



Prognostic factors of mortality after surgery in infective endocarditis: systematic review and meta-analysis

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Abstract

Purpose There is a lack of consensus about which endocarditis-specific preoperative characteristics have an actual impact over postoperative mortality. Our objective was the identification and quantification of these factors.

Methods We performed a systematic review of all the studies which reported factors related to in-hospital mortality after surgery for acute infective endocarditis, conducted according to PRISMA recommendations. A search string was constructed and applied on three different databases. Two investigators independently reviewed the retrieved references. Quality assessment was performed for identification of potential biases. All the variables that were included in at least two validated risk scores were meta-analyzed independently, and the pooled estimates were expressed as odds ratios (OR) with their confidence intervals (CI).

Results The final sample consisted on 16 studies, comprising a total of 7484 patients. The overall pooled OR were statistically significant ($p < 0.05$) for: age (OR 1.03, 95% CI 1.00–1.05), female sex (OR 1.56, 95% CI 1.35–1.81), urgent or emergency surgery (OR 2.39 95% CI 1.91–3.00), previous cardiac surgery (OR 2.19, 95% CI 1.84–2.61), NYHA \geq III (OR 1.84, 95% CI 1.33–2.55), cardiogenic shock (OR 4.15, 95% CI 3.06–5.64), prosthetic valve (OR 1.98, 95% CI 1.68–2.33), multivalvular affection (OR 1.35, 95% CI 1.01–1.82), renal failure (OR 2.57, 95% CI 2.15–3.06), paravalvular abscess (OR 2.39, 95% CI 1.77–3.22) and *S. aureus* infection (OR 2.27, 95% CI 1.89–2.73).

Conclusions After a systematic review, we identified 11 preoperative factors related to an increased postoperative mortality. The meta-analysis of each of these factors showed a significant association with an increased in-hospital mortality after surgery for active infective endocarditis.

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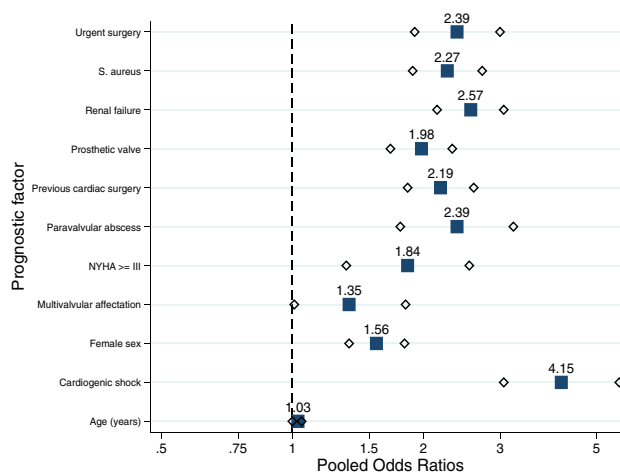
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Graphic abstract

Graph summary of the Pooled Odds Ratios of the 11 preoperative factors analyzed after the systematic review and meta-analysis.



Keywords Infective endocarditis · Prognostic factors · Systematic review · Meta-analysis

Introduction

The mortality rate in patients operated on after the diagnosis of infective endocarditis (IE) is reported to range from 15% to more than 45%, depending on several factors, such as patient baseline characteristics, preoperative status, offending pathogen, intraoperative difficulties and hospital expertise variations [1]. In spite of the improvement of antimicrobial therapy, the advances in surgical techniques and the shortening of waiting time to surgery, the mortality associated with IE continues to be very high [1, 2]. In that context, although cardiac surgery is an essential procedure in the treatment of IE, a proportion of patients who have surgical indication do not undergo surgical treatment because of their high surgical risk, which could lead to surgery rejection [3–6]. It is estimated that less than half of the patients who have a surgical indication finally undergo surgical intervention [7–10]. However, it is well known that patients who have indication for surgery and are not operated on have a dismal prognosis [11], whereas long-term survival in patients who survive the cardiac surgery is acceptable [12].

Therefore, accurate surgical risk estimation is crucial for the surgical decision-making process. In the recent years, several new IE-specific risk scores have been developed. They incorporate some IE-specific factors that are thought to be independent mortality factors [8, 13]. However, the impact of all these specific factors in postoperative mortality continues to be in doubt.

The aim of the present systematic review and meta-analysis was to clarify which are the main pre-operative factors

related to in-hospital mortality after valve surgery for active IE. An adequate knowledge of the impact on survival of these factors may help to guide the surgical decision process, through the identification of patients with a higher risk of suffering a poor outcome after surgery.

Methods

Data sources

The systematic review was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [14], and it followed the recommendations of Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group [15]. The literature search was carried out with the help of an experienced librarian. The review question and the complete search strategy [16] are detailed in Fig. 1-1.

Study selection

The inclusion criteria for the eligible studies were studies whose study population comprised adult subjects with active IE who underwent valve surgery. The investigation of the association between a prognostic factor and in-hospital postoperative mortality was required for inclusion, or raw data from which this association could be determined instead. Active endocarditis was defined as on-going active infection under antimicrobial treatment at the time of surgery [17].

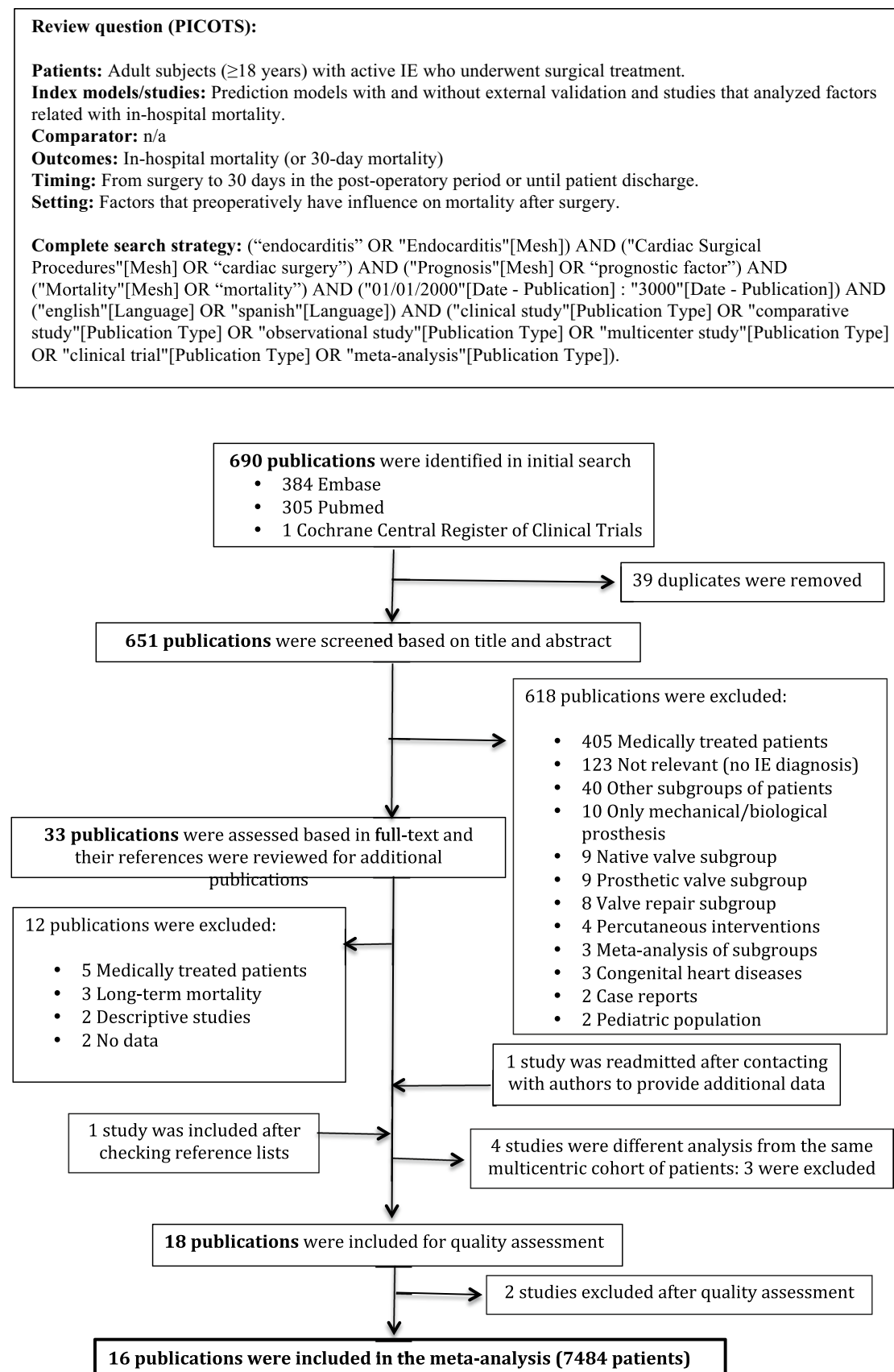


Fig. 1 Search strategy. 1: Review question and complete search strategy. 2: Flow chart of included/excluded studies

Observational studies, randomized controlled trials, and systematic reviews and meta-analysis were included. Redundancies and overlaps between studies were managed and controlled after quality assessment. Studies that included participants who were managed with medical treatment alone, and those studies focused exclusively on specific subgroups (e.g., valve repair, native valves, congenital diseases, etc.) were excluded. The main reason for exclusion of those specific subgroups publications was the lack of availability of full-sample data, with a high risk of selection bias. The search was limited to articles published in English or Spanish languages, in peer-reviewed journals, involving human subjects. In addition, the bibliographic search was limited to studies published from 2000, because of the change in surgical indications and diagnosis with the development of the IE guidelines [18–20]. The selected search string was applied on three databases (Medline, Cochrane and EMBASE). Meeting abstracts, case reports, conference presentations, editorials, and expert opinions were excluded.

Figure 1-2 shows the flow chart of the process of selection of the eligible references, and the reasons for inclusion/exclusion at each step are summarized.

Data extraction and quality assessment

Two reviewers (JLM and LVB) independently reviewed the full-text articles of the remaining references, and eligibility against the predefined criteria was evaluated. Discrepancies between the two reviewers were resolved by discussion and consensus. Complete References list of the eligible studies was checked for possible additional unidentified references. Finally, information was extracted from article text, tables, and figures of each selected study (Table 2).

The methodological quality of the selected studies was assessed using the Quality in Prognostic Studies tool (QUIPS), using the criteria previously published by Hayden et al. [21]. Studies with an unacceptable risk of bias were excluded, considered as those with more than one aspect classified as “high risk of bias”.

Prognostic factor selection and definitions

Through the systematic review of the literature, we identified the most common IE-specific variables (Table 1). All those variables that were considered as risk factors for mortality in two or more IE-specific scores were included in the meta-analysis. Therefore, a total of 11 possible pre-operative prognostic factors related to pre-surgical conditions were identified:

1. Age (considered as a continuous variable, expressed in years).
2. Female sex.

3. Urgent surgery: surgery required within 24 h of its indication [22].
4. Emergency surgery: surgery required on the day of admission [22].
5. Previous cardiac surgery: previous surgical procedure with opening of the pericardium.
6. Functional class \geq III before valve surgery, according to New York Heart Association (NYHA) classification [23].
7. Cardiogenic shock: acute myocardial dysfunction, with systolic pressure $<$ 90 mmHg, tissue hypoperfusion and low cardiac output [24].
8. Prosthetic valve IE: IE affecting a previous prosthetic valve.
9. Multivalvular involvement: IE affecting more than one heart valve.
10. Renal failure: presence of a serum creatinine concentration $>$ 2 mg/dl before surgery.
11. Paravalvular abscess: purulent cavity with necrosis and capacity to invade adjacent structures [25].
12. *Staphylococcus aureus* as the causative agent of the IE episode.

The analyzed outcome was postoperative death, considered as in-hospital mortality and/or death in the first 30 days after surgery [26, 27].

Statistical analysis

All statistical analyses were performed using Stata/IC 14.2 (Stata Statistical Software: Release 14. College Station, TX: StataCorp LP), implemented with the meta-analysis OR, RR, RD, IR, ID, B, MD & R Combined: User-written command [28].

The meta-analysis was performed pooling all the data of reported in hospital mortality in every study, stratified by each of the previously identified IE-specific prognostic factors.

The calculated univariate OR for in-hospital mortality of each of the selected studies were used as the individual summary statistic to obtain the pooled estimation. Heterogeneity across the studies was assessed using the I^2 statistic. An I^2 greater than 25% was considered as substantial heterogeneity [29, 30]. The weighting method used was the inverse of variance fixed-effects model (FEM), if there was no significant heterogeneity across the studies, or random-effects model (REM) if substantial heterogeneity was observed [31].

Forest plot graphs were used to graphically depict the association between early mortality and each of the analyzed factors. Empirical correction of zeros methodology was used if zero mortality events were observed in 1 group. However, forest plot graphs were presented after excluding studies with zero mortality for graphical quality improvement.

Table 1 Variables included in the IE-specific scores (STS-IE, PALSUSE, De Feo-Cotrufo, Costa score, Risk-E, AEPEI, Endoscore and Specific Euroscores I and II) with the corresponding value given in each of them

	STS-IE	PALSUSE	De Feo-Cotrufo	Costa	Risk-E	AEPEI	Endoscore	SpecificES1'	SpecificES2'
Age		> 70:1	40–49:5 50–59:7 60–69:9 70–79:11 > 80:13	≥ 40:4	≤ 51:0 61:9 65:13 ≥ 73:14		60–70:0.46 70–80:0.88 > 80:1.53	≤ 60:0 65:11 70:22 75:33 80:44 90:67 100:78	≤ 60:0 65:11 70:22 75:33 80:44 90:67 100:78
Sex (female)		1					0.51		
Urgent surgery	6	1						Emergent:30	42 Emergent:70
Cardiogenic shock	17 In/IABP:10	∅	Critical state:11 NYHA IV:9	5	15	Critical:1.5 NYHA IV:1.3	1.46	42	37
Multivalvular	9						2:0.5 3:1.5		
Prosthetic IE		1	Not applicable		6				
Prior cardiac surgery	CABG:7 Valve:7	∅						42	35
Renal failure	12	∅	5		5	2.2	0.5	18	
Arrhythmia	8			8 AV block:5					
Active IE	10								
Positive blood cultures		<i>S. aureus</i> :1	5		<i>Virulent</i> :9		<i>P. aureginosa</i> :1.46 <i>S. aureus</i> :1.24 Fungi:1.66 Other:0.60	<i>Staphyl</i> :20	<i>Staphyl</i> :19
Abscess cardiac destruct		1	5	TEE anom:5	5		1.09	Fistulae:46	Fistulae:41
Other variable	IDDM:8 NIDDM:6 Hypert:5 COPD:5	ES ≥ 10%:1		Veg ≥ 10:4 Sepsis:6	Trombop:7 Septic shock:7	BMI > 27:1 sPAP > 55:1	LVEF: -0.03	NYHA > 1:26 Pulm HT:48 Mitral:14	NYHA > 1:22 Mitral:14

Fernández-Hidalgo et al. study

IE infective endocarditis, In inotropes, IABP intra-aortic balloon pump, CABG coronary artery bypass grafting, Hyper high blood pressure, COPD chronic obstructive pulmonary disease, ES EuroScore, NYHA New York Heart Association, AV atrio-ventricular, TEE transesophageal echocardiography, Veg vegetations, Trombop thrombocytopenia, BMI body mass index, sPAP systolic pulmonary artery pressure, LVEF left ventricular ejection fraction, Pulm HT pulmonary hypertension

[∅]Included in EuroSCORE calculation

Publication bias was assessed using Egger method [32] and Funnel plot graphs [33]. All *p* values were two-sided. In addition, to assess the influence of each individual study on the pooled estimates, we performed an influence analysis by sequentially removing each individual study, to analyze the robustness of the estimated ORs.

Results

Description of included studies and patients

Figure 1-2 shows the flow chart for study selection. After full-text review, 18 observational studies were included [9,

Table 2 Main characteristics of included studies

Study	Pub year	Design	Outcomes	Prognostic factors	Sample size	IE	Age	Mort.	Native prosthetic ID	Valve affected
David et al.	2007	RU	In-hospital ^m Long term ^m	3, 6–11	383	LR	51 ± 16	12.0% (45)	69%N 31%P	56%A 27%M 15%MA
Mestres et al.	2007	RU	In-hospital ^m EuroSCORE validation	1–5, 8, 11	180	LR	57.2 ± 15.6	28.8% (55)	n/a	57.1%A 25.7%M 9.9%MA
Hanai et al.	2008	RU	In-hospital ^m	1, 2, 4, 5, 7, 8, 10, 11	94	LR	50.1 ± 15.9	15.0% (14)	84.04%N 17.02%P	55.32%A 29.78%M 11.70%MA
Fayad G. et al.	2011	RU	In-hospital ^m	1, 2, 5, 7, 8, 10, 11	141	LR	56.3 ± 14.9	16.0% (22)	87%N 13%P	39%A 34.75%M 9.93%MA
Caes et al.	2013	RU	In-hospital ^m Long term ^m	1–5, 9, 11	186	LR	57.8 ± 15.3	13.0% (24)	82%N 18%P	45%A 35%M 16%MA
Hussain et al.	2014	RU	In-hospital ^m Long term ^m	1, 7, 10	775	L	n/a	8.0% (62)	53%N 47%P	51%A 31%M 18%MA
Martínez-Sellés et al.	2014	PM	In-hospital ^m Score develop.	1–3, 7, 10, 11	437	LR ID	65.9 ± 16.4	24.3% (106)	61.1%N 27.9%P 11%ID	52.6%A 42.1%M n/a
Spilopoulos et al.	2014	RU	In-hospital ^m Long term ^m	1–3, 5, 7, 8, 9–11	94	LR	58.3 ± 13.1	8.5% (8)	90.4%N 9.6%P	57.4%A 29.8%M 8.5%MA
Marks et al.	2014	RU	30-days ^m	1, 2, 4	336	LR	52	12.2% (41)	79.2%N 20.8%P	56%A 53.9%M 23.5%MA
Oh et al.	2014	RU	In-hospital ^m Long term ^m Morbidity Scores valid	1, 2, 4–6, 8–11	146	LR	48.8 ± 16	6.8% (10)	66.4%N 33.6%P 14.4%ID	64.4%A 42.5%M 14.4%MA
Olmos et al.	2017	PM	In-hospital ^m Score develop.	1, 2, 4–6, 8–11	424	L	61	29.3% (124)	61.1%N 38.9%P	n/a
Di Mauro et al.	2017	RM	In-hospital ^m	1, 2, 4–6, 7–11	2715	LR	59.6 ± 15.1	11.0% (298)	79.6%N 20.4%P	42.5%A 33%M 18%MA
Farag et al.	2017	RU	30 days ^m	1–5, 7–10	360	LR	58.7 ± 14.7	18.3% (68)	86.1%N 13.9%P	45.6%A 31.1%M 13.3%MA
Perrota et al.	2017	RU	In-hospital ^m Medium term ^m Morbidity	1, 2, 7, 8, 10	254	LR	56 ± 16	8.9% (22)	72%N 28%P	57%A 31%M 9%MA

Table 2 (continued)

Study	Pub year	Design	Outcomes	Prognostic factors	Sample size	IE	Age	Mort.	Native prosthetic ID	Valve affected
Varela et al.	2017	RU	In-hospital ^m Scores valid	1-3, 5-11	180	L	61.8 ± 14.3	26.8% (48)	62.78%N 37.22%P	36.84%A 36.84%M 26.32%MA
Fernández-Hidalgo et al.	2018	RM	30 days ^m Score develop	1-6, 8-11	779	LR	58 ± 15.4	26.8% (208)	n/a	62.5%A 41.8%M 12.2%MA

Age: years ± standard deviation

Pub Year publication year, *IE* infective endocarditis, *R* retrospective, *P* prospective, *U* unicentric, *M* multicentric, *L* left, *R* right, *ID* implantable devices, ^m mortality, *PO* post-operative, *A* aortic, *M* mitral, *MA* mitro-aortic, *Mort.* mortality (% of patients)

^ 1: age, 2: female sex, 3: urgent surgery, 4: previous surgery, 5: NYHA ≥ III, 6: cardiogenic shock, 7: prosthetic valve, 8: multivalvular, 9: renal failure, 10: abscess, 11: *S. aureus*

10, 34–49]. The demographic details, distribution, methods and designs of these studies are shown in Table 2.

Four of the initially selected studies analyzed the same multipurpose database, in three different time periods [2, 9, 50, 51]. Therefore, to avoid selection bias because of repeated studies from the same cohort, only one study of these series was included [9].

Quality assessment

To assess the potential biases in the included studies, QuIPS [21] was employed by two reviewers independently in the selected references (Fig. 2-1). Two studies were excluded from the meta-analysis due to a moderate to severe risk of bias [34, 38]. Rob summary table [52] adapted to observational studies was used to show overall risk of bias (Fig. 2-2).

Outcomes

1. Age

Age was analyzed in 15 of the included studies; however, the pooled estimation was only possible in five of them, where age was considered as a continuous variable, comprising a total of 1393 patients. Significant heterogeneity was found across the studies (I^2 53.10%; $p=0.07$). The overall REM pooled OR (Fig. 3-1) was statistically significant (OR 1.03, 95% CI 1.00–1.05, $p<0.01$).

2. Female sex

Fourteen studies reported enough data to estimate the association of sex with the event of interest, comprising a total of 6326 patients (Fig. 3-2). I^2 was 3.96% ($p=0.41$). The overall FEM pooled OR was 1.56 (95% CI 1.35–1.81, $p<0.001$).

3. Urgent or emergency surgery

9 studies analyzed the relation between urgent/emergent surgery and in-hospital mortality (2809 patients). I^2 resulted 38.27% ($p=0.12$). The overall pooled OR after zero correction was statistically significant (OR 2.39, 95% CI 1.91–3.00, $p<0.001$) (Fig. 3-3).

4. Previous cardiac surgery

It was analyzed in 8 of the included studies (4796 patients). I^2 was 24.90%, ($p=0.23$). The overall pooled OR was 2.19 (95% CI 1.84–2.61, $p<0.001$) (Fig. 3-4).

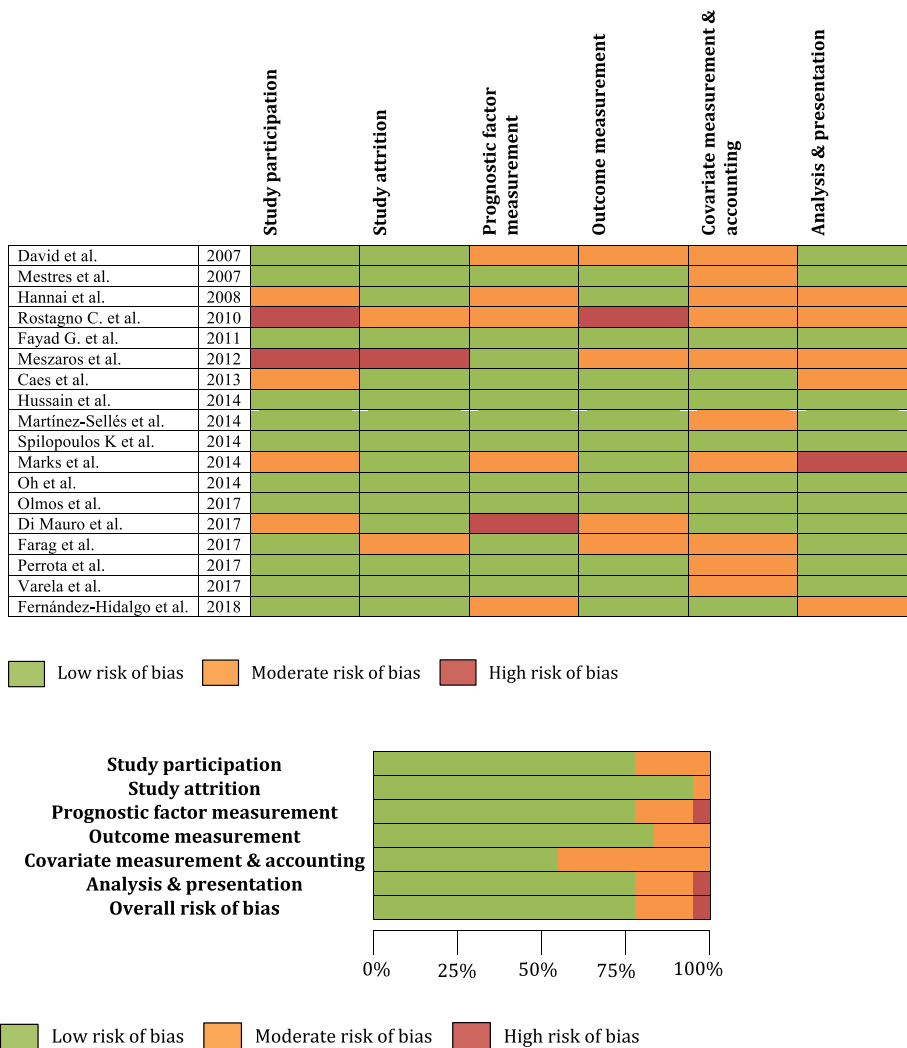
5. NYHA functional class ≥ III

NYHA ≥ III was considered in 10 studies (5119 patients). I^2 resulted 32.90% ($p=0.15$). The REM pooled OR, adjusted for zero correction, was 1.84 (95% CI 1.33–2.55, $p=0.002$) (Fig. 3-5).

6. Cardiogenic shock

Acute circulatory failure was analyzed in 6 studies, comprising a total of 4627 patients. There was significant heterogeneity across the studies ($I^2=43.82%$,

Fig. 2 Quality assessment. 1: Risk of bias table and 2: Rob summary



$p=0.11$). REM pooled estimation resulted in a significant association (OR 4.15, 95% CI 3.06–5.64, $p < 0.001$) (Fig. 3-6).

7. Prosthetic valve IE

Among the 16 studies included in the analysis, 11 analyzed prosthetic valve IE comprising a total of 5857 patients. No heterogeneity was observed across the studies (I^2 0%, $p=0.89$). The overall pooled OR was 1.98 (95% CI 1.68–2.33, $p < 0.001$) (Fig. 3-7).

8. Multivalvular involvement

Multivalvular IE was analyzed in 12 studies (5750 patients). The meta-analysis showed a significant heterogeneity (I^2 37.92%, $p=0.11$). REM pooled estimation (after zero correction) showed a significant association (OR 1.35, 95% CI 1.01–1.82, $p=0.003$) (Fig. 3-8).

9. Renal failure

9 studies analyzed the relation between renal failure and in-hospital mortality, comprising a total of 5267 patients. The overall pooled OR was statistically sig-

nificant (OR 2.57, 95% CI 2.15–3.06, $p < 0.001$) without heterogeneity across the studies (I^2 0%, $p=0.87$) (Fig. 3-9).

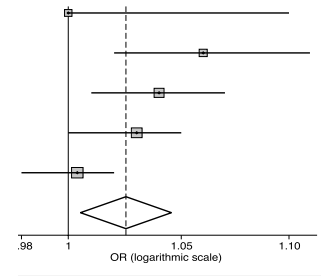
10. Paravalvular abscess

Figure 3-10 shows the estimated OR of in-hospital mortality and abscess formation. Twelve analyzed paravalvular abscess, comprising a total of 6422 patients. The pooled OR was statistically significant (OR 2.39, 95% CI 1.77–3.22, $p < 0.001$) using REM (I^2 64.68%, $p=0.001$).

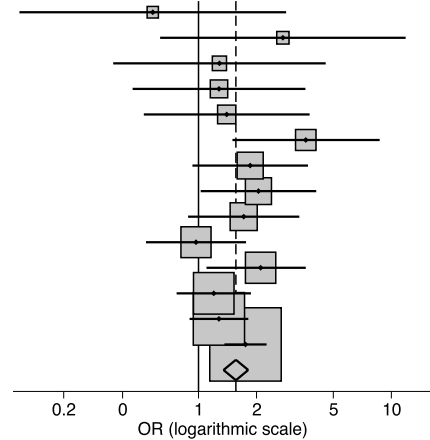
11. *Staphylococcus aureus* infection

Staphylococcus aureus as the causative agent of the IE episode was analyzed in 11 studies (5759 patients). No heterogeneity was observed across the studies (I^2 0%, $p=0.48$). The overall pooled OR was statistically significant (OR 2.27, 95% CI 1.89–2.73, $p < 0.001$) (Fig. 3-11).

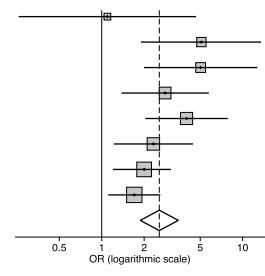
Study	Year	OR	95% CI		Weight (%)
			Lower	Upper	
Caes et al.	2013	1.02	1.00	1.05	11.9
Perrota et al.	2017	1.01	1.00	1.04	14.0
Varela et al.	2017	1.02	0.99	1.05	21.4
Martínez-Sellés et al.	2014	1.02	0.99	1.05	24.6
Marks et al.	2014	1.03	1.01	1.05	28.1
Total		1.03	1.00	1.05	100



Study	Year	OR	95% CI		Weight (%)
			Lower	Upper	
Oh et al.	2014	0.58	0.11	2.85	0.86
Spilopoulos K et al.	2014	2.74	0.63	11.87	1.01
Hanai et al.	2008	1.28	0.36	4.56	1.35
Fayad G. et al.	2011	1.28	0.46	3.58	2.05
Perrota et al.	2017	1.4	0.52	3.77	2.23
Caes et al.	2013	3.6	1.5	8.7	2.82
Marks et al.	2014	1.85	0.93	3.69	4.58
Varela et al.	2017	2.05	1.02	4.08	4.59
Mestres et al.	2007	1.72	0.88	3.33	4.94
Farag et al.	2017	0.97	0.53	1.76	6.11
Martínez-Sellés et al.	2014	2.1	1.1	3.6	6.20
Olmos et al.	2017	1.2	0.77	1.87	11.1
Fernández-Hidalgo et al.	2018	1.28	0.89	1.81	17.6
Di Mauro et al.	2017	1.75	1.36	2.25	34.4
Total		1.56	1.35	1.81	100



Study	Year	OR	95% CI		Weights
			Lower	Upper	
Spilopoulos K et al.	2014	1.09	0.26	4.67	4.06
Caes et al.	2013	5.1	1.9	13.5	7.79
Fernández-Hidalgo et al.	2018	5.04	1.99	12.69	8.51
Varela et al.	2017	2.81	1.38	5.76	12.3
Mestres et al.	2007	4	2.04	7.84	13.2
David et al.	2007	2.32	1.21	4.44	13.9
Martínez-Sellés et al.	2014	2	1.2	3.1	19.2
Olmos et al.	2017	1.70	1.11	2.60	21.1
Total		2.56	1.87	3.49	100



Study	Year	OR	95% CI		Weights
			Lower	Upper	
Oh et al.	2014	2.48	0.68	9.07	1.81
Hanai et al.	2008	2.62	0.76	9.01	1.98
Marks et al.	2014	3.85	1.15	12.5	2.13
Caes et al.	2013	2.4	1	6.1	3.71
Mestres et al.	2007	2.23	1.16	4.31	7.02
Farag et al.	2017	1.36	0.77	2.41	9.28
Fernández-Hidalgo et al.	2018	3.11	2.22	4.35	26.8
Di Mauro et al.	2017	1.87	1.45	2.42	47.3
Total		2.19	1.84	2.61	100

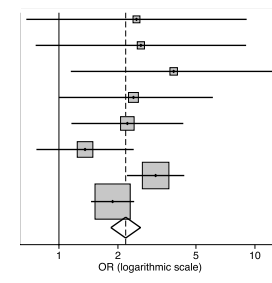
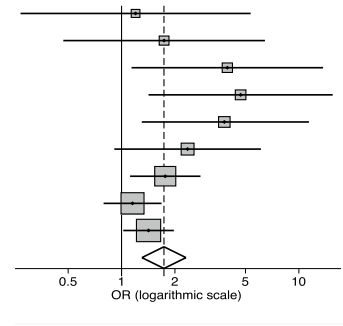
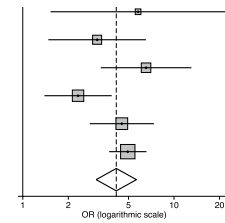


Fig. 3 Forest plot graphs. 1: Age, 2: Female sex, 3: Urgent surgery, 4: Previous cardiac surgery, 5: NYHA ≥ III, 6: Cardiogenic shock, 7: Prosthetic valve IE, 8: Multivalvular IE, 9: Renal failure, 10: Paravalvular abscess, 11: *S. aureus*. *OR odds ratio; CI confidence interval

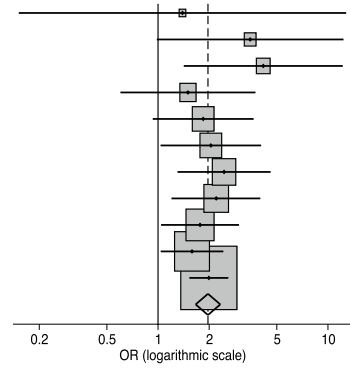
Study	Year	OR	95% CI		Weights
			Lower	Upper	
Spilopoulos K et al.	2014	1.2	0.27	5.35	3.36
Oh et al.	2014	1.74	0.47	6.44	4.26
Hanai et al.	2008	3.95	1.14	13.71	4.67
Farag et al.	2017	4.69	1.42	15.52	5.01
Caes et al.	2013	3.8	1.3	11.4	5.91
Fayad G. et al.	2011	2.36	0.91	6.11	7.36
Olmos et al.	2017	1.76	1.11	2.79	19.7
Di Mauro et al.	2017	1.15	0.79	1.68	23.6
Fernández-Hidalgo et al.	2018	1.42	1.02	1.97	26.1
Total		1.73	1.30	2.30	100



Study	Year	OR	95% CI		Weights
			Lower	Upper	
Oh et al.	2014	5.78	1.52	21.92	4.70
Varela et al.	2017	3.10	1.48	6.53	12.1
David et al.	2007	6.53	3.28	13.02	13.4
Olmos et al.	2017	2.32	1.39	3.82	19.2
Fernández-Hidalgo et al.	2018	4.52	2.77	7.35	20.2
Di Mauro et al.	2017	4.95	3.72	6.57	30.5
Total		4.15	3.06	5.64	100



Study	Year	OR	95% CI		Weights
			Lower	Upper	
Spilopoulos K et al.	2014	1.39	0.15	12.79	0.56
Hanai et al.	2008	3.48	0.98	12.35	1.74
Fayad G. et al.	2011	4.16	1.42	12.22	2.40
Perrota et al.	2017	1.5	0.60	3.75	3.32
Farag et al.	2017	1.84	0.93	3.65	5.96
Varela et al.	2017	2.05	1.04	4.04	6.00
David et al.	2007	2.25	1.30	4.59	6.99
Martínez-Sellés et al.	2014	2.2	1.2	4	7.68
Hussain et al.	2014	1.77	1.04	2.99	9.97
Olmos et al.	2017	1.59	1.04	2.42	15.4
Di Mauro et al.	2017	1.99	1.52	2.59	39.9
Total		1.98	1.68	2.33	100



Study	Year	OR	95% CI		Weights
			Lower	Upper	
Hanai et al.	2008	0.54	0.06	4.57	1.81
Farag et al.	2017	0.71	0.08	6.00	1.81
Fayad G. et al.	2011	1.55	0.39	6.08	4.08
Perrota et al.	2017	1.67	0.46	6.14	4.44
Mestres et al.	2007	1.15	0.41	3.22	6.62
Varela et al.	2017	4.42	2.12	9.20	10.8
David et al.	2007	1.33	0.67	2.67	11.6
Olmos et al.	2017	0.88	0.53	1.44	16.8
Fernández-Hidalgo et al.	2018	1.24	0.78	1.98	17.7
Di Mauro et al.	2017	1.39	1.05	1.86	24.4
Total		1.38	1.03	1.86	100

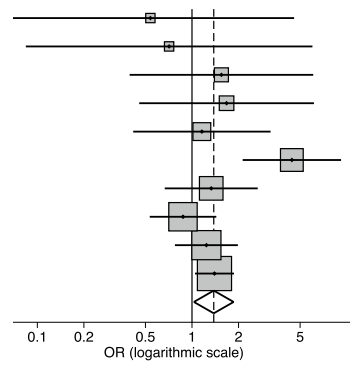
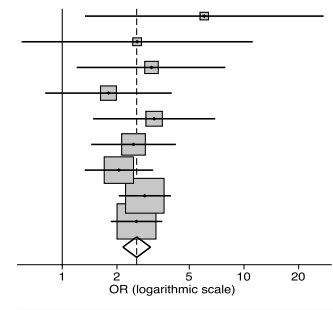
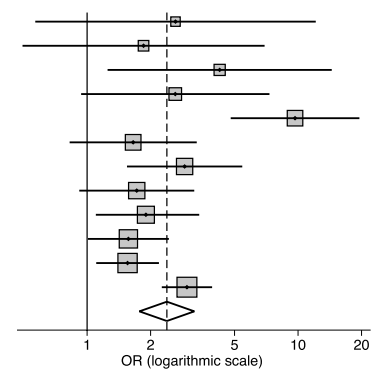


Fig. 3 (continued)

Study	Year	OR	95% CI		Weights
			Lower	Upper	
Oh et al.	2014	6.04	1.33	27.43	1.34
Spilopoulos K et al.	2014	2.58	0.59	11.17	1.43
Caes et al.	2013	3.1	1.2	7.9	3.45
Varela et al.	2017	1.79	0.81	4.00	4.77
David et al.	2007	3.2	1.48	6.95	5.12
Farag et al.	2017	2.47	1.44	4.22	10.6
Olmos et al.	2017	2.05	1.33	3.16	16.3
Di Mauro et al.	2017	2.84	2.05	3.96	28.1
Fernández-Hidalgo et al.	2018	2.56	1.84	3.55	28.8
Total		2.56	2.15	3.06	100



Study	Year	OR	95% CI		Weights
			Lower	Upper	
Spilopoulos K et al.	2014	2.63	0.57	12.13	3.08
Oh et al.	2014	1.85	0.49	6.94	3.87
Hanai et al.	2008	4.25	1.25	14.45	4.33
Fayad G. et al.	2011	2.62	0.94	7.31	5.49
Perrota et al.	2017	9.68	4.79	19.53	8.36
Varela et al.	2017	1.65	0.83	3.31	8.45
Hussain et al.	2014	2.89	1.55	5.44	9.19
David et al.	2007	1.72	0.92	3.22	9.21
Martínez-Sellés et al.	2014	1.9	1.1	3.4	9.98
Olmos et al.	2017	1.57	1.01	2.44	11.6
Fernández-Hidalgo et al.	2018	1.56	1.10	2.19	12.8
Di Mauro et al.	2017	2.97	2.26	3.91	13.7
Total		2.39	1.77	3.22	100



Study	Year	OR	95% CI		Weights
			Lower	Upper	
Spilopoulos K et al.	2014	2.11	0.46	9.66	1.43
Hanai et al.	2008	1.41	0.34	5.75	1.66
Oh et al.	2014	2.58	0.71	9.42	1.96
Fayad G. et al.	2011	1.22	0.43	3.41	3.11
Caes et al.	2013	3.5	1.5	8.5	4.37
Varela et al.	2017	1.7	0.77	3.78	5.18
Mestres et al.	2007	1.60	0.74	3.47	5.53
David et al.	2007	1.85	0.94	3.62	7.28
Martínez-Sellés et al.	2014	2.3	1.3	4.1	9.98
Olmos et al.	2017	1.49	0.88	2.54	11.8
Di Mauro et al.	2017	2.83	2.18	3.68	47.7
Total		2.27	1.89	2.73	100

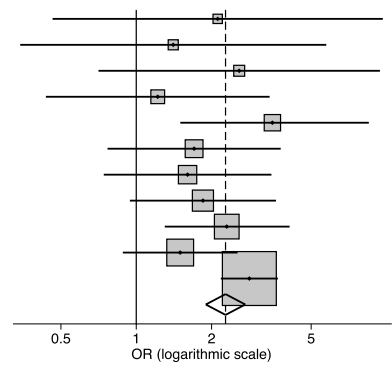


Fig. 3 (continued)

Other data

There was a possible publication bias, according to Egger’s method in 7 of the analyzed variables; however, no important asymmetries were observed regarding Funnel plots (Fig. 4).

Regarding the influence analysis, the pooled estimates were robust and independent of the deletion of any individual study.

Discussion

We performed a systematic review of all the studies that reported factors related to in-hospital mortality after cardiac surgery for IE, trying to address which of those previously described factors are related to poor prognosis. After the development of 11 independent meta-analysis, in order to assess the relative influence of each one on mortality, we found that the 11 possible pre-operative prognostic factors analyzed were associated with poor outcome after surgery.

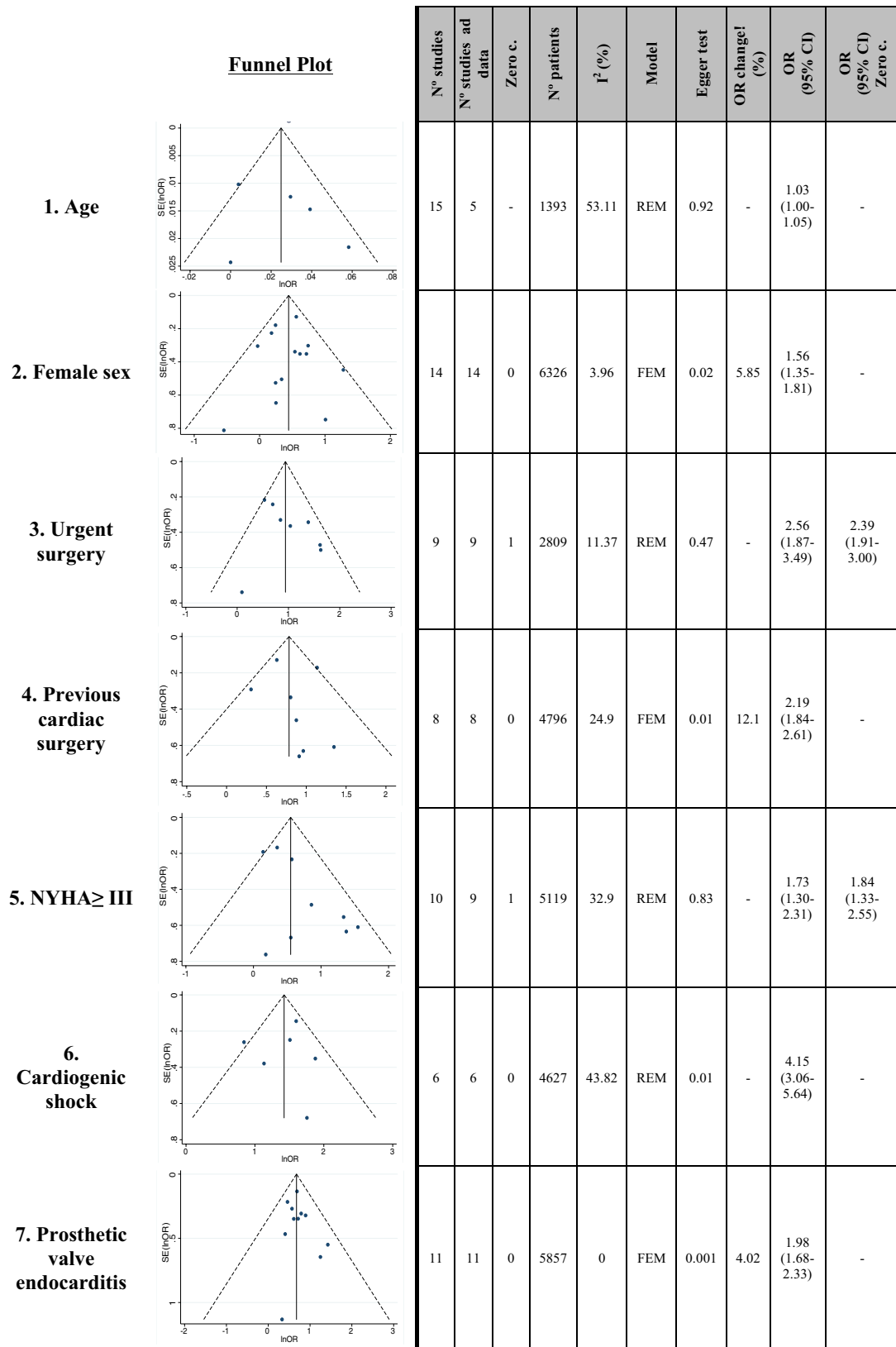


Fig. 4 Funnel plots and results in each of the meta-analysis conducted. *N° number, *Stud ad. data* studies with adequate data for pooled calculations, *FIM* fixed effects model, *REM* random effects

model, *OR* odds ratio, *CI* confidence interval, *Zero c* zero correction needed. OR change ^ after influence analysis, maximum change in the pooled OR

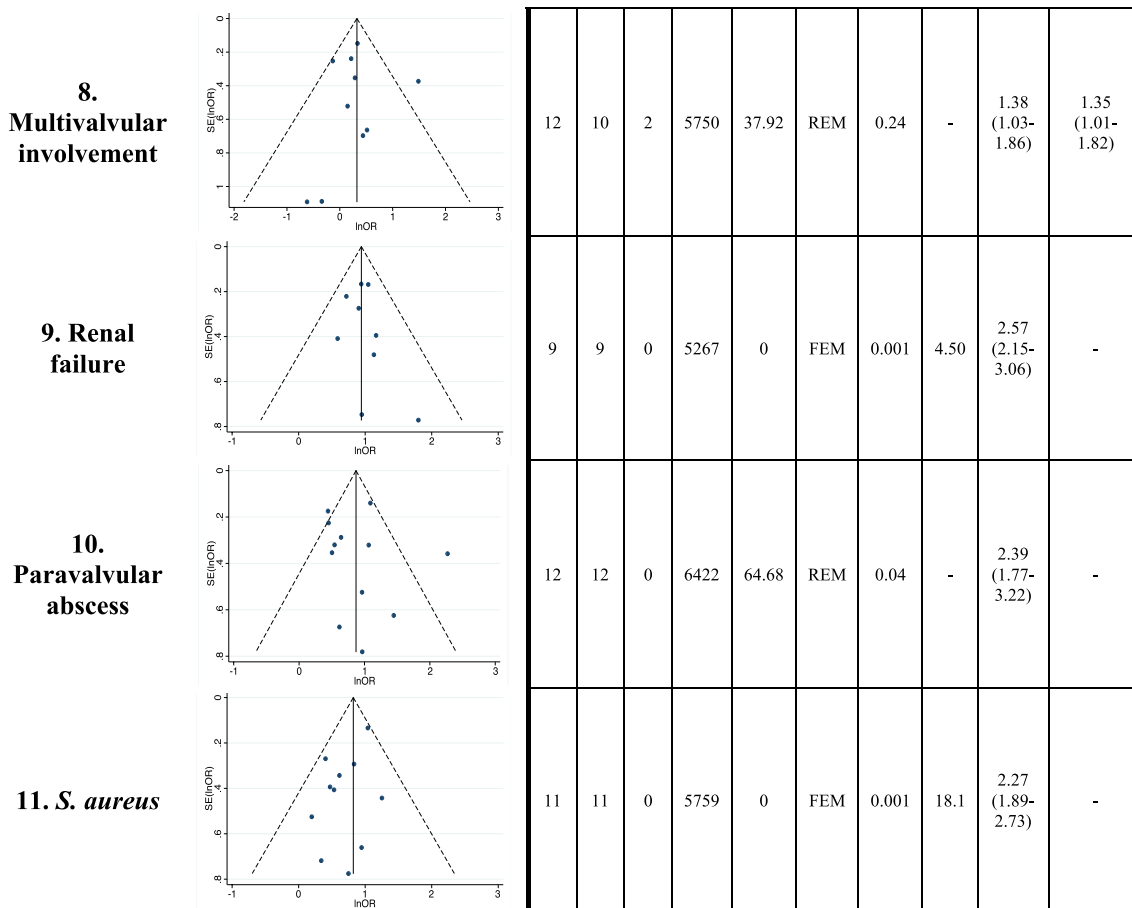


Fig. 4 (continued)

In the last years, some new endocarditis specific scores have been published [8, 9, 41, 45, 48, 53–55] trying to improve prognostic accuracy. And, at the same time, a lot of retrospective and prospective observational studies with limited sample sizes were published describing independent factors for mortality. Several IE-specific factors have been previously defined as independent mortality predictors in patients with IE [8–10, 47, 56]. However, the impact of these specific factors on postoperative mortality is debated, since the ones considered in each study are different, and with varied effect-sizes.

Regarding age, although it is one of the most important factors employed in risk calculation [41, 44, 47], it was only considered as a continuous variable in 5 of the included studies. There is an important lack of consensus when categorizing this variable, with different cut-off points when age was considered as a categorical variable. Therefore, it is not possible to combine every study’s individual results. Nevertheless, we observed the huge importance that age has in the prognosis after cardiac surgery, with a 3% of increase in mortality for each additional year.

Several studies found that although women suffered from IE less frequently than men, females have more severe manifestations and are more likely to have worse outcomes [57]. Although female sex is considered as a risk factor in the majority of cardiac surgery scores, it is only present in half of the IE-specific scores [47]. The individual studies included in our systematic review did not find female sex as a significant mortality factor, probably because of a relatively small sample size. Therefore, the pooled estimation found that female sex had a significant association with mortality (OR 1.56).

Both IE-specific scores and classic cardiac surgery risk scores take into account the priority of the surgical intervention to estimate mortality risk [47]. Urgent or emergency surgeries had a significant association with mortality in almost every individual study; consequently, the pooled OR was also statistically significant. Similarly, a history of previous cardiac surgery also increases the difficulty of the surgical approach and increases the mortality risk. Probably for that reason, it also showed a significant association with mortality.

Regarding the clinical presentation of IE, a poor preoperative hemodynamic condition is the greatest predictor of mortality, therefore, it is present in all the published risk models [8, 47]. Cardiogenic shock showed the strongest association with mortality in our meta-analysis (OR 4.15). Likewise, in patients without a critical hemodynamic condition, the presence of heart failure also was an indicator of worse prognosis after surgery [5], with a pooled OR for NYHA \geq III of 1.84. Regarding valvular invasion, on the one hand, the prognostic implications of prosthetic valve IE have been reported elsewhere [58, 59]. On the other hand, the involvement of more than one cardiac valve has been described as a marker of non-controlled infection and greater severity of IE [8]. Although few studies analyzed the risk of death in multivalvular IE, high mortality rates were reported [60, 61]. Our pooled estimations confirmed an association with mortality of both prosthetic valve IE and multivalvular invasion.

Preoperative renal insufficiency is associated with poor prognosis [62, 63] and longer hospitalization in patients with IE [64]. Nine articles considered renal failure as a prognostic factor, and their results were consistent. Paravalvular abscess increases complexity of the procedure and complications associated with IE surgery and mortality [13]. It is probably associated with higher microorganism virulence, poor prognosis and a delay in the surgical treatment [65]. Twelve studies analyzed paravalvular abscesses, and the pooled OR was 2.39, which agrees with the studies that specifically analyzed outcomes in IE complicated with paravalvular abscesses [13, 65]. *Staphylococcus aureus* is being recognized as the most common cause of IE [1, 66] and also has been shown to be an independent predictor of mortality. *Staphylococcus aureus* is related to severity of the local invasion, with increased likelihood of abscesses formation, fistulae and prosthesis dehiscence. Our results confirmed a significant relation with mortality of this etiologic agent.

We believe that an adequate knowledge of the impact on survival of the analyzed risk factors may help to guide the surgical decision process in IE patients. Some meta-analyses were developed to assess the optimal time to surgery, compared biological versus mechanical prosthesis, or compared valve replacement versus valve repair in IE patients. But to our knowledge, our study is the first meta-analysis of prognostic factors in IE surgery in which 11 factors associated with poor outcome were assessed. Recently, Wang et al. published a meta-analysis of risk-scores in surgery for IE [67], comparing the prognostic utility of EuroSCORE I and II, which included 8 studies (1743 patients), and they calculated pooled c-statistics for operative mortality for both scores. They concluded that EuroSCORE had a trend to over-estimate mortality, and suggested that EuroSCORE II would be a better estimator, but in addition, the authors made great emphasis on the need to develop new endocarditis-specific

risk scores. One possible future study, after identification of these preoperative factors related to in-hospital mortality, could be the use of the obtained regression coefficients in the development of a new specific-IE score derived from the literature search.

Study limitations

The major limitation of this report is that our meta-analysis included both prospective and retrospective observational studies, with a small to moderate number of patients. Therefore, because of their observational nature, there could be some unidentified differences between the studies, regarding different disease spectrum, referring population size, epidemiological factors, hospital differences, referral bias [68] or surgical indications. For example, the aggressiveness of endocarditis could be different between the included studies, since some of them included only left side IE; whereas other studies included also right side IE. In addition, some studies considered in-hospital mortality as their main outcome, whereas other calculated 30-day mortality. However, predefined criteria insured the inclusion of exclusively active IE. Unfortunately, the results of the individual studies included were not adjusted for baseline differences, since we reported the OR from the univariate analysis or the ones obtained from raw data calculations; so there is risk of bias because of unknown confounders. Of the 16 studies finally included in the meta-analysis, it is important to note that none of them included as much as these 11 factors altogether.

Statistical analysis revealed a possible publication bias in some of the analyzed factors. In addition, some of the funnel plot showed slight asymmetries. The role of chance is critical for interpretation of funnel plots because most of our meta-analyses contained few studies. Relations across studies in meta-analysis are seriously prone to false positive findings when there is heterogeneity and a few numbers of studies are included, which may affect funnel plot symmetry [33].

In reference to age, as we previously mentioned, there is an important lack of consensus in the cut-off points for categorization of age across the studies. Categorization of continuous variables carries a loss of information, and it is not recommended. Therefore, it could only be analyzed when continuous age OR were reported.

All those variables that were considered as risk factors for mortality in two or more IE-specific scores were included in the meta-analysis; however, some other possible risk factors were not analyzed, such as vegetations, thrombocytopenia, LVEF, stroke or embolism. We tried to follow a strict criterion to choose the most studied variables in risk assessment by reviewing previously published IE-specific scores; however the analysis of those other risk factors could be performed to further improve mortality risk prediction.

Conclusions

After a systematic review, we identified 11 preoperative factors related with an increased postoperative mortality: Cardiogenic shock, urgent surgery, paravalvular abscess, preoperative renal failure, previous cardiac surgery, *S. aureus*, female sex, age, NHYA class \geq III, prosthetic valve IE, and multivalvular involvement.

The meta-analysis of each of these factors showed a significant association with an increased in-hospital mortality after surgery for active infective endocarditis.

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Compliance with ethical standards

Conflict of interest There was no conflict of interest.

Ethical approval The Ethical Review Board (ERB) of the Hospital approved the implementation of this study (ERB number 313/2016, approved on November 28, 2016).

Informed consent The requirement for informed written consent was waived. Patient identification was encoded, complying with the requirements of the Organic Law on Data Protection 15/1999.

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