for liver, kidney, and myocardial dysfunction.

Univariate analysis

Clinical symptoms and signs

A total of 14 clinical symptoms and signs (Table 2) were analyzed by single-variable logistic regression analysis. The results showed five variables to be significantly associated with the risk of death; these were (1) disturbance of consciousness, i.e., drowsiness, confusion, lethargy, or a severe disturbance of consciousness (no Glasgow Coma Score evaluation was done); (2) pulse–temperature deficit, i.e., acceleration of the pulse is not proportional to the degree of increase in body temperature; (3) nervous system signs, i.e., abnormalities of the cranial nerves, abnormalities of motor system function (such as muscle wasting, muscle tone and power, posture and gait, involuntary movements, and ataxia), abnormalities of sensory function (hypoesthesia and paresthesia), abnormal neural reflexes (such as superficial reflex, deep reflex, pathological reflex, and signs of meningeal irritation), and abnormalities of the autonomic system; (4) hemorrhagic manifestations, i.e., internal or external bleeding; (5) pulmonary infection.

Nervous system signs were seen in all 20 patients who died. The signs included shaking limbs, muscular tremors, slurred speech, and other manifestations. Pyramidal signs were seen in three patients and signs of meningeal irritation in one patient. Hemorrhagic manifestations were seen in eight patients; they

Table 1
Comparison of general characteristics in the two study groups.

General information	Death group (20 cases)	Survivor group (40 cases)	Statistical analysis value	*p*-Value
Age, years	68.24 ± 10.40	63.95 ± 9.41	$\tau = 1.542$	0.129
Time from onset to admission, days	5 (5–7)	6 (4–7)	$Z = 0.188$	0.851
Underlying diseases, *n*	13 (65%)	16 (40%)	$\chi^2 = 3.337$	0.068
History of tick bite, *n*	6 (30%)	10 (25%)	$\chi^2 = 0.170$	0.680
Ct value	24.91 (18.79–28.42)	24.84 (21.40–29.19)	$Z = -0.063$	0.963

Ct, cycle threshold.

Table 2
Comparison of clinical symptoms and signs between the two groups.[a]

Symptoms and signs	Death group (20 cases)	Survivor group (40 cases)	Wald χ^2 value	*p*-Value	OR (95% CI)
Fever	19 (95)	39 (97.5)	0.259	0.611	0.487 (0.029–8.219)
Fatigue	13 (65)	23 (57.5)	0.312	0.577	1.373 (0.451–4.175)
Myalgia	9 (45)	21 (52.5)	0.299	0.548	0.740 (0.252–2.175)
Headache	2 (10)	6 (15)	0.285	0.594	0.630 (0.115–3.444)
Cough	6 (30)	1 (2.5)	3.754	0.053	0.123 (0.15–1.025)
Diarrhea	5 (25)	8 (20)	0.196	0.658	1.333 (0.373–4.770)
Vomiting	5 (25)	9 (22.5)	0.047	0.829	1.148 (0.327–4.028)
Anorexia	19 (95)	35 (87.5)	0.778	0.378	2.714 (0.295–24.954)
Disturbance of consciousness	12 (60)	1 (27.5)	5.664	0.017	3.955 (1.275–12.269)
Pulse-temperature deficit	10 (50)	31 (77.5)	4.660	0.031	3.444 (1.092–10.862)
Lymphadenopathy	7 (35)	17 (42.5)	0.312	0.577	0.729 (0.240–2.216)
Neurological signs	20 (100)	17 (42.5)	7.160	0.000	18.857 (4.811–73.905)
Hemorrhagic manifestations	8 (40)	3 (7.5)	7.805	0.005	8.222 (1.875–36.049)
Pulmonary infection	10 (50)	32 (80)	5.714	0.017	4.000 (1.242–12.886)

OR, odds ratio; CI, confidence interval.
[a] Note: Assignment, positive = 1, negative = 0.

included four patients with subcutaneous petechiae and ecchymosis, three patients with gastrointestinal bleeding (two cases of hematemesis and one case of melena), and one patient with pulmonary hemorrhage.

The prevalence of fever, fatigue, muscular soreness, and other factors were comparable in the two groups (Table 2).

Laboratory test results

The association of 18 laboratory parameters with mortality was also assessed using single-variable logistic regression (Table 3).

Table 3
Assignment of variables in the logistic regression analysis of laboratory test indicators.

Factor	Abbreviation	Value
Leukocyte count	WBC	$<2.0\times10^9$/l = 1 $\geq2.0\times10^9$/l = 0
Platelet count	PLT	$<30\times10^9$/l = 1 $\geq30\times10^9$/l = 0
Percentage of lymphocytes	L%	<20% = 1 ≥20% = 0
Alanine aminotransferase	ALT	≥200 U/l = 1 <200 U/l = 0
Aspartate aminotransferase	AST	≥400 U/l = 1 <400 U/l = 0
Albumin	ALB	<35 g/l = 1 ≥35 g/l = 0
Total bilirubin	TBil	≥20.5 μmol/l = 1 <20.5 μmol/l = 0
Lactate dehydrogenase	LDH	≥1000 U/l = 1 <1000 U/l = 0
Creatine kinase	CK	≥1000 U/l = 1 <1000 U/l = 0
Creatine kinase isoenzyme	CK-MB	≥100 U/l = 1 <100 U/l = 0
Serum creatinine	SCr	≥130 μmol/l = 1 <130 μmol/l = 0
Urea nitrogen	BUN	≥6.4 mmol/l = 1 <6.4 mmol/l = 0
Activated partial thromboplastin time	APTT	≥40 s = 1 <40 s = 0
Prothrombin time	PT	≥14 s = 1 <14 s = 0
D-dimer	DD	≥2.7 mg/l = 1 <2.7 mg/l = 0
C-reactive protein	CRP	≥20 mg/l = 1 <20 mg/l = 0
Serum sodium	Na	<136 mmol/l = 1 ≥136 mmol/l = 0
Serum calcium	Ca	<2.1 mmol/l = 1 ≥2.1 mmol/l = 0

The results showed that nine of these parameters were significantly associated with an increased risk of death in SFTS. These included a percentage of lymphocytes (L%) <20%, serum lactate dehydrogenase (LDH) ≥1000 U/l, serum creatine kinase (CK) ≥1000 U/l, serum creatinine ≥130 μmol/l, blood urea nitrogen (BUN) ≥6.4 mmol/l, activated partial thromboplastin time (APTT) ≥40 s, prothrombin time (PT) ≥14 s, C-reactive protein (CRP) ≥20 mg/l, and serum sodium <136 mmol/l (Table 4).

Multivariate analysis

The 14 factors that were found to be significant on univariate analysis were entered into the multivariate logistic regression analysis. The results showed neurological signs, hemorrhagic manifestations, disturbances of consciousness, serum sodium <136 mmol/l, CRP ≥20 mg/l, APTT ≥40 s, and serum creatinine ≥130 μmol/l to be independent risk factors for death in SFTS patients (Table 5).

Discussion

SFTS is characterized by rapid disease progression and a high case-fatality rate; therefore the early identification of critically ill patients is essential. In the present study, the median time from disease onset to hospital admission in both groups was ≤6 days. Laboratory tests performed within 1–2 days after admission could serve as indicators of the early course of disease (Gai et al., 2012). The mean Ct value was comparable in the two groups: death group and survivor group. This finding is consistent with a previous report (Gai et al., 2012). In that report, patients in both groups had similarly high viral loads at the onset of SFTS. However, in the second phase of the disease – the multiple organ dysfunction phase – the viral load increased in the death group but decreased in the survivor group. Therefore, continuous monitoring of changes in viral load may be useful in determining the prognosis of SFTS.

The SFTSV can cause damage to different organs. In this study a disturbance of consciousness and nervous system signs were risk factors for death; this finding is consistent with previous reports (Gai et al., 2012; You et al., 2014). The mechanism of neurological damage is not clear. Some studies have reported that brain magnetic resonance imaging (MRI) and cerebrospinal fluid show changes typical of acute viral encephalitis. Serum electrolyte imbalances may also contribute to the abnormal performance of the nervous system (Deng et al., 2013).

Zhao et al. (2016) compared the laboratory parameters of patients who survived SFTS and those who died and found APTT

Table 4
Univariate analysis of laboratory test indicators.

Clinical manifestations	Death group (20 cases)	Survivor group (40 cases)	Wald χ^2 value	*p*-Value	OR (95% CI)
WBC $<2.0 \times 10^9$/l	7 (35)	15 (37.5)	0.047	0.829	0.891 (0.248–3.055)
PLT $<30 \times 10^9$/l	4 (20)	2 (5)	3.354	0.077	4.750 (0.789–28.595)
L% <20%	15 (75)	14 (35)	8.142	0.003	5.571 (1.674–18.548)
ALT ≥200 U/l	7 (35)	8 (20)	2.427	0.119	1.531 (0.896–2.616)
AST ≥400 U/l	10 (50)	7 (17.5)	6.121	0.013	2.049 (1.161–3.617)
ALB <35 g/l	12 (60)	29 (72.5)	0.924	0.336	2.250 (0.431–11.758)
TBil ≥20.5 μmol/l	6 (30)	4 (10)	3.532	0.060	3.857 (0.944–15.763)
LDH ≥1000 U/l	8 (40)	2 (5)	8.617	0.003	3.068 (1.451–6.486)
CK ≥1000 U/l	10 (50)	10 (25)	7.873	0.005	2.397 (1.302–4.414)
CK-MB ≥100 U/l	6 (30)	4 (10)	3.532	0.060	3.857 (0.944–15.763)
SCr ≥130 μmol/l	7 (35)	3 (7.5)	6.179	0.013	6.641 (1.492–29.551)
BUN ≥6.4 mmol/l	14 (70)	14 (35)	6.179	0.013	4.333 (1.364–13.770)
APTT ≥40 s	14 (70)	10 (25)	10.195	0.001	7.000 (2.120–23.113)
PT ≥14 s	13 (65)	8 (20)	8.774	0.003	2.511 (1.365–4.616)
DD ≥2.7 mg/l	4 (20)	4 (10)	1.114	0.291	2.250 (0.499–10.143)
CRP ≥20 mg/l	8 (40)	4 (10)	8.798	0.003	3.164 (1.478–6.773)
Na <136 mmol/l	12 (60)	8 (20)	6.621	0.010	4.5 (1.431–14.150)
Ca <2.1 mmol/l	18 (90)	34 (85)	0.264	0.601	1.588 (0.290–8.687)

OR, odds ratio; CI, confidence interval.

Table 5
Multivariate logistic regression analysis of risk factors for death.

Clinical manifestations	β-value	S*x* value	Wald χ^2 value	*p*-Value	OR (95% CI)
Neurological signs	3.442	0.954	13.006	0.000	31.247 (4.813–202.853)
Hemorrhagic manifestations	3.008	1.167	6.644	0.010	20.251 (2.056–199.443)
Disturbance of consciousness	2.732	1.006	7.377	0.007	15.359 (2.139–110.268)
Na <136 mmol/l	1.664	0.741	5.037	0.025	5.280 (1.235–22.575)
CRP ≥20 mg/l	0.971	0.451	4.629	0.031	2.641 (1.090–6.396)
APTT ≥40 s	1.795	0.726	6.109	0.013	6.018 (1.450–24.975)
SCr ≥130 μmol/l	1.913	0.953	4.034	0.045	6.776 (1.047–43.840)

OR, odds ratio; CI, confidence interval.

prolongation in the first week of illness in both groups; however, the prolongation was much more obvious in the group of patients who died in the course of 8–10 days. The authors also reported that from day 11 to day 13, the prolonged APTT and PT were significantly correlated with the risk of death. In the present study, single-variable analysis showed significantly greater prolongation of PT and APTT and a higher incidence of hemorrhagic manifestations in the death group than in the survivor group in the early stage of illness. On multivariate analysis, APTT prolongation and hemorrhagic manifestations were independent predictors of death. This finding is consistent with that of Deng et al. (2013). Therefore, a close watch for hemorrhagic manifestations and changes in APTT and PT in the early stages of the disease is advisable, as they could predict a deterioration in the patient's condition. The cause of coagulopathy in SFTS is still unclear. Some researchers have suggested that a decrease in coagulation factor synthesis due to SFTSV-induced acute liver injury may be responsible (Zhang et al., 2012).

Liver function damage plays a vital role in the pathogenesis of SFTS (Yu et al., 2011). Increased serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and LDH, and decreased serum albumin are common findings in SFTS patients. An increase in AST/ALT ratio indicates serious liver parenchymal damage. Some studies have indicated that elevated AST may be an indicator of a poor outcome in SFTS (Cui et al., 2012). However, in the present study, AST elevation was not a risk factor for mortality; this is consistent with the results of Zhao et al. (2016) who also analyzed the early indicators of the prognosis. This may be because abnormal liver function is prevalent in the early course of the disease, while more severe liver function damage is found in the middle to late stages in patients who die. Obviously an increased AST was found in SFTS patients who died, indicating that it may be an indicator of death.

Previous studies have suggested that the kidneys may be a target of the SFTSV (Jin et al., 2012). Kidney damage usually occurs in the later stages of SFTS (Cui et al., 2014). In the present study, increased serum creatinine in the initial stage was a risk factor for SFTS death. The increase in serum creatinine was not marked, but it was sufficient to suggest the existence of some renal parenchymal damage (which has not yet reached the standard of acute renal failure), but the damage is likely high in the renal afferent arterioles and glomerular basement membrane. Increased BUN has also been found to be a risk factor for death (Cui et al., 2012); however, it must be noted that BUN only increases when the glomerular filtration rate is ≤50% of normal, and therefore its sensitivity to early lesions is far less than that of serum creatinine.

Electrolyte imbalances, especially hyponatremia and hypocalcemia, are common in SFTS. In the present study, hyponatremia was found to be an independent risk factor for death in SFTS. You et al. (2014) also believed that hyponatremia is related to more serious disease and poorer outcomes in SFTS patients. In the present study, patients in both the death and survivor groups had reduced serum calcium in the early stage of disease. Although it was not selected by multivariate analysis in this study, it is considered to be an indicator of disease severity (Zivin et al., 2001). Severe hypocalcemia is an independent risk factor for death in critically ill patients (Egi et al., 2011). Therefore, the clinician should pay close attention to serum calcium levels during the treatment of SFTS patients.

Viral infections generally cause mild elevation or no change in CRP. This is because viral proliferation occurs mostly in the cells; there is no damage to the cell membrane and therefore no phospholipoprotein exposure to trigger CRP production. However, severe viral infections may cause extensive damage to the tissues and cause a substantial rise in CRP in the early stages of disease (Suberviola et al., 2012; Liang et al., 2010; Wang and Jiang, 2011). This study found an increased CRP in the early stage of SFTSV infection to be an indicator of a worse outcome; this may have been because more serious tissue damage occurred in these patients.

Older age and the presence of underlying diseases have been reported to be associated with increased mortality in SFTS (Gai et al., 2012; You et al., 2014; Zhang et al., 2012; Yang et al., 2016). However, in the present study, age and underlying diseases were not independent risk factors for death from SFTS. These results are consistent with those of Sun et al. (2016). The mean age of patients was >60 years in both groups in the present study, and most patients were farmers by occupation. This was probably because the young had migrated to the cities in search of work, while the elderly continued with agricultural work and therefore had an increased risk of exposure to the SFTSV (Peng et al., 2010). Older age is associated with an increased risk of various other diseases and with reduced immunity, which may also increase the risk of morbidity and mortality (Ding et al., 2014). Therefore, special efforts must be made for the prevention of SFTS in the elderly and close attention must be paid to risk factors during treatment.

All patients in this study received ribavirin on admission, which has been shown to inhibit the SFTSV in vitro (Shimojima et al., 2014). However, follow-up studies have found that ribavirin does not reduce mortality in SFTS (Liu et al., 2013). Shimojima et al. found that the combination of a type I or II interferon with ribavirin markedly reduced the SFTSV viral load, and this could be a potential new approach for pharmacotherapy of SFTS (Shimojima et al., 2015).

The infusion of platelets improves coagulation function in patients with SFTS and is considered to have a positive effect on the prognosis (Chen et al., 2017). However, due to factors such as the cost of treatment, the compliance of patients with blood products is not high, which affects the therapeutic effect to some extent.

A limitation of this study is that all patients were selected from one general hospital; a selection bias is therefore likely to be present. Multicenter studies involving different grades of hospitals from different regions are necessary to confirm the findings. Regarding the matching factors, using sex and age as matching factors is more conducive to reveal the risk factors. However, the number of confirmed cases was limited, and the majority of the patients were in the older age group.

In this study, the majority of research variables were obtained from clinical and laboratory examinations and were therefore objective and accurate. This avoids interference due to inaccurate patient recall. In the selection of study subjects, the patients were matched by sex, and the control group was a good match. Therefore, the results of this study can be extrapolated to a certain extent.

In conclusion, neurological signs and disturbances of consciousness, hemorrhagic manifestations, hyponatremia, prolonged APTT, and increased CRP and serum creatinine at an early stage are risk factors for mortality in SFTS patients. In future studies, patient clinical and laboratory indicators could be monitored dynamically during the different stages of the disease course in order to evaluate the warning indicators of SFTS in a comprehensive way.

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Ethics statement

This study did not involve human participants or human experimentation. The only human materials used were blood samples collected from SFTS patients for public health purposes, and written informed consent for the use of their clinical samples was obtained from these patients. This study was approved by the Ethics Review Committee of the Yantai Center for Disease Control and Prevention, and the methods were carried out in accordance with the approved guidelines.

Conflict of interest

All authors declare no competing interests.

Author contributions

Xiaowen Xu performed part of the data collection, statistics, and writing of the paper. Zhenlu Sun performed part of the experiment and writing of the paper. Jingyu Liu, Jianjun Zhang, Tao Liu, and Xiaodong Mu all performed the data collection and statistics. Mei Jiang contributed to the revision of the paper.

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