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Operator Experience and Procedural Results of Transcatheter Mitral Valve Repair in the United States

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Brief Title: Operator Learning Curve for MitraClip

Disclosures

Dr. Chhatriwalla is a proctor for Edwards Lifesciences and Medtronic Inc. and is on the Speaker Bureau for Abbott Vascular, Edwards Lifesciences and Medtronic Inc.
Dr. Vemulapalli has grants from Abbott Vascular, Boston Scientific, HeartFlow, American College of Cardiology, Society of Thoracic Surgeons, National Institutes of Health and Patient Centered Outcomes Research Institute. He serves as a consultant to Boston Scientific, Premiere, Janssen, and Zafgen.
Dr. Szerlip has served as a speaker and proctor for Edwards Lifesciences and as a speaker for Medtronic Inc.
Dr. Kodali has received consulting fees from Edwards Lifesciences, Abbott Vascular, Meril Lifesciences, Claret Medical, Admedus; is on the Advisory Board of Dura Biotech, Thubrikar Aortic Valve, Inc., and Biotrace Medical has received honoraria from Abbott Vascular, Meril Lifesciences, Claret Medical, and Admedus; and has equity in Thubrikar Aortic Valve Inc., Dura Biotech, and Biotrace Medical. R. Hahn reports speaker fees from Boston Scientific Corporation, Baylis Medical and Philips Healthcare; consulting for Abbott Structural, Edwards Lifesciences, Medtronic, NaviGATE, Philips Healthcare.
Dr. Mack has served as co-principal investigator for the Edwards Lifesciences PARTNER trial and Abbott COAPT Trial; and has served as study chair for the Medtronic APOLLO Trial.
Dr. Ailawadi is a consultant with Abbott Vascular, Atricure, Edwards Lifesciences, Medtronic Inc., Gore and Admedus.
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Tweet: For TMVr with MitraClip, procedural success, procedure time, and procedural complications improve with increasing operator experience.

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Abstract

Background: Transcatheter mitral valve repair (TMVr) for the treatment of mitral regurgitation (MR) is a complex procedure that requires development of a unique skillset.

Objective: To examine the relationship between operator experience and procedural results of TMVr with MitraClip (Abbott Structural, Santa Clara, CA).

Methods: TMVr device procedures from the STS/ACC TVT Registry were analyzed with operator case number as a continuous and categorical (1-25, 26-50, and >50) variable. Outcomes of procedural success, procedural time, and in-hospital procedural complications were examined. The learning curve for the procedure was evaluated using generalized linear mixed models adjusting for baseline clinical variables.

Results: All TMVr device procedures (n=14,923) performed by 562 operators at 290 sites between November 2013 and March 2018 were analyzed. Optimal procedural success (≤ 1+ residual MR without death or cardiac surgery) increased across categories of operator experience (63.9%, 68.4%, and 75.1%; p<0.001), while procedural time and procedural complications decreased. Acceptable procedural success (≤ 2+ residual MR without death or cardiac surgery) also increased with operator experience, but the differences were smaller (91.4%, 92.4%, and 93.8%, p<0.001). These associations remained significant in adjusted, continuous variable analyses. Visual inflection points in the learning curves for procedural time, procedural success, and procedural complications were evident after approximately 50 cases, with continued improvements observed up to 200 cases.

Conclusions: For TMVr device proceedures, operator experience was associated with improvements in procedural success, procedure time, and procedural complications. The impact of operator experience was greater when considering the goal of achieving 1+ residual MR.

Key Words: mitral regurgitation; learning curve; operator; TMVr

Condensed Abstract: In this study, 14,923 TMVr procedures with MitraClip from the STS/ACC TVT Registry were categorized based on operator case number. Procedural success, procedural time, and procedural complications were examined, and generalized linear mixed models were developed to adjust for baseline variables. Procedural success increased with increasing operator experience, while procedural time and procedural complications decreased. In a continuous variable analysis, visual inflection points for procedural time, procedural success, and procedural complications were evident after ~50 cases, with continued improvements observed up to 200 cases. These findings demonstrate the key role of operator experience in optimizing outcomes with transcatheter mitral repair.

Abbreviations:

TMVr: transcatheter mitral valve repair
MR: mitral regurgitation
TVT: Transcatheter Valve Therapy
STS: Society of Thoracic Surgery
ACC: American College of Cardiology
IQR: Interquartile range
NYHA: New York Heart Association
CHF: congestive heart failure
STS PROM: Society of Thoracic Surgery predicted risk of mortality

Introduction

Transcatheter mitral valve repair (TMVr) with MitraClip (Abbott Structural, Santa Clara, CA) is an established therapy for patients with mitral regurgitation (MR) and, for appropriate patients, is associated with improvement in symptom status and quality of life, and greater survival (1-4). MitraClip has been commercially available in the United States since 2013 and is a relatively novel procedure that requires a complex and unique skill set on behalf of both the operator and echocardiographer to ensure optimal procedural results while minimizing complications.

Procedural success of TMVr with MitraClip, as defined by acceptable reduction in MR and absence of major procedural complications,(5) has been reported to be as high as >90% in post-market registries, and the safety profile has been favorable. However, procedural success is variable, and complications, including death and device detachment, can occur. Multiple factors, including procedural experience, may impact procedural success.(6) As a relatively complex procedure, TMVr requires close collaboration among multidisciplinary specialists for patient selection and technical performance, and indeed, prior studies have demonstrated that procedural outcomes of TMVr improve with increasing institutional experience.(7) However, few data are available regarding the level of individual operator experience necessary to optimize clinical outcomes of TMVr.

Accordingly, the aim of the present study was to examine the association between individual operator experience and clinical outcomes of TMVr with Mitraclip. Using data from the Society of Thoracic Surgeons/ American College of Cardiology (STS/ACC) Transcatheter Valve Therapy (TVT) registry, we examined cumulative operator case experience and its association with procedural success, procedure time, and procedural complications.

Methods

Data Source and Study Population

The STS/ACC TVT Registry is a voluntary U.S. multicenter reporting system for structural heart procedures, jointly sponsored by STS and ACC, and data submission to the registry is a required by the Center for Medicare and Medicaid Services (CMS) for reimbursement of commercial MitraClip procedures performed in the U.S.(8). Demographic, clinical, procedural, and institutional data are collected and entered into a secure centralized database. Within the registry, up to two operators performing MitraClip procedures are identified based on National Provider Identifier (NPI) numbers. Automatic system validation, reporting of data completeness, random auditing of participating centers, and education and training of data site managers is performed to promote quality assurance. Data from adult patients undergoing a first MitraClip procedure between November 2013 and March 2018 were collected from the TVT Registry for this study. Patients with a history of prior transcatheter mitral valve intervention, patients undergoing concomitant transcatheter aortic valve replacement and patients with cardiogenic shock within 24 hours prior to the procedure were excluded from this analysis.

Outcomes Definitions

The primary outcome variable for this study was in-hospital procedural success, analyzed according to two definitions: (1) “optimal” MR reduction, defined as post-implant residual MR grade ≤1 without mortality or need for cardiac surgery; and (2) “acceptable” MR reduction, defined as post-implant residual MR grade ≤2 without mortality or need for cardiac surgery.(5) Procedure time was defined as the time from first vascular or transesophageal echocardiogram (TEE) access to last catheter or TEE removal. Procedural complications were analyzed individually and as a composite endpoint that included in-hospital death, stroke, single leaflet device detachment, unplanned cardiac surgery or intervention, cardiac perforation, major bleeding, major vascular access complication, retroperitoneal bleeding, unplanned vascular surgery or intervention, trans-septal complication, complete device detachment, device embolization, device thrombosis, or other device/delivery system related event.

Statistical Analysis

Procedures were categorized based on individual operator case sequence (1-25, 26-50, and >50). In the case of two operators with different levels of case experience performing a procedure together, the case was categorized based on the higher case sequence number. Baseline patient demographics, procedural data, and complications were examined across categories of case experience. Data were described across categories of operator case sequence number as median with interquartile range (IQR) for continuous variables and number (%) for categorical variables. Comparisons across these categories were performed using Kruskal-Wallis test for continuous variables and Pearson's chi-square test (or Fisher's exact test) for categorical variables.

To examine the relationship between individual operator case sequence number and procedural success, procedure time, and the composite endpoint of procedural complications, generalized linear mixed models were developed by using operator case sequence as a continuous variable. Restricted cubic splines were used to explore potential nonlinear relationships between case number and outcomes. Relationships were plotted as curves for operator case sequence versus outcome such that any given slope along the curve represents the rate of change in outcome with increasing procedural experience. A hierarchical structure was adopted, with random effects placed on the intercept for each operator and operators further nested within institution, assuming standard variance components. This mixed model also accounts for operator-specific effects. As a result, the data relating to all operators in the present analysis necessarily includes each operator's "learning curve." The applied methodology allows for visual estimation of the overall learning curve. For adjusted models, all patient risk factors for each model were first combined into a single risk score before constructing the hierarchical model. The risk score was used, rather than individual variables, to simplify the model and decrease the likelihood of non-convergence (failure of the program to find a model that fits the observed data), which is a particular problem with hierarchical models. To create this score, we performed an ordinary logistic regression model and used the predicted log odds for the outcome rather than the predicted probability because log odds are linear with respect to the model's variables. The risk score was then added as a single independent variable in the subsequent hierarchical model. The covariates in the adjusted mixed models are listed in Online Table 1.

In addition, sensitivity analyses were performed using 3-level hierarchical generalized linear mixed models, in which we compared outcomes for less experienced operators at high- or low-volume centers. Two separate analyses were performed using cutoffs of 25th percentile and 50th percentile to define operator case experience and institutional volume. Finally, an additional sensitivity analysis was performed using 3-level hierarchical generalized linear mixed models adjusting for mitral valve regurgitation etiology (degenerative vs. functional vs. other).

Missing data occurred at a rate of less than 5% for all covariates and missing data were imputed with the median for continuous variables and with the mode for categorical variables. All statistical analyses were performed by the Duke University Clinical Research Institute using SAS v. 9.4.

RESULTS

Patient and Procedural Characteristics

During the study period, 14,923 TMVr procedures with MitraClip were performed by 562 operators at 290 U.S. sites (**Table 1**). Patients were commonly elderly (median age, 81 years; IQR, 74 to 86 years) and Caucasian (88.9%), with a high prevalence of morbidities such as diabetes mellitus (27.6%), prior cardiac surgery (33.8%), prior myocardial infarction (MI, 26.6%), prior percutaneous coronary intervention (PCI, 30.6%) and prior coronary artery bypass grafting (CABG, 27.5%). The vast majority of patients had 3+ or 4+ mitral regurgitation (92.9%), and degenerative mitral disease (86.3%). Overall, the median STS predicted risk of mortality (STS PROM) was 5.7% (3.4, 9.2%) for mitral valve repair, and 8.7% (5.5, 13.3%) for mitral valve replacement. The distribution of operator case experience by site is shown in Figure 1. This corresponded to 549 operators with a case experience of 1-25, 230 operators with a case experience of 26-50, and 116 operators with a case experience of >50 during the study period. Patient baseline characteristics were largely comparable for these three categories. However, small but statistically significant differences were observed in patient age, prior MI, prior PCI, prior CABG, procedural acuity, carotid stenosis, prior stroke, peripheral arterial disease, hypertension, current dialysis, left ventricular ejection fraction, New York Heart Association (NYHA) classification, home oxygen use, severity of MR, mitral valve stenosis, mitral annular calcification, mitral leaflet calcification, etiology of MR (degenerative vs functional) and STS PROM.

Procedural characteristics of the total analytic cohort are represented in. **Table 2**The majority of cases were elective (87.2%). In most procedures, a single clip was deployed (53.3%), and the majority of clips were deployed at the A2-P2 location (86.4%). Procedure time decreased across categories of case experience (145, 118, and 99 minutes, respectively,

$p<0.001$), as did radiation exposure as measured by cumulative air Kerma (578, 475, and 383 mGy, respectively, $p<0.001$). Operators in the higher categories of case experience more frequently used > 1 MitraClip and more frequently placed clips in the A2-P2 and A3-P3 segments, with less frequent placement in the A1-P1 segments. Frequency of atrial septal defect (ASD) closure was higher in the higher categories of operator experience (0.9%, 1.4%, and 2.2%, respectively, $p<0.001$).

Clinical Outcomes

Procedural success improved with increasing operator case experience (Figure 2). Optimal procedural success increased across categories of operator case experience (63.9%, 68.4%, and 75.1%, respectively, $p<0.001$). Rates of acceptable procedural success were higher in all categories of operator experience, and the improvement in rates of procedural success with increasing operator experience was smaller (91.4%, 92.4%, and 93.8%, respectively, $p<0.001$). Procedural complications were lower in the higher categories of operator case experience (Table 3). This included fewer composite complications (9.7%, 8.1%, and 7.3%, respectively, $p<0.001$), including less frequent cardiac perforation (1.0%, 1.1%, and 0.4%, respectively, $p<0.001$) and less frequent blood transfusion (9.6%, 8.6%, and 6.5%, respectively, $p<0.001$). Of note, no difference in the rates of stroke ($p=0.26$), single leaflet device attachments ($p=0.11$), trans-septal complications ($p=0.25$), urgent cardiac surgery (0.42), or in-hospital mortality ($p=0.55$) were observed across categories of operator experience.

Continuous Variable Analyses

Unadjusted and adjusted 'learning curves' for both definitions of procedural success, procedure time, and procedural complications were constructed using operator experience as a continuous variable (**Central Illustration**). In unadjusted analyses, inflection points in the adjusted learning curves for procedural success were visually evident after approximately 50 cases, and continued improvement in clinical outcomes was observed for the entire case sequence up to 200 cases. Similar findings for a relation between a threshold of 50 cases and shorter procedural time and lower procedural complications also were evident. These associations remained statistically significant in adjusted analyses. Procedural success rates at various steps of the 'learning curve' are shown in **Table 4**.

Sensitivity Analyses

The 25th percentile of case experience equaled 13 cases for operators and 15 cases for sites. No differences in procedural success, procedure time, or procedural complications were observed between operators with a case experience ≤ 13 performing procedures at higher-volume (> 15 cases) as compared to lower-volume (≤ 15 cases) sites (Online Table 2). The 50th percentile of case experience equaled 31 cases for operators and 33 cases for sites. No differences in procedural success or procedural complications were observed between operators with a case experience ≤ 31 performing procedures at higher-volume (> 33 cases) as compared to lower-volume (≤ 33 cases) sites (Online Table 3). Procedure time was significantly higher for operators with a case experience ≤ 31 performing procedures at higher-volume (> 33 cases) sites +13.2 min (5.82, 20.5 min), p<0.001. No interaction between mitral valve regurgitation etiology and procedural success, procedure time, or procedural complications was observed (Online Table 4).

Discussion

The present investigation is an analysis of the impact of operator experience in a large multicenter cohort of patients representing the U.S. commercial TMVr experience with MitraClip. In this study, clinical outcomes, including procedural success, procedure duration, and procedural complications, improved with increasing operator case experience. Importantly, this association persisted in generalized linear mixed models adjusting for patient baseline characteristics, indicating that these improvements cannot be attributed solely to patient selection. The impact of operator experience was particularly evident for the endpoint of optimal MR reduction (≤ 1+ residual MR), as compared to the commonly used endpoint of acceptable MR reduction (≤ 2+ residual MR). Prior analyses have shown that increasing institutional experience is similarly associated with improved outcomes following TMVr;(7) therefore, these findings suggest that both operator and institutional experience play important roles in the procedural outcomes of TMVr with MitraClip. In addition, no interaction was observed between the mechanism of mitral valve regurgitation and procedural outcomes in this study.

These findings demonstrate that acceptable procedural success with residual moderate MR was achievable with a high rate (>90%) even early in the operator experience, but that procedural success further improves and procedural complications lessen with greater operator experience. As with surgery, (9,10) prior studies have suggested that residual MR is an important prognostic marker following TMVr. Less residual MR following TMVr has been associated with fewer rehospitalizations for CHF and better survival (6). In this study, we found residual MR grade ≤ 1 is achieved in only approximately 2/3 of patients undergoing TMVr with Mitraclip and that there is a steeper rise in the learning curve for “optimal” procedural success. Therefore, if the goal of TMVr is to optimally reduce MR while minimizing complications, and, if in the future, transcatheter therapy is to be considered as an alternative to surgery in eligible patients, operator experience may play an important role in the procedural outcomes achievable with TMVr. Furthermore, as TMVr becomes more prevalent in the U.S., it may be prudent for less experienced operators to be cognizant of where they sit on the ‘learning curve’ and to pay particular attention to case selection early in their early experience, considering that more complex patients may be referred to more experienced centers for treatment when prudent.

Importantly, the improvements in procedural success, procedure time, and procedure complications observed in this study may be related not only to the procedural skills and technique of the operator(s) performing the procedure, but also to the collective knowledge base of the Heart Team, which requires multidisciplinary input throughout the procedure. Small iterations in device placement can greatly impact procedural results, and typically, decisions regarding the location of the regurgitant jet, device placement or adjustment and the placement of additional devices are made through discussion between multiple team members. While the TVT Registry provides sufficient data to evaluate the association between operator experience and procedural outcomes, data regarding the experience of echocardiographers, anesthesiologists, and other members of the Heart Team are lacking. However, individual operators represent a crucial component of the Heart Team, and new operators may experience a 'learning curve' irrespective of the overall site experience or experience of other members of the Heart Team. Therefore, operator-level analyses such as the present analysis are of great interest and add to prior studies evaluating the site-level learning curve for TMVr with Mitraclip.

Several differences in procedural characteristics were present between procedures performed early and later in operators' experience. The proportion of patients with functional as opposed to degenerative, MR increased with increasing operator experience, and whether procedural success and complication rates are different for this patient population is unknown. More experienced operators were more likely to use more than 1 clip per case, and more frequently treated A2-P2 (central) and A3-P3 (medial), as opposed to the A1-P1 (lateral), pathology. Notably, procedure time decreased with increasing operator experience even as the number of clips deployed per case increased, and the relative impact of these procedural differences on procedural and clinical outcomes was not assessed in this study. Regarding complications, while the composite endpoint of overall complications decreased with increasing operator experience, this appears to be driven by fewer bleeding complications including cardiac perforation and blood transfusion. Importantly, no differences in death or stroke were observed with increasing operator experience. ASD closure was performed more frequently as operator experience increased, the incidence of trans-septal complications was no different, suggesting that operators' thresholds for closing iatrogenic ASDs after TMVR may decrease with increasing case experience. Alternatively, given that experienced operators were more likely to perform urgent procedures, this difference in practice may be related to a presumed benefit of iatrogenic ASD closure in a sicker patient population, for example in patients with pulmonary hypertension or right heart failure with elevated right atrial pressure, who may experience right to left shunting through an ASD.

Case selection is crucial and requires knowledge of a patient's suitability for a surgical procedure along with the attributes and limitations of TMVr, particularly as it relates to appropriate mitral valve anatomy for MitraClip and the identification of patients most likely to benefit from the procedure. However, because the improvements in procedural outcomes observed in this study despite adjustment for baseline patient characteristics, these improvements cannot be attributed to patients selection alone, and instead confirm that an operator learning curve exists for TMVr with Mitraclip. Importantly, patients treated with MitraClip later in operators' experience differed from patients treated early in operators' experience in several meaningful ways. To that end, operators with a case experience >50 were less likely to treat patients with pre-existing mitral stenosis or requiring home oxygen, presumably because they were less likely to achieve procedural success in these patients or because these patients were less likely to have a clinical benefit. Conversely, the frequency of urgent, as opposed to elective, cases was higher for operators with a case experience >50, suggesting that more experienced operators were more comfortable performing the procedure for unstable patients, when appropriate. The proportion of patients with functional MR treated with MitraClip also increased with increasing operator experience. Whether, this observation is simply reflective of the application of the MitraClip procedure to broader populations over time or more experienced operators' greater comfort level for treating this mechanism of MR is unknown. Importantly, no interaction was observed between the mechanism of mitral valve regurgitation and outcomes of procedural success, procedure time, or procedural complications in this study.

While volume-outcome relationships have been established for many medical procedures, including general surgery, cardiovascular surgery and transcatheter therapies,(11-16) yearly operator volumes were not analyzed in this study. Future studies examining the volume-outcome relationship for TMVr are needed to determine whether minimum annual volume thresholds for procedural success exist. A greater understanding of the relationship of MitraClip procedure volume on outcomes could have an impact on hospital and physician criteria for initiating and maintaining MitraClip programs.

Taken together, our findings emphasize the importance of experience in optimizing outcomes of TMVr with MitraClip and multidisciplinary collaboration for the treatment of patients with MR. The importance of operator experience for the procedure in our study incorporates the learning curves for patient selection and the procedural learning curves of multiple team members with varied roles. Of note, our study focused only on short-term procedural and in-hospital outcomes, and further research into long-term results is needed, particularly as these patients commonly have severe morbidities that may impact their survival despite early procedural success.

Study Limitations

This was a retrospective, observational study, and despite adjustment for various demographic, clinical, and procedural factors, unmeasured variables can confound the results of this analysis. Data in the TVT registry are site-reported, and baseline and residual MR severity were not adjudicated by a core laboratory. However, sites are instructed to report echocardiographic findings in accordance with American Society of Echocardiography Guidelines.(17,18) Furthermore, there were relatively few operators with very high case experience (e.g., >150 cases) in this analysis, which may have limited the ability to fully assess the learning curve for TMVr in this study. Similarly, operator experience with TMVr and MitraClip outside of the TVT Registry (for example in the setting of clinical trials) was not accounted for in this study. Finally, the present analysis represents the earliest U.S. clinical experience with TMVr, and iterations of the Mitraclip device that were adopted after the time period in the present study could impact future outcomes and the learning curve for the procedure. However, techniques for TMVr with MitraClip have not significantly changed since commercialization, and the commercial introduction facilitated an analysis for a learning curve through an examination of many sites that were new to the therapy and rapidly adopting it into clinical practice.

Conclusions

For TMVr with Mitraclip, increasing operator case experience was associated with improvements in procedural outcomes, including procedural success, procedure time, and procedural complications. These findings suggest that a relatively greater attention to case selection may be important during the early operator experience. Further research is needed to understand the specific factors associated with operator and site experience that impact long-term clinical outcomes.

Perspectives:

Competency in Medical Knowledge: Clinical outcomes of TMVr with Mitraclip, including procedural success, procedure duration, and procedural complications, improve with increasing operator case experience.

Competency in Patient Care: Associations between procedural outcomes and operator experience persisted despite adjustment for baseline patient characteristics, indicating that a procedural learning curve does exist for TMVR with Mitraclip.

Translational Outlook: Further research is needed to understand the impact of site and operator experience on longer-term outcomes following TMVr with Mitraclip.

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Figure Legends

Figure 1: MitraClip Volume. Cumulative commercial MitraClip case count by operators during the study period, as captured in the TVT Registry.

Figure 2: Association between Operator Experience and Procedural Success – Unadjusted Data. Unadjusted comparisons demonstrating higher procedural success rates with increasing operator experience. MR = mitral regurgitation

Central Illustration: Learning Curves for Procedural Success, Procedure Time, and Procedural Complications. Plots depicting the association between operator case count and procedural outcomes. Panel A = "optimal" procedural success; Panel B = "acceptable" procedural success; Panel C = procedure time; Panel D = procedural complications. Red line with red transparent band = unadjusted predicted curve with 95% confidence interval; Blue line with blue transparent band = adjusted predicted curve with 95% confidence interval. MR = mitral regurgitation

Table 1: Patient Characteristics

	Overall (N=14,923)	*Group 1 1-25 (N=6,431)*	*Group 2 26-50 (N=3,467)*	*Group 3 >50 (N=5,025)*	*p-value**
Age, Median (IQR)	81 (74,86)	82 (74,86)	80 (73,86)	81 (73,86)	<0.01
Female gender, n (%)	7,083 (47.5)	3,035 (47.2)	1,685 (48.6)	2,363 (47.0)	0.31
Caucasian race, n (%)	13,266 (88.9)	5,727 (89.1)	3,072 (88.6)	4,467 (88.9)	0.80
Endocarditis, n (%)	220 (1.5)	88 (1.4)	43 (1.2)	89 (1.8)	0.09
Implanted Cardioverter/Defibrillator, n (%)	2,085 (14.0)	860 (13.4)	492 (14.2)	733 (14.6)	0.16
Prior Percutaneous Coronary Intervention, n (%)	4,569 (30.6)	1,923 (29.9)	1,131 (32.6)	1,515 (30.1)	0.01
Prior Coronary Artery Bypass Surgery, n (%)	4,097 (27.5)	1,837 (28.6)	1,000 (28.8)	1,260 (25.1)	<0.01
Prior MV Repair	228 (0.01)	73 (0.01)	52(0.01)	103 (0.02)	0.54
Prior MV Ring	137 (0.01)	43 (0.01)	30 (0.01)	64 (0.01)	0.89
Prior Stroke or Transient Ischemic Attack, n (%)	2,470 (16.6)	1066 (16.6)	616 (17.8)	788 (15.7)	0.04
Carotid Stenosis, n (%)	1,698 (11.4)	784 (12.2)	395 (11.4)	519 (10.3)	<0.01
Peripheral Arterial Disease, n (%)	2,754 (18.5)	1,238 (19.3)	672 (19.4)	844 (16.8)	<0.01
Current/Recent Smoker, n (%)	925 (6.2)	409 (6.4)	226 (6.5)	290 (5.8)	0.29
Hypertension, n (%)	12,848 (86.1)	5,467 (85.0)	3,006 (86.7)	4,375 (87.1)	<0.01
Diabetes, n (%)	4,119 (27.6)	1,719 (26.7)	999 (28.8	1,401 (27.9)	0.07
Dialysis, n (%)	571 (3.8)	215 (3.3)	125 (3.6)	231 (4.6)	<0.01
Severe Chronic Lung Disease, n (%)	1,655 (11.1)	710 (11.0)	411 (11.9)	534 (10.6)	0.21
Home Oxygen, n (%)	1,975 (13.2)	909 (14.1)	499 (14.4)	567 (11.3)	<0.01
Prior Myocardial Infarction	3,969 (26.6)	1,674 (26.0)	1,015 (29.3)	1,280 (25.5)	<0.01
NYHA Class, n (%)					<0.01
I	241 (1.6)	118 (1.8)	67 (1.9)	56 (1.1)	
II	1,933 (13.0)	755 (11.7)	411 (11.9)	767 (15.3)	
III	9,471 (63.5)	4,106 (63.8)	2,205 (63.6)	3,160 (62.9)	
IV	3,139 (21.0)	1,398 (21.7)	741 (21.4)	1,000 (19.9)	
Atrial Fibrillation/Flutter, n (%)	9,333(62.5)	3,996 (62.1)	2,183 (63.0)	3,154 (62.8)	0.61
Body Surface Area (m^2, median, IQR)	1.8 (1.6,2.0)	1.8 (1.6,2.0)	1.8 (1.6,2.0)	1.8 (1.7,2.0)	0.20
Creatinine (mg/dL, median, IQR)	1.2 (0.9,1.6)	1.2 (0.9,1.6)	1.2 (0.9,1.6)	1.2 (0.9,1.6)	0.75
Hemoglobin (g/dL, median, IQR)	12.0 (10.7,13.3)	12.0 (10.6,13.3)	12.0 (10.7,13.2)	12.1 (10.7,13.3)	0.10
LV ejection fraction (median, IQR)	55 (40,60)	55 (40,60)	55 (40,60)	55 (40,60)	<0.01

	Overall (N=14,923)	Group 1 1-25 (N=6,431)	Group 2 26-50 (N=3,467)	Group 3 >50 (N=5,025)	p-value*
MR Severity, n (%)					0.01
moderate-severe or severe (3+/4+)	13,796 (92.9)	5,972 (93.4)	3,217 (93.3)	4,607 (92.0)	
none, trace, mild or moderate (0-2+)	990 (6.7)	393 (6.1)	220 (6.4)	377 (7.5)	
Mitral Stenosis, n (%)	769 (5.2)	371 (5.8)	188 (5.5)	210 (4.2)	<0.01
Functional MR, n (%)	2,816 (18.9)	976 (15.2)	649 (18.7)	1191 (23.7)	<0.01
Degenerative MR, n (%)	12,879 (86.3)	5,529 (86.0)	3,024 (87.2)	4,326 (86.1)	0.20
Mitral Leaflet Calcification, n (%)	2,999 (20.1)	1,297 (20.2)	686 (19.8)	1,016 (20.2)	<0.01
Mitral Annular Calcification, n (%)	5,381 (36.1)	2,343 (36.4)	1,228 (35.4)	1,810 (36.0)	<0.01
STS PROM-MV Replacement (median, IQR)	8.7 (5.5,13.3)	8.9 (5.6,13.6)	8.6 (5.5,13.1)	8.5 (5.3,12.9)	<0.01
STS PROM-Score-MV Repair (median, IQR)	5.7 (3.4,9.2)	5.8 (3.5,9.5)	5.7 (3.5,9.0)	5.4 (3.3,8.9)	<0.01

MV = mitral valve; NYHA = New York Heart Association; LV = left ventricle; MR = mitral regurgitation; STS PROM = Society of Thoracic Surgery predicted risk of mortality

*** p-values refer to comparisons among the three categories of operator experience (1-25 cases, 26-50 cases, and >50 cases)**

Table 2: Procedural Characteristics

	Overall (N=14,923)	*Group 1 1-25 (N=6,431)*	*Group 2 26-50 (N=3,467)*	*Group 3 >50 (N=5,025)*	*p-value**
Procedure Status, n (%)					0.01
Elective	13,019 (87.2)	5,668 (88.1)	2,996 (86.4)	4,355 (86.7)	
Urgent	1,165 (7.8)	456 (7.1)	282 (8.1)	427 (8.5)	
Emergent	681 (4.6)	287 (4.5)	167 (4.8)	227 (4.5)	
Salvage	58 (0.4)	20 (0.3)	22 (0.6)	16 (0.3)	
Number of Leaflet Clips, n (%)					<0.01
0	355 (2.4)	181 (2.8)	93 (2.7)	81 (1.6)	
1	7,957 (53.3)	3,600 (56.0)	1,825 (52.6)	2,532 (50.4)	
2+	6,479 (43.4)	2,582 (40.1)	1,524 (44.0)	2,373 (47.2)	
Number of Leaflet Clips, n(%) in A1P1 Location					<0.01
0	13,542 (90.7)	5,783 (89.9)	3,146 (90.7)	4,613 (91.8)	
1	1,166 (7.8)	552 (8.6)	279 (8.0)	335 (6.7)	
2+	151 (1.0)	58 (0.9)	28 (0.8)	65 (1.3)	
Number of Leaflet Clips, n(%) in A2P2 Location					<0.01
0	1,968 (13.2)	954 (14.8)	461 (13.3)	553 (11.0)	
1	8,187 (54.9)	3,624 (56.0)	1,900 (54.8)	2,663 (53.0)	
2+	4,704 (31.5)	1,815 (28.2)	1,092 (31.5)	1,797 (35.8)	
Number of Leaflet Clips, n(%) in A3P3 Location					0.04
0	13,239 (89.1)	5,724 (89.0)	3,062 (88.3)	4,453 (88.6)	
1	1,411 (9.5)	598 (9.3)	342 (9.9)	471 (9.4)	
2+	209 (1.4)	71 (1.1)	49 (1.4)	89 (1.8)	
Procedure time (mins, median, IQR)	122 (88,165)	145 (109,191)	118 (87,158)	99 (73,135)	<0.01
Cumulative Air Kerma (mGy, median, IQR)	481 (221,1019)	578 (268,1234)	475 (226,963)	383 (182,821)	<0.01

	Overall (N=14,923)	*Group 1 1-25 (N=6,431)*	*Group 2 26-50 (N=3,467)*	*Group 3 >50 (N=5,025)*	*p-value**
Mitral Regurgitation, n (%)					<0.01
≤ 1+ (none/trace/mild)	10,303 (69.0)	4,127 (64.2)	2,383 (68.7)	3,793 (75.5)	
2+ (moderate)	3,654 (24.5)	1,819 (28.3)	862 (24.9)	973 (19.4)	
3+/4+ (moderate-severe/severe)	889 (6.0)	448 (7.0)	206 (5.9)	235 (4.7)	
Mean Mitral Valve Gradient (mmHg, median, IQR)	3.0 (2.0,5.0)	3.0 (2.0,5.0)	3.0 (2.0,5.0)	3.0 (2.0,5.0)	0.20
ASD closure	217 (1.5)	61 (0.9)	47 (1.4)	109 (2.2)	<0.01

ASD = atrial septal defect

***p-values refer to comparisons among the three categories of operator experience (1-25 cases, 26-50 cases, and >50 cases)**

Table 3: Adverse Clinical Outcomes

	Overall (N=14,920)	*Group 1 1-25 (N=6,429)*	*Group 2 26-50 (N=3,466)*	*Group 3 >50 (N=5,025)*	*p-value**
Post Implant					
Composite of Complications	1,266 (8.5)	621 (9.7)	280 (8.1)	365 (7.3)	<0.01
In-hospital Death	280 (1.9)	128 (2.0)	66 (1.9)	86 (1.7)	0.55
Conversion to Open Heart Surgery	69 (0.5)	35 (0.5)	13 (0.5)	21 (0.4)	0.42
Cardiac perforation	121 (0.8)	62 (1.0)	37 (1.1)	22 (0.4)	<0.01
Transient Ischemic Attack	18 (0.1)	7 (0.1)	3 (0.1)	8 (0.2)	0.60
Any stroke	103 (0.7)	42 (0.7)	19 (0.5)	42 (0.8)	0.26
Single Leaflet Device Attachment	160 (1.1)	82 (1.3)	33 (1.0)	45 (0.9)	0.11
Complete Detachment of Leaflet Clip	22 (0.1)	8 (0.1)	4 (0.1)	10 (0.2)	0.50
Device Embolization	13 (0.1)	4 (0.1)	1 (0.0)	8 (0.2)	0.09
Device Thrombosis	3 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)	0.91
Other Device/Delivery System Related Event	78 (0.5)	34 (0.5)	24 (0.7)	20 (0.4)	0.18
Bleeding at Access Site	119 (0.8)	59 (0.9)	30 (0.9)	30 (0.6)	0.14
Retroperitoneal Bleeding	35 (0.2)	18 (0.3)	11 (0.3)	6 (0.1)	0.11
Trans-septal Complication	62 (0.4)	29 (0.5)	18 (0.5)	15 (0.3)	0.25
Major Vascular Access Complication	49 (0.3)	20 (0.3)	15 (0.4)	14 (0.3)	0.45
Minor Vascular Access Complication	93 (0.6)	46 (0.7)	18 (0.5)	29 (0.6)	0.44
Unplanned Other Cardiac Surgery/Intervention	194 (1.3)	75 (1.2)	40 (1.2)	79 (1.6)	0.11
Unplanned Vascular Surgery/Intervention	81 (0.5)	35 (0.5)	21 (0.6)	25 (0.5)	0.80
RBC/Whole Blood Transfusion	1,243 (8.3)	619 (9.6)	298 (8.6)	326 (6.5)	<0.01
Hospital length of stay (median, IQR)	2.0 (1.0, 4.0)	2.0 (1.0, 5.0)	2.0 (1.0, 4.0)	2.0 (1.0, 4.0)	<0.01

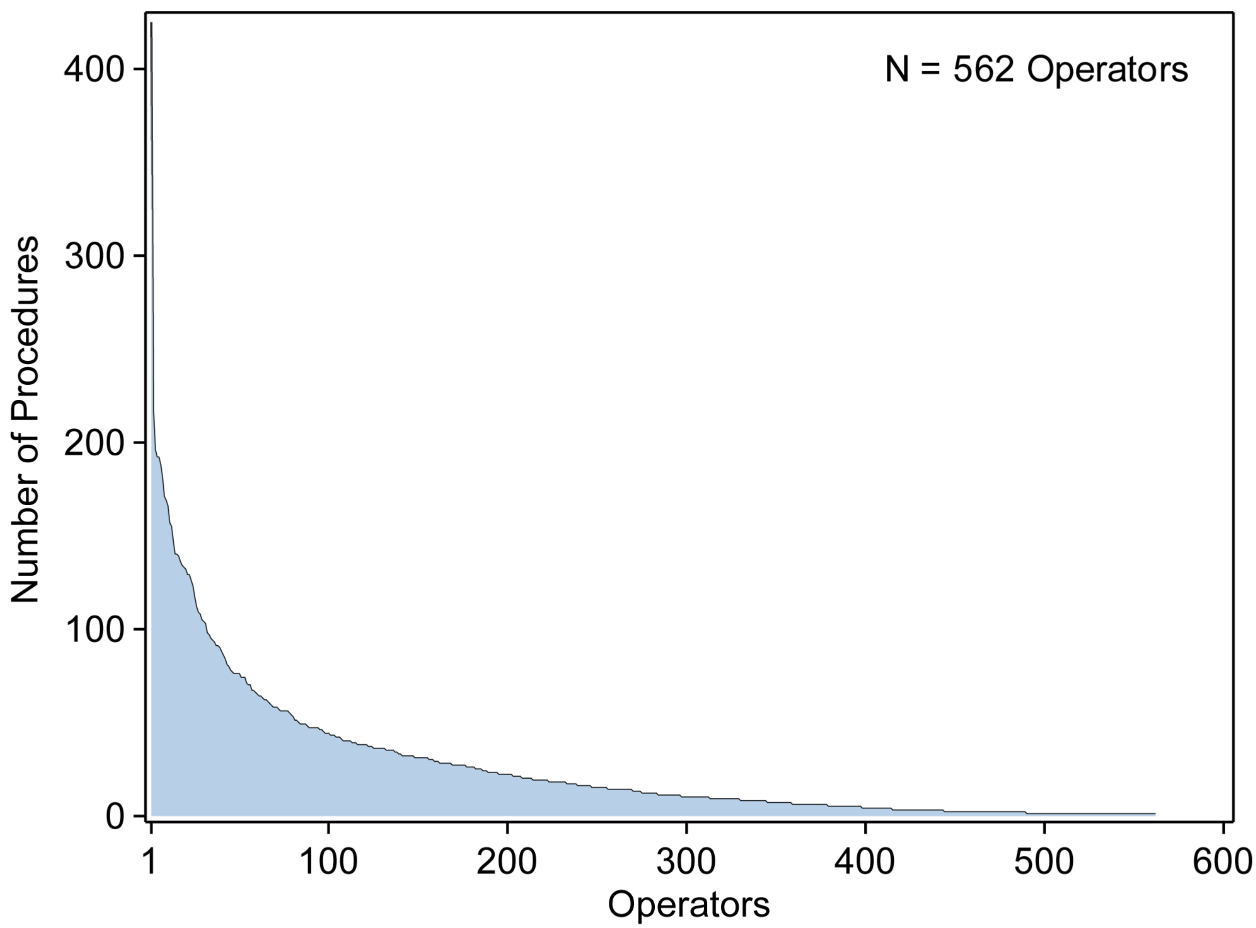
RBC = red blood cell

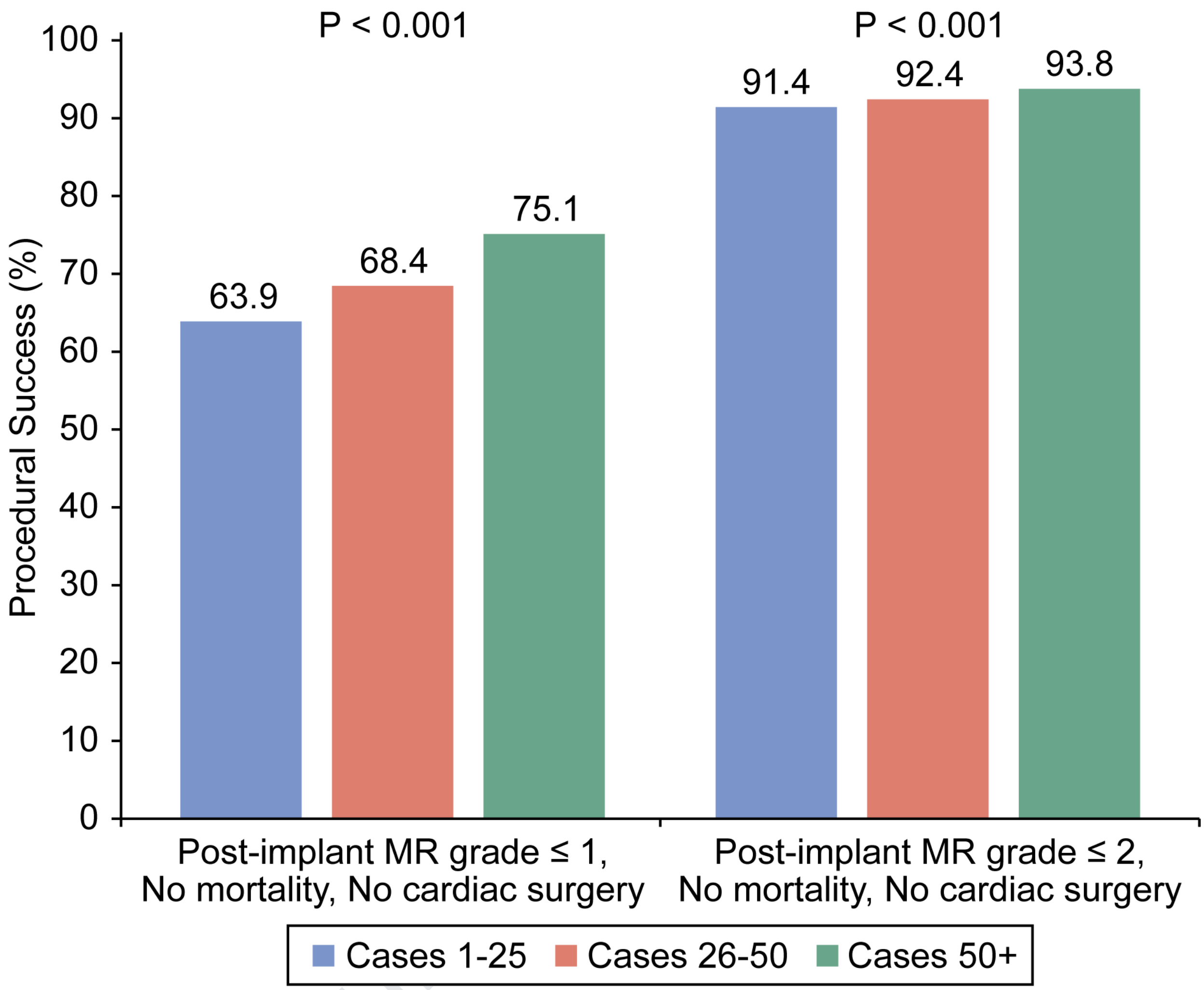
***p-values refer to comparisons among the three categories of operator experience (1-25 cases, 26-50 cases, and >50 cases)**

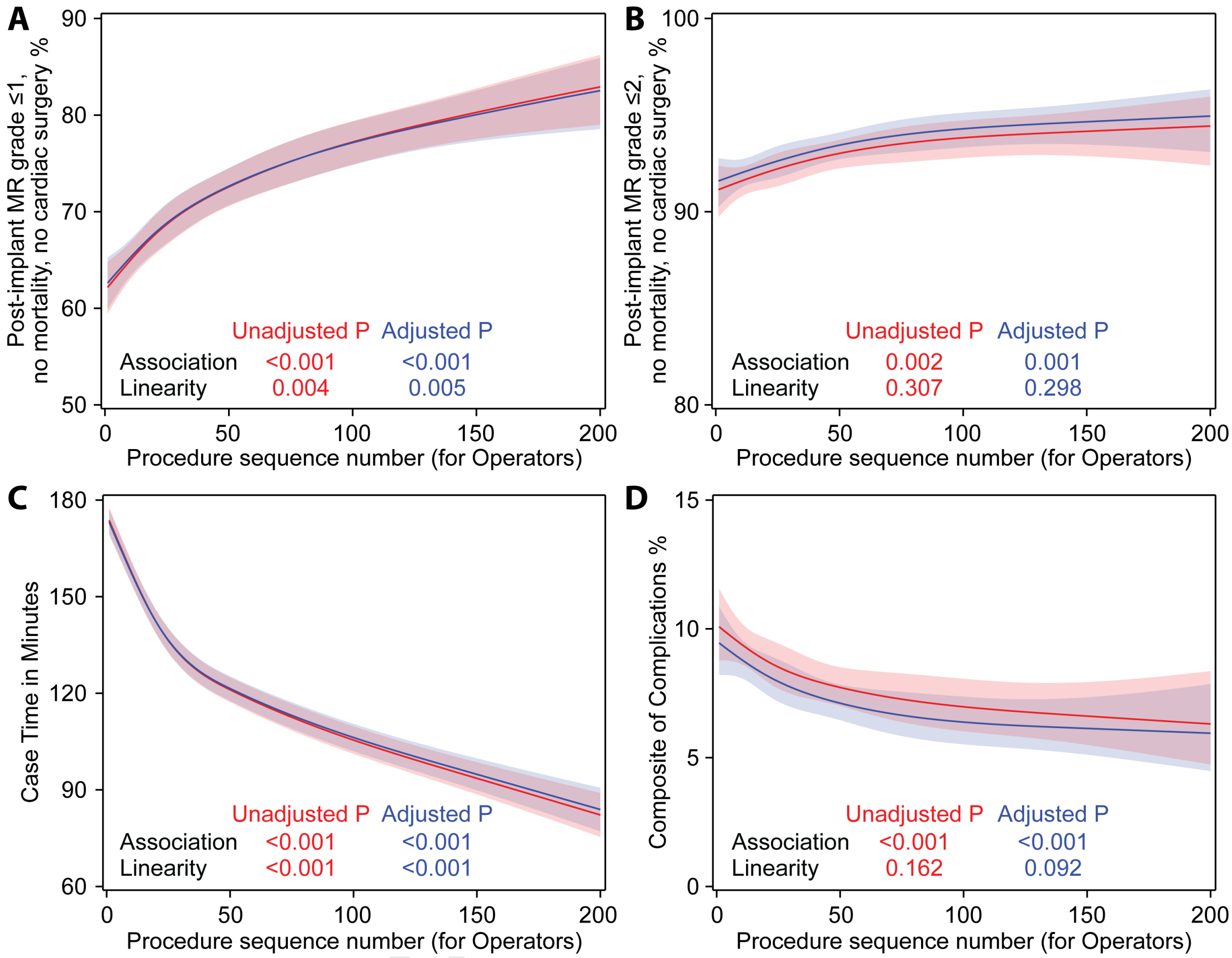
Table 4: Procedural Success Stratified by Operator Case Count

Case Count	Procedural Success (residual MR grade ≤1, no mortality or need for cardiac surgery)		Procedural Success (residual MR grade ≤2, no mortality or need for cardiac surgery)	
	Unadjusted (%, 95% CI)	Adjusted (%, 95% CI)	Unadjusted (%, 95% CI)	Adjusted (%, 95% CI)
10	64.9 (63.0, 66.8)	65.2 (63.3, 67.1)	91.6 (90.8, 92.3)	92.0 (91.2, 92.7)
25	68.7 (66.6, 70.7)	68.8 (66.8, 70.8)	92.2 (91.3, 93.0)	92.6 (91.8, 93.4)
50	72.6 (70.6, 74.5)	72.6 (70.7, 74.5)	93.0 (92.2, 93.7)	93.4 (92.7, 94.1)
100	77.2 (74.9, 79.4)	77.1 (74.8, 79.3)	93.8 (92.8, 94.7)	94.3 (93.3, 95.1)
150	80.3 (77.5, 82.8)	80.0 (77.3, 82.5)	94.2 (92.9, 95.2)	94.7 (93.5, 95.6)
200	82.9 (79.0, 86.2)	82.5 (78.5, 85.9)	94.4 (92.4, 96.0)	94.9 (93.1, 96.3)

MR = mitral regurgitation


N = 562 Operators
Number of Procedures
400
300
200
100
0
1
100
200
300
400
500
600
Operators


P < 0.001
P < 0.001
100
90
80
70
60
50
40
30
20
10
0
Procedural Success (%)
63.9
68.4
75.1
91.4
92.4
93.8
Post-implant MR grade ≤ 1,
No mortality, No cardiac surgery
Post-implant MR grade ≤ 2,
No mortality, No cardiac surgery
Cases 1-25
Cases 26-50
Cases 50+


A
Post-implant MR grade ≤1, no mortality, no cardiac surgery %
Unadjusted P Adjusted P
Association <0.001 <0.001
Linearity 0.004 0.005
Procedure sequence number (for Operators)
B
Post-implant MR grade ≤2, no mortality, no cardiac surgery %
Unadjusted P Adjusted P
Association 0.002 0.001
Linearity 0.307 0.298
Procedure sequence number (for Operators)
C
Case Time in Minutes
Unadjusted P Adjusted P
Association <0.001 <0.001
Linearity <0.001 <0.001
Procedure sequence number (for Operators)
D
Composite of Complications %
Unadjusted P Adjusted P
Association <0.001 <0.001
Linearity 0.162 0.092
Procedure sequence number (for Operators)

Online Table 1: Covariates used in the Adjusted Mixed Models

Age	Smoking Status
Sex	Diabetes Mellitus
Race	New York Heart Association Class
Hispanic/Latino Ethnicity	Atrial Fibrillation or Atrial Flutter
Body Surface Area	Chronic Lung Disease (Severe)
Left Ventricular Ejection Fraction	Home Oxygen
Hemoglobin	Prior Percutaneous Coronary Intervention
Glomerular Filtration Rate	Prior Coronary Artery Bypass Grafting
Current Dialysis	Prior Mitral Valve Repair or Annuloplasty Ring
Left Main Stenosis ≥50%	Number of Prior Cardiac Surgeries
Prior Myocardial Infarction	Aortic Insufficiency
Infective Endocarditis	Acuity of Procedure (Elective, Urgent, Emergent, or Salvage)
Prior Stroke or Transient Ischemic Attack	Mitral Valve Disease Etiology (Degenerative or Functional)
Carotid Stenosis	Mitral Annular Calcification
Peripheral Arterial Disease	Mitral Leaflet Calcification

Online Table 2: Comparison of outcomes for lower volume operators at higher vs lower volume institutions – 25th percentile cutoff

	Higher Vs. Lower Volume Sites	
Outcome	*Odds Ratio*	*p-value*
Optimal Procedure Success	1.06 (0.82,1.39)	0.649
Acceptable Procedure Success	0.96 (0.67,1.37)	0.821
Composite of Complication	1.04 (0.75,1.44)	0.821
Outcome	*Estimate*	*p-value*
Case Time	9.46 (-.88,19.8)	0.073

Lower Operator experience is defined as ≤13 procedures.
Lower Volume Site is defined as sites with ≤15 total procedures.
Optimal Procedure Success is defined as residual MR grade ≤1, no mortality, no cardiac surgery
Acceptable Procedure Success is defined as residual MR grade ≤2, no mortality, no cardiac surgery

Online Table 3: Comparison of outcomes for lower volume operators at higher vs lower volume institutions – 50th percentile cutoff

	Higher Vs. Lower Volume Sites	
Outcome	*Odds Ratio*	*p-value*
Optimal Procedure Success	1.13 (0.95,1.34)	0.174
Acceptable Procedure Success	1.05 (0.86,1.30)	0.613
Composite of Complication	0.99 (0.81,1.20)	0.613
Outcome	Estimate	p-value
Case Time	13.2 (5.82,20.5)	<.001

Lower Operator experience is defined as ≤31 procedures.
Lower Volume Site is defined as sites with ≤33 total procedures.
Optimal Procedure Success is defined as residual MR grade ≤1, no mortality, no cardiac surgery
Acceptable Procedure Success is defined as residual MR grade ≤2, no mortality, no cardiac surgery

Online Table 4: Sensitivity analysis adjusting for etiology of mitral valve regurgitation

	Functional vs. Degenerative		*Other* vs. Degenerative*	
Outcome	*Odds Ratio*	*p-value*	*Odds Ratio*	*p-value*
Optimal Procedure Success	0.98 (0.88,1.08)	0.632	1.02 (0.86,1.20)	0.834
Acceptable Procedure Success	0.95 (0.81,1.13)	0.585	0.92 (0.71,1.21)	0.556
Composite of Complication	0.94 (0.80,1.10)	0.585	0.93 (0.71,1.21)	0.556
	Estimate	*p-value*	*Estimate*	*p-value*
Case Time	1.36 (-1.1,3.80)	0.274	2.32 (-1.9,6.58)	0.286

Optimal Procedure Success is defined as residual MR grade ≤1, no mortality, no cardiac surgery
Acceptable Procedure Success is defined as residual MR grade ≤2, no mortality, no cardiac surgery

* Post-Inflammatory, Endocarditis and Other/Indeterminate Mitral Valve Disease Etiology