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Sex-specific differences in infective endocarditis: A systematic review and meta-analysis of clinical profiles and management outcomes

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ABSTRACT

Background: Infective endocarditis (IE) presents significant morbidity and mortality, with potential sex differences in clinical profile and outcomes. This is the first meta-analysis that aims to compare the clinical profile and outcomes of IE between males and females.

Methods: We conducted a meta-analysis of nine studies evaluating the clinical profile and outcomes of IE in males versus females extracted from PubMed, EMBASE, SCOPUS, and Cochrane databases up to 1st of Jan 2024.

Results: Our meta-analysis revealed notable sex differences in the incidence and complications of IE. Males exhibited a higher incidence of aortic valve IE (RR 1.57, 95 % CI [1.31, 1.88]), surgical indications for IE (RR 1.38, [1.12, 1.70]), Streptococci infection (RR 1.36, [1.04, 1.77]), intracardiac abscess (RR 1.22, [1.05, 1.42]), and Enterococci IE (RR 1.44, [1.28, 1.61]). In contrast, females had a higher incidence of mitral valve IE (RR 0.79, [0.67, 0.94]) and a higher in-hospital mortality rate (RR 0.84, [0.74, 0.96]). No significant sex differences were found in the incidence of valve vegetations, tricuspid valve IE, embolization, and Staphylococcus IE. In-hospital stay was longer in male patients, however, with borderline significance (RR 3.15, [-0.16, 6.45], $p = 0.06$). In patients who underwent surgery for IE, mortality rates were significantly lower in male patients (RR: 0.67 [0.59, 0.76], $p < 0.01$).

Conclusions: Compared to females, males exhibit higher rates of aortic valve IE, intracardiac abscess, streptococci IE, enterococci IE and IE-related surgery indication. In contrast, females have higher rates of mitral valve IE and in-hospital mortality.

1. Introduction

Infective endocarditis (IE) is a potentially fatal inflammation affecting the heart's inner lining, with an annual incidence of 5 per 100,000 people and a mortality rate up to 30 % [1,2]. Bacterial infection is the most common cause of IE and is responsible for 80–90 % of all IE cases with staphylococcus aureus being the most frequent microorganism [3]. Literature suggests major differences driven by sex in cardiovascular diseases such as hypertrophic cardiomyopathy [4], myocarditis [5], as well as valvular heart diseases [6]. Previous studies suggest epidemiological differences between both sexes in prevalence, comorbidities, mortality rate, response to treatment and outcomes in patients with IE. IE affects males more frequently, with a male-to-female ratio ranging between 2:1 and 9:1, however female sex has been associated with a higher mortality rate [7–9]. Moreover, older males tend to present with native aortic valve IE, compared to younger females who usually present with mitral valve involvement. Also, comorbidities vary between both sexes; females tend to have atrial fibrillation, chronic kidney disease, psychiatric disorders, and taking immunosuppressants compared to males who suffer from chronic liver disease, underlying valve disease, and peripheral artery disease, contributing to the ease of developing IE [10]. Also, females were more likely to have culture-

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negative IE, however males were more likely to be infected with streptococcus viridians [11]. This systematic review and epidemiological meta-analysis is the first that aims at providing summary of evidence on the sex driven differences in clinical profiles and outcomes of IE.

2. Methods

2.1. Literature Search

This protocol of this meta-analysis was registered to PROSPERO (CRD42024596277). We formulated search terms using the Population, Intervention, Comparator, and Outcome framework to identify relevant studies that report sex-stratified comparisons of clinical profile and outcomes in adults diagnosed with IE. Our search encompassed multiple databases, including PubMed, EMBASE, SCOPUS, and Cochrane up until January 2024. This study was conducted in line with the Updated 2020 Version of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12]. The search terms employed were "infective endocarditis" or "IE" and "sex" or "gender" or "male" and "female" or "men" and "women". Table S1 highlights the search strings used to search different databases. To augment our search results, we did a meticulous backward and forward citation check to ensure the inclusion of all relevant studies.

2.2. Studies selection

The final selection of studies was based on the predetermined inclusion and exclusion criteria. During the abstract and full-text review stages, two independent reviewers meticulously evaluated each study, and any discrepancies were resolved by a third reviewer. The inclusion criteria for the study were as follows: (1) the study must compare the clinical profile and outcomes in both sexes; (2) the number of study subjects for the male and female groups should be clearly defined; (3) only studies involving human participants will be included; (4) the published study must be in English; (5) all study participants must be adults (age > 18 years); (6) study design is an observational cohort studies (prospective or retrospective) or post-hoc analyses of clinical trials; and (7) abstracts can be included if they meet all the previously mentioned criteria and are the only available source of information. The exclusion criteria for the study were as follows: (1) studies published in languages other than English; (2) studies that do not provide sex-stratified data for clinical profile and outcomes; (3) excluded study designs were systematic reviews, meta-analyses, narrative reviews, case reports/series, editorials, study protocols, and abstracts that do not meet the inclusion criteria.

2.3. Data extraction and quality assessment

Data extraction was carried out by two independent investigators. Revision was conducted and discrepancies were resolved by two additional reviewers to maintain accuracy and consistency. For categorical data, event and total numbers were extracted for each group, while continuous data were recorded as means and standard deviation (SD). If the continuous data were reported in other formats, the method by Wan and colleagues [13] was used to estimate the mean and the SD. Study details, key demographic characteristics and clinical variables were extracted, including patient demographics, comorbidities, and microbiological profiles. The data was analyzed in two categories, the clinical profile, and the outcomes. Clinical profile data was extracted from studies reporting the overall number of patients admitted with IE. It included valve affection, causative organisms, intra-cardiac abscess, embolization, and vegetations. In-hospital outcomes included in-hospital mortality, indication for surgery, stroke, and in-hospital stay. For patients who were indicated and underwent surgery, we extracted data on postoperative mortality, stroke, and requirement for permanent pacemaker (PPM) implantation. The quality of the included studies was assessed using the Newcastle-Ottawa Scale.

2.4. Statistical Analysis

This meta-analysis followed the guidelines of the Cochrane Collaboration and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) [14]. Data analysis was carried out using STATA BE 18 provided by StataCorp, Texas, United States. The inverse-variance random effects model was used to calculate the risk ratio (RR) with 95 % confidence intervals (CI) for binary outcome measures. To assess statistical heterogeneity, we used the Q-test for heterogeneity (Cochrane, 1954) and I2 statistics. An I2 value above 50 % indicated substantial heterogeneity among the included studies. Statistical significance was defined as a p-value less than 0.05. To test the robustness of our results, a sensitivity analysis was performed. Publication bias was examined using funnel plots and Egger's regression test when the analysis included eight or more studies.

3. Results

3.1. Included studies and population

From a total of 1,656 unique articles identified in the primary search, we included 11 studies reporting general IE patients and four studies reporting patients who were indicated for and underwent surgery. The PRISMA flowchart is included in the supplementary material (Fig. S1). All the included studies were of good quality. Total number of general IE patients were 16,754 including 10,308 (61.5 %) males and 6,446 (38.5 %) females. On the other hand, total number of patients who were indicated for surgery were 9520 including 6624 (69.6 %) males and 2896 (30.4 %) females. Several studies showed that female patients tends to be older at presentation and at the time surgery was indicated. However, such differences were inconsistent across the included studies, were not valve-specific, and yielded no significant difference. Table 1 presents the defining characteristics of these studies and definitions used to establish the diagnosis of IE. Table S2 summarizes the quality assessment results using the Newcastle-Ottawa Scale.

3.2. Sex differences in clinical profiles of general IE patients

In terms of valve involvement, male patients had more frequent aortic valve involvement (Risk ratio (RR): 1.57, 95 %CI [1.31, 1.88], p = 0.001, reference: female). Fig. 1. On the other hand, mitral valve involvement was more frequent in females compared to males (RR: 0.79, 95 %CI [0.67, 0.94], p = 0.01). Fig. 2. There were no significant differences in the distribution of right-sided IE including tricuspid or pulmonic valve affection between males and females. Table 2 provides a summary of the pooled results. In terms of microbiological profile, male patients were more likely to be infected with Enterococci IE (RR: 1.44, 95 %CI [1.28, 1.61], p = 0.001) and Streptococcal IE (RR: 1.36, 95 %CI [1.04, 1.77], p = 0.02) in comparison to female patients. Staphylococcus aureus and Coagulase-negative Staphylococcus did not exhibit notable differences in distribution between males and females. Male patients manifested higher rates of intra-cardiac abscess at admission (RR: 1.22, 95 %CI [1.05, 1.42], p = 0.01) but no significant difference was noted in terms of vegetations between both sexes (RR: 1.01, 95CI [0.98, 1.03], p = 0.71).

3.3. In-hospital outcomes in general IE patients

In-hospital mortality was significantly lower in male patients (RR: 0.84, 95 %CI [0.74, 0.96], p = 0.01) when compared to female patients. Fig. 3. Indication for surgery was also significantly higher in male patients (RR: 1.38, 95 %CI [1.12, 1.70], p = 0.00). Fig. 4. Consequently, male patients tended to have longer in-hospital stays, however the results came out with borderline significance (mean difference (MD): 3.15,

Table 1
Overview of the included studies in this meta-analysis.

Study ID	Location	Study Center	Study Duration	Population	Patients	
					Male	Female
Barca 2021 [15]	Spain	Multi-Centre	2008–2018	General IE	2346	1105
Elamragy 2020 [16]	Egypt	Single-Centre	2005–2016	General IE	243	155
Sousa 2021 [17]	Portugal	National Multicenter	2010–2018	General IE	4308	3266
Aksoy 2007 [18]	USA	Duke University	1996–2004	General IE	252	187
Polishchuk 2021 [19]	Israel	Soroka University	2004–2013	General IE	131	83
Bhandari 2022 [20]	USA	Multicenter	2014–2018	General IE	390	390
Sambola 2010 [21]	Spain	Single-Centre	2000–2008	General IE	183	88
Ahtela 2021 [22]	Finland.	National Multicenter	2005–2014	General IE	1469	697
Sevilla 2010 [23]	Spain	Multi-Centre	1996–2007	Left sided IE	395	226
Curlier 2014 [24]	France	Multi-Centre	1999–2008	Left sided IE	466	154
Hamda 2010 [25]	Tunisia	Single-Centre	1997–2007	General IE	125	95
Patients who were indicated and underwent surgery						
Weber 2019 [26]	Germany	University of Cologne	2009–2016	Underwent IE Surgery	229	76
Bansal 2021 [27]	USA	National Multicenter	2004–2015	Underwent IE Surgery	5529	2518
Friedrich 2022 [28]	Germany	Schleswig Holstein University	2002–2020	Underwent IE Surgery	308	105
Dohmen 2016 [29]	Germany	Leipzig Heart Center	1994–2011	Underwent IE Surgery	558	297

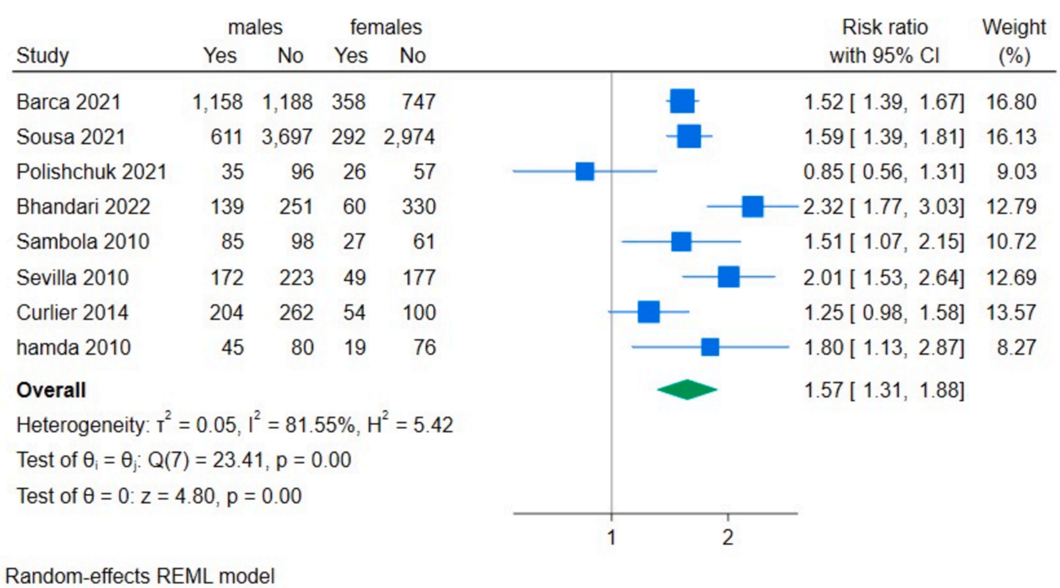

Fig. 1. Forest plot summarizing differences in aortic valve IE rates between both sexes.

95 %CI (−0.16, 6.45), p = 0.06). Any vascular embolization and stroke showed no significant differences in frequency between both sexes. Fig. 5.

3.4. Outcomes in patients who were indicated and underwent surgery for IE

At the time of surgery, male patients tended to be younger, however with no significant difference. In-hospital mortality was significantly lower in male patients who underwent surgery (RR: 0.67, 95 %CI [0.59, 0.76], p = 0.001). No differences in postoperative stroke, permanent pacemaker requirement, or in-hospital stay between males and females after undergoing surgery for IE (Table 2, IE surgery outcomes).

4. Discussion

IE significantly contributes to morbidity and mortality among affected patients. Beyond its infectious nature, IE profoundly impacts intracardiac hemodynamics, valve integrity, and can lead to severe cerebral and systemic embolization which further worsen outcomes [30–32]. Understanding the profile and clinical course of IE can contribute to optimizing outcomes in this severely ill population. In this systematic review and meta-analysis, male patients were more likely to present with aortic valve IE in contrast to female patients who presented with more mitral valve affection. Enterococci and Streptococci were more frequently observed in male patients. In terms of outcomes, male patients were more likely to present with intracardiac abscess and were indicated for surgery more frequently. Mortality rates were higher in female patients admitted for IE as well as those who were indicated for and underwent surgery.

4.1. Sex differences in valve involvement among IE patients

Our meta-analysis revealed notable sex differences in valve involvement among IE patients. Specifically, males show a higher incidence of aortic valve involvement, whereas females are more often affected by mitral valve IE. These findings align with previous studies suggesting that males are more susceptible to aortic valve issues, while females are more likely to have mitral valve involvement. Additionally, a recent systematic review indicated that females tend to develop IE in

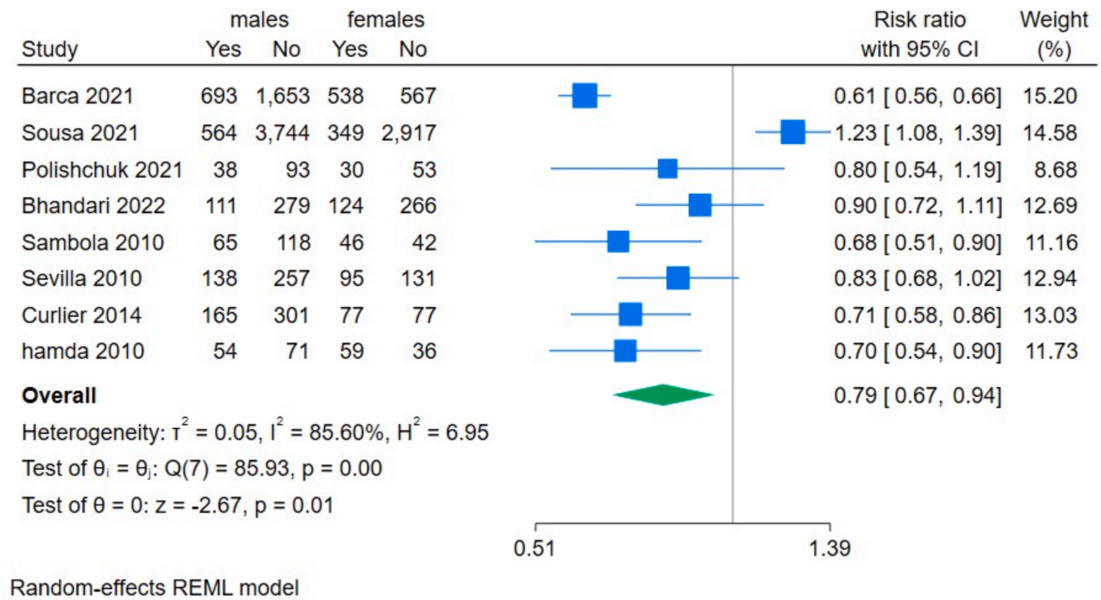

Fig. 2. Forest plot summarizing differences in mitral valve IE rates between both sexes.

Table 2
Overall summary of meta-analysis results.

Outcome	Patients analyzed	Effect Estimate (Ref. Female)	Significance
Surgical indications for IE	13,588	1.38 (1.12, 1.70)	**p = 0.00***
Intracardiac abscess	5,800	1.22 (1.05, 1.42)	**p = 0.01***
Valve vegetations	5,391	1.01 (0.98, 1.03)	p = 0.71
Stroke	13,136	1.03 (0.90, 1.17)	p = 0.69
Embolization	13,375	1.03 (0.95, 1.11)	p = 0.52
In-hospital mortality rate	13,808	0.84 (0.74, 0.96)	**p = 0.01***
In-hospital stay duration#	10,030	3.15 (−0.16, 6.45)	p = 0.06
Valve Involvement			
Aortic valve IE	13,751	1.57 (1.31, 1.88)	**p = 0.00***
Mitral valve IE	13,751	0.79 (0.67, 0.94)	**p = 0.01***
Tricuspid valve IE	4,716	0.94 (0.65, 1.35)	p = 0.73
Pulmonary valve IE	4,716	1.07 (0.69, 1.68)	p = 0.76
Microbiological Profile			
Enterococci IE	13,970	1.44 (1.28, 1.61)	**p = 0.00***
Streptococci infection	12,911	1.36 (1.04, 1.77)	**p = 0.02***
Staphylococcus aureus IE	13,970	0.96 (0.81, 1.14)	p = 0.63
Coagulase-negative Staphylococcus IE	13,190	1.16 (0.89, 1.50)	p = 0.27
IE Surgery Outcomes			
Age at Surgery#	9610	−1.70 [-3.61, 0.20]	p = 0.08
In-hospital Mortality	9610	0.67 [0.59, 0.76]	**p = 0.00***
Post-op Stroke	9610	0.93 [0.84, 1.04]	p = 0.23
PPM Requirement	1573	0.95 [0.63, 1.45]	p = 0.18
In-hospital Stay#	8352	−0.01 [-2.50, 2.49]	p = 1.00

IE: Infective Endocarditis. PPM, Permanent pacemaker, # continuous outcome reported as mean-difference.

the mitral and tricuspid valves more frequently, while males are more prone to aortic valve IE, consistent with our results [33]. One potential explanation for this distribution is the influence of age and comorbidities. Males with IE are typically older and have a higher prevalence of chronic conditions such as chronic liver disease and peripheral artery disease, which are risk factors for aortic valve involvement [34,35]. Conversely, females are more likely to have conditions like atrial fibrillation and chronic kidney disease, which may predispose them to mitral valve involvement at a younger age [34]. In addition, anatomical and physiological differences between the sexes may also contribute to this distribution. The aortic valve is subjected to higher pressures, making it more susceptible to damage and subsequent infection in older males with hypertension and other cardiovascular risk factors [36]. On the other hand, the mitral valve is often involved in conditions like mitral valve prolapse, which is more common in females, making it more vulnerable to infection in this patient population [37]. Moreover, studies indicates that males often exhibit more calcified and sclerotic aortic valves, which can create a favorable environment for bacterial colonization and subsequent endocarditis [38,39]. In contrast, the higher incidence of mitral valve IE in females might be associated with the increased prevalence of connective tissue disorders and rheumatic heart disease conditions that predominantly affect the mitral valve [40].

4.2. Sex differences in microbiological profiles among IE patients

Our study found that males were more frequently infected with Enterococci, while no significant sex differences were observed for Staphylococcus aureus and Coagulase-negative Staphylococcus infections. This discrepancy in microbiological profiles may be attributed to several factors. First, males are more often exposed to risk factors such as invasive procedures, gastrointestinal surgeries, and urological conditions, which are associated with Enterococci infections [41]. Furthermore, males may have different health-seeking behaviors and hygiene practices compared to females, potentially increasing their exposure to these pathogens [42]. Hormonal differences might also play a role in susceptibility to certain infections. For instance, testosterone has been shown to influence immune response and bacterial colonization differently than estrogen, which may contribute to the higher incidence of Enterococci and Streptococci infections in males [43,44]. Additionally, males may have a higher prevalence of conditions such as diabetes, drug abuse disorders, and chronic liver disease, which also increases the risk for such infections [45,46].

4.3. Sex differences in surgery frequency and indications among IE patients

Several studies have highlighted that male patients with IE are more frequently indicated for surgery compared to their female counterparts [15,21,23,24]. This disparity can be attributed to several interrelated factors. Our meta-analysis demonstrated that men exhibit higher rates of

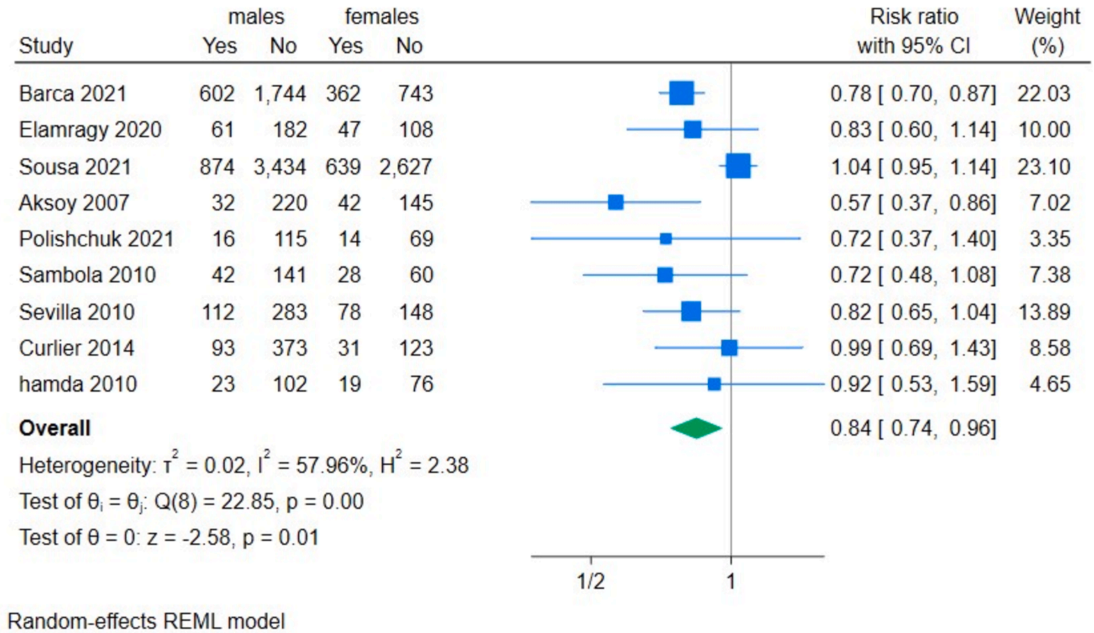

Fig. 3. Forest plot summarizing differences in short-term mortality between both sexes.

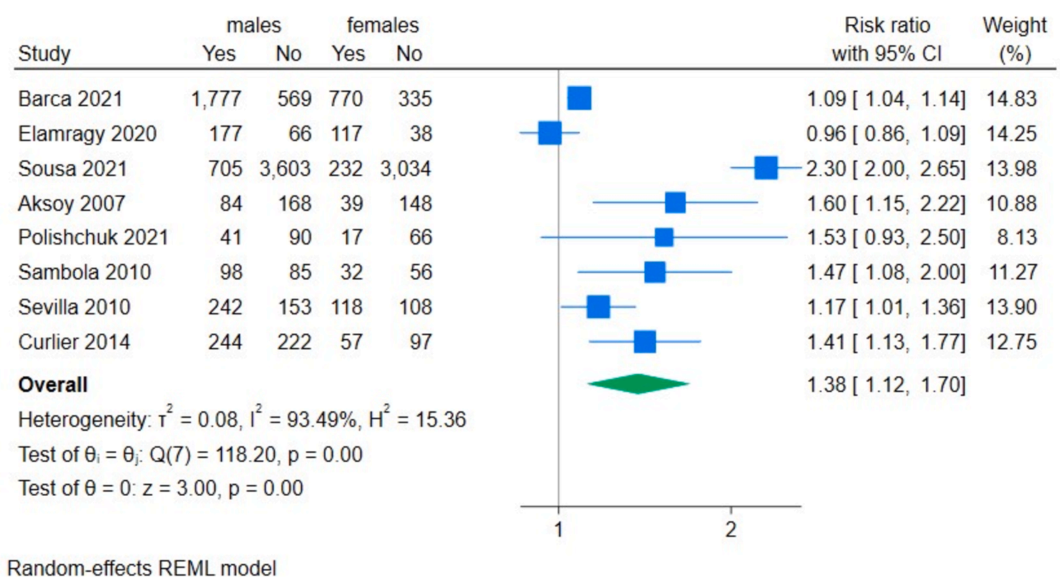

Fig. 4. Forest plot summarizing differences in indication for IE surgery between both sexes.

intracardiac abscesses, a severe complication of IE that often necessitates surgical intervention. The development of intracardiac abscesses in men could be attributed to the more frequent aortic valve involvement at older age, which correlates with more advanced disease and extensive cardiac damage at the time of diagnosis. Furthermore, the aortic valve is more commonly affected in men and is in close proximity to critical structures such as the conduction system and coronary arteries. This anatomical positioning necessitates more frequent surgical intervention in males to address complications arising from the involvement of these critical structures [15]. Additionally, men with IE are more likely to have predisposing factors such as prosthetic valves and previous cardiac surgery, complicating their clinical course and necessitating surgical intervention [47].

On the other hand, the need to address complications such as heart failure and uncontrolled infection, which are more prevalent in males, also drives the higher frequency of surgical intervention in this population [30]. In women, studies have suggested a systematic bias in the decision to perform surgery, potentially due to the higher age and greater comorbidities present in female patients. [21] This bias may lead to women being less frequently indicated for surgery despite having similar clinical course to men [23]. The consistent finding across multiple studies that men undergo surgery more frequently than women could be influenced by clinical decisions based on sex. For instance, in the study by Sambola et al., male gender was independently associated with surgical treatment, despite controlling for other factors such as the presence of severe aortic regurgitation and *peri*-annular complications [21]. This suggests a potential bias in clinical decision-making where men are more readily referred for surgery. Whereas, Curlier et al. noted that although women underwent surgery less frequently, sex was not an independent predictor of surgical intervention, implying other underlying factors possibly influencing this disparity [24].

The female disadvantage in cardiovascular diseases

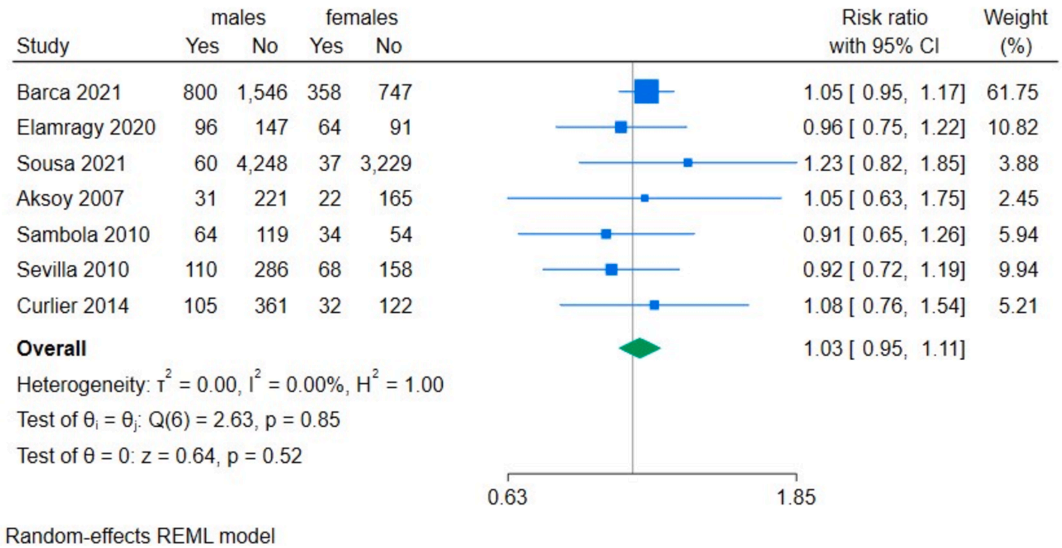

Fig. 5. Forest plot summarizing differences in IE-caused embolization between both sexes.

A myriad of biological, medical and behavioral factors likely contribute to the cardiovascular health disadvantage for women along with potential diagnostic biases. Women undergo remarkable and intricately orchestrated physiological changes during distinct stages of life, encompassing puberty, periodical menstrual cycles, pregnancy, and menopause [48]. These pivotal transitions are accompanied by dynamic alterations in hormonal profile, especially after menopause increasing the vulnerability of women to cardiovascular diseases. Although women have lower age-adjusted rates of cardiovascular disease compared to men, it is still the leading cause of death among women worldwide and a major contributor to the burden of disability-adjusted life-years lost [48,49]. Furthermore, when it comes to women's health, there is a prejudiced restriction of discussing reproductive, maternal and child health. Whereas the long-term implications on general health, especially cardiovascular health, is limited. This is evidently seen in the world of clinical medicine and research, where women are still under-represented in clinical trials. As we progress into the era of precision medicine, it is crucial to recognize that sex differences play a significant role in clinical presentation and influence the health outcomes across different cardiovascular diseases [4–6]. Accordingly, practices must strive to address these inequities through rigorous research and the implementation of sex-equitable practices within the clinical setting. The outcomes of surgical cardiac procedures, particularly coronary and valvular surgery, have been recognized as inferior in female patients. A recent interesting article by Doenst et al. [50] discusses how the surgical challenges may differ between male and female patients. Female patients are often referred to cardiac surgery later in life and tend to have more comorbidities at the time of surgery. Additionally, in coronary surgery, smaller coronary arteries and thinner graft material in female patients, which are more prone to spasm, may contribute to the disparity in outcomes. Such challenging cases typically require more skill to achieve comparable results. This challenge may also apply to surgical patients with valvular disease and IE, contributing to the understanding of outcomes disparity.

4.4. Limitations and future recommendations

To our knowledge, this meta-analysis is the first to provide a comprehensive report on sex differences in infective endocarditis (IE). However, there are several limitations that should be addressed in future research. First, incomplete data regarding the stage of presentation, initial antibiotic strategies, and referral for surgery across the included studies may introduce confounding factors. Also, the urgency of surgical decisions, when indicated, were not consistently reported between both sexes. Second, specific differences in valve-specific outcomes were not reported, nor were outcomes for cases of double valve IE. Future research could explore, for example, how outcomes differ between mitral and aortic valve IE in patients undergoing surgery. While the included studies provide real-world observational data, future studies with matched analyses could offer a more balanced comparison of sex differences.

5. Conclusion

In conclusion, men were more likely to present with aortic valve IE while women showed higher rates of mitral valve IE. Additionally, males also exhibited higher rates of developing intracardiac abscess, Streptococcal or Enterococcal IE, and more frequently underwent surgical intervention for IE. However, the in-hospital mortality was noted to be greater among women. The distinct microbiological and clinical profiles between sexes suggest that sex-based diagnostic and management plans could optimize the outcomes. Future research should aim to develop and implement clinical protocols that address these sex-based differences to ensure equitable and precise treatment strategies for all IE patients.

CRediT authorship contribution statement

Heba T. Salim: Writing – review & editing, Writing – original draft, Software, Investigation, Formal analysis, Data curation. **Yousef A. Hamad:** Writing – original draft, Software, Methodology, Investigation, Formal analysis, Data curation. **Huda Alwadiya:** Writing – review & editing, Writing – original draft, Methodology, Data curation. **Woroud Siriya:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation. **Baraa Mansour:** Writing – original draft, Investigation, Data curation. **Haya Alhadad:** Writing – original draft, Investigation, Data curation. **Walid Marouf:** Investigation, Data curation. **Mohammed Ayyad:** Writing – original draft, Methodology, Investigation. **Ragavendar Saravanabavanandan:** Writing – review & editing, Writing – original draft, Investigation. **Saif Almaghrabi:** Writing – original draft, Investigation. **Mohammed Al-Tawil:** Writing – original draft, Methodology, Investigation. **Assad Haneya:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2025.101607.

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