

Systematic Meta-Analysis

Does Sex Predict the Development of Mediastinitis?

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Abstract

Objectives: We aimed to analyze whether sex was a risk factor for the development of mediastinitis after cardiac surgery.

Methods: Literature screening was performed using PubMed database without date limitation. Trial results were evaluated with random or fixed-effect model according to the heterogeneity. Statistical evaluation was performed.

Results: In total, 4044 articles were obtained after database searching. Of all these articles, 32 articles containing 1.11.303 patients, which satisfied the inclusion criteria, were included in the meta-analysis. The rate of mediastinitis was 2.19%. The effect size was observed as heterogeneous (Q: 89.09, df(Q): 31, p:0.00, I²:65.20%). Analysis results according to the random effect model were as follows: OR (odds ratio), 1.09; 95% CI, 0.90–1.32; and p=0.34 (p>0.05).

Conclusion: The results of the quantitative analysis showed that a patient's sex does not predict the development of mediastinitis after cardiac surgery for children and/or adults.

Keywords: Cardiac surgery, mediastinitis, meta-analysis, sex

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The rate of developing mediastinitis after cardiac surgery is approximately 0.8%–5.6%.^[1,2] Although the rate of occurrence of mediastinitis is low, mediastinitis causes complications, such as the need for intra-aortic balloon pump or inotropic drug support, ventricular or supraventricular arrhythmias, stroke, and myocardial ischemia, leading to reduction in long-term survival.^[3,4]

Mediastinal infections can be caused by direct contamination, hematogenous spread, or through extension of infection from the neck, retroperitoneum, lung, pleura, or chest wall.^[5] Mediastinal infections are defined as microbiological or clinical infection of presternal tissue. There are two types of mediastinal infections: superficial or deep wound infections (mediastinitis).^[6] Superficial wound infections involve only the skin and subcutaneous tissue; however, mediastinitis is the wound infection that includes sternal osteomyelitis which spreads to retrosternal space.^[6]

There are many risk factors for the development of mediastinitis: diabetes mellitus, obesity, age, peripheral artery disease, smoking, previous cardiac surgery, >5-h long surgery, and length of stay in intensive care unit.^[7,8] There are few clinical studies alleging that sex is a risk factor for the development of mediastinitis after cardiac surgery;^[9,10] however, there is no evidence. Therefore, we aimed to analyze whether sex is a risk factor for the development of mediastinitis after cardiac surgery.

Methods

Search Strategy

We searched PubMed database for articles according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA)^[11] to determine whether the sex of patients could predict devel-

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opment of mediastinitis after cardiac surgery. Two authors (S.O and I.O.) searched the database through May 20, 2017. There were no limitations for the date of articles. Articles in English were searched with a combination of keywords (cardiac surgery, heart surgery, valve surgery, coronary artery bypass grafting, mediastinitis, male, and female). The methods of studies were limited with “clinical trial, comparative study, multicenter study, observational study, randomized controlled trial, controlled clinical trial, and evaluation studies.”

Selection of Studies

Retrospective or prospective clinical studies, regardless of the sample size, were included. The inclusion criteria were as follows: Clinical study, open cardiac surgery with off-pump or extracorporeal circulation, and article in English. The exclusion criteria were as follows: Experimental studies, articles in a language other than English, and noncardiac surgery. Furthermore, articles not containing information about the rate of mediastinitis according to the patient’s sex were also excluded. Articles containing data in figures, and not in numerical values, were also excluded.

Data Extraction

Two reviewers (S.O. and I.O.) independently extracted data from relevant studies. We extracted publication information (first author’s name, publication year, patient population, and type of surgery), characteristics of participants (sex, sample size, and type of study), and outcome information (mediastinitis rate, number of males or females, and definition of mediastinitis). Any disagreement was resolved by consensus. The number of patients with mediastinitis and non-mediastinitis according to sex were recorded.

Statistical Analysis

The meta-analysis program Comprehensive Meta-Analysis Version 2.0 (Biostat, Englewood, New Jersey, USA) was used for the statistical analysis. The odds ratio (OR) and 95% confidence interval (CI) was used for analysis. The heterogeneity was evaluated with the analysis of moderators and statistics of I^2 , and it was accepted as significant if $I^2 \geq 50\%$. Meta-analysis was applied using fixed or random effect models. We performed random effect model in the presence of heterogeneity ($I^2 > 50\%$) and fixed-effect model in the absence of heterogeneity ($I^2 < 50\%$). The overall effect was analyzed using the Z score. Publication bias was evaluated with funnel plot and Begg’s test.

Results

Figure 1 shows the flow diaphragm of the database search. A total of 4044 records were identified through the data-

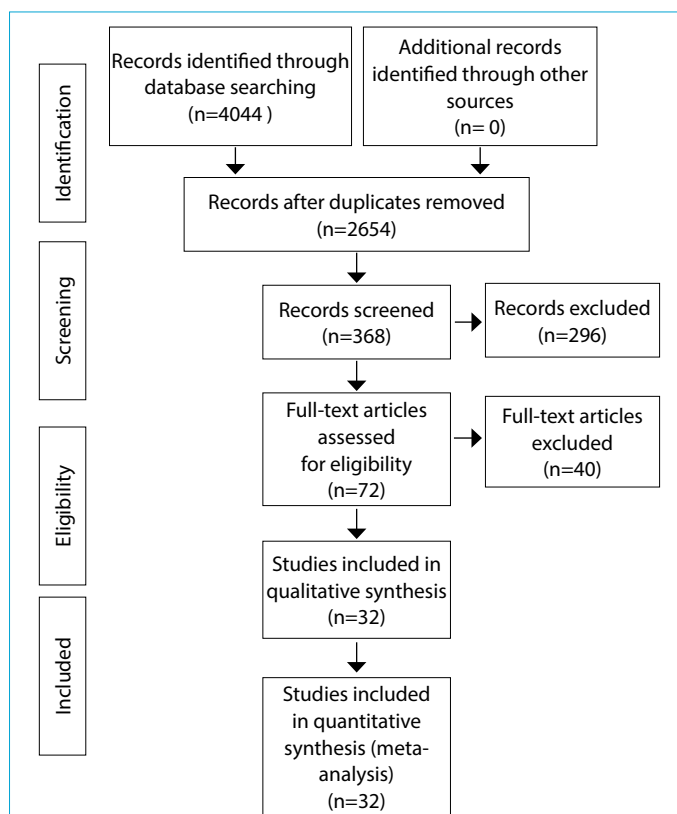


Figure 1. Flow diagram.

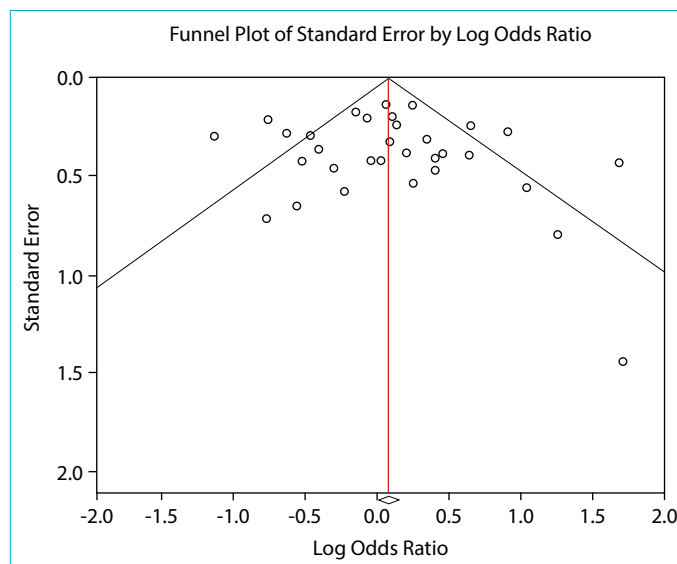


Figure 2. Funnel plot of publication bias.

base search. After removing the duplicate records, 2654 records were included. After screening, unrelated records ($n=2286$) were excluded. The complete text of 72 articles was assessed for eligibility, and 32 of them were excluded because of the absence of detailed data about rates of sex in each group. Finally, 32 articles were included for the quantitative synthesis.^[1, 2, 4, 7, 9, 10, 12-37] Table 1 shows the

Table 1. The studies included in the analysis

| Author | Year | M/F | n | Study design | Population | Type of surgery |
|-------------------------------------|------|--------|-------|---------------|------------|-----------------|
| Nakano et al. ^[9] | 2008 | 55/43 | 1500 | Prospective | Adult | CABG |
| Lopez Gude et al. ^[26] | 2006 | 109/54 | 490 | Prospective | Adult | Combined |
| Filsoufi et al. ^[21] | 2009 | 42/64 | 5798 | Retrospective | Adult | CABG |
| Ridderstolpe et al. ^[31] | 2001 | 213/78 | 3008 | Retrospective | Adult | Combined |
| Tiveron et al. ^[25] | 2012 | 26/9 | 2768 | Prospective | Adult | Combined |
| Newman et al. ^[35] | 1988 | 58/10 | 204 | Retrospective | Adult | Combined |
| Wouters et al. ^[27] | 1994 | 16/7 | 1368 | Retrospective | Adult | CABG |
| Sa et al. ^[37] | 2011 | 19/9 | 528 | Retrospective | Adult | CABG |
| Stahle et al. ^[30] | 1997 | 153/15 | 10157 | Prospective | Adult | Combined |
| Omran et al. ^[10] | 2007 | 21/23 | 9201 | Prospective | Adult | CABG |
| Risnes et al. ^[4] | 2010 | 101/6 | 551 | Retrospective | Adult | CABG |
| Diez et al. ^[17] | 2007 | 37/8 | 1699 | Retrospective | Adult | Combined |
| Parissis et al. ^[32] | 2011 | 44/8 | 3948 | Prospective | Adult | Combined |
| Eklund et al. ^[2] | 2006 | 95/20 | 10713 | Prospective | Adult | Combined |
| Dial et al. ^[16] | 2003 | 6/5 | 44 | Retrospective | Adult | Combined |
| Ottino et al. ^[33] | 1987 | 33/15 | 2627 | Prospective | Adult | Combined |
| Sakamoto et al. ^[34] | 2003 | 12/5 | 863 | Retrospective | Adult | Combined |
| Ghotaslou et al. ^[18] | 2008 | 13/10 | 1827 | Retrospective | Adult | Combined |
| Elenbaas et al. ^[1] | 2010 | 79/21 | 11748 | Prospective | Adult | CABG |
| Abboud et al. ^[12] | 2004 | 25/14 | 117 | Retrospective | Adult | Combined |
| Lin et al. ^[24] | 2003 | 28/20 | 113 | Retrospective | Both | Combined |
| Robinson et al. ^[29] | 2007 | 105/48 | 12001 | Retrospective | Adult | Combined |
| Antunes et al. ^[13] | 1997 | 55/5 | 2572 | Prospective | Adult | CABG |
| Koch et al. ^[23] | 2003 | 7/2 | 1890 | Prospective | Adult | Combined |
| Colombier et al. ^[19] | 2013 | 55/19 | 222 | Retrospective | Adult | Combined |
| Gualis et al. ^[22] | 2009 | 18/4 | 838 | Prospective | Adult | Combined |
| Ashley et al. ^[7] | 2004 | 84/59 | 223 | Prospective | Adult | Combined |
| Baillot et al. ^[14] | 2010 | 201/66 | 23499 | Combined | Adult | Combined |
| Ben-Ami et al. ^[15] | 2008 | 20/27 | 141 | Retrospective | Pediatric | Congenital |
| San Juan et al. ^[28] | 2007 | 6/11 | 68 | Prospective | Adult | Combined |
| Karwande et al. ^[20] | 1992 | 12/0 | 420 | Retrospective | Adult | Transplantation |
| Sa et al. ^[36] | 2011 | 4/7 | 157 | Retrospective | Adult | CABG |

CABG: coronary artery bypass grafting.

demographical features of studies. The rate of developing mediastinitis was 2.19% (2.444 out 1.11.303 cases).

The analysis results of the 32 studies are as follows: OR, 1.09; 95% CI, 0.90–1.32; Z value, 0.94; and $p=0.34$ ($p>0.05$). According to the random effect model, Ridderstolpe et al.'s study^[31] (5.14%) had the largest effect weight and Karwande et al.'s study^[20] (0.42%) had the smallest effect weight. The effect weight of trials were not homogenous ($Q: 89.09$, $df(Q): 31$, $p:0.00$, $I^2:65.20\%$). Figure 2 summarizes analysis results.

The result of publication bias evaluation was not significant according to the Begg's test ($\tau b=0.23$). The number of possible articles that escaped notice during the database search was 0 (classic fail-safe N). Table 2 shows the funnel plot.

The heterogeneity depended on the type of surgery (CABG $I^2=81.89\%$, congenital heart surgery $I^2=0.00\%$, heart transplantation $I^2=0.00\%$ and combined $I^2=42.63\%$), method of trials (retrospective $I^2=40.87\%$, prospective $I^2=78.39\%$, and combined $I^2=0.00\%$), type of patient population (pediatric $I^2=0.00\%$, adult $I^2=66.73\%$, and both $I^2=0.00\%$), and definition of mediastinitis (Center of Disease Control and Prevention-CDC $I^2=76.43\%$, undefined $I^2=45.96\%$, and defined except CDC $I^2=6.00\%$).

Discussion

It is known that individual features of patients such as age, height, and weight may affect the outcomes of surgical procedures. Sex is one such individual feature. Male sex was determined as a predictor of major infections after sur-

Table 2. Analysis of the studies

| Study name | Time point | Statistics for each study | | | | | Odds ratio and 95% CI | Relative weight |
|---------------------|------------|---------------------------|-------------|-------------|--------|-------|-----------------------|-----------------|
| | | Odds ratio | Lower limit | Upper limit | Z | P | | |
| Abboud et al. | 2004 | 0.575 | 0.250 | 1.324 | -1.300 | 0.193 | | 2.73 |
| Antunes et al. | 1997 | 1.469 | 0.584 | 3.700 | 0.817 | 0.414 | | 2.44 |
| Ashley et al. | 2004 | 0.610 | 0.341 | 1.093 | -1.662 | 0.097 | | 3.73 |
| Baillet et al. | 2010 | 1.262 | 0.954 | 1.669 | 1.633 | 0.103 | | 5.11 |
| Ben-Ami et al. | 2008 | 0.652 | 0.322 | 1.321 | -1.188 | 0.235 | | 3.21 |
| Chotaslou et al. | 2008 | 0.949 | 0.414 | 2.175 | -0.125 | 0.901 | | 2.74 |
| Colombier et al. | 2013 | 1.072 | 0.568 | 2.024 | 0.215 | 0.830 | | 3.50 |
| Dial et al. | 2003 | 0.450 | 0.110 | 1.848 | -1.108 | 0.268 | | 1.38 |
| Diez et al. | 2007 | 1.885 | 0.872 | 4.078 | 1.611 | 0.107 | | 2.95 |
| Eklund et al. | 2006 | 1.900 | 1.171 | 3.083 | 2.599 | 0.009 | | 4.19 |
| Elenbaas et al. | 2010 | 1.121 | 0.692 | 1.818 | 0.465 | 0.642 | | 4.19 |
| Filsoufi et al. | 2009 | 1.091 | 0.736 | 1.616 | 0.434 | 0.664 | | 4.62 |
| Gualis et al. | 2009 | 2.829 | 0.949 | 8.437 | 1.866 | 0.062 | | 1.98 |
| Karwande et al. | 1992 | 5.568 | 0.326 | 95.094 | 1.186 | 0.236 | | 0.42 |
| Koch et al. | 2003 | 3.519 | 0.729 | 16.982 | 1.567 | 0.117 | | 1.16 |
| Lin et al. | 2003 | 1.200 | 0.565 | 2.548 | 0.475 | 0.635 | | 3.02 |
| Lopez Gude et al. | 2006 | 0.915 | 0.613 | 1.367 | -0.433 | 0.665 | | 4.58 |
| Nakano et al. | 2008 | 0.454 | 0.299 | 0.688 | -3.722 | 0.000 | | 4.51 |
| Newman et al. | 1988 | 1.000 | 0.440 | 2.275 | 0.000 | 1.000 | | 2.77 |
| Omran et al. | 2007 | 0.313 | 0.173 | 0.566 | -3.842 | 0.000 | | 3.68 |
| Ottino et al. | 1987 | 1.400 | 0.757 | 2.591 | 1.072 | 0.284 | | 3.59 |
| Parissis et al. | 2011 | 1.551 | 0.727 | 3.307 | 1.136 | 0.256 | | 3.01 |
| Ridderstolpe et al. | 2001 | 1.039 | 0.791 | 1.365 | 0.277 | 0.782 | | 5.14 |
| Risnes et al. | 2010 | 5.411 | 2.309 | 12.680 | 3.886 | 0.000 | | 2.67 |
| Robinson et al. | 2007 | 0.846 | 0.600 | 1.193 | -0.956 | 0.339 | | 4.84 |
| Sa et al.* | 2011 | 1.467 | 0.651 | 3.307 | 0.924 | 0.355 | | 2.80 |
| Sa et al.** | 2011 | 0.556 | 0.156 | 1.981 | -0.906 | 0.365 | | 1.61 |
| Sakamoto et al. | 2003 | 1.272 | 0.444 | 3.644 | 0.447 | 0.655 | | 2.08 |
| San Juan et al. | 2007 | 0.779 | 0.249 | 2.437 | -0.429 | 0.668 | | 1.87 |
| Stahle et al. | 1997 | 2.473 | 1.452 | 4.212 | 3.331 | 0.001 | | 3.96 |
| Tiveron et al. | 2012 | 1.574 | 0.735 | 3.373 | 1.167 | 0.243 | | 2.99 |
| Wouters et al. | 1994 | 0.719 | 0.293 | 1.764 | -0.719 | 0.472 | | 2.52 |
| | | 1.095 | 0.905 | 1.324 | 0.936 | 0.346 | | |

gery following trauma.^[38] Mansur et al.^[39] found that women with *Staphylococcus aureus* bacteremia had a greater risk of 30-day all-cause mortality than men; however, the reason for this was not explained. Haring et al.^[40] observed that men have a generally higher risk of incident cardiovascular morbidity and mortality and alleged that low testosterone concentrations were the risk factors.

In literature, some of the trials showed that morbidity and mortality after CABG have been higher for women than for men.^[41, 42] In contrast to those reports, Koch et al.^[23] alleged that female sex was not associated with increased mortality for well-matched patients. However, they observed

that sex had minimal impact on morbidity after CABG.^[23] In this study, propensity matching women and men was difficult because only 26% of women could be matched with men. Furthermore, the characteristics of patients according to demographical features (age, height, weight, and body surface area; $p < 0.01$) and laboratory values (hematocrit, bilirubin, albumin, and blood urea creatinine levels; $p < 0.01$) were significantly different between unmatched and matched women. These significant differences (well-matched women/unmatched women=26%) were the most important point of the results of Koch et al.'s^[23] study.

Except that study,^[23] nine of 34 four trials used the matched

population for the analysis.^[4, 7, 12, 15, 19, 24, 26, 28, 35] They included 3.186 of 72.633 patients for statistical analysis by 1:2 or 1:3 matching.^[15, 30] Individual features (age, cigarette smoking, alcoholism, obesity/body mass index, prior cardiac surgery) of these patients were not available in the text of articles. Also, the percentages of co-existing diseases such as diabetes mellitus, chronic obstructive pulmonary disease, or peripheral artery disease were not given in the studies. Both individual features and co-existing disease of patients are possible risk factors for the development of postoperative mediastinitis after cardiac surgery. When the difficulty of well-matching of patients only for sex is considered,^[23] it is more difficult for the other possible risk factors. At that point, Koch et al.'s^[23] study was well designed for our aim of analyzing sex as a constant variable for population.

Among the abovementioned studies, the determined significant differences between the case and control groups were body mass index, hypertension, chronic obstructive pulmonary disease, and diabetes in the study by Risnes et al.^[4]; obesity, diabetes, dyslipidemia, and previous acute myocardial infarction in the study by Abboud et al.^[12]; obesity, diabetes, pulmonary hypertension, and chronic obstructive pulmonary disease in the study by Lopez Gude et al.^[26]; age and weight in the study by Ben-Ami et al.^[15] and previous hospitalization in the study by Lin et al.^[24] Conversely, Colombier et al.^[19] did not find difference for these variables between the groups. Therefore, we thought that the results of these studies are disputable for overall analysis. However, when we performed the analysis by excluding eleven studies,^[4, 7, 12, 15, 19, 23, 24, 26, 28, 35] analysis results did not change (OR, 1.11; 95% CI, 0.89–1.39; $p=0.33$).

We reviewed 32 articles for heterogeneity. The type of surgery, method of trial, definition of mediastinitis, and patient population were evaluated.

The methods of studies were prospective^[1, 2, 7, 9, 10, 13, 22, 23, 25, 26, 28, 30, 32, 33] or retrospective.^[4, 12, 15-21, 27, 29, 31, 34-37] One of them was performed both prospectively and retrospectively.^[14] However, neither retrospective nor prospective designs affected the overall result of our analysis.

We observed the articles by classifying them into four groups according to the type of surgery. The type of surgery was a reason for heterogeneity. Sex was not a predictor of mediastinitis for CABG, heart transplantation, congenital heart surgery, or combined cardiac surgeries.

When we evaluated the articles according to the definition of mediastinitis, they were divided into three groups: CDC, undefined, and other definitions. Heterogeneity reduced in the studies that defined mediastinitis, except for CDC criteria. However, the type of definition did not change the analysis result.

Limitations

The main limitation of our analysis was the lesser number of studies containing pediatric patients. One trial studied only pediatric patients^[15] and one studied both adult and pediatric patients.^[24]

Conclusion

Although female and male patients have co-existing disease at different ratios, we found that the patient's sex was not a predictor for the development of postoperative mediastinitis after cardiac procedures.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship contributions: Concept – S.O., I.O.; Design – S.O., I.O.; Supervision – S.O., I.O.; Materials – S.O., I.O.; Data collection &/or processing – S.O., I.O.; Analysis and/or interpretation – S.O., I.O.; Literature search – S.O., I.O.; Writing – S.O., I.O.; Critical review – S.O., I.O.

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