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VASCULAR DISEASE

Utility of GERAADA Score for Predicting Long-term Survival Following Surgical Repair of Aortic Dissection

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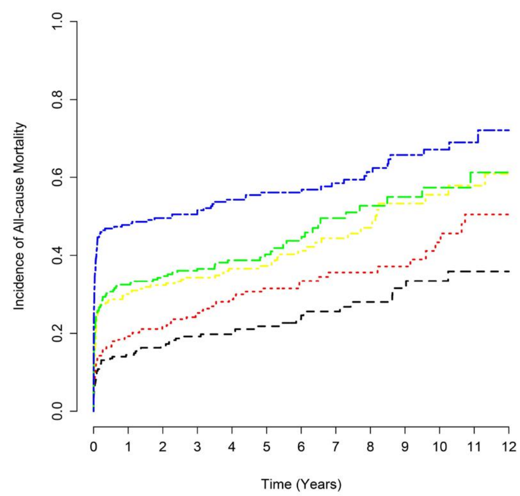
Graphical abstract

Utility of GERAADA score for predicting long-term survival

Summary

We matched the clinical data of 1110 patients following surgical repair of ATAAD with the tax registry. The Kaplan-Meier estimates of survival at 5 and 10 years were respectively 62.5%±1.5%, and 48.5%±2.1%. Long-term survival was analysed according to baseline GERAADA-score founding significant differences.



Legend: mortality at long-term follow-up according to baseline GERAADA score.

Abstract

Objectives: We aimed to assess the long-term survival following surgical repair because of acute type A aortic dissection (ATAAD) and the correlation with the preoperative GERAADA (German Registry for Acute Type A Aortic Dissection)-score value.

Methods: We enrolled patients who underwent emergent aortic surgery because of ATAAD from 2010 to 2022 from 9 hospitals. Follow-up information was obtained by matching the clinical patient data with a national administrative database. Discrimination and calibration of GERAADA were tested at 1, 2, 5, and 10 years. The relationship between long-term outcome and score was also tested through time-to-event methods.

Results: A total of 1110 patients were analysed: Median age was 67 years [IQR 57-75], and 30.8% of subjects were female. Median GERAADA score was 14.3% [10.2-22]. Mean length of follow-up was 4.19 years. The Kaplan-Meier estimates of survival at 5 and 10 years were, respectively, 62.5% ± 1.5%, and 48.5% ± 2.1%. Discrimination was poor but remained stable over the time (area under the curve [AUC] at 1-year follow-up: 0.66; 95% CI 0.63-0.70. AUC at 10-year follow-up: 0.64; 95% CI 0.61-0.68). Calibration plots showed underprediction until 50%-predicted probability and progressive overprediction afterward. There is a steep mortality in the first couple of months after surgery while afterward the mortality rate is constantly lower. GERAADA score was found to be a predictor of long-term mortality with a nonlinear association.

Conclusions: GERAADA score showed a poor performance in predicting long-term survival.

Keywords: aortic dissection; long-term outcomes; risk scores.

INTRODUCTION

Acute type A aortic dissection (ATAAD) is a life-threatening condition and emergency surgical treatment is still the gold standard, also if burdened by a high perioperative mortality risk.[1] Due to the severity of aortic disease, which may involve several vital organs, as well as the invasiveness of surgical treatment (which varies depending on the strategy chosen), and the risk of reoperations at follow-up, patients who survive surgical treatment are at risk of mortality and morbidity even after hospital discharge. The rate of readmission and mortality in a long-term follow-up can burden the patient's quality of life and represent a significant cost for the heat-care system. Risk stratification on long-term outcomes is also fundamental to tailor the health care to the patient. In the recent years, a plethora of mortality scores aimed to identify patients at higher risk for perioperative death. Among those, the score based on the German Registry for Acute Type A Aortic Dissection (GERAADA) data set proven to be the most reliable.[2] However, the fate of those patients who survive the surgical repair of aorta as well as the possible correlation of preoperative GERAADA-score values with the long-term outcome, meaning over the 30 days postoperatively for which it was designed, have been so far not investigated. For these reasons, we aimed to assess the long-term mortality following surgical repair for ATAAD as well as its correlation with the preoperative GERAADA score.

METHODS

The study is an initiative of the Italian Research Group on the Outcomes in Cardiac Surgery (*Gruppo Italiano di Ricerca sugli Outcome in Cardiochirurgia*; GIROC). Details regarding GIROC, steering committee, and study conduction are reported in the Supplementary Material. All described procedures were in accordance with the ethical standards of the Helsinki Declaration, which were developed by the World Medical Association (WMA). This study was firstly approved by the Ethics Committee of Trieste (Comitato Etico Unico Regionale del Friuli Venezia Giulia, CEUR FVG; reference number CEUR-2022-Os-78 on April 26, 2022, Trieste, Italy) and later approved by the local institutional study centres, and was conducted in accordance with the principles of the Declaration of Helsinki. The study population included all adult patients who underwent surgery for type A dissection from January 2010 to December 2022 within the departments of cardiac surgery of 9 hospitals from Italy. Preoperative and demographic information, operative data and perioperative mortality for all patients were retrieved from the institutional databases that were prospectively collected by trained clinicians under the supervision of data managers and are composed by electronic patient's records. The GERAADA score was calculated for each patient in accordance with published guidelines manually on the internet site of Germany society.[3]

Follow-up information was obtained by matching the clinical patient data with a national administrative database, the Tax Register (TR) Information System, which retrieves the status (death/alive) and the date of event. The methodologies employed for record-linkage among databases have been previously described and linkage was based on Hospital Discharge Record number, date of birth, date of surgery, and date of discharge.[4] Data from the TR were available only from the beginning of 2010. The final study population included all adult patients who underwent cardiac surgery in the clinical dataset whose information was matched with the TR Information System. Follow-up was truncated on May 31, 2023; patients who did not experience the events were considered as right-censored. A written consent was waived from patients due to the retrospective nature of the study. Data from the 9 centres were matched and stored in a dedicated dataset in accordance with requirements outlined in the WMA Declaration of Taipei.

Data analysis

The performance of GERAADA score was analysed focusing on discrimination power and calibration, as previously described.[5] The discrimination was evaluated by constructing receiver operating characteristic curve and calculating the area under the curve (AUC) with 95% confidence intervals. The accuracy of the models was also tested calculating the Brier score (quadratic difference between predicted probability and observed outcome for each patient), an overall performance measure that is 0 when the prediction is perfect. The calibration performance was evaluated by generating calibration plots that visually compare the prediction with the observed probability.[5] The comparison of actual slope and intercept with the ideal value of 1 and 0 was performed with the U statistic and tested against a c^2 distribution with 2 degrees of freedom. For testing whether the calibration curve is ideal, we employed even the single degree of freedom (d.f.) Spiegelhalter *Z*-test for calibration accuracy with its 2-tailed *P*-value. Moreover, calibration was tested with Hosmer-Lemeshow goodness-of-fit test, which compares observed to predicted values by deciles of predicted probability.

The relationship between long-term mortality and GERAADA was also tested through time-to-event methods,[5,6] with both grouped frailty fully parametric models (accelerated failure time, "AFT", model), accounting for heterogeneity among trials with a random-intercept parameter. The Akaike information criterion (AIC) was employed to select the distribution that best fit data (Exponential, Weibull, Log-logistic, Log-normal, Gompertz distributions). Nonlinear effect of continuous covariates (GERAADA) was modelled with a restricted cubic spline function, as described by Harrell.[5] The final models were validated by bootstrap (1000 runs) adjusted by the degree of optimism in bootstrap estimates.

Two-sided statistics were performed with a significance level of .05. Analyses were performed with R language (R 4.3.2; R Development Core Team (2023). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL: http://www.R-project.org/).

RESULTS

The record-linkage of administrative and clinical datasets led to 87.0% link and hence the cohort of the study finally included 1110 patients. Median age was 67 years [IQR 57-75], and 30.8% of subjects were female. Mean GERAADA score was 19.14%. There were no significant differences in the baseline clinical characteristics and surgical procedures between the study cohort and the unmatched group. Similarly, there were no significant differences in terms of GERAADA score of the 87 patients who died intraoperatively (mean GERAADA value = 20.4%), excluded from the population before matching, and survivors of surgery. **Table 1** reports baseline characteristics of the study cohort. The median follow-up time was 3.6 years (third quartile 6.5 years; mean 4.19 years ± 3.74) and 467 patients (42.07%) died at follow-up.

Performance of GERAADA score in predicting mortality at different time-points

The performance analysis of GERAADA in predicting perioperative 1-, 2-, 5-, and 10-year mortality is shown in **Figure 1**. The AUC did not demonstrate a good performance (AUC at 1-year follow-up: 0.66; 95% CI 0.63-0.70; AUC at 10-year follow-up: 0.64; 95% CI 0.61-0.68). However, the discrimination power remains stable increasing the follow-up time, with no difference among receiver operating characteristic (ROC) curves (De Long test of AUC 1 year vs AUC 5 years: *P*-value = .40; De Long test of AUC 1 year vs AUC 10 years: *P*-value = .41; De Long test of AUC 5 years vs AUC 10 years: *P*-value = .98).

Table 1. Descriptive Statistics of the GERAADA Score Risk Factors and Surgical Data in the Study Population

	Study population size *N* = 1110
Preoperative data and comorbidities	
Age (years), median [IQ range][a]	67 [57-75]
Gender (female), *n* (%)[a]	342 (30.8)
Body mass index, median [IQ range]	26.51 [24.31-29.39]
Body surface area, mean ± SD	1.95 ± 0.23
Marfan or Loyes-Dietz' s Syndrome, *n* (%)	35 (3.15)
Serum creatinine (mg/dL), median [IQ range]	1.00 [0.80-1.24]
Chronic dialysis	10 (1)
Extracardiac arteriopathy	372 (34)
Diabetes mellitus	139 (14)
Chronic obstructive pulmonary disease	91 (11)
LVEF (%), median [IQ range]	55.00 [53-60]
Migrating pain, *n* (%)	64 (13.5)
Previous cardiac surgery, *n* (%)[a]	53 (4.8)
Resuscitation before surgery, *n* (%)[a]	27 (3.2)
Intubation at referral, *n* (%)[a]	190 (17.2)
Catecholamines at referral, *n* (%)[a]	162 (17.8)
Aortic regurgitation, *n* (%)[a] (Echo, *N* = 936)	
• None	396 (35.67)
• I or II	280 (25.23)
• III or IV	260 (23.42)
Preoperative organ malperfusion, *n* (%)[a]	
• Coronary malperfusion	99 (11.0)
• Visceral malperfusion	160 (18.0)
• Peripheral malperfusion	102 (11.5)
Neurological deficit at referral, *n* (%)	318 (28.65)
Preoperative hemiparesis[a]	84 (9.3)
Descending aorta involvement, *n* (%)[a]	552 (62.9)
Surgical data	
Aortic valve surgery, *n* (%)	391(35.23)
Valve replacement	110 (9.9)
Aortic arch surgery, *n* (%)	195 (17.8)
Frozen elephant trunk, *n* (%)	30 (2.7)
Concomitant CABG, *n* (%)	66 (6.0)
Due to coronary malperfusion	39 (6.7)
CPB time (minutes), median [IQ range]	180.00 [128.75-239.00]
CPB temperature (°C), median [IQ range]	26.00 [25-28]
X-clamp time (minutes), median [IQ range]	102.00 [75.00-142.00]
Cerebral perfusion time (minutes), median [IQ range]	30.00 [17-50]
Arterial cannulation site	
• Right axillary artery	454
• Femoral artery	485
• Aortic arch or ascending aorta	64
• Innominate artery	22
• Combined sites	85
Observed and predicted mortality	
GERAADA score, mean ± SD	19.14 ± 13.76
In-hospital survivors, *n* (%)	848 (76.4)
30-day survivors, *n* (%)	813 (75.4)
1-year survival	95.0% ± 0.2%
5-year survival[b]	62.5% ± 1.5%
10-year survival	48.5% ± 2.1%

Abbreviations: CPB, cardiopulmonary bypass; LVEF, left ventricle ejection fraction.

[a]As reported into GERAADA score model.

[b]36.94% of 1110 patients with a follow-up longer than 5 years.

Calibration plots showed a similar pattern among follow-up times, with underprediction until 50%-predicted probability and progressive overprediction afterward (**Figure 1**). The overprediction in the low-risk GERAADA was accentuated for higher follow-up. In all plots, GERAADA had significant *P*-values for the related summary statistics (Unreliability, Hosmer-Lemeshow test, Spiegelhalter *Z*-test) indicating that they do not provide accurate probabilities (**Table 2**).

Relationship between GERAADA and long-term mortality

The Kaplan-Meier estimates of survival at 5 and 10 years were, respectively, 62.5% ± 1.5%, and 48.5% ± 2.1% (**Figures 2A** and **3**). There is a steep mortality in the first couple of months after surgery while afterward the mortality rate is constantly lower. Kaplan-Meier estimates of long-term survival in patients classified within quintiles of GERAADA score demonstrated a significant relationship between increasing GERAADA and long-term mortality (long-rank test *P*-value $< .0001$, **Figure 2B**). GERAADA was confirmed to be an independent predictor of long-term mortality estimated by semiparametric models. However, the assumption of hazards proportionality for the Cox model was not met by the analysis of Schoenfeld residuals (Grambsch-Therneau test *P*-value $< .01$). We moved to fully parametric AFT models and the best fit was found for the log-normal model, whose hazard function increases to a maximum and then decreases approaching 0 at time becomes large. In this case, hazard ratio (HR) cannot be estimated as measure of effect, and the effect of covariates is expressed in term of survival time ratio (sTR). GERAADA score was found to be a predictor of long-term mortality with a nonlinear association. The sTR of GERAADA was 0.07 (95% CI 0.03-0.16, $P < .001$). Validation of the reduced model by bootstrapping with 1000 repetitions did not show significant overfitting.

Figure 4 shows the predicted 10-year survival for patients with GERAADA score of 10, 20, and 30; the predicted curves demonstrated a similar effect of nonparametric Kaplan-Meier curve, with GERAADA being highly related to mortality in the first months, while afterward the effect is similar for increasing scores. The nonlinear association between long-term mortality and GERAADA is underlined by nonproportional effect of different scores. The predicted hazard trend by GERAADA score is depicted in **Figure 4**; again, the hazard of GERAADA is maximum in the first months after surgery and decreased toward 0 afterward.

DISCUSSION

The main findings of our study are as follows: (1) The all-cause mortality following surgical repair of ATAAD is concentrated in the first months following the procedure, and afterward shows a lower trend; (2) GERAADA-score's effect on survival is dynamic, with a higher influence in the first period, and tendency to 0 in the longer follow-up.

Unlike other risk scores, a specific score for dissecting aortic disease can hardly be used to manage the surgical risk or the expectations of the patient or his relatives. Patients are often referred during the night, without relatives, and maybe already intubated (and therefore unconscious).[7] Alternatively, the prediction of long-term outcome is also an important aspect of patient's care as well of comparative clinical analyses. However, prior reporting in literature for patients operated for ATAAD with an observation time longer than 1 year are few. Mosbahi et al[8] showed a similar mortality rate (33.56%) in their study considering 733 patients from Pennsylvania with a mean

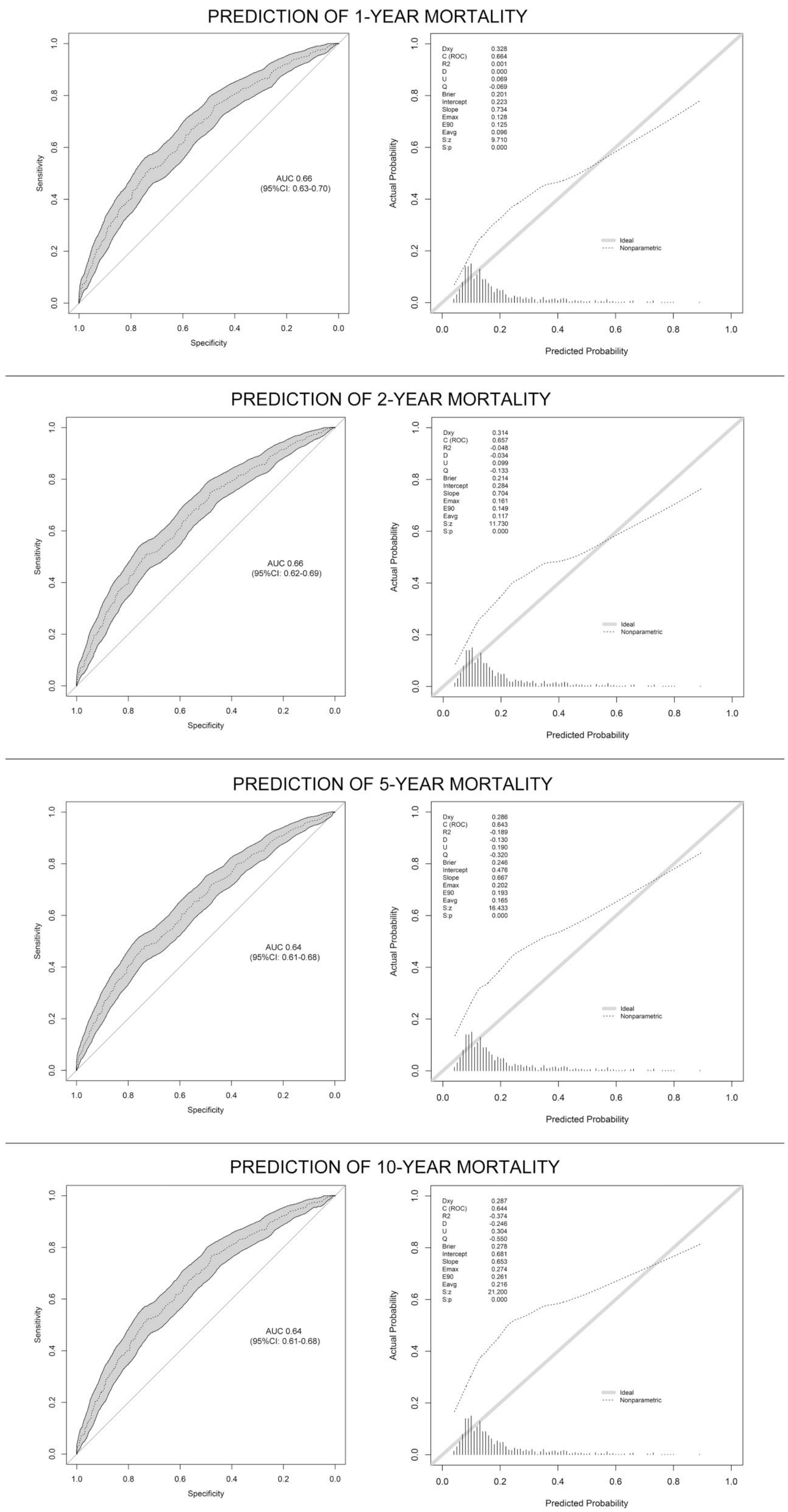


Figure 1. Performances of GERAADA Score in 1-, 2-, 5-, and 10-Year Mortality

observation time of 5.1 ± 4.4 years. Titsworth et al[9] recorded a 10-year survival of 66% in 655 patients from Michigan. The above-mentioned studies attempted to assess the variables associated with a long-term mortality through a Cox-regression analysis: Although both found age as significantly associated with higher mortality at follow-up, they diverged about the significance of other factors (eg, prior cardiac surgery,[8] and coronary artery disease, and acute paralysis[9]). Unfortunately, none but the study of Mosbahi et al[8] investigated the role of any score: The latter included the Penn classification in the analysis,

Table 2. Performance of the GERAADA Score in Predicting 1-Year, 5-Year, and 10-Year Mortality[a]

	1-year mortality	5-year mortality	10-year mortality
Overall performance			
Brier score	0.201	0.246	0.278
AUC (95% CI)	0.66 (0.63-0.70)	0.64 (0.61-0.68)	0.64 (0.61-0.68)
Discrimination			
De Long test *P*-value		.40 (vs 1-year)	.41 (vs 1-year)
Calibration			
U statistic *P*-value	<.01	<.01	<.01
Hosmer-Lemeshow test *P*-value	<.01	<.01	<.01
Spiegelhalter *Z*-test *P*-value	<.01	<.01	<.01

[a]Best performance for: Brier score = 0, AUC = 1, Slope = 1, Intercept = 0, nonsignificant *P*-values of the U statistic, Spiegelhalter *Z*-test, and Hosmer-Lemeshow test.

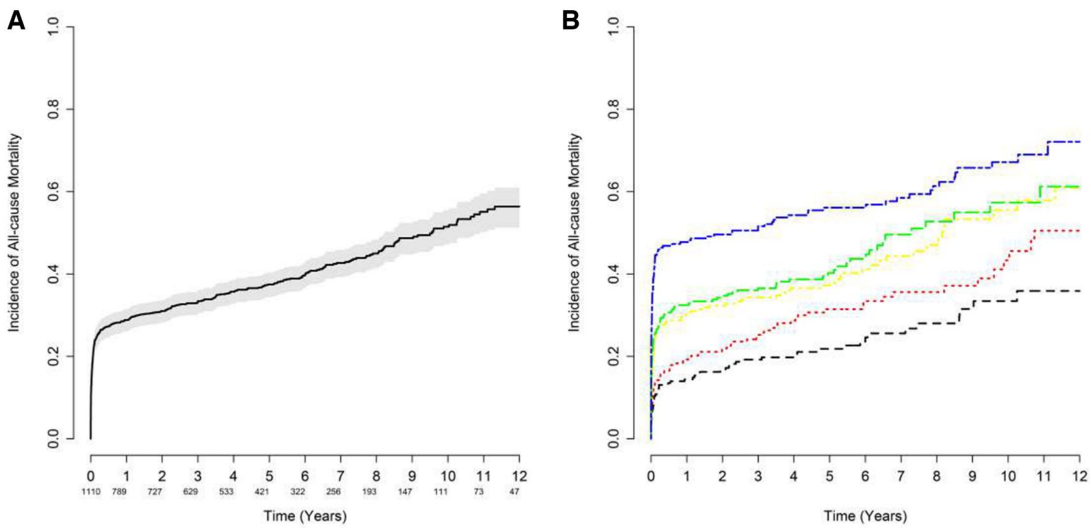


Figure 2. (A) The Kaplan-Meier Estimates of Survival of the Study Cohort. Survival Rates at 1, 5, and 10 Years Were, Respectively, 95.0% ± 0.2%, 84.7% ± 0.4%, and 67.6% ± 1.2%. (B) Kaplan-Meier Estimates of Long-Term Survival in Patients Classified Within Quintiles of GERAADA Score. A Significant Relationship between Quintiles of GERAADA Score and Survival Is Evident (Long-Rank Test *P*-value < .0001)

which however was not significantly associated with the long-term mortality. Finally, Onorati et al[10] reported a 47% 10-year survival in a European registry involving 3902 patients with a mean follow-up time of 3.9 ± 4.2 years. In addition to the correspondence of the long-term cumulative mortality, it is interesting to note that the trend of our survival curves is also superimposable to that of above-mentioned studies. In particular, most of the events are concentrated in the period immediately following the intervention and then stabilize in the long term. Since our follow-up method is based exclusively on the national tax register that is updated instantly, and is therefore certain, this finding confirms the quality of the above-mentioned studies. At the same time, this correspondence suggests that the results of our study based on an Italian population are translatable to American and European countries.

To the best of our knowledge, none did investigate the possibility to predict the long-term outcome. The GERAADA score, although not designed for this purpose, could have had the characteristics suitable to be taken into consideration for this scope. Indeed, its calculation considers anatomical/radiological (such as the extension of the dissection) and functional/metabolic variables (such as the presence of organ malperfusion) in addition to the demographic (gender and age) ones. The above-mentioned variables have a logical influence not only on the risk of death, but also and above all on the probability of postoperative complications (such as lower limb ischemia or stroke), which in turn can influence the need for rehospitalization, reoperation, and indirectly the longer-term survival. Nonetheless, the possible progression of aortic disease remains an important part of the risk of new events in follow-up. Our study, the first validating this score for the long-term survival after ATAAD, showed a poor but constant discrimination at different time points, as well the tendence to overestimate the lower risk patients. An overestimation in low-risk predicted patients has been already observed in relation to 30-day mortality.[2] These results discourage its employ for the long-term outcome but open the possibility to include it as variable in a new model which could also include, for example, further variable such the presence of a pulmonary artery intramural hematoma,[11] the onset of postoperative stroke[12] or acute kidney injury,[13] or the need of reintervention on the aorta. In the latter case, it should be distinguished about the reintervention on the proximal aorta

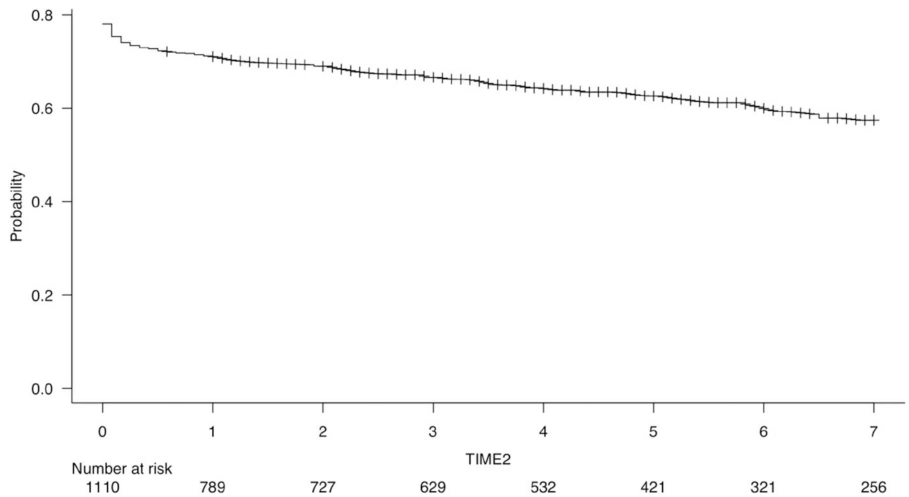


Figure 3. Kaplan-Meier Estimates of Survival Truncated at 7 Years with Numbers of Patients at Risk

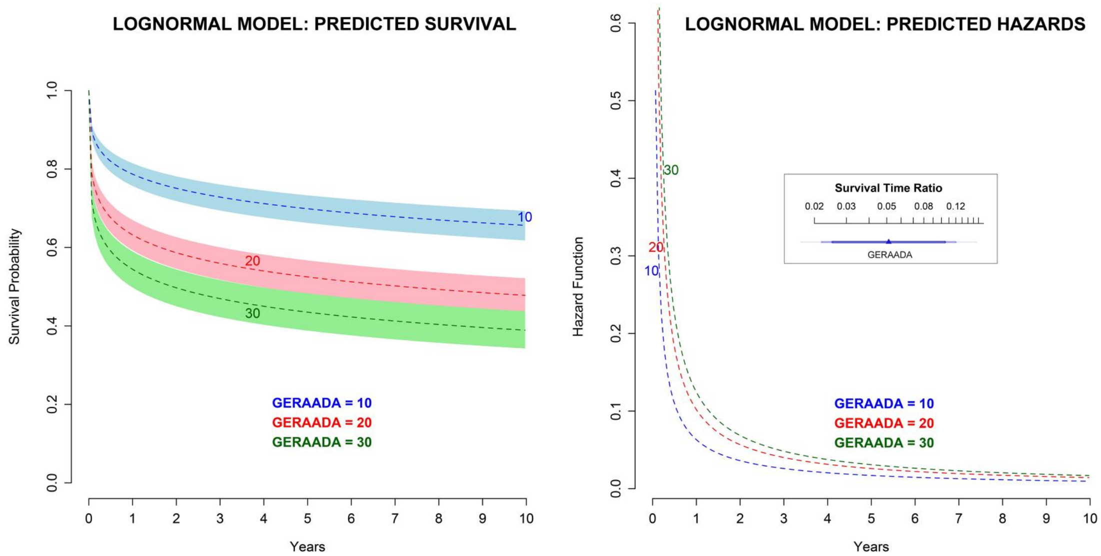


Figure 4. Left: Prediction of Survival of 3 Different Risk Profiles. Right: Predicted hazards. As Evident, the Survival Curves Are Consistent With the Preoperative Predicted Mortality; Nonetheless, the Effects of Singular Risk Factors Are Different on Short and Long-Term Outcomes

(due to incomplete or failed repair) from the reintervention on the distal part (due to completion of the treatment of a thoracoabdominal disease).[9]

The analysis of the survival curves according to GERAADA score shows, after the perioperative period, a quite parallel course: This underlines that once the perioperative period—when the risk of death is highly correlated to the GERAADA score value—is over, the risk of mortality in the subsequent period is no longer influenced by the GERAADA value and remains constant. This is evident in predicted survival: Different scores have different steep impact on mortality in the beginning, afterward the survival curves tend to be parallel (being their underlying hazard superimposable). Consequently, it may be concluded that medical surveillance should be more intensive (or personalized) in the first 6 months after the procedure, especially for those patients with a GERAADA value above 10%. After this period, the risk seems to stabilize uniformly for all GERAADA values, so routine checks can be performed regardless of the score value and probably with a standardized protocol. Individual surveillance protocols following acute aortic events are recommended by the guidelines.[1] However, there is no consensus regarding the criterion that should guide it. The surveillance following ATAAD is a controversial topic. The 2010 American College of Cardiology/American Heart Association guidelines suggest computed tomography or magnetic resonance imaging before discharge; at 1, 6, and 12 months; and yearly thereafter in acute aortic dissection.[14] Nevertheless, evidence from the real world found that adherence to guidelines was extremely poor, with only 14% of patients having guideline-directed imaging surveillance during their follow-up period.[15] Given the low adherence to the guideline, a tailored approach to selecting patients for strict imaging surveillance rather than a generalized protocol for imaging surveillance has been suggested. Although this evidence refers to imaging surveillance, which probably plays a key role in this type of patients, other forms of nonimaging surveillance such as recognition and pharmacological control of cardiovascular risk factors (ie, arterial hypertension) should not be underestimated. The use of an objective score to customize the surveillance could be an easy and practical tool for healthcare givers.

Limitations

The results of this study should be interpreted with caution considering its limitations. The study has been designed to evaluate the performance of GERAADA score in predicting long-term mortality and not to derive a new score based on GERAADA variables for estimating long-term risk; hence, it analyses the correlation of GERAADA with long-term mortality and checks the GERAADA performance's increase by applying time-to-event models. No adjustment with other variables was included, as the nature of the data is not uniform. The present analysis did not consider some variable possibly affecting the outcome, such as the treatment of distal aorta in case of thoracoabdominal aneurysm or the presence of coronary artery disease as well as post-discharge medication.[9] Reason of death is not retrievable from the national administrative registry. As with all observational retrospective studies, unmeasured or unknown confounders may bias the outcome, needing external validation.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

FUNDING

No fundings were received for this study.

CONFLICTS OF INTEREST

Authors have no conflict of interest in relation to this topic.

DATA AVAILABILITY

The data underlying this article will be shared on reasonable request to the corresponding author.

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