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ORIGINAL ARTICLE

The Influence of the Charlson Comorbidity Index on Procedural Characteristics, VARC-2 Endpoints and 30-Day Mortality Among Patients Who Undergo Transcatheter Aortic Valve Implantation

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Background Aortic stenosis (AS) is a common valvular abnormality and transcatheter aortic valve implantation (TAVI) is being increasingly used to treat patients considered too high risk for conventional surgery. We aimed to assess the prevalence of comorbid conditions in patients undergoing TAVI using the Charlson Comorbidity Index (CCI) and to assess their impact on clinical and procedural outcomes.

Methods We analysed 158 patients who underwent a TAVI at our institution between June 2009 and September 2015 to define their co-morbid burden as measured with CCI, and study its impact on procedural characteristics and mortality at 30 days.

Results One hundred fifty-eight (158) patients with a mean age of 82 ± 8 years and a mean CCI score of 2.67 underwent a TAVI. Only 12/158 patients had a CCI of 0. The commonest cardiovascular comorbidities were previous myocardial infarction (24%), congestive heart failure (15%) and diabetes mellitus (23%) whilst the commonest non-cardiovascular comorbidities were renal disease (46%) and chronic obstructive pulmonary disease (COPD) (29%). After multivariable adjustment, CCI was not independently associated with adverse clinical outcomes. The addition of CCI to scoring systems such as Logistic EuroScore (LES) and Society of Thoracic Surgeons (STS) risk models improved the area under the curve from 0.75 (95%CI: 0.44–1.00) and 0.83 (95%CI: 0.64–1.00) to 0.78 (95%CI: 0.53–1.00) and 0.89 (95%CI: 0.78–1.00) respectively.

Conclusions The burden of comorbid conditions in patients undergoing TAVI is significant. The CCI score was not independently associated with a higher risk of death but can be useful in addition to LES and STS risk models in informing decision making on the selection of patients for TAVI.

Keywords Aortic valve disease • Transcatheter valve implantation • Health care outcomes

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Introduction

Aortic stenosis is the commonest form of valvular heart disease in Europe and in North America, affecting between 2–7% of the population over the age of 65 [1,2]. In patients with symptomatic severe aortic stenosis, surgical aortic valve replacement (SAVR) remains the definitive treatment with a mortality of only 1–3% in younger patients and a mortality of 4–8% in selected patients over the age of 70 [3–5]. In patients with a high surgical risk, transcatheter aortic valve implantation (TAVI) via the transfemoral or transapical route achieves similar survival at 1 year to SAVR [6]. In patients deemed inoperable due to a prohibitive risk, TAVI significantly reduces mortality and symptoms compared to best medical therapy [7]. Both American and European guidelines recommend TAVI in patients with prohibitive or high surgical risk for SAVR after appropriate review by a heart team [1,8].

Transcatheter aortic valve implantation procedures have a mortality rate of between 6–15% [7,9,10] and complications including stroke, requirement for permanent pacemaker, vascular access complications and paravalvular regurgitation [6,7].

The prevalence of aortic stenosis increases with age [11]. Comorbidity burden also significantly increases with age. In a Medicare population of over one million, 85% of patients over the age of 65 had at least one significant comorbid condition and 65% of patients had two or more significant comorbid conditions [12]. Therefore, it is unsurprising that many patients with aortic stenosis are elderly with multiple co-morbidities [13]. The presence of significant comorbidities can make the selection of appropriate patients who would benefit from TAVI challenging and may influence outcomes. Previous studies in patients undergoing TAVI have considered only co-morbidities as either cardiovascular risk factors and or the presence of coronary artery disease that frequently coexists with aortic stenosis rather than systematic measures of general co-morbidity burden [14,15]. The Charlson Comorbidity Index (CCI) is a measure of comorbidity burden, which quantifies the prognostic impact of 22 comorbid conditions on the basis of their number and their individual prognostic impact by means of a score that was developed as a prognostic indicator for patients with a variety of medical conditions [16]. A score of zero indicates that no comorbidities were present whilst a score of 33 is the maximum; a higher score is associated with a higher risk of death. The CCI is well validated and has been shown to be a good predictor of outcome in a range of conditions including surgery for small cell lung cancer [17], surgery following hip fracture [18], percutaneous coronary intervention (PCI) [19] and patients with aortic stenosis [20]. It has also been shown that CCI has a similar ability to assess risk of in-hospital mortality to EuroSCORE in patients undergoing coronary artery bypass grafting (CABG) [21].

However, less is known about the distribution of other comorbid conditions in patients undergoing TAVI and their association with clinical outcomes with limited data derived from small single centre registries. The CCI has only been evaluated in three studies of patients undergoing TAVI. A high CCI has been shown to be associated with a worse outcome in two small single centre studies [22,23], although another study failed to observe such a relationship [24]. We sought to assess the prevalence and distribution of comorbid conditions in patients undergoing TAVI using CCI and to assess their impact on clinical and procedural outcomes.

Methods

This study analysed all patients who underwent TAVI at the Royal Stoke Hospital, University Hospitals of North Midlands (UHNM) between June 2009 and September 2015. The procedures were performed under general anaesthetic using the Sapien and Sapien XT valves (Edwards Lifesciences, Irvine, CA, USA) via the transfemoral route in 89% and the transapical route in 11% of cases. Data was collected from our local TAVI registry that is submitted annually to the National Institute of Cardiovascular Outcomes Research for the UK TAVI Registry for national reporting [25]. Using their NHS number as the link, electronic patient records for these patients were retrieved from the hospital patient administration system (PAS) and linked to their National Institute for Cardiovascular Outcomes Research (NICOR) TAVI dataset records. The components of CCI include: previous myocardial infarction, congestive cardiac failure, peripheral vascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, diabetes, renal disease, hemiplegia, leukaemia, lymphoma, solid tumour with or without metastatic disease, liver disease and Acquired Immune Deficiency Syndrome (AIDS) status (Table 1).

Outcomes collected include Valve Academic Research Consortium (VARC)-2 combined safety endpoints (mortality, all cause stroke, life-threatening bleeding, acute kidney injury, coronary artery obstruction, major vascular complication, valve-related dysfunction) [26], 30-day mortality, intraoperative radiation dose, intraoperative radio-contrast exposure, length of procedure and length of stay.

Statistical Analysis

Statistical analysis was performed on STATA 13.1 (StataCorp LLC, College Station, TX, USA) and R version 3.3.1 [27]. The CCI score was calculated for each patient and the frequency of each CCI score in the cohort is shown graphically. The patients were then split into four groups based on CCI score of: CCI = 0, CCI = 1, CCI = 2 and CCI $\geq$ 3, which are based on commonly used categories in existing studies [28–30]. Descriptive statistics were presented for each variable per CCI group. Differences across CCI groups were tested using Fisher's Exact Test and one-way analysis of variance for categorical and continuous variables, respectively.

Univariate and multivariable regression analyses were performed to determine the association between incremental unit increases in CCI score and each outcome. Binary

Table 1 Charlson Comorbidity Index.

Variable	Points
Myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic obstructive pulmonary disease	1
Connective tissue disease	1
Peptic ulcer disease	1
Diabetes mellitus	1 if uncomplicated 2 if end-organ damage
Moderate to severe chronic kidney disease	2
Hemiplegia	2
Leukaemia	2
Malignant lymphoma	2
Solid tumour	2 6 if metastatic
Liver disease	1 if mild 3 if moderate to severe
AIDS	6

outcomes (30-day mortality and VARC-2 composite early safety) were analysed using logistic regression, continuous variables (intraoperative radiation dose and intraoperative radio-contrast exposure) were analysed using linear regression and time-to-event outcomes (length of stay and length of procedure) were analysed using Cox proportional hazards models. In the latter case, the proportionality assumption was checked. Multivariable models adjusted for age, sex, apical access and any of following demographic or procedural variables that were identified significant ($p < 0.05$) by univariable analysis for each outcome: smoking status, calcification of ascending aorta, atrial fibrillation/flutter, previous balloon aortic valvuloplasty (BAV), New York Heart Association (NYHA) Class ≥III, body mass index (BMI), Canadian Cardiovascular Society (CCS) Class 4 angina, aortic valve area, left ventricular ejection fraction (LVEF) <50%, one or more diseased vessels, left main stem disease and non-elective procedure indication. Additionally, a sensitivity analysis was performed that analysed all outcomes in transfemoral access patients only. Rates of the individual components of VARC-2 were also evaluated according to CCI group.

The predicted risk of mortality was retrospectively calculated for each patient using the Logistic EuroScore (LES) and Society of Thoracic Surgeons (STS) risk models using the variables and coefficients previously reported [31,32]. Any LES or STS variable that was not available in the dataset or missing for a patient was assumed risk factor absent. Subsequently, CCI total was added into to each risk model by fitting a logistic regression model to 30-day mortality with both the linear predictor of that risk model and CCI total as covariates [33]. The area under the receiver operator characteristic curve (AUC) was calculated for the LES and STS, which were compared with those for the updated risk models (i.e. those with CCI added) using a DeLong comparison [34]. This was similarly undertaken for the VARC-2 composite endpoint.

Results

Between 2009 and 2015, 158 patients with a mean age of 82.1 (SD 7.5) years underwent TAVI at our centre. The majority of patients were male (64%) and their CCI scores ranged from 0 (no comorbidity) to 8 (very significant comorbidity) (Figure 1). The mean CCI was 2.67 (SD 1.72).

Table 2 shows the characteristics of the cohort under examination as a whole cohort and across the four defined CCI groups. There were 12 (8%) patients with a CCI of 0, 35 patients (22%) with a CCI of 1, 29 patients (18%) with a CCI of 2, 36 patients (23%) with a CCI of 3 and 46 (29%) patients with CCI of 4 or above. There was no significant difference in age or sex of patients between the CCI groups ($p = 0.194$, $p = 0.117$). The majority were also either current or ex-smokers (55%) and overweight with a mean BMI of 27.6. Smoking status ($p < 0.001$), creatinine ($p < 0.001$), previous BAV ($p = 0.015$) and previous PCI ($p = 0.027$) were all significantly different between CCI groups. Conversely, BMI ($p = 0.272$), cardiac operation ($p = 0.593$), aortic valve area ($p = 0.975$), atrial fibrillation/flutter ($p = 0.387$) and extra-cardiac arteriopathy ($p = 0.199$) were not significantly different between the groups, and neither were procedural variables of emergency procedure ($p = 0.754$) and apical procedure ($p = 0.556$). The Logistic EuroSCORE and STS score were also similar across the groups ($p = 0.099$, $p = 0.067$).

Table 3 shows the prevalence of the elements making up the CCI in our cohort. The commonest cardiovascular comorbidities were previous myocardial infarction (38 patients, 24%), congestive heart failure (24 patients, 15%) and diabetes mellitus (37 patients, 23%); the commonest non-cardiovascular comorbidities were chronic renal disease (73 patients, 46%) and COPD (46 patients, 29%) (Table 3). Peripheral vascular disease ($p < 0.001$), COPD ($p = 0.004$), diabetes ($p < 0.001$), renal disease ($p < 0.001$) and solid tumour ($p < 0.001$) were significantly more common amongst the CCI ≥ 3 group; there were no significant differences in the prevalence of the other risk factors.

When unadjusted patient outcomes were considered according to comorbid burden, no significant differences were seen between the CCI groups in VARC-2 ($p = 0.903$), 30-day mortality ($p = 0.583$), contrast ($p = 0.731$), mean procedure length ($p = 0.051$) or mean length of stay ($p = 0.375$)

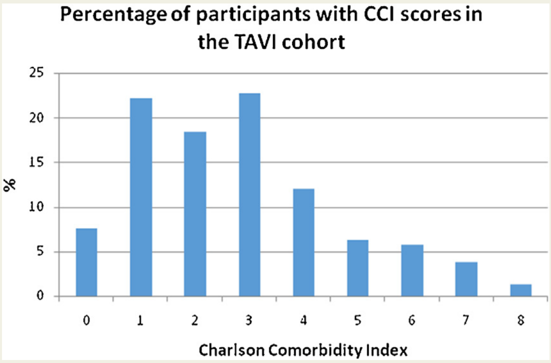

Figure 1 Percentage of participants with CCI scores in the TAVI cohort.
Abbreviations: CCI, Charlson Comorbidity Index; TAVI, transcatheter aortic valve implantation.

(Table 3). A significant difference was observed for radiation dose (p = 0.021). Additionally, there was no significant difference in the cumulative event rates of length of stay (log-rank test, p = 0.894) or in length of procedure (log-rank test, p = 0.261) by CCI group. Rates of the individual components of VARC-2 were also evaluated according to CCI group and are shown in Supplementary Table 1.

Increases per unit CCI score were significantly associated with increased 30-day mortality (p = 0.009), radiation dose (p = 0.006) and length of procedure (p = 0.002) when adjusted for age and sex (Table 4). However, after multivariable adjustment for age, sex, apical access and other significant predictors, unit increases in CCI were not significantly associated with outcome. The multivariable adjustment for VARC-2 composite early safety, 30-day mortality and contrast all included age, sex and apical access. Multivariable adjustment of radiation dose included age, sex apical access and smoking status. Length of stay was adjusted for age, sex, apical access, smoking status, aortic valve area and left main stem disease. Finally, length of procedure was adjusted for age, sex, apical access, smoking status and non-elective procedure indication. The sensitivity analyses that examined only transfemoral access patients indicated no significant differences in outcomes for unit increases in CCI, after multivariable adjustment.

The AUC for 30-day mortality prediction were 0.75 (95% CI: 0.44, 1.00) and 0.83 (95% CI: 0.64, 1.00) for LES and STS, respectively. The addition of CCI total into the LES and STS score increased the AUCs to 0.78 (95% CI: 0.53, 1.00; DeLong p = 0.71), and 0.89 (95% CI: 0.78, 0.99; DeLong p = 0.43), respectively. Similarly, for VARC-2 composite early safety, the AUC for LES was 0.57 (95% CI: 0.41, 0.74) and for STS score was 0.46 (95% CI: 0.30, 0.63). Again, adding CCI increased these to 0.60 (95% CI: 0.46, 0.75; DeLong p = 0.59) and 0.58 (95% CI: 0.43, 0.73; DeLong p = 0.36) for LES and STS, respectively.

Table 2 **Participant characteristics by Charlson Comorbidity Index.**

Variable	CCI = 0–1 (N = 47)	CCI = 2–3 (N=65)	CCI ≥ 4 (N = 46)	Whole Cohort (N = 158)	P-value
Age (SD)	83.8 (6.84)	81.5 (8.44)	81.3 (6.68)	82.1 (7.53)	0.194
Male (%)	27 (57%)	39 (60%)	35 (76%)	101 (64%)	0.117
Smoker (%)	19 (41%)	25 (38%)	35 (76%)	79 (50%) 8 (5%)	**<0.001**
Ex-smoker	0 (0%)	6 (9%)	2 (4%)		
Current smoker					
BMI (SD)	26.7 (4.57)	28.2 (5.82)	27.8 (4.91)	27.6 (5.24)	0.272
NYHA ≥III (%)	46 (98%)	62 (95%)	43 (93%)	151 (96%)	0.491
Mean creatinine (SD)	76.4 (14.4)	127.6 (100.8)	152.9 (90.7)	119.8 (86.4)	**<0.001**
Aortic valve area (SD)	0.75 (0.25)	0.76 (0.25)	0.76 (0.21)	0.76 (0.24)	0.975
Atrial fibrillation/flutter (%)	14 (30%)	25 (38%)	20 (43%)	59 (37%)	0.387
Extracardiac arteriopathy (%)	13 (28%)	14 (22%)	17 (37%)	44 (28%)	0.199
LVEF < 50% (%)	19 (40%)	27 (42%)	27 (59%)	73 (46%)	0.127
Previous BAV [d1] (%)	9 (19%)	14 (22%)	20 (43%)	43 (27%)	**0.015**
Previous PCI (%)	6 (13%)	17 (26%)	17 (37%)	40 (25%)	**0.027**
Previous cardiac operation (%)	17 (36%)	18 (28%)	13 (28%)	48 (30%)	0.593
Emergency (%)	0 (0%)	1 (2%)	1 (2%)	2 (1%)	0.754
Apical procedure (%)	4 (9%)	6 (9%)	7 (15%)	17 (11%)	0.556
Logistic EuroSCORE (SD)	17.0 (9.0)	18.9 (13.9)	22.8 (16.2)	19.5 (13.5)	0.099
STS Score (SD)	3.3 (1.7)	3.8 (2.2)	4.3 (2.4)	3.8 (2.1)	0.067

Abbreviations: SD, standard deviation; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; BMI, body mass index; CCI, Charlson Comorbidity Index; BAV, Balloon aortic valvuloplasty.
Values have been highlighted in bold where they are deemed to have ''statistical significance'' with a p value of <0.05.

Table 3 Charlson Comorbidity Index variables and outcomes for participants.

Variable in Charlson Comorbidity Index	CCI = 0–1 (N = 47)	CCI = 2–3 (N = 65)	CCI ≥ 4 (N = 46)	Whole Cohort (N = 158)	P-value
Previous MI (%)	9 (19%)	13 (20%)	16 (35%)	38 (24%)	0.142
Congestive Cardiac Failure (%)	4 (9%)	9 (14%)	11 (24%)	24 (15%)	0.121
PVD (%)	2 (4.3%)	6 (9.2%)	15 (32.6%)	23 (14.6%)	**<0.001**
Cerebrovascular disease (%)	6 (13%)	16 (26%)	20 (43%)	43 (27%)	**0.004**
Dementia (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	–
COPD (%)	7 (15%)	18 (28%)	21 (46%)	46 (29%)	**0.004**
Connective Tissue Disease (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	–
Peptic Ulcer Disease (%)	1 (2%)	2 (3%)	4 (9%)	7 (4%)	0.298
Diabetes without end organ damage (%)	6 (13%)	10 (15%)	4 (9%)	20 (13%)	**<0.001**
Diabetes with end organ damage (%)	0 (0%)	0 (0%)	17 (37%)	17 (11%)	
Renal Disease (%)	0 (%)	35 (54%)	38 (83%)	73 (46%)	**<0.001**
Hemiplegia (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	–
Leukaemia (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	–
Lymphoma (%)	0 (0%)	2 (3%)	1 (2%)	3 (2%)	0.631
Solid Tumour (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	**<0.001**
Solid Tumour + metastasis (%)	0 (0%)	5 (8%)	12 (26%)	17 (11%)	
Liver Disease Mild (%)	0 (0%)	0 (0%)	1 (2%)	1 (1%)	0.083
Liver Disease Moderate-Severe (%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	
AIDS (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	–
Outcomes					
VARC-2 (%)	5 (11%)	7 (11%)	6 (13%)	18 (11%)	0.903
30-day mortality (%)	1 (2%)	2 (3%)	3 (7%)	6 (4%)	0.583
Radiation dose (SD)	3526 (2636)	3937 (5195)	5195 (3552)	4183 (3046)	**0.021**
Contrast (SD)	44.4 (28.8)	45.9 (35.1)	41.3 (22.1)	44.1 (29.7)	0.731
Length of Procedure (SD)	87.0 (29.8)	87.7 (34.3%)	103.6 (47.1)	92.1 (37.8)	0.051
Length of Stay (SD)	8.3 (8.3)	7.1 (4.9)	9.7 (14.9)	8.2 (9.8)	0.375

Abbreviations: MI, myocardial infarction; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; AIDS, Acquired Immune Deficiency Syndrome; SD, standard deviation.

Values have been highlighted in bold where they are deemed to have ''statistical significance'' with a p value of <0.05.

Discussion

Our analysis showed that patients undergoing TAVI had a large range in the severity of comorbidities as measured by the CCI. A CCI score of >2 is considered to represent significant comorbidity and our patients had a mean CCI of 2.67 (SD 1.72). Unsurprisingly, less than 8% of patients undergoing TAVI at our centre had no comorbidities, since patients with very low comorbid burden are likely to have been appropriate for SAVR and patients with very high scores would have a very poor prognosis regardless of aortic valve intervention. Patients with higher CCI were significantly more likely to have smoked, have worse renal function, worse left ventricular function and to have had a previous BAV. This population of multi-morbid elderly patients (mean age 82) is likely to be representative of the types of patients undergoing the procedure elsewhere. Our 30-day mortality rate of less than 5%, and VARC-2 safety endpoints observed in 11% of patients is broadly similar to patient groups and outcomes reported elsewhere [6,7,35–37]. Although there was no difference in any unadjusted outcome measure between the four groups, we observed a significant association between higher CCI (per unit increase) and higher radiation dose, length of procedure and 30-day mortality in both unadjusted analyses, and those adjusted for age and gender. However, after multivariable analysis (age, sex, apical access and other significant variables), CCI score was not significantly linked to any outcome measure, although non-significant trends were evident.

Our analysis found that CCI score contributes to predicting mortality following TAVI when added to established risk scoring systems such as LES and STS. The LES uses a composite score based on a combination of patient demographics (age and sex), cardiac (previous cardiac surgery, endocarditis, recent myocardial infarction (MI), LV function, presence of unstable angina) and extra-cardiac comorbidities (COPD, peripheral vascular disease (PVD), neurological dysfunction, renal failure, pulmonary hypertension) and details of planned surgical procedure (emergency, valve surgery, aortic surgery, post-infarct septal defect) to give a risk of 30-day (or in-hospital) mortality following cardiothoracic surgery [31]. The STS score also gives a risk of 30-day mortality but uses a more extensive list of 40 patient and operative variables [32]. Both scoring systems are good at predicting operative mortality following open heart surgery [38] but are suboptimal if used

Table 4 Linear and logistic regression for outcomes by Charlson Comorbidity Index.

Outcome from logistic regression	N	Odds ratio (95% CI)	P-value
30-day mortality			
Unadjusted	158	1.69 (1.08, 2.76)	**0.023**
Age Adjusted	158	1.72 (1.10, 2.81)	**0.020**
Age & Sex Adjusted	158	1.91 (1.20, 3.24)	**0.009**
Multivariable Adjusted*	158	1.62 (0.99, 2.74)	0.055
VARC-2 composite early safety			
Univariate	158	1.22 (0.93, 1.61)	0.151
Age Adjusted	158	1.24 (0.94, 1.64)	0.126
Age & Sex Adjusted	158	1.25 (0.94, 1.67)	0.114
Multivariable Adjusted*	158	1.17 (0.87, 1.57)	0.284
Outcomes from linear regression	**N**	**Coefficient (95% CI)**	**P-value**
Radiation dose			
Univariate	157	431 (159, 704)	**0.002**
Age Adjusted	157	443 (169, 718)	**0.002**
Age & Sex Adjusted	157	377 (109, 644)	**0.006**
Multivariable Adjusted*	157	224 (−54, 501)	0.114
Contrast			
Univariate	156	−0.04 (−2.79, 2.71)	0.979
Age Adjusted	156	0.45 (−2.25, 3.15)	0.743
Age & Sex Adjusted	156	0.39 (−2.35, 3.13)	0.781
Multivariable Adjusted*	156	0.60 (−2.17, 3.37)	0.670
Outcomes from Cox proportional hazards model	**N**	**Hazard Ratio (95% CI)**	**P-value**
Length of Procedure			
Univariate	156	0.88 (0.80, 0.96)	**0.005**
Age Adjusted	156	0.86 (0.78, 0.94)	**0.001**
Age & Sex Adjusted	156	0.86 (0.78, 0.94)	**0.002**
Multivariable Adjusted*	156	0.90 (0.81, 1.00)	0.051
Length of Stay			
Univariate	158	0.96 (0.88, 1.05)	0.330
Age Adjusted	158	0.92 (0.84, 1.01)	0.085
Age & Sex Adjusted	158	0.94 (0.85, 1.03)	0.162
Multivariable Adjusted*	158	0.99 (0.90, 1.10)	0.869

Bold items indicate significant results.

*Multivariable Adjusted: such models included age, sex, transapical access indication and any other demographic or procedural variables identified significant ($p < 0.05$) by univariable analysis for each outcome.

in assessment of patients for TAVI [39]. In this study, the AUC for 30-day mortality is 0.75 (95% CI: 0.44, 1.00) and 0.83 (95% CI: 0.64, 1.00) for LES and STS, which improve to 0.78 (95% CI: 0.53, 1.00) and 0.89 (95% CI: 0.78, 1.00) respectively with the addition of CCI. Similarly, for VARC-2 composite early safety, the AUC for LES was 0.57 (95% CI: 0.41, 0.74) and for STS score was 0.46 (95% CI: 0.30, 0.63). Adding CCI increased these to 0.60 (95% CI: 0.46, 0.75) and 0.58 (95% CI: 0.43, 0.78).

Research by Bouleti et al. examining survival following TAVI has shown that a higher CCI is associated with higher rates of late (non-hospital) mortality following TAVI [22]. Their study of 123 patients with a mean age of 81.5 ± 8.4 underwent TAVI using a combination of the Sapien valve (Edwards Lifesciences, Irvine, CA, USA) and the CoreValve (Medtronic, Minneapolis, MN, USA) via the transfemoral (68.3%), transapical (30.1%), subclavian and retroperitoneal routes (1.6%). Their patients were significantly more comorbid than our own with a mean CCI of 5.3 ± 2.3 and, therefore, had a relatively high in-hospital mortality of 13%. During late follow-up, they found that CCI was associated with a higher rate of mortality for as long as 6 years (CCI per 1 unit increase had a hazard ratio of 1.12, $p = 0.03$) and that the majority of deaths in this population of patients were attributable to non-cardiac causes. Their outcome data did not include radiation dose or length of procedure.

Muñoz-García et al. also found that high CCI is associated with increased mortality after 30 days [23]. Their study of 133 high risk patients with a mean age of 79.5 ± 6.7 years underwent TAVI with the CoreValve (Medtronic). As well as using a different valve, their procedure differed from ours in that the majority of their patients (96%) underwent the procedure under local anaesthetic with sedation rather than general anaesthetic. Most (91%) of the patients had TAVI via the femoral route with subclavian access used in the remainder. Their patients also had significant comorbidities with a mean CCI of 3.57 $\pm$ 1.9 which is higher than our own cohort. Mortality at 30 days was 4.5% with CCI having a significant effect (OR 1.44, $p < 0.10$).

The two studies described found a clear association between CCI and mortality following TAVI. Our study did not find any clear association between CCI and mortality following multivariate analysis. This may have been related to the lower risk population that our TAVI cohort represented compared to the two studies described. Another recent study by Hiltrop et al. examined 145 patients with a median age of 84 (IQR 80–87) undergoing TAVI [24] in which cases were performed under general anaesthetic using the Sapien or Sapien XT valves (Edwards Lifesciences). Patients had a similar CCI (median 3, IQR 2–4) with 61% of access via the femoral artery and 39% transapical and the authors reported no difference in the baseline CCI between those patients who died and those who survived up to 2 years in following TAVI.

Our study adds significant information to the field of outcome following TAVI in elderly, heavily comorbid patients. Although we did not find a statistically significant association between CCI and outcome following TAVI, there was a trend towards higher radiation dose, length of procedure and 30-day mortality. We also found that the addition of CCI to either the LES or the STS improved the model in predicting death within 30 days following TAVI. This is unsurprising as increasing age is associated both with severe aortic stenosis and other comorbidities. The leading causes of death within 30 days of a TAVI procedure are infection, heart failure, stroke and multi-organ failure [40,41]. Heavily comorbid patients can reasonably be expected to be more at risk from these conditions as kidney disease, cerebrovascular disease and heart failure make up part of the scoring of CCI. Our study has limitations. It reflects the experience of a single centre using the Sapien and Sapien XT TAVI devices and will be subject to biases around local practices, particularly the type of patients accepted onto the TAVI program by our heart team. Additionally, we had only a modest sample size, reflecting the lower number of these procedures compared to other interventions. It is also possible that there are factors which influence outcomes in TAVI, such as frailty, which we were unable to capture. It has been shown that frailty (measured by grip strength, gait speed, serum albumin and activities of daily living) can be associated with long-term outcome after TAVI [42]. In addition, we were also unable to capture any post-procedure management which could have affected 30-day mortality and safety endpoints. We found that higher CCI score was associated with significantly higher radiation dose and reduced length of procedure but after adjustments these were no longer significant. There are other important factors such as operator experience which may influence length of procedure and radiation dose which we were unable to account for in the current study.

Conclusions

Our work suggests that patients undergoing TAVI have a significant comorbid burden that is mainly cardiovascular. The most common non-cardiovascular comorbidities are renal impairment and COPD. A high CCI is associated with a non-statistically significant trend towards a longer procedure, higher radiation dose and higher 30-day mortality. The addition of CCI to other scoring systems such as LES or STS improved the performance of the models. It is important that comorbidity burden is carefully evaluated in an objective manner as part of the assessment of patients prior to TAVI.

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Conflicts of Interest

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.hlc.2018.11.006.

References

[1] Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, et al. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg 2012;42:S1–44.

[2] Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet 2006;368:1005–11.

[3] Bridgewater B, Kinsman R, Walton P, Gummert J, Kappetein AP. The 4th European Association for Cardio-Thoracic Surgery adult cardiac surgery database report. Interact Cardiovasc Thorac Surg 2011;12:4–5.

[4] Beckmann A, Funkat A-K, Lewandowski J, Frie M, Ernst M, Hekmat K, et al. Cardiac surgery in Germany during 2014: A Report on Behalf of the German Society for Thoracic and Cardiovascular Surgery. Thorac Cardiovasc Surg 2015;63:258–69.

[5] Barreto-Filho J, Wang Y, Dodson JA, Desai MM, Sugeng L, Geirsson A, et al. Trends in aortic valve replacement for elderly patients in the United States 1999-2011. JAMA 2013;310:2078–84.

[6] Smith CR, Leon MB, Mack MJ, Miller C, Moses JW, Svensson LG, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187–98.
[7] Leon MB, Smith CR, Mack M, Miller C, Moses JW, Svensson LG, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597–607.
[8] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:e521–643.
[9] Thomas M, Schymik G, Walther T, Himbert D, Lefevre T, Treede H, et al. Thirty-day results of the SAPIEN aortic Bioprosthesis European Outcome (SOURCE) Registry: a European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. Circulation 2010;122:62–9.
[10] Piazza N, Grube E, Gerckens U, den Heijer P, Linke A, Luha O, et al. Procedural and 30-day outcomes following transcatheter aortic valve implantation using the third generation (18 Fr) corevalve revalving system: results from the multicentre, expanded evaluation registry 1-year following CE mark approval. EuroIntervention 2008;4:242–9.
[11] Osnabrugge RLJ, Mylotte D, Head SJ, Van Mieghem NM, Nkomo VT, LeReun CM, et al. Aortic stenosis in the elderly disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. J Am Coll Cardiol 2013;62:1002–12.
[12] Wolff JL, Starfield B, Anderson G. Prevalence expenditures, and complications of multiple chronic conditions in the elderly. Arch Intern Med 2002;162:2269–76.
[13] Faggiano P, Frattini S, Zilioli V, Rossi A, Nistri S, Dini FL, et al. Prevalence of comorbidities and associated cardiac diseases in patients with valve aortic stenosis. Potential implications for the decision-making process. Int J Cardiol 2012;159:94–9.
[14] Dewey TM, Brown DL, Herbert MA, Cuclica D, Smith CR, Leon MB, et al. Effect of concomitant coronary artery disease on procedural and late outcomes of transcatheter aortic valve implantation. Ann Thorac Surg 2010;89:758–67. discussion 767.
[15] Snow TM, Ludman P, Banya W, De Belder M, MacCarthy PM, Davies SW, et al. Management of concomitant coronary artery disease in patients undergoing transcatheter aortic valve implantation: the United Kingdom TAVI Registry. Int J Cardiol 2015;199:253–60.
[16] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.
[17] Ö Birim, Kappetein AP, AJJC Bogers. Charlson comorbidity index as a predictor of long-term outcome after surgery for nonsmall cell lung cancer. Eur J Cardiothorac Surg 2005;28:759–62.
[18] Kirkland LL, Kashiwagi DT, Burton MC, Cha S, Varkey P. The Charlson Comorbidity Index Score as a Predictor of 30-Day Mortality After Hip Fracture Surgery. Am J Med Qual 2011;26:461–7.
[19] Mamas MA, Fath-Ordoubadi F, Danzi GB, Spaepen E, Kwok CS, Buchan I, et al. Prevalence and impact of co-morbidity burden as defined by the charlson co-morbidity index on 30-day and 1- and 5-year outcomes after coronary stent implantation (from the nobori-2 study). Am J Cardiol 2015;116:364–71.
[20] Kearney L, Ord M, Buxton B, Matalanis G, Patel S, Burrell L, et al. Usefulness of the Charlson co-morbidity index to predict outcomes in patients >60 years old with aortic stenosis during 18 years of follow-up. Am J Cardiol 2012;110:695–701.
[21] Ugolini C, Nobilio L. Risk adjustment for coronary artery bypass graft surgery: an administrative approach versus EuroSCORE. Int J Qual Health Care 2004;16:157–64.
[22] Bouleti C, Himbert D, Iung B, Alos B, Kerneis C, Ghodbane W, et al. Long-term outcome after transcatheter aortic valve implantation. Heart 2015;101:936–42.
[23] Muñoz-García AJ, Hernández-García JM, Jiménez-Navarro MF, Alonso-Briales JH, Dominquez-Franco AJ, Rodriguez-Bailon I, et al. Survival and predictive factors of mortality after 30 days in patients treated with percutaneous implantation of the CoreValve aortic prosthesis. Am Heart J 2012;163:288–94.
[24] Hiltrop N, Belmans A, Claes M, Hornikx M, Peeters B, Flamaing J, et al. Functional performance and quality of life in high-risk comorbid patients undergoing transcatheter aortic valve implantation for symptomatic aortic valve stenosis. Eur Heart J Qual Care Clin Outcomes 2016;2:184–92.
[25] Ludman PF, Moat N, de Belder MA, Blackman DJ, Duncan A, Banya W, et al. Transcatheter aortic valve implantation in the United Kingdom: temporal trends, predictors of outcome, and 6-year follow-up: a report from the UK Transcatheter Aortic Valve Implantation (TAVI) Registry, 2007 to 2012. Circulation 2015;131:1181–90.
[26] Kappetein AP, Head SJ, Genereux P, Piazza N, van Miegham NM, Blackstone EH, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol 2012;60:1438–54.
[27] R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2016 Available from:https://www.R-project.org/.
[28] Eberli F, Valdes M, Menown I, Alhaddad I, Oldroyd K, Roffi M, et al. Comorbidities determine prognosis in patients undergoing coronary stenting: results from two large registries evaluating biolimus-A 9-eluting from biodegradable polymer stents. EuroPCR abstracts 2013 Available from:http://www.pcronline.com/eurointervention/Abstracts2013_issue/europcr-abstracts-2013/194/comorbidities-determine-prognosis-in-patients-undergoing-coronary-stenting-results-from-two-large-registries-evaluating-biolimus-a9-eluting-from-biodegradable-polymer-stents.html.
[29] Jong P, Vowinckel E, Liu PP, Gong Y, Tu JV. Prognosis and determinants of survival in patients newly hospitalized for heart failure: a population-based study. Arch Intern Med 2002;162:1689–94.
[30] Radovanovic D, Seifert B, Urban P, Erberli FR, Rickli H, Bertel O, et al. Validity of Charlson Comorbidity Index in patients hospitalised with acute coronary syndromeInsights from the nationwide AMIS Plus Registry 2002-2012. Heart 2014;100:288–94.
[31] Roques F, Michel P, Goldsonte AR, Nashef SA. The logistic EuroSCORE. Eur Heart J 2003;24:881–2.
[32] Anderson RP. First publications from the Society of Thoracic Surgeons National Database. Ann Thorac Surg 1994;57:6–7.
[33] Steyerberg EW, Borsboom GJJM, van Houwelingen HC, Eijkemans MJC, Habbema JDF. Validation and updating of predictive logistic regression models: a study on sample size and shrinkage. Stat Med 2004;23:2567–86.
[34] DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44:837–45.
[35] Toggweiler S, Humphries KH, Lee M, Binder RK, Moss RR, Freeman M, et al. 5-Year outcome after transcatheter aortic valve implantation. J Am Coll Cardiol 2013;61:413–9.
[36] Arsalan M, Szerlip M, Vemulapalli S, Holper EM, Arnold SV, Li Z, et al. Should transcatheter aortic valve replacement be performed in nonagenarians? Insights from the STS/ACC TVT Registry. J Am Coll Cardiol 2016;67:1387–95.
[37] Moat NE, Ludman P, de Belder MA, Bridgewater B, Cunningham AD, Young CP, et al. Long-term outcomes after transcatheter aortic valve implantation in high-risk patients with severe aortic stenosis: the U.K. TAVI (United Kingdom Transcatheter Aortic Valve Implantation) Registry. J Am Coll Cardiol 2011;58:2130–8.
[38] Ad N, Barnett SD, Speir AM. The performance of the EuroSCORE and the Society of Thoracic Surgeons mortality risk score: the gender factor. Interact Cardiovasc Thorac Surg 2007;6:192–5.
[39] Piazza N, Wenaweser P, van Gameren M, Pilgrim T, Tzikas A, Otten A, et al. Relationship between the logistic EuroSCORE and the Society of Thoracic Surgeons Predicted Risk of Mortality score in patients implanted the CoreValve ReValving system-a Bern-Rotterdam Study. Am Heart J 2010;159:323–9.
[40] Xiong TY, Liao YB, Zhao ZG, Xu YN, Wei X, Zuo ZL, et al. Causes of death following transcatheter aortic valve replacement: a systematic review and meta-analysis. J Am Heart Assoc 2015;4:e002096.
[41] Van Mieghem NM, van der Boon RM, Nuis RJ, Schultz C, van Geuns RJ, Serruys PW, et al. Cause of death after transcatheter aortic valve implantation. Catheter Cardiovasc Interv 2014;83:E277–82.
[42] Green P, Woglom AE, Genereux P, Daneault B, Paradis JM, Schnell S, et al. The impact of frailty status on survival after transcatheter aortic valve replacement in older adults with severe aortic stenosis: a single-center experience. JACC Cardiovasc Interv 2012;5:974–81.