This is the **accepted version** of the journal article:

Belahnech, Yassin [et al.]. «Impact of a Successful Percutaneous Mitral Paravalvular Leak Closure on Long-term Major Clinical Outcomes». *Canadian Journal of Cardiology*, Vol. 40, Num. 7 (July 2024), p. 1213-1222 DOI 10.1016/j.cjca.2023.11.025

This version is available at https://ddd.uab.cat/record/327683

under the terms of the IN COPYRIGHT license.

Impact of a successful percutaneous mitral paravalvular leak closure on long-term major clinical outcomes.

Yassin Belahnech, MD[a], Gerard Martí Aguasca MD[a,b,*], Bruno García del Blanco, MD, PhD[a,b], Eduard Ródenas-Alesina, MD[a], Teresa González Alujas, MD, PhD[a,b], Laura Gutiérrez García-Moreno, MD[a,b], Laura Galian-Gay, MD, PhD[a,b], Rubén Fernández-Galera MD[a], Imanol Otaegui Irurueta, MD[a,b], Viçens Serra, MD[a,b], Neus Bellera, MD, PhD[a,b], Bernat Serra, MD[a], Alvaro Calabuig, MD, PhD[a], Maria Calvo Barceló, MD[a], José A. Barrabés, MD, PhD[a,b], Ignacio Ferreira González, MD PhD[a,c].

[a] Cardiology Department, Vall d'Hebron University Hospital. Vall d'Hebron Research Institute. Universitat Autònoma de Barcelona. Barcelona, Spain.

[b] Centro de Investigación Biomédica en Red en Enfermedades Cardiovasculares (CIBERCV), Instituto de Salud Carlos III, Madrid, Spain.

[c] Centro de Investigación Biomédica en Red en Epidemiología y Salud Pública (CIBERESP), Instituto de Salud Carlos III, Madrid, Spain.

Short title: Impact of mitral PVL closure on clinical outcomes

Word count (including reference and legends): 4746

***Address for correpondence:**

Dr Gerard Martí Aguasca, MD

Vall d'Hebron Hospital, Barcelona, Passeig de la Vall d'Hebron, 119, 08035 Barcelona.

E-mail: E-mail: drgmarti@googlemail.com

Funding: Yassin Belahnech is supported by a non-conditioned research grant (Rio Hortega [CM22/00242] Instituto de Salud Carlos III and Ajut_AulaVH/2021-01).

Disclosure Statement: All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Consent Statements: The authors confirm that we obtained an informed consent waiver from the Institutional Review Board due to the retrospective nature of the study.

Key-words: mitral valve, paravalvular leak, percutaneous closure, survival

Abbreviations and acronyms:

CI	Confidence interval
CKD	Chronic kidney disease
HF	Heart Failure
HR	Hazard Ratio
NYHA	New York Heart Association
OR	Odd ratio
PVL	Paravalvular leak
TEE	Transesophageal echocardiography
TTE	Transthoracic echocardiography

ABSTRACT

Background

Percutaneous mitral paravalvular leak (PVL) closure techniques are an effective and safe alternative to surgical treatment, but data regarding long-term outcomes are scarce. We aim to describe the impact of successful percutaneous mitral PVL closure on long-term outcomes.

Methods

All consecutive patients in whom a first-attempt percutaneous mitral PVL closure was performed in a single tertiary center between January 2010 and October 2021 were included. Clinical variables, procedural details and procedural success were collected. Patients were classified based on procedural success, defined as no more than mild residual leak. All-cause mortality was the primary endpoint. Cardiovascular death and heart failure hospitalizations (HFH) were key secondary endpoints.

Results

Ninety patients (median age 72.5 years [66.0-78.4]; median Euroscore-II 8.2 [5.3-12.46]) were included. Although reduction of at least one degree in PVL severity was achieved in 82 (91.1%), procedural success was achieved in 47 (52.2%). Chronic kidney disease, previous surgery for PVL, and the presence of multiple jets, were independently associated with procedural failure. After a median follow-up of 3.2 (1.2-5.2) years, mortality rate was higher in the procedural failure group (27.3 per 100 patients-years) compared to the group with successful closure (8.2 per 100 patient-years). Procedural failure was associated with all-cause death (adjusted hazard ratio [aHR]:2.59; 95%CI:1.41-4.78), cardiovascular death (aHR:3.53, 95%CI:1.67–7.49) and HFH (aHR:3.27, 95%CI:1.72–6.20).

Conclusions

A successful reduction in PVL to absent or less than mild may convey a survival benefit with improved rates of all-cause death , cardiovascular death and HFH.

INTRODUCTION

A paravalvular leak (PVL) is a complication that occurs in 7-17% of patients undergoing mitral valve replacement, especially in those receiving mechanical valves (1,2). It results from an incomplete seal between the prosthetic sewing ring and the native valve annulus, which causes a paravalvular mitral regurgitation. Although many PVLs are subclinical, others may deteriorate over time, which can lead to heart failure (HF) or hemolytic anemia and consequently a higher risk of major cardiovascular outcomes and impaired quality of life (3,4). For this reason, surgical correction of PVLs with a prosthetic valve replacement or patch repair is recommended by current guidelines (5,6). However, this invasive procedure carries a high risk of mortality and a non-negligible risk of recurrence of PVL, which has led to a decrease in its widespread use (7,8).

Transcatheter percutaneous PVL closure techniques have emerged as an effective and safe alternative to surgery in patients with moderate to high surgical risk (7–10). Successful closure of mitral PVL is hampered by anatomic considerations, a friable and irregular surrounding tissue and multiple jet origins. Thus, a multimodal imaging approach is usually required for assessment of the PVL (11). Although some reports suggest that percutaneous closure of PVL is associated with improved functional class and may improve survival if the residual leak is less than mild (12,13), other studies have failed to show any benefit on hard clinical outcomes. Since these discrepancies may be related to differences in definitions of procedural success or PVL severity grading, in 2017 the Paravalvular Leak Academic Research Consortium addressed the issue by establishing a new 5-Class Grading Scheme (14,15) in order to standardize mitral PVL characterization and provide uniform criteria for procedural success.

Even if PVL closure is routinely performed in selected high-volume catheterization laboratories, clinical factors associated to procedural failure are not well determined. In addition, the impact of procedural failure on long-term mortality and need for HF hospitalizations has not been well established according to the new recommendations for PVL grading. The present study aims to address these questions in a cohort of non-selected consecutive patients undergoing PVL at a high-volume tertiary referral center that were followed systematically for a minimum of one year.

METHODS

Study population

This is a single-center retrospective cohort of all consecutive patients in whom a first-attempt percutaneous mitral PVL closure was performed between January 2010 and October 2021 at Vall d'Hebron University Hospital, a high-volume tertiary referral center in Barcelona, Spain. The indication for PVL closure and post-procedural management were determined by a multidisciplinary heart team. All patients included had either a mitral PVL considered at least moderate with symptomatic HF (New York Heart Association -NYHA- functional class III or IV) or a PVL of any severity associated with symptomatic hemolytic anemia (hemoglobin less than 10 g/dL with signs of intravascular hemolysis requiring recurrent blood transfusions). Active endocarditis was ruled out prior to PVL closure. Demographic, clinical, and procedural details, laboratory tests and outcomes occurring during follow-up were retrospectively extracted from the electronic medical records. The PVL severity was graded as per the Unifying 5-Class Grading Scheme recommendations (14,15) using images from transthoracic (TTE) and transesophageal echocardiography

(TEE) that were retrospectively reviewed by two expert cardiologists who were blinded to clinical outcomes. Patients were followed up until death or censored if they were still alive at the last available follow-up. The follow-up was completed in November 2022. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local Institutional Review Board (PR(AG)635/2021).

Definitions

Technical success was defined as successful release of the device correctly, without any interference with the prosthetic leaflets' movement. Procedural success was considered when technical success was achieved, and the residual leak was equal or less than mild, assessed by TEE at the end of the procedure. Conversely, procedural failure was defined as a residual leak greater than mild. The primary endpoint was all-cause mortality. Secondary endpoints were cardiovascular death, non-cardiovascular mortality, HF admission and surgical or percutaneous reintervention due to recurrent PVL. The causes of death were established by chart review or telephone calls with physicians or family members of the deceased patient. Cardiovascular death was defined according to the Paravalvular Leak Academic Research Consortium (14,15). Stage III-V chronic kidney disease (CKD) was defined as CKD-EPI less than 60 mL/min/1.73m^2 (16).

PVL closure techniques

All procedures were guided by TEE under general anesthesia and intubation except for one patient in whom intracardiac echocardiography was used due to severe restrictive lung disease. The use of vascular ultrasound for obtaining femoral access was not routinely performed throughout the cohort, being systematically implemented from 2015 onwards.

An antegrade transseptal approach was used to cannulate the PVL in most patients, while transapical access was used in a minority of cases to create an arteriovenous rail. Intravenous heparin was administered after transseptal puncture and cefazolin was administered for prophylaxis. An AMPLATZER Vascular Plug III (AVP-III; St. Jude Medical, St. Paul, MN) was used for PVL closure in most patients. The procedural approach was determined by the number, location, and size of the PVL. Several percutaneous techniques were used, including single device placement, sequential or simultaneous deployment.

Statistical analysis

Patients were compared according to the success or failure of the procedure. Categorical variables are presented as counts (%) and continuous variables as median [interquartile range] or mean (± standard deviation [SD]), as appropriate. Comparison of the continuous variables was performed using a Student t test or the Wilcoxon rank sum test, depending on the normality of the distribution as assessed with the Shapiro-Wilk test. The chi-square test or Fisher's exact test was used to compare categorical variables, as appropriate. Potential predictors of procedural failure were analyzed using a univariate and multivariate logistic regression model using complete cases analysis, as there were no missing values. The association of procedural failure with the primary and secondary endpoints was analyzed using a multivariable Cox proportional hazards model, and the hazard ratios (HR) and 95% confidence intervals (CI) are provided. Additionally, the results were adjusted for variables associated with mortality. The incidence rates of primary and secondary endpoints were compared between groups. The survival function for all-cause death was plotted using a Kaplan-Meier model, and significance was tested with the log rank test. A two-tailed p-value of < 0.05 was considered statistically significant for all analyses. The statistical analyses were performed using Stata, version 15.1.0 (StataCorp, College Station, TX, USA).

RESULTS

During the study period, 90 patients underwent a percutaneous closure of a mitral PVL for the first time. The mean age was 72.5 years old, 51.1% of the patients were women and the average surgical risk was moderate to high (median Euroscore II score 8.2%). Technical success was achieved in 94.4% of the procedures, and a reduction in at least one degree of mitral regurgitation was observed in 91.1% of the cases. However, procedural failure occurred in 47.8% of the patients, mainly due to the inability to reduce the leak to mild or less degree (**Supplementary Figure 1**). Procedural failure was more common among the first 30 procedures compared to the remaining two-thirds of the cohort (**Supplementary Figure 2**).

Clinical characteristics and echocardiographic findings of the study population are summarized in **Table 1**. Patients with procedural failure had a lower body mass index, a more advanced NYHA class, more severe anemia and a higher transfusion requirement compared with patients with a successful closure. Chronic kidney disease, history of cerebrovascular accident, previous sternotomy and previous surgery for PVL were more common among patients with procedural failure. There were no differences between the groups based on the type of prosthesis or a prior history of endocarditis, but patients with procedural failure had more frequently complex PVL with multiple jets and a more severe regurgitation. Among the variables related to the procedure, only the absence of 3D-guided TEE was associated with procedural failure (**Table 2**).

Several clinical factors associated with procedural failure were identified in the univariate analysis (**Table 3**). In the multivariable model, however, only chronic kidney disease (OR 7.09, 95% CI 2.26-22.21, p=0.001), previous surgery due to PVL (OR 4.03, 95% CI 1.17-13.92, p=0.03), and the presence of multiple jet origins (OR 4.41, 95%CI 1.49-13.06, p=0.003) were associated with an increased risk of procedural failure.

Periprocedural complications occurred in 15 (16.7%) patients and were mostly related to vascular access (**Table 4**). There were two patients who died within the initial 30 days after the procedure: one death was related to the perforation of the free wall with a guidewire which led to cardiac tamponade and subsequent electromechanical dissociation during the procedure and the other was related to respiratory failure and prolonged ventilatory support in the intensive care unit. At one year, 16 (37.2%) patients with procedural failure had died compared to 1 (2.1%) among those with a successful repair (p<0.001). One year after the procedure, the NYHA class had improved by more than 1 grade in 46.5% patients with procedural failure, compared to 76.6% of those with a successful closure (p=0.005). No patient experienced a late embolization of the closure device.

Follow-up at 1 year was complete for 97.8% of the patients. After a median follow-up of 3.2 (1.2-5.2) years (mean 3.7±3.2), 57.8% the patients had died. At the end of follow-up, 17 (36.2%) patients with a successful closure had died compared to 35 (81.4%) among those with procedural failure (p<0.001). The incidence rate of all-cause death was higher in patients with procedural failure (27.3 events per 100 patient-years) compared with that of patients with a successful closure (8.2 deaths per 100 patient-years), so that procedural failure was associated with a HR for all-cause death of 3.56 (95% CI 1.98-6.40) in univariate analysis. Other variables associated with all-cause death were age, NYHA class IV, CKD, higher Euroscore II score, diabetes mellitus and transfusion requirement in the last 6 months (**Table 5**). In the multivariate analysis, procedure failure remained associated with a more than 2-fold increase in mortality risk (adjusted hazard ratio [aHR] 2.61, 95% CI 1.42-4.77). The median survival in the procedural failure group was 1.6 years, compared to 6.8 years among those with a successful closure (**Figure 1A**, log rank $p<0.001$). A significant association between procedural failure and all-cause mortality remained when a landmark survival analysis after 30 days was performed (aHR 2.54, 95% CI 1.38-4.67, log rank $p<0.001$, **Supplementary Figure 3**).

To assess the impact of reducing the leak by at least one grade, patients were analyzed in three groups using Kaplan-Meier curve analysis. Group A represented patients who achieved a residual leak no more than mild. Group B consisted of patients who had a leak reduction of at least one grade but still had a residual leak more than mild. Group C included patients who did not achieve any reduction in leak severity. When comparing patients in group B with those in group C, no differences in mortality were observed (**Figure 1B**, log rank = 0.454). However, group A had a significantly better survival when compared to groups B and C (**Figure 1B,** log rank < 0.001 for both comparisons).

The incidence rates of HF hospitalization, cardiovascular mortality, and percutaneous re-do procedures were all significantly higher in the procedural failure group. In adjusted analyses, procedural failure was also found to be associated with significant increases in HF hospitalization (aHR: 3.27, 95% CI: 1.72–6.20), cardiovascular mortality (aHR: 3.53, 95% CI: 1.67–7.49) and percutaneous re-do procedures (aHR: 2.81, 95% CI:

1.15-6.87). However, there was no difference between groups in non-cardiovascular death (**Table 6**).

When we analyzed the survival curves based on the presence of hemolysis, there was a similar mortality in patients with prior hemolysis when compared to those without hemolysis (**Supplementary Figure 4A**). Among patients with a successful PVL closure, there was no association between hemolysis and survival. Similarly, among patients who had a failed PVL closure, hemolysis did not impact on prognosis (**Supplementary Figure 4B**).

DISCUSSION

This study shows that, even in a tertiary referral center, PVL closure failure, defined as the presence of a residual PVL greater than mild, is frequent and it is associated with complex PVLs with multiple jets, previous failed surgery for PVL and CKD stage III or IV. Procedural failure was associated with more than a 2-fold increase in the adjusted risk of all-cause death, cardiovascular death, and HF hospitalization. However, there was no significant reduction in non-cardiovascular death after a median follow-up of 3.2 years. This suggests that successful PVL closure may have a positive impact on survival.

A crucial aspect of percutaneous closure techniques is how the medical community evaluates procedural success. In the percutaneous mitral repair field this seems to be of especial relevance. Despite the recommendations established in 2017 by the PVL Academic Research Consortium, each center still uses their own definitions for procedural success, thus hampering the comparison of results between centers and the assessment of predictors for procedural failure (17, 18, 19). Successful closure of mitral PVL in our cohort was

52.2% as per the recommended criteria, which constitutes a success rate lower than previously reported. In a metanalysis including 362 patients (70% mitral PVL) from 12 different cohorts, a technical success was reported in 82.3% patients, with procedural success rate of 73.3% (20). However, procedural success was defined as an immediate reduction of more than 1 degree in mitral PVL severity. Should we follow this criterion, procedural success in our cohort would have been reached in 91.1%. In our study the criterion states that comparing patients with a reduction in leakage of at least one-degree, but still having leakage greater than mild, with those who did not have any reduction in leakage, did not show a correlation with a reduction in mortality. As a result, we consider this criterion to be outdated because it overestimates the success and fails to accurately discriminate clinical events.

In several other studies, procedural failure has been reported from 70% to 75% using less permissive definitions, although without consistent correlation with long-term outcomes (12,21,22). The association observed in our cohort between procedural failure and all-cause death using the stringent PVL Academic Research Consortium definition suggests that near complete resolution of the PVL would be required to positively impact on patient prognosis. The AMPLATZER Vascular Plug III was the most commonly used in our study. Even if this device was not designed for PVL closure, it remains the most commonly used for this purpose (12,23). Devices specifically designed for PVL closure, such as the Occlutech PLD has been associated with improvement in long-term outcomes in a large series of complex PVLs, attaining a reduction in PVL severity of one or more grade in over 90% of cases (18).

Previously described risk factors for procedural failure included multiple jets, prolonged time since surgery, other devices than AVP III and pulmonary hypertension

(13,23). In our cohort, median time from surgery to PVL closure was 7.4 years (similar to the one in the Spanish registry (23)) and 40% of patients have multiple leaks. In addition, we also identified prior surgery for PVL repair and CKD as independent risk factors for procedural failure previously not described.

Although other groups have not reported a clear impact of the learning curve on outcomes (24), we observed a clear temporal trend in our institution. In our center, the initial experience with a heterogeneous assortment of percutaneous devices led to discouraging clinical results. However, the use of multiple devices and steerable sheaths along with improved understanding of the anatomy through multimodal imaging and increasing technical expertise likely contributed to better outcomes in the recent era. We believe that a more liberal and systematic use of 3D-echocardiography was a major determinant of improved outcomes during the last two tertiles, as previously suggested by other groups (25). Due to a less restrictive patient selection criteria and more complex cases in recent times, with larger and multiple PVLs, we have seen a slight deterioration in procedural success in the last tertile, although not significant when compared to the second tertile.

Despite being associated with higher risks than aortic PVL closure (19), few adverse events occurred after the mitral procedure in our series, with only 2 patients dying early after the mitral PVL closure (one of them unrelated to the procedure).

The effectiveness of mitral PVL closure to improve functional class, HF symptoms and hemolytic anemia observed in our series has been described previously (8,9,26,27). However, the question about whether PVL closure could reduce all-cause mortality in the long term remained elusive (12,13,22). In this sense, a multicentric report based on 259 patients (44% mitral, 48% aortic and 8% others PVLs) from 20 hospitals in the United

Kingdom and Ireland showed that procedural failure increased by 2-fold the risk of all-cause death. Although median follow-up was notably shorter than ours (110 days, IQR 7-452 days) (12) and the analysis included both mitral and aortic PVL closures, it indicates the likelihood of this positive association. A similar result was observed in a smaller cohort also combining aortic and mitral PVL closure procedures (22). These positive results conflict with those of the largest published, single-center cohort, in which a mortality benefit was observed in the initial 30 days following the procedure, but a landmark analysis showed no reduction in all-cause death in those surviving at least 30 days, despite a median follow-up of 2.0 years (13). Moreover, a contemporary single-center Spanish cohort has also failed to report a decrease in all-cause death associated to the procedural success. However, procedural success, which was achieved in 79.2% of patients, was defined in this study as a reduction in only one degree in the severity of regurgitation (19). Therefore, the potential benefit of the procedure success, if any, may have been diluted if the differences in the post-procedure PVL between the two groups were attenuated due to the definition of success and failure. In fact, a smaller cohort of 80 patients undergoing percutaneous PVL closure (of which 65 had a mitral PVL) observed a long-term survival benefit when the Paravalvular Leak Academic Research Consortium definition was used (28), as in our study. Our results, which show large differences between groups in the median survival, support that successful PVL closure and the adherence to the strict PVL consortium recommendations for leak quantification to guide the procedure may improve survival in patients with severe mitral PVL. In any case, the differences reported in the prognosis among studies emphasize the need to use homogeneous definitions both for the success of the procedure and for the results.

Additionally, it is important to consider the impact of hemolysis on patient outcomes. In some studies, the presence of hemolysis has been associated with higher mortality and worse survival compared to patients without hemolysis (17,19,,29). In comparison with previous literature, our observations reveal that prior hemolysis does not have an impact on survival by itself; instead, leaving a residual leak more than mild seems to confer an equally poor prognosis in both patients with and without prior hemolysis. This finding supports that in patients presenting with isolated HF and without prior hemolysis achieving a final leak of less or equal than mild is as important as in patients with prior hemolysis to improve long-term survival.

As observed in our cohort, prior hemolysis may reflect a more complex PVL with a more challenging anatomy and higher rates of procedural failure, thus being a confounder in other series. Therefore, it is important to emphasize that successful closure of the leak can lead to comparable survival outcomes for all patients, regardless of the presence of hemolysis at baseline.

Limitations

As an observational, single-center retrospective study limitations must be acknowledged, and causality cannot be inferred from the association observed between procedural failure and death despite adjustment for several covariates. Although this is one of the largest single center reports of mitral PVL closure procedures, sample size remains relatively limited and precludes subgroup analysis. The generalizability of our results may be compromised, as we observed a trend towards higher rates of procedural success in other studies. In addition, the data obtained from this study is derived from a specific high-risk cohort undergoing percutaneous PVL closure, and the results may not be extended to a surgical population, nor supports a percutaneous approach instead of surgery. Finally, these findings do not apply to cardiac surgeries, that were not included in the study, and data cannot be inferred from percutaneous PVL closure.

CONCLUSIONS

Procedural failure defined as a residual leak greater than mild, which may occur despite an initial technical success, leads to a higher risk of all-cause death, cardiovascular death and HF hospitalization. Therefore, perseverance in the reduction of the regurgitant jet to less than mild, as recommended by current consensus documents, may be required improve long-term clinical outcomes.

BIBLIOGRAPHY

1. Hammermeister K, Sethi GK, Henderson WG, Grover FL, Oprian C, Rahimtoola SH. Outcomes 15 Years After Valve Replacement With a Mechanical Versus a Bioprosthetic Valve: Final Report of the Veterans Affairs Randomized Trial, J Am Coll Cardiol. 2000 Oct; 36(4):1152-8.

2. Dávila-Román VG, Waggoner AD, Kennard ED, Holubkov R, Jamieson WR, Englberger L, Carrel TP, Schaff HV. Prevalence and severity of paravalvular regurgitation in the Artificial Valve Endocarditis Reduction Trial (AVERT) echocardiography study. J Am Coll Cardiol. 2004 Oct 6; 44(7):1467–72.

3. O'rourke DJ, Palac RT, Malenka DJ, Marrin CAS, Arbuckle BE, Plehn JF. Outcome of Mild Periprosthetic Regurgitation Detected by Intraoperative Transesophageal Echocardiography. J Am Coll Cardiol. 2001 Jul;38(1):163-6.

4. Jindani A, Neville EM, Venn G, Williams BT. Paraprosthetic leak: A complication of cardiac valve replacement. Journal of Cardiovascular Surgery. 1991;32(4):503–8.

5. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, Capodanno D, Conradi L, De Bonis M, De Paulis R, Delgado V, Freemantle N, Gilard M, Haugaa KH, Jeppsson A, Jüni P, Pierard L, Prendergast BD, Sádaba JR, Tribouilloy C, Wojakowski WESC/EACTS Scientific Document Group. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2022 Feb 12;43(7):561-632.

6. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, Jneid H, Krieger EV, Mack M, McLeod C, O'Gara PT, Rigolin VH, Sundt TM 3rd, Thompson A, Toly C. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American

Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021 Feb 2;143(5):e35-e71.

7. Hourihan M, Perry SB, Mandell VS, Keane JF, Rome JJ, Bittl JA, Lock JE. Transcatheter umbrella closure of valvular and paravalvular leaks. J Am Coll Cardiol. 1992 Nov 15;20(6):1371–7.

8. Sorajja P, Cabalka AK, Hagler DJ, Rihal CS. Percutaneous repair of paravalvular prosthetic regurgitation: acute and 30-day outcomes in 115 patients. Circ Cardiovasc Interv. 2011 Aug;4(4):314-21.

9. Ruiz CE, Jelnin V, Kronzon I, Dudiy Y, Del Valle-Fernandez R, Einhorn BN, Chiam PT, Martinez C, Eiros R, Roubin G, Cohen HA. Clinical outcomes in patients undergoing percutaneous closure of periprosthetic paravalvular leaks. J Am Coll Cardiol. 2011 Nov 15;58(21):2210–7.

10. Busu T, Alqahtani F, Badhwar V, Cook CC, Rihal CS, Alkhouli M. Meta-analysis Comparing Transcatheter and Surgical Treatments of Paravalvular Leaks. American Journal of Cardiology. 2018 Jul 15;122(2):302–9.

11. Hascoet S, Smolka G, Bagate F, Guihaire J, Potier A, Hadeed K, Lavie-Badie Y, Bouvaist H, Dauphin C, Bauer F, Nejjari M, Pillière R, Brochet E, Mangin L, Bonnet G, Ciobotaru V, Leurent G, Hammoudi N, Aminian A, Karsenty C, Spaulding C, Armero S, Collet F, Champagnac D, Ternacle J, Kloeckner M, Gerardin B, Isorni MA. Multimodality imaging guidance for percutaneous paravalvular leak closure: Insights from the multi-centre FFPP register. Arch Cardiovasc Dis 2018 Jun;111(6–7):421–31.

12. Calvert PA, Northridge DB, Malik IS, Shapiro L, Ludman P, Qureshi SA, Mullen M, Henderson R, Turner M, Been M, Walsh KP, Casserly I, Morrison L, Walker NL, Thomson J, Spence MS, Mahadevan VS, Hoye A, MacCarthy PA, Daniels MJ, Clift P, Davies WR,

Adamson PD, Morgan G, Aggarwal SK, Ismail Y, Ormerod JO, Khan HR, Chandran SS, de Giovanni J, Rana BS, Ormerod O, Hildick-Smith D.. Percutaneous device closure of paravalvular leak. Circulation. 2016 Sep 27;134(13):934–44.

13. Alkhouli M, Zack CJ, Sarraf M, Eleid MF, Cabalka AK, Reeder GS, Hagler DJ, Maalouf JF, Nkomo VT, Rihal CS. Successful Percutaneous Mitral Paravalvular Leak Closure Is Associated with Improved Midterm Survival. Circ Cardiovasc Interv. 2017 Dec 1;10(12).

14. Ruiz CE, Hahn RT, Berrebi A, Borer JS, Cutlip DE, Fontana G, Gerosa G, Ibrahim R, Jelnin V, Jilaihawi H, Jolicoeur EM, Kliger C, Kronzon I, Leipsic J, Maisano F, Millan X, Nataf P, O'Gara PT, Pibarot P, Ramee SR, Rihal CS, Rodes-Cabau J, Sorajja P, Suri R, Swain JA, Turi ZG, Tuzcu EM, Weissman NJ, Zamorano JL, Serruys PW, Leon MB. Paravalvular Leak Academic Research Consortium. Clinical Trial Principles and Endpoint Definitions for Paravalvular Leaks in Surgical Prosthesis: An Expert Statement. J Am Coll Cardiol. 2017 Apr 25;69(16):2067-2087.

15. Ruiz CE, Hahn RT, Berrebi A, Borer JS, Cutlip DE, Fontana G, Gerosa G, Ibrahim R, Jelnin V, Jilaihawi H, Jolicoeur EM, Kliger C, Kronzon I, Leipsic J, Maisano F, Millan X, Nataf P, O'Gara PT, Pibarot P, Ramee SR, Rihal CS, Rodes-Cabau J, Sorajja P, Suri R, Swain JA, Turi ZG, Tuzcu EM, Weissman NJ, Zamorano JL, Serruys PW, Leon MB. Clinical Trial Principles and Endpoint Definitions for Paravalvular Leaks in Surgical Prosthesis: An Expert Statement. Eur Heart J (2018) 39, 1224–1245.

16. Stevens PE, Levin A. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med 2013 Jun;158(11):825–30.

17. Hascoët S, Smolka G, Blanchard D, Kloëckner M, Brochet E, Bouisset F, Leurent G, Thambo JB, Combes N, Dumonteil N, Bauer F, Nejjari M, Pillière R, Dauphin C, Bonnet G, Ciobotaru V, Ketelers R, Gallet R, Hammoudi N, Mangin L, Bouvaist H, Spaulding C, Aminian A, Kilic T, Popovic B, Armero S, Champagnac D, Gérardin B. Predictors of Clinical Success After Transcatheter Paravalvular Leak Closure: An International Prospective Multicenter Registry. Circ Cardiovasc Interv. 2022 Oct;15(10):e012193.

18. Onorato EM, Alamanni F, Muratori M, Smolka G, Wojakowski W, Pysz P, Zorinas A, Zakarkaite D, Eltchaninoff H, Litzer PY, Godart F, Calvert P, Christou C, Mussayev A, Missiroli B, Buzaev I, Curello S, Tesorio T, Bartorelli AL. Safety, Efficacy and Long-Term Outcomes of Patients Treated with the Occlutech Paravalvular Leak Device for Significant Paravalvular Regurgitation. J Clin Med. 2022 Apr 1;11(7):1978.

19. Cruz-González I, Luengo-Mondéjar P, Trejo-Velasco B, Núñez-García JC, González-Ferreiro R, Moreno-Samos JC, Fuertes-Barahona M, Rama-Merchán JC, Antúnez-Muiños P, López-Tejero S, Barreira de Sousa G, Rodríguez-Collado J, Martín-Moreiras J, Diego-Nieto A, Herrero-Garibi J, Barreiro-Pérez M, Díaz-Peláez E, Sánchez Fernández PL. Percutaneous Closure of Mitral Paravalvular Leak: Long-Term Results in a Single-Center Experience. J Clin Med. 2022 Aug 18;11(16):4835.

20. Millán X, Skaf S, Joseph L, Ruiz C, García E, Smolka G, Noble S, Cruz-González I, Arzamendi D, Serra A, Kliger C, Sia YT, Asgar A, Ibrahim R, Jolicœur EM.. Transcatheter Reduction of Paravalvular Leaks: A Systematic Review and Meta-analysis. Vol. 31, Can J Cardiol. Pulsus Group Inc.; 2015. P. 260–9.

21. Alkhouli M, Rihal CS, Zack CJ, Eleid MF, Maor E, Sarraf M, Cabalka AK, Reeder GS, Hagler DJ, Maalouf JF, Nkomo VT, Schaff HV, Said SM. Transcatheter and Surgical

Management of Mitral Paravalvular Leak: Long-Term Outcomes. JACC Cardiovasc Interv. 2017 Oct 9;10(19):1946-1956.

22. Perl L, Cohen A, Dadashev A, Shapira Y, Vaknin-Assa H, Yahalom V, Sagie A, Kornowski R, Hirsch R. Long-term outcomes of catheter-based intervention for clinically significant paravalvular leak. EuroIntervention. 2021 Oct 1;17(9):736–43.

23. García E, Arzamendi D, Jimenez-Quevedo P, Sarnago F, Martí G, Sanchez-Recalde A, Lasa-Larraya G, Sancho M, Iñiguez A, Goicolea J, Garcia-San Roman K, Alonso-Briales JH, Molina E, Calabuig J, Freixa X, Berenguer A, Valdes-Chavarri M, Vazquez N, Diaz JF, Cruz-Gonzalez I. Outcomes and predictors of success and complications for paravalvular leak closure: An analysis of the SpanisH real-wOrld paravalvular LEaks closure (HOLE) registry. EuroIntervention. 2017 Mar 1;12(16):1962–8.

24. Sorajja P, Cabalka AK, Hagler DJ, Rihal CS. The learning curve in percutaneous repair of paravalvular prosthetic regurgitation: an analysis of 200 cases. JACC Cardiovasc Interv. 2014 May;7(5):521-9.

25. García-Fernández MA, Cortés M, García-Robles JA, Gomez de Diego JJ, Perez-David E, García E. Utility of real-time three-dimensional transesophageal echocardiography in evaluating the success of percutaneous transcatheter closure of mitral paravalvular leaks. J Am Soc Echocardiogr. 2010 Jan;23(1):26-32.

26. Cruz-Gonzalez I, Rama-Merchan JC, et al. Paravalvular leak closure with the Amplatzer Vascular Plug III device: immediate and short-term results. Rev Esp Cardiol 2014 Aug;67(8):608–14.

27. Noble S, Jolicoeur EM, Basmadjian A, Levesque S, Nozza A, Potvin J, Crépeau J, Ibrahim R. Percutaneous paravalvular leak reduction: procedural and long-term clinical outcomes. Can J Cardiol. 2013 Nov;29(11):1422-8.

28. Millán X, Bouhout I, Nozza A, Samman K, Stevens LM, Lamarche Y, Serra A, Asgar AW, El-Hamamsy I, Cartier R, Pellerin M, Noble S, Demers P, Ibrahim R, Jolicœur EM, Bouchard D. Surgery Versus Transcatheter Interventions for Significant Paravalvular Prosthetic Leaks. JACC Cardiovasc Interv. 2017 Oct 9;10(19):1959-1969.

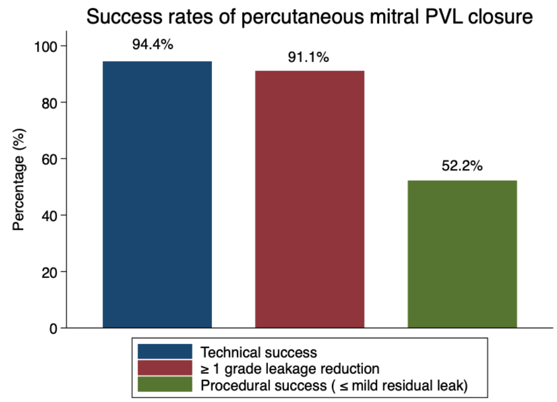
29. Smolka G, Pysz P, Ochała A, Kozłowski M, Zasada W, Parma Z, Tendera M, Wojakowski W. Transcatheter paravalvular leak closure and hemolysis - a prospective registry. Arch Med Sci. 2017 Apr 1;13(3):575-584. doi: 10.5114/aoms.2016.60435.

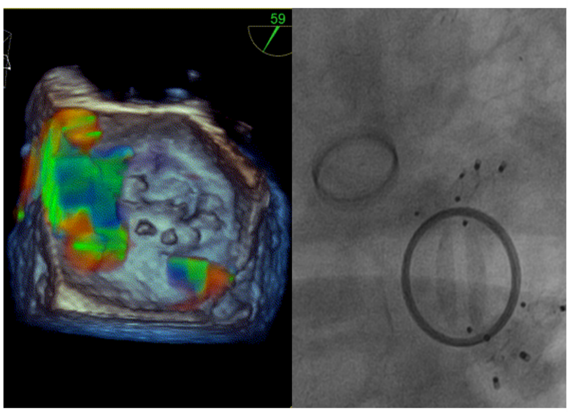
CENTRAL ILLUSTRATION

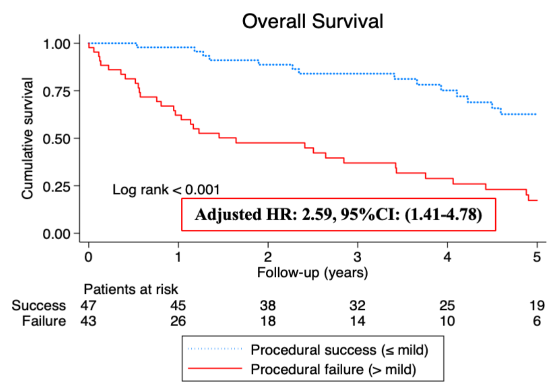
90 consecutive patients with percutaneous mitral PVL closure (2010-2020)

Independent predictors of procedural failure:
1) Multiple leaks
2) Previous mitral PVL surgery
3) Stage III-V chronic kidney disease

Incidence rate for all-cause death:
-Procedural failure: 27.3 per 100 patient-years
-Procedural success: 8.2 per 100 patient-years

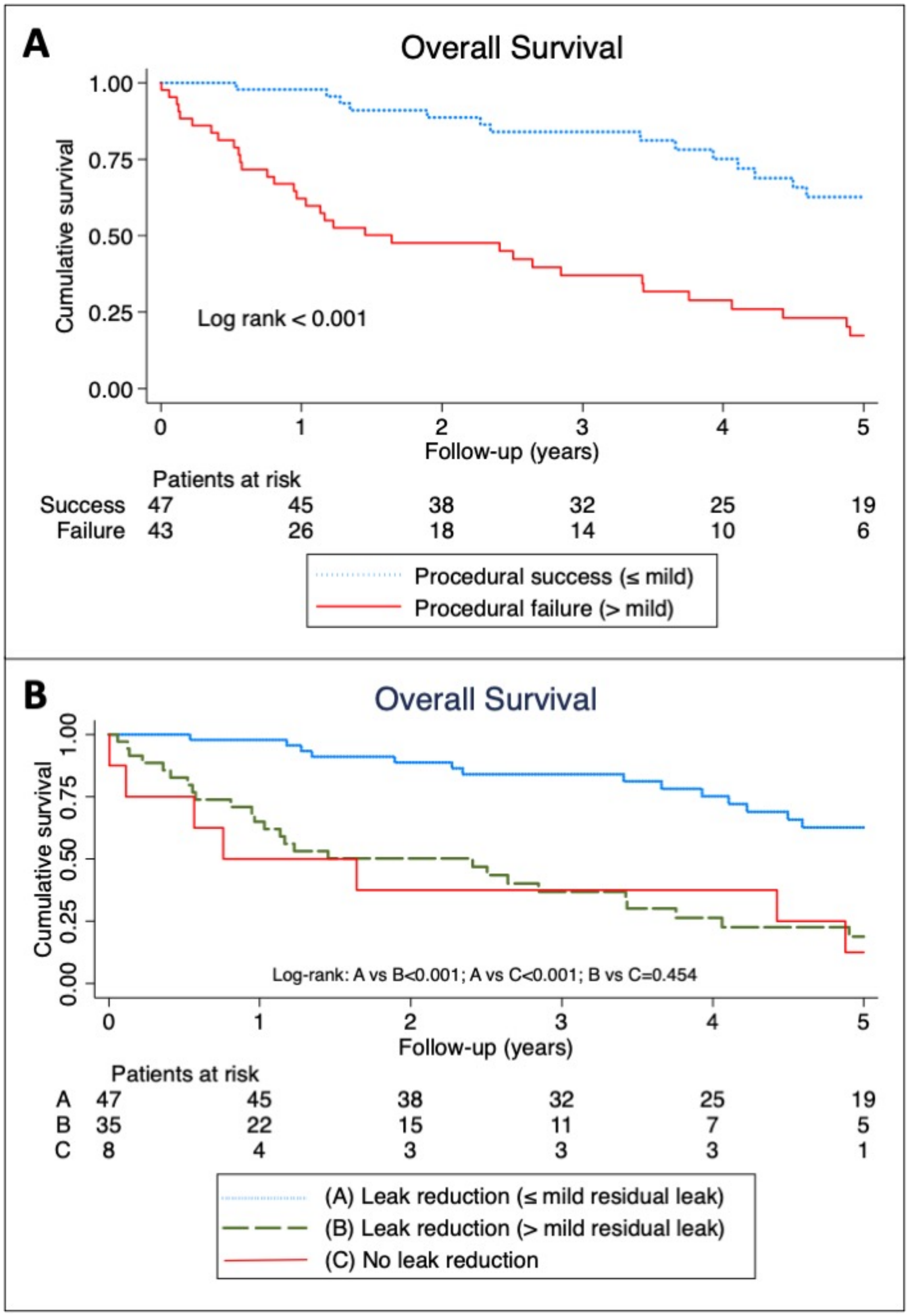






FIGURES

Figure 1: Kaplan-Meier plot showing cumulative survival free from death based on the result of procedure. A: Based on procedural success. B: Based on leak reduction.



TABLES

Table 1. Demographic and echocardiography baseline characteristics in patients undergoing percutaneous closure of a paravalvular mitral leak.

		All patients (n=90)	Procedural Success† (n=47)	Procedural Failure (n=43)	P value
Clinical characteristics					
Age, years		72.5 (66.0-78.4)	71.8 (63.4-76.4)	73.4 (68.5-79.2)	0.180
Women		46 (51.1)	19 (40.4)	27 (62.8)	**0.034**
Body mass index (kg/m2)		25.6 (22.3-29.1)	27.4 (24.3-29.8)	23.7 (21.1-26.4)	**<0.001**
Diabetes mellitus		22 (24.4)	10 (21.3)	12 (27.9)	0.465
Procedure indication	Heart failure	34 (37.8)	24 (51.1)	10 (23.3)	**0.024**
	Hemolysis	10 (11.1)	4 (8.5)	6 (14.0)	
	Both	46 (51.1)	19 (40.4)	27 (62.8)	
NYHA functional class	Class II	8 (8.9)	8 (17.02)	0 (0)	**<0.001**
	Class III	58 (64.4)	33 (70.2)	25 (58.1)	
	Class IV	24 (26.7)	6 (12.8)	18 (41.9)	
Transfusion requirement		45 (50.0)	16 (34.0)	29 (67.4)	**0.002**
Chronic kidney disease		29 (32.2)	7 (14.9)	22 (51.2)	**<0.001**
Cerebrovascular disease		19 (21.1)	5 (10.6)	14 (32.6)	**0.011**
COPD		15 (16.7)	5 (10.6)	10 (23.3)	0.109
Coronary artery disease		11 (12.2)	8 (17.0)	3 (7.0)	0.146
Atrial fibrillation		80 (88.9)	42 (89.4)	38 (88.4)	0.881
Prior endocarditis		28 (31.1)	14 (29.8)	14 (32.6)	0.777
Mechanical prosthesis		79 (87.8)	43 (91.5)	36 (83.7)	0.261
≥ 2 sternotomies		54 (60.0)	23 (48.9)	31 (72.1)	**0.025**
Previous PVL repair surgery		23 (25.6)	8 (17.0)	15 (34.9)	**0.052**
Time since last surgery		7.4 (2.2-15.3)	9.7 (2.6-18.1)	6.3 (1.9-13.6)	0.343
EUROSCORE II (%)		8.2 (5.3-12.5)	7.0 (4.8-11.2)	9.3 (6.1-13.9)	0,061
Echocardiographic features					
PVL grade	Moderate	1 (1.1)	1 (2.1)	0 (0)	**0.004**
	Moderate to severe	17 (18.9)	14 (29.8)	3 (7.0)	
	Severe	72 (80.0)	32 (68.1)	40 (93.0)	
PVL type	Simple jet	54(60.0)	35 (74.5)	19 (44.2)	**0.003**
	Multiple jets	36 (40.0)	12 (25.5)	24 (55.8)	
PVL location	Anterior	25 (27.8)	16 (34.0)	9 (20.9)	0.408
	Posterior	27 (30.0)	11(23.4)	16 (37.1)	
	Lateral	16 (17.8)	8 (17.0)	8 (18.6)	
	Medial	22 (24.4)	12 (25.5)	10 (23.3)	
LVEF (%)		56 (48-62)	55 (47-61)	56 (50-62)	0.294
Systolic PAP (mmHg)		60 (46-76)	58 (45-78)	60 (46-73)	0.887
Laboratory values					

Basal hemoglobin g/dL	9.7 (9-11.9)	10.7 (9.5-13.2)	9.4 (8.7-9.7)	**<0.001**
Basal LDH (UI/L)	1483 (741-2443)	1188 (615-2372)	1596 (970-2712)	0.091

Values are median (Q1-Q3) or n (%). NYHA: New York Heart Association, eGFR: estimated glomerular filtration rate., COPD: chronic obstructive pulmonary disease., PVL: paravalvular leak, LVEF: left ventricular ejection fraction, PAP: pulmonary artery pressure, LDH: lactate dehydrogenase. † Procedural success was considered when residual leak was equal or less than mild. *Chronic kidney disease was considered as CKD-EPI less than 60 mL/min/1.73m^2

Table 2. Procedural features in patients undergoing mitral paravalvular leak closure.

	All patients (n=90)	Procedural Success† (n=47)	Procedural Failure (n=43)	P value
Procedure				
Ambulatory	68 (75.6)	40 (85.1)	28 (65.1)	**0.049**
Hospitalized	20 (22.2)	7 (14.9)	13 (30.2)	
Emergent	2(2.2)	0 (0.0)	2 (4.7)	
General anesthesia	89 (98.9)	46 (97.9)	43 (100)	0.522
Intraprocedural image guidance				
TEE 2D	23 (25.6)	4 (8.5)	19 (44.2)	**<0.001**
TEE 3D	66 (73.3)	42 (89.4)	24 (55.8)	
ICE	1(1.1)	1(2.1)	0 (0)	
Approach				
Transseptal	86 (95.6)	44(93.6)	43 (97.7)	0.343
Transapical	4 (4.4)	3 (6.4)	1(2.3)	
Arteriovenous loop	19 (21.1)	8 (17.0)	11 (25.6)	0.320
Number of devices				
Multiple devices	51 (56.7)	27 (57.5)	24 (55.8)	0.876
0	1 (1.1)	0 (0.0)	1 (2.3)	0.169
1	38 (42.2)	20 (42.6)	18 (41.9)	
2	24 (26.7)	16 (34.0)	8 (18.6)	
≥ 3	27 (30.0)	11 (23.4)	16 (37.2)	
Implanted devices	183	94	89	
AVP III	118/183 (64.5)	59/94 (62.8)	59/89 (66.3)	-
AVP II	47/183 (25.7)	23/94 (24.6)	26/89 (29.2)	-
AVP IV	7/183 (3.8)	5/94 (5.3)	2/89 (2.3)	-
ADO	2/183 (1.1)	0/94 (0.0)	2/89 (2.3)	-
VSD	2/183 (1.1)	2/94 (2.1)	0/89 (0)	-
Coils	5/183 (2.7)	5/94 (5.3)	0/89 (0)	-
Other details				
Procedure time (min)	211 (177-260)	194 (160-248)	222 (185-272)	0.057
Fluoroscopy time (min)	46 (29-72)	42 (28-66)	52 (34-77)	0.351
X-ray dose (Gy/cm2)	546 (286-856)	487 (267-753)	636 (342-935)	0.239
Iodinated contrast (ml)	75 (40-96)	84 (28-116)	63 (40-90)	0.185
Hospitalization (days)	2 (1-6)	2 (1-6)	2 (1-9)	0.564

Values are median (Q1-Q3) or n (%). ICE: Intracardiac echocardiography, TEE: Transesophageal echocardiography, 3D: Three-dimensional, 2D: Two-dimensional, AVP: Amplatzer Vascular Plug. ADO: Amplatzer Ductal Occluder. VSD: Ventricular Septal Defect Occluder. † Procedural success was considered when residual leak was equal or less than mild.

Table 3. Univariate and multivariate predictors of > mild residual leak in patients undergoing percutaneous paravalvular leak (PVL) closure.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age, years	1.04 (0.99-1.08)	**0.093**	1.06 (0.99 -1.12)	0.073
Women	2.49 (1.06-5.82)	**0.036**	2.58(0.90-7.36)	0.076
Body mass index (kg/m2)	1.00 (0.99-1.00)	0.774		
NYHA class IV	4.92 (1.72-14.05)	**0.003**		
Hemolysis	3.04 (1.24-7.41)	**0.015**		
Transfusion requirement (last 6 m)	4.01 (1.67-9.66)	**0.002**		
Chronic kidney disease*	5.99 (2.20-16.29)	**<0.001**	7.09 (2.26-22.21)	**0.001**
Cerebrovascular disease	4.06 (1.32-12.50)	**0.015**		
Prior endocarditis	1.14 (0.47-2.78)	0.777		
EUROSCORE II, (%)	0.05 (-0.02-0.13)	0.161		
Time since last surgery, years	0.98 (0.94 -1.03)	0.468		
≥ 2 sternotomies	2.70 (1.12-6.49)	**0.027**		
Previous PVL repair surgery	2.61 (0.97-7.0)	**0.056**	4.03 (1.17-13.92)	**0.028**
Mechanical prosthesis	0.48 (0.13-1.77)	0.268		
Severe basal PVL grade	6.25 (1.67-23.49)	**0.007**		
Multiple jets	3.68 (1.51-8.97)	**0.004**	4.41(1.49-13.06)	**0.003**
SPAP > 60mmHg	0.99 (0.41- 2.36)	0.979		
First 45 procedures	2.69 (1.14-6.33)	**0.023**		
Intraprocedural 3D TEE imaging	0.18 (0.04-0.39)	**<0.001**		

OR: Odds Ratio, CI: Confidence Interval, NYHA: New York Heart Association, eGFR: estimated glomerular filtration rate, PVL: paravalvular leak, 3D TEE: Three-dimensional transesophageal echocardiography, SPAP: Systolic pulmonary artery pressure, m: months. *Chronic kidney disease was considered as CKD-EPI less than 60 mL/min/1.73m^2

Table 4. Thirty-day complications after percutaneous paravalvular leak closure.

30-day complications		
Number of patients with complications		15 (16.7)
Total number of complications		22
Number of patients with major complications		9 (10.0)
Total number of major complications		12
Type of complications		
Conversion to surgery		0 (0)
Leaflet impingement		4 (4.4)
Leaflet impingement (surgically resolved)		0 (0)
Device embolization (percutaneously resolved)		1 (1.1)
Pericardial effusion		2 (2.2)
Vascular complication	Total	11 (12.2)
	Surgical requirement	1 (1.1)
	Transfusion requirement	3 (3.3)
	Pseudoaneurysm	4 (4.4)
	Arteriovenous fistulas	1 (1.1)
	Hematoma	6 (6.7)
Stroke		0 (0)
Transient ischemic attack		1 (1.1)
Ventilator-dependent respiratory failure		1 (1.1)
30-day mortality		2 (2.2)

Values are n (%).

Table 5. Univariate and multivariate factors associated with all-cause death in patients undergoing percutaneous paravalvular leak (PVL) closure.

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P-value	HR (95%CI)	P-value
Age, (years)	1.06 (1.03-1.09)	**<0.001**	1.06 (1.02-1.09)	**0.002**
Women	1.33 (0.76-2.32)	0.320		
Diabetes	2.50 (1.37-4.58)	**0.003**	2.19 (1.17-4.12)	**0.015**
NYHA class IV	4.36 (2.47-7.7)	**<0.001**	2.60 (1.39-4.85)	**0.003**
Hemolysis	1.09 (0.62-1.93)	0.754		
Transfusion requirement (last 6 months)	2.0 (1.14-3.51)	**0.015**		
Chronic kidney disease *	3.21 (1.85-5.59)	**<0.001**	1.64 (0.88-3.06)	0.118
EUROSCORE II	1.07 (1.04-1.11)	**<0.001**		
≥ 2 sternotomies	1.38 (0.76-2.49)	0.291		
Previous PVL repair surgery	1.46 (0.80-2.66)	0.220		
Severe basal regurgitation grade PVL	1.15 (0.66-2.01)	0.627		
Multiple jets	1.15 (0.66-2.01)	0.627		
Pulmonary hypertension (SPAP >60mmHg)	1.10 (0.62-1.96)	0.743		
Left ventricular ejection fraction	1.02 (0.10-1.05)	0.108		
Intraprocedural 3D TEE imaging	0.97 (0.52-1.81)	0.927		
Procedural failure (residual leak > mild)	3.56 (1.98-6.40)	**<0.001**	2.61 (1.42-4.77)	**0.002**

HR: Hazard Ratio, CI: confidence interval, NYHA: New York Heart Association, SPAP: Systolic pulmonary artery pressure, TEE: transesophageal echocardiography *Chronic kidney disease was considered as CKD-EPI less than 60 mL/min/1.73m^2

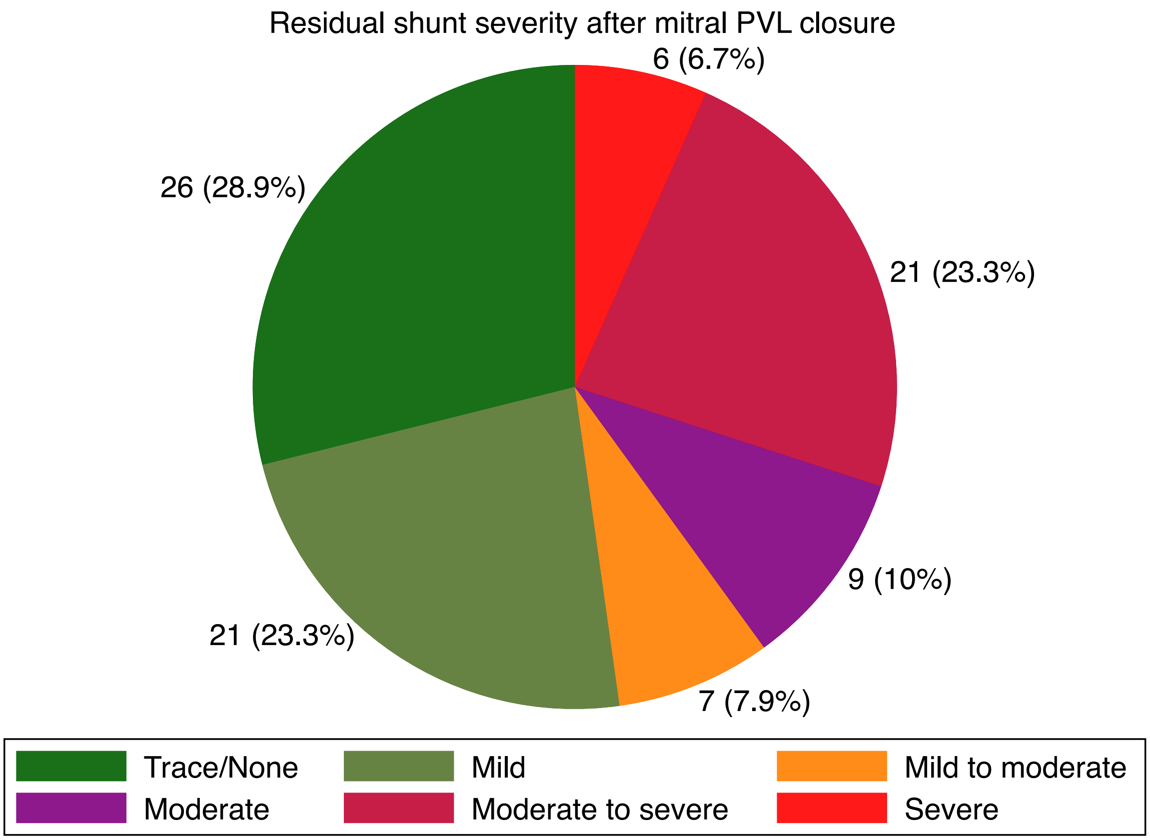
Table 6. Differences in incidence rates and risks of each endpoint according to the result of the procedure.

Endpoints	All patients (n=90), IR	Procedural Success † (n=47), IR	Procedural Failure † (n=43), IR	CI 95% of IR ratio	Non-adjusted HR (CI 95%)	Adjusted HR†‡ (CI 95%)
All-cause death	15.5	8.2	27.3	(1.81-6.34)	3.56 (1.98-6.40)	2.59 (1.41-4.78)
Cardiovascular death	10.7	4.8	20.3	(1.96-9.78)	4.74 (2.27-9.88)	3.53 (1.67-7.49)
Non-cardiovascular death	4.8	3.4	7.0	(0.69-6.58)	1.14 (0.40-3.32)	1.29 (0.36-4.66)
Heart failure admission	14.3	7.7	25.0	(1.73-6.32)	3.77 (2.05-6.93)	3.27 (1.72-6.20)
Surgical redo	3.3	2.4	4.7	(0.49-8.05)	1.30 (0.37-4.55)	0.99 (0.01-65.71)
Percutaneous redo	7.5	4.8	11.7	(1.02-6.04)	2.69 (1.17-6.14)	2.81 (1.15-6.87)

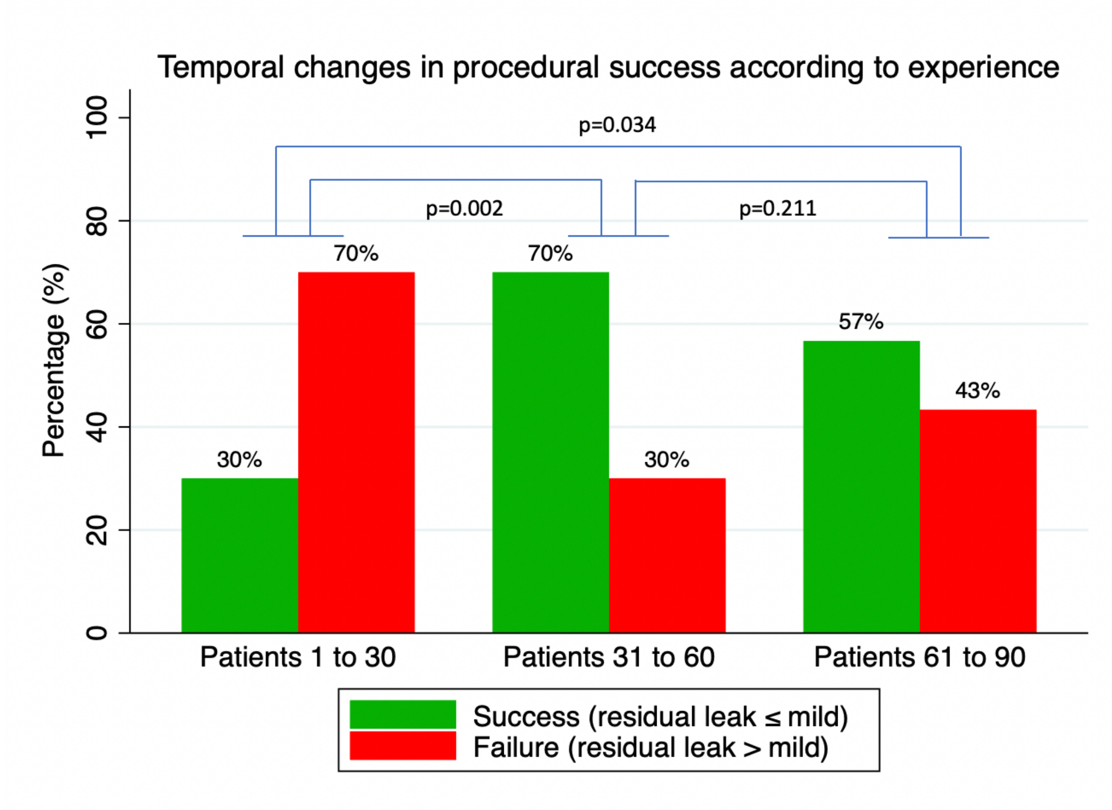
IR: incidence rate (100 person/year); HR: Hazard Ratio. † Procedural success was considered when residual leak was equal or less than mild. ‡Adjusted by age, New York Heart association class IV, chronic kidney disease, transfusion requirement and diabetes.

SUPPLEMENTARY MATERIALS

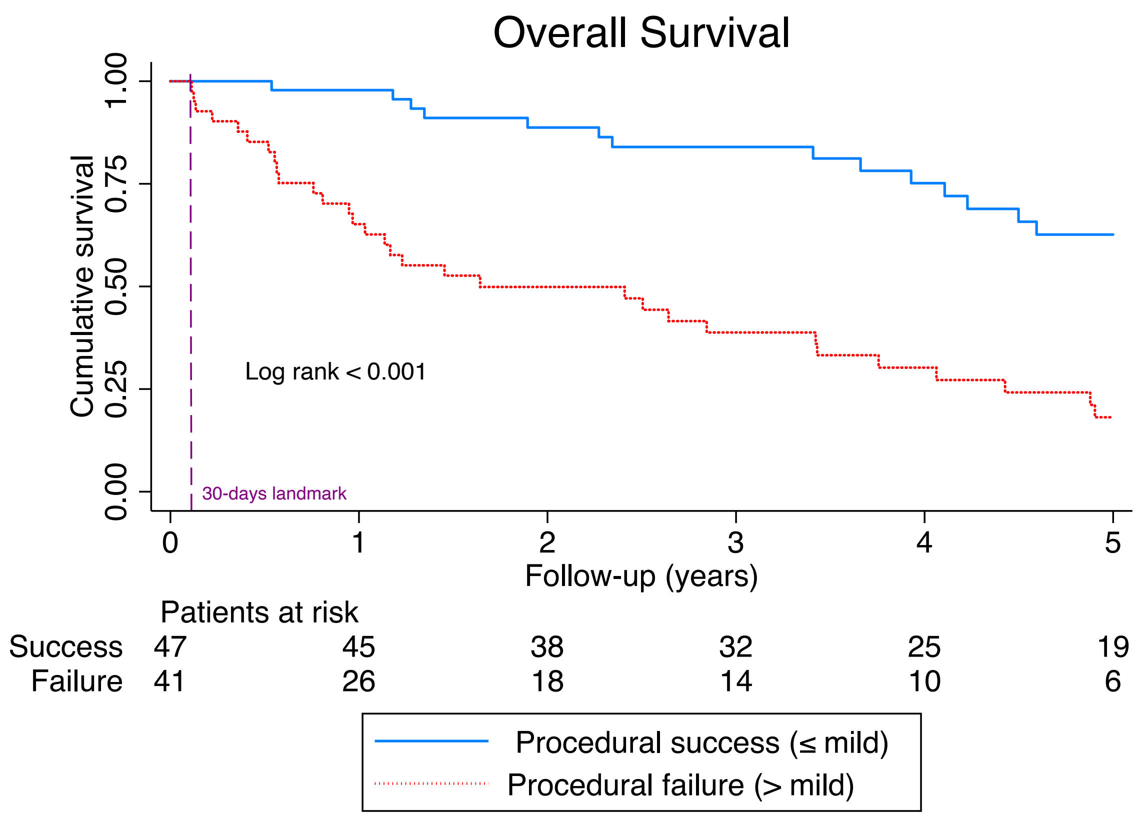
Supplemental Figure S1: Residual shunt severity assessment using the 5-Class Grading Scheme after mitral paravalvular leak (PVL) closure.



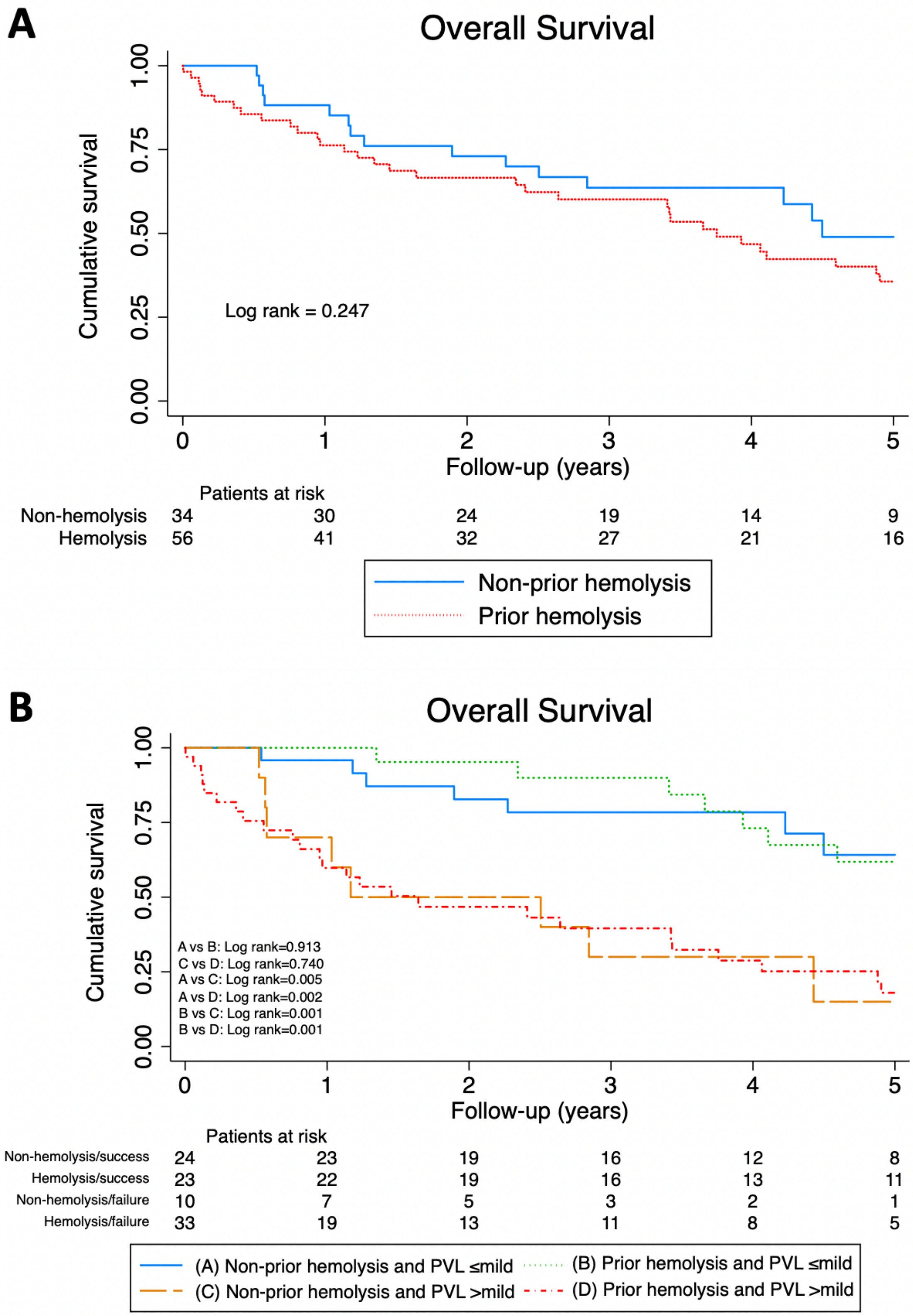
Supplemental Figure S2: Bar Chart illustrating temporal divisions of the cohort into three tiers, depicting changes in procedural success according to experience.



Supplemental Figure S3: Landmark analysis of patients who survived beyond 30 days.



Supplemental Figure S4: Overall survival according to the presence or absence of hemolysis (A) and according to the presence of hemolysis and procedural success (B).


A
Overall Survival
Cumulative survival
1.00
0.75
0.50
0.25
0.00
Log rank = 0.247
0
1
2
3
4
5
Follow-up (years)
Patients at risk
Non-hemolysis 34 30 24 19 14 9
Hemolysis 56 41 32 27 21 16
Non-prior hemolysis
Prior hemolysis
B
Overall Survival
Cumulative survival
A vs B: Log rank=0.913
C vs D: Log rank=0.740
A vs C: Log rank=0.005
A vs D: Log rank=0.002
B vs C: Log rank=0.001
B vs D: Log rank=0.001
Follow-up (years)
Patients at risk
Non-hemolysis/success 24 23 19 16 12 8
Hemolysis/success 23 22 19 16 13 11
Non-hemolysis/failure 10 7 5 3 2 1
Hemolysis/failure 33 19 13 11 8 5
(A) Non-prior hemolysis and PVL ≤mild
(B) Prior hemolysis and PVL ≤mild
(C) Non-prior hemolysis and PVL >mild
(D) Prior hemolysis and PVL >mild