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REVIEW ARTICLE

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Patient survival in severe low-flow, low-gradient aortic stenosis after aortic valve replacement or conservative management

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Abstract

Background and aim: Classical and paradoxical low-flow, low-gradient (LFLG) aortic stenosis (AS) are the most challenging subtypes of AS. The current therapeutic options are aortic valve replacement (AVR) and conservative management: AVR promotes long-term survival but is invasive, while conservative management yields a poor prognosis but is noninvasive since it uses no aortic valve replacement (noAVR). The present meta-analysis investigated the rate of survival of patients with LFLG AS undergoing either AVR or noAVR interventions.

Methods: The meta-analysis compared the outcomes of AVR with those of noAVR in terms of patient survival. In both groups, a meta-regression was conducted to investigate the impact on patient survival of the left ventricular ejection fraction (LVEF), either preserved (paradoxical LFLG AS) or reduced (classical LFLG AS).

Results: The relative risk of survival between the AVR and noAVR groups was 1.99 [1.40, 2.82] ($p = .0001$), suggesting that survival tends to be better in AVR patients than in noAVR patients. The meta-regression revealed that a reduced LVEF may be related to a higher survival in AVR patients when compared to a preserved LVEF ($p = .04$). Finally, the analysis indicated that LVEF seems not to be prognostic of survival in noAVR patients ($p = .18$).

Conclusions: Patients with LFLG AS have better survival if they undergo AVR. In AVR patients, reduced LVEF rather than preserved LVEF is related to better survival, whereas there seems to be no difference in prognostic value between reduced and preserved LVEF in noAVR patients.

KEYWORDS

aortic stenosis, aortic valve replacement, ventricular function

Linda R. Micali and Salma Algargoosh equally contributed to the paper.

1 | INTRODUCTION

Low-flow, low-gradient (LFLG) aortic stenosis (AS) is the most challenging AS subtype, regardless of whether it is accompanied by either depressed left ventricular ejection fraction (LVEF) (i.e., classical LFLG AS) or preserved LVEF (i.e., paradoxical LFLG AS).[1,2] The challenge derives from the impossibility of choosing the right therapeutic approach because a realistic assessment of the extent of stenosis is not always possible due to the discrepancy between aortic valve area (AVA) and pressure gradient.[3]

Currently, the available therapeutic management for LFLG AS is either aortic valve replacement (AVR)—performed either percutaneously (transcatheter valve replacement [TAVR]) or surgically (surgical valve replacement [SAVR]) in symptomatic patients with left ventricular (LV) dysfunction—or conservative management.[4] AVR promotes long-term survival and improvement of the functional status of patients in both classical and paradoxical LFLG AS. Nonetheless, it is more invasive and is associated with high operative mortality risk in patients with reduced LV contractile reserve.[4-7] In contrast, a no aortic valve replacement (noAVR) approach carried out mainly by medical management is considered to be the treatment of choice in elderly patients and subjects with high preoperative risk, because it is noninvasive.[8] However, noAVR approaches predispose patients to a poorer prognosis in both classical and paradoxical LFLG AS.[8]

Since a noAVR approach leads to a poor prognosis and AVR is burdened by a high operative risk, the literature reports conflicting results about the superiority of one type of management over the other. Accordingly, the present meta-analysis aims to investigate the survival rate of patients with LFLG AS undergoing AVR versus noAVR interventions.

2 | MATERIALS AND METHODS

2.1 | Search strategy

We conducted our study using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) investigation guidelines. We searched for all available articles that reported the survival rate in patients with LFLG AS after they underwent either AVR or noAVR.[9] A literature search was conducted in Embase and Medline databases through PubMed, as well as in Google Scholar and Cochrane Library. Additionally, we checked both the relevant articles contained in these databases and the relevant references listed in these articles but not in the databases. We used both free text words and MeSH terms.

The search terms were: “conservative therapy” AND “valve replacement” AND “aortic valve replacement” AND “aortic stenosis” AND “low flow” AND “low gradient”; “aortic stenosis” AND “low flow low gradient” AND “aortic valve replacement” AND “medical management”; “aortic stenosis” AND “low flow low gradient” AND surgery AND medical.

2.2 | Selection criteria

We included articles that met the following criteria: (a) performed on humans, (b) studies with more than 20 patients, (c) articles comparing AVR to noAVR procedures, (d) articles focused on LFLG AS, (e) studies published in English and (f) articles published within the last 15 years (2004–2019). We excluded articles with the following conditions: (a) performed on animals, (b) not in English, (c) literature reviews and meta-analyses, (d) population studies of 20 or less, (e) articles older than 15 years, (f) studies not focusing on LFLG AS, (g) studies that did not report a comparison between AVR and noAVR; (h) studies conducted on patients selected on the basis of their baseline characteristics (e.g., studies specifically carried out on elderly patients or on patients with coronary artery disease); (i) studies on AVR patients the majority of which underwent other concomitant procedures.

All studies were approved by local Ethical Committees, in retrospective studies the consent was waived and in prospective studies patients were excluded if they did not provide their informed consent.

2.3 | Methodological quality assessment

To evaluate the quality of the included studies, we used a modified tool of Down and Black's Checklist for Measuring Quality.[10] This tool consists of 18 questions evaluating five criteria: (a) the overall quality of the study, (b) the external validity, (c) study bias, (d) confounding and selection bias, and (e) power of the study. These questions are graded on a 0–1 scale, except for two questions that are graded one on a 0–2 and one on a 0–5 scale.

Two researchers (S.A. and L.M.) conducted the evaluation. A third researcher was involved in reviewing (O.P.). The agreement was quantified using Cohen's kappa.[11]

2.4 | Endpoints

The primary endpoint of our study was the survival rate at follow up in patients with LFLG AS, treated with AVR or noAVR. We also investigated the impact of LVEF on survival. In the AVR group, we included both SAVR and TAVR, while in the noAVR group we included conservative medical management and valvuloplasty.[3]

LFLG AS was defined as an AVA of $\leq 1\,cm^2$ or an indexed AVA $<0.6\,cm^2/m^2$, a stroke volume indexed (SVI) $\leq 35\,ml/m^2$ and a transvalvular mean pressure gradient ≤ 40 mmHg. Preserved LVEF was identified as >55% (paradoxical LFLG AS), while reduced LVEF was defined as <50% (classical LFLG AS).[3]

2.5 | Statistical analysis

This meta-analysis was conducted using V.3.6.1 (R Foundation for Statistical Computing). We used relative risk (RR) and proportions as main statistical indices. The I^2 test was used to evaluate heterogeneity and the Egger regression test to evaluate publication bias. Furthermore, meta-regression was performed to evaluate the impact of LVEF on survival in both the AVR and noAVR groups. We defined statistical significance for $p < .05$.

3 | RESULTS

3.1 | Characteristics of the studies

The steps that we followed in selecting the articles are shown in the PRISMA flow diagram in Figure 1. In the end, there were 13 articles included in our meta-analysis.[12-24]

The overall population size was 2013 patients, 1066 (53%), and 947 (47%) in the AVR and noAVR groups, respectively.

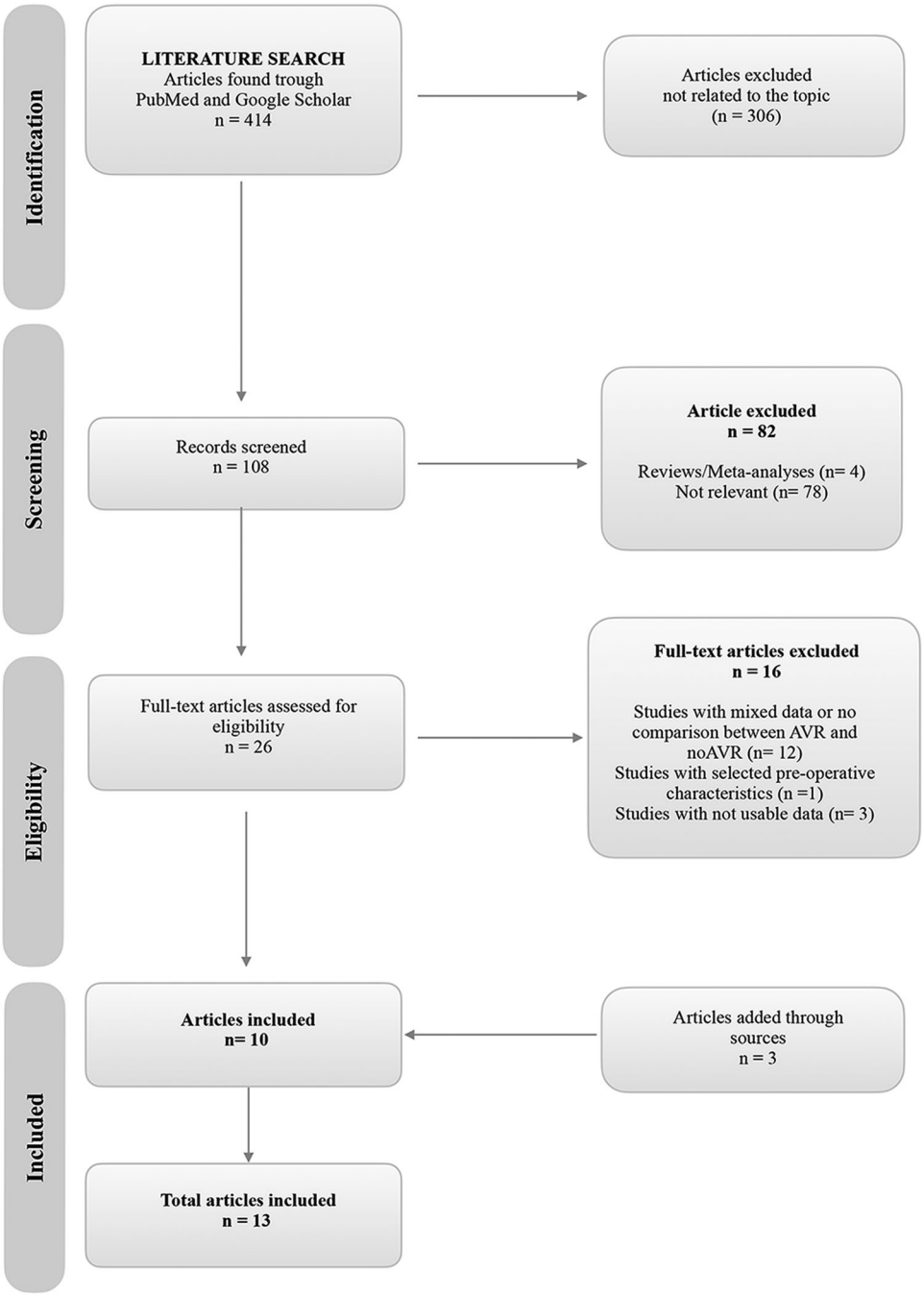

FIGURE 1 PRISMA flowchart of the selection process. noAVR, no aortic valve replacement

TABLE 1 Patient characteristics

Author (year)	Study design	No. patients	No. patients		Age	Female	Symptoms	AVA (cm^2)	SVi (ml/m^2)	Mean gradient (mmHg)	LVEF (%)	Classical LFLGAS/ Paradoxical LFLGAS	CAD	Follow up (months)
			AVR	noAVR										
Hachicha et al. (2007)	RCS	171	80	91	73 ± 13	92 (51)	–	0.76 ± 0.23	–	32 ± 17	62 ± 8	Paradoxical LFLGAS	46 (65)	60[a]
Clavel et al. (2008)	MPOS	101	44	57	71 ± 10	23 (23)	49 (49)	0.92 ± 0.24	–	21 ± 8	29 ± 9	Classical LFLGAS	76 (75)	20 ± 15
Pai et al. (2008)	RCS	167	46	121	72 ± 13	–	–	–	–	–	–	Classical LFLGAS: 115 (68.9) Paradoxical LFLGAS: 52 (31.1)	–	28.8 ± 32.4
Tarantini et al. (2011)	RCS	101	72	29	78 [72–81]	59 (58)	90 (88)	0.80 [0.70-0.89]	46 ± 13	33 [27–38]	0.69 [0.61–0.74]	Paradoxical LFLGAS	63 (62.4)	42 [23–75]
Clavel et al. (2012)	RCS	187	83	104	74 ± 12	96 (51)	44 (22)[b] 104 (56)[c]	0.82 ± 0.16	30 ± 4	22 ± 8	62 ± 8	Paradoxical LFLGAS	120 (64)	50.4 ± 28.8
Mohty et al. (2013)	RCS	99	83	16	77 ± 6	50 (51)	88 (89)	0.72 ± 0.17	29 ± 5	30 ± 7	70 ± 11	Paradoxical LFLGAS	54 (54.5)	55.2 ± 36
Melis et al. (2013)	RCS	40	18	22	78 [73.0-83.0]	25 (59.5)	–	0.77 [0.73-0.81]	31 [30–32]	26 [24–29]	64 [62–67]	Paradoxical LFLGAS	22 (55)	26.1 [14.6-36.1]
Herrmann et al. (2013)	RCS	130	105	25	–	–	–	–	–	–	–	Classical LFLGAS	–	24[a]
Eleid et al. (2013)	RCS	53	27	26	77 ± 12	18 (34)	41 (77)	0.87 ± 0.11	31 ± 3	30 ± 6	60 ± 7	Paradoxical LFLGAS	23 (43)	27.6 ± 22.8
Ozkan et al. (2013)	PCS	135	54	81	–	–	–	–	–	–	–	Paradoxical LFLGAS	–	60[a]
Tribouilloy et al. (2015)	RCS	114	57	57	78.5 [73.5–86.3]	33 (57.9)	9 (15.8)	0.8 [0.7–0.9]	30.1 [27.2–32.2]	30 [20.5–34.5]	60 [55–67]	Paradoxical LFLGAS	22 (13.3)	39 [11–69]

(Continues)

TABLE 1 (Continued)

Author (year)	Study design	No. patients	No. patients		Age	Female	Symptoms	AVA (cm^2)	SVi (ml/m^2)	Mean gradient (mmHg)	LVEF (%)	Classical LFLGAS/ Paradoxical LFLGAS	CAD	Follow up (months)
			AVR	noAVR										
Annabi et al. (2019)	PCS	480	269	211	75 ± 10	136 (28.3)		0.79 ± 0.15	-	26 ± 7	-	Classical LFLGAS: 341 (71) Paradoxical LFLGAS: 139 (29)	-	36[a]
Sato et al. (2019)	ROS	235	128	107	80 [73–85]	61 (26)	-	0.75 [0.65–0.92]	25 [20–33]	22 ± 7	29 [23–37]	Classical LFLGAS	172 (74)	27.6 [8.4-44.4]

Note: Values are expressed as mean ± *SD*, median [interquartile range] or number (%).

Abbreviations: AVA, aortic valve area; AVR, aortic valve replacement; CAD, coronary artery disease; LFLGAS, low-flow, low-gradient aortic stenosis; LVEF, left ventricle ejection fraction; MCD, multivessel coronary disease; MPOS, Multicenter Prospective Observational Study; No, number; RCS, Retrospective Cohort Study; ROS, Retrospective Observational Study; SVi, stroke volume index.

[a]Maximum follow up.

[b]Mild symptoms.

[c]Moderate/severe symptom.

The baseline characteristics of the included patients are reported in Table 1. Twelve papers specified whether their cohort of patients presented a preserved or reduced LVEF.[12-19,21-24] Out of 1533 patients, 952 (62.1%) patients had preserved LVEF, and 581 (37.9%) had low LVEF. The mean age of the total population was 74.9 [73.3–76.6] years old,[12-16,18-21,23,24] specifically 73.2 [69.7-76.7] years old in the AVR group and 77.7 [74.8–80.7] years old in the noAVR group. Overall, the AVA was 0.81 [0.77–0.84] cm^2,[12-16,18-21,24] the mean gradient was 27.21 [24.43–29.98] mmHg,[12-16,18-21,24] and the SVI was 34.82 [27.61– 42.04] ml/m^2.[13-16,18,19,21,24]

The number of patients undergoing either SAVR or TAVR was determined from 11 papers.[12-19,21,23,24] It turned out that 607 (81.7%) patients were treated with SAVR and 136 (18.3%) with TAVR (Table 2). In the AVR group, 124 (11.6%) patients underwent concomitant coronary artery bypass grafting (CABG). In the noAVR group, almost all patients were treated medically rather than with valvuloplasty (99.9% vs. 0.1%).

3.2 | Methodological quality

The average overall quality rating was 0.81 ± 0.53, with ratings ranging from 0 to 1.81. Appendix A reports the mean scores assigned to the checklist items. The analysis revealed lower scores of internal validity for bias, selection bias, and power analysis, which may be related to the quality of reporting. These low values are due to the studies being of a retrospective nature without randomized samples. There was an acceptable interrater agreement ($\kappa = 0.89$; %-agree = 94.9).

3.3 | Follow up

The mean follow-up period, calculated from nine papers, was 35.66 [27.50–43.81] months.[12-16,18,19,23,24] The longest follow-up period was 55.2 months.[15] Follow-up was 100% complete in nine studies.[12-15,17,18,21-23]

3.4 | Main endpoints

Figure 2A shows that the RR of survival between the AVR and noAVR groups was 1.99 [1.40, 2.82] ($p = .0001$; $I^2 = 56.46\%$, p-value $I^2 = 0.006$; Egger's test: 0.21 [−0.16, 0.58], p-value Egger's test = 0.004). This suggests that overall survival was significantly better in the AVR group compared to the noAVR group. The funnel plot is shown in Figure 2B (funnel plot asymmetry test: $p = .11$). Moreover, the meta- regression revealed that low LVEF was related to higher survival rates in the AVR group ($p = .04$) when compared to preserved LVEF (Figure 3A). Conversely, LVEF had no impact on survival in the noAVR group ($p = .18$), as shown in Figure 3B.

TABLE 2 Surgical data of AVR

Author (year)	AVR		
	TAVR/SAVR	Concomitant CABG	Operative mortality
Hachicha et al. (2007)	SAVR	–	–
Clavel et al. (2008)	SAVR	30 (68.2)	–
Pai et al. (2008)	SAVR	–	–
Tarantini et al. (2011)	SAVR	38 (52)	2 (2.7)
Clavel et al. (2012)	SAVR	44 (53)	–
Mohty et al. (2013)	SAVR	–	8 (9.8)
Melis et al. (2013)	SAVR	–	1 (5.6)
Herrmann et al. (2013)	SAVR: 56 (53.3)		
	TAVR: 49 (46.7)	–	–
Eleid et al. (2013)	SAVR: 26 (98)		
	TAVR: 1 (2)	12 (23)	–
Ozkan et al. (2013)	SAVR: NS		
	TAVR: NS	–	–
Tribouilloy et al. (2015)	SAVR	–	–
Annabi et al. (2019)	SAVR: NS		
	TAVR: NS	–	–
Sato et al. (2019)	SAVR: 42 (32.8)		
	TAVR: 86 (67.2)	–	–

Note: Values are expressed as number (%).

Abbreviations: AVR, aortic valve replacement; CABG, coronary artery bypass graft; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

4 | DISCUSSION

LFLG AS is associated with a higher risk of a cardiac event and heart failure, increasing the rate of all-cause mortality, and of both cardiovascular-related and valvular-related deaths.[25] The therapeutic choice for LFLG AS is complex and it is unclear what treatment to opt for, as there is no explicit recommendation in cardiology guidelines.[26] Some authors claim that AVR is effective in either classical or paradoxical LFLG AS.[27] Some studies have shown that AVR is able to reduce the rate of adverse events and improve LVEF, enhancing long-term survival when compared to noAVR approaches. However, controversy arises because, in patients with concomitant coronary artery disease (CAD) and reduced contractile reserve (CR), the preoperative risk is too high to opt for AVR.[28,29] Furthermore, patients with irreversible LV impairment do not benefit from AVR. In all these cases, medical management is the recommended alternative approach, despite its reduced long-term survival rates.[26] The aim of approaches other than AVR is to treat those patients who are inoperable because of concomitant life-threatening comorbidities and have reduced life expectancy.[30] Nevertheless, medical therapy is more palliative than curative, although it predisposes to complications such as stroke, aortic regurgitation, myocardial infarction,[31] restenosis, and deterioration of the AV.[32,33]

The main finding of our meta-analysis is the superiority of AVR over noAVR in enhancing survival in patients with LFLG AS. Our result is consistent with studies reporting improved outcomes following AVR rather than noAVR.[34] AVR involves an elevated preoperative risk, but its benefits still outweigh the disadvantages when compared to noAVR. This superiority of AVR may be attributable to the fact that medication with or without valvuloplasty in high-risk patients with low life expectancy represents a mere palliative cure not aimed at achieving therapeutic responses. The noAVR approach is mainly oriented toward the management of cardiovascular risk factors, which include controlling hypertension and volume status. Valvuloplasty may indeed accompany medication but it has lower survival rates when compared to noAVR because of increased risk of restenosis occurring after the procedure, which may lead to deterioration of the valve already 1 year after surgery.[35,36] Indeed, despite the fact that valvuloplasty reduces the transvalvular pressure gradient and improves symptoms, it does not fully resolve the stenosis, because the postvalvuloplasty AVA usually does not exceed 1.0 cm^2.[31,37] This fact suggests that mild stenosis still persists even after the procedure.

The second finding of our meta-analysis was the increased survival at follow up in patients with reduced LVEF compared to those with preserved LVEF in the AVR group. Although this result could at first sound counterintuitive, it is critical to acknowledge that it has been

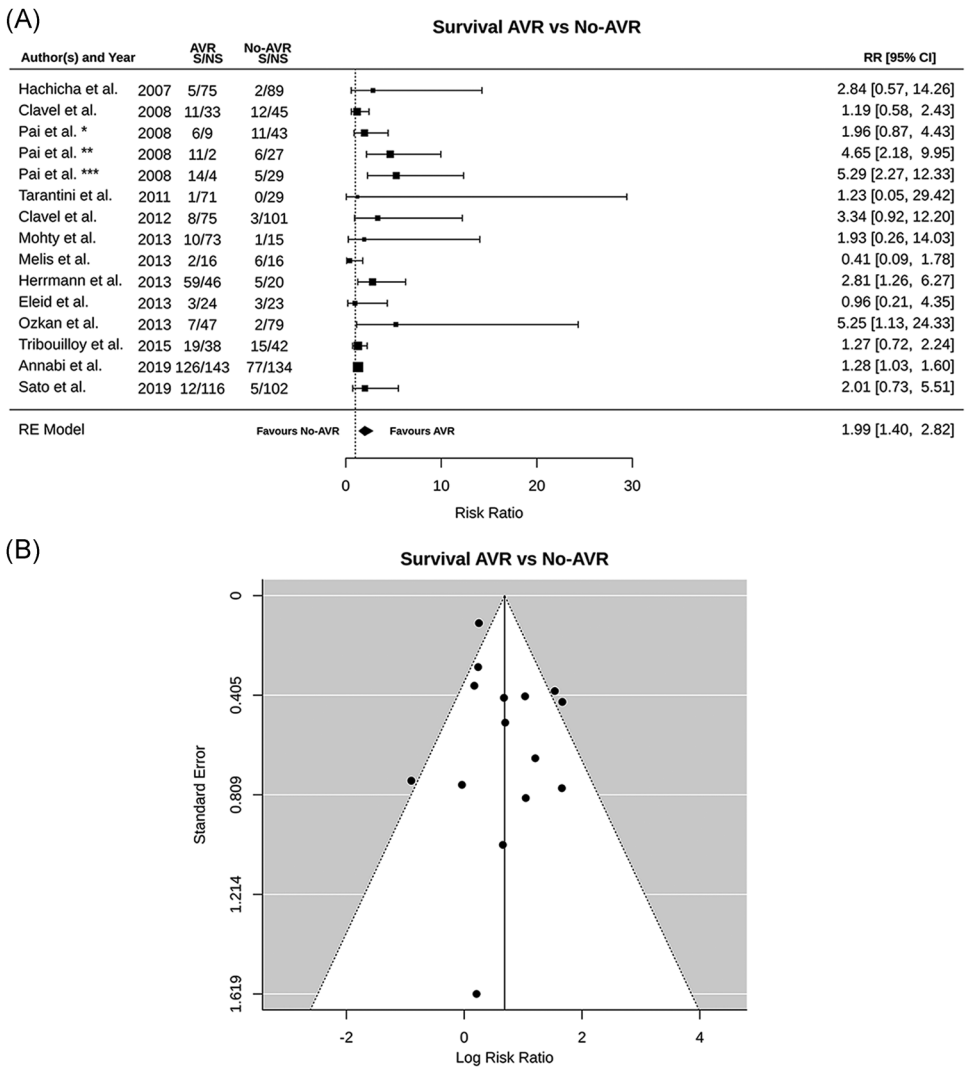

FIGURE 2 Survival AVR vs noAVR. (A) Forest plot. (B) Funnel plot. *LVEF < 35%; **LVEF between 35% and 54%; ***LVEF > 55%. AVR, aortic valve replacement; LVEF, left ventricular ejection fraction; noAVR, no aortic valve replacement

widely proven that LV dysfunction is present even with preserved LVEF. Indeed, studies employing speckle-tracking echocardiography have shown that in patients with LFLG AS and normal LVEF, LV systolic longitudinal dysfunction manifests as a result of the increased afterload.[38] Additionally, in patients with a low LVEF undergoing CABG concomitantly to AVR, long-term survival appears to be enhanced. CABG makes the myocardium viable in certain areas, increasing the LV function and exerting a protective effect [33,39] leading to an improvement in the LVEF that had been reduced due to the concomitant CAD. Since in our meta-analysis some patients were operated on AVR + CABG, it is possible that in patients with low LVEF, the simultaneous CABG procedure might have been beneficial.[2]

Furthermore, we found that LVEF did not impact survival in the noAVR group. These results may be attributable to the fact that conservative management has only palliative purposes dealing only with symptoms, without actually improving cardiac function.[26] This is because there are different mechanisms by which both classical and paradoxical LFLG AS can induce heart failure. Patients with classical LFLG AS have low survival rates because their cardiac function is severely compromised by a small LV cavity size due to LV hypertrophy, severe myocardial fibrosis, and the restrictive pattern of LV filling.[2] Conversely, some studies suggest that conservative management is not particularly useful in increasing survival in the case of paradoxical LFLG AS as a result of the advanced stage of myocardial fibrosis, the systolic and diastolic dysfunction, and the reduced stroke volume index.[2] Moreover, patients with paradoxical AS mostly have diffused atherosclerosis and increased stiffness of arterial walls, which decreases arterial compliance.[2] In the case just described, medical management is only useful for treating the resulting hypertension rather than affecting the aortic valve.[3]

5 | LIMITATIONS

The present meta-analysis has some limitations that need to be addressed. First, the number of patients is not large enough to draw definitive conclusions. Second, the majority of papers were

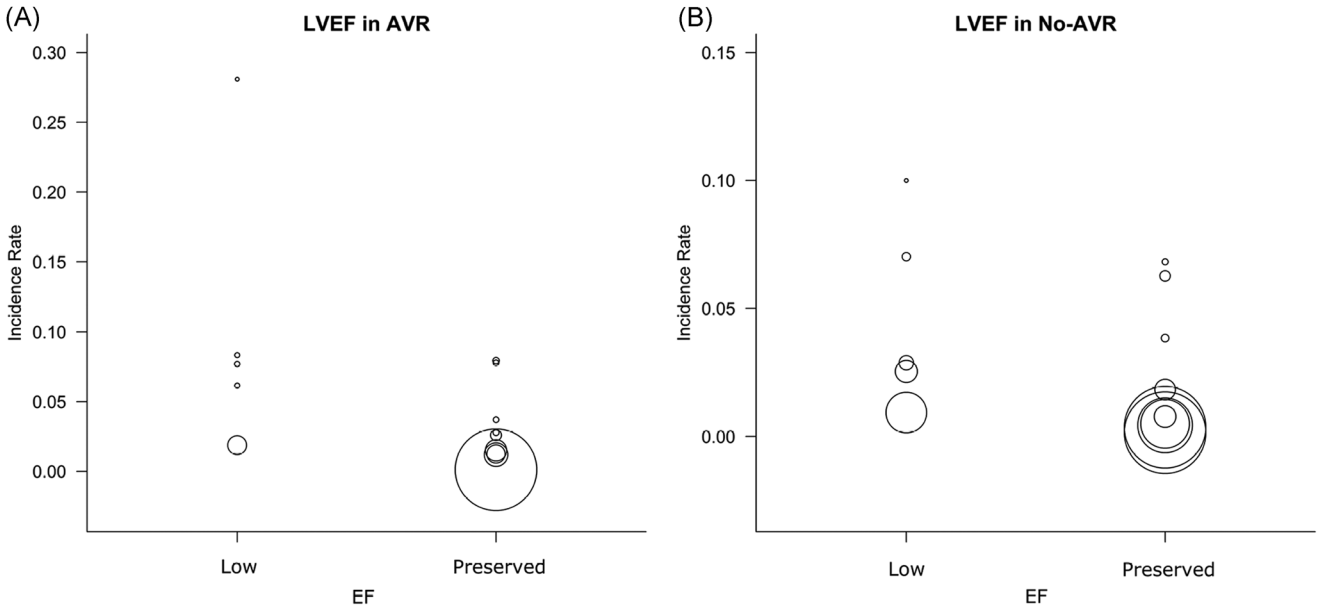

FIGURE 3 Meta regression on the impact of LVEF on survival in (A) AVR and (B) noAVR. AVR, aortic valve replacement; LVEF, left ventricular ejection fraction; noAVR, no aortic valve replacement

retrospective studies, so this might have led to an inherent selection bias. Third, one included review was an abstract so that we could only retrieve limited data from it. Fourth, the papers about reduced LVEF and preserved LVEF were not evenly distributed. Fifth, when we consider that AVR is a class I intervention for symptomatic AS in our current practice, a selection bias could occur between AVR and noAVR patients. An adjusted analysis would have probably addressed this issued but unfortunately data were unavailable for this analysis and for propensity scores that could allow adjustment of preoperative imbalances. Sixth, the majority of the papers included in the analysis did not provide separate data on TAVR and SAVR, making it impossible to conduct a subgroup analysis (i.e., TAVR vs. SAVR, TAVR vs. noAVR, and SAVR vs. noAVR).

6 | CONCLUSION

Patients with LFLG AS have a better survival rate following AVR rather than noAVR. Additionally, patients in the AVR group with reduced LVEF seem to have better survival than patients with preserved LVEF. No difference between low and protected LVEF was found in the noAVR group.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

Data sharing not applicable—no new data generated.

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APPENDIX A: QUALITY ASSESSMENT

Item		Mean	*SD*
1	Study hypothesis/aim/objective described?	0.92	0.27
2	Main outcomes described in the introduction or methods?	1.00	0.00
3	Participant characteristics described?	1.00	0.00
4	Contacted participants representative?	0.04	0.20
5	Prepared participants representative?	0.08	0.27
6	Participants recruited from the same population?	0.50	0.51
7	Participants recruited over the same time?	0.71	0.46
8	Measures and experimental tasks described?	0.83	0.38
9	Main outcome measures valid and reliable?	1.00	0.00
10	Task engagement assessed?	0.33	0.48
11	Confounders described and controlled for?	1.81	0.57
12	Statistical tests appropriate?	1.00	0.00
13	Main findings described?	1.00	0.00
14	Estimates of the random variability in data main outcomes?	1.00	0.00
15	Probability values reported?	0.96	0.20
16	Withdrawals and drop-outs reported?	0.27	0.45
17	Data dredging made clear?	0.86	0.35
18	Sufficient power analysis provided?	0.00	0.00

(Continues)