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ORIGINAL ARTICLE

The MAGGIC risk score predicts mortality in patients undergoing transcatheter aortic valve replacement: sub-analysis of the OCEAN-TAVI registry

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Abstract

This study is aimed to evaluate the performance of MAGGIC risk score for predicting mortality by external validation using multicenter transcatheter aortic valve replacement (TAVR) registry. We assessed 1383 patients who underwent TAVR from October 2013 to April 2016. Patients were divided into 2 groups according to the median of MAGGIC score and we compared the incidence of all-cause death between high and low MAGGIC score. To assess whether the MAGGIC risk score add prognostic value on STS risk score, we also compared the incidence of all-cause death between the 2 groups according to low, intermediate, and high STS score. The median of MAGGIC score was 29 (interquartile range: 13–46). Within 2 years, 147 cases of all-cause death were observed. The high MAGGIC (30–46) risk score was significantly associated with an increased risk of all-cause death as compared to low MAGGIC (11–29) risk score and this relationship was also observed in patients with high STS risk score. However, this relationship was not observed in patients with low and intermediate STS score. Multivariate analysis showed that the MAGGIC risk score was an independent predictor of all-cause death (hazard ratio, 1.07; 95% confidence interval, 1.03–1.11). Our results demonstrated that the MAGGIC score predicts all-cause death in TAVR population and provides better risk stratification, particularly in patients with high STS risk.

Keywords Transcatheter aortic valve replacement · Mortality · MAGGIC risk score

Introduction

Transcatheter aortic valve replacement (TAVR) became mainstream and standard care for severe aortic valve stenosis (AS) [1, 2]. Moreover, its indication has been shifted

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and spread from high-operative risk to intermediate risk patients [3]. Due to expanded application of TAVR, a precise risk prediction is key to achieve the best clinical result. Recently, the Society of Thoracic Surgeons/American College of Cardiology (STS/ACC) TAVR score, developed from STS/ACC Transcatheter Valve Therapy Registry, provided better prediction model for in-hospital mortality [4] and externally validated in the German Cohort [5]. On the other hand, there are no risk scoring system to predict long-term adverse events after TAVR.

The most common symptom of AS on admission is exertional dyspnea due to heart failure (HF) [6]. The Meta-Analysis Global Group in Chronic (MAGGIC) heart failure risk score has been developed from 30 cohort studies to predict mortality in patients who admitted to hospital due to HF [7]. In current TAVR practice, we usually identify high-risk population based on the pre-procedural STS risk score. No data are so far available whether the MAGGIC risk score predicts mortality and could provide additional prognostic value on risk stratification using STS score in TAVR cohort or not.

Therefore, we sought to evaluate the clinical validation of MAGGIC risk score for predicting mortality in patients who underwent TAVR and to assess its prognostic value according to low, intermediate, and high STS risk score.

Methods

Study population

Retrospective analysis was performed using data from the OCEAN (Optimized transCathEter vAlvular interveNtion) TAVI registry. The OCEAN-TAVI is a prospective, multicenter, observational registry of symptomatic severe AS patients who undergo TAVR at 14 hospitals in Japan. This trial was registered with the University Hospital Medical Information Network Clinical Trials Registry, as accepted by the International Committee of Medical Journal Editors (UMIN000020423). AS patients with following conditions were included: a) degenerative AS; b) a mean gradient > 40 mmHg or a jet velocity greater than 4.0 m/s; and/or c) an aortic valve area < 1.0 cm^2 (or an effective orifice area Index < 0.6 cm^2/m^2). An indication of TAVR was determined based on clinical consensus of heart team including cardiac surgeons, interventional cardiologists, anesthetists, and imaging specialists. Exclusion criteria were: (a) failed surgical bioprosthesis implantation and/or (b) severe aortic regurgitation. The study protocol was developed in accordance with the Declaration of Helsinki and was approved by the ethics committee of each participating hospital. All patients gave informed consent before participating in this study.

Assessment of meta-analysis global group in chronic (MAGGIC) heart failure risk score

All participants were calculated with the MAGGIC risk score according baseline patients' characteristics. The details of the MAGGIC risk score has been reported previously [7]. Briefly, the MAGGIC risk score consisted 13 variables including age, gender, body mass index (BMI), smoking history, diabetes mellitus (DM), New York Heart Association (NYHA) class, left ventricular ejection fraction (LVEF), chronic obstructive pulmonary disease (COPD), heart failure duration, serum creatinine, beta-blocker and angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB). This score was developed from 30 cohort studies including 39372 patients with HF to predict the mortality. Its clinical utility was externally validated in the Swedish Heart Failure Registry [8].

Clinical endpoint

The endpoint of this study was all-cause death after TAVR. The procedural complications were determined based on the definition of Valve Academic Research Consortium (VARC–2) criteria [9].

Statistical analysis

Continuous variables were assessed for normal distribution using the Shapiro–Wilk test and presented as mean ± standard deviation or median and interquartile range (IQR), as appropriate. Dichotomous variables were described as numbers and percentages. To stratify simple category, we divided all patients into two groups according to the median value of MAGGIC risk score on admission. Two groups were classified as low MAGGIC group (the MAGGIC score was lower than or equal to the median value of the MAGGIC risk score) and high MAGGIC score (the MAGGIC score was higher than the median value of the MAGGIC risk score). Differences between the two groups were compared using the Chi-square test for categorical variables and Student's *t* tests or Wilcoxon rank-sum tests, as appropriate, for continuous variables. The Kaplan–Meier test was used to estimate the incidence of all-cause death after TAVR and the difference of survival between two MAGGIC groups was compared using log-rank test. Multivariate Cox regression analysis was applied to evaluate the impact of MAGGIC level on all-cause death after TAVR. Confounders in multivariate analysis were determined based on clinical significance and multicollinearity. Age, gender, BMI, DM, current smoking, COPD, NYHA class on admission, LVEF, systolic blood pressure, serum creatinine level, history of

chronic heart failure, an administration of ACE-I or ARB, and an administration of beta blocker were not included in multivariate model because these variables were included in the MAGGIC risk score. Finally, the following confounders were entered in multivariate Cox model: clinical frail scale (CFS); atrial fibrillation (AF); low serum albumin level (< 3.5 g/dL); stroke; peripheral artery disease (PAD); coronary artery disease (CAD); diuretic use; and mean aortic valve pressure gradient. To assess whether the MAGGIC risk score add an additional prognostic value on STS risk score among different STS risk score, Kaplan–Meier tests and Cox-regression analysis using the same confounders were also performed according to low, intermediate, and high STS score subgroups. Statistical analysis was performed using the Statistical Package for Social Sciences, version 21 (SPSS Inc., Chicago, IL, USA) software. A p value was 2-sided and a value < 0.05 was considered statistically significant.

Results

Baseline characteristics

Out of 1613 patients in the OCEAN-TAVI registry, 230 patients (14.3%) with data of missing blood pressure were excluded. The remaining 1383 patients (85.7%) were included in this analysis (Fig. 1).

The median value of the MAGGIC risk score was 29 (IQR: 26–32). Patients' clinical and procedural characteristics are shown in Table 1. The patients with high MAGGIC score had significantly higher proportion of elderly and male, lower BMI, higher CFS, higher incidence of advanced NYHA class, DM, chronic kidney disease (CKD), COPD, AF, CAD, PAD, stroke, low serum albumin, low systolic blood pressure and high STS score as compared to those with low MAGGIC score. In index of echocardiographic findings, mean aortic valve pressure gradient and left ventricular ejection fraction were significantly lower in patients with high MAGGIC score than those with low MAGGIC score. There were no differences of procedure indices between two groups. The patients with high MAGGIC score had higher incidence of in-hospital mortality (4.4% vs. 1.4%, $p < 0.01$), life-threatening bleeding (8.0% vs. 4.0%, $p < 0.01$), and acute kidney injury (10.0% vs. 7.1%, $p = 0.05$) after TAVR. Moreover, these entities required longer hospital stay than those with low MAGGIC score [17 (11–28) days vs. 15 (10–22) days, $p < 0.01$].

Incidence of endpoints

During 2-year follow-up, there were 147 cases (10.6%) of all-cause death, including 38.1% ($n = 56$) of cardiovascular death and 61.9% ($n = 91$) of non-cardiovascular death.

The Kaplan–Meier curve demonstrated that the patients with high MAGGIC score had higher incidence of all-cause death as compared to those with low MAGGIC score (14.4% vs. 7.3%, log-rank $P < 0.01$) (Fig. 2). Multivariate Cox regression analysis demonstrated that the MAGGIC risk score, as a continuous variable, was significantly associated with the higher incidence of all-cause death (HR, 1.07; 95% CI, 1.07–1.11) (Table 2). To assess whether this prognostic value of MAGGIC risk score was consistent among low, intermediate, and high STS risk score, we assessed Kaplan–Meier tests and multivariate Cox regression analysis in these three sub-group. Of 1383 analyzed patients, 18.0% ($n = 249$) had low STS risk score, 47.0% ($n = 650$) had intermediate STS risk score, and 35.0% ($n = 484$) had high STS risk score. The Kaplan–Meier test demonstrated that the high MAGGIC risk score was associated with higher mortality as compared to low MAGGIC risk score in patients with high STS risk score (19.8% vs. 9.4%, log-rank $p < 0.01$) (Fig. 3c). On contrary, the incidence of mortality was not significantly different between high and low MAGGIC risk score in patients with intermediate STS risk score (9.5% vs. 6.0%, log-rank $p = 0.17$) (Fig. 3b) and those with low STS

Fig. 1 Study population

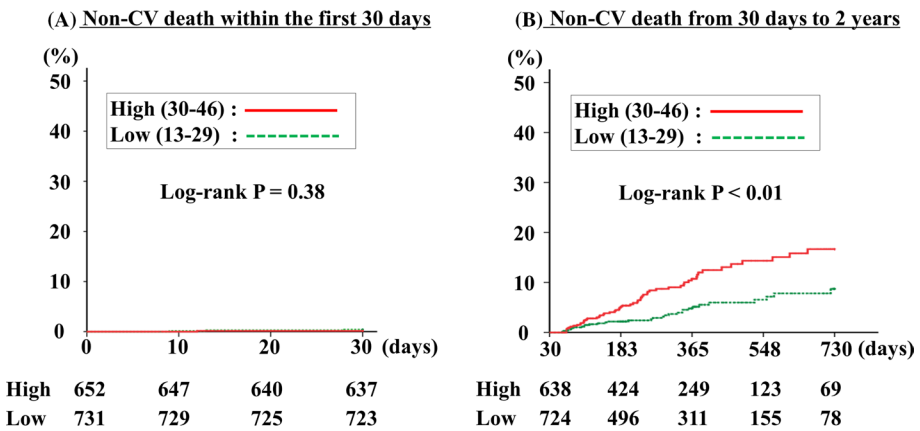

Table 1 Patients' characteristics

Variables	Overall ($n=1383$)	Low MAGGIC score ($n=731$)	High MAGGIC score ($n=652$)	p value
Age (years)	85 [81–88]	84 [80–87]	86 [82–89]	<0.01
Men	413 (29.9%)	178 (24.4%)	235 (36.0%)	<0.01
Body mass index (kg/m^2)	22.0 [19.6–24.4]	22.8 [20.5–25.1]	21.0 [18.9–23.4]	<0.01
Clinical frailty scale	4 [3–5]	4 [3, 4]	4 [3–5]	<0.01
Congestive heart failure	1135 (82.1%)	538 (73.6%)	597 (91.6%)	<0.01
NYHA class III/IV	701 (50.7%)	174 (23.8%)	527 (80.8%)	<0.01
Current smoking	40 (2.9%)	19 (2.6%)	21 (3.2%)	0.49
Dyslipidemia	605 (43.7%)	322 (44.0%)	283 (43.4%)	0.81
Diabetes mellitus	367 (26.5%)	117 (16.0%)	250 (38.3%)	<0.01
Hypertension	1089 (78.7%)	576 (78.8%)	513 (78.7%)	0.96
Chronic kidney disease	825 (59.7%)	364 (49.8%)	461 (70.7%)	<0.01
Chronic obstructive pulmonary disease	259 (18.7%)	89 (12.2%)	170 (26.1%)	<0.01
Atrial fibrillation	289 (20.9%)	123 (16.8%)	166 (25.5%)	<0.01
Coronary artery disease	409 (29.6%)	191 (26.1%)	218 (33.4%)	<0.01
Peripheral artery disease	201 (14.5%)	79 (10.8%)	122 (18.7%)	<0.01
Stroke	213 (15.4%)	98 (13.4%)	115 (17.6%)	0.03
Serum albumin (g/dL)	3.8 [3.5–4.1]	3.9 [3.6–4.1]	3.7 [3.3–4.0]	<0.01
STS score	6.59 [4.90–9.33]	5.53 [3.80–7.60]	7.91 [5.80–11.80]	<0.01
Systolic blood pressure on admission	126 [114–138]	130 [118–141]	122 [110–135]	<0.01
Echocardiogram finding				
Mean aortic valve pressure gradient (mmHg)	48 [38–61]	49 [39–62]	46 [36–60]	0.01
Aortic valve area index (cm^2/m^2)	0.44 [0.36–0.52]	0.44 [0.36–0.52]	0.43 [0.36–0.51]	0.12
Left ventricular ejection fraction (%)	62 [53–68]	63 [56–68]	61 [49–67]	<0.01
Medications on admission				
Angiotensin converting enzyme inhibitor or Angiotensin receptor blocker	754 (54.5%)	427 (58.4%)	327 (50.2%)	<0.01
Beta blocker	457 (33.0%)	293 (40.1%)	164 (25.2%)	<0.01
Diuretics	747 (54.0%)	323 (44.2%)	424 (65.0%)	<0.01
Procedure index				
Transfemoral approach	1110 (80.3%)	595 (81.4%)	515 (79.0%)	0.26
Valve type				
Balloon-expandable valve	1254 (90.7%)	667 (91.2%)	587 (90.0%)	0.44
Self-expandable valve	129 (9.3%)	64 (8.8%)	65 (10.0%)	
Local anesthesia	168 (12.1%)	84 (11.5%)	84 (12.9%)	0.43
Pre-dilatation	1078 (77.9%)	568 (77.7%)	510 (78.2%)	0.82
Post-dilatation	280 (20.2%)	152 (20.8%)	128 (19.6%)	0.59
Procedure time (min)	80 [58–103]	81 [59–102]	79 [58–105]	0.86

Data are presented as mean ± standard deviation, median [interquartile ranges], or n (percentages)

risk score (6.8% vs. 7.8%, log-rank $p=0.95$) (Fig. 3a). Multivariate analysis demonstrated that the prognostic value of MAGGIC risk score was also observed in patients with high STS risk score (Table 2). Within the patients with intermediate STS risk score, there was a trend that the MAGGIC risk score might be related to an increased incidence of all-cause death after TAVR. On contrary, in patients with low STS risk score, the MAGGIC risk score had no additional prognostic value on predicting mortality after TAVR.

Discussion

The main findings of current study on patients who underwent TAVR are: (1) the high MAGGIC score (ranging 30–44) was significantly associated with higher incidence of all-cause death; and (2) the MAGGIC risk score provided further risk stratification for mortality, particularly in patients with high STS risk score. To our best knowledge, this is the first report to verify the clinical validation

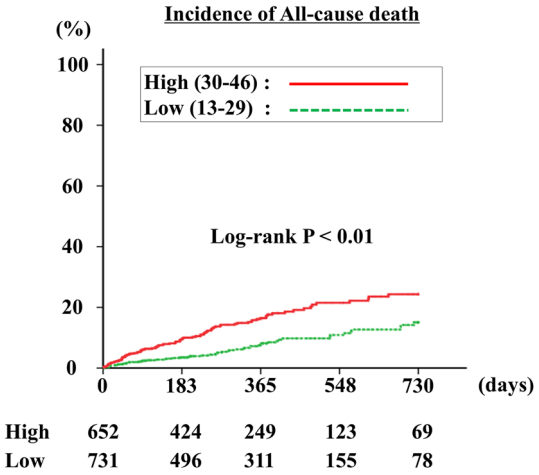

Fig. 2 Kaplan–Meier analysis of all-cause death according to MAGGIC risk score. The incidence of all-cause death was significantly higher in patients with high MAGGIC risk score (30–46) than those with low MAGGIC risk score (11–29) (14.4% vs. 7.3%, log-rank $p < 0.01$)

of MAGGIC risk score for predicting all-cause death after TAVR.

HF was highly associated with mortality and, therefore, the simple scoring system has been warranted to predict the mortality in HF patients. Recent study has demonstrated the best accuracy to predict mortality using MAGGIC risk score as compared with other prognostic risk score in general HF patients [11]. The previous large registries have showed that an approximately 80% of patients who undergo TAVR have NYHA functional class III or IV on admission [12–14]. For these reasons, the current analysis mainly focused on whether the MAGGIC risk score could be validated in patients who undergo TAVR or not.

We showed that high MAGGIC score, coded as higher than the median value of the MAGGIC risk score, was related to higher incidence of all-cause death. Within the component of MAGGIC risk score, the previous studies have reported that CKD, low EF, low BMI, male, COPD, and DM were associated with higher mortality after TAVR [15–20]. So far, no literature has mentioned the impact of impaired NYHA functional status on morality in TAVR population. However, an advanced NYHA functional class (III or IV) was associated with higher incidence of mortality in general HF population [21]. Therefore, the impaired NYHA class could be an independent predictor of mortality in patients who undergo TAVR. Though medical therapy, using renin–angiotensin system blocker or beta-blocker, might be prone to hypotension and considered as contraindication in patients with severe aortic stenosis, the previous studies have demonstrated their safety and efficacy on clinical outcome [22, 23]. These might be reason why high MAGGIC risk score was associated with higher incidence of all-cause death in patients undergoing TAVR.

Another interesting finding of our study was the MAGGIC risk score could provide further risk stratification on mortality, particularly in patients with high STS risk. Indeed, even in high STS risk score, patients with low MAGGIC risk score had comparable incidence of all-cause death as compared with patients with intermediate STS risk score. The previous studies demonstrated that each of the MAGGIC and STS risk score could predict long-term survival after TAVR [7, 10]. Moreover, in terms of variables used in risk score, characteristics of the MAAGIC risk score include duration of heart failure as variable. The previous study demonstrated that duration of heart failure predicts mortality independently of risk factors such as advanced age, severe NYHA class, renal dysfunction, and atherosclerotic disease [24]. Therefore, these might be reason why the MAGGIC risk score could add an additional predictive value for predicting mortality on STS risk score in TAVR population. Though the patients with high STS risk score were considered to have worse clinical outcome, our results might be very useful for TAVR operator to stratify lower risk

Table 2 Impact of the MAGGIC risk score on all-cause death after TAVR

	Unadjusted		Adjusted	
	HR (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Overall	1.12 (1.08–1.15)	< 0.01	1.07 (1.03–1.11)	< 0.01
Sub-group analysis				
Low STS score	1.07 (0.96–1.19)	0.26	1.05 (0.93–1.18)	0.42
Intermediate STS score	1.10 (1.02–1.18)	0.01	1.07 (0.99–1.16)	0.08
High STS score	1.10 (1.05–1.15)	< 0.01	1.07 (1.02–1.13)	< 0.01

In the multivariate model, the adjusted hazard ratio (HR) of the Meta-Analysis Global Group in Chronic (MAGGIC) risk score, as a continuous variable, for all-cause death was calculated by adjusting variables. The adjusting variables in multivariate model included clinical frail score; atrial fibrillation; low serum albumin level (< 3.5 g/dL); history of coronary artery disease; history of peripheral artery disease; history of stroke; diuretic use; and mean aortic valve pressure gradient

CI confidence interval, *TAVR* transcatheter aortic valve replacement

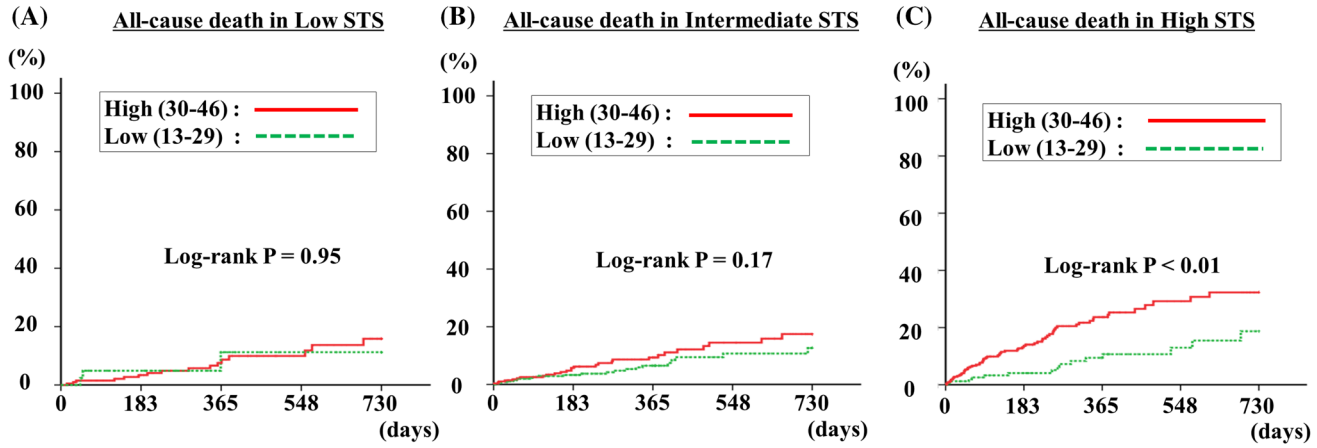

Fig. 3 Kaplan–Meier analysis of all-cause death according to MAGGIC risk score among STS subgroups. **a**, **b** In patients with low and intermediate STS risk score, the incidence of all-cause death was comparable between high MAGGIC risk score (30–46) and low MAGGIC risk score (11–29) (6.8% vs. 7.8%, log-rank $p=0.95$; 9.5 vs. 6.0%, log-rank $p=0.17$, respectively). **c** In patients with high STS risk score, the incidence of all-cause death was significantly higher in patients with high MAGGIC risk score as compared to those with low MAGGIC risk score (19.8% vs. 9.4%, log-rank $p<0.01$)

subgroup using the MAGGIC risk score even in the patients with high STS risk score.

Eventually, the high MAGGIC risk score, particularly coded as the higher value of median MAGGIC risk score, could predict all-cause death after TAVR, mainly derived from non-cardiovascular death. Several studies have demonstrated that obesity, DM, blood pressure, and smoking, which were included in the MAGGIC risk score, were associated with higher incidence of death by malignant disease [25]. Furthermore, the presence of COPD, reduced glomerular filtration rate, and DM were highly related with infection-related mortality in general elderly population [26–28]. According to these studies, prevention and early intensive management for infection should be done to achieve lower morality after TAVR. Further research is required to assess whether the combination of the MAGGIC risk score and patients' frailty, i.e. gait speed or clinical frailty scale, could provide further prognostic value on mortality after TAVR, as another scientific interest.

Limitations

There were several limitations in this analysis. First, this is a retrospective analysis of prospective multicenter study. Second, about 15% of patients were excluded due to lack of data, particularly blood pressure on admission. However, variables, which include in the MAGGIC risk score, were not different between patients included and excluded (Supplementary Table). And third, because the MAGGIC risk score was developed from 13 studies including HF patients aged 60–70 years, this risk score did not include the patients' condition, particularly frailty. Therefore, it might be underpowered to apply this risk score for patients undergoing TAVR who had generally advanced age. Further study is required to assess whether the combination of MAGGIC risk score and patients' frailty have better prognostic value in patients undergoing TAVR.

Conclusion

In TAVR population, high MAGGIC risk score was significantly associated with higher incidence of all-cause death as compared with low MAGGIC risk score. Even in high STS risk score, patients with low MAGGIC risk score had lower incidence of all-cause death as comparable as the patients with intermediate STS risk score. Another clinical study is warranted to further investigate the impact of combination of MAGGIC risk score and frailty on mortality to predict clinical outcome after TAVR.

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Compliance with ethical standards

Conflict of interest The authors report no relationships that could be construed as conflict of interest.

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