A validated score to predict one-year and long-term mortality in patients with significant tricuspid regurgitation

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Received 16 June 2022; revised 12 September 2022; online publish-ahead-of-print 14 October 2022

Handling Editor: Patrizio Lancellotti

Aims

Most patients with significant (defined as ≥ moderate) tricuspid regurgitation (TR) are treated conservatively. Individual mortality rates are markedly variable. We developed a risk score based on comprehensive clinical and echocardiographic evaluation, predicting mortality on an individual patient level.

Methods and results

The cohort included 1701 consecutive patients with significant TR, half with isolated TR, admitted to a single hospital, treated conservatively. We derived a scoring system predicting 1-year mortality and validated it using k-fold cross-validation and with external validation on another cohort of 5141 patients. Score utility was compared with matched patients without significant TR. One-year mortality rate was 31.3%. The risk score ranged 0–17 points and included 11 parameters: age (0–3), body mass index ≤ 25 (0–1), history of liver disease (0–2), history of chronic lung disease (0–2), estimated glomerular filtration rate (0–5), haemoglobin (0–2), left-ventricular ejection fraction (0–1), right-ventricular dysfunction (0–1), right atrial pressure (0–2), stroke volume index (SVI) (0–1) and left-ventricular end-diastolic diameter (0–1). One-year mortality rates increased from 0 to 100%, as the score increased up to ≥16. Areas under the receiver operating curves were 0.78, 0.70, and 0.73, for the original, external validation, and external validation with SVI measured cohorts. The score remained valid in subpopulations of patients with quantified RV function, quantified TR and isolated TR. Significant TR compared to no TR, affected 1-year mortality stronger with higher scores, with a significantly positive interaction term.

Conclusion

We suggest a robust risk score for inpatients with significant TR, assisting risk stratification and decision-making. Our findings underscore the burden of TR providing benchmarks for clinical trial design.

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Graphical Abstract

Aims: Predicting mortality in patient with significant TR

Methods:
1,701 Consecutive patients with significant TR with clinical, laboratory and echocardiographic parameters

0-17 Score predicting 1-year survival

Results:

Internal validation

External validation on 5,141 patients from another cohort

Conclusions:
A relatively simple 17-point score can predict 1-year and long-term mortality in patients with TR. The score has shown high external validity and is robust to other cardiac pathologies and comorbidities.

Keywords
Tricuspid regurgitation • Risk score • Mortality

Introduction
Prevalence of significant, moderate or severe, tricuspid regurgitation (TR) is ≈ 0.6% in the general population, and up to 3% after the age of 75 years, similar to that of aortic stenosis.1 Epidemiological studies suggest that significant TR is associated with almost doubling of mortality after adjustment for potential confounders.2,3 In spite of the high prevalence of significant TR, and its poor prognosis, it is rarely managed surgically.4–6 However, mortality post tricuspid surgery is variable and predicted by the severity of the clinical presentation.7–9 Furthermore, with the recent development of trans-catheter interventions, associated with lower in-hospital mortality10 there is a critical need to accurately predict individual mortality rates with conservative therapy, in order to support individual decisions about timing of surgery or trans-catheter interventions.

Relying on two centres’ consecutive cohort of hospitalized patients with significant TR, treated conservatively, we aimed to develop a dedicated risk score model to predict the 1-year mortality of these patients.

Methods
Data collected retrospectively of all admitted patients who undergone echocardiography in the Tel-Aviv medical center from January 2011 until August 2019 and had at least 1-year of follow-up was used. In total, 1719 patients with significant TR were found. Six patients underwent previous tricuspid surgery, and another 12 patients underwent tricuspid surgery during follow-up resulting in a final cohort of 1701 patients with significant TR treated conservatively for analysis. We collected demographic, clinical and echocardiographic data to create a score to predict 1-year mortality in patients with significant TR. We chose hospitalized patients to get comprehensive clinical and laboratory data, unavailable for most outpatients. The utility of the score was compared with patients without significant TR, patients with quantified TR, patients with quantified right-ventricular (RV) function and patients with isolated TR. Isolated TR was defined as TR without any other valvular disease classified as moderate or above.11,12 The score was also externally validated using data of 5141 consecutive in-patients with significant TR from the Sheba Medical Center between January 2011 and December 2019, who were treated conservatively. As only 18.2% of the patients in the Sheba Medical Center database had left-ventricular stroke volume index (SVI) measured, we did a sensitivity analysis for the 948 patients with SVI measured.

Patients’ co-morbid conditions were evaluated by the patients’ personal physician. Medical history of relevant diagnoses was procured from patients’ electronic medical record, after chart review. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation.13 Treating physicians were responsible for implementing contemporary heart failure guidelines in all patients, reflecting routine clinical practice. Mortality data were available for all patients of both institutions from national registry.

The ethics committee of the Tel-Aviv Medical Center approved the study.

Echocardiography
All patients had comprehensive two-dimensional and Doppler echocardiography. LV diameters, volumes, ejection fraction (LVEF) were measured as recommended.14 Measurements of mitral inflow included the peak early filling (E-wave) and late diastolic filling (A-wave) velocities, and E-wave deceleration time. Early diastolic mitral septal and lateral annular velocities (e’) were measured in the apical 4-chamber view. Left atrial (LA) volume was calculated using the biplane area length method at end-systole.
Detection and gradation of TR was visually assessed using an integrative, semi-quantitative approach, including assessment of colour Doppler jet area, tricuspid valve morphology, right atrial (RA) and RV size, inferior vena cava size, jet density, and contour colour Doppler, as recommended by guidelines. Apart from gradation, TR was quantified in 566 patients. TR quantitation used proximal flow convergence (proximal isovelocity surface area—PISA) method which allowed calculation of effective-regurgitant-orifice (ERO) area and regurgitant volume. RV size was qualitatively assessed from an apical 4-chamber view. Right ventricle larger than the left in this view, or right ventricle displacing the left ventricle and occupying the apex signified right ventricle dilatation. Right-ventricular systolic function was qualitatively graded using all views available. Using multiple views, an integrative qualitative grading was formulated according to published guidelines. Apart from gradation, RV function was evaluated by tricuspid annular plane systolic excursion (TAPSE) or systolic tricuspid lateral annular velocity (RV’S) measured in the apical four-chamber view, in 496 patients. Haemodynamic assessment measured the tricuspid regurgitant velocity and estimated right atrial pressure (RAP) using the inferior vena cava to calculate the systolic pulmonary artery pressure (SPAP). Forward stroke volume was calculated from left-ventricular outflow tract with subsequent calculation of cardiac output and index. TR was assessed by standard qualitative assessment, and significant TR was defined as ≥ moderate TR. All echocardiographic findings were assessed by a senior cardiologist with experience in echocardiographic assessment blinded to the patients’ clinical characteristics.

Building to the score, validation, and investigation

To identify demographic, clinical, and echocardiographic variables which significantly affect 1-year mortality, we evaluated them using univariable logistic regression. All variables with a significant relationship were entered as a seed to a multivariable logistic regression, which was optimized to a model with the minimal number of relevant variables. All significant variables in this model were used to create the final score. To simplify the model, we categorized all continuous variables to an optimal number of bins. These were put into another regression to extract numerical values assigned to each variable creating a formula for a simple score predicting 1-year mortality.

The score’s utility in prediction of 1-year mortality was assessed with both logistic regression and receiver operating curves (ROC) area under the curve (AUC). Predictive usefulness for long-term survival (upto 5 years) was also determined. To determine external validity, the score was calculated on a different database of 5141 patients and its utility in prediction of 1-year and long-term mortality was assessed using the same methods.

To compare the specific utility of the suggested score in patients with and without TR the entire database was used, and patients with significant TR were matched in a 2:1 ratio to patients without TR. Patients were matched by age, renal function, body mass index (BMI), minimal haemoglobin levels, presence of chronic lung disease, left-ventricular ejection fraction (LVEF), and left-ventricular end-diastolic diameter (LVEDD), these variables were selected on one hand to control confounding and on the other to evaluate morbidity specific to TR. The relative predictive ability of the score was assessed in patients with and without TR using an interaction term.

Statistical methods

Results are reported as Mean ±SD or median (IQR) for continuous variables, number (%) for categorical variables and ratios with their respective 95% confidence intervals (CIs). Comparison of proportions was performed using fishers’ exact method, while comparison of continuous variables was performed using a Wilcoxon test. Multivariable and univariable predictors of 1-year mortality were evaluated using binary logistic regression. Variables with P-values <0.2 level in univariate logistic regression were entered into multivariate analysis, using a step-wise procedure based on the Akaike information criterion (AIC) for variable selection. Binning of continuous variables was done using conditional inference trees. Long-term mortality was described using the Kaplan–Meier method with Cox proportional hazards models used for calculating the hazard ratios and the log-rank test for the P-values. Internal cross-validation was done using a k-fold cross-validation using 10 folds. Comparison of the AUCs of different ROC curves was done using the Delong method. Matching of patients with and without TR was done using greedy nearest neighbour propensity score matching.

To reduce bias, all multivariable analyses were performed on databases with missing values imputed using a random forest algorithm, all fields had non-missing values in at least 80% of cases. Findings were considered statistically significant when P<0.05. All calculations were performed using R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The primary cohort consisted of 1701 patients aged 76 ±14 years of whom 845 (50%) female. Overall, 1-year mortality was 31.3% (n=533). Baseline clinical and echocardiographic characteristics along with the results of the univariate analyses for 1-year mortality are presented in Table 1. Using the methods described, a risk score consisting of 0–3 points for age, a point for BMI ≤25, 2 points for liver disease, 2 points for chronic lung disease, 0–5 points for eGFR, 0–2 points for minimal haemoglobin during admission, a point for LVEF ≤30%, a point for RV dysfunction, 0–2 points for estimated RAP, a point for SVI ≤30 mL/m² and a point for LVEDD ≤45 mm was constructed (Table 2). The score ranged between 0 and 17 with a median of 6 and an IQR of 4–9. Patient’s distribution according to each score value is shown in Figure 1.

Score utility

The score showed significant predictive ability for 1-year mortality with an odds ratio (OR) of 1.47 per point increase (95% CI: 1.41–1.54, P<0.001). Rate of 1-year mortality for the various score ranged from 0% for patients with a scores of 0–1 to 100% for patients with scores of 16–17 (Figure 2). ROC curves for the model show good predictive ability with an AUC of 0.78 (95% CI: 0.76–0.81, Figure 3). Long-term mortality was also well predicted using the score, with an HR of 1.28 (95% CI of 1.25–1.31) and a log-rank P-value for trend <0.0001(Figure 4).

Score validation

The score was validated using k-fold cross-validation that showed almost identical results with AUC of 0.78 and 95% CI of 0.75–0.81. Furthermore, sensitivity analyses of specified subpopulations shown similar discriminative ability for the 566 patients with quantified TR (AUC: 0.76, 95% CI: 0.71–0.80, P=0.25 for difference with the original population), the 496 patients with quantified RV dysfunction (AUC: 0.77, 95% CI: 0.73–0.81, P=0.68 for the difference with the original population) and the 835 patients with isolated TR (AUC 0.76, 95% CI 0.73–0.80, P=0.390 for the difference with the original population). To enhance external validity, we calculated the score on a different database of 5141 consecutive patients with significant TR without tricuspid valve intervention (see baseline clinical and echocardiographic characteristics of patients in the validation cohort in Supplementary material online.
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Table S1. The score performed well on the validation cohort with an OR for 1-year mortality of 1.35 (95% CI: 1.32–1.39, P < 0.001) per point and an HR for long-term (5 years) mortality of 1.25 (95% CI: 1.24–1.27, P < 0.001) per point. The score accuracy was, however, lower than from the original database with an ROC AUC of 0.70 (95% CI: 0.68–0.72, Figure 3).

As the validation cohort had an extremely high number of missing values of SVI (81.8%, n = 4204) we performed a sensitivity analysis for the 937 patients who had SVI measured, that showed more accurate results with an OR of 1.43 (95% CI: 1.35–1.53, P < 0.001) for 1-year mortality, HR of 1.26 (95% CI: 1.23–1.30, P < 0.001) and an ROC AUC of 0.73 (95% CI: 0.69–0.76; Figure 3).

Comparison to patients without significant TR

Applying the score to the full database, including all inpatients, the score predicted mortality also in the non-TR patients with a ROC AUC of 0.76 (95% CI: 0.76–0.77, P = 0.14, in comparison with TR patients).

### Table 1 Baseline characteristics and odds ratios for 1-year mortality in patients with significant tricuspid regurgitation

| Parameter                                         | Odds ratio (95% confidence interval) | P-value |
|---------------------------------------------------|--------------------------------------|---------|
| N                                                 | 1701                                 |         |
| Age—years (mean ± SD)                             | 76.24 (13.74)                       | 1.04 (1.03–1.05) | <0.001 |
| Female gender (%)                                 | 845 (49.7)                          | 0.98 (0.8–1.2) | 0.853  |
| BMI (mean ± SD)                                   | 25.90 (4.45)                        | 0.96 (0.94–0.99) | 0.002 |
| eGFR—mL/min (mean ± SD)                           | 44.53 (23.42)                       | 0.96 (0.96–0.97) | <0.001 |
| Minimal haemoglobin—g/dL (mean ± SD)              | 10.42 (2.27)                        | 0.82 (0.78–0.86) | <0.001 |
| Past pacemaker or ICD (%)                         | 69 (4.4)                            | 1.66 (1.01–2.7) | 0.042  |
| Heart failure diagnosis (%)                       | 346 (22.0)                          | 1.52 (1.19–1.95) | 0.001 |
| Atrial fibrillation diagnosis (%)                 | 463 (29.4)                          | 1.32 (1.05–1.65) | 0.018  |
| Ischemic heart disease diagnosis (%)              | 556 (35.3)                          | 1.41 (1.13–1.75) | 0.002  |
| History of coronary bypass (%)                    | 13 (0.8)                            | 0.63 (0.14–2.07) | 0.485  |
| Essential hypertension (%)                        | 1048 (66.5)                         | 1.28 (1.02–1.62) | 0.031  |
| Diabetes mellitus (%)                             | 456 (28.9)                          | 1.14 (0.9–1.43) | 0.269  |
| Chronic lung disease (%)                          | 67 (4.3)                            | 1.75 (1.06–2.87) | 0.026  |
| Liver disease diagnosis (%)                       | 33 (2.0)                            | 2.07 (1.03–4.15) | 0.038  |
| LVEDD (mean ± SD)                                 | 52.62 (9.16)                        | 0.98 (0.97–0.99) | 0.002  |
| LVESD (mean ± SD)                                 | 37.36 (11.54)                       | 0.99 (0.99–1–01) | 0.903  |
| Estimated LVEF—% (mean ± SD)                      | 46.44 (13.97)                       | 0.98 (0.98–0.99) | <0.001 |
| LV mass index—g/m^2 (mean ± SD)                   | 184.44 (42.49)                      | 1 (0.99–1–01) | 0.918  |
| LV SVI—mL/m² (mean ± SD)                          | 33.30 (11.96)                       | 0.98 (0.97–0.99) | <0.001 |
| Cardiac index—L/min/m² (mean ± SD)                | 25.55 (12.1)                        | 0.93 (0.79–1.06) | 0.362  |
| Mitral E velocity—cm/s (mean ± SD)                | 1.08 (0.31)                         | 1 (0.7–1.44) | 0.984  |
| Mitral A velocity—cm/s (mean ± SD)                | 0.76 (0.33)                         | 1.04 (0.67–1.62) | 0.849  |
| Mitral E/A ratio (mean ± SD)                       | 1.67 (0.85)                         | 0.93 (0.78–1.1) | 0.405  |
| Mitral E/e'                                       | 17.91 (7.80)                        | 1.02 (1.01–1.04) | 0.009  |
| LA volume index—mL/m² (mean ± SD)                  | 57.45 (17.04)                       | 1 (0.99–1–01) | 0.812  |
| Severe AS (%)                                     | 85 (5.0)                            | 1.08 (0.67–1.7) | 0.743  |
| Severe MR (%)                                     | 333 (19.6)                          | 0.79 (0.6–1.02) | 0.079  |
| Right-ventricular dilatation (%)                   | 623 (36.6)                          | 1.7 (1.38–2.09) | <0.001 |
| Right-ventricular dysfunction (%)                  | 521 (30.6)                          | 1.86 (1.5–2.31) | <0.001 |
| TAPSE—mm (mean ± SD)                              | 17.51 (5.57)                        | 0.97 (0.94–1) | 0.035  |
| TV s’—cm/s (mean ± SD)                            | 9.79 (3.20)                         | 0.94 (0.89–0.98) | 0.006  |
| Estimated systolic PAP—mmHg (mean ± SD)           | 30.39 (16.40)                       | 1.02 (1.01–1.03) | <0.001 |
| RAP—mmHg (mean ± SD)                              | 10.99 (6.09)                        | 1.08 (1.06–1.1) | <0.001 |
| Diuretic use (%)                                   | 203 (11.9)                          | 0.91 (0.66–1.25) | 0.561  |
| ACEI/ARB use (%)                                   | 45 (2.6)                            | 0.54 (0.24–1.08) | 0.102  |
| Beta-Blockers use (%)                              | 205 (12.1)                          | 0.66 (0.46–0.91) | 0.015  |

AS, aortic stenosis; BMI, body mass index; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter device; LVEF, left-ventricular ejection fraction; LV, left ventricle; LA, left atrium; LVEDD, left ventricle end-diastolic diameter; LVESD, left ventricle end-systolic diameter; MR, mitral regurgitation; PAP, pulmonary artery pressure; RAP, right atrial pressure; RV, right ventricle; SPAP, systolic pulmonary pressure; TAPSE, tricuspid annular plane systolic excursion; TV, tricuspid valve. ACEI/ARB, angiotensin converting enzyme inhibitors/angiotensin receptor blockers.
In order to diminish selection bias, we matched each significant TR patient with two non-TR patients by age, renal function, BMI, Minimal haemoglobin levels, presence of chronic lung disease, LVEF and LVEDD. The matched database showed that TR patients had higher RAP, lower SVI, and higher prevalence of RV dysfunction (Table 3). Patients with significant TR had higher 1-year and long-term mortality (OR: 1.21, 95% CI: 1.06–1.37, \( P = 0.004 \) for 1-year mortality, HR: 1.12, 95% CI: 1.03–1.22, \( P = 0.006 \) for up to 5 years). The effect of significant TR on mortality was stronger with higher score levels as manifested by a positive interaction of significant TR with the score (OR: 1.07, 95% CI: 1.02–1.13, \( P = 0.009 \)).

**Table 2** Final simplified score calculation from multivariate analysis and scoring system

| Parameter                                      | Points |
|------------------------------------------------|--------|
| Age \( \geq 65 \) and <80 years                | +1     |
| Age \( \geq 80 \) and <85 years                | +2     |
| Age \( \geq 85 \) years                       | +3     |
| BMI \( \leq 25 \)                             | +1     |
| Diagnosis of liver disease                    | +2     |
| Diagnosis of chronic lung disease             | +2     |
| eGFR \( \leq 50 \) and >30 mL/h/1.73m²         | +1     |
| eGFR \( \leq 30 \) and >20 mL/h/1.73m²         | +3     |
| eGFR \( \leq 20 \) mL/h/1.73m²                | +5     |
| Minimal Hgb \( \leq 12.5 \) g/dL              | +1     |
| Minimal Hgb \( \leq 8 \) g/dL                 | +2     |
| LVEF \( \leq 30\% \)                          | +1     |
| RAP >5 and \( \leq 15 \) mmHg                 | +1     |
| RAP >15 mmHg                                  | +2     |
| Left-ventricular SVI \( \leq 30 \)            | +1     |
| LVEDD \( \leq 45 \)                           | +1     |
| Echocardiographic signs of RV dysfunction      | +1     |

Egfr, estimated glomerular filtration rate; BMI, body mass index; LVEDD, left ventricle end-diastolic diameter; Hgb, haemoglobin; LVEF, left ventricle ejection fraction; RAP, right atrial pressure; RV, right ventricle; SVI, stroke volume index.

**Figure 1** Distribution of patients with significant tricuspid regurgitation presenting with each score value.

**Discussion**

In this study, we developed a dedicated risk score predicting 1-year mortality. The risk score showed both an excellent discrimination and calibration. Although designed to predict 1-year mortality, it also predicted long-term mortality with good accuracy. Of note, despite the increased mortality of TR, only 12 (>1%) patients admitted with significant TR were referred for an intervention during long-term follow-up.

Management of patients with severe TR is misled by several erroneous beliefs. The first is that TR is benign and/or improves once left sided cardiac disease is corrected. The second is that we should intervene only when patients have florid symptoms of right heart failure. The third is that surgical risk for TR is very high. In contrast to left sided valvular disease, TR’s symptoms are vague and progress slowly. Its first and most common symptom is effort intolerance, usually attributed to old age. Oedema, ascites, or end organ damage usually occur after many years, after severe RV dysfunction prevails. Unfortunately, patients are usually sent for intervention only at this advanced stage, explaining the falsely malignant reputation of TR surgery. Recent literature showed an overall high 1-year mortality of ≈25–30% in hospitalized patients with significant TR, consistent with our cohort. However, our data show that mortality rate is extremely heterogeneous, with rates ranging from 0 to 100%. Previous natural history studies have shown that the outcome is predicted by the severity of TR, and on its clinical presentation. However, these findings were of limited clinical use to predict mortality of TR at the individual level.

In the present study, we developed a simple and accurate model for 1-year mortality in patients with significant TR. Our model is based on 11 (four clinical, two laboratory, and five echocardiographic) easily measured parameters. Our risk score, on a 0–17 point scale, provided both valuable discrimination (AUC = 0.78) and calibration with a predicted mortality ranging from 0–100%.

Interestingly, although SPAP was associated with higher mortality in non-adjusted analysis, it was not an independent predictor of outcome, and was excluded from the final model. In the setting of severe TR, laminar flow between the right ventricle and right atrium is usually observed and the assumptions behind the simplified Bernoulli equation are not valid, underestimating the pulmonary pressure. Furthermore, with low RV stroke volume, due to TR, pulmonary pressure may ‘pseudo-normalize’ not capturing the true malignant nature of TR.
However, RAP and SVI were the only hemodynamic parameters reflecting right-ventricular performance entered the risk model. This is not surprising, since the combination of filling pressure and forward flow reflects RV’s Frank–Starling curve, in which as the RV function deteriorates, filling pressures rise to maintain output, and ultimately fail to produce sufficient output despite further elevation in filling pressure. Importantly, our risk score model designed to predict 1-year mortality also predicted long-term mortality which is important when tricuspid interventions are considered.

Recently a risk score for predicting mortality in the population of patients with isolated TR was developed, our score carries a complementary value to it as it is robust to predicting mortality in multivalvular disease ($P=0.390$ between patients with isolated TR and the entire cohort) which was relatively common in our database (49.1%). This robustness may be attributed to inclusion of echocardiographic hemodynamic measurements such as SVI and LVEDD which may indicate the severity of other left sided valvular disease. This fact also explains how the multivariable model did not show significance for severe mitral and aortic regurgitation or stenosis as their hemodynamic effects were already accounted for. Furthermore, the model described here had slightly better discerning ability than the model presented by Wang et al. (0.78 vs. 0.73) and was also validated both internally and externally.

The present risk score model, combined with the recently developed surgical TRISCORE risk score can support individual clinical decisions. For example, a patient with estimated 5% 1-year mortality under...
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conservative treatment and calculated post-surgical 30-day mortality of 20% (based on the TRISCORE surgical risk score), should probably be followed up. On the other hand, a patient with estimated 50% 1-year mortality and calculated post-surgical 30-day mortality of 10%, should be recommended a tricuspid intervention.

The effect of significant TR on 1-year mortality, compared with patients without TR was stronger with higher score levels, indicating that a significant excess mortality is caused by the TR itself rather than the TR being a surrogate marker for severe illness. Although the risk score predict mortality in non-TR patients as well albeit to a lesser accuracy, the significant interaction between the score value and TR suggests that TR patients have a worse prognosis per score point which makes it unique towards predicting mortality in TR. Furthermore, the score contains measures of RV dysfunction, hepatic failure and lung disease that are relatively specific to TR and less for other structural diseases.

Importantly, we only provided evidence that no intervention is likely to be detrimental for some patients, yet timing, and intervention type remains to be determined. With the rapid development of trans-catheter interventions, and future development of risk score for mortality post trans-catheter procedures, our risk score model may provide a unique tool to select the patients who might be better suitable for conservative treatment vs. those that will benefit from trans-catheter interventions.

Study limitations

First, our sample size was relatively small (1701 patients), especially considering a very small number of patients in very low and very high scores groups. Nevertheless, it was validated using a larger cohort (5141 patients) from another centre. Second, our study is retrospective, and includes only hospitalized patients. Third, not all variables were available for each patient, and we performed imputation for missing variables. However, all variables had at least 80% non-missing data. Fourth, assessment of RV function relied on an integrative approach and not a single parameter with a well-defined threshold. Yet, each echocardiographic parameter proposed for the assessment of RV systolic function suffers from limitations, and none have been well validated in the setting of severe TR. Thus, an integrative approach seems to be a preferable way to assess RV function and is recommended by recent guidelines. Furthermore, sensitivity analysis performed on patients with quantitative RV systolic assessment revealed similar results.

In the validation cohort AUC was 0.7 implying about 30% residual mortality not predicted by the model. As this cohort included all admitted patients with both combined and isolated TR, sumo with a substantial co-morbidities.it is reasonable to believe the residual mortality not predicted by the model is not related to TR and probably is not cardiac related.
Table 3  Significant tricuspid regurgitation patients matched 1:2 with non-tricuspid regurgitation patients by age, renal function, BMI, minimal haemoglobin levels, presence of chronic lung disease, LVEF, and LVDD

| Parameter                      | Non-tricuspid regurgitation | Sig. tricuspid regurgitation | P-value |
|--------------------------------|----------------------------|-----------------------------|---------|
| N                              | 3402                       | 1701                        |         |
| Age—years (mean ± SD)          | 76.73 (12.37)              | 76.24 (13.74)              | 0.202   |
| eGFR—ml/L (mean ± SD)          | 44.27 (22.87)              | 44.73 (23.42)              | 0.501   |
| Estimated LVEF—% (mean ± SD)   | 46.96 (12.98)              | 46.59 (13.68)              | 0.350   |
| Estimated RAP—mmHg (mean ± SD) | 7.85 (4.47)                | 10.75 (5.89)               | <0.001  |
| SVI—ml/m2 (mean ± SD)          | 38.54 (11.21)              | 34.23 (11.09)              | <0.001  |
| Diagnosis of liver disease (%) | 49 (1.4)                   | 33 (1.9)                   | 0.222   |
| LVEDD—mm (mean ± SD)           | 52.24 (8.51)               | 52.57 (8.93)               | 0.201   |
| Minimal Hgb—g/dL (mean ± SD)   | 10.40 (2.43)               | 10.44 (2.26)               | 0.554   |
| BMI kg/m2 (mean ± SD)          | 26.00 (4.17)               | 26.07 (4.34)               | 0.549   |
| Chronic lung disease (%)       | 128 (3.8)                  | 67 (3.9)                   | 0.816   |
| RV dysfunction (%)             | 484 (14.2)                 | 521 (30.6)                 | <0.001  |
| Risk score value [median (IQR)]| 6.00 (4.00, 8.00)          | 6.00 (4.00, 9.00)          | <0.001  |

Egfr, estimated glomerular filtration rate; BMI, body mass index; LVEDD, left ventricle end-diastolic diameter; Hgb, haemoglobin; LVEF, left ventricle ejection fraction; RAP, right atrial pressure; RV, right ventricle; SVI, stroke volume index.

**Conclusion**

We propose a risk score model based on easily measured parameters to advise patients and physicians regarding the individual risk of TR both isolated and combined under conservative therapy. This risk score can guide the clinical decision-making process, leading to earlier intervention for patients with significant TR, before irreversible RV dysfunction, RV failure, or end organ damage occur.

**Data availability**

Data can be made available in accordance to the participating acenter data sharing policy and IRB approval.

**References**

1. Topilsky Y, Maltais S, Medina Inojosa J, Oguz D, Michelena H, Maalouf J, Mahoney DW, Enriquez-Sarano M. Burden of tricuspid regurgitation in patients diagnosed in the community setting. *JACC Cardiovasc Imaging* 2019;12:433–442.
2. Wang N, Fulcher J, Abeyasurya N, McGrady M, Wilcox I, Celermaier D, Lal S. Tricuspid regurgitation is associated with increased mortality independent of pulmonary pressures and right heart failure: a systematic review and meta-analysis. *Eur Heart J* 2019;40:476–494.
3. Messika-Zeitoun D, Verta P, Gregerson J, Pocock SJ, Boero I, Feldman TE, Abraham WT, Lindenfeld J, Bax J, Leon M, Enriquez-Sarano M. Impact of tricuspid regurgitation on survival in patients with heart failure: a large electronic health record patient-level database analysis. *Eur J Heart Fail* 2020;22:1803–1813.
4. Dreyfus J, Ghalem N, Garbar E, Gimalev C, Natala P, Vahanian A, Caranhag H, Messika-Zeitoun D. Timing of referral of patients with severe isolated tricuspid valve regurgitation to surgeons (from a French nationwide database). *Am J Cardiol* 2018;122:323–326.
5. Zack CJ, Fender EA, Chandrashekar P, Reddy YNV, Bennett CE, Stulak JM, Miller VM, Nishimura RA. National trends and outcomes in isolated tricuspid valve surgery. *J Am Coll Cardiol* 2017;70:2953–2960.
6. Messika-Zeitoun D, Cadorpi P, Dreyfus J, Burwash IG, Iung B, Philippon J-F, Toussaint J-M, Verta P, Feldman TE, Obadia J-F, Vahanian A, Mesana T, Enriquez-Sarano M. Management and outcome of patients admitted with tricuspid regurgitation in France. *Can J Cardiol* 2021;37:1078–1085.
7. Topilsky Y, Khanna AD, Oh JK, Nishimura RA, Enriquez-Sarano M, Jeon YB, Sundt TM, Schaff HV, Park SJ. Preoperative factors associated with adverse outcome after tricuspid valve replacement. *Circulation* 2011;123:1929–1939.
8. Kim Y-J, Kwon D-A, Kim H-K, Park J-S, Hahn S, Kim K-H, Kim K-B, Sohn D-W, Ahn H, Oh B-H, Park Y-B. Determinants of surgical outcome in patients with isolated tricuspid regurgitation. *Circulation* 2009;120:1672–1678.
9. Dreyfus J, Audureau E, Bohlert Y, Coisse A, Lavey-Badie Y, Bouchary M, Flageollet M, Baize B, Ezapenitier F, Vial F, Riant E, Mtsaki Y, Ehyarts D, Senage T, Modine T, Nicol M, Dognett F, Nguyen V, Le Tourneau T, Triboloyl C, Donal E, Tomasi J, Habib G, Selton-Suty C, Raffoul R, Iung B, Obadia J-F, Messika-Zeitoun D. TRI-Score: a new risk score for in-hospital mortality prediction after isolated tricuspid valve surgery. *Eur Heart J* 2022;43:654–662.
10. Taramasso M, Benfari G, van der Bijl P, Alessandrini H, Attinger-Toller A, Biasco L, Lurz P, Braun D, Brochet E, Connelly KA, de Brujin S, Denti P, Deuschl F, Estevez-Loureiro R, Fam N, Freker C, Gavazzoni M, Hausleiter J, Ho E, Juliard J-M, Kaple R, Besler C, Kodali S, Kreidel F, Kuck K-H, Latib A, Lauten A, Morivas V, Mehr M, Muntané-Carol G, Nazif T, Nickering G, Pedrazzini G, Philippon F, Pozzoli A, Praz F, Puri R, Rodés-Cabau J, **Supplementary material**

Supplementary material is available at European Heart Journal Open online.

**Funding**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Conflict of interest:** None declared.

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A validated score to predict one-year and long-term mortality in patients with significant tricuspid regurgitation

Schäfer U, Schofer J, Sievert H, Tang GHL, Thiele H, Topilsky Y, Rommel K-P, Delgado V, Vahanian A, Van Bardeleben RS, Webb JG, Weber M, Windecker S, Winkel M, Zuber M, Leon MB, Hahn RT, Bañ J, Enriquez-Sarano M, Maisano F. Transcatheter versus medical treatment of patients with symptomatic severe tricuspid regurgitation. J Am Coll Cardiol 2019;74:2998–3008.

11. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, Hahn RT, Han Y, Hung J, Lang RM, Little SH, Shah DJ, Sherman S, Thavendiranathan P, Thomas JD, Weissman NJ. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American society of echocardiography developed in collaboration with the society for cardiovascular magnetic resonance. J Am Soc Echocardiogr 2017;30:303–371.

12. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, O’Gara PT, Ruz CE, Skubas NJ, Sorajja P, Sundt TM, Thomas JD. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary. Circulation 2014;129:2440–2492.

13. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–612.

14. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Mor-Avi V, Mor-Avi V, Mor-Avi V. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American society of echocardiography and the European association of cardiovascular imaging. J Am Soc Echocardiogr 2015;28:1–39.e14.

15. Lindman BR, Maniar HS, Jaber WA, Leralsis S, Mack MJ, Suri RM, Thoumani VH, Babalaros V, Kereakesi DJ, Whisenant B, Miller DC, Tuzcu EM, Svensson LG, Xu K, Doshi D, Leon MB, Zajarias A. Effect of tricuspid regurgitation and the right heart on survival after transcatheter aortic valve replacement. Circ Cardiovasc Interv 2015;8:e002073.

16. Vahanian A, Beyersdorf F, Praz F, Mileovic M, Baldus S, Bauersachs J, Capodanno D, Conradi L, De Bonis M, De Paulis R, Delgado V, Freemantele N, Gilard M, Haugaa KH, Jeppsson A, Jüni P, Pierard L, Prendergast BD, Sădaba JR, Tribouilloy C, Wójcikowski W, ESC/EACTS Scientific Document Group. 2021 ESC/EACTS guidelines for the management of valvular heart disease: developed by the task force for the management of valvular heart disease of the European society of cardiology (ESC) and the European association for cardio-thoracic surgery (EACTS). Eur Heart J 2022;43:561–632.

17. Braunwald N, Ross J, Morrow AG. Conservative management of tricuspid regurgitation in patients undergoing mitral valve replacement. Circulation 1967;35:63.

18. Arbulo A, Holmes RJ, Afdhal I. Tricuspid valvulotomy without replacement. Twenty years’ experience. J Thorac Cardiovasc Surg 1991;102:917–922.

19. Topilsky Y, Inojosa JM, Benfari F, Vaturi O, Malais S, Michelena H, Mankad S, Enriquez-Sarano M. Clinical presentation and outcome of tricuspid regurgitation in patients with systolic dysfunction. Eur Heart J 2018;39:3584–3592.

20. Topilsky Y, Nikomy VT, Vatary O, Michelena H, Letourneau T, Suri RM, Pislaru S, Park S, Mahoney DW, Biner S, Enriquez-Sarano M. Clinical outcome of isolated tricuspid regurgitation. JACC Cardiovasc Imaging 2014;7:1185–1194.

21. Bar N, Schwartz LA, Biner S, Aviram G, Ingbir M, Nachmany I, Margolis G, Sadeh B, Barashi R, Keren G, Topilsky Y. Clinical outcome of isolated tricuspid regurgitation in patients with preserved left ventricular ejection fraction and pulmonary hypertension. J Am Soc Echocardiogr 2018;31:34–41.

22. Chorin E, Rozenbaum Z, Topilsky Y, Konigstein M, Ziv-Baran T, Richert E, Keren G, Banai S. Tricuspid regurgitation and long-term clinical outcomes. Eur Heart J Cardiovasc Imaging 2020;21:157–165.

23. Tsai P, Szekely Y, Lupo L, Ghantous E, Borohovitz A, Sadon S, Lichter Y, Ben-Gal Y, Banai A, Hochstadt A, Merdler I, Sapir O, Granot Y, Laufer-Perl M, Banai S, Topilsky Y. Risk prediction in patients with COVID-19 based on haemodynamic assessment of left and right ventricular function. Eur Heart J Cardiovasc Imaging 2021;22:1241–1254.

24. Wang TKM, Akyuz K, Mentias A, Kirinich E, Duran Crane A, Xu S, Popovic ZB, Xu B, Gillinov AM, Pettersson GB, Griffin BP, Desai MT. Contemporary etiologies, outcomes, and novel risk score for isolated tricuspid regurgitation. JACC Cardiovasc Imaging 2021;15(5):731–744.