# Clinical and bacteriological influence of diabetes mellitus on deep neck infection: Systematic review and meta-analysis

Hiroshi Hidaka, MD, PhD,[1] *Takuhiro Yamaguchi, PhD,[2] Jun Hasegawa, MD, PhD,[1] Hisakazu Yano, MD, PhD,[3] Risako Kakuta, MD,[1,3] Daiki Ozawa, MD,[1,3] Kazuhiro Nomura, MD, PhD,[1] Yukio Katori, MD, PhD[1]

[1]Department of Otolaryngology–Head and Neck Surgery, Tohoku University Graduate School of Medicine, Sendai, Japan, [2]Division of Biostatistics, Tohoku University Graduate School of Medicine, Sendai, Japan, [3]Department of Infection Control and Laboratory Diagnostics, Internal Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan.

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**ABSTRACT:** *Background.* Diabetes mellitus has been recognized as the most common systemic disease associated with deep neck infection. We report the first systematic review and meta-analysis of the influence of diabetes on clinical and bacteriological characteristics of deep neck infection.

*Methods.* Articles were retrieved from PubMed, EMBASE, and the Japan Medical Abstracts Society database. A critical review of 227 studies identified 20 studies eligible for quantitative synthesis.

*Results.* Diabetes was associated with higher prevalences of multispace spread of infection, complications, and failure to identify pathogenesis, with risk ratios (RRs) of 1.96, 2.42, and 1.29, respectively. Bacteriologically, patients with diabetes showed a higher prevalence of culture identification of *Klebsiella pneumoniae* (RR, 3.28), and lower prevalences of *Streptococcus* spp. (RR, 0.57) and anaerobes (RR, 0.54).

*Conclusion.* Deep neck infection with diabetes differs from that without in several clinical aspects. Again, bacteriological differences imply that diabetic infections might be populated by different bacterial flora.  *Head Neck* **37:** 1536–1546, 2015

**KEY WORDS:** **deep neck infections, diabetes mellitus, complications, systematic review, meta-analysis**

## INTRODUCTION

Deep neck infection represents a serious disorder in the potential spaces and fascial planes of the neck, developing as either abscess formation or cellulitis.[1–3] Despite the administration of antibiotics and ongoing improvements in dental care, these infections can still cause significant morbidity, including airway compromise, pneumonia, mediastinal involvement, pericarditis, emphysema, jugular vein thrombosis, arterial erosion, and cranial extension.[4–7]

Diabetes mellitus has been recognized as the systemic disease most commonly associated with deep neck infection. Huang et al[8] reported that patients with deep neck infection who have diabetes usually display a clinical picture distinct from that in patients without diabetes, and thus should be treated in a different manner. We recently reported that the presence of diabetes in patients with deep neck infection is associated with aggravating and widespread inflammation.[3,9] However, studies addressing these topics have been retrospective case series and case-control cohorts, and several questions regarding the influence of hyperglycemia on deep neck infection have not been fully explored.[10] Thus, the goal of the present study was to perform a systematic review and meta-analysis to clarify the influence of diabetes on clinical outcomes and bacteriological characteristics of deep neck infection.

***Corresponding author:** H. Hidaka, Department of Otolaryngology–Head and Neck Surgery, Tohoku University Graduate School of Medicine, 1-1 Seiryomachi, Aoba-ku, Sendai 980-8575, Japan. E-mail: ZAY00015@nifty.com

## MATERIALS AND METHODS

### Search strategy and study selection

A systematic search of the literature for articles published between 1990 and May 2013 was performed using the PubMed, Ovid, and Japan Medical Abstracts Society databases, with no language restrictions. We used the following search terms: "deep neck infection" OR "neck abscess" AND "diabetes mellitus." Studies that were acceptable for inclusion were those addressing differences in clinical or bacteriological characteristics according to the presence of diabetes in deep neck infections and that included more than 20 patients. All studies were independently screened for eligibility by 2 reviewers in compliance with Cochrane guidance.[11] We screened duplicate collections based on the same data sets; namely, where data overlapped with data from other included studies. In such studies, only the most recently published report reviewing the largest number of cases was included. The only exceptions were studies by Huang et al[2,8] from 2005 and 2006. The former study addressed both clinical and bacteriological aspects of 185 patients, whereas the latter addressed bacteriological aspects, focusing on 128 patients for whom bacteria were isolated from culture

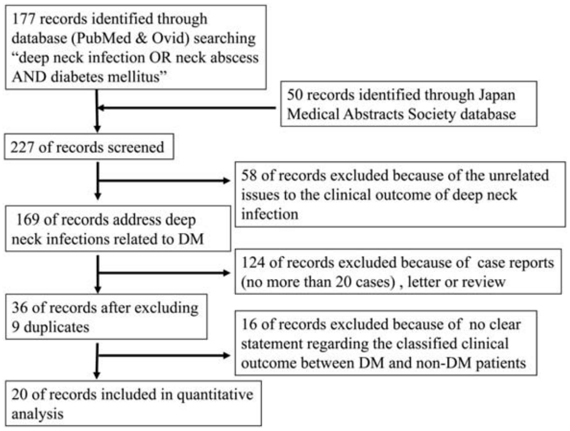


**FIGURE 1. Flow diagram of the systematic review, showing the search strategy for the period from January 1990 to May 2013. DM, diabetes mellitus.**

analysis. The former study was therefore selected for qualitative analysis.

## Data extraction

For each study, the following data were extracted: study design, sample size, age, hospitalization period, prevalence of multispace spread (ie, infections involving 2 or more potential head and neck spaces), complications (including airway obstruction, mediastinitis, pleural effusion, hypoproteinemia, pneumonia, intracranial infection, skin defect, diabetic ketoacidosis, pericarditis, and mortality), prevalence of failure to identify the primary source of infection (unknown pathogenesis), and bacteriological organisms.

## Statistical analyses

A quantitative synthesis for meta-analysis was performed on the eligible studies. For continuous outcomes, specifically age and hospitalization period, we calculated a weighted mean difference from the mean, SD, and sample size of each study. Regarding outcomes reported by event rates, statistical analysis for comparison in each study was performed with the inverse-variance weighted analysis of variance, and forest plots were used to analyze the difference between diabetic and nondiabetic groups of populations with Comprehensive Meta-Analysis version 2 (Biostat, Englewood, CA). Pooled estimates of risk ratios (RRs) and 95% confidence intervals (CIs) for the estimates were derived using a random-effects model. Heterogeneity was assessed and quantified by calculating $I^2$ (inconsistency) and $p$ values. In addition, Egger's test and funnel plots were used to measure possible publication bias in terms of each factor.

# RESULTS

## Study characteristics

Figure 1 represents a flow chart showing inclusion and exclusion criteria. Among the total of 227 records identified using the key words "deep neck infection" OR "neck abscess" AND "diabetes mellitus," 58 records were excluded because of issues unrelated to the clinical outcomes of deep neck infection. In addition, 124 reports were excluded because they were letters or reviews, or case reports consisting of no more than 20 cases. After excluding 9 reports addressing duplicate results, 16 reports were noted to have addressed the clinical features of deep neck infection without clarifying differences between diabetic and nondiabetic groups of patients. Quantitative synthesis was performed on the remaining 20 eligible studies.[3,7,8,10,12–27] The study by Srivanitchapoom et al[14] categorized 177 patients into those with diabetes mellitus or human immunodeficiency virus (HIV; $n = 34$) and an immunocompetent host group. Whereas diabetes mellitus and patients with HIV were categorized to the same immunocompromised group, diabetes mellitus was present in most patients (30 of the 34 cases). We therefore did not exclude that study, because inclusion of the 4 patients with HIV was presumed to have not contributed to the clinical characteristics of the other 30 patients with diabetes mellitus.

The meta-analysis regarding clinical outcomes in diabetic and nondiabetic patients for the 20 reports is summarized in Table 1.

## Years of age

Eight studies compared age between diabetic and nondiabetic groups, providing data on mean and SD. Figure 2 shows the results of meta-analysis after combining these available unadjusted effect sizes, as shown by the forest plot. Patients complicated with diabetes mellitus were significantly older than patients without diabetes (standardized mean difference [SMD], 0.61; 95% CI, 0.41–0.81). No significant heterogeneity was observed between studies ($I^2 = 31.1\%$; $p = .18$).

## Hospitalization period

Eleven studies compared hospitalization period between diabetic and nondiabetic groups, using mean and SD. Figure 3 shows the results of meta-analysis after combining these available unadjusted effect sizes, as shown by the forest plot. Although the heterogeneity among studies was significant ($I^2 = 59.8\%$; $p < .01$), patients complicated with diabetes showed significantly longer hospitalization than patients without diabetes (SMD, 0.64; 95% CI, 0.38–0.90).

## Multispace spread of infection

Seven studies compared the difference in prevalence of affected head and neck spaces between patients with and without diabetes. Almost all of the studies defined multispace extended infection as the concurrent involvement of 2 or more spaces. The exception, by Zhang et al,[12] focused only on cases in which 2 or more spaces in the head and neck (ie, excluding single-space infection) were affected, defining cases involving 3 or more spaces as multispace infection.

Figure 4 shows the results of meta-analysis using the forest plot, including the study by Zhang et al.[12] Although heterogeneity testing yielded significant results ($I^2 = 69.0\%$; $p = .004$), the incidence of multispace spread

TABLE 1. Summary of meta-analysis addressing clinical and bacteriological outcomes, comparing patients with and without diabetes.

| Description | Year | Country | Definition of diabetes mellitus | Category | Total cases | Age, y, mean ± SD | Hospitalization, d, mean ± SD | Etiology unknown | Multispace spread (+) | Complication (+) | No. of available culture tests | *Streptococcus spp.* (+) | *Klebsiella pneumoniae* (+) | *Streptococcus milleri* group (+) | Anaerobes (+) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zheng et al[12] | 2012 | China | Know history or diagnosed during admission | DM | 77 | 54.0 ± 16.0 | NA | 8 | 41 | 20 | 77 | 11 | 13 | NA | 8 |
| | | | | Non-DM | 114 | 45.0 ± 19.0 | NA | 18 | 48 | 15 | 114 | 26 | 6 | NA | 9 |
| Boscolo–Rizzo et al[13] | 2012 | Italy | Not clearly mentioned | DM | 52 | NA | NA | NA | NA | 27 | NA | NA | NA | NA | NA |
| | | | | Non-DM | 313 | NA | NA | NA | NA | 40 | NA | NA | NA | NA | NA |
| Srivanitchapoom et al[14] | 2012 | Thailand | Know history or diagnosed during admission | DM or HIV | 34 | NA | 23.0 ± 10.0 | 4 | 18 | 11 | 34 | 11 | 8 | NA | NA |
| | | | | Non-DM or HIV | 143 | NA | 14.0 ± 13.6 | 15 | 69 | 25 | 143 | 72 | 8 | NA | NA |
| Hohchi et al[15] | 2012 | Japan | Not clearly mentioned | DM | 8 | 62.4 ± 14.6 | 42.0 ± 20.5 | NA | NA | NA | 8 | NA | NA | 4 | NA |
| | | | | Non-DM | 33 | 58.1 ± 23.3 | 21.8 ± 15.0 | NA | NA | NA | 33 | NA | NA | 9 | NA |
| Lee and Kanagalingam[16] | 2011 | Singapore | Not clearly mentioned | DM | 54 | 58.0 ± 11.0 | 12.5 ± 10.6 | NA | NA | 20 | 44 | NA | 22 | 5 | 3 |
| | | | | Non-DM | 77 | 43.7 ± 17.0 | 8.8 ± 10.9 | NA | NA | 22 | 52 | NA | 4 | 16 | 17 |
| Hasegawa et al[3] | 2011 | Japan | Know history or diagnosed during admission | DM | 17 | 61.3 ± 17.4 | 17.4 ± 8.1 | 7 | 11 | 7 | 15 | 6 | 1 | 1 | 3 |
| | | | | Non-DM | 48 | 48.0 ± 23.4 | 14.6 ± 7.7 | 7 | 16 | 17 | 41 | 21 | 1 | 12 | 10 |
| Rao et al[17] | 2010 | India | A fasting blood glucose of >130 mg/dL or known history | DM | 31 | 48.0 ± 10.1 | 9.5 ± 8.2 | 0 | NA | NA | 31 | 5 | 4 | NA | 0 |
| | | | | Non-DM | 80 | 43.7 ± 14.6 | 6.2 ± 3.6 | 0 | NA | NA | 80 | 21 | 3 | NA | 1 |
| Wang LF et al[18] | 2010 | Taiwan | Not clearly mentioned | DM | 143 | NA | 13.7 | NA | NA | NA | 111 | 10 | 68 | NA | 15 |
| | | | | Non-DM | 196 | NA | 8.1 | NA | NA | NA | 165 | 49 | 38 | NA | 51 |
| Daramola et al[19] | 2009 | USA | Not clearly mentioned | DM | 6 | NA | NA | NA | NA | NA | 6 | 1 | 0 | 0 | 0 |
| | | | | Non-DM | 100 | NA | NA | NA | NA | NA | 78 | 35 | 0 | 5 | 6 |
| Roccia et al[20] | 2007 | Italy | Not clearly mentioned | DM | 6 | 54.5 ± 10.2 | 25.2 ± 14.1 | 0 | 6 | 6 | 6 | 2 | 0 | 1 | 1 |
| | | | | Non-DM | 17 | 48.1 ± 17.0 | 35.6 ± 15.4 | 0 | 17 | 17 | 17 | 4 | 0 | 1 | 3 |
| Bagnati et al[21] | 2007 | Italy | Not clearly mentioned | DM | 21 | 63.5 | 18.1 | 11 | 4 | 6 | NA | NA | NA | NA | NA |
| | | | | Non-DM | 58 | 39.5 | 12.0 | 26 | 6 | 6 | NA | NA | NA | NA | NA |
| Lee et al[7] | 2007 | Korea | Not clearly mentioned | DM | 27 | NA | NA | NA | NA | 9 | 27 | NA | 7 | NA | NA |
| | | | | Non-DM | 131 | NA | NA | NA | NA | 14 | 131 | NA | 3 | NA | NA |
| Nakano et al[22] | 2007 | Japan | Not clearly mentioned | DM | 7 | NA | 30.1 ± 19.1 | NA | NA | NA | NA | NA | NA | NA | NA |
| | | | | Non-DM | 24 | NA | 20.1 ± 5.3 | NA | NA | NA | NA | NA | NA | NA | NA |
| Lin et al[10] | 2006 | Taiwan | Fasting blood glucose of ≥126 mg/dL or post-prandia blood glucose level of ≥200 mg/dL, accompanied by symptoms or history | DM | 40 | 60.5 | 24.3 | 16 | 29 | 19 | 33 | 6 | 18 | NA | 5 |
| | | | | Non-DM | 91 | 45.0 | 12.9 | 37 | 18 | 12 | 55 | 14 | NA | NA | 28 |

**TABLE 1.** *Continued*

| Description | Year | Country | Definition of diabetes mellitus | Category | Total cases | Age, y, mean ± SD | Hospitalization, d, mean ± SD | Etiology unknown | Multispace spread (+) | Complication (+) | No. of available culture tests | *Streptococcus spp.* (+) | *Klebsiella pneumoniae* (+) | *Streptococcus milleri* group (+) | Anaerobes (+) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ohata et al[23] | 2006 | Japan | Not clearly mentioned | DM | 20 | NA | 39.2 ± 28.5 | NA | NA | NA | NA | NA | NA | NA | NA |
| | | | | Non-DM | 49 | NA | 18.0 ± 8.2 | NA | NA | NA | NA | NA | NA | NA | NA |
| Mazita A et al[24] | 2006 | Malaysia | Known history or diagnosed during admission | DM | 12 | NA | NA | 10 | NA | NA | 12 | NA | 4 | NA | NA |
| | | | | Non-DM | 24 | NA | NA | 15 | NA | NA | 24 | NA | 0 | NA | NA |
| Huang et al[8] | 2005 | Taiwan | Not clearly mentioned | DM | 56 | 57.2 ± 21.1 | 19.7 ± 13.7 | 37 | 9 | 19 | 43 | 9 | 23 | 1 | 6 |
| | | | | Non-DM | 129 | 46.2 ± 16.5 | 10.2 ± 7.3 | 69 | 6 | 11 | 84 | 41 | 15 | 0 | 33 |
| Sakashita et al[25] | 2005 | Japan | Not clearly mentioned | DM | 7 | NA | 22.4 ± 14.5 | NA | NA | 2 | NA | NA | NA | NA | NA |
| | | | | Non-DM | 20 | NA | 20.8 ± 34.9 | NA | NA | 0 | NA | NA | NA | NA | NA |
| Chen et al[26] | 2000 | Taiwan | Not clearly mentioned | DM | 30 | 57.8 | 12.7 | 16 | 16 | 10 | NA | NA | 22 | NA | NA |
| | | | | Non-DM | 75 | 43.1 | 6.7 | 18 | 16 | 7 | NA | NA | NA | NA | NA |
| Okuno et al[27] | 1997 | Japan | Not clearly mentioned | DM | 9 | 55.2 ± 13.7 | 30.3 ± 13.8 | 0 | NA | 5 | 9 | 4 | 0 | NA | 4 |
| | | | | Non-DM | 28 | 34.3 ± 16.5 | 23.5 ± 11.1 | 0 | NA | 10 | 23 | 12 | 1 | NA | 9 |

Abbreviations: DM, diabetes mellitus; Non-DM, nondiabetic; NA, not available; HIV, human immunodeficiency virus.

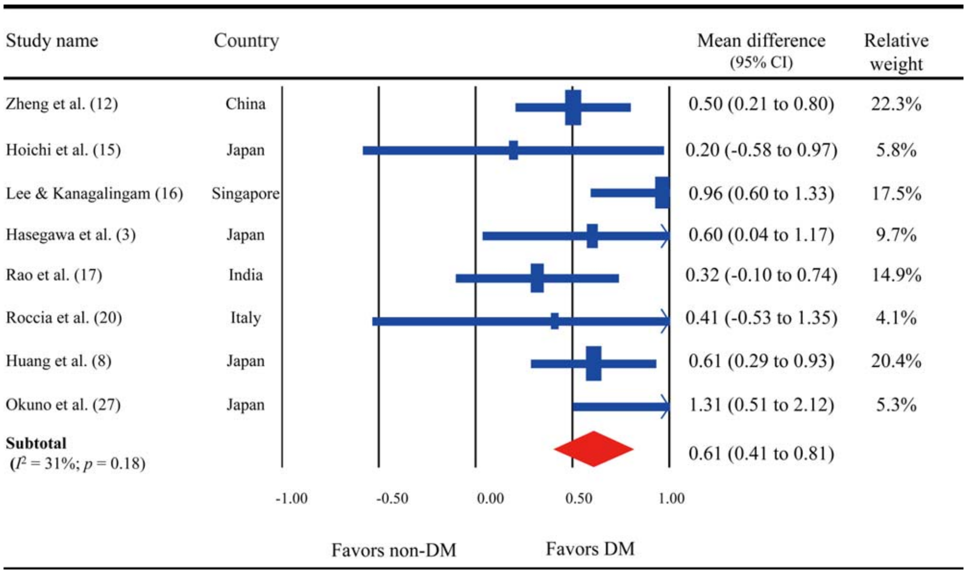


FIGURE 2. Forest plots of unadjusted standard mean difference in years of age between patients with and without diabetes mellitus (DM). CI, confidence interval. Study names and countries are shown in reverse chronological order. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

was significantly higher in patients with diabetes than in those without (RR, 1.96; 95% CI, 1.32–2.90).

Even if we excluded the study by Zhang et al[12] because of the difference in definitions of multispace spread, the incidence of complications remained significantly higher in patients with a history of diabetes (RR, 2.17; 95% CI, 1.36–3.47).

## Complications

Thirteen studies compared the difference in prevalence of life-threatening complications between diabetic and nondiabetic patients with deep neck infection. Figure 5 shows the results of meta-analysis combining these available unadjusted effect sizes, as shown by the forest plot. Although the heterogeneity among studies was significant ($I^2 = 57.6\%$; $p = .01$), the incidence of complications was significantly higher in patients with a history of diabetes than in those without diabetes (RR, 2.43; 95% CI, 1.80–3.30).

## Prevalence of unknown pathogenesis

Eleven studies compared differences in the identification of etiology between patients with and without diabetes. Figure 6 shows the results of meta-analysis for the available unadjusted effect sizes, as shown by the forest

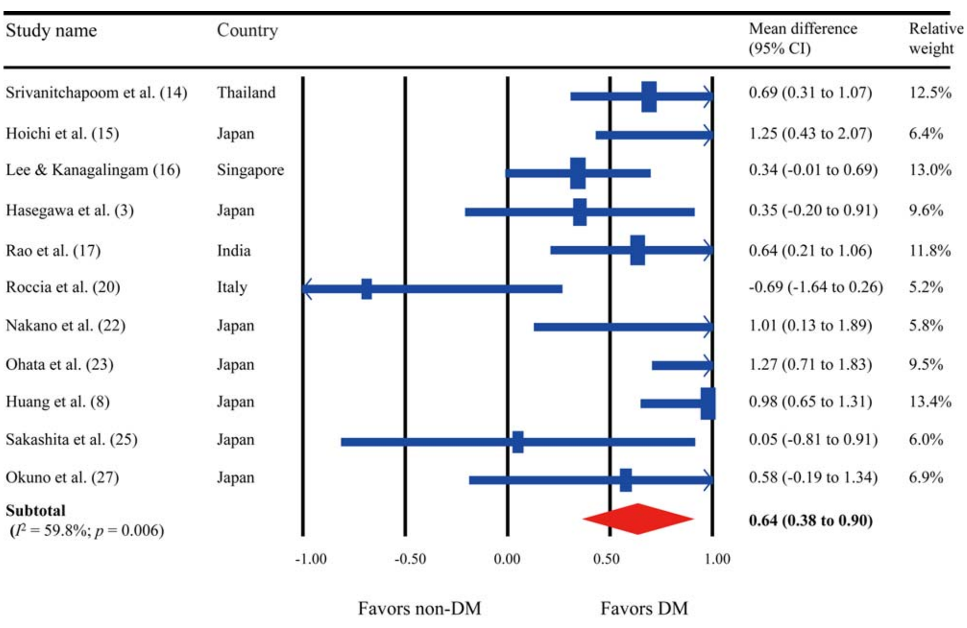


FIGURE 3. Forest plots of unadjusted standard mean difference in hospitalization period between patients with and without diabetes mellitus (DM). CI, confidence interval. Study names and countries are shown in reverse chronological order. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

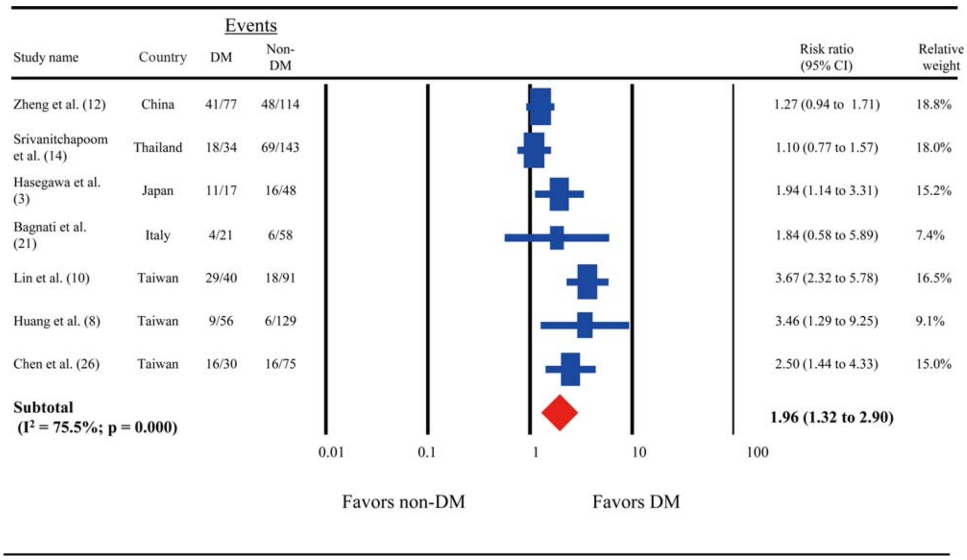


**FIGURE 4.** Forest plot of studies regarding the prevalence of multispace spread of infection in deep neck infections, comparing patients with and without diabetes mellitus (DM). CI, confidence interval. Study names and countries are shown in reverse chronological order. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

plot. Because 3 studies[17,20,27] identified the etiology of all cases regardless of diabetic complications (ie, failure to identify the pathogenesis was not seen in any cases), forest plot was performed for the remaining 8 studies. The incidence of unknown pathogenesis was significantly higher in patients with a history of diabetes (RR, 1.29; 95% CI, 1.02–1.63). Heterogeneity between studies was not significant ($I^2 = 40.1\%$; $p = .11$).

## Bacteriology: Identification of *Klebsiella pneumoniae*

Comparisons of differences in the identification of *K. pneumoniae* between diabetic and nondiabetic patients were available in 10 studies. Figure 7 shows the results of meta-analysis combining the available unadjusted effect sizes, as shown by the forest plot. The incidence of isolating *K. pneumoniae* was significantly higher in patients with diabetes than in those without (RR, 3.28; 95% CI,

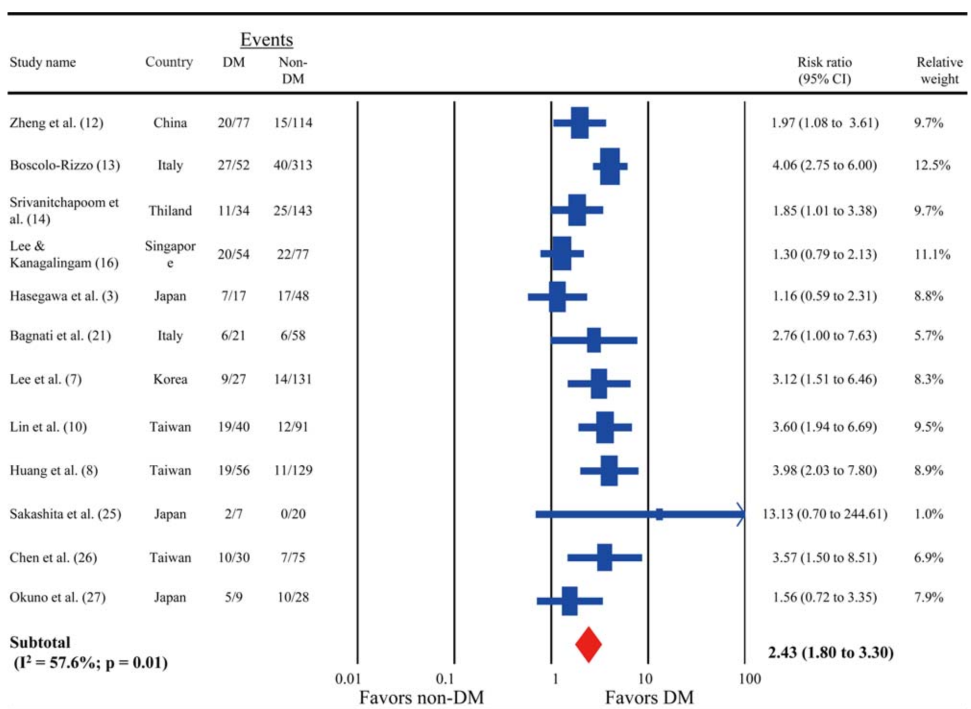


**FIGURE 5.** Forest plot of studies regarding the prevalence of complications in deep neck infections, comparing patients with and without diabetes mellitus (DM). Study names and countries are shown in reverse chronological order. CI, confidence interval. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

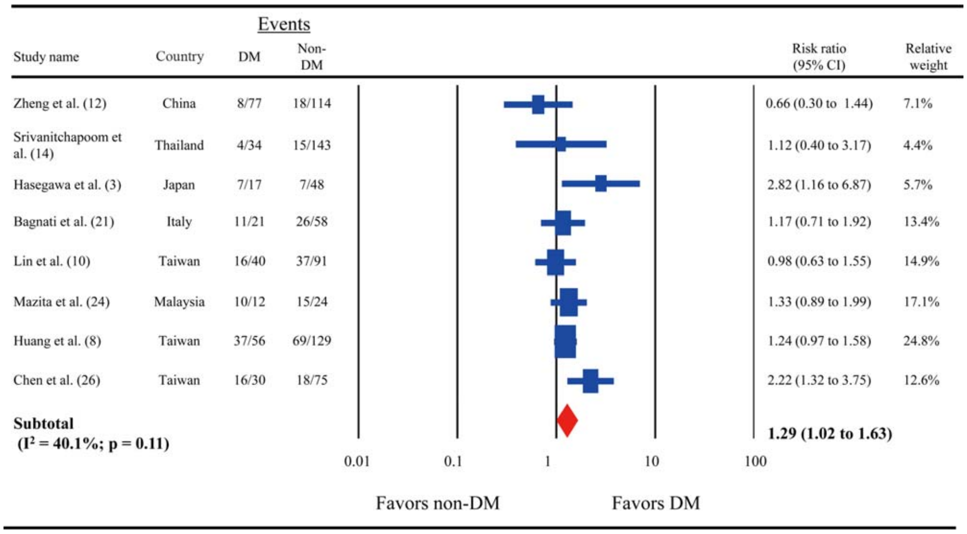


FIGURE 6. Forest plot of studies regarding the prevalence of unknown pathogenesis or failure to identify pathogenesis in deep neck infections, comparing patients with and without diabetes mellitus (DM). Study names and countries are shown in reverse chronological order. CI, confidence interval. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

2.52–4.26). Heterogeneity between studies was not significant ($I^2 = 5.6\%$; $p = .39$).

## Bacteriology: Identification of *Streptococcus* spp.

Eleven studies compared the difference in identification of *Streptococcus* spp. between patients with and without diabetes. Figure 8 shows the results of meta-analysis combining the available unadjusted effect sizes, as shown by the forest plot. The incidence of isolating *Streptococcus* spp. was significantly lower in patients with a history of diabetes than in those without (RR, 0.57; 95% CI, 0.46–0.73). Heterogeneity between studies was not significant ($I^2 = 0\%$; $p = .48$).

Among these 11 studies, 4 studies also addressed identifications of the *Streptococcus milleri* group. Moreover, 2 studies[15,16] presented an association between diabetes and *Streptococcus* focusing only on the *Streptococcus milleri* group. Results of meta-analysis of the resulting 6 cases are shown in Figure 9. In contrast to the overall results for *Streptococcus* spp., the incidence of isolating the *Streptococcus milleri* group did not differ significantly between patients with and without diabetes (RR, 0.91; 95% CI, 0.35–2.40).

## Bacteriology: Identification of anaerobes

Comparisons of the differences in identifying anaerobes between diabetic and nondiabetic patients were available in 10 studies. Figure 10 shows the results of meta-analysis combining the available unadjusted effect sizes, as shown by the forest plot. Similar to the results for

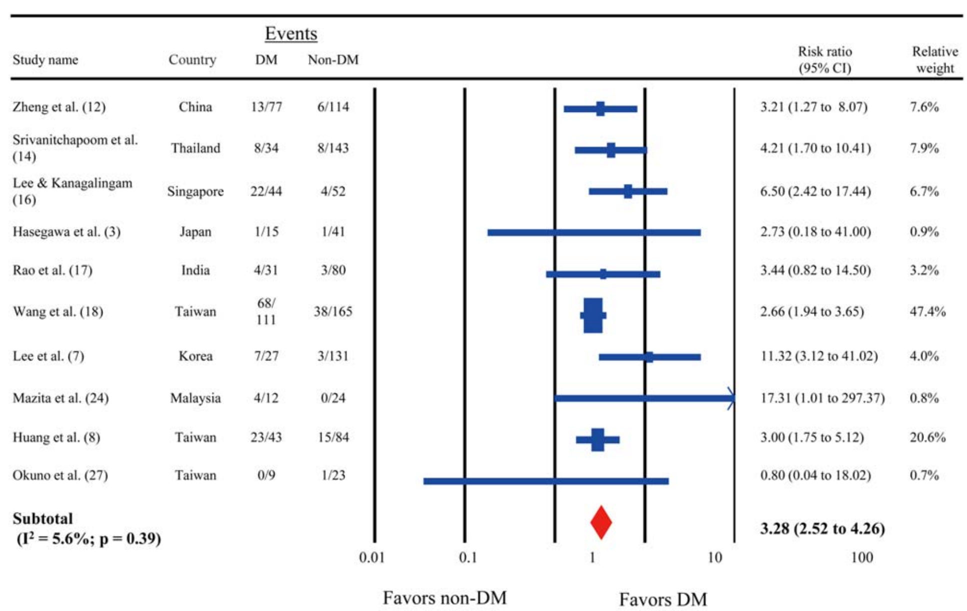


FIGURE 7. Forest plot of studies regarding the prevalence of identification of *Klebsiella pneumoniae* according to culture tests in deep neck infections, comparing patients with and without diabetes mellitus (DM). Study names and countries are shown in reverse chronological order. CI, confidence interval. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

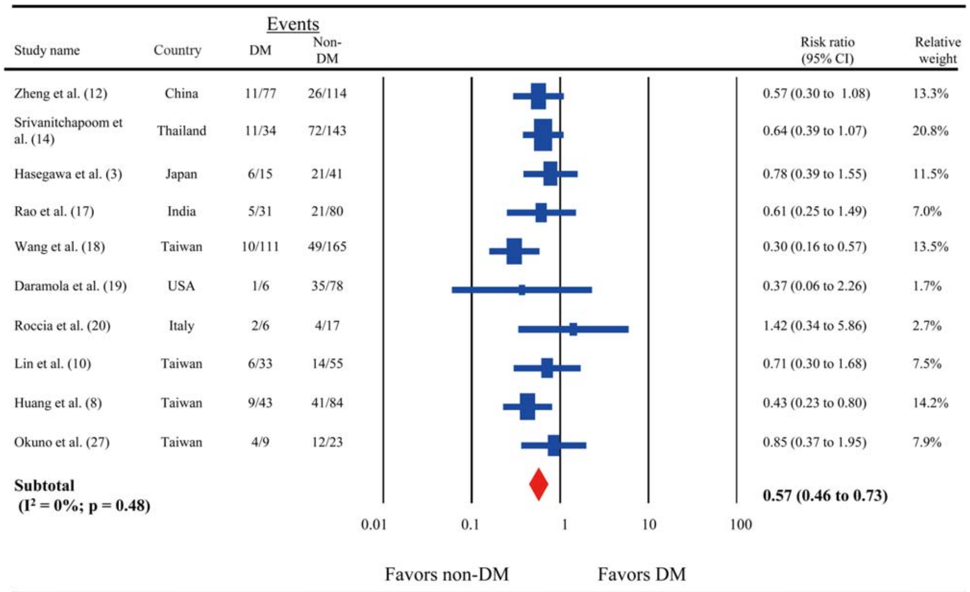

FIGURE 8. Forest plot of studies regarding the prevalence of identification of *Streptococcus* spp. according to bacteriological culture tests in deep neck infections, comparing patients with and without diabetes mellitus (DM). Study names and countries are shown in reverse chronological order. CI, confidence interval. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

*Streptococcus* spp., the incidence of isolating anaerobes was significantly lower in patients with a history of diabetes than in those without (RR, 0.54; 95% CI, 0.36–0.82). Heterogeneity between studies was not significant ($I^2 = 33.3\%$; $p = .14$).

## Publication bias

The funnel plot and Egger's test were performed for each factor to evaluate the potential for publication bias. For all clinical and bacteriological factors, funnel plots did not show an asymmetrical pattern (data not shown). Statistical tests did not reveal significant publication bias (ie, $p > .10$ on Egger's regression test) for any factors (Table 2).

## DISCUSSION

Diabetes mellitus is considered to adversely impact the immune system, along with causing vascular insufficiency.[8,12,28] Although several reports have described clinical features of deep neck infection in patients with diabetes compared to nondiabetic patients,[7–10,12–28] all such reports have been retrospective observational studies, including our own previous report.[3] Systematic reviews and meta-analyses are essential for developing new hypotheses that can then be tested in interventional studies.[29] To the best of our knowledge, this report features the first systematic review and meta-analysis comparing the effects of diabetes mellitus on the clinical and bacteriological features of deep neck infection with representation of several factors contributing to infection-related morbidity.

First, mean age was significantly higher in patients with diabetes than in nondiabetic patients, without significant heterogeneity among studies (Table 2). These results are consistent with the clinical experience that elderly patients with diabetes are particularly prone to infection, and senescence of the immune system can also alter host

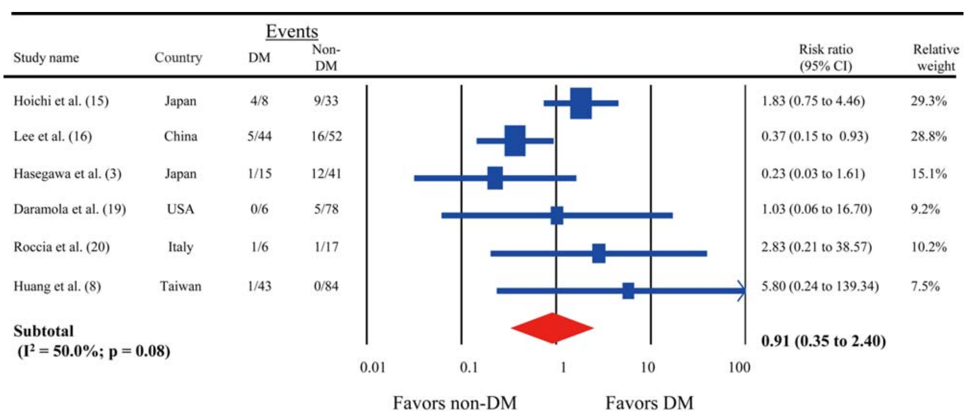

FIGURE 9. Forest plot of studies regarding the prevalence of identification of *Streptococcus milleri* group according to bacteriological culture tests in deep neck infections, comparing patients with and without diabetes mellitus (DM). Study names and countries are shown in reverse chronological order. CI, confidence interval. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

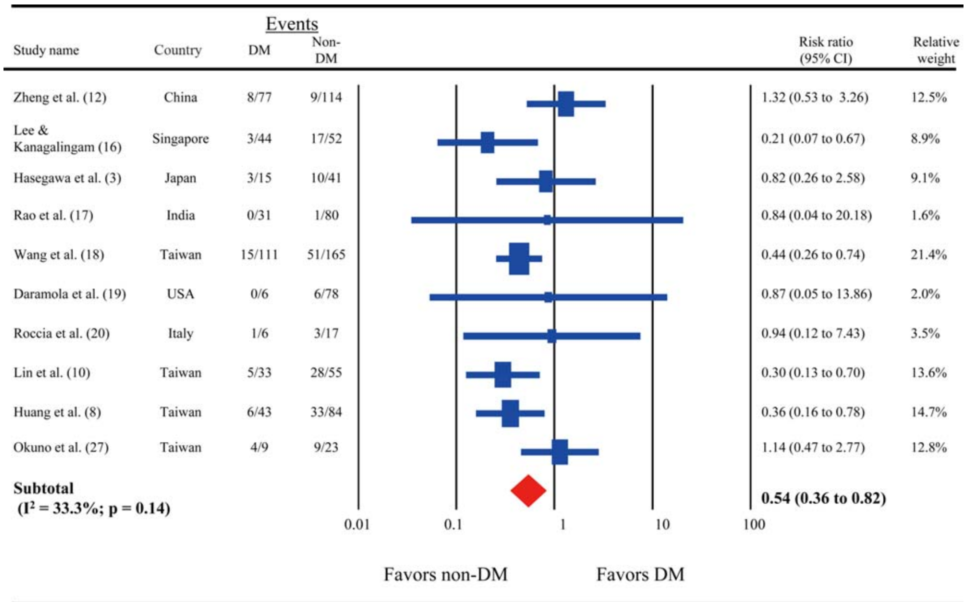


FIGURE 10. Forest plot of studies regarding the prevalence of identification of anaerobes according to bacteriological culture tests in deep neck infections, comparing patients with and without diabetes mellitus (DM). Study names and countries are shown in reverse chronological order. CI, confidence interval. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

defense mechanisms.[26,28,30] Moreover, the prevalence of diabetes has been reported to increase in older groups in the general population.[26]

Second, several studies have found that patients with diabetes spend longer periods of time in the hospital than those without.[3,8,14–17,20,22,23,25,27] In the present meta-analysis, the mean difference between hospitalization periods was significantly longer in patients with diabetes than in nondiabetic patients, with significant heterogeneity among studies (Table 2). One reason for this heterogeneity would presumably be the report by Roccia et al,[20] which focused on 23 cases of deep neck infection complicated by descending necrotizing mediastinitis. After excluding that study, SMD was 0.71 (95% CI, 0.48–0.93) without significant heterogeneity ($I^2 = 46.6\%$; $p = .051$).

Although the pattern of spread for deep neck infection varies among patients, a relatively constant trend in the extension into spaces seemed to be evident because of the relationship of the cervical fascia, which directs and limits the spread of these infections.[3,9] The interrelationship of these spaces is important in the spread of infection, because these spaces communicate fairly freely and easily with others.[26] Moreover, the severity of infection usually depends on the number of spaces involved.[17] According to the present meta-analysis, all except 1 study defined the multispace spread of infection as that extending into 2 or more spaces. The exception was a study by Zhang et al,[12] which focused on deep neck infections involving 2 or more spaces. Excluding that study, RR increased slightly from 1.96 (95% CI, 1.32–2.90) to 2.17 (95% CI, 1.36–3.47). A patient with diabetes would thus be approximately twice as likely to suffer from deep neck infection extending into multiple spaces as a patient without diabetes.

A higher prevalence of extended space infection in patients with diabetes also leads to a high frequency of

TABLE 2. Summary of the meta-analysis addressing overall estimates and 95% confidence intervals for each clinical and bacteriological factor, comparing patients with and without diabetes. Results of heterogeneity and publication bias are also shown.

| | | | | | | | Heterogeneity | | Publication bias |
|---|---|---|---|---|---|---|---|---|---|
| | | Weighted mean difference | RR | 95% CI | Z-value | *p* value | $I^2$ | *p* value | *p* value |
| 1 | Age, y | 0.61 | | 0.41–0.81 | 5.99 | .000 | 31.1 | .18 | .92 |
| 2 | Hospitalization period, d | 0.64 | | 0.38–0.90 | 4.79 | .000 | 59.8 | .01 | .55 |
| 3 | Multispace spread | | 1.96 | 1.32–2.90 | 3.34 | .001 | 75.5 | .00 | .20 |
| 4 | Complication | | 2.43 | 1.80–3.30 | 5.74 | .000 | 57.6 | .01 | .92 |
| 4 | Unknown pathogenesis | | 1.29 | 1.02–1.63 | 2.15 | .032 | 40.1 | .11 | .79 |
| 5 | Bacteriology | | | | | | | | |
| | *Klebsiella pneumonia* | | 3.28 | 2.52–4.26 | 8.90 | .000 | 5.6 | .39 | .13 |
| | *Streptococcus spp.* | | 0.57 | 0.46–0.73 | −4.65 | .000 | 0.0 | .48 | .45 |
| | *Streptococcus milleri* group | | 0.91 | 0.35–2.40 | −0.18 | .852 | 50.0 | .08 | .71 |
| | *Anaerobes* | | 0.54 | 0.36–0.82 | −2.94 | .003 | 33.3 | .14 | .48 |

Abbreviations: RR, risk ratio; CI, confidence interval.

complications, including airway obstruction, mediastinitis, pleural effusion, hypoproteinemia, pneumonia, intracranial infection, skin defect, diabetic ketoacidosis, pericarditis, and mortality.[3,7,8,10,12–14,16,21,25–27] We found a significant prevalence of these complications in patients with diabetes (RR, 2.43; 95% CI, 1.80–3.30) compared to those without (Table 2). These results support the previous findings[3] that patients with diabetes showing deep neck infection should immediately undergo more aggressive treatment, including immediate diagnostic imaging, airway management, and surgical drainage during the clinical course. Moreover, control of blood sugar levels is essential in the control of infection.[8]

Although dental infections, pharyngitis, and sialoadenitis have been considered as the main causes of deep neck infection, these pathogeneses vary according to the standards applied or patients surveyed,[31–33] as well as the demographic factors involved.[34,35] The prevalence of cases with difficulty in discerning the primary source of infection has been reported as 17% to 67%.[3,31,32,36] The present meta-analysis revealed that the prevalence of unknown causes was significantly higher in patients with diabetes (RR, 1.29; 95% CI, 1.02–1.63) than in patients without, showing no significant heterogeneity (Table 2). Although no background mechanisms have been confirmed to explain why deep neck infection with diabetes is associated with a higher prevalence of unknown causes, multispace spread of infection may contribute to difficulties in identifying the primary infection. Chen et al[26] hypothesized that the immunocompromised status in diabetes would contribute to the progression of severe infection, even if the primary infection site was minor. Another hypothesis is that the inciting infection can precede deep neck infection by weeks, and discerning the primary source of infection is often difficult because of prior out-patient treatment with antibiotics.[18,19]

Many previous bacteriological analyses have shown that the most commonly isolated organism in patients with diabetes with facial space infections is *K. pneumoniae*, followed by *Streptococcus* spp., whereas the most common organisms isolated from nonpatients with diabetes were *Streptococcus* spp. followed by *Staphylococcus* spp.[8,12,28] In the present meta-analysis, patients with diabetes displayed a significantly higher prevalence of identifying *K. pneumoniae* (RR, 3.28; 95% CI, 2.52–4.26) than nonpatients with diabetes without heterogeneity. This higher prevalence in patients with diabetes was attributed to impaired neutrophilic functions and complement activation.[26,37,38] Such reduced immunity, coupled with the increased oropharyngeal *K. pneumoniae* colonization in immunocompromised hosts, has been considered to explain the predominance of *K. pneumoniae*.[12,26,28,38] Empirical antimicrobial coverage of *K. pneumoniae* should thus be considered mandatory in patients with diabetes showing deep neck infections.

In contrast to the results for *K. pneumoniae*, the present meta-analysis revealed some interesting features with regard to other bacteria. Specifically, patients with diabetes showed a lower prevalence of identifying *Streptococcus* spp. (RR, 0.57; 95% CI, 0.46–0.73) compared to nondiabetic patients without heterogeneity. Although *Streptococcus* spp. were the major commonly isolated organisms in both diabetic and nondiabetic patents, these species would play a more important role as a pathogen in patients without diabetes. In recent years, the *Streptococcus milleri* group have been reported to be involved in more than 30% of cases with deep neck infection, including peritonsillar abscess.[39–42] Such findings suggest that the presence of the *Streptococcus milleri* group might promote abscess formation, and increase the need for surgical drainage, specifically in patients without diabetes mellitus.[3,43] In contrast to the results for *Streptococcus* spp., the prevalence of identifying the *Streptococcus milleri* group did not differ significantly between diabetic and nondiabetic patients (RR, 0.91; 95% CI, 0.35–2.40). These results are consistent with a previous report[3] that the *Streptococcus milleri* group plays a critical role in the pathogenesis of deep neck infections, regardless of complications of diabetes mellitus.

Similar to the results for *Streptococcus* spp., patients with diabetes showed a lower prevalence of identifying anaerobes (RR, 0.54; 95% CI, 0.36–0.82) than nondiabetic patients, without significant heterogeneity ($I^2 = 33.3\%$). Anaerobes express significant virulence factors, including adherence and spreading factors, such as hyaluronidase, collagenase, and fibrinolysin, which may promote the dissemination of a localized infection.[43] Such bacteriological differences between patients with and without diabetes imply that diabetic infections might be populated with different bacterial flora, making culture and sensitivity data more important in their global management.

Several limitations to the current study must be considered when interpreting the results. First, studies included for the meta-analysis used a case-control or cohort design. These observational studies may lack the experimental element of random allocation to an evaluation or intervention, and may rely on differences in an outcome of interest.[29] Given these limitations, the current studies revealed no significant publication bias in all of the clinical and bacteriological characteristics (Table 2). Second, diabetes mellitus was defined by various methods among the analyzed studies, including history and/or cutoff values. Third, the selected studies contained no details regarding diabetes interventions that were sufficient in addressing the effects of diabetes. Finally, bacteriological results from the included studies were based on culture tests. These factors may contribute to the relatively low prevalence of positive culture rates (*Streptococcus* spp., 20% to 48%; anaerobes, 7% to 38%; and *K. pneumoniae*, 4% to 30%). The prevalence of no bacterial growth has been estimated as approximately 20%, presumably because of the prompt use of high-dose antimicrobials early in the course of the disease.[1,41] Moreover, none of the studies for the meta-analysis clarified microbiological methodology, with the sole exception being the study by Rao et al,[17] in which inoculation was performed on blood agar and MacCokey's agar at 37°C for 24 hours, identified by standard technique. The use of methods adequate for recovering anaerobes thus could also influence isolation of the organism. Recently, bacterial identification using 16S ribosomal RNA (16S rRNA) sequencing has been applied for identifying uncultivable or culture-negative infections.[44,45] Multi-institutional prospective research assessing the association between deep neck infection and diabetes mellitus by applying 16S rRNA techniques would be helpful to overcome these limitations and to verify causative pathogens in detail.

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