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Benefits of mitral valve repair over replacement in the elderly: a systematic review and meta-analysis

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Abstract
Objectives: Mitral valve (MV) repair has demonstrated excellent short- and long-term outcomes, however, its merit in the elderly population is still debated. We conducted a meta-analysis of studies that have compared the MV repair to replacement in the elderly population.

Methods: A systematic literature search was conducted for any study published on MV surgery on elderly patients (≥75 years old). A pooled risk-ratio meta-analysis was done to evaluate short-term mortality, postoperative complications, surgical timings, and long-term survival rates.

Results: A total of nine retrospective observational studies were included in the quantitative meta-analysis. Pooled meta-analysis showed a reduced risk of short-term mortality for the MV repair group (risk ratio [RR] = 0.41 [0.24–0.71], p-value = .005). Postoperative neurological complications were in favor of repair, although not significantly (RR = 0.49 [0.21–1.11], p-value = .07). Operative timings (cardiopulmonary bypass and crossclamp time) were not different between the groups although no data were available on the complexity of the repairs. Long-term survival rates were in favor of the repairs (pooled treatment effect of −0.47 [−0.64; −0.29], p = .005).

Conclusions: MV surgery is a safe and effective procedure for the elderly. MV repair demonstrated better short-term outcomes compared to replacement. Long-term survival rates are significantly better after repair.

Keywords
elderly, meta-analysis, mitral valve, mitral valve repair

Abbreviations: CI, confidence intervals; CPB, cardiopulmonary bypass; IQR, interquartile range; MV, mitral valve; MVR, mitral valve repair; MVR, mitral valve replacement; PRISMA, preferred reporting items for systematic reviews and meta-analyses; PS, propensity score; RR, risk ratio; TE, treatment effect.
INTRODUCTION

Over the last decades, there has been a significant growth in life expectancy in the developed countries. Hence, the aging portion of the population has consistently increased over the years and it has been predicted that by 2030 the number of people aged 65 years and above will represent around 20% of the entire population in United States\(^1\) while in Europe the median age will increase by 3.8 years by 2050.\(^2\) Currently more than half of cardiac surgical procedures are performed in patients older than 75 years\(^3\) and it has been estimated than more than 10% of the hospitalized patients aged \(\geq 75\) years have a considerable degree of mitral valve (MV) regurgitation\(^4\) that may require intervention. Mitral valve repair (MVR) is currently preferred to mitral valve replacement (MVR) for the surgical management of degenerative MV disease\(^5\) as it provides better short- and long-term outcomes and a lesser tendency to thromboembolic events\(^6\) and although the durability of MVR and MVR are similar, there is a survival advantage for the former.\(^6\) Despite these obvious advantages, the use of MVR in the elderly is still debated and some surgeons believe that reducing the cross-clamp time with a “quick” valve replacement would be beneficial for this subgroup of patients. It has been previously shown that elderly patients are less likely to receive MV repair compared to a series of all-comers.\(^7\) We examined the current evidence on the surgical outcome of MVR and MVR in elderly patients by conducting a contemporary systematic review and meta-analysis of previously published studies on this topic.

MATERIALS AND METHODS

LITERATURE SEARCH STRATEGY

A systematic literature search was conducted through PubMed for any study published on MV surgery in the elderly population with the intent to select the studies evaluating and compare the short- and long-term surgical outcomes of MVR and MVR in this subgroup of patients. Searching expressions were: [“Mitral Valve Repair” (all fields)] and [“Mitral Valve Surgery” (all fields)] and a combination of these terms with the subsequent terms: [elderly (all fields)], [elderly [MeSH term]], [aged (all fields)], [aged [MeSH term]], [octogenarians (all fields)], [octogenarians [MeSH term]]. Two reviewers (V.D.B. and E.D.T.) independently assessed the online database (last access on May 12th, 2020), screening titles and abstracts. The full-text articles were then obtained for all potentially eligible articles that clearly met the inclusion criteria and were reviewed separately if either reviewer considered the manuscript as being eligible. When the full articles were not available data were extracted from the abstract whenever possible. Any disagreement was resolved by consensus.

ELIGIBILITY CRITERIA

Case reports, editorials, reviews, and meta-analysis were excluded. Nonclinical or post-mortem reports were also excluded. The inclusion criteria were: (I) articles addressing MV surgery and or MVR; (II) including age groups specifications (or available from published data); (III) reporting short term mortality and/or postoperative complications and/or long-term survival data. The patient’s eligibility criteria were as follow: (I) elderly defined as \(\geq 75\) years old; (II) any type of cardiac surgery operations requiring an intervention on the MV; (III) comparative analysis between repair and replacement; (IV) additional cardiac procedures were included. All publications were limited to human subjects and written in English.

DATA EXTRACTION AND CRITICAL APPRAISAL

All data were independently extracted from the studies by two investigators (V.D.B. and E.D.T.). After the initial screening, a further selection and evaluation of the full-text articles were conducted by four authors (V.D.B., E.D.T., F.R., and G.G.). All authors have reviewed the final selection of studies and agreed with the appropriateness of

| Authors       | Year | Age cut-off (years) | No of repair | No of replacement | Op mortality rate repair (No %) | Op mortality rate replacement (No %) | Longest survival rate for repair (years) |
|---------------|------|---------------------|--------------|-------------------|---------------------------------|--------------------------------------|-----------------------------------------|
| Goldsmith et al. | 1999 | 75                  | 22           | 21                | 5 (23)                          | 8 (38)                               | -                                       |
| DiGregorio et al. | 2004 | 80                  | 46           | 13                | 1 (2)                           | 0                                    | -                                       |
| Ailawadi et al. | 2008 | 75                  | 70           | 47                | 5 (7.1)                         | 11 (23.4)                            | 5-years: 63% 5-years: 51%                |
| Chikwe et al.  | 2011 | 80                  | 227          | 95                | 25 (11)                         | 18 (18.9)                            | 5-years: 59% 5-years: 45%               |
| Nloga et al.   | 2011 | 80                  | 75           | 54                | 2 (2.7)                         | 10 (18.5)                            | 1-year: 81.3% 1-year: 65%              |
| Silaschi et al. | 2016 | 75                  | 221          | 120               | 12 (5.4)                         | 11 (9.2)                             | 5-years: 81.8% 5-years: 64.9%           |
| Chivasso et al. | 2018 | 80                  | 150          | 97                | 7 (4.7)                         | 18 (18.6)                            | 10-years: 51.8% 10-years: 35.5%         |
| Farid et al.   | 2019 | 75                  | 145          | 115               | 0                               | 6 (7.7)                              | -                                       |
| Seese et al.   | 2020 | 75                  | 301          | 171               | 17 (5.65)                        | 12 (7.02)                            | 5-years: 100% 5-years: 86%              |
The included studies. The main outcomes of interest were short-term postoperative mortality, postoperative stroke rates, surgical timings, and long-term survival rates. Data on those outcomes were retrieved from the original articles and/or from the available abstracts or supplemental files if available. Short-term mortality was defined as in-hospital or 30-days postoperative mortality. Stroke was defined as permanent postoperative neurological events as specified by the papers. The definition of "elderly" was different among the selected studies: we included in the meta-analysis only the studies involving patients with age ≥75 years in the study population. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol used is represented in the supplemental file.

2.4 Statistical analysis

Study characteristics are presented as raw values and percentages for categorical values and as mean and 95% confidence interval (CI) for continuous numerical variables. Short-term mortality and stroke rates have been analysed using the risk ratio (RR) random effects model using Mantel-Haenszel method. For short-term mortality rates, stroke incidence, and long-term survival rates, a subanalysis of the studies that have used a propensity score (PS) was conducted to avoid potential bias related to the nonrandomized nature of the studies. Continuous numerical outcomes have been analysed using random effects estimates and inverse variance weighting for pooling. Sample means and standard deviations for numerical data were obtained directly from the studies: if they were reported as median and IQR, the mean and SD were estimated using the methods proposed by Wan et al.8 For the analysis of time-to-event data, the estimated treatment effect and the relative standard error were calculated from the estimated HR and the log-rank variance.9 Patient-level raw data that were calculated directly from the Kaplan Meier curves using WebPlotDigitizer (https://automeris.io/WebPlotDigitizer). We did not consider the hazard ratio derived from multivariable models because of the extensive heterogeneity of the covariates included in those models and the inconsistency of adjustment methods used to build them. Forest plots were used to describe the results reporting relative risk and 95% CIs and treatment effect (TE) and relative SE. The heterogeneity between studies was estimated using $\chi^2$-based Q statistics, and $I^2$ test. Statistical significance was set at $p < .05$. Statistical analysis was conducted with R statistical software version 3.6.0 (R Foundation for Statistical Computing).

3 RESULTS

3.1 Quantity of the evidence

A total of 9251 studies were initially found on PubMed. After the initial screening, 56 studies were considered relevant. A further
screening of abstracts and full texts was conducted and a final sample of nine studies considered relevant to our analysis. Two studies\(^5,10\) were PS matched, while another study\(^11\) presented both PS and nonpropensity score-adjusted analysis; we have included both analysis in our study, therefore we used data from 10 comparative analysis. Table 1 describes the main characteristics of the studies included in the meta-analysis. All the selected studies provided information on short-term mortality, while seven studies reported data on cardiopulmonary bypass (CPB) time and six on cross-clamp time. Postoperative stroke rates were available in all studies and long-term survival data were retrieved from seven studies. Table 2 shows the critical appraisal of the included studies (Newcastle-Ottawa Quality Assessment Scale for Cohort Studies).

### Table 1

| Study                  | Events Total | Events Total | Risk Ratio | RR  | 95%-CI | Weight |
|------------------------|--------------|--------------|------------|-----|--------|--------|
| Goldsmith 1999         | 5            | 22           | 8          | 21  | 0.60   | [0.23; 1.53] | 13.5% |
| DiGregorio 2004        | 1            | 46           | 0          | 13  | 3.13   | [0.00; 1966.66] | 1.1%  |
| Ailawadi 2008          | 25           | 227          | 18         | 95  | 0.31   | [0.11; 0.82] | 13.1% |
| Chikwe 2011 (PS)       | 2            | 75           | 10         | 54  | 0.14   | [0.03; 0.63] | 9.8%  |
| Silaschi 2016          | 12           | 221          | 11         | 120 | 0.59   | [0.27; 1.30] | 14.6% |
| Silaschi 2016 (PS)     | 0            | 63           | 4          | 63  | 0.02   | [0.00; 12.80] | 1.1%  |
| Chivasso 2018          | 7            | 150          | 18         | 97  | 0.25   | [0.11; 0.58] | 14.3% |
| Farid 2018 (PS)        | 0            | 78           | 6          | 78  | 0.02   | [0.00; 8.41] | 1.1%  |
| Seese 2020             | 17           | 301          | 12         | 171 | 0.80   | [0.39; 1.64] | 15.1% |
| Overall effect         | 1253         | 759          |            |     | 0.41   | [0.24; 0.71] | 100.0% |

**Prediction interval**

| Heterogeneity: \(I^2 = 17\%\), \(\tau^2 = 0.6702\), \(p = 0.28\) | Test for overall effect: \(t = -3.65\) \((p < 0.01)\) |
|---------------------------------------------------------------|---------------------------------------------------|
| 0.001 0.1 1 10 1000                                           | |

**Figure 1** Forest plot of postoperative mortality following mitral valve repair or replacement in the elderly population. PS, propensity score adjusted.

### 3.2 Postoperative mortality

Nine studies\(^5,10-17\) provided data on postoperative mortality for both groups representing a total of 1202 patients (1253 repairs vs. 759 replacements). Three of these studies have conducted a PS matched or adjusted analysis.\(^5,10,11\) The studies from Farid\(^5\) and Silaschi\(^11\) reported a PS matched analysis in addition to a larger unmatched analysis, while Chikwe et al.\(^10\) described a PS adjusted analysis. The short-term mortality rates were lower in the MVr group with a pooled mortality rate (random effect model) of 4.5% \([2.4-8.2]\) in this group versus 13.11% \([8.86-18.97]\) in the MVR group. The relative risk was in favor of MVr with a value of 0.41 \([0.24-0.71]\) with a \(p\) value of .005; the degree of heterogeneity for this outcome was low with an \(I^2\) of 17.5% (Figure 1).

### Table 2

| Study                  | TE  | seTE | 95%-CI            | Weight |
|------------------------|-----|------|-------------------|--------|
| Silaschi 2016          | -0.62 | 0.2397 | -0.62 [-1.09; -0.15] | 14.0%  |
| Silaschi 2016 (PS)     | -0.78 | 0.3536 | -0.78 [-1.47; -0.08] | 6.4%   |
| Seese 2020             | -0.07 | 0.1963 | -0.07 [-0.46; 0.31] | 20.9%  |
| Nlenga 2011            | -0.56 | 0.2751 | -0.56 [-1.10; -0.02] | 10.6%  |
| Chivasso 2018          | -0.63 | 0.2246 | -0.63 [-1.08; -0.19] | 15.9%  |
| Chikwe 2011 (PS)       | -0.39 | 0.2194 | -0.39 [-0.82; 0.04] | 16.7%  |
| Farid 2018 (PS)        | -0.80 | 0.3650 | -0.80 [-1.51; -0.08] | 6.0%   |
| Ailawadi 2008          | -0.48 | 0.2921 | -0.48 [-1.05; 0.09] | 9.4%   |

**Random effects model**

| Heterogeneity: \(I^2 = 0\%\), \(\tau^2 = 0\), \(p = 0.45\) | Test for overall effect: \(z = -5.24\) \((p < 0.01)\) |
|---------------------------------------------------------------|---------------------------------------------------|
| -0.47 [-0.65; -0.29]                                          | 100.0%                                            |

**Figure 2** Forest plot of survival data following mitral valve repair or replacement in the elderly population. PS, propensity score adjusted; seTE, standard error of the treatment effect; TE, treatment effect.
3.3 | Long term survival

A comparative survival analysis was reported in seven studies.5,10–15 One study11 reported two separate survival curves for unmatched and PS matched analysis. The benefits of MVr are evident in each survival curve represented, with a pooled treatment effect of $-0.47 [-0.65; -0.29]$ ($p = < .01$, Figure 2).

3.4 | Operative surgical times

Seven studies11–13,15–17 reported data on CPB time. There was a high heterogeneity between the studies in this parameter, but majority of them reported a shorter CPB time in the MVr group. The mean CPB time was 112.35 [96.62–128.08] minutes in the repair group versus 115.79 [91.51–140.08] minutes in the replacement group. The random effect model showed an overall standardized mean difference of −0.03 and a 95% CI of −0.47 and 0.41 ($p$ value = .88, Figure 3). Six studies reported data on the cross-clamp time.12–16 Even in this case the heterogeneity between the studies was high with majority of the studies reporting a shorter cross-clamp time in the MVr group. The pooled mean cross-clamp time was 79.36 [66.57–92.15] min in the repair group vs 86.21 [69.11–103.31] min in the replacement group. The overall effect, in this case, was −0.16 [95% CI: -0.54; 0.21] with a $p$ value of .32. Figure 3. No data were available on regards of the complexity of the repairs and this might have had an impact on the operative timings.

3.5 | Postoperative stroke

Nine studies reported the postoperative incidence of stroke: the pooled incidence of postoperative stroke in the MVr patients was 2.1% [1.4–3.03] while this was 4.8% [3.3–7.1] in the MVR patients. The relative risk for this complication was in favor of MVr with a RR of 0.49 [0.21–1.11] with a $p$-value = .07 (Figure 4).
For surgery because they are considered high-risk patients or too old to undergo surgery. In terms of operative timings, we found no evidence of prolonged surgical times when performing a repair although this is not consistent across the different studies. Indeed, MV repair is becoming the standard treatment for MV disease and more centers are conducting repairs routinely with improvements in operative timings and outcomes. It has to be noted that a previously published randomized study showed a prolonged CPB and cross-clamp time in the repair group, and the authors suggested that this was the leading cause for a prolonged ventilatory support. The current meta-analysis confirms that there is no direct influence of the type of surgery on the duration of the operation and we believe this is important in elderly patients in whom shortening CPB and cross-clamp time might determine an improvement in clinical outcomes.

There are several limitations to the current analysis: a certain degree of statistical heterogeneity is present for some outcomes although it has been addressed using random effects models. As for any meta-analysis there is always the risk of publication bias and or extreme outliers: we have run bias and influential analysis to evaluate the importance of these factors (supplemental file). Another limitation is the fact that this meta-analysis includes only retrospective studies and no data are available on the complexity of the repairs that might have affected prolonged surgical timings in this group.

5 | CONCLUSION

In conclusion, our study demonstrates that MV surgery can be safely conducted in the elderly population with good short- and long-term outcomes. Short- and long-term survival rates are favorable for the MVr technique. MV repair should be offered to elderly patients and
timely referrals for surgery should be granted even in this cohort of patients.

CONFLICT OF INTERESTS
The authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION
Additional Supporting Information may be found online in the supporting information tab for this article.

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