The analysis of left ventricular ejection fraction after minimally invasive surgery for primary mitral valve regurgitation

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Abstract

Background: Although minimally invasive mitral valve surgery (MIMVS) has become the first choice for primary mitral regurgitation (MR) in recent years, clinical evidence in this field is yet limited. The main focus of this study was the analysis of preoperative (Pre), postoperative (Post), and 1-year follow-up (Fu) data in our series of MIMVS to identify factors that have an impact on the left ventricular ejection fraction (LVEF) evolution after MIMVS.

Methods: We reviewed the perioperative and 1-year follow-up data from 436 patients with primary MR (338 isolated MIMVS and 98 MIMVS combined with tricuspid valve repair) to analyze patients’ baseline characteristics, the change of LV size, the postoperative evolution of LVEF and its factors, and the clinical outcomes.

Results: The overall mean value of ejection fraction (EF) slightly decreased at 1-year follow-up (mean change of LVEF: \(-2.63 \pm 9.00\%\)). A significant correlation was observed for preoperative EF (PreEF) and EF evolution, the higher PreEF the more pronounced decreased EF evolution (in all 436 patients; \(r = -0.54, p < .001\), in isolated MIMVS; \(r = -0.54, p < .001\), in combined MIMVS; \(r = -0.53, p < .001\)). Statistically significant differences for negative EF evolution were evident in patients with mild or greater tricuspid valve regurgitation (TR) in all patients; \(p < .05\), odds ratio [OR] = 1.64, in isolated MIMVS; \(p < .01\), OR = 1.93, respectively). Overall clinical outcome in New York Heart Association classification at 1 year was remarkably improved.
Conclusions: Our results suggest an excellent clinical outcome at 1 year, although mean LVEF slightly declined over time. TR could be a predictor of worsened follow-up LVEF in patients undergoing MIMVS.

KEYWORDS
left ventricular ejection fraction, minimally invasive surgery, mitral valve surgery, tricuspid valve regurgitation

1 INTRODUCTION

Mitral valve regurgitation (MR) is a pathological condition in which the anterior-posterior leaflet coaptation is reduced for various reasons, whereby left ventricular (LV) preload and diastolic volume increase, and the risk of LV remodeling and irreversible cardiac dysfunction increases. As one of the changes in the guidelines for surgical intervention on the mitral valve (MV), the 2017 guidelines of the American College of Cardiology/American Heart Association provide a Class IIa recommendation for MV surgery in case of Stage C1 (sever valve disease but asymptomatic, normal left ventricular ejection fraction [LVEF]) when LVEF is diminished below 60% or left ventricular end systolic diameter (LVESD) is increased to 40 mm or more.1 The 2017 European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) guidelines also have issued almost the same recommendation for MV disease. Asymptomatic primary severe MR has been classified according to LVEF, LVESD, and atrial fibrillation (AF) and the presence or absence of pulmonary hypertension (PH).2 According to these recommendations, LVEF represents one of the essential preoperative factors in the process of decision finding for surgical indication. Surgery is recommended when LVEF is reduced below 60% but yet greater than 30%. On the contrary, the recommendation for surgery is remarkably restricted in case of normal LVEF or severely depressed LVEF of less than 30%.2

However, preoperative ejection fraction (EF) (PreEF) in the presence of severe MR may be technically overestimated, and a case in which follow-up LVEF (FuEF) occasionally deteriorates after surgery despite good PreEF is observed, whereas frequently improved FuEF is observed in clinical practice after successful MV repair. We conclude that the prediction of how LVEF will develop postoperatively (i.e., LVEF evolution = FuEF – PreEF) is cumbersome, particularly when PreEF is considered primarily. Current evidence with this respect is quite scarce, and it remains unclear which factors contribute to an improvement or a deterioration of FuEF.

Here, we analyzed our 436 consecutive patients who underwent isolated or combined minimally invasive mitral valve surgery (MIMVS) to evaluate (1) How does LVEF change after MIMVS for primary MR which was performed according to the guideline? (2) According to the results of Question 1., how does the change of EF (delta EF) affects clinical results (NYHA classification)? (3) Which factors have a negative impact on LVEF in the setting of MIMVS for primary MR?

2 METHODS

2.1 Study population and data collection

Four hundred thirty-six consecutive patients undergoing MIMVS for primary MR as an isolated procedure (n = 338; 84.9%) or in combination with tricuspid valve (TV) surgery (n = 98; 15.1%) between September 2009 and December 2016 at a single institution were evaluated in this study. Data on the clinical course were prospectively collected in our data system as well as 1-year follow-up data that were systematically performed via telephone interview.

The local ethics committee approved this study (Approval No.: 3650).

2.2 Surgical indication and procedure

The indication of MV and TV operation was determined by based on EACTS guideline.2 All patients received a minimally invasive surgical approach via right anterolateral mini-thoracotomy with peripheral vascular cannulation for extracorporeal circulation via femoral vessels or subclavian artery as described in detail before.3–5

2.3 Echocardiographic evaluation

All patients underwent transthoracic echocardiographic evaluation preoperatively and at 1 year postoperatively. Echocardiography was performed as part of the institutional routine procedure.6 We measured ordinal variables with 2-dimensional echocardiography and Doppler color echocardiography. LV dimensions were evaluated in the parasternal long-axis view, and LVEF was measured by using the biplanar Simpson method. The evaluation of regurgitation severity for each valve was performed according to the current ESC guideline.7 LVEF evolution was defined as [FuEF–PreEF].

2.4 Statistical analysis

All statistical analyses were administrated with SPSS Statistics version 25 software (IBM). Data are presented as mean ± SDs of the mean as well as the median values for continuous variables, or as proportions in case of categorical variables. Analysis of
statistical correlation was performed using Spearman’s correlation coefficient. Chi-Quadrat-Test and odds ratio (OR) were conducted for nominal scaled variables, whereas the Student t tests or Mann–Whitney U tests were used for the comparison of values as required. For comparisons between multiple groups, one-way analysis of variance (ANOVA), and in case of multiple time points, two-way ANOVA, each with Bonferroni post hoc tests, were applied. The p values less than .05 were considered statistically significant. Finally, we performed linear and logistic regression analysis with variables for which a significant difference has been shown in previous analysis.

### 3 RESULTS

#### 3.1 Baseline characteristics

The baseline characteristics of the analyzed patients are presented in Table 1. A total of 221 (50.7%) men and 215 (49.3%) women were assigned with a mean age of 64.0 ± 12.9 years. TV repair was performed in 98 patients (22.5%). As part of the institutional policy, MV repair was favored over MVR whenever deemed feasible and durable, but MVR was also performed in 77 patients (17.3%) with a consideration of age, pathophysiology of MR and concomitant diseases.

| TABLE 1 Patient characteristics       | All patients (n = 436) | Median       | Surgical characteristics | All patients (n = 436) | Median       |
|---------------------------------------|-----------------------|--------------|--------------------------|-----------------------|--------------|
| Clinical characteristics              |                        |              |                          |                       |              |
| Age (y)                               | 64.0 ± 12.9 (n=436)   | 66.5 (n=384) | Elective OP, n (%)        | 384 (88.1)            |              |
| Male, n (%)                           | 221 (50.7)            |              | OP time (min)             | 236.2 ± 58.7          | 230          |
| BMI (kg/m²)                           | 25.2 ± 4.2 (n=436)    | 24.6 (n=359) | ECC time (min)            | 164.5 ± 47.1          | 159          |
| Nicotine abuses, n (%)                | 73 (16.7)             | 1.54 (n=41)  | Aortic crossclamp time (min) | 96.0 ± 33.1           | 91           |
| Euroscore II                          | 2.47 ± 2.63 (n=436)   |              | MV repair, n (%)          | 359 (82.7)            |              |
| NYHA class                            | 2.32 ± 0.81 (n=436)   | 2 (n=44)     | AML neochordae implantation, n (%) | 41 (9.4)            |              |
| Atrial fibrillation, n (%)            | 157 (36.2)            |              | PML neochordae implantation, n (%) | 161 (37.1)            |              |
| History of CAD or nonsignificant CAD, n (%) | 71 (16.7) |              | AML resection, n (%)      | 5 (1.2)              |              |
| Peripheral vascular disease, n (%)    | 16 (3.7)              |              | PML resection, n (%)      | 112 (26.4)            |              |
| Diabetes, n (%)                       | 30 (6.9)              |              | MAZE procedure, n (%)     | 54 (12.5)             |              |
| Hyperlipidemia, n (%)                 | 123 (28.2)            |              | TV repair, n (%)          | 98 (22.5)             |              |
| COPD, n (%)                           | 44 (10.1)             |              |                           |                       |              |
| Arterial hypertension, n (%)          | 295 (68.1)            |              |                           |                       |              |
| Pulmonary hypertension, n (%)         | 169 (38.8)            |              |                           |                       |              |
| Chronic kidney disease, n (%)         | 67 (15.4)             |              |                           |                       |              |
| Creatinine (mg/dl)                    | 1.06 ± 0.73 (n=436)   | 1 (n=31)     | Residual MR, n (%)        | 22 (5.3)             |              |
| Endocarditis, n (%)                   | 31 (7.2)              |              |                           |                       |              |
| Aortic valve regurgitation, n (%)     | 119 (27.5)            |              |                           |                       |              |
| Tricuspid valve regurgitation, n (%)  | 315 (72.4)            |              |                           |                       |              |
| Barlow, n (%)                         | 36 (8.3)              |              |                           |                       |              |
| AML prolapse, n (%)                   | 98 (22.7)             |              |                           |                       |              |
| PML prolapse, n (%)                   | 254 (58.9)            |              |                           |                       |              |
| Bileaflet prolapse, n (%)             | 7 (1.6)               |              |                           |                       |              |
| Preoperative LVEF (%)                 | 60.3 ± 9.73 (n=436)   |              |                           | 60                    |              |

Note: Data documented as n (%) or mean ± SD.

Abbreviations: AML, anterior mitral leaflet; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; ECC, extracorporeal circulation; LVEF, left ventricular ejection fraction; MR, mitral valve regurgitation; MV, mitral valve; NYHA, New York Heart Association; OP, operation; PML, posterior mitral leaflet; SAM, systolic anterior motion; TV, tricuspid valve.
The LV function is presented in Figure 1. In all groups, we identified 3.2 \% (246 [56.4\%]) had an EF decline. The change of mean LVEF at different time points after MIMVS for whole patients group comprising 436 patients, patients undergoing isolated MIMVS, and patients undergoing combined MIMVS with other concomitant procedures. \( p < .005, \ p < .001 \). EF, ejection fraction; FuEF, follow-up EF; LV, left ventricular; MIMVS, minimally invasive mitral valve surgery; PostEF, postoperative EF; PreEF, preoperative EF

There were five cases of conversion from MV repair to MVR during surgery in the study period; these cases were excluded from further analysis. The mean preoperative LVEF was 60.3 ± 9.73\%. As far as EF evolution is concerned, the overall mean value of EF evolution was negative within the evaluated postoperative period of 1 year (mean evolution is presented in Figure 2. Overall, we found a significant influence of PreEF on EF evolution (0 > EF evolution); in comparison to PreEF (EF evolution = 0) for each group. For whole patients group, this cut-off value was PreEF = 54.8\%, in isolated MIMVS PreEF = 55.4\%; and in combined MIMVS at a cut-off PreEF = 54.4\%. Based on these cut-off values of PreEF where EF evolution equaled 0, we classified 6 subcohorts:

A, a subcohort of patients with preoperative LVEF greater than the defined cut-off (PreEF ≥ cut off) and postoperative LVEF increase (0 ≤ EF evolution);
B, patients with preoperative LVEF greater than the defined cut-off (PreEF ≥ cut off), however a postoperative decrease (0 > EF evolution);
C, patients with preoperative LVEF lower than the defined cut-off (PreEF ≤ cut off) but a postoperative LVEF increase (0 ≤ EF evolution);
D, patients with preoperative LVEF lower than the defined cut-off (PreEF ≤ cut off) and a further postoperative decline in LVEF (0 > EF evolution);
I = A + C; subcohort of patients with a postoperatively stable or increased LVEF (0 ≤ EF evolution);
II = B + D; subcohort of patients with a postoperative decrease in LVEF (0 > EF evolution; Figure 3).

### 3.3 Follow-up on clinical outcome according to NYHA classification at 1 year postoperatively

We analyzed the 1-year follow-up in NYHA classification for all patients. The follow-up NYHA classification was remarkably improved in comparison with preoperative data (Figure 4).

### 3.4 Analysis of predictive factors of EF decline at 1 year postoperatively

According to classifications mentioned above, we conducted an analysis of predictive factors of EF decline in all subcohorts in each group. We performed the univariable analysis as well as multivariable analysis of each factor (Table 2).

### 3.5 Univariable analysis

In all 436 patients, statistically significant differences for negative EF evolution were evident in patients with mild or greater TR (subcohort I in comparison with II; \( p < .05, OR = 1.64 \)). Interestingly, this trend was stronger in patients with good PreEF (subcohort A vs. B; \( p < .05, OR = 1.68 \)). This tendency was also observed in isolated MIMVS group (I vs. II; \( p < .01, OR = 1.93 \), A vs. B; \( p < .01, OR = 2.10 \)). We evaluated LV end diastolic diameter (LVEDD) and right ventricular end diastolic diameter (RVEDD) only for 316 patients and
The correlation graphic between PreEF and EF evolution, defined as FuEF-PreEF, is shown for whole patients group comprising 436 patients, patients undergoing isolated MIMVS, and patients undergoing combined MIMVS with other concomitant procedures. Cut-off value of PreEF is 54.8%, 55.4%, and 54.4%, in the whole patients group, group of isolated and combined MIMVS, respectively. EF, ejection fraction; MIMVS, minimally invasive mitral valve surgery; PreEF, preoperative EF.
259 patients in all patients group, respectively. Both values proved as nonpredictive for worsening of FuEF (LVEDD; $I$ vs. $II$; $p = .18$, RVEDD; $I$ vs. $II$; $p = .07$). Regarding cardiac index (CI), preoperative values were available only for 92 patients in isolated MIMVS group. CI was not a worsening predictor of FuEF in this limited study size.

### 3.6 | Multivariable analysis

Subsequently, we performed logistic regression analysis. Mild or greater TR was showed as the significant preoperative factor of negative EF evolution in all 436 patients ($p < .005$; OR = 1.46; confidence interval (C.I.): 1.12–1.88). TR was also identified as the factor in the setting of subcohorts $A$ and $B$ ($p < .05$; OR = 1.36; C.I.: 1.04–1.77), however not in the setting of subcohorts $C$ and $D$ ($p = .39$). Further, in isolated MIMVS groups, TR would be a preoperative factor of negative EF evolution not only in all patients ($p < .05$; OR = 1.50; C.I.: 1.15–1.97) but also in the setting of subcohorts $A$ and $B$ ($p < .05$; OR = 1.62; C.I.: 1.12–1.88).

### 4 | DISCUSSION

Although MIMVS is becoming the first choice for MV surgery in recent years, the choice of surgical approach has not been addressed in the current ESC guidelines. There are a few reports about postoperative EF decline after MV surgery. However, clinical evidence in this field is yet limited and with respect to MIMVS even more scarce.

The key findings of this study are: (1) PreEF and EF evolution show a significant negative correlation in all groups; (2) a preoperative LVEF of 55% prove as cut-off value for FuEF decline in all groups; (3) a preoperative TR of mild or greater severity is associated with reduced LVEF postoperatively; (4) however, TV repair shows no correlation with FuEF decline; (5) in comparison to past reports, age, PH, AF show no impact on decreased LVEF at 1 year; (6) CI does not predict FuEF in isolated MIMVS. And finally; (7) Overall clinical outcome in NYHA classification at 1 year was remarkably improved, although on the mere numeric level mean LVEF slightly declined over time.

As already well known, PreEF in MR is overestimated due to relevant regurgitant stroke volume. In other words, PreEF measured by routine echocardiography underestimates the myocardial systolic
TABLE 2  Representative uni- and multivariable analysis of predictive factors of LVEF decline at 1 year postoperatively

|                     | All patients (n = 436) | A (n = 135) versus B (n = 225) | C (n = 55) versus D (n = 21) |
|---------------------|------------------------|---------------------------------|-----------------------------|
|                     | OR (95% CI) p          | OR (95% CI) p                   | OR (95% CI) p               |
| **Univariable analysis** |                        |                                 |                             |
| PH                  | 0.99 (0.67–1.45) .94   | 1.06 (0.68–1.65) .8             | 1.49 (0.54–4.1) .44         |
| TR (≥mild)          | 1.64 (1.07–2.50) .03   | 1.68 (1.05–2.69) .03            | 2.46 (0.64–9.53) .18        |
| MV repair           | 0.71 (0.43–1.16) .17   | 0.72 (0.41–1.26) .25            | 0.84 (0.24–2.98) .79        |
| TV repair           | 0.76 (0.48–1.19) .22   | 0.76 (0.45–1.28) .3             | 1.21 (0.42–3.58) .72        |
| SAM                 | 1.12 (0.35–3.60) .85   | 1.09 (0.31–3.79) .9             |                       |
| Residual MR         | 0.72 (0.31–1.68) .45   | 1.04 (0.37–2.95) .93            | 0.44 (0.05–3.87) .44        |
| **Multivariable analysis** |                    |                                 |                             |
| PH                  |                        |                                 |                             |
| TR (≥mild)          | 1.46 (1.13–1.88) <.01  | 1.36 (1.04–1.77) .02            |                       |
| MV repair           |                        |                                 |                             |
| TV repair           |                        |                                 |                             |
| SAM                 |                        |                                 |                             |
| Residual MR         |                        |                                 |                             |

|                     | Isolated MIMVS (n = 338) | A (n = 96) versus B (n = 177) | C (n = 46) versus D (n = 19) |
|---------------------|-------------------------|---------------------------------|-----------------------------|
|                     | OR (95% CI) p          | OR (95% CI) p                   | OR (95% CI) p               |
| **Univariable analysis** |                        |                                 |                             |
| PH                  | 1.32 (0.27–0.73) .24   | 1.46 (0.84–2.56) .18            | 2.67 (0.88–8.05) .07        |
| TR (≥mild)          | 1.931 (1.23–3.04) <.01 | 2.104 (1.26–3.52) <.01          | 1.8 (0.55–5.86) .33         |
| MV repair           | 0.59 (0.32–1.09) .09   | 0.76 (0.38–1.55) .45            | 0.18 (0.02–1.48) .08        |
| SAM                 | 1.16 (0.32–4.18) .82   | 1.15 (0.28–4.70) .85            |                       |
| Residual MR         | 0.68 (0.27–1.71) .41   | 0.91 (0.29–2.88) .88            | 0.48 (0.05–4.44) .51        |
| **Multivariable analysis** |                    |                                 |                             |
| PH                  |                        |                                 |                             |
| TR (≥mild)          | 1.5 (1.15–1.97) .03    | 1.62 (1.19–2.20) .02            |                       |
| MV repair           |                        |                                 |                             |
| TV repair           |                        |                                 |                             |
| SAM                 |                        |                                 |                             |
| Residual MR         |                        |                                 |                             |

|                     | Combined MIMVS (n = 98) | A (n = 32) versus B (n = 43) | C (n = 16) versus D (n = 7) |
|---------------------|------------------------|---------------------------------|-----------------------------|
|                     | OR (95% CI) p          | OR (95% CI) p                   | OR (95% CI) p               |
| PH                  | 0.5 (0.22–1.13) .1     | 0.55 (0.21–1.41) .21            | 0.34 (0.06–2.13) .24        |
| MV repair           | 1.17 (0.48–2.87) .74   | 1.03 (0.36–2.96) .95            | 2.3 (0.35–14.7) .39        |
| SAM                 | 0.92 (0.06–15.1) .95   | 0.71 (0.04–11.8) .81            |                       |
| Residual MR         | 0.94 (0.13–6.93) .95   | 1.5 (0.13–17.3) .75            |                       |

|                     | Isolated MIMVS (n = 92) |
|---------------------|-------------------------|
|                     | CI                      |
| I (n = 41)          | 2.62 ± 0.82             |
| II (n = 51)         | 2.46 ± 0.58             |
| A (n = 31)          | 2.59 ± 0.81             |
| B (n = 45)          | 2.45 ± 0.57             |
| C (n = 10)          | 2.7 ± 0.90              |
| D (n = 6)           | 2.56 ± 0.64             |

Note: Data documented as mean ± SD. CI, cardiac index; MIMVS, minimally invasive mitral valve surgery.

Abbreviations: CI, confidence interval; LVEF, left ventricular ejection fraction; MIMVS, minimally invasive mitral valve surgery; MR, mitral valve regurgitation; MV, mitral valve; OR, odds ratio; PH, pulmonal hypertension; SAM, systolic anterior motion; TR, tricupid valve regurgitation; TV, tricuspid valve.
dysfunction.\textsuperscript{14} In the presence of MR, much of the ejected blood flows into the left atrium. As a result, the afterload of the left heart system is low, and there is a limited decrease in LVEF for a while, even if some deterioration in ventricular function occurs. This results in the clinical dilemma that potential cardiac dysfunction is progressing even if the preoperative cardiac function apparently is reasonable.

Furthermore, if functional TR is involved, there is still controversy whether LVEF with low preload by TR reflects the true cardiac function. Under such circumstances, some authors have reported that preoperative “forward LVEF,” also referred to as LV forward stroke,\textsuperscript{15} may well correlate with postoperative “total” LVEF.\textsuperscript{16} Forward LVEF less than 35% has been demonstrated as a cut off value to predict higher short-term mortality after MV surgery.\textsuperscript{17} Therefore, forward LVEF may be a superior parameter to the “total” LVEF and may be employed to predict LV dysfunction after MV surgery.\textsuperscript{18} On the other hand, it has been shown that a postoperative (6 months) LVEF less than 50% indicates decreased long-term survival in patients undergoing surgery for MR.\textsuperscript{19} Recently Quintana et al.\textsuperscript{11} have indicated that more severely depressed immediate postoperative EF (here 4 postoperative days) less than 40% may indicate an adverse outcome. We think that our result, as above mentioned, may have a further impact on the preoperative estimation of expected FuEF.

Concerning the evolution of LV size and function when PreEF is preserved, the past report suggested that LVEDD and LVESD significantly decreased. At this point, it can be inferred whether LV reverse remodeling has occurred or not.\textsuperscript{10} Thus, we think that preoperative TR could indicate a decreased capacity for reverse remodeling after MIMVS.

In past studies, some authors have noted that smaller LVESD, younger age, and sinus rhythms represent important preoperative determinants for preserved postoperative EF.\textsuperscript{10–12} Our study could not provide the same results. However, these factors can also be a prognostic factor for overall favorable outcome, and hence, it seems necessary to consider them as postoperative predictive factors.

With the emerging notion of limitations adherent to LVEF other parameters have been discussed as alternative measures for assessment of cardiac function and particularly functional reserve. One of the alternative ordinal indicators of cardiac function is CI. Before this study, we speculated that CI might be a predictive factor for estimating cardiac deterioration after surgery. All patients preoperatively subjected to diagnostic workup at our cardiovascular center and referred to surgery for MR receive a right heart catheterization with a determination of cardiac output and CI. To evaluate our hypothesis on the value of CI, we analyzed data from patients without TR. Against our assumption, there was no correlation between preoperative CI and EF evolution. This “unexpected” result has caught our attention as it indicates that CI maybe even less critical than PreEF in the context of preoperative evaluation and risk assessment for patients with severe MR. However, CI was not routinely measured in every patient and datasets were available in a minority of patients.

There are several limitations to this study. First, our study was a nonrandomized series from a single center with retrospective analysis. Second, we did not analyze long-term prognosis, as our institutional standard procedure encounters 1-year follow-up only. A long-term follow-up may add some insight into the progressive remodeling of LV and the evolution of LVEF. Third, due to incomplete datasets, our study could not conclude the analysis of all echocardiographic parameters. Further studies are certainly warranted for comparative evaluation of these diagnostic values.

5 CONCLUSION

Patients with greater PreEF are at higher risk for decreased LVEF at 1 year after MIMVS. Moreover, the concomitant TR at the time of MIMVS for severe MR might be a predictive factor for the decline of LVEF; in other words, worsened LV reverse remodeling at 1 year. Therefore, there could be a need to pay attention of overestimated PreEF and reconsider surgical indication to primary MR regarding this study results.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Conception of the work: Yukiharu Sugimura and Payam Akhyari. Analysis and interpretation of data: Yukiharu Sugimura, Shintaro Katahira, Philipp Rellbecke, Jan-Philipp Minol, Moritz Benjamin Immohr, and Payam Akhyari. Drafting of the manuscript: Yukiharu Sugimura. Critical revision of the manuscript: Hiroyuki Kamiya, Hug Aubin, Stephan Urs Sixt, Patrick Horn, Ralf Westenfeld, Torsten Doenst, Artur Lichtenberg, and Payam Akhyari. Responsibility for treatment decisions: Philipp Rellbecke, Artur Lichtenberg, and Payam Akhyari. Supervision: Artur Lichtenberg and Payam Akhyari.

DATA AVAILABILITY STATEMENT

Primary data and datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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