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ORIGINAL ARTICLE

# Cystatin C in risk prediction after transcatheter aortic valve replacement: a retrospective analysis

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## Abstract

**Aims** No study has evaluated the prognostic value of the chronic kidney disease (CKD) classification by cystatin C-based estimated glomerular filtration rate (eGFR) ($CKD_{Cys}$ classification) in patients undergoing transcatheter aortic valve replacement (TAVR). This study aimed to compare the prognostic value of $CKD_{Cys}$ classification and CKD classification by creatinine-based eGFR ($CKD_{Cr}$ classification) in risk prediction after TAVR.

**Methods and results** We retrospectively analysed consecutive 219 patients with symptomatic severe aortic stenosis who underwent TAVR at our institute between December 2016 and June 2019. Pre-operative $CKD_{Cr}$ and $CKD_{Cys}$ classifications were evaluated for their prognostic value of 2-year major adverse cardiovascular and cerebrovascular events (MACCE) after TAVR. MACCE was defined as the composite of all-cause mortality, non-fatal myocardial infarction, stroke, and rehospitalization for worsening congestive heart failure. Participants had a median age of 86.0 years and were predominantly female (76.9%). In 96.6% of the cases, TAVR was performed using transfemoral access. The median creatinine-based eGFR (52.85 mL/min/1.73 $m^2$) was higher than the cystatin C-based eGFR (41.50 mL/min/1.73 $m^2$). Downward reclassification in CKD stages based on $eGFR_{Cys}$ was observed in 49.0% of patients. During a median follow-up period of 575.5 (interquartile range: 367.0–730.0) days, 58 patients presented with MACCE. $CKD_{Cys}$ classification, but not $CKD_{Cr}$ classification, significantly stratified the risk of 2-year MACCE in patients after TAVR by log-rank test ($P$ = 0.003). In multivariate Cox regression analysis, only $CKD_{Cys}$ stage 3b [hazard ratio (HR) = 4.37; 95% confidence interval (CI): 1.28–14.91; $P$ = 0.019] and $CKD_{Cys}$ stage 4 + 5 (HR = 3.72; 95% CI: 1.06–12.99; $P$ = 0.040) were significant predictors of MACCE after adjustment for potential confounders.

**Conclusions** The $CKD_{Cys}$ classification could better assess the risk than the $CKD_{Cr}$ classification in patients undergoing TAVR. $CKD_{Cys}$ stage 3b and stage 4 + 5 correlated with adverse outcomes.

**Keywords** CKD; Creatinine; Cystatin C; Glomerular filtration rate; Transcatheter aortic valve replacement

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## Introduction

Chronic kidney disease (CKD) has been an independent predictor of adverse outcomes in patients after transcatheter aortic valve replacement (TAVR).[1,2] In addition, the classification of CKD based on estimated glomerular filtration rate (eGFR) was reported to be useful in the stratification of risk after the procedure.[3–6] Creatinine-based eGFR ($eGFR_{Cr}$) has been used most commonly in clinical practice. However, serum creatinine levels are influenced by several other factors besides the glomerular filtration rate (GFR) such as age, sex, race, and muscle mass,[7,8] resulting in inaccuracy in estimating GFR.

Cystatin C, an alternative marker of GFR that is less influenced by age, sex, race, and muscle mass than other markers,[7,8] is reported to be superior to creatinine for estimating GFR in elderly patients.[9] Cystatin C-based eGFR ($eGFR_{Cys}$) is also known to be a more powerful predictor of mortality than $eGFR_{Cr}$ in the general population cohort.[10]

No study has evaluated the prognostic meaning of CKD classification based on $eGFR_{Cys}$ ($CKD_{Cys}$ classification) in

patients undergoing TAVR. This study aimed to compare the prognostic value of $CKD_{Cys}$ classification and CKD classification based on $eGFR_{Cr}$ ($CKD_{Cr}$ classification) in the prediction of risk after TAVR.

# Methods

## Study design

Herein, we describe a single-centre retrospective observational study that consecutively enrolled 219 patients with symptomatic severe aortic stenosis who underwent TAVR at our institute between December 2016 and June 2019. TAVR is indicated for inoperable patients or those at high risk of surgical aortic valve replacement based on the consensus of the institutional heart team. The review board of the Kyoto Prefectural University of Medicine approved a study protocol conforming to the Declaration of Helsinki, and informed consent was obtained in the form of opt-out via the institutional website. Those who rejected it were excluded from this study.

## Assessment of renal function

Pre-operative creatinine and cystatin C values were measured for samples obtained at the same time point after the admission for TAVR. The measurements were taken up to 1 day before TAVR to avoid the influence of pre-operative hydration. Then, $eGFR_{Cys}$ was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula,[11] and $eGFR_{Cr}$ was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula modified with Japanese coefficient (0.813).[12] Based on the pre-operative $eGFR_{Cr}$ and $eGFR_{Cys}$, the study cohort was classified into four groups: eGFR $\geq$ 60 mL/min/1.73 $m^2$ (CKD stage 1 + 2), 60 $>$ eGFR $\geq$ 45 mL/min/1.73 $m^2$ (CKD stage 3a), 45 $>$ eGFR $\geq$ 30 mL/min/1.73 $m^2$ (CKD stage 3b), and 30 $>$ eGFR mL/min/1.73 $m^2$ (CKD stage 4 + 5).[13] Patients on regular haemodialysis were not included in this cohort because TAVR was not applicable for them in Japan during the study period. CKD classifications by $eGFR_{Cr}$ ($CKD_{Cr}$ classification) and $eGFR_{Cys}$ ($CKD_{Cys}$ classification) were evaluated for their prognostic value for adverse events after TAVR. Eleven patients were excluded for missing pre-operative cystatin C values. The final study cohort included 208 patients.

## Endpoint and patient follow-up

The endpoint of this study was the 2-year cumulative incidence of major adverse cardiovascular and cerebrovascular events (MACCE). MACCE was defined as the composite of all-cause mortality, non-fatal myocardial infarction, stroke, and rehospitalization for worsening congestive heart failure. Other TAVR-related outcomes and complications were classified according to the Valve Academic Research Consortium-2 criteria.[14] The follow-up started on the day of TAVR, and the peri-interventional complications were also rated as MACCE during follow-up in our study. All information was retrospectively obtained from patients' medical records or telephone interviews.

## Transcatheter aortic valve replacement procedures

All patients received either a balloon-expandable device (Edwards SAPIEN XT or SAPIEN 3 prosthesis, Edwards Lifesciences, Irvine, CA) or a self-expandable device (CoreValve, Evolut R, or Evolut PRO, Medtronic, Minneapolis, MN). The choice of the prosthesis and approach (transfemoral, trans-subclavian, or transaortic) was at the operator's decision based on the pre-procedural assessment by multidetector computed tomography and echocardiography. All patients except for one were treated under general anaesthesia.

## Statistical analysis

Continuous variables are presented as the mean ± standard deviation (SD) or median and interquartile range (IQR; 25–75%) depending on the variable distribution. Data normality was assessed using the Shapiro–Wilk test. Categorical valuables are expressed as numbers with percentages. Intergroup comparisons for continuous variables were performed using the one-way analysis of variance for parametric variables or the Kruskal–Wallis test for non-parametric variables. Categorical variables were compared using the $\chi^2$ test. The agreement between $eGFR_{Cr}$ and $eGFR_{Cys}$ was analysed using a Bland–Altman plot. The Kaplan–Meier method was used to estimate the cumulative rates of 2-year MACCE in the four groups stratified by $CKD_{Cr}$ or $CKD_{Cys}$ classification. Survival differences in each group were compared using log-rank tests. Bonferroni test for post hoc comparisons was conducted when the log-rank test determined significance. A univariate Cox regression analysis was performed to obtain the hazard ratio (HR) of each variable on 2-year MACCE. Then, a multivariate analysis was performed using the variables with $P$ values $< 0.1$ in the univariate analysis to examine the independent association of $CKD_{Cr}$ or $CKD_{Cys}$ classification with 2-year MACCE. Although not significant in univariate analysis, age and sex were forced into the multivariate analysis because they were highly related to long-term outcomes. All statistical tests were two-sided, and $P$ values $< 0.05$ were considered significant. All statistical analyses were performed


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**Table 1** Baseline patient characteristics

| Variable | Overall ($n$ = 208) | $CKD_{Cys}$ stage 1 + 2 ($n$ = 33) | $CKD_{Cys}$ stage 3a ($n$ = 57) | $CKD_{Cys}$ stage 3b ($n$ = 60) | $CKD_{Cys}$ stage 4 + 5 ($n$ = 58) | $P$ value |
|---|---|---|---|---|---|---|
| Age (years) | 86.0 [84.0, 89.0] | 85.0 [82.0, 86.0] | 86.0 [84.0, 88.0] | 87.0 [84.0, 89.0] | 88.5 [84.3, 91.0] | 0.003 |
| Male | 48 (23.1) | 7 (21.2) | 11 (19.3) | 21 (35.0) | 9 (15.5) | 0.066 |
| BMI (kg/m$^2$) | 21.03 [19.02, 23.66] | 21.11 [18.83, 23.69] | 21.50 [18.44, 24.24] | 20.21 [19.11, 22.51] | 21.05 [19.18, 23.50] | 0.850 |
| Logistic EuroSCORE (%) | 13.57 [10.74, 19.27] | 12.08 [8.99, 15.46] | 12.50 [10.74, 18.26] | 13.97 [10.61, 20.12] | 15.65 [11.56, 24.03] | 0.006 |
| STS score (%) | 6.26 [4.83, 9.16] | 4.86 [4.05, 6.00] | 5.74 [4.63, 7.92] | 7.04 [5.36, 8.96] | 8.63 [5.74, 12.16] | <0.001 |
| NYHA class III or IV | 81 (38.9) | 7 (21.2) | 19 (33.3) | 23 (38.3) | 32 (55.2) | 0.009 |
| Peripheral artery disease | 45 (21.6) | 3 (9.1) | 12 (21.1) | 11 (18.3) | 19 (32.8) | 0.053 |
| Prior MI | 14 (6.7) | 3 (9.1) | 3 (5.3) | 3 (5.0) | 5 (8.6) | 0.776 |
| Prior PCI | 59 (28.4) | 8 (24.2) | 16 (28.1) | 14 (23.3) | 21 (36.2) | 0.427 |
| Prior CABG | 9 (4.3) | 1 (3.0) | 3 (5.3) | 2 (3.3) | 3 (5.2) | 0.919 |
| Prior other cardiac surgery | 3 (1.4) | 0 (0.0) | 1 (1.8) | 1 (1.7) | 1 (1.7) | 0.902 |
| Prior balloon aortic valvuloplasty | 16 (7.7) | 0 (0.0) | 6 (10.5) | 1 (1.7) | 9 (15.5) | 0.009 |
| Prior stroke | 30 (14.4) | 6 (18.2) | 15 (26.3) | 6 (10.0) | 3 (5.2) | 0.008 |
| Prior PPM | 17 (8.2) | 0 (0.0) | 6 (10.5) | 6 (10.0) | 5 (8.6) | 0.303 |
| Atrial fibrillation | 56 (26.9) | 4 (12.1) | 12 (21.1) | 18 (30.0) | 22 (37.9) | 0.036 |
| COPD | 19 (9.1) | 2 (6.1) | 2 (3.5) | 8 (13.3) | 7 (12.1) | 0.219 |
| Smoking | 40 (19.2) | 7 (21.2) | 8 (14.0) | 14 (23.3) | 11 (19.0) | 0.631 |
| Hypertension | 139 (66.8) | 23 (69.7) | 35 (61.4) | 42 (70.0) | 39 (67.2) | 0.764 |
| Dyslipidaemia | 87 (41.8) | 20 (60.6) | 26 (45.6) | 27 (45.0) | 14 (24.1) | 0.005 |
| Diabetes mellitus | 37 (17.8) | 8 (24.2) | 8 (14.0) | 9 (15.0) | 12 (20.7) | 0.543 |
| Treatment | | | | | | |
| ACEI/ARB | 97 (46.6) | 14 (42.4) | 26 (45.6) | 28 (46.7) | 29 (50.0) | 0.914 |
| Beta-blockers | 90 (43.3) | 16 (48.5) | 22 (38.6) | 22 (36.7) | 30 (51.7) | 0.305 |
| Diuretics | 136 (65.4) | 7 (21.2) | 34 (59.6) | 47 (78.3) | 48 (82.8) | <0.001 |
| Anticoagulants | 54 (26.0) | 3 (9.1) | 13 (22.8) | 17 (28.3) | 21 (36.2) | 0.036 |
| Pre-procedural laboratory data | | | | | | |
| Haemoglobin (g/dL) | 10.93 ± 1.67 | 11.76 ± 1.71 | 10.81 ± 1.53 | 11.41 ± 1.46 | 10.07 ± 1.59 | <0.001 |
| Albumin (g/dL) | 3.70 [3.40, 4.10] | 3.80 [3.60, 4.20] | 3.80 [3.40, 4.10] | 3.70 [3.48, 3.92] | 3.60 [3.23, 3.98] | 0.058 |
| BNP (pg/mL) | 300.05 [138.77, 562.52] | 183.20 [77.60, 431.10] | 214.40 [87.10, 541.60] | 313.50 [160.35, 522.77] | 404.85 [222.53, 898.92] | 0.001 |
| Creatinine (mg/dL) | 0.88 [0.69, 1.17] | 0.64 [0.56, 0.73] | 0.75 [0.62, 0.80] | 0.93 [0.81, 1.10] | 1.28 [1.14, 1.64] | <0.001 |
| $eGFR_{Cr}$ (mL/min/1.73 m$^2$) | 52.85 [36.59, 64.23] | 67.48 [64.23, 70.73] | 61.79 [56.10, 66.67] | 47.97 [42.28, 56.30] | 30.89 [25.41, 36.38] | <0.001 |
| Cyctatin C (mg/L) | 1.43 [1.17, 1.93] | 0.96 [0.91, 1.02] | 1.25 [1.15, 1.30] | 1.54 [1.44, 1.66] | 2.13 [1.99, 2.41] | <0.001 |
| $eGFR_{Cys}$ (mL/min/1.73 m$^2$) | 41.50 [28.00, 54.00] | 71.00 [64.00, 75.00] | 50.00 [46.00, 56.00] | 38.50 [33.75, 41.00] | 23.50 [20.25, 26.75] | <0.001 |
| Echocardiographic data | | | | | | |
| LVEF (%) | 61.00 [51.00, 68.00] | 62.00 [54.00, 68.00] | 61.00 [54.00, 68.00] | 59.50 [50.75, 70.00] | 60.00 [49.25, 66.00] | 0.761 |
| AVA (cm$^2$) | 0.55 [0.41, 0.67] | 0.60 [0.50, 0.69] | 0.58 [0.43, 0.68] | 0.50 [0.40, 0.60] | 0.60 [0.48, 0.70] | 0.091 |
| Peak velocity (m/s) | 4.56 ± 0.72 | 4.76 ± 0.80 | 4.63 ± 0.66 | 4.55 ± 0.72 | 4.40 ± 0.72 | 0.123 |
| Mean aortic valve gradient (mmHg) | 49.50 [40.00, 62.00] | 54.00 [41.00, 71.00] | 51.00 [41.00, 62.00] | 51.50 [41.50, 62.25] | 46.05 [37.10, 57.38] | 0.168 |
| AR grade ≧ 2 | 59 (28.4) | 8 (24.2) | 14 (24.6) | 16 (26.7) | 21 (36.2) | 0.471 |
| MR grade ≧ 2 | 33 (15.9) | 0 (0.0) | 10 (17.5) | 8 (13.3) | 15 (25.9) | 0.012 |

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AR, aortic regurgitation; AVA, aortic valve area; BMI, body mass index; BNP, B-type natriuretic peptide; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; $eGFR_{Cr}$, creatinine-based eGFR; $eGFR_{Cys}$, cystatin C-based eGFR; EuroSCORE, European System for Cardiac Operative Risk Evaluation; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MR, mitral regurgitation; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PPM, permanent pacemaker; STS, Society of Thoracic Surgeons.
Values are expressed as mean ± standard deviation, median [interquartile range], or $n$ (%).

**Figure 1** Bland–Altman plot showing the within-person difference between creatinine-based eGFR ($eGFR_{Cr}$) and cystatin C-based eGFR ($eGFR_{Cys}$) obtained by the Chronic Kidney Disease Epidemiology Collaboration formula. eGFR, estimated glomerular filtration rate; SD, standard deviation.

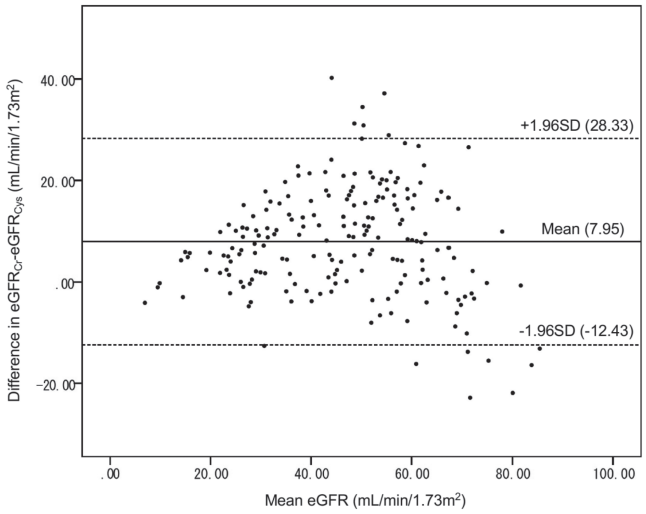


**Table 2** Reclassification across CKD stages by cystatin C-based eGFR from CKD stages by creatinine-based eGFR

| | | CKD classification by $eGFR_{Cys}$ | | | | |
|---|---|---|---|---|---|---|
| | | $CKD_{Cys}$ stage 1 + 2 | $CKD_{Cys}$ stage 3a | $CKD_{Cys}$ stage 3b | $CKD_{Cys}$ stage 4 + 5 | Total |
| CKD classification by $eGFR_{Cr}$ | $CKD_{Cr}$ stage 1 + 2 | 31 (42.5%) | 31 (42.5%) | 10 (13.7%) | 1 (1.4%) | 73 |
| | $CKD_{Cr}$ stage 3a | 2 (3.4%) | 24 (41.4%) | 29 (50.0%) | 3 (5.2%) | 58 |
| | $CKD_{Cr}$ stage 3b | 0 (%) | 2 (4.2%) | 18 (37.5%) | 28 (58.3%) | 48 |
| | $CKD_{Cr}$ stage 4 + 5 | 0 (%) | 0 (0%) | 3 (10.3%) | 26 (89.7%) | 29 |
| | Total | 33 | 57 | 60 | 58 | 208 |

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; $eGFR_{Cr}$, creatinine-based eGFR; $eGFR_{Cys}$, cystatin C-based eGFR. The number (percentage) of participants reclassified to the corresponding $CKD_{Cys}$ stages is shown.

using R software packages (Version 3.6.3; R Development Core Team, Auckland, New Zealand) or SPSS statistics Version 22 (IBM Corporation, Armonk, NY).

# Results

## Baseline patient characteristics

The patient baseline characteristics are summarized in *Table 1*. The median age of the entire cohort was 86.0 years, and 76.9% were female. The median Society of Thoracic Surgeons (STS) score was 6.26%. The percentage of patients categorized as NYHA class III or IV was 38.9%. The median $eGFR_{Cr}$ was 52.85 mL/min/1.73 $m^2$ and the median $eGFR_{Cys}$ was 41.50 mL/min/1.73 $m^2$. Age, Logistic EuroSCORE, STS score, and the proportion of patients with NYHA class III or IV were significantly higher at the more advanced CKD stages.

The Bland–Altman plot showed a mean difference of 7.95 ± 10.43 mL/min/1.73 $m^2$, ranging from −22.84 to 40.23 mL/min/1.73 $m^2$ between $eGFR_{Cr}$ and $eGFR_{Cys}$ with proportional bias (*Figure 1*). The reclassification of the $eGFR_{Cr}$ CKD stages by $eGFR_{Cys}$ is shown in *Table 2*. Forty-nine per cent of patients were reclassified to more advanced CKD stages, including 32.8% patients in $CKD_{Cr}$ stage 1 + 2 or stage 3a that were reclassified to $CKD_{Cys}$ stage 3b or stage 4 + 5.

## Procedural characteristics and periprocedural complications

Procedural characteristics and periprocedural complications are shown in *Table 3*. The transfemoral approach was used in 201 patients (96.6%), and general anaesthesia was used in 207 patients (99.5%). No significant difference was observed among the $CKD_{Cys}$ stages concerning the device, approach, anaesthesia, and procedure time. Contrast doses

**Table 3** Procedural characteristics and periprocedural complications

| | Overall ($n$ = 208) | $CKD_{Cys}$ stage 1 + 2 ($n$ = 33) | $CKD_{Cys}$ stage 3a ($n$ = 57) | $CKD_{Cys}$ stage 3b ($n$ = 60) | $CKD_{Cys}$ stage 4 + 5 ($n$ = 58) | $P$ value |
|---|---|---|---|---|---|---|
| Balloon-expandable valve | 107 (51.4) | 20 (60.6) | 27 (47.4) | 32 (53.3) | 28 (48.3) | 0.613 |
| Transfemoral approach | 201 (96.6) | 32 (97.0) | 54 (94.7) | 60 (100.0) | 55 (94.8) | 0.346 |
| General anaesthesia | 207 (99.5) | 32 (97.0) | 57 (100.0) | 60 (100.0) | 58 (100.0) | 0.149 |
| Procedure time (min) | 93.0 [81.0, 115.5] | 88.0 [78.0, 116.3] | 92.0 [81.0, 107.0] | 94.0 [81.0, 111.0] | 99.0 [83.5, 130.0] | 0.577 |
| Contrast medium volume (mL) | 60.0 [40.0, 80.0] | 65.0 [50.0, 90.0] | 63.3 [50.0, 80.0] | 62.9 [40.0, 87.4] | 43.3 [36.2, 60.0] | 0.001 |
| Device success | 202 (97.1) | 33 (100.0) | 57 (100.0) | 56 (93.3) | 56 (96.6) | 0.122 |
| Periprocedural myocardial infarction | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | NA |
| Life-threatening or major bleeding | 23 (11.1) | 2 (6.1) | 7 (12.3) | 7 (11.7) | 7 (12.1) | 0.799 |
| Major vascular complications | 17 (8.2) | 1 (3.0) | 6 (10.5) | 6 (10.0) | 4 (6.9) | 0.577 |
| PPM implantation | 16 (7.7) | 2 (6.1) | 4 (7.0) | 5 (8.3) | 5 (8.6) | 0.966 |
| AKIN stage 3 or new dialysis | 3 (1.4) | 0 (0.0) | 0 (0.0) | 2 (3.3) | 1 (1.7) | 0.414 |
| Conversion to open surgery | 1 (0.5) | 1 (3.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0.149 |
| Unplanned use of cardiopulmonary bypass | 4 (1.9) | 0 (0.0) | 0 (0.0) | 2 (3.3) | 2 (3.4) | 0.375 |
| Coronary obstruction | 2 (1.0) | 1 (3.0) | 0 (0.0) | 0 (0.0) | 1 (1.7) | 0.396 |
| Valve embolization | 1 (0.5) | 0 (0.0) | 0 (0.0) | 1 (1.7) | 0 (0.0) | 0.479 |

AKIN, Acute Kidney Injury Network; CKD, chronic kidney disease; NA, not applicable; PPM, permanent pacemaker.
Values are expressed as median [interquartile range], or $n$ (%).

differed significantly ($P$ = 0.001), and the $CKD_{Cys}$ stage 4 + 5 patients were treated with the lowest dose. The device success rate was similar between the four groups. Acute kidney injury was observed only in $CKD_{Cys}$ stage 3b and $CKD_{Cys}$ stage 4 + 5, although they did not reach statistical significance.

### Clinical outcomes at 30 days and 2 years

During the median follow-up period of 575.5 days (IQR: 367.0–730.0 days), there were 58 MACCE, including 26 all-cause mortality, 1 non-fatal myocardial infarction, 16 strokes, and 15 rehospitalizations for worsening congestive heart failure. *Table 4* showed the clinical outcomes both at 30 days and 2 years classified by $CKD_{Cr}$ or $CKD_{Cys}$ stages. The information on the number of cardiovascular mortality and disabling stroke was available only at 30 days.

### Two-year cumulative MACCE and $CKD_{Cr}$/$CKD_{Cys}$ classification

Kaplan–Meier analyses of 2-year cumulative MACCE stratified by the CKD stages based on the baseline $eGFR_{Cr}$ or $eGFR_{Cys}$ are presented in *Figure 2*. The MACCE rates did not significantly differ among CKD stages based on $eGFR_{Cr}$ ($P$ = 0.081) (*Figure 2A*). In contrast, the MACCE rates were significantly increased in $CKD_{Cys}$ stage 3b ($P$ = 0.012) and $CKD_{Cys}$ stage 4 + 5 ($P$ = 0.022) compared with that of $CKD_{Cys}$ stage 1 + 2 (*Figure 2B*).

### Prognostic value of $CKD_{Cys}$ classification after TAVR

The univariate Cox regression analysis results for the association between 2-year cumulative MACCE and clinical findings are presented in Supporting information, *Table S1*. The STS score, NYHA class III or IV, diabetes mellitus, albumin, $CKD_{Cr}$ stage 3b, $CKD_{Cr}$ stage 4 + 5, $CKD_{Cys}$ stage 3b, and $CKD_{Cys}$ stage 4 + 5 were significantly associated with MACCE after TAVR. In the multivariate Cox regression analysis, only $CKD_{Cys}$ stage 3b [HR = 4.37; 95% confidence interval (CI): 1.28–14.91; $P$ = 0.019] and $CKD_{Cys}$ stage 4 + 5 (HR = 3.72; 95% CI: 1.06–12.99; $P$ = 0.040) were the significant predictors of MACCE after adjustment for age, sex, STS score, NYHA class III or IV, diabetes mellitus, and albumin (*Table 5*).

## Discussion

The primary findings of the present analysis were as follows: (i) there was a considerable discrepancy between $eGFR_{Cys}$ and $eGFR_{Cr}$ in the TAVR patient cohort; (ii) the CKD classification based on $eGFR_{Cys}$, but not $eGFR_{Cr}$, significantly stratified the risk of 2-year MACCE in patients after TAVR; and (iii) $CKD_{Cys}$ stage 3b and $CKD_{Cys}$ stage 4 + 5 were shown to be the significant predictors of 2-year MACCE after TAVR.

Previous studies reported on the difference between $eGFR_{Cys}$ and $eGFR_{Cr}$ in the old general population. In SPRINT trial, $eGFR_{Cys}$ was shown to be higher than $eGFR_{Cr}$ with the mean difference of 0.5 ± 15 mL/min/1.73 $m^2$ in a large pop-

**Table 4** Clinical outcomes at 30 days and 2 years

| | Overall ($n$ = 208) | $CKD_{Cys}$ stage 1 + 2 ($n$ = 33) | $CKD_{Cys}$ stage 3a ($n$ = 57) | $CKD_{Cys}$ stage 3b ($n$ = 60) | $CKD_{Cys}$ stage 4 + 5 ($n$ = 58) | $P$ value |
|---|---|---|---|---|---|---|
| Outcomes at 30 days | | | | | | |
| Major adverse cardiovascular and cerebrovascular events | 14 (6.7) | 0 (0.0) | 1 (1.8) | 7 (11.7) | 6 (10.3) | 0.044 |
| All-cause mortality | 5 (2.4) | 0 (0.0) | 0 (0.0) | 4 (6.7) | 1 (1.7) | 0.07 |
| Cardiovascular mortality | 4 (1.9) | 0 (0.0) | 0 (0.0) | 3 (5.0) | 1 (1.7) | 0.18 |
| Non-fatal myocardial infarction | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | NA |
| Stroke | 10 (4.8) | 0 (0.0) | 1 (1.8) | 5 (8.4) | 4 (6.9) | 0.17 |
| Disabling stroke | 8 (3.9) | 0 (0.0) | 0 (0.0) | 4 (6.8) | 4 (6.9) | 0.097 |
| Rehospitalization for worsening congestive heart failure | 1 (0.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (1.7) | 0.47 |
| Outcomes at 2 years | | | | | | |
| Major adverse cardiovascular and cerebrovascular events | 58 (33.9) | 3 (10.0) | 11 (28.6) | 23 (45.6) | 21 (42.3) | 0.003 |
| All-cause mortality | 36 (21.7) | 2 (6.6) | 8 (22.3) | 14 (28.7) | 12 (23.8) | 0.11 |
| Non-fatal myocardial infarction | 1 (0.5) | 0 (0.0) | 0 (0.0) | 1 (2.1) | 0 (0.0) | 0.42 |
| Stroke | 17 (10.4) | 1 (3.6) | 3 (7.3) | 7 (14.3) | 6 (13.3) | 0.32 |
| Rehospitalization for worsening congestive heart failure | 18 (10.3) | 0 (0.0) | 1 (1.8) | 7 (15.5) | 10 (20.3) | 0.004 |

| | Overall ($n$ = 208) | $CKD_{Cr}$ stage 1 + 2 ($n$ = 73) | $CKD_{Cr}$ stage 3a ($n$ = 58) | $CKD_{Cr}$ stage 3b ($n$ = 48) | $CKD_{Cr}$ stage 4 + 5 ($n$ = 29) | $P$ value |
|---|---|---|---|---|---|---|
| Outcomes at 30 days | | | | | | |
| Major adverse cardiovascular and cerebrovascular events | 14 (6.7) | 2 (2.7) | 5 (8.6) | 4 (8.3) | 3 (10.3) | 0.4 |
| All-cause mortality | 5 (2.4) | 1 (1.4) | 3 (5.2) | 0 (0.0) | 1 (3.4) | 0.31 |
| Cardiovascular mortality | 4 (1.9) | 1(1.4) | 2 (3.4) | 0 (0.0) | 1 (3.4) | 0.54 |
| Non-fatal myocardial infarction | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | NA |
| Stroke | 10 (4.8) | 1 (1.4) | 4 (7.0) | 4 (8.3) | 1 (3.4) | 0.28 |
| Disabling stroke | 8 (3.9) | 0 (0.0) | 3 (5.2) | 4 (8.3) | 1 (3.4) | 0.12 |
| Rehospitalization for worsening congestive heart failure | 1 (0.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (3.4) | 0.11 |
| Outcomes at 2 years | | | | | | |
| Major adverse cardiovascular and cerebrovascular events | 58 (33.9) | 13 (21.7) | 18 (37.4) | 17 (46.5) | 10 (38.4) | 0.081 |
| All-cause mortality | 36 (21.7) | 9 (15.4) | 10 (21.2) | 11 (32.4) | 6 (23.2) | 0.39 |
| Non-fatal myocardial infarction | 1 (0.5) | 0 (0.0) | 1 (1.9) | 0 (0.0) | 0 (0.0) | 0.47 |
| Stroke | 17 (10.4) | 4 (7.0) | 6 (13.8) | 5 (14.9) | 2 (7.3) | 0.62 |
| Rehospitalization for worsening congestive heart failure | 18 (10.3) | 2 (3.3) | 5 (9.4) | 4 (11.1) | 7 (29.9) | 0.004 |

CKD, chronic kidney disease; NA, not applicable.
Values are expressed as $n$ (%). All percentages are Kaplan–Meier estimates at 30 days or 2 years. Major adverse cardiovascular and cerebrovascular event was a composite of all-cause mortality, non-fatal myocardial infarction, stroke, and rehospitalization for worsening congestive heart failure. The information on the number of cardiovascular mortality and disabling stroke was available only at 30 days.

ulation of hypertensive patients older than 50 years.[15] Furthermore, in the Cardiovascular Health Study, which assessed community-dwelling adults older than 65 years, $eGFR_{Cys}$ was lower than $eGFR_{Cr}$ with the mean difference of 1.4 ± 14 mL/min/1.73 $m^2$.[16] However, the difference between $eGFR_{Cys}$ and $eGFR_{Cr}$ in patients undergoing TAVR has not been previously investigated. In the present study, we first showed that $eGFR_{Cr}$, with a mean of 7.95 ± 10.43 mL/min/1.73 $m^2$, was higher than $eGFR_{Cys}$ among the patients undergoing TAVR, with decreasing agreement at the higher mean eGFR values. The overestimation of GFR by creatinine possibly explains this discrepancy. Sarcopenia with reduced muscle mass was reported to be highly prevalent in patients undergoing TAVR.[17,18] As creatinine is a breakdown product of muscle, $eGFR_{Cr}$ is prone to be overestimated in this patient cohort. In addition, the creatinine levels cannot track the mild to moderate renal impairment due to the non-linear relationship with GFR.[19] In contrast, cystatin C is a low molecular weight protease inhibitor produced by all nucleated cells at a constant rate. After free filtration by the glomeruli, it is almost completely reabsorbed and catabolized by the proximal tubule without return to the blood flow.[20] Therefore, cystatin C is less affected by age, sex, and muscle mass[7,8] and is a more sensitive marker to detect early renal impairment compared with creatinine.[20] Considering the advantages of cystatin C and the comparable difference between $eGFR_{Cr}$ and $eGFR_{Cys}$ observed in this study, it might be better to use $eGFR_{Cys}$ for the precise renal function assessment and CKD classification in patients undergoing TAVR.

**Figure 2** Kaplan–Meier analysis for MACCE by CKD classification in accordance with (A) creatinine-based eGFR ($CKD_{Cr}$ classification) and (B) cystatin C-based eGFR ($CKD_{Cys}$ classification). MACCE, major adverse cardiovascular and cerebrovascular events; TAVR, transcatheter aortic valve replacement.

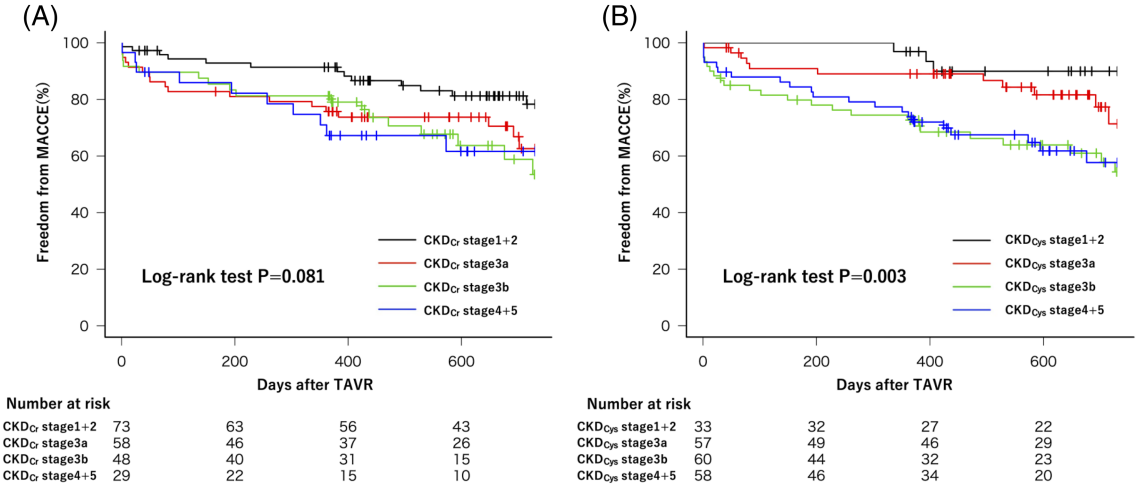


**Table 5** Multivariate Cox regression analysis for the association between cumulative MACCE and clinical findings

| | Multivariate analysis model 1 | | | Multivariate analysis model 2 | | |
|---|---|---|---|---|---|---|
| Variable | Hazard ratio | 95% CI | *P* value | Hazard ratio | 95% CI | *P* value |
| Age | 1.02 | (0.95–1.08) | 0.63 | 1.01 | (0.94–1.07) | 0.86 |
| Male (for female) | 1.29 | (0.71–2.37) | 0.4 | 1.22 | (0.66–2.25) | 0.53 |
| STS score | 1.02 | (0.95–1.10) | 0.53 | 1.02 | (0.95–1.10) | 0.6 |
| NYHA class III or IV | 1.26 | (0.67–2.37) | 0.48 | 1.23 | (0.66–2.31) | 0.51 |
| Diabetes mellitus | 0.41 | (0.16–1.09) | 0.075 | 0.40 | (0.15–1.06) | 0.066 |
| Albumin | 0.56 | (0.31–1.00) | 0.051 | 0.58 | (0.33–1.03) | 0.063 |
| CKD classification by $eGFR_{Cr}$ | | | | | | |
| $CKD_{Cr}$ stage 1 + 2 | 1.00 | | | | | |
| $CKD_{Cr}$ stage 3a | 1.84 | (0.88–3.85) | 0.1 | | | |
| $CKD_{Cr}$ stage 3b | 2.07 | (0.99–4.34) | 0.054 | | | |
| $CKD_{Cr}$ stage 4 + 5 | 1.74 | (0.71–4.25) | 0.22 | | | |
| CKD classification by $eGFR_{Cys}$ | | | | | | |
| $CKD_{Cys}$ stage 1 + 2 | | | | 1.00 | | |
| $CKD_{Cys}$ stage 3a | | | | 1.93 | (0.53–6.99) | 0.32 |
| $CKD_{Cys}$ stage 3b | | | | 4.37 | (1.28–14.91) | 0.019 |
| $CKD_{Cys}$ stage 4 + 5 | | | | 3.72 | (1.06–12.99) | 0.04 |

CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; $eGFR_{Cr}$, creatinine-based eGFR; $eGFR_{Cys}$, cystatin C-based eGFR; MACCE, major adverse cardiovascular and cerebrovascular events; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons.

Accurate classification of CKD is vital in clinical practice because there is much evidence of its association with morbidity and mortality in cardiovascular diseases.[21–23] A study showed that misclassification of CKD stages by creatinine-based GFR equations is higher than that of cystatin C-based GFR equations.[24] In the present study, reclassification of CKD stages using $eGFR_{Cys}$ was very common, and only the $CKD_{Cys}$ classification, not $CKD_{Cr}$ classification, had prognostic value in predicting adverse events after TAVR. This is inconsistent with the previous reports showing the prognostic utility of $CKD_{Cr}$ classification in patients undergoing TAVR.[4,5] For the possible explanation, the limited number of the present study cohort might attenuate the prognostic utility of $CKD_{Cr}$ classification. The more accurate classification of CKD stages by $eGFR_{Cys}$ might enable the risk stratification following TAVR even in a relatively small patient cohort.

Our study showed that $CKD_{Cys}$ stage 3b and stage 4 + 5 were the significant predictors of 2-year MACCE after TAVR. Previous reports showed creatinine-based eGFR $<$ 45 mL/min/1.73 $m^2$ as the optimal cut-off value predicting late adverse events after TAVR.[4,5] In the present study, almost all the patients with $eGFR_{Cr}$ $<$ 45 mL/min/1.73 $m^2$ were classified into $CKD_{Cys}$ stage 3b or stage 4 + 5 ($eGFR_{Cys}$ $<$ 45 mL/min/1.73 $m^2$). However, 32.8% of patients with $eGFR_{Cr}$ $\geq$ 45 mL/min/1.73 $m^2$ were reclassified into $CKD_{Cys}$ stage 3b or stage 4 + 5, which was associated with adverse


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clinical outcomes in our study. Therefore, the risk after TAVR among patients with $eGFR_{Cr} \geq 45$ mL/min/1.73 $m^2$, but $eGFR_{Cys} < 45$ mL/min/1.73 $m^2$ should be overlooked during $CKD_{Cr}$ classification. The reclassification of CKD stages by $eGFR_{Cys}$ might enable the improvement in the risk prediction after TAVR.

In this study, diabetes mellitus significantly lowered the risk of MACCE in univariate analysis. This should not result from diabetes itself but some possible confounders in patients with diabetes in our cohort. As shown in *Table S2*, even in patients with diabetes, the control of the disease was good with a median HbA1c of 6.2%. Moreover, patients with diabetes were significantly younger, with higher albumin than patients without diabetes. Additionally, although insignificant, the percentage of patients with NYHA class III or IV was lower in the diabetes group. Those confounders possibly lowered the risk of MACCE in patients with diabetes.

### Limitations

The present study has some limitations. First, this was a retrospective, single-centre study. Second, pre-operative eGFR was established with a single-point measurement of creatinine and cystatin C. It is possible that GFR was estimated inaccurately in our study. To avoid the influence of dehydration, we adjusted the dose of diuretics before TAVR to maintain the stable condition of heart failure without prerenal kidney injury. Third, we did not perform urine analysis or kidney imaging in our study cohort; therefore, the diagnosis of CKD depends solely on the GFR categories. Thus, CKD stage 1 + 2 possibly includes patients without CKD. Fourth, the number of subjects was relatively small, which might be insufficient to fully understand the prognostic value of $CKD_{Cys}$ and $CKD_{Cr}$ classifications after TAVR. Finally, all the patients in this study were Japanese; thus, caution must be taken when generalizing the results of this study for a different population. Further studies are warranted to validate the prognostic utility of $CKD_{Cys}$ classification after TAVR in a wider range of patients.

## Conclusions

In conclusion, $CKD_{Cys}$ classification, but not $CKD_{Cr}$ classification, significantly stratified the risk after TAVR. The use of $CKD_{Cys}$ classification could provide better risk assessment in patients undergoing TAVR, and $CKD_{Cys}$ stage 3b and stage 4 + 5 correlated with adverse outcomes.

## Conflict of interest

Dr Zen is a clinical proctor for Edwards Lifesciences and Medtronic. The other authors have no conflicts of interest to declare.

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None.

## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Univariate Cox regression analysis for the association between cumulative MACCE and clinical findings.
**Table S2.** Baseline patient characteristics stratified by diabetes status.

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