Risk factors of community-associated infections in Chinese patients with diabetes: A meta-analysis

Guang-Dan Zhao, Jia-Ying Sun, Ming-Jing Zhao, Ling-Ling Wang, Fang-Zhi Li, Shuo Liu, Dan Liu, Xiao-Ge Wang

Department of Respiration, the Fourth Hospital Affiliated to China Medical University, Shenyang, China

ABSTRACT

Objective: To identify the common sites and risk factors of community-associated infections in Chinese patients with diabetes. **Materials and Methods:** The Wanfang, CNKI, PUBMED and VIP databases restricting to Chinese patients with diabetes were queried without restriction to time period. Randomized controlled trials (RCTs) on the risk factors of community-associated infections in Chinese patients with diabetes were considered. Polled odd ratios (OR) and 95% confidence intervals (95% CI) were used for each factor in fixed or random-effect meta-analyses. **Results:** Twelve studies were identified that investigated seven risk factors of community-associated infections in Chinese patients with diabetes. The average infection incidence was 39.55%. The respiratory tract and urology tract were the predilection sites. Meta-analysis results are as follows: Diabetic patients with chronic complications (OR: 1.63; 95% CI 1.45-1.82), advanced age (OR: 1.30; 95% CI 1.19-1.42), longer duration (OR: 1.47; 95% CI 1.35-1.61) or ketoacidosis (OR: 1.37; 95% CI 1.13-1.66) were more prone to suffer from infections. Those with better glycemic control (OR: 0.68; 95% CI 0.61-0.76) or males (OR: 0.69; 95% CI 0.64-0.75) were less prone to suffer from infections. **Conclusion:** Chinese patients with diabetes had a high incidence of community-associated infections. We should highlight the risk factors that might provide a reference for the same.

Key words: Community-associated infections, diabetes, risk factors

Address for Correspondence:
Dr. Xiao-Ge Wang,
Department of Respiration, the Fourth Hospital Affiliated to China Medical University, Shenyang - 110 032, China.
E-mail: cm4hwxgn2005@126.com

Access this article online
Website: www.intern-med.com
DOI: 10.4103/2224-4018.154290
Quick Response Code:

INTRODUCTION

Diabetes mellitus is one of the most prevalent conditions and leading causes of mobility worldwide. It is not solely a disturbance of glucose metabolism but, instead, is a chronic inflammatory condition characterized by multiple alterations in lipid profiles and neuropathy as well as chronic vascular and renal diseases. Type 2 diabetes mellitus used to be mainly a disease of aged people, but early-onset diabetes is increasingly being diagnosed in young adults. The incidence of diabetes was 26.9% for people older than 65 years in the USA, compared with 11% in China.[1]

It is a common belief that people with diabetes are generally more susceptible to infections.[2] Over the past decades, several attempts have been made to investigate the association between risk factors and infections in Chinese patients with diabetes, but still there have been no systematic reviews of the published literature on the same.

In this study, we aimed to observe the incidence and common infection sites of Chinese patients with diabetes and estimate the association between the risk factors and infections in those patients.

MATERIALS AND METHODS

Searching

Four databases (Chinese academic journals full-text database CNKI, Wanfang database, PUBMED and VIP database) were searched for relevant articles using the search terms of diabetes, infection and risk factor; study subjects were limited to Chinese.

Selection

Two researchers independently reviewed the titles and abstracts of all relevant citations and then retrieved all potentially relevant articles identified by either reviewer. The following selection criteria were applied to the full manuscripts in duplicate and independently:

1. Design: Cohort study or case — control study;
2. Population: Chinese patients with diabetes;
3. Infectious type: Community acquired;
4. Outcomes: Incidence, risk factors and mortality.

We excluded the following studies: Reviews, no risk factor, no control group, could not get available results, disagreement were resolved by discussion.

Data extraction

The titles, abstracts and full articles were reviewed independently by two authors. Abstracted data included type of study, first author, year of publication, study population, characteristics, incidence of infection and mortality.

Statistical analysis

Statistical analyses were performed using the Stata 11.0 software to quantify the risk factors of infections. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using the Mantel–Haenszed fixed-effect or the Dersimonian–Laird random-effects models, and Z-statistic test for over effect was performed. $P < 0.05$ was considered to be statistically significant. For all analyses, the fixed-effect model was used only when there was no heterogeneity between reports; otherwise, the random-effect model was used. The heterogeneity between reports was assessed by using the I^2 statistic test, with $I^2 > 50\%$ indicating heterogeneity. The Beggs and Egger method were used to monitor publication bias and Funnel plots were drawn.

RESULTS

The selection process applied to identify relevant studies included in the meta-analysis is shown by a flow diagram [Figure 1]. Through searching the CNKI, Wanfang, PUBMED and VIP databases, 1503 articles were retrieved; 1471 articles were excluded by reading the titles and extracts, 20 of them were extracted by reading the whole paper and 12 trials were included in the present meta-analysis.[3-14]

Characteristics of the included studies

The time of publication was from 1988 to 2012 and all of them were case - control studies. The number of diabetics with infections was 3287 and that of diabetics without infections was 8311, and all trials were published in Chinese [Table 1].

Incidence of infections in Chinese patients with diabetes

The incidence of infections in Chinese patients with diabetes ranged from 22.12% to 55.86%, on average

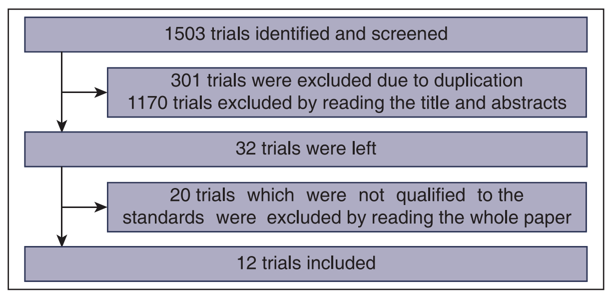

Figure 1: Selection of studies for review

Table 1: Characteristics of included studies

First author	year	Risk factors	Setting	cases/controls	NOS
Shan Ping	2012	Age, duration and gender	In all hospital	36/66	7
Nan Guo-zhen	2000	Age, duration, glycelnic control and gender	In all hospital	891/930	8
Ye Qi	2006	age, duration, glycelnic control, gender, ketoacidosis, chronic complications	In all hospital	229/344	8
Wu Hong-yan	2001	age, duration, glycelnic control, gender, chronic complications	In all hospital	118/218	8
Wu He-mei	2010	age, duration, glycelnic control, chronic complications	In all hospital	339/282	8
Yao Jun-li	1999	age, duration, gender, diabetes type, ketoacidosis, chronic complications	In all hospital	269/577	8
Zhang Hua-ping	2002	age, duration, gender, diabetes type, ketoacidosis, chronic complications	In all hospital	488/1039	7
Xu Gong-fu	1999	gender	endocrinology unit	115/405	8
Wang Xiao-li	2012	age, duration, glycelnic control, gender, ketoacidosis	In all hospital	61/127	8
Wang Ai-min	2003	age, duration, gender, chronic complications	In all hospital	471/714	8
He Dong-feng	2003	age, duration, glycelnic control, gender, chronic complications	In all hospital	108/204	7
Gao Li-min	1988	age, duration, glycelnic control, gender, ketoacidosis	endocrinology unit	162/128	8

39.55%. The respiratory tract (40.74%) and the urology tract (27.35%) were the most common sites [Table 2]. Five of the studies[3,4,8,13,14] analyzed gender differences in diabetics with urinary tract infection, which found that females were two to eight times more than males.

Risk factors

Seven risk factors were analyzed, including age, duration, glycelmic control, gender, diabetes type, ketoacidosis and chronic complications. Of them, three were studied in a fixed effects model (diabetes type, ketoacidosis and chronic complications) and four were studied in a random-effects models (age, duration, glycelmic control and gender).

Chronic complications

Seven documents[5-9,12,13] were included. There were 1371 patients in the Exposed group (diabetics with chronic complications) and 3113 patients in the Unexposed group (diabetics without chronic complications). There was a significant increased risk of infection among patients in the Exposed group (OR: 1.63, 95% CI 1.45-1.82, $I^2 = 3.3\%$, $n = 7$, $Z = 8.3$ $P = 0.000$). There was statistical significance and the Begg's test, Egger's test and funnel chart were used to monitor publication bias. All sensitivity analyses were used to observe the effect on the results of each article [Figures 2 and 3].

Age

Eleven documents[3-9,11-14] were included; patients who were older than 60 years were included in the Exposed group and others were included in the Unexposed group. In the Exposed group, the risk of infection was increased (OR: 1.30, 95% CI 1.19-1.42, $I^2 = 86.3\%$, $n = 11$, $Z = 5.95$, $P = 0.000$) and there was a statistical significance [Figure 4].

Duration

Eleven documents were included;[3-9,11-14] patients whose durations were more than 5 years were included in the Exposed group and others were included in the Unexposed group. As presented, patients in the Exposed group were more prone to suffer from infections (OR: 1.47, 95% CI 1.35-1.61, $I^2 = 54.7\%$, $n = 11$, $Z = 8.92$, $P = 0.000$) [Figure 5].

Glycemic control

Seven papers were included;[4-7,11,13,14] patients with good glycelmic control were included in the Exposed group and others were included in the Unexposed group. As shown in this study, patients of the Exposed group were not prone to suffer from infections (OR: 0.68, 95% CI 0.61-0.72, $I^2 = 78\%$, $n = 7$, $Z = 6.71$, $P = 0.000$) and there was a statistical significance [Figure 6].

Table 2: The incidence of infections of included studies

First author	Infection cases	urology tract male:female	Respiratory tract	skin and soft tissue	hepatobiliary system	Gastrointestinal system	Mouth Mucosa	tuberculosis	septicemia	Fungal infection	Diabetic foot infection	Genitale system	Others	infection rate
Shan Ping*	36	13 (3:10)	11	10		9							6	35.29
Nan Guo-zhen	891	258 (30:228)	370	89	48			96					30	48.93
Ye Qi*	229	83	165	51	8		3	18					17	39.97
Wu Hong-yan	118	36	49	4	6	6	2	8			3		4	35.12
Wu He-mei*	339	30	171	30	27	12	9	45		12			12	54.59
Yao Jun-li*	269	52 (15:37)	135	24	49		6	22	5		13	4	23	31.8
Zhang Hua-ping*	488	72	124	36	27	32		96	10		42	42	41	31.96
Xu Gong-fu*	115	47	51		2			11		5			15	22.12
Wang Xiao-li	61	22	15	9		8							7	34.27
Wang Ai-min	471	210	163	29				32			37			39.75
He Dong-feng	108	31 (4:27)	46	6	5		4	8					8	34.62
Gao Li-min	162	45 (5:40)	39	14	11	12	9	19	4	2			7	55.86

*Some patients had two or more kinds of infections, which all listed; the rest studies listed the main infection

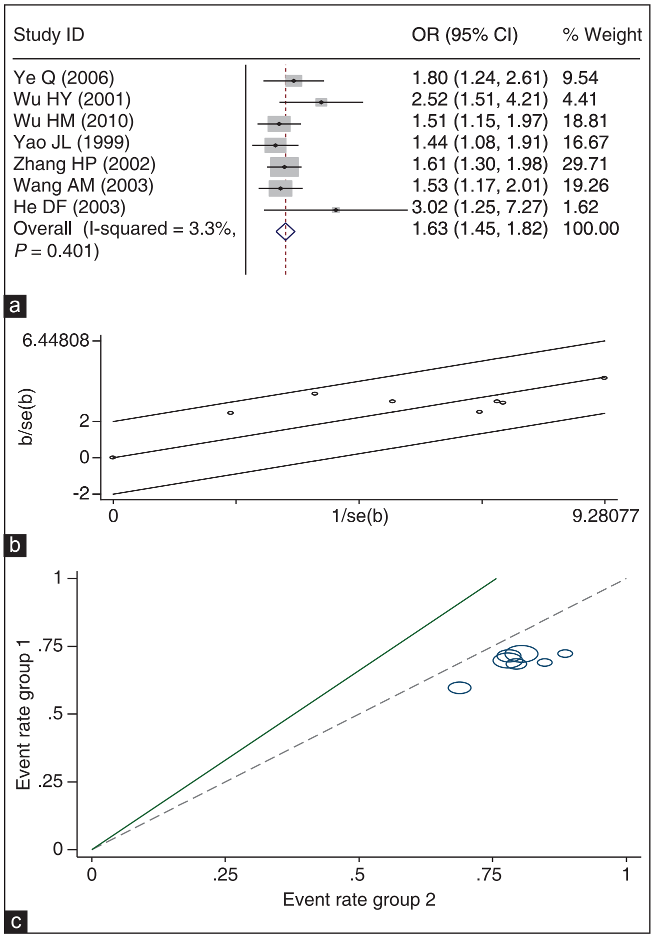

Figure 2: The forest plot (a), Galbraith plot (b) and L'Abbe plot (c) of the influence of complications to incidence of community-acquired infections of diabetics

Gender

Male diabetics were included in the Exposed group and females were included in the Unexposed group. A total of 12 documents were included.[3-14] The incidence of infections was lesser in the Exposed group than in the Unexposed group (OR: 0.69, 95% CI 0.64-0.75, $I^2 = 75.9\%$, $n = 12$, $Z = 8.86$, $P = 0.000$) and there was a statistical significance [Figure 7].

Ketoacidosis

Four papers were included.[5,8,11,14] Patients with ketoacidosis were included in the Exposed group and those without ketoacidosis were included in the Unexposed group. The result showed that patients in the Exposed group were more prone to suffer from infections (OR: 1.37, 95% CI 1.13-1.66, $I^2 = 49.9\%$, $n = 4$, $Z = 3.24$, $P = 0.001$) and there was a statistical significance [Figure 8].

Diabetes type

Three documents were included;[5,8,9] patients with type 1 diabetes were included in the Exposed group and those with type 2 diabetes were included in the Unexposed group.

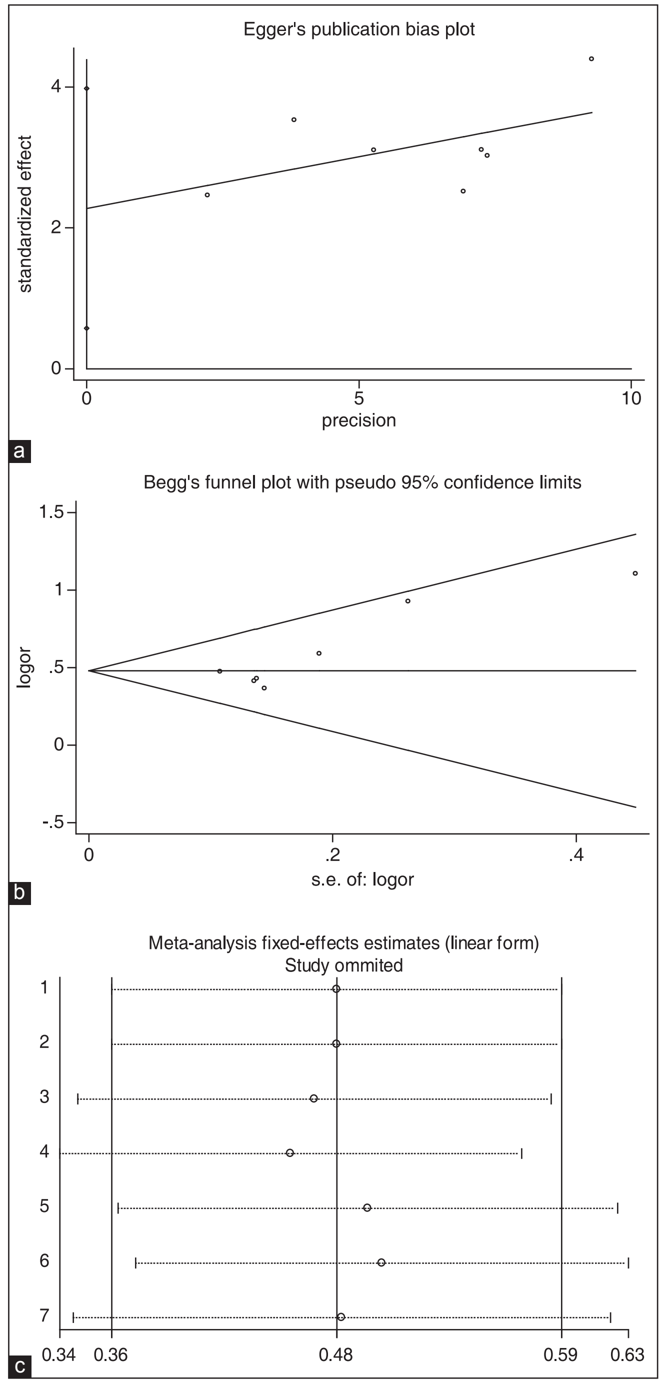

Figure 3: (a) The funnel plot of the influence of complications to incidence of community-acquired infections of diabetics through Begg's test; (b) The funnel plot of the influence of complications to incidence of community-acquired infections of diabetics through Egger's test; (c) The influence of each document for the outcome of the Meta-analysis

The incidence of infections had no difference (OR: 0.87, 95% CI 0.62-1.23, $I^2 = 4.2\%$, $n = 3$, $Z = 0.75$, $P = 0.432$) [Figure 9].

Mortality

Diabetic patients with infections were classified as the Exposed group and others were classified as the Unexposed

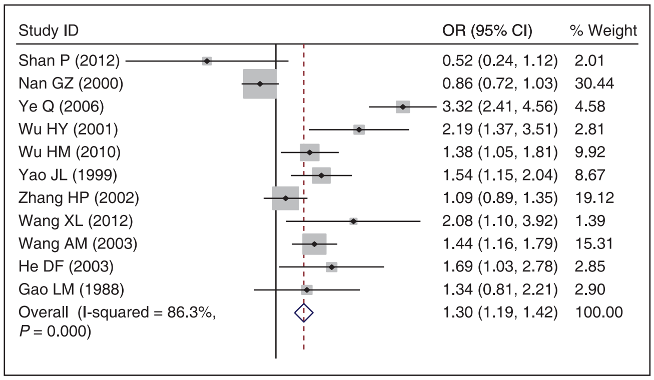

Figure 4: Forest plot of age and incidence of community-acquired infections of diabetes

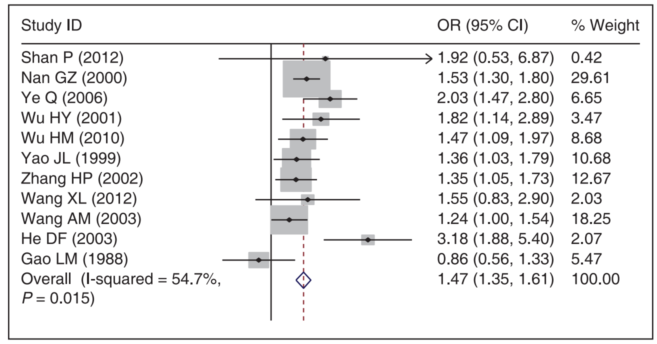

Figure 5: Forest plot of Course of disease and incidence of community-acquired infections of diabetes

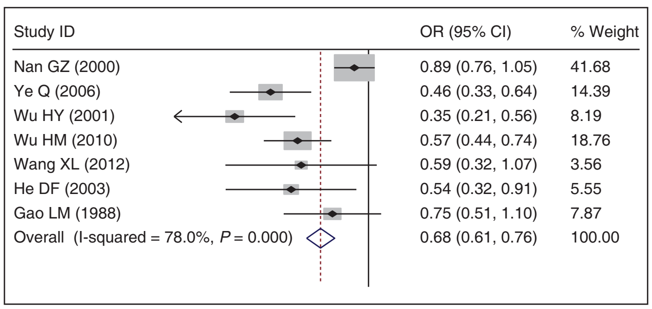

Figure 6: Forest plot of glycelnic control and incidence of community-acquired infections of diabetes

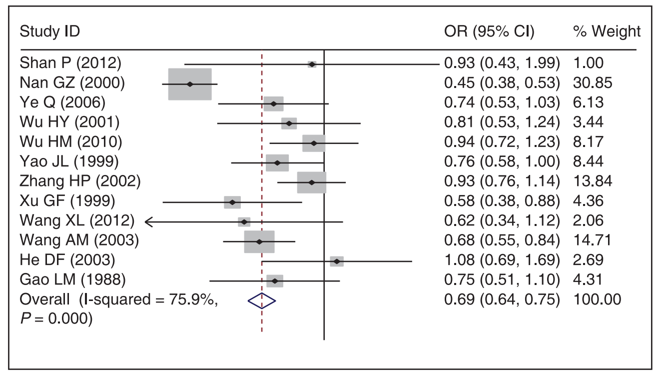

Figure 7: Forest plot of sex and incidence of community-acquired infections of diabetes

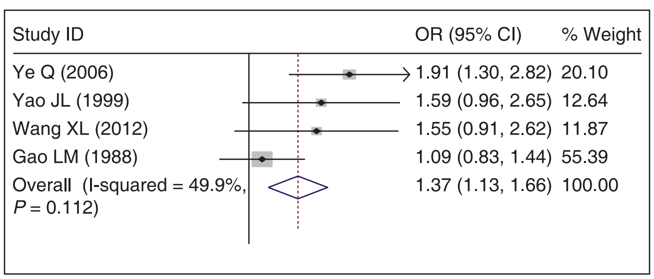

Figure 8: Forest plot of ketoacidosis and incidence of community-acquired infections of diabetes

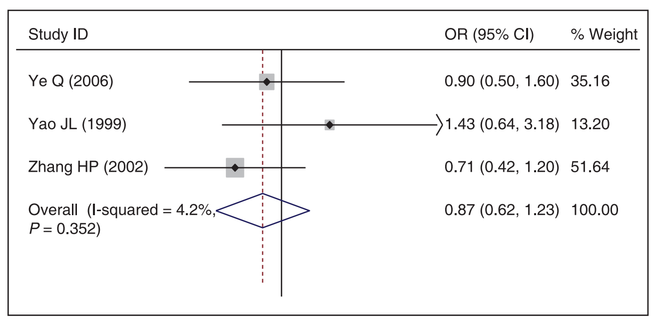

Figure 9: Forest plot of types and incidence of community-acquired infections of diabetes

group. A total of three documents were included.[6,8,11] The incidence of mortality was high in the Exposed group (OR: 3.2, 95% CI 2.0-5.13, $I^2 = 36.7\%$, $n = 3$, Z = 4.84, $P = 0.000$) [Figure 10].

DISCUSSION

In clinical work, we found that people with diabetics were prone to suffer from infections, some of who were hard to treat and finally died. A recent study analyzed the death rates of more than 800,000 participants and identified the presence of diabetes as a major risk factor for premature death. The study showed an average 6 years earlier death of a 50-year-old patient with diabetes as compared with a nondiabetic person of the same age. In detail, the study showed that beside cardiovascular causes and cancer, infectious diseases substantially contribute to the reduced life expectancy of diabetic people.[1,2,15,16] Diabetics were prone to suffer from infections, the mechanisms of which may be as follow:[17-19]

1. The body's defense system was weakened: Each stage of the body's defense to invading microorganisms was suppressed in diabetics, including leukocyte chemotaxis, phagocytosis, weakened intracellular bactericidal effect, neutralized toxin, decreased serum opsonin and cellular immune function, etc.,
2. Complications of diabetes:
   a. Urinary retention and usually catheterization caused by neurogenic bladder could be complicated by urinary tract infection;

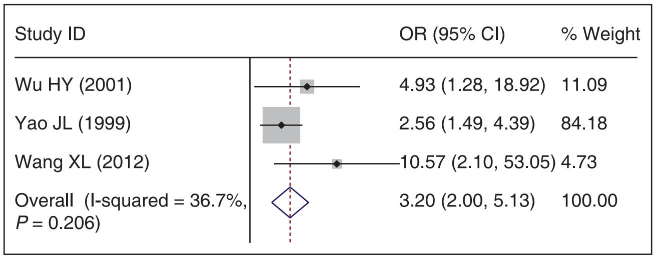

Figure 10: Forest plot of the mortality between infection group and non-infection group

b. Peripheral neuropathy and sensory disturbances could cause the damage of skin, making it hard to detect, finally developing to infection;
c. Because of diabetic vascular disease, surrounding tissue's blood flow was decreased, where there were hypoxia, anaerobic bacteria could grow easily, and it also changed the oxygen-dependent bactericidal action of white blood cells,

3. High sugar: Some bacteria grow better in favor of a high-sugar environment,
4. In diabetics, sugar, protein and fat metabolism were disordered.

If glycemic control is unstable, the body's resistance is weakened, coupled with malnutrition and dehydration, making diabetics more vulnerable to infection. The glycemic control was hard in infected patients and high blood sugar further aggravated the infection, which was a vicious cycle. To study about common infection in diabetics and the risk factors can be conducive to clinicians to judge the patient's condition, to treat them timely and correctly and, finally, to reduce patient's pain, financial burden and mortality.

In the 12 comprehensive documents, we observed that the rate of community-acquired infections in Chinese patients with diabetes ranged from 22.12% to 55.86%, with an average of 39.55%. The common sites of infection and infection rates were as follows: Respiratory tract (40.74%), urinary tract (27.35%), tuberculosis (10.80%), skin and mucous membranes (9.19%) and hepatobiliary (5.57%). In foreign studies, the incidence of infection was slightly lower (30.4%) and skin and mucous membrane infections and urinary tract infections were common, followed by respiratory tract infections.[20] This difference may be related to race, attendance rates, population surveys and other relevant factors. Risk factors of infection in diabetics included gender, age, disease duration, glycemic control and complications, etc. The results of this study showed that there was a large probability of infection in patients who were female, elder, with longer duration, poor glycemic control and diabetic complications, regardless of the type of diabetes. Studies have shown that gender is an independent risk factor for diabetics with urinary tract infection, which is probably due to the structural characteristics of the female urinary tract. High blood sugar is an independent risk factor for lung infections, which may be because of the increasing secretion of sugar by the respiratory mucosa, which increases bacterial colonization infection. Vascular lesions were the risk factors of gastrointestinal infections and lipids were the risk factors of skin infections. However, because of data limitations, we only observed that the incidence of urinary tract infection in females was two to eight times higher than that in male diabetic patients.

In diabetics, the risk of bacterial colonization infection increased, particular intestinal bacteria. Pathogenic examination of sputum, urine and blood showed that the bacteria were mostly Gram negative bacilli and the detection rate ranged from 43.2% to 80%, which was similar to foreign reports. The common bacteria detected were *Escherichia coli* and *Klebsiella pneumonia*.[21,22] Because of the special immune status, patients with diabetes were easier to merge resistant and *Mycobacterium tuberculosis*. Because only one pair of the studies involved described pathogens, no further analysis was conducted. Infected patients with diabetes compared with noninfected patients had high mortality (OR: 3.2, 95% CI: 2.00, 5.13, $Z = 4.84$, $P = 0.000$) and there was a statistical significance, which is similar to foreign researches.[1,23-25]

In this study, the inclusion and exclusion criteria were strictly limited, case — control studies were included in the study and, therefore, the results are more reliable. In addition, a number of databases queried the literatures to avoid missing any relevant studies. Like any observational study, the findings of the studies incorporated into this meta-analysis could have been biased by methodological flaws, including issues of control selection, misclassification of both outcomes and exposures and residual confounding. Further in-depth follow-up studies are needed.

In our study, the average incidence of infection in diabetics was 39.55% and the common sites were the respiratory tract, urinary tract and skin and soft tissue. In general, diabetics who were female, elder, with longer duration, poor glycemic control and complications were more susceptible to infection.

REFERENCES

1. Emerging Risk Factors Collaboration, Seshasai SR, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, Sarwar N, *et al*. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 2011;364:829-41.

2. Knapp S. Diabetes and infection: Is there a link? -A mini-review. Gerontology 2013;59:99-104.
3. Shan P, Shi RX, Li XC , Lv L, Yang JH. Analysis on common factors of diabetes complicated with infections and its countermeasures. Pract Prev Med 2012;19:1380-1.
4. Nan GZ, Zhou H, Zhang LH, Wang SY, Sun BJ. Clinical analysis on 891 cases of complicated infection with diabetes mellitus. J Hebei Med Univ 2000;21:70-1.
5. Ye Q. A Clinical relative factors analysis on 229 cases of complicated infection with diabetes mellitus. Med World 2006;12:10-2.
6. Wu HY, Xiang MZ. Clinical analysis of 118 case of diabetes with infection. Practi Clin Med 2001;2:50-1.
7. Wu HM. Clinical analysis of type 2 diabetes complicated by infection. Chin J Mod Doct 2010;48:115.
8. Yao JL. Clinical type of infection and risk factor analysis in diabetic patients. Chinese Journal of Prevention and Control of Chronic Non-Communicable Diseases 1999;7:147-9.
9. Zhang HP. Analysis of Diabetes complicated by infection and its risk factors. Clin Med China 2002;18:809-10.
10. Xu GF, Huang Q, Zou DJ, Xu MJ. Diabetes and infection in clinical analysis. Acad J Sec Mil Med Univ 1999;20:821-2.
11. Wang XL, Zhang J. Analysis of the risk factors of infection among patients with diabetes mellitus. Chin J Microecol 2012;24:257-8.
12. Wang AM, Lei MX, Liu ZY, Zhang J, Chen ZX, Sun SG. Clinical analysis of diabetic patients with infection. Bull Hunan Med Univ 2003;28:541-2.
13. He DF, Wu SH. Infection factors analysis among diabetics. Shanghai J Prev Med 2003;15:406-8.
14. Gao LM, Bian WB. Clinical analysis of 162 cases of diabetes with infection. Chin J Endocrinol Metab 1988;4:178-9.
15. Bertoni AG, Saydah S, Brancati FL. Diabetes and the risk of infection-related mortality in the U.S. Diabetes Care 2001;24:1044-9.
16. Yende S, van der Poll T, Lee M, Huang DT, Newman AB, Kong L, *et al*. The influence of pre-existing diabetes mellitus on the host immune response and outcome of pneumonia: Analysis of two multicentre cohort studies. Thorax 2010;65:870-7.
17. Chen HS, Su LT, Lin SZ, Sung FC, Ko MC, Li CY. Increased risk of urinary tract calculi among patients with diabetes mellitus — a population-based cohort study. Urology 2012;79:86-92.
18. Jalil A, Barlaam PI, Fung BK, Ip JW. Hand infection in diabetic patients. Hand Surg 2011;16:307-12.
19. Berrou J, Fougeray S, Venot M, Chardiny V, Gautier JF, Dulphy N, *et al*. Natural killer cell function, an important target for infection and tumor protection, is impaired in type 2 diabetes. PLoS One 2013;8:e62418.
20. Rawat V, Singhai M, Kumar A, Jha PK, Goyal R. Bacteriological and resistance profile in isolates from diabetic patients. N Am J Med Sci 2012;4:563-8.
21. Feng Y, Zuo Z, Gong XN. Monitoring results analysis of pathogens infected in diabetic patients. Chin J Nosocomiol 2010;20:2168-70.
22. Thomsen RW, Hundborg HH, Lervang HH, Johnsen SP, Schønheyder HC, Sørensen HT. Diabetes mellitus as a risk and Prognostic Factor for community-acquired bacteremia due to enterobacteria: A 10-Year, population-based study among adults. Clin Infect Dis 2005;40:628-31.
23. Muller LM, Gorter KJ, Hak E, Goudzwaard WL, Schellevis FG, Hoepelman AI, *et al*. Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus. Clin Infect Dis 2005;41:281-8.
24. Marble A, White HJ, Fernald AT. The nature of the lowered resistance to infection in diabetes mellitus. J Clin Invest 1938;17:423-30.
25. Zubair M, Abida M, Jamal A. Clinicobacteriology and risk factors for the diabetic foot infection with multidrug resistant microorganisms in North India. Biol Med 2010;2:22-34.

How to cite this article: Zhao GD, Sun JY, Zhao MJ, Wang LL, Li FZ, Liu S, *et al*. Risk factors of community-associated infections in Chinese patients with diabetes: A meta-analysis. J Transl Intern Med 2015;3:17-23.
Source of Support: Liaoning Provincial Science and Technology Department Project (20132253030); Technology Bureau of Shenyang (F12-277-1-71), **Conflict of Interest:** We declare that there is no conflict of interest in the paper.