The predictive value of intraprocedural mitral gradient for outcomes after MitraClip and its peri-interventional dynamics

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Abstract

Background: The current data on the impact of the increased mitral gradient (MG) on outcomes are ambiguous, and intraprocedural assessment of MG can be challenging. Therefore, we aimed to evaluate (a) peri-interventional dynamics of MG, (b) the impact of intraprocedural MG on clinical outcomes, and (c) predictors for unfavorable MG values after MitraClip.

Methods: We prospectively included patients who underwent MitraClip. All patients underwent echocardiography at baseline, intraprocedurally, at discharge, and after 6 months. 12-month survival was documented.

Results: One hundred and seventy five patients (age 81.2 ± 8.2 years, 61.2% male) with severe mitral regurgitation (MR) were included. We divided our cohort into two groups according to intraprocedural MG with a threshold of 4.5 mm Hg, determined by a multivariate analysis of predictors for 12-month mortality (<4.5 mm Hg: Group 1, ≥4.5 mm Hg: Group 2).

Intraprocedural MG ≥4.5 mm Hg was found to be the strongest independent predictor for 12-month mortality (HR: 2.33, P = .03, OR: 1.70, P = .05), and >3.9 mm Hg was associated with adverse functional outcomes (OR: 1.96, P = .04).

The baseline leaflet-to-annulus index >1.1 was found to be the strongest independent predictor (OR: 9.74, P = .001) for unfavorable intraprocedural MG, followed by the number of implanted clips (P = .01), MG at baseline (P = .02), and central clip implantation (P = .05).

Conclusion: An intraprocedural MG <3.9 mm Hg appears to be the best strategy for 1-year survival and favorable functional outcomes after edge-to-edge MV repair with MitraClip independently from MR etiology. Peri-interventional echocardiographic and procedural parameters are useful for the adequate assessment of intraprocedural MG.

Keywords
MitraClip, mitral gradient, mitral regurgitation, outcome
Transcatheter edge-to-edge mitral valve (MV) repair with the MitraClip system is increasingly regarded as a successful and effective therapeutic alternative to surgical therapy for relevant refractory mitral regurgitation (MR) in patients at high surgical risk.¹–³ The MitraClip procedure reduces the MV area and generates at least two new orifices, followed by an increase in the mean transmitral pressure gradient (MG). An MG over 5 mm Hg after clip attachment has been shown to be associated with adverse outcomes and should thus be avoided according to the current guidelines.⁴,⁵ On the contrary, some recent studies found no predictive value of MG for clinical outcomes after interventional therapy for functional MR.⁶,⁷

Mean transmitral pressure gradient is assessed by transesophageal echocardiography using the MV peak-systolic velocity from intraprocedural continuous-wave Doppler measurements. Intraprocedural assessment of MG can be influenced by various factors: heart rate and rhythm, hemodynamics during general anesthesia and presence of inotropes, as well as measurement-related factors, such as angulation errors. Furthermore, there are additional heart-related factors: (a) left atrial compliance, (b) left ventricular end-diastolic pressure, and (c) valvular parameters.⁸–¹⁰ Therefore, intraprocedural MG should be carefully and individually anticipated since the cofactors mentioned are dynamic and time-varying parameters and might lead to over- or underestimation of MG. Taken together, it is unknown how much the intraprocedurally measured MG values change following general anesthesia and restoration of "normal" hemodynamic conditions or following epithelialization of the clip devices.

We, therefore, aimed to (a) evaluate the dynamic changes of MG, both peri-interventionally and during the follow-up (FU), (b) assess the impact of peri-interventionally measured MG on clinical outcomes, and (c) analyze predictors for unfavorable MG after MitraClip.

2 | METHODS

2.1 | Patients, follow-up, and endpoints

We prospectively included consecutive patients with symptomatic moderate-to-severe or severe refractory MR undergoing the MitraClip™ procedure (NTR/XTR Clip Delivery System, Abbot Vascular, Inc) at the Heart Center of the University Hospital Bonn between February 2017 and January 2019.

All patients underwent standardized echocardiographic examinations for noninvasive MG assessments at baseline, intraprocedurally, at discharge, and 6 months after MitraClip. Clinical examinations comprised an evaluation of NYHA functional class, a 6-minute walk test (6MWT), and a comprehensive blood test, which included serum levels of NT pro-BNP. The 6-month FU was performed in our outpatient clinic and included transthoracic echocardiography, a routine physical examination, an electrocardiogram, and a blood test.

Survival status was reassessed by either a FU visit in the outpatient clinic or a phone call 12 months after the procedure.

We defined all-cause mortality at 12-month FU as the primary endpoint in line with MVARC (Mitral Valve Academic Research Consortium) definitions.¹¹ Secondary endpoints were defined as follows: NYHA functional class at FU <II, amelioration in the walk distance of 25%, intraprocedural MG ≥4.5 mm Hg, residual MR>II at discharge, and MR at FU >II.

The study was authorized by the local ethics committee (Medical Faculty of University Bonn, Bonn, Germany) and in accordance with the Declaration of Helsinki. All patients signed their written informed consent before inclusion in the study. All patients’ data were anonymized before use in the study. Echocardiographers and clinicians from the in- and outpatient clinics were blinded to the study parameters. Trained study nurses carried out clinical FU evaluation, unattended by the interventionalists or the procedural echocardiographer.

2.2 | Echocardiographic assessment

Echocardiographic assessments were performed in line with the current recommendations and guidelines of the European Association of Echocardiography, including comprehensive echocardiography.¹² All echocardiograms were performed after a relaxing time of 5 minutes to occasion a resting condition to avoid misinterpretations due to hemodynamic undulations. We presented LV volumes as indexed values – absolute value/body surface area. The severity of MR was assessed by the semiquantitative PISA method, using the radius of proximal isovelocity surface area (PISA radius), the effective regurgitant orifice area (EROA), as well as the vena contracta width (VC) and the regurgitant volume (RegVol).¹³ Residual MR was assessed by a multiparametric approach consisting of a systemically visual estimation—eyeballing—by experts, determination of color Doppler jet (area, count, and localization), flow convergence, the peak velocity, and the density of the CW Doppler, as well as semiquantitative measurements based on residual PISAs—in case of single residual jet—and VCs intra- and postprocedurally.¹⁴ MG was estimated from the peak-systolic velocity from continuous-wave Doppler imaging of the MV inflow profile. Multiple measurements were done to minimize angulation- and acquisition-related errors and exclude any relevant mitral valve stenosis (>5 mm Hg) during each examination or directly after clip deployment before clip release and at the end of the procedure after removing all catheters. We assessed intraprocedural MG only using transeophageal echocardiography. Right ventricular systolic pressure (RVSP) was estimated by the tricuspid systolic-peak velocity using the modified Bernoulli equation (instantaneous pressure gradient [ΔP] = 4 x velocity). The leaflet-to-annulus index (LAI) was calculated by a formula defined as the ratio between the summation of the lengths of the mitral valve leaflets (anterior mitral leaflet +posterior mitral leaflet) and the anteroposterior diameter (AP diameter), as published previously.¹⁵ The leaflet lengths and AP diameter were measured at 120-150° (three-chamber view).
and SL diameter at 0–20° (four-chamber view) in transesophageal echocardiography. The echocardiographic studies were performed with currently available ultrasound machines (IE33, Philips Medical Systems; E9, GE Healthcare Vingmed Ultrasound).

2.3 | Statistical analysis

The normal distribution of continuous variables was examined using the Shapiro–Wilk test. Continuous data were expressed as mean values ± the standard deviation if normally distributed. Categorical data were presented as a percentage. The Student’s two-sample t test or the Man–Whitney U test was performed to compare continuous variables. Fisher’s exact test or the chi-square test was used to compare categorical data. To compare more than two variables, we used the one-way variance analysis or the Kruskal–Wallis test as an extension of the Student’s t test. Univariate analysis was performed to assess the predictors of clinical outcomes. The predictors of 12-month mortality were estimated by multivariate regression analysis. Cumulative survival incidence was compared using the log-rank test between the groups and presented by the Kaplan–Meier curve. A ROC analysis was performed to determine independent predictors’ sensitivity and specificity for unfavorable outcomes and mortality with defined cutoff values. Two-tailed p-values were considered to be significant if ranging below 0.05. Statistics were performed using SPSS (PASW statistic, Version 25.0.0.0, SPSS Inc) and MedCalc Statistical Software (Version 19.2, MedCalc Software Ltd).

3 | RESULTS

3.1 | Defining the groups

According to multivariate regression analysis and a receiver operating characteristic (ROC) analysis, we found intraprocedural MG— with a cutoff value of 4.5 mm Hg— was the only statically significant predictor for the primary endpoint. Consequently, we divided our patient cohort into two groups— patients with an intraprocedural MG <4.5 mm Hg were defined as group 1 and ≥4.5 mm Hg as group 2.

3.2 | Baseline characteristics

One hundred and seventy five consecutive patients (61.2% male) with symptomatic (100% NYHA functional class >II), moderate-to-severe or severe MR (PISA: 0.8 ± 0.2 cm, VC: 0.8 ± 1.2 cm, EROA; 0.5 ± 0.3 cm², RegVol: 51.1 ± 19.7 mL) were included. 40% (n = 70) of the patients showed degenerative MR (DMR), 42.8% (n = 75) of patients had functional MR (FMR), and 17.2% (n = 30) of patients had a mixed etiology. At baseline, all patients were on guideline-directed medical heart failure therapy or device therapy, if needed. All patients were classified as inoperable or at a high surgical risk by the heart team owing to advanced comorbidities (Logistic EuroScore: 17.8 ± 5.2%), advanced age (mean age: 81.2 ± 8.2 years), and frailty assessed by clinicians’ estimations.

Concerning the baseline demographical and clinical characteristics, there were no statistically significant differences between the groups. Of note, the serum level of NT pro-BNP was more elevated in group 2 than group 1, but without reaching the level of statistical significance (3382 pg/mL vs 3634 pg/mL, P = .1). The baseline demographical and clinical characteristics are presented in Table 1.

In the overall cohort, baseline echocardiography showed a relevant left ventricular (LV) dilation (end-diastolic volume [LV-EDV]: 96.9 ± 40.5 mL, end-systolic volume [LV-ESV]: 56.6 ± 34.6 mL) with a decreased LV ejection fraction (LV-EF: 44.7 ± 16.3%). There was no relevant mitral valve stenosis observed at baseline (1.5 ± 1.1 mm Hg). Furthermore, we found increased RVSP (45.4 ± 14.8 mm Hg) as a sign of pulmonary hypertension at baseline. The baseline echocardiographic parameters were comparable between the groups (Table 2).

3.3 | Interventional outcomes and technical success

All patients underwent a successful transcatheter edge-to-edge mitral valve repair using the MitraClip™ NTR/XTR Delivery System with a reduction in MR of at least one grade or to an MR grade <moderate-to-severe as previously described.16–18 To maintain optimal procedural conditions and outcomes, all procedures were performed under general anesthesia with controlled hemodynamic conditions such as systolic blood pressure in the range of 110–130 mm Hg and the heart rate between 60 and 80 bpm.

54% (n = 95) of patients received one-clip device, and 43% (n = 75) of patients were treated using two clip devices. Three clip devices were implanted in 3% (n = 5) of patients, without a significant difference in the arithmetic mean of the number of clip devices used between the groups; however, the one-clip approach was performed significantly more often in group 1 (1.43 ± 0.58 vs 1.41 ± 0.7, P = .9). There was no significant difference in postprocedural residual MR between the groups (MR-II: Group 1: 94.2% [n = 145] vs Group 2: 86% [n = 18], P = .3). No major periprocedural complications, such as pericardial tamponade or vascular injury requiring additional surgical or interventional therapy, occurred. Furthermore, no relevant peri-interventional bleeding and related laboratory changes were documented.

3.4 | Follow-up in all patients

Regarding MG’s peri-interventional dynamics, we found a decrease in MG to values below 4.5 mm Hg in 11 patients (52%) from group 2 at discharge. In total, 94% of patients (n = 165) presented with an MG <4.5 mm Hg and only 6% of patients (n = 10) had persistent increased MG ≥4.5 mm Hg at discharge.
Two patients (1.1%) were deceased during the 30-day FU due to cardiovascular causes. The 6-month all-cause mortality rate was 8.5% (n = 15), and the 12-month all-cause mortality rate was 23.4% (n = 41).

At 6-month FU, we found significantly improved NYHA functional class (NYHA≥II: 100%–31.66%, P = .001) and increased 6-minute walk distance (247.23 ± 33.4 m–333.45 ± 60.5 m, P = .001) in the overall cohort.

Echocardiography at 6-month FU showed no significant changes in LV dimensions and function (LV-EDV: group 1, P = .6 vs group 2, P = .3; LV-ESV: group 1, P = .4 vs group 2, P = .5; LV-EF: group 1, P = .5 vs group 2, P = .9). We found a significant and sustained
reduction in MR for the overall cohort 6 months after the procedure (MR >II; 91.36%–2.48%, P < .001). Moreover, RVSP significantly decreased within the 6-month FU period (45.4 ± 14.8 mm Hg, 34.7 ± 10.5 mm Hg, P = .01).

### 3.5 Dynamic changes in MG

Mean transmitral pressure gradient significantly increased after the MitraClip procedure (1.5 ± 1.1 mm Hg–3.5 ± 1.7 mm Hg, P = .03)
in the overall cohort. Elevated MG values above 4.5 mm Hg were measured intraprocedurally in 21 patients (12%)—group 2.

At 6-month FU, the following MG values were documented: (a) increase to values above 4.5 mm Hg in nine patients (5.45%) from group 1 and (b) decrease to values below 4.5 mm Hg in two patients (20%) from group 2, in addition to 11 patients with a predischarge reduction in MG. Overall, we found 146 patients (91%) with MG <4.5 mm Hg and 14 patients (9%) with MG ≥4.5 mm Hg at 6-month FU. The dynamics of MG values over time are presented in Figure 1.

3.6 | Comparison of the groups

Concerning baseline echocardiography, we found higher MG in group 2 (1.5 ± 1 mm Hg vs 2.6 ± 1.1 mm Hg, P = .001), as expected. However, the MV geometry was comparable the groups—baseline AP diameter (37.3 ± 0.5 mm vs 37.5 ± 0.5 mm, P = .9) and baseline SL diameter (39.9 ± 6.9 mm vs 39.2 ± 5.9 mm, P = .9). The remaining baseline echocardiographic parameters were statistically comparable between the groups. Of note, there were no significant differences concerning MR etiology between the groups (Table 2).

At 6-month FU in survived patients (n = 160), the NYHA functional class was found to be significantly improved in group 1 (NYHA >II; 100%–26%, P < .001), but not in group 2 (NYHA >II; 100%–73%, P = .5). We, furthermore, found an increased walk distance (6MWT) in group 1 (252.2 ± 127.8 m–348.3 ± 80.7 m, P = .05), but this value was unchanged in group 2 (210.8 ± 46.5 m–223.3 ± 25.8 m, P = .3). Serum levels of NT pro-BNP tended to decrease in group 1 and increase in group 2 at 6-month FU (2874 pg/mL–2436 pg/mL, P = .3 vs 2836 pg/mL–3462 pg/mL, P = .6) (Table 3).

We found a significant and sustained reduction in MR severity in both groups 6 months after the procedure (MR ≥III; 91%–2%, P < .001, 94%–6%, P < .001). RVSP significantly decreased only in group 1 (44.6 ± 11.3 mm Hg–33.3 ± 4.2 mm Hg, P = .016). Patients with an intraprocedural MG ≥4.5 mm Hg showed no significant RVSP changes (49.4 ± 18.3 mm Hg–45.6 ± 18.7 mm Hg, P = .5) at FU (Table 3).

3.7 | Predictors for clinical outcomes

There was a statistically significant difference in 12-month mortality between the groups (20.7% [n = 32] vs 42.8% [n = 9], P = .02). Survival status within the 12-month FU period is graphically depicted by the Kaplan–Meier curve (Figure 2). A Cox-regression analysis showed significantly higher 12-month mortality in group 2 compared to group 1 (HR: 2.33, 95% CI: 1.11–4.88, P = .03), and a multivariate analysis relieved that intraprocedural MG is the strongest predictor (OR: 1.70, 95% CI: 0.95–3.05, P = .05) for 12-month mortality compared to MGs at another time points, residual MR >II at discharge and residual MR >II at FU (Table 4).

According to multivariate regression analysis, including ROC curve analysis of MGs at three different time points (intraprocedurally, at discharge, and 6-month FU) concerning the prediction of adverse functional outcomes (NYHA at FU >II, improvement in walk distance <25%), we found intraprocedural MG to be the strongest predictor for unfavorable clinical outcomes (OR: 1.96, 95% CI: 1.02–3.75, P = .04) with a cutoff value of 3.9 mm Hg (specificity of 80% and sensitivity of 63.9%) followed by MG at FU (OR: 1.56, 95% CI: 0.85–2.86, P = .14) with a cutoff value of 2.6 mm Hg; however, this finding was without statistical significance (Table S1).
According to the one-way variance analysis of group 1, group 2 without predischarge MG reduction, and group 2 with predischarge MG reduction concerning adverse functional outcome—higher NYHA functional class (>II) and lower walk distance (improvement <25%)—we found a significant difference between the groups (24% vs 75% vs 55%, P < .001). Group 2—with/without predischarge MG reduction—showed a somewhat higher 12-month mortality rate than group 1 but without statistical significance (40% vs 33%, vs 29%, P = .4). Remarkably, the worst outcomes—functional and mortality—occurred in group 2 without predischarge MG reduction.

### 3.8 Predictors for unfavorable intraprocedural MG

We evaluated the impact of clip localization on intraprocedural MG in patients with one-clip implantation (n = 95) using the Kruskal-Wallis test. Central clip implantation (segment A2-P2) was found to induce higher intraprocedural MG (3.58 ± 1.7 mm Hg), followed by the technique with cross-clipping (ie, segment A2-P3, A2-P1; 3.2 ± 1.7 mm Hg). Noncentral noncross clip implantation (segment A3-P3; 2.98 ± 1.3 mm Hg or A1-P1; 2.66 ± 1.04 mm Hg) led to a lower MG after clipping in our cohort. Of note, there was a significant
The major findings of the present study are as follows:

1. Intraprocedural MG was found to be a strong predictor for 12-month mortality (cutoff value: 4.5 mm Hg) and adverse functional outcomes (cutoff value: 3.9 mm Hg) independently from MR etiology.

2. Leaflet-to-annulus index (<1.11) was found to be the strongest predictor for unfavorable intraprocedural MG followed by baseline MG, the number of implanted clips, and central clip localization.

3. Concerning 12-month mortality and functional outcomes, intraprocedural MG ≥4.5 mm Hg was more influential than residual MR II.

It is recommended that an intraprocedural MG above 5 mm Hg should be avoided due to associated adverse outcomes. On the other hand, some contradicting studies currently show no relevant association between MG and outcomes after the MitraClip procedure, particularly in patients with functional MR. Therefore, the effect of MG on outcomes after MitraClip is ambiguous.

Intraprocedural echocardiographic assessment of mitral inflow patterns and hemodynamics might be challenging and inadequate owing to altered mitral geometry, such as multi-orifice MVs after transcatheter MV repair. Despite difficulties in MG assessment...
using continuous-wave Doppler in the setting of catheter-based MV repair, it was proven to be superior over planimetric evaluation of MVA for intraprocedural stenosis assessment due to unacceptably time-consuming assessment and misestimations, in a study with 38 patients by Biaggi and coworkers.\(^{19}\) Accordingly, we used the Doppler-based assessment of MG in the present study.

In a monocentric study including 51 elderly patients (mean age: 75 years), Boerlage–van Dijk et al demonstrated that intraprocedural assessment of MG systematically underestimates the value compared to real life. Of note, the authors found no correlation between higher intraprocedural MG and increased heart failure symptoms at FU.\(^6\) In contrast, we found worse clinical outcomes—lower functional capacity and higher 1-year mortality—in patients with intraprocedural MG ≥4.5 mm Hg, which might be due to the fact that the majority of patients included in the cited study suffered from chronic heart failure with concomitant FMR (74%). This might hamper discerning persistent advanced heart failure symptoms and symptoms due to elevated MG at FU—high competing risk. Our cohort comprised a balanced number of MR etiologies (DMR: 40%, FMR: 42.8%, mixed: 17.2%), which might be a reason for the divergent finding.

An intraprocedural MG >4.4 mm Hg was shown by Patzelt et al to be predictive for a combined endpoint consisting of all-cause mortality, redo procedure, and LVAD implantation after MitraClip only in patients with DMR, but not with FMR. The authors found the patient’s age to be the strongest independent predictor for the combined endpoint, followed by residual MR >II and intraprocedural MG.\(^7\) Differently, we found intraprocedural MG more influential than residual MR concerning clinical outcomes in our patients’ cohort in more advanced stages of heart failure with more FMR (42.5%). Additionally, we found a negative influence of elevated intraprocedural MG on clinical outcomes regardless of MR etiology.

Itabashi et al\(^{23}\) showed that increased LV and MV dimensions might be accountable for a somewhat lower intraprocedural MG in a comparable cohort after one-clip implantation. Contrary to our findings, patients with FMR showed a tendency for developing higher intraprocedural MG in this study, which might be due to smaller annular dimensions in their study cohort (AP diameter: 32 vs 38 mm).

We found LAI as a surrogate parameter of MV geometry to be the strongest predictor for unfavorable MG after clip deployment. This new parameter, which reflects on the length of the leaflets in relation to annular dimensions and offers an adequate geometrical assessment of the MV, was not assessed in all of the studies cited but seemed to be associated with residual MR, MG, and outcomes after the MitraClip procedure.\(^{15}\)

Apart from residual MR as a well-known prognostic parameter, postinterventional MG appears to be an independent predictor for clinical outcomes. It shows a dynamic postinterventional process and is influenced by various hemodynamic parameters such as blood pressure, heart frequency, volume condition of the patient, sedation or anesthesia, hemoglobin, and inotropes. Therefore, its sporadic assessment may lead to misestimations intrainterventionally. Understanding of MG dynamics, its predictors, and its effect of outcomes is desirable to get more favorable outcomes after MitraClip compared to just residual MR based decision-making. In the present study, intraprocedural MG appears to be more influential on all-cause mortality and clinical outcomes compared to residual MR>II. The definite pathomechanism of this clinical entity stays still unexplained as an encouraging reason for further prospective multicentric studies. Considering that higher postprocedural MG is associated with worse clinical outcome and increased mortality, forthcoming procedural and device/system-related improvements are desirable.

### 4.1 Limitations

This single-center study has several limitations. It was performed with a limited sample size and short FU duration. Echocardiographic analyses were not performed or validated by an independent core laboratory. Neither an invasive assessment of the left atrial pressure and intraprocedural MG nor exercise echocardiography was done in every patient. There was no assessment of postinterventional interatrial shunt. Further evaluation of the MG’s impact on outcomes based on the MR etiology (FMR vs DMR) was not possible owing to the too low number of patients with elevated MG. To validate the predictive value of parameters for adverse outcomes and unfavorable MG appropriately powered multicentric studies with a larger patient cohort, a longer FU and subgroup and multivariate analysis according to cutoff values and/or propensity matching are required.

### 5 Conclusion

Intraprocedural MG was found to be a strong predictor for 12-month mortality (cutoff value: 4.5 mm Hg) and adverse functional outcomes (cutoff value: 3.9 mm Hg), irrespective of the etiology of MR. Moreover, intraprocedural MG≥4.5 mm Hg appears more influential than residual MR>II regarding clinical outcomes. To aim for an MG of <3.9 mm Hg would be the safest strategy for not negatively influencing survival and functional outcomes after edge-to-edge repair of the MV with the MitraClip system. Additionally, LAI (>1.11) as a surrogate parameter of MV geometry was the strongest predictor for unfavorable intraprocedural MG, followed by MG at baseline, the number of implanted clips, and central implantation. These parameters might help for appropriate patient selection, sufficient intraprocedural decision-making, and more favorable clinical outcomes.

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### Conflict of Interest

Öztürk C, Sprenger Kim, Sugiura A, Weber M, Tabata N, and Schueler R have no conflict of interest. Nickenig G has received speaker honoraria and research grants from Medtronic, Boston Scientific, Edwards Lifesciences, and Abbott.
DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Table S1. Predictors for adverse functional outcome. A, Predictive values of MGs assessed by the ROC analysis. B, Comparison of outcome-predicting parameters by the multivariate regression analysis concerning functional outcomes.

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