Prognostic value of left ventricular apical four-chamber longitudinal strain after heart valve surgery in real-world practice

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Running title: Longitudinal strain and heart valve surgery

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Running title: Longitudinal strain and valve surgery
Abstract

**Background:** Left ventricular longitudinal strain is an emerging marker of ventricular systolic function. However, the prognostic value of apical four-chamber longitudinal strain after heart valve surgery in real-world clinical practice is uncertain.

**Methods:** This observational cohort study was conducted in patients who underwent heart valve surgery between January 2014 and December 2018 at a tertiary hospital in South Korea. The exposure of interest was preoperative left ventricular apical four-chamber strain. The primary outcome was postoperative all-cause mortality.

**Results:** Among 1773 study patients (median age, 63 years; female, 45.9%), 132 (7.4%) died during a median follow-up of 27.2 months. Preoperative left ventricular longitudinal strain was significantly associated with all-cause mortality (adjusted hazard ratio, 0.94 per 1% increment in absolute value; 95% confidence interval, 0.90–0.99; p = 0.022), whereas ejection fraction was not significantly associated with all-cause mortality (adjusted hazard ratio, 1.01; 95% confidence interval, 0.99–1.03; p = 0.222). Moreover, combining longitudinal strain to the ejection fraction and conventional prognostic factors enhance the prognostic model for all-cause mortality (p = 0.022).

**Conclusions:** In patients undergoing heart valve surgery without coronary artery disease, left ventricular longitudinal strain measured in real-world clinical practice was independently associated with postoperative survival. Left ventricular longitudinal strain measurement may be helpful for outcome prediction after valve surgery.

**Keywords:** Strain; Speckle-tracking; Cardiac surgery; Valvular heart disease; Mortality; Morbidity.
Introduction

In patients with advanced valvular heart disease, surgical treatment is one of the key management options. However, considering that cardiac surgery entails substantial operative risks, accurate prediction of both the risks and benefits of surgery in each patient is crucial. Evaluating the left ventricular systolic function carries a vital role in making treatment decisions; specifically, left ventricular ejection fraction (LVEF) has been a cornerstone in determining surgical intervention and risk prediction [1-4].

Left ventricular longitudinal strain has recently gained interest as a marker of left ventricular systolic function. Strain is a mechanical term representing the degree of deformation relative to the material’s reference length; accordingly, left ventricular longitudinal strain directly reflects longitudinal myocardial shortening during a cardiac cycle. Recently, longitudinal strain has shown significant prognostic value in a variety of cardiac diseases, such as heart failure [5,6], acute myocardial infarction [7], cardiomyopathy [8].

In terms of valvular surgery, several studies have shown that left ventricular longitudinal strain was independently associated with long-term postoperative survival [9,10]. However, as previous studies were exclusively conducted in patients with mitral regurgitation (MR), the prognostic value of longitudinal strain in patients with other types of heart conditions is less clear. Furthermore, strain analyses in previous studies were performed post-hoc using stored echocardiography data for research purposes. Hence, it is unclear whether longitudinal strain can confer significant incremental prognostic values over conventional risk factors in real-world clinical settings. In addition, while the above-mentioned studies used global longitudinal strain, several reports have demonstrated the feasibility and reliability of apical four-chamber longitudinal strain [11,12].

Thus, we investigated whether left ventricular four-chamber longitudinal strain measured in clinical practice can be helpful for predicting postoperative survival in patients with various types of
valvular heart diseases including MR. We also examined the predictive value of longitudinal strain for postoperative complications.
Materials and Methods

Design and Participants
This observational cohort study was conducted at a tertiary hospital in South Korea. All patients who underwent heart valve surgery at our institution between January 2014 and December 2018 were screened for eligibility. We excluded patients under 20 years of age, those who underwent urgent or emergent surgery, and those who underwent combined coronary artery bypass surgery. Patients who did not undergo left ventricular longitudinal strain analysis preoperatively were also excluded.

The institutional review board approved the study protocol and waived the need for informed consent considering the retrospective nature of the study. Clinical data of the study population was collected from the electronic medical record and institutional echocardiography database. This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement[13].

Echocardiography and strain analysis
All candidates for heart valve surgery were preoperatively evaluated with transthoracic echocardiography using standard machines and techniques in accordance with the American Society of Echocardiography guidelines [14]. At our institution, the incorporation of longitudinal strain measurement as a part of transthoracic echocardiography began in late 2013. This new policy encouraged the provision of formal left ventricular longitudinal strain reporting. In the initial phase of the left ventricular longitudinal strain reporting, speckle tracking analysis was performed with EchoPAC (GE Healthcare, Chicago, IL, United States) or QLAB (Philips Healthcare, Amsterdam, Netherlands) according to the availability of ultrasound machines. Afterward, they have been replaced by a vendor-independent software, Image-Arena™ (TomTec, Unterschleissheim, Germany) since 2015. In this transitional phase, only the apical four-chamber strain was measured and reported, thus
highlighting the expansion of strain reporting against resource limitation. Strain measurements were performed by experienced sonographers. After acquiring an adequate apical four-chamber view, the region of interest is automatically traced by strain software. Endocardial border tracing was manually adjusted if appropriate. A four-chamber strain curve throughout the cardiac cycle was derived and peak longitudinal strain value was calculated from the average of the six segments. This strain reporting policy was phased in over six years, and the final strain analysis implementation with global longitudinal strain was adopted in 2020; however, the data acquired in the final phase was not included in this study.

Study exposure and outcomes
The primary exposure of this study was four-chamber longitudinal strain measured from the last echocardiography prior to heart valve surgery. In its original definition, left ventricular longitudinal strain has a negative value; however, in this study, we converted the longitudinal strain to an absolute value for a more straightforward interpretation.

In the primary analysis, the outcome was all-cause mortality after surgery. The mortality data were obtained from our medical record and the National Health Insurance status. The data on the survival status were collected until July 31, 2020. Patients who survived over five years were censored at five years, and those who underwent redo-cardiac surgery were censored at the time of redo-surgery. The secondary outcome was operative morbidity defined by the Society of Thoracic Surgeons risk calculator (i.e., composite of operative mortality, stroke, renal failure, prolonged ventilation, mediastinitis/deep sternal wound infection, and reoperation). The detailed definitions of the secondary outcomes are provided in Table S1 in the Supplement.
**Statistical analysis**

Sample size was driven by all eligible patients from 2014 to 2018. Missing values were replaced with mode or median. Categorical variables are presented as frequency (proportion), and continuous variables are presented as mean ± standard deviation or median (interquartile range). Comparison of descriptive statistics between groups was performed with chi-square test for categorical variables and Student's *t*-test or Mann–Whitney *U* test for continuous variables according to the normality of the data. Correlation between continuous variables was assessed with Pearson's or Spearman's correlation test depending on the normality of the variables.

In order to determine the association between predictors and outcomes, univariate Cox proportional hazard regression analysis and univariate logistic regression were performed for the primary outcome and the secondary outcome, respectively. For continuous variables, the univariate association with outcomes was explored using the restricted cubic spline. If there were significant non-linear relationships between continuous variables and the study outcomes, the variables were transformed or categorized as appropriate.

To examine the independent associations between longitudinal strain and outcomes, multivariable regression analyses were performed. Multivariable Cox proportional models for the primary outcome were adjusted for LVEF, age, sex, Charlson Comorbidity Index (CCI), pulmonary hypertension, mitral stenosis (MS), mitral regurgitation (MR), aortic stenosis (AS), aortic regurgitation (AR), tricuspid regurgitation (TR), New York Heart Association (NYHA) classification, and atrial fibrillation. Multivariable logistic regression for the secondary outcome was adjusted for LVEF, age, sex, CCI, redo surgery, pulmonary hypertension, body mass index, hematocrit, hypertension, MS, MR, AS, AR, TR, smoking, combined surgery, NYHA classification, and atrial fibrillation. Possible confounders from background knowledge were selected as adjusted variables.
To assess the incremental value of longitudinal strain as a prognostic factor, the likelihood test was used to compare the prediction performance between models with and without longitudinal strain. Additional interaction analyses were performed to evaluate the effect-modification of longitudinal strain according to prespecified subgroups (LVEF $\geq 50\%$ or $<50\%$; patients with or without MR). Two sensitivity analyses—multivariable Cox regression including other echocardiographic parameters as potential confounders and multivariable logistic regression with different outcome definitions—were performed, and their details are provided in Table S2 in the Supplement.

We also performed post-hoc analyses to obtain more straightforward interpretations of our results. These post-hoc analyses categorized preoperative left ventricular function according to longitudinal strain and LVEF (LVEF $\geq 50\%$ and longitudinal strain $\geq 16.3\%$ vs. LVEF $\geq 50\%$ and longitudinal strain $< 16.3\%$ vs. LVEF $< 50\%$). For the comparison of patients with preserved and reduced LVEF, a cut-off value of 50% was used [15]. A cut-off value for the longitudinal strain was based on the median value of the population (16.3%). Multivariable Cox regression, logistic regression, and Kaplan–Meier survival curve analyses were used as appropriate.

All statistical analyses were two-tailed with a significance level of 0.05. Statistical analysis was performed with R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).
Results

Patient population and characteristics

A total of 3666 patients underwent heart valve surgery at our institution during the study period. Of them, 1773 were included in the final analysis (Figure S1A in the Supplement). The leading cause of exclusion was the absence of strain analysis, which was primarily due to the low availability of strain during the early study period. The proportion of strain reporting has gradually increased, with 92% of patients in 2018 having strain results (Figure S1B in the Supplement).

The baseline characteristics of the study patients are shown in Table 1. The median age was 63 years (interquartile range [IQR], 54–70), and 45.9% were female. The median LVEF was 61% (interquartile range, 56%–65%), and the median longitudinal strain was 16.3% (IQR, 13.2%–19.0%). Left ventricular strain and LVEF had a moderate degree of positive correlation (Spearman's ρ = 0.56, p < 0.001). At each level of the LVEF, the longitudinal strain had a broad distribution, especially in higher LVEF levels (Figure 1). The majority (92.4%) of longitudinal strain data were analyzed with Image-Arena™ (TomTec). The median (interquartile range) time interval between preoperative TTE and surgery was 23 (7–56) days.

Primary analysis: Postoperative all-cause mortality

During a median follow-up of 27.2 months (IQR, 19.1–38.9), 132 (7.4%) patients died. Patients who survived had higher preoperative longitudinal strain values than did non-survivors (16.4 [13.4–19.2] vs. 14.9 [11.5–17.2], p < 0.001; Table 1); in contrast, the preoperative LVEF was not significantly different between the survivors and non-survivors (61.0 [56.0–66.0] vs. 61.0 [52.0–65.0], p = 0.071). Univariate associations between longitudinal strain, LVEF, and all-cause mortality are shown in Figure S2 in the Supplement. While longitudinal strain had a statistically significant linear negative relationship with all-cause mortality (p-value for univariate Cox regression with restricted cubic
spline = 0.005, p-value for non-linearity = 0.062), LVEF did not show a significant relationship with all-cause mortality (p-value for univariate Cox regression with restricted cubic spline = 0.17).

The negative relationship between longitudinal strain and all-cause mortality remained statistically significant in a multivariable-adjusted Cox proportional hazard model (Figure 2A). On the contrary, LVEF did not have a statistically significant relationship with all-cause mortality (Figure 2B, Table S3 in the Supplement). Combining longitudinal strain to the conventional prognostic factors (i.e., age, sex, CCI, PHTN, MS, MR, AS, AR, TR, NYHA class, atrial fibrillation) and LVEF significantly enhanced prognostic model for all-cause mortality (p = 0.022; Figure 2C).

**Secondary analysis: operative morbidity**

During index hospitalization or within 30 days postoperatively, 251 (14.2%) had operative morbidity; of them, 40 (2.3%) patients died, 175 (9.9%) had prolonged mechanical ventilation or reintubation, 81 (4.6%) underwent reoperation, 60 (3.5%) had renal failure, 40 (2.3%) had a stroke, and 11 (0.6%) had mediastinitis or deep sternal wound infection.

Descriptive statistics according to the occurrence of morbidity are presented in Table S4 in the Supplement. Patients with operative morbidity had a lower value of preoperative longitudinal strain than those without morbidity (15.1 [12.8–18.0] vs. 16.5 [13.4–19.1], p < 0.001). LVEF was also lower in patients with morbidity than those without (60.0 [52.5–64.0] vs. 62.0 [56.0–66.0], p < 0.001).

Univariate analysis showed that both longitudinal strain and LVEF had negative linear relationships with operative morbidity (Figure S3 in the Supplement, p-values for univariate logistic regression with restricted cubic spline < 0.05). After adjusting for potential confounders, the negative relationship between LVEF and operative morbidity remained statistically significant (odds ratio [OR], 0.99; 95% confidence interval [CI], 0.97–1.00; p = 0.049; Table S5 in the Supplement); however, after further adjustment with longitudinal strain, the association between LVEF and
operative morbidity was no longer statistically significant (OR, 0.99; 95% CI, 0.98–1.01; p = 0.543; Figure 3B). Likewise, longitudinal strain did not have a statistically significant relationship with operative morbidity in this final model (OR, 0.97; 95% CI, 0.93–1.01; p = 0.163; Figure 3A). Furthermore, combining longitudinal strain to the LVEF and conventional risk factors did not show a significant incremental prognostic value for predicting operative morbidity (Figure 3C).

**Subgroup and sensitivity analysis**

In subgroup analysis, the association between preoperative longitudinal strain and all-cause mortality was different across different levels of LVEF, albeit without statistical significance (p-value for interaction = 0.086; Figure 4A). The presence of moderate/severe MR did not significantly alter the relationship between longitudinal strain and all-cause mortality as well (p-value for interaction = 0.613). On the contrary, there was a significant interaction between longitudinal strain and the presence of moderate/severe MR in terms of operative morbidity (p-value for interaction = 0.047), as a conditional negative relationship between longitudinal strain and operative morbidity was shown in the moderate/severe MR group (Figure 4B).

Sensitivity analyses showed similar results to the main analyses in terms of the relationships of longitudinal strain and LVEF with all-cause mortality and operative morbidity. The results are shown in Table S6 and Table S7 in the Supplement, respectively.

**Post-hoc survival analysis according to the strain and LVEF strata**

All-cause mortality according to the strain and LVEF strata (LVEF ≥ 50% and longitudinal strain ≥ 16.3% vs. LVEF ≥ 50% and longitudinal strain < 16.3% vs. LVEF < 50%) is shown in Figure 5. Patients with preserved LVEF (≥ 50%) and normal strain (≥ 16.3%) had the lowest risk of death. Moreover, patients with preserved LVEF and low strain (< 16.3%) had a significantly high mortality.
rate, which was comparable to that of patients with low LVEF. Patients with preserved LVEF and normal strain also had the lowest risk of operative morbidity. Patients with preserved LVEF and low strain (adjusted OR, 1.56; 95% CI, 1.12–2.16; p = 0.009) and patients with low LVEF (adjusted OR, 1.74; 95% CI, 1.15–2.65; p = 0.009) had significantly higher risks of operative morbidity.
Discussion

In this observational study of 1773 patients who underwent heart valve surgery, we showed that left ventricular longitudinal strain was significantly associated with all-cause mortality after surgery. Furthermore, longitudinal strain had incremental value for predicting all-cause mortality beyond previously known risk factors including LVEF. However, longitudinal strain did not provide a significant benefit over LVEF in predicting operative morbidity.

Left ventricular longitudinal strain is an emerging parameter of systolic function. Previous studies constantly reported that longitudinal strain was a valuable predictor of long-term mortality in a variety of cardiac diseases. In terms of valvular surgery, left ventricular longitudinal strain was also independently associated with long-term survival and had incremental prognostic value beyond LVEF [9,10]. However, most of the existing studies only included patients who underwent surgery to correct MR. In patients with significant MR, the LVEF is a limited parameter of the systolic function because LVEF is overestimated due to the regurgitant fraction. Therefore, the impaired systolic function may be masked in the preoperative LVEF, and become overt after mitral valve surgery. In contrast, left ventricular strain directly reflects the myocardial shortening and is less dependent on loading conditions than LVEF [16]. In this respect, preoperative longitudinal strain may be a superior parameter of systolic function to LVEF in patients with MR. Indeed, the correlation between preoperative longitudinal strain and immediate postoperative LVEF was stronger than that between preoperative LVEF and immediate postoperative LVEF [17,18]. The pronounced association between longitudinal strain and operative morbidity in patients with MR in our study further supports the prognostic value of longitudinal strain in patients with MR.

Notably, the significant relationship between longitudinal strain and long-term mortality shown in this study was not limited to patients with MR. Longitudinal strain is regarded to detect subtle left ventricular dysfunction, which LVEF cannot detect. Longitudinal myocardial fibers, which are
predominantly presented in the subendocardial layer, are more vulnerable to injury than oblique and circumferential fibers [19-21]. Thus, longitudinal shortening can deteriorate in the early stage of valve disease. In contrast, compensatory ventricular remodeling can lead to preserved LVEF until the manifestation of overt myocardial damage [22-24]. Accordingly, our results also showed that a substantial proportion of patients had impaired longitudinal strain while having an LVEF of above 50%. Furthermore, we showed that longitudinal strain can differentiate long-term survival among patients with preserved LVEF. Thus, our results also support the current concept that longitudinal strain can detect subtle myocardial dysfunction, which can impact the clinical outcomes.

In patients undergoing valve surgery, it should also be considered that longitudinal strain may reflect not only the negative myocardial impact of valve diseases but also the reversibility of myocardial damage. For example, Kim et al. reported that patients with preserved longitudinal strain had a more significant reduction of left ventricular end-diastolic diameter after mitral valve surgery [10]. Another study also showed that preoperative longitudinal strain was associated with remodeling status three months after mitral valve replacement [25]. Thus, impairments in longitudinal strain may imply a low likelihood of reverse remodeling after surgery. This is especially important considering that early intervention before the occurrence of irreversible myocardial damage may lead to better survival outcomes. As the aforementioned studies have been conducted in patients with MR, it is unknown whether reverse remodeling can differ according to preoperative longitudinal strain in other valve diseases. Our results also do not provide direct evidence on this topic, and further studies are needed to test this hypothesis.

In contrast to long-term survival, left ventricular longitudinal strain did not have a significant incremental predictive value above LVEF regarding operative morbidity. Instead, the statistical significance of LVEF disappeared after longitudinal strain was incorporated into the multivariable model. Thus, our results did not support incorporating longitudinal strain as a predictor of operative
morbidity. Longitudinal strain may have limited role in specific situations such as the presence of significant MR.

Limitations

Our study has several limitations. First, this study is from a single tertiary referral center and the study population exclusively consisted of Asian patients. Thus, our findings should be validated in different clinical settings. Second, more than one-third of the eligible patients did not have strain measurements. This is presumed to be largely due to the limited availability of strain analysis in the initial phase of the introduction of the strain measurement, but we cannot preclude the possibility of other patient-specific reasons, such as suboptimal endocardial tracing, atrial fibrillation, and tachycardia. Finally, the strain analysis in our study had a few practical limitations. All values were from the strain adaptation period in clinical practice; accordingly, a tradeoff between clinical feasibility and measurement precision was inevitable. There were heterogeneities in the vendors and versions of the strain softwares used. Also, the experience levels of the sonographers might have been different and interobserver variability also existed. However, in the mid-2010s, inter-vendor variability decreased to a level similar to conventional echocardiogram parameters [26,27]. Also, the reproducibility of longitudinal strain was better than that of LVEF, and competency could be achieved with a short learning curve [26,28,29].

Nevertheless, the most critical limitation of our strain measurement was that longitudinal strain values were not a global one and obtained from apical four-chamber view. Global longitudinal strain is the standard method that averages four, two, and three-chamber longitudinal strain. Thus, some valuable prognostic information from other views might have been ignored in the apical four-chamber strain. Nevertheless, a few studies advocated the apical four-chamber strain. For example, Alenzi et al. reported that there was little difference between apical four-chamber longitudinal strain with global
longitudinal strain in patients with heart failure without regional wall motion abnormality (Median difference, -0.03%; interquartile range, -0.3% to 0.27%; 95% pairwise difference < 2% in absolute magnitude) [12]. Similarly, a study of patients with moderate to severe aortic stenosis showed that apical four-chamber longitudinal strain was in good agreement with global longitudinal strain (mean bias, -0.09%; 95% limits, -3.6 to 3.4%) [11]. Moreover, apical four-chamber longitudinal strain was independently associated with mortality, suggesting it may serve as a new prognostic factor for patients with aortic stenosis [11]. Considering the above-mentioned studies and our findings, the apical four-chamber longitudinal strain measurement could be a useful alternative. As an example, apical four-chamber strain could be implemented more easily in routine clinical practice, as we have experienced. It may be also useful as a substitute for global longitudinal strain when the imaging quality from apical two or three-chamber view is poor. Nevertheless, it should be noted that studies investigating apical four-chamber longitudinal strain excluded patients with regional wall motion abnormality or significant coronary artery disease. Also, the apical four-chamber strain needs to be validated in other cardiac diseases, such as amyloidosis, congenital heart disease, etc.

**Clinical implications**

Although the value of longitudinal strain for risk prediction in a broad spectrum of cardiac diseases has been repeatedly studied, the widespread clinical implementation of longitudinal strain has been slow [20]. This may be due to the lack of availability and concern about standardization [21,22]. However, our study showed that the gradual implementation of longitudinal strain may be feasible. Moreover, even in its limited form, longitudinal strain provided additional prognostic information in the actual clinical setting. Although further validation is needed, our results suggest that it may be worthwhile to implement strain analysis according to the availability of each institution while considering the current limitation of strain measurement described above. Newer systems that allow
fully automated analysis may facilitate the clinical implementation of longitudinal strain in the future. Along with the widespread clinical implementation of longitudinal strain, a future pragmatic trial can answer whether strain-based surgical decisions can improve the clinical outcomes in patients with valve disease.

Conclusions

In patients undergoing heart valve surgery without coronary artery disease, apical four-chamber left ventricular longitudinal strain measured in a real-world clinical practice was independently associated with postoperative survival. Left ventricular longitudinal strain may be successfully implemented in clinical practice and aid the outcome prediction after valve surgery.
References


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Table 1. Baseline characteristics of the study patients

<table>
<thead>
<tr>
<th></th>
<th>Total population (n = 1773)</th>
<th>Survivors (n = 1641)</th>
<th>Non-survivors (n =132)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.0 (54.0–70.0)</td>
<td>62.0 (53.0–70.0)</td>
<td>69.0 (60.5–75.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>814 (45.9)</td>
<td>756 (46.1)</td>
<td>58 (43.9)</td>
<td>0.703</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>24.0 (21.9–26.2)</td>
<td>24.1 (22.0–26.3)</td>
<td>22.5 (20.2–25.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Current smoker*</td>
<td>181 (10.2)</td>
<td>166 (10.1)</td>
<td>15 (11.4)</td>
<td>0.759</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>3.0 (1.0–4.0)</td>
<td>3.0 (1.0–4.0)</td>
<td>4.0 (3.0–6.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>750 (42.3)</td>
<td>684 (41.7)</td>
<td>66 (50.0)</td>
<td>0.077</td>
</tr>
<tr>
<td>Pulmonary hypertension†‡</td>
<td>722 (41.0)</td>
<td>649 (39.8)</td>
<td>73 (55.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Atrial fibrillation‡</td>
<td>640 (36.1)</td>
<td>578 (35.2)</td>
<td>62 (47.0)</td>
<td>0.009</td>
</tr>
<tr>
<td>NYHA class ≥ 2†</td>
<td>1263 (73.7)</td>
<td>1157 (72.9)</td>
<td>106 (83.5)</td>
<td>0.013</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>39.0 (35.5–42.2)</td>
<td>39.1 (35.8–42.5)</td>
<td>35.0 (30.4–39.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Redo surgery</td>
<td>216 (12.2)</td>
<td>189 (11.5)</td>
<td>27 (20.5)</td>
<td>0.004</td>
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<tr>
<td>Combined surgery§</td>
<td>262 (14.8)</td>
<td>233 (14.2)</td>
<td>29 (22.0)</td>
<td>0.022</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>61.0 (56.0–65.0)</td>
<td>61.0 (56.0–66.0)</td>
<td>61.0 (52.0–65.0)</td>
<td>0.071</td>
</tr>
<tr>
<td>Longitudinal strain (%)</td>
<td>16.3 (13.2–19.0)</td>
<td>16.4 (13.4–19.2)</td>
<td>14.9 (11.5–17.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mitral stenosis§</td>
<td>276 (15.6)</td>
<td>256 (15.6)</td>
<td>20 (15.2)</td>
<td>0.990</td>
</tr>
<tr>
<td>Mitral regurgitation§</td>
<td>608 (34.3)</td>
<td>564 (34.4)</td>
<td>44 (33.3)</td>
<td>0.884</td>
</tr>
<tr>
<td>Aortic stenosis§</td>
<td>693 (39.1)</td>
<td>641 (39.1)</td>
<td>52 (39.4)</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>497 (28.0)</td>
<td>458 (27.9)</td>
<td>39 (29.5)</td>
<td>0.763</td>
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<tr>
<td>--------------------------</td>
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<tr>
<td>Aortic regurgitation§</td>
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<td></td>
<td></td>
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<tr>
<td>Tricuspid regurgitation§</td>
<td>369 (20.8)</td>
<td>323 (19.7)</td>
<td>46 (34.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>54.0 (48.0–61.0)</td>
<td>54.0 (48.0–61.0)</td>
<td>53.0 (47.5–59.0)</td>
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<td>LVESD (mm)</td>
<td>35.0 (29.0–42.0)</td>
<td>35.0 (29.0–42.0)</td>
<td>35.0 (30.0–42.0)</td>
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<td>LAD† (mm)</td>
<td>47.0 (40.0–54.0)</td>
<td>47.0 (40.0–54.0)</td>
<td>48.0 (42.5–58.0)</td>
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<td>Strain software vendor</td>
<td></td>
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<td></td>
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<tr>
<td>TomTec</td>
<td>1638 (92.4)</td>
<td>39 (2.4)</td>
<td>3 (2.3)</td>
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<td>Philips</td>
<td>93 (5.2)</td>
<td>85 (5.2)</td>
<td>8 (6.1)</td>
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<td>General Electric</td>
<td>42 (2.4)</td>
<td>1517 (92.4)</td>
<td>121 (91.7)</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as the number of patients (%) or median (interquartile range).

Abbreviations: LAD, left atrial dimension; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; NYHA class, New York Heart Association Functional Classification.

*Smoking history within eight weeks before surgery.

*Variables with missing values: pulmonary hypertension (10/1773; 0.6%), atrial fibrillation (1/1773; 0.1%), NYHA class (59/1773; 3.3%), LAD (3/1773; 0.2%).

*Mean pulmonary artery pressure ≥ 25 mmHg assessed by right heart catheterization, peak tricuspid regurgitation velocity ≥ 2.9 m/s, or early diastolic pulmonary regurgitation velocity > 2.2 m/s on preoperative echocardiography.

*More than or equal to the moderate grade.
<table>
<thead>
<tr>
<th>Subgroup</th>
<th>For all-cause mortality</th>
<th>For operative morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio (95% confidence interval)</td>
<td>Odds ratio (95% confidence interval)</td>
</tr>
<tr>
<td>Adjusted</td>
<td>0.94 (0.90–0.99)</td>
<td>0.97 (0.93–1.01)</td>
</tr>
<tr>
<td>Subgroup</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF &lt; 50%</td>
<td>1.04 (0.93–1.16)</td>
<td>0.98 (0.90–1.08)</td>
</tr>
<tr>
<td>LVEF ≥ 50%</td>
<td>0.94 (0.89–0.99)</td>
<td>0.96 (0.92–1.01)</td>
</tr>
<tr>
<td>Moderate/severe MR</td>
<td>0.93 (0.87–1.00)</td>
<td>0.93 (0.88–0.99)</td>
</tr>
<tr>
<td>No moderate/severe MR</td>
<td>0.95 (0.90–1.01)</td>
<td>1.00 (0.95–1.05)</td>
</tr>
</tbody>
</table>

Abbreviations: LVEF, left ventricular ejection fraction; MR, mitral regurgitation.
Figure 1. Relationship between left ventricular longitudinal strain and ejection fraction

A scatter plot showing the relationship between left ventricular longitudinal strain and ejection fraction. Spearman’s coefficient indicated a moderate correlation between left ventricular longitudinal strain and ejection fraction.
Figure 2. Adjusted relationship of (A) left ventricular longitudinal strain and (B) ejection fraction with all-cause mortality and (C) incremental value of longitudinal strain for predicting all-cause mortality

(A,B) Solid lines represent adjusted hazard ratios and the shaded areas indicate 95% confidence intervals. Longitudinal strain of 16.3% and ejection fraction of 50% were used as references. Hazard ratios were estimated per 1% increase in longitudinal strain or ejection fraction. (C) Bar plots represent the Chi-Square statistics of each model. P-values are from the likelihood ratio test to compare the nested models (including conventional risk factors with or without longitudinal strain).

AR, aortic regurgitation; AS, aortic stenosis; CCI, Charlson Comorbidity Index; CI, confidence interval; EF, ejection fraction; HR, hazard ratio; MR, mitral regurgitation; MS, mitral stenosis; NYHA class, New York Heart Association Functional Classification; PHTN, pulmonary hypertension; TR, tricuspid regurgitation.
Figure 3. Adjusted relationship between (A) left ventricular longitudinal strain and (B) ejection fraction with operative morbidity and (C) incremental value of longitudinal strain for predicting operative morbidity.

(A,B) Solid lines represent the adjusted odds ratios, and the shaded areas indicate the 95% confidence intervals. Longitudinal strain of 16.3% and ejection fraction of 50% were used as references. The odds ratios were estimated per 1% increase in longitudinal strain or ejection fraction. (C) Bar plots represent the Chi-Square statistics of each model. P-values are from the likelihood ratio test to compare the nested models (including conventional risk factors with or without longitudinal strain).

A. fib, atrial fibrillation; AR, aortic regurgitation; AS, aortic stenosis; BMI, body mass index; CCI, Charlson Comorbidity Index; EF, ejection fraction; Hct, hematocrit; HTN, hypertension; MR, mitral regurgitation; MS, mitral stenosis; NYHA class, New York Heart Association Functional Classification; OR, odds ratio; PHTN, pulmonary hypertension; TR, tricuspid regurgitation.
Figure 4. Subgroup analyses for (A) all-cause mortality and (B) operative morbidity

Dots indicate the (A) adjusted hazard ratio and (B) odds ratio. Horizontal lines represent 95% confidence intervals.

CI; confidence interval, MR; mitral regurgitation.
Figure 5. Kaplan–Meier survival curve according to longitudinal strain and ejection fraction strata

Kaplan–Meier curve for all-cause mortality. Preoperative left ventricular systolic function is categorized into three strata (EF ≥ 50% and longitudinal strain ≥ 16.3% vs. EF ≥ 50% and longitudinal strain < 16.3% vs. EF < 50%). The median value of longitudinal strain (16.3%) was used as the cut-off value.

CI, confidence interval; HR, hazard ratio; EF, ejection fraction.