



## Policy Review



## Clinical outcomes of transcatheter aortic valve replacement stratified by left ventricular ejection fraction: A single centre pilot study

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## ABSTRACT

**Introduction:** To define baseline echocardiographic, electrocardiographic (ECG) and computed tomographic (CT) findings of patients with heart failure undergoing transcatheter aortic valve replacement (TAVR) and analyze their overall procedural outcomes.

**Methods:** Between 2018 and 2021, patients with severe aortic stenosis (AS) who performed transcatheter aortic valve replacement (TAVR) in Sabah Al Ahmad Cardiac Centre, Al Amiri Hospital were identified. A retrospective review of patients' parameters including pre-, intra-, and post-procedural data was conducted. Patients were grouped in 2 subgroups according to their EF: EF <40% (HFReEF) and EF ≥ 40%. The data included patients' baseline characteristics, electrocardiographic and echocardiographic details along with pre-procedural CT assessment of aortic valve dimensions. Primary outcomes including post-operative disturbances, pacemaker implantation and in-hospital mortality following TAVR were additionally analyzed.

**Results:** A total of 61 patients with severe AS underwent TAVR. The mean age was 73.5 ± 9, and 21 (34%) of the patients were males. The mean ejection fraction (EF) was 55.5 ± 9.7%. Of 61 patients, 12 (20%) were identified as heart failure with reduced EF (<40%). These patients were younger, more often males, and were more likely to have coronary artery disease (75% versus 53.1%). Left ventricular hypertrophy and diastolic dysfunction was documented in 75% and 58.3% of patients with heart failure with reduced ejection fraction (HFReEF) respectively. Post TAVR conduction disturbances, with the commonest being LBBB was observed in 41.7%. Permanent pacemaker was implanted in 3 of patients with HFReEF (25%). There were no significant differences between the two groups with regards to in hospital mortality (p = 0.618).

**Conclusion:** Severe AS with EF <40% constitute a remarkable proportion of patients undergoing TAVR. Preliminary results of post-operative conduction disturbances and in hospital mortality in HFReEF patients were concluded to not differ from patients with LVEF ≥40%.

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## 1. Introduction

As the aging population increases, a concurrent rise in aortic stenosis is similarly projected [1,2]. Subsequently, the utilization of a minimally invasive procedure such as transcatheter aortic valve replacement

### Abbreviations definitions

TAVR	Transcatheter aortic valve replacement
AS	Aortic stenosis
EF	Ejection fraction
LBBB	Left bundle branch block
HFrEF	Heart failure with reduced ejection fraction
AVA	Aortic valve area
MPG	Mean pressure gradient
SVI	Stroke volume index
Vmax	Peak aortic velocity
CT	Computed tomography

(TAVR) has been validated for patients at high risk for surgical intervention [3,4]. In terms of prognosis, several parameters have been established to predict poor outcomes in patients with AS, including low transvalvular gradient (MPG), low stroke volume index (SVI), and low ejection fraction (EF) [5–8]. Systolic dysfunction has long been established to confer poor outcomes after surgical aortic valve replacement (SAVR) [9]. In regards to TAVR outcomes, however, the prognostic role of baseline LVEF varies in different cohorts, resulting in conflicting evidence. Despite the risks and uncertainty of TAVR in patients with severe systolic dysfunction, clear survival benefits have been established in patients with milder degrees of LV dysfunction [10,11].

Since patients with HFrEF represent a significant proportion of high-risk patients referred for TAVR [12], it is essential to distinguish prognostic parameters implicated in the overall outcomes of such patients. Therefore, our study aims to define baseline characteristics, echocardiographic and CT parameters of patients with HFrEF and analyze their overall procedural outcomes.

## 2. Methods

Between 2018 and 2021, 61 patients with severe aortic stenosis (AS) performing transcatheter aortic valve replacement (TAVR) with the Edwards SAPIEN 3 valve in Sabah Al Ahmad Cardiac Centre, Al Amiri Hospital were identified. A retrospective review of patients' parameters including pre-, intra-, and post-procedural data was conducted. Patients were grouped in 2 subgroups according to their EF: EF <40% (HFrEF) and EF ≥ 40%.

The data included patients' baseline characteristics, electrocardiographic and echocardiographic details including: peak gradient (PG), peak aortic velocity (Vmax), mean pressure gradient (MPG), aortic valve area (AVA) and the presence of left ventricular hypertrophy (LVH) or other valvular lesions. Pre-procedural CT assessment of aortic valve dimensions and bioprosthetic size were additionally analyzed. Post-operative outcomes including conduction disturbances, pacemaker implantation and in-hospital mortality following TAVR were further examined. The ethics committee at the Ministry of Health approved the study protocol. This study has been submitted in line with the STROCSS statement [13]. This study has been registered with the Research Registry with a (UID: 7627).

### 2.1. Statistical techniques

Continuous variables were presented as mean and standard deviation, whereas categorical variables were presented as frequencies and

percentages. Pearson's chi-squared test was used to analyze statistical differences in categorical variables. Continuous variables were analyzed through Linear Model ANOVA. A p value of ≤0.05 was used as a measure of statistical significance. For measuring the association using Chi-square (with α0.025; power = 0.800; a small effect size = 0.30; number of predictors = 3), total desired sample size was 61. Based on the probability of type I error of 0.05, power (1-beta) of 0.8, and medium effect size of 0.30, the minimal sample size is 58 for paired t-test analyses.

## 3. Results

### 3.1. Subject characteristics

A total of 61 severe AS patients underwent TAVR between 2018 and 2021. Of the 61 patients, 20% were categorized to reduced LVEF group (LVEF <40%). Table 1 compares the baseline characteristics of patients in the two subgroups. In patients with HFrEF, 50% were male, with a mean age of 70.5 ± 9. The mean body mass index (BMI) was 32.1.

In terms of cardiovascular risk factors, 16.7% were identified as smokers, and the prevalence of hypertension, diabetes mellitus, and dyslipidemia were found to be 83.3%, 75%, 41.7% respectively in HFrEF patients. Baseline cardiovascular disease including coronary artery disease (75%), prior myocardial infarction (58.3), and stroke (8.3%) were captured. In comparison to patients with EF ≥ 40%, patients with HFrEF were significantly more likely to have undergone percutaneous coronary intervention (p = 0.044).

Pre-admission medications were analyzed in both subgroups (Table 2). The most prevalent medications prescribed in the total study group included bisoprolol (59%), statins (55.7%), clopidogrel (54.1), and aspirin (52.5%).

**Table 1**  
Demographic and clinical characteristics of the study population (N = 61).

Characteristics n (%), unless otherwise specified	Total (N = 61)	HFrEF (EF <40%) (N = 12)	Others (N = 49)	p- value
<b>Demographic data</b>				
Age, yrs	73.5 ± 9	70.5 ± 9	74.2 ± 9	<b>0.203</b>
Mean ± SD				
Male	21 (34.4)	6 (50)	15 (30.6)	<b>0.205</b>
Body mass index	32.6	32.1	32.6	<b>0.893</b>
Mean (Range)	(22.2–54)	(24.2–42)	(22.2–54)	
Smoking	4 (6.6)	2 (16.7)	2 (4.1)	<b>0.114</b>
Chronic kidney disease	17 (27.9)	4 (33.3)	13 (26.5)	<b>0.638</b>
<b>Risk factors</b>				
Hypertension	52 (85.2)	10 (83.3)	42 (85.7)	<b>0.835</b>
Diabetes mellitus	41 (67.2)	9 (75)	32 (65.3)	<b>0.521</b>
Dyslipidemia	28 (45.9)	5 (41.7)	23 (46.9)	<b>0.743</b>
<b>Clinical data</b>				
NYHA class III-IV	7 (11.6)	2 (16.6)	5 (11.6)	<b>0.650</b>
Dyspnea	19 (31.1)	5 (41.7)	14 (28.6)	<b>0.380</b>
Angina	9 (14.8)	2 (16.7)	7 (14.3)	<b>0.835</b>
<b>Cardiovascular disease</b>				
Coronary artery disease	35 (57.4)	9 (75)	26 (53.1)	<b>0.168</b>
Prior MI	47 (77)	7 (58.3)	40 (81.6)	<b>0.147</b>
PCI	25 (41)	8 (66.7)	17 (34.7)	<b>0.044*</b>
CABG	4 (6.6)	1 (8.3)	3 (6.1)	<b>0.782</b>
Stroke	6 (9.8)	1 (8.3)	5 (10.2)	<b>0.845</b>
Pulmonary HTN	9 (14.8)	2 (16.7)	7 (14.3)	<b>0.835</b>

Table 1. Demographic and clinical characteristics of patients undergoing TAVR. Mean ± SD is shown. CABG: Coronary artery bypass surgery; HTN: hypertension; MI: Myocardial infarction; NYHA: New York heart association; PCI: Percutaneous coronary intervention; SD: standard deviation. (\*) denotes statistical significance.

**Table 2**  
Pre-admission medications.

n (%), unless otherwise specified	Total (N = 61)	HFrEF (EF <40%) (N = 12)	Others (N = 49)	p-value
Statins	34 (55.7)	7 (58.3)	27 (55.1)	<b>0.840</b>
Aspirin	32 (52.5)	8 (66.7)	24 (49)	<b>0.272</b>
Clopidogrel	33 (54.1)	8 (66.7)	25 (51)	<b>0.33</b>
Amlodipine	3 (4.9)	1 (8.3)	2 (4.1)	<b>0.542</b>
Warfarin	4 (6.6)	1 (8.3)	3 (6.1)	<b>0.782</b>
Enoxaparin	4 (6.6)	1 (8.3)	3 (6.1)	<b>0.782</b>
Bisoprolol	36 (59)	8 (66.7)	28 (57.1)	<b>0.548</b>
Furesomide	15 (24.6)	2 (16.7)	13 (26.5)	<b>0.477</b>
Apixaban	6 (9.8)	1 (8.3)	5 (10.2)	<b>0.845</b>
Lisinopril	1 (1.6)	1 (8.3)	0	<b>0.042*</b>
Valsartan	5 (8.2)	1 (8.3)	4 (8.2)	<b>0.985</b>
Nitroglycerine	5 (8.2)	3 (25.0)	2 (4.1)	<b>0.018*</b>
Dabigatran	2 (3.3)	0	2 (4.1)	<b>0.477</b>
Rivaroxaban	2 (3.3)	0	2 (4.1)	<b>0.477</b>
Metformin	7 (11.5)	2 (16.7)	5 (10.2)	<b>0.529</b>
Insulin glargine	16 (26.2)	5 (41.7)	11 (22.4)	<b>0.175</b>

**Table 2:** Pre-TAVR baseline medications. (\*) denotes statistical significance.

3.2. Baseline echocardiography

**Table 3** compares baseline echocardiographic parameters in the two subgroups. The mean LVEF in patients with HFrEF was 38.8%, compared to 59.6% in their counterparts. In regards to measures of aortic stenosis severity, the mean aortic gradient and peak aortic velocity were significantly lower in those with left ventricular dysfunction (34.5 mmHg & 3.9 m/s). However, the mean aortic valve area (AVA) was similar in both subgroups (p < 0.952). Moderate or severe aortic regurgitation and tricuspid regurgitation were found in 33.3% and 50% of patients with LVEF <40%. A higher trend of left ventricular hypertrophy and diastolic dysfunction was observed in patients with systolic dysfunction compared to patients with normal ejection fraction (75% & 58% vs. 81.6 & 71.4%). Additionally, echocardiographic parameters including left ventricular hypertrophy was prevalent in 80% of the total study population, with no significant association with mortality (p = 0.618).

**Table 3**  
Baseline Echocardiographic and ECG parameters.

n (%), unless otherwise specified	Total (N = 61)	HFrEF (EF <40%) (N = 12)	Others (N = 49)	p-value
Echocardiography				
LVEF, %	55.5 ± 9.7	38.8 ± 6.8	59.6 ± 4.3	< <b>0.001*</b>
Mean ± SD				
Mean aortic gradient (mmHg)	44.5 ± 11.6	34.5 ± 5	46.7 ± 11.5	<b>0.003*</b>
Mean ± SD				
Peak aortic velocity (m/s)	4.3 ± 0.5	3.9 ± 0.2	4.4 ± 0.5	<b>0.046*</b>
Mean ± SD				
Aortic valve area (cm <sup>2</sup> )	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	<b>0.952</b>
Mean ± SD				
Peak aortic gradient (mmHg)	74.2 ± 17.5	65.7 ± 10.2	75.7 ± 18.2	<b>0.167</b>
Mean ± SD				
Moderate-severe AR	17 (27.9)	4 (33.3)	13 (26.5)	<b>0.638</b>
Moderate-severe TR	26 (42.6)	6 (50)	20 (40.8)	<b>0.564</b>
LVH	49 (8.3)	9 (75)	40 (81.6)	<b>0.604</b>
Diastolic dysfunction	42 (68.9)	7 (58.3)	35 (71.4)	<b>0.380</b>

**Table 3:** Baseline pre-TAVR echocardiographic parameters. Mean ± SD. AR: aortic regurgitation; TR: tricuspid regurgitation; LVH: left ventricular hypertrophy; SD: standard deviation; (\*) denotes statistical significance.

3.3. Baseline multidetector CT (MDCT)

Preprocedural CT imaging (TAVR protocol) findings in patients with HFrEF and their counterparts are compared in (**Table 4**). Severe calcifications were more likely in patients with systolic dysfunction (p = 0.033). Additionally, distance to right coronary artery was shorter (13.2 ± 3.7) in patients with HFrEF (p = 0.048). The mean bioprosthetic size was 25.8 ± 2.4 for patients with systolic dysfunction.

3.4. Procedural outcomes

Post TAVR procedural outcomes including conduction disturbances and pacemaker implantation is demonstrated in (**Table 5**). LBBB was most common conduction disturbance induced by TAVR, with a prevalence of 29.5% in the total study population. It was reported in 41.7% and 26.5% in patients with HFrEF and their counterparts, respectively (p = 0.303). Other arrhythmias induced by TAVR in patients with systolic dysfunction include first-degree heart block (16.7%), complete heart block (8.3%), and atrial fibrillation (16.7%), with no statistical difference between the two-subgroups.

Of the total study population, 7 patients (11.5%) implanted a permanent pacemaker secondary to 2nd degree and complete heart block, out of which 3 constituted heart failure patients. In terms of in hospital outcomes post-TAVR, only 1 mortality was observed in LVEF ≥40% subgroup, due to asystole complicating 2:1 heart block. Furthermore, post-operative LBBB was not a predictor of mortality outcomes (p = 0.119).

**Table 4**  
Pre-procedural MDCT assessment.

n (%), unless otherwise specified	Total (N = 61)	HFrEF (EF <40%) (N = 12)	Others (N = 49)	p-value
Maximum leaflet length (mm)	17 ± 3.7	17.9 ± 2.3	16.8 ± 3.9	<b>0.616</b>
Mean ± SD				
Degree of calcifications	6 (9.8)	1 (8.3)	5 (10.2)	<b>0.033*</b>
o Mild				
o Moderate	24 (39.3)	1 (8.3)	23 (46.9)	
o Severe	31 (50.8)	10 (83.3)	21 (42.9)	
Short axis diameter (mm)	21.8 ± 2.5	22.1 ± 2.5	21.8 ± 2.5	<b>0.713</b>
Mean ± SD				
Long axis diameter (mm)	26.8 ± 3.3	26.3 ± 2.8	26.9 ± 3.5	<b>0.623</b>
Mean ± SD				
Annular area (mm)	464.7 ± 100.3	447.1 ± 92.7	469 ± 102.6	<b>0.521</b>
Mean ± SD				
Annular circumference (mm)	76.8 (7.6)	75.5 (7.9)	77.1 (7.7)	<b>0.560</b>
ST junction diameter (mm)	25.8 ± 3.5	27.4 ± 3.8	25.5 ± 3.4	<b>0.222</b>
Mean ± SD				
Height of valsava (mm)	22 ± 4	21.7 ± 2.1	22.1 ± 4.3	<b>0.801</b>
Mean ± SD				
Area of sinus of valsava (mm)	742.2 ± 204.6	841.3 ± 148.7	730.4 ± 209.4	<b>0.385</b>
Mean ± SD				
Distance to LCA	12.9 ± 2.8	11.9 ± 3.2	13.2 ± 2.7	<b>0.155</b>
Mean ± SD				
Distance to RCA	15 ± 3.4	13.2 ± 3.7	15.5 ± 3.2	<b>0.048*</b>
Mean ± SD				
Bioprosthetic size	24.8 ± 2	25.8 ± 2.4	24.5 ± 1.8	<b>0.058</b>
Mean ± SD				

**Table 4:** Baseline pre-TAVR computed tomographic findings. Mean ± SD. LCA: left coronary artery; RCA: right coronary artery; SD: standard deviation; (\*) denotes statistical significance.

**Table 5**  
Baseline ECG, Conduction disturbances and Pacemaker implantation Post-TAVR.

n (%), unless otherwise specified	Total (N = 61)	HFrEF (EF <40%) (N = 12)	Others (N = 49)	p-value
Baseline ECG	40 (66.7)	9 (75)	31 (64.6)	<b>0.729</b>
o SR				
oLBBB	3 [5]	1 (8.3)	2 (4.2)	
oAF	16 (26.7)	2 (16.7)	14 (29.2)	
oAVNRT	1 (8.3)	0	1 (2.1)	
Post-TAVR	18 (29.5)	5 (41.7)	13 (26.5)	<b>0.303</b>
oLBBB				
oRBBB	4 (6.6)	0	4 (8.2)	<b>0.306</b>
o1st degree HB	4 (6.6)	2 (16.7)	2 (4.1)	<b>0.114</b>
o2nd degree HB	1 (1.6)	0	1 [2]	<b>0.618</b>
oBifascicular block	1 (1.6)	0	1 [2]	<b>0.618</b>
oCHB	5 (8.2)	1 (8.3)	4 (8.2)	<b>0.985</b>
oAF	4 (6.6)	2 (16.7)	2 (4.1)	<b>0.114</b>
Pacemaker implantation	7 (11.5)	3 [25]	4 (8.2)	<b>0.101</b>

**Table 5:** Baseline pre-TAVR ECG and conduction disturbances post TAVR. Mean ± SD. AF: atrial fibrillation; AVNRT: atrioventricular re-entry tachycardia; CHB: complete heart block; ECG: electrocardiography; HB: heart block; LBBB: left bundle branch block; RBBB: right bundle branch block; SR: sinus rhythm; SD: standard deviation; (\*) denotes statistical significance.

**4. Discussion**

This single-centre experience of TAVR outcomes in Kuwait analyzed baseline characteristics of patients with HFrEF along with their overall procedural outcomes. Patients with systolic dysfunction constituted 20% of patients with severe AS undergoing TAVR. Baseline characteristics were non-significantly different between the two sub-groups; however, a significantly larger proportion of patients with heart failure had a history of PCI, suggesting a higher comorbidity of coronary artery disease and ultimately systolic dysfunction. In regards to their baseline echocardiography, both peak aortic velocity and mean aortic gradient were significantly lower in patients with heart failure, implying the presence of a low-flow low-gradient state. Pre-procedural CT further revealed a higher degree of valvular calcifications in patients with systolic dysfunction, further contributing to the low-flow low-gradient state.

Moreover, results revealed non-significant differences in major outcomes including conduction disturbances, pacemaker implantation, and in hospital mortality in patients with HFrEF. A higher trend of LBBB was observed in patients with systolic dysfunction compared to patients with LVEF ≥40%. Only three patients with heart failure required pacemaker implantation secondary to 2nd degree and complete heart block. In-hospital mortality was reported in 1 patient within the LVEF ≥40% subgroup.

Left ventricular dysfunction has long been established as a marker for poor outcomes after surgical aortic valve replacement (SAVR), despite an increased survival in comparison to medical therapy [14,15]. The mortality of patients with reduced EF undergoing aortic valve replacement was originally reported to be 12% higher than patients with preserved ejection fraction, allowing the utility of systolic function as a surrogate for survival outcomes [16]. This was further supported in the CURRENT AS registry, with results revealing impaired survival in patients with LVEF <60% undergoing AVR [17]. The advent of TAVR has clearly transformed the conventional management of such patients, with results revealing favorable hemodynamic changes with TAVR in comparison to SAVR [18]. The impact of baseline systolic dysfunction on TAVR outcomes has been controversial, however, with conflicting results. In a cohort of 11,292 AS patients undergoing TAVR, systolic dysfunction (LVEF <30%) was not significantly associated with higher rates of mortality [19]. These results were further replicated in the

PARTNER trial, where results revealed similar early and late mortality rates in AS patients, regardless of their LVEF % [20]. In the more recent PARTNER 2 cohort, however, baseline LVEF % was an independent predictor of 2-year cardiovascular mortality, contradicting the results of previous studies [21].

The main clinical implication suggested by this finding involves the necessity of early intervention in patients with systolic dysfunction, with the use of higher LVEF cut-off values to improve their outcomes. Future trials and investigations should analyze the prognostic significance of early intervention in patients with milder degrees of systolic dysfunction, potentially improving their overall survival after TAVR. The possible benefits of early intervention in patients with moderate AS and low LVEF is currently studied in the TAVR UNLOAD trial (NCT0266145), comparing transfemoral TAVR with standard heart failure regimens.

Our cohort revealed a significantly higher proportion of HFrEF patients with LFLG states. In terms of prognosis, LFLG severe AS has been previously established to confer poor outcomes in patients undergoing aortic valve replacement [22,23]. More recently, however, the TOPAS registry revealed similar clinical outcomes in patients with severe systolic dysfunction and LFLG states, favoring TAVR over SAVR in such population [24]. The recovery of systolic function was additionally suggested to be significantly higher in patients with severe heart failure in comparison to patients with preserved ejection fraction [25], further delineating the positive advent of TAVR in such at-risk population. Future trials should further analyze the overall outcomes of patients with heart failure undergoing TAVR, as they constitute a substantial proportion of high-risk patients referred for TAVR. The limitations of the study are related to single centre data acquisition resulting in a smaller sample size, which may limit statistical power. Additionally, this study was retrospective in nature with a short-follow up period, which limits the ability to detect delayed complications and out of hospital mortality outcomes post-TAVR. In addition, selection bias and inter-observer variability for clinical and echocardiographic evaluations performed by different physicians may contribute to limitations encountered by this retrospective analysis.

**5. Conclusion**

This is the first reported outcome study of TAVR in patients with HFrEF in Kuwait. Post-TAVR conduction disturbances were observed in almost half of patients with systolic dysfunction. In addition, requirement for pacemaker implantation was observed in both subgroups, regardless of the LVEF%. In terms of their in-hospital outcomes, systolic dysfunction was not a predictor of mortality. This association needs to be further clarified by future follow-up and additional studies.

**Ethics approval statement**

This study was approved by the ethics committee and Ministry of Health Kuwait.

**Funding statement**

No funding available for this study.

**Author contributions**

Joud Al Balool contributed to study concept, design, data collection, analysis, draft preparation, and final submission.

Mohammed Al Jarallah contributed to study concept, design, data collection, analysis, draft preparation, and final submission.

Rajesh Rajan contributed to study concept, design, data collection, analysis, draft preparation, and final submission Raja Dashti contributed to study concept, design, data collection, analysis, draft preparation, and final submission.

Nader Alasousi contributed to study concept, design, data collection, analysis, draft preparation, and final submission.

Vladimir Koteivski contributed to study concept, design, data collection, analysis, draft preparation, and final submission.

Ahmed Said contributed to study concept, design, data collection, analysis, draft preparation, and final submission.

Taha Mousa contributed to study concept, design, data collection, analysis, draft preparation, and final submission.

Retaj Al Haroun contributed to study concept, design, data collection, analysis, draft preparation, and final submission.

Gary Tse contributed to study concept, design, data collection, analysis, draft preparation, and final submission.

Kobalava D. Zhanna contributed to study concept, design, data collection, analysis, draft preparation, and final submission.

Parul Setiya contributed to study concept, design, data collection, analysis, draft preparation, and final submission.

Ahmad Al-Saber contributed to study concept, design, data collection, analysis, draft preparation, and final submission.

Peter A Brady contributed to study concept, design, data collection, analysis, draft preparation, and final submission.

### Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

### Registration of research studies

1. Name of the registry: researchregistry7627
2. Unique Identifying number or registration ID: researchregistry7627
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): <https://www.researchregistry.com/browse-the-registry/#home/>

### Clinical trial registration

Researchregistry7627.

### Guarantor

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### Patient consent statement

Patient consented was not mandated for this retrospective observational study. Permission to reproduce material from other sources: No material from other sources is included in this study.

### Declaration of competing interest

No conflict of interest exists for any author on this manuscript.

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