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ORIGINAL RESEARCH

VALVULAR HEART DISEASE

Comorbidities and Symptom Status in Moderate and Severe Aortic Stenosis

A Multicenter Clinical Cohort Study

David Playford, MBBS, PhD,[a,b] Nisha Schwarz, PhD,[a] Enayet Chowdhury, PhD,[a] Anna Williamson, PhD,[a] MyNgan Duong, PhD,[a] Leighton Kearney, MBBS, PhD,[a,c] Simon Stewart, PhD,[d,e] Geoff Strange, PhD[b,f,g]

ABSTRACT

BACKGROUND Symptoms associated with severe aortic stenosis (AS) are used to guide management.

OBJECTIVES The purpose of this study was to examine the pattern of symptoms, comorbidities, and cardiac damage in moderate and severe AS.

METHODS A total of 846,198 echocardiographic investigations from 330,940 individuals aged >18 years were selected for the most recent echocardiogram, moderate or severe AS (mean gradient 20.0-39.9 mm Hg, aortic valve peak gradient 3.0-3.9 m/s and aortic valve area >1.0 cm^2; or ≥ 40.0 mm Hg, ≥4.0 m/s or ≤1.0 cm^2, respectively), and a cardiologist consultation. Natural Language Processing was applied to letters to extract comorbidities, dyspnea, chest pain, and syncope. Patients with prior aortic valve replacement were excluded.

RESULTS 2,213 patients (0.7% overall, 32.8% females) had moderate and 3,416 (1.0%, 47.3% females) had severe AS. Comorbidities were common, including hypertension, (56.6% moderate AS, 53.1% severe AS, $P = 0.01$), coronary disease (46.0% and 46.8%, respectively, $P = 0.58$) and atrial fibrillation (29.6% and 34.8%, respectively, $P < 0.001$). Symptoms were also common in *both* moderate (n = 915, 41.3%) and severe (n = 1,630, 47.7%) AS ($P < 0.001$). Comorbidities were more likely in symptomatic vs asymptomatic patients ($P < 0.001$). Dyspnea was more likely in severe AS, whereas angina and syncope were similar in moderate vs severe AS. In multivariable analysis, only dyspnea was associated with severe (vs moderate) AS (OR: 1.73, 95% CI: 1.41-2.13, $P < 0.001$). In both adjusted and unadjusted models, the degree of cardiac damage did not relate to presence of any symptoms but was associated with AS severity.

CONCLUSIONS Dyspnea is common in *both* moderate and severe AS, is associated with comorbidities and is not related to the degree of cardiac damage. Symptom-guided management decisions in AS may need revision. (JACC Adv 2023;2:100356) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Advara Heart Care, Leabrook, Adelaide, Australia; [b]School of Medicine, The University of Notre Dame, Fremantle, Australia; [c]Cardiology, Warringal Private Hospital, Heidelberg, Victoria, Australia; [d]Institute for Health Research, The University of Notre Dame, Fremantle, Australia; [e]School of Medicine, Dentistry and Nursing, University of Glasgow, Glasgow, United Kingdom; [f]Heart Research Institute, Sydney, Australia; and the [g]Department of Cardiology, Royal Prince Alfred Hospital, Sydney, Australia.
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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AS = aortic stenosis

AV = aortic valve

AVA = aortic valve area

AVR = aortic valve replacement

BMI = body mass index

CAD = coronary artery disease

CKD = chronic kidney disease

EMR = electronic medical record

LV = left ventricular

LVEF = left ventricular ejection fraction

LVOT = left ventricular outflow tract

NLP = Natural Language Processing

TR = tricuspid regurgitation

Aortic stenosis (AS) is the most prevalent form of valvular heart disease,[1-3] and is clinically silent in its earlier forms. By convention, symptoms are thought to only become apparent when the AS is severe enough to provoke ventricular decompensation. At this critical juncture, surgical aortic valve replacement (AVR), or in suitable patients, transcatheter AVR is recommended.[4] However, recent evidence has shown that less severe forms of AS are also associated with high mortality.[5] This creates a clinical conundrum as to the ideal management strategies for these individuals.[5,6] Recent clinical trial data has supported consideration of AVR in critical asymptomatic AS,[7,8] associated with a 2- to 3-fold lower cardiovascular mortality among patients who underwent early surgical intervention than those who received conservative care.[9] The current evidence gap relating to valve intervention in various forms of moderate AS is currently the subject of ongoing clinical trials.

Despite conventional clinical wisdom, the true prevalence of symptoms in moderate AS is poorly understood. A recent publication[6] suggested just under half of all patients with moderate AS were symptomatic. This included 17% of patients who were highly symptomatic (NYHA functional class III-IV). However, the results were not corrected for the presence of clinical comorbidities and their treatments. Symptoms observed in the setting of moderate and severe AS may be due to comorbidities typically found in those of similar age and with common risk factors. These include coronary artery disease, heart failure, chronic kidney disease, or hypertension and may result in spurious associations with AS. Further, any symptoms due to AS are likely to be associated with the degree of cardiac damage and its independent association with mortality,[10,11] indicating late stage disease and a strong determinant of outcome after AVR.[12]

Because of the potential importance of symptoms as a risk marker in AS, we studied a clinical cohort being routinely investigated for heart disease, to assess whether the pattern or association of symptoms typically ascribed to AS remained associated after adjusting for their demographic and clinical characteristics.

METHODS

STUDY DESIGN. Advara Heart Care is a large private cardiology service in Australia with over 80 clinical practice locations, including echocardiography and clinical cardiology services. A single, unified electronic medical record (EMR) comprising all echocardiography studies, clinical outpatient consultation letters, invasive cardiac procedures, implanted device registries, hospitalizations, comorbidities, and treatments allows for the extraction of health-related data.

PATIENT DATA SELECTION. Deidentified patient-level data from echocardiographic reports (inclusive of aortic valve [AV] profiling), clinical characteristics, and clinical consultation letters were extracted from the EMR system. A total of 846,198 echocardiographic investigations from 330,940 unique individuals were extracted, shown in **Figure 1**, representing 80 separate testing locations across Australia. One echocardiogram report was evaluated per patient. If a patient had multiple echocardiograms, the most recently recorded echocardiogram was used. Patients aged <18 years at their first echocardiography study, or those without consultation letters, were excluded from the study. Appropriate ethics approval was obtained to perform this study by a National Human Research Ethics Committee HREC#2022/ETH00918 and adheres to the Declaration of Helsinki.

CALCULATIONS TO DETERMINE PRESENCE AND SEVERITY OF AS. AS severity was determined using current guidelines,[4] with aortic valve area (AVA) calculated according to the formula:

$$\mathrm{AVA} = \left(\pi(\mathrm{LVOTd})^2 \,/\, 4\right) \times \left(\mathrm{LVOTV}_{\mathrm{Vpeak}} \,/\, \mathrm{AV}_{\mathrm{Vpeak}}\right)$$

where LVOTd = LVOT diameter (cm)

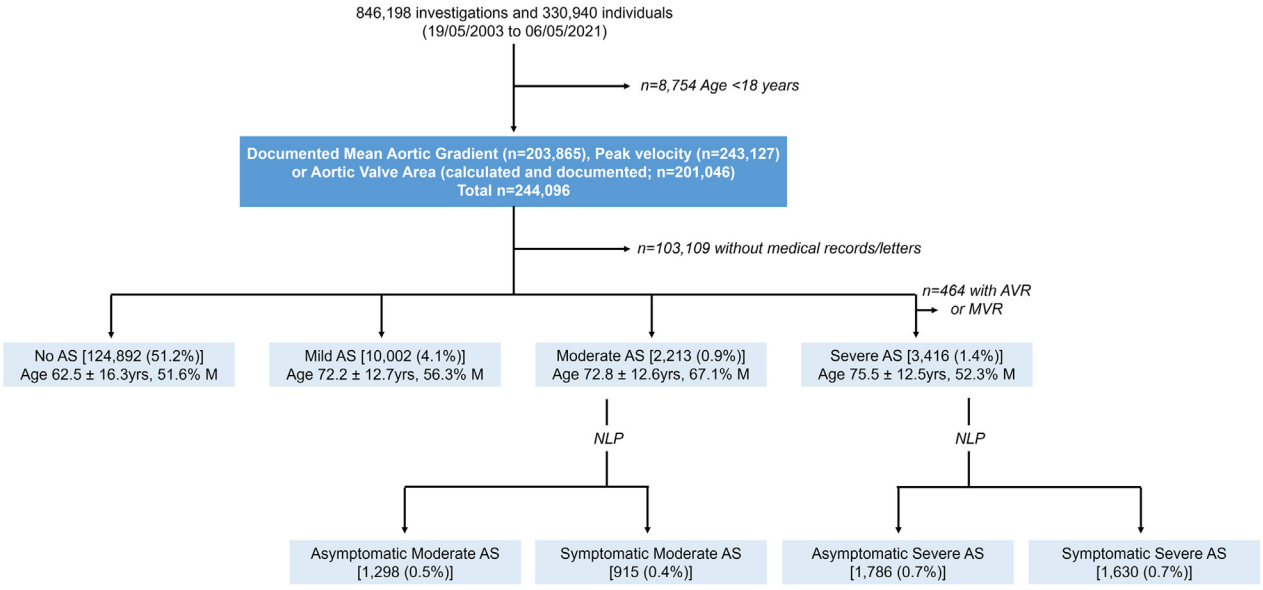
All individuals were categorized based on standard echocardiographic criteria as having:

a) No AS (mean AV gradient <10.0 mm Hg or peak AV velocity <2.0 m/s), AND AVA ≥1.0 cm^2,
b) Mild AS (10.0-19.9 mm Hg/2.0-2.9 m/s and AVA ≥1.0 cm^2),
c) Moderate AS (20.0-39.9 mm Hg/3.0-3.9 m/s and AVA >1.0 cm^2), or
d) Severe AS (≥40.0 mm Hg/≥4.0 m/s or AVA ≤1.0 cm^2), using the last documented echocardiogram (for those with multiple echocardiograms) to define AS severity.

Also consistent with contemporary guidelines,[4] an AVA of <1.0 cm^2 was used to further reclassify those with severe, low-gradient AS (AVA <1.0 cm^2) despite having a mean AV gradient <40.0 mm Hg and/or peak AV velocity <4.0 m/s.

To further refine the results and remove any potential sources of error, echocardiographic

FIGURE 1 Study Flowchart for Identifying AS Clinical Cohort



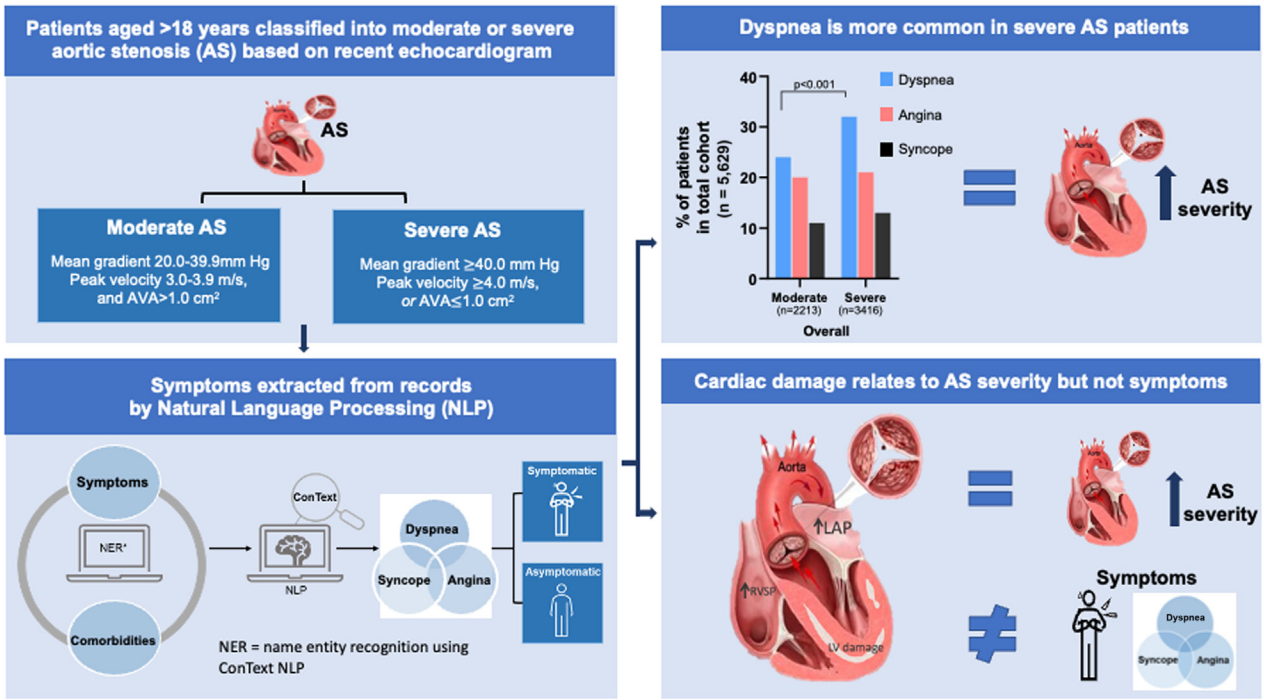
AS = aortic stenosis; AVR = aortic valve replacement; MVR = mitral valve replacement.

measurements were reviewed for normality and clinically relevant distributions.

NATURAL LANGUAGE PROCESSING OF CLINICAL LETTERS TO IDENTIFY SYMPTOMS. To identify patients with or without symptoms in the moderate and severe AS cohorts, a supervised machine-learning classifier was developed, which analyzed clinical consultation letters to search for specified terminology using Named Entity Recognition (Supplemental Figure 1). Once these terminologies were found, a ConText algorithm was used to determine the context of that term (ie, negated, hypothetical, historical, or experienced).[12] This allowed indication of the patient's symptoms, comorbidities, past treatments, family history, medication, and referral to treatments. The algorithm was adjudicated for specificity and sensitivity by manually reading through the letters and evaluating 881 terms in 100 documents randomly chosen (1 document per patient). The accuracy of term extraction for the algorithm was calculated as >98% for sensitivity and >90% for specificity in symptom recognition. Dates of when terms were identified were evaluated and extracted enabling distinction between multiple clinical consultation letters per patient. The 3 symptoms of interest were dyspnea (including incline, walking, and exertion), angina, and syncope. Patient records with any AVR were excluded from moderate and severe AS groups if AVR had occurred prior to and up to 1-week post baseline echocardiography.

According to the above criteria, moderate and severe AS patients and cardiology consults had their letters (for all consultations) (n = 5,629) processed for symptomology and comorbidities using the algorithm (**Central Illustration**). Once unstructured data was processed, the patient cohort was classified based on the presence or absence of symptoms of AS. The main assumption made in the study was that *missing data* for any of the symptoms and comorbidities were interpreted as *not present/absent* for that specific symptom or comorbidity. Sensitivity analyzes were performed on definite vs assumptive symptoms to determine the impact of this assumption. A second assumption was made if symptoms occurred before 2 years of the first echocardiogram date and were not recurrent, the patient was classified as asymptomatic. Symptomatic AS patients were defined if symptoms occurred within 2 years of the first echocardiography date and/or if symptoms occurred after the echocardiography date.

CENTRAL ILLUSTRATION Comorbidities and Symptoms in Moderate and Severe Aortic Stenosis



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The cohort was then categorized into the following AS groups: 1) symptomatic moderate; 2) asymptomatic moderate; 3) symptomatic severe; and 4) asymptomatic severe (Figure 1). Asymptomatic moderate AS was excluded from the correlation and assumption analyzes but included in baseline analyzes.

Additional patient characteristics and comorbidities collected using the Natural Language Processing (NLP) system coronary artery disease (CAD) including patients who had a prior myocardial infarction, coronary artery bypass grafting, or coronary angioplasty/stenting procedure. A history of heart failure, pacemaker, hypertension, diabetes, chronic kidney disease, atrial fibrillation, dementia or cancer, was also collected from the NLP system. If a comorbidity was not mentioned in letters/EMR, it was interpreted as the absence of comorbidity.

STATISTICAL ANALYSIS. We compared baseline characteristics of the patients by asymptomatic and symptomatic status among moderate and severe AS patients. Categorical variables were reported as numbers with percentages and compared using the chi-square test. Continuous variables were reported either as mean ± SD or median (IQR) depending on distribution of variables whether symmetric or skewed. Data sets were tested for normality of distribution by Skewness-Kurtosis test. Differences in continuous variables were compared using analysis of variance for normally distributed data and Wilcoxon rank sum (Mann-Whitney *U* test) test for non-normally distributed variables. No data were imputed.

To evaluate the association between moderate and severe AS, and the risk of symptoms (any symptom, dyspnea, angina, syncope, or presence of all 3 symptoms), we used univariable and multivariable logistic regression models. Multivariable models were adjusted for: 1) age, sex, body mass index (BMI) and left ventricular ejection fraction (LVEF); 2) age, sex, BMI, LVEF and echocardiographic parameters (left ventricular [LV] mass index, tricuspid regurgitation [TR] velocity, septal e′ velocity and E/e′ ratio); 3) age, sex, BMI, LVEF and the presence of comorbidities; 4) age, sex, BMI, LVEF, presence of comorbidities and echocardiographic parameters; and 5) age, sex, and presence of comorbidities.

To explore the predictors of symptoms with moderate and severe AS characteristics, we firstly used a univariable logistic regression model to explore the association of the characteristics with symptoms

(ie, any symptom, dyspnea, angina, or syncope). Thereafter, characteristics with a univariable *P* value of <0.10 were included in a multivariable logistic regression model to identify the predictors that were strongly associated with symptoms. All statistical analyzes were performed using Stata version 17.0 for Windows.

RESULTS

BASELINE CLINICAL CHARACTERISTICS BASED ON THE PRESENCE OF SYMPTOMS. Overall, 2,213 patients (0.7% overall, 32.8% females) had moderate and 3,416 (1.0%, 47.3% females) had severe AS based on echocardiographic profiling. Symptoms were documented in the patient's clinical record in 45.2% (n = 2,545) of cases. In the moderate AS group, symptoms were documented in 41.3% (n = 915) of patients, and in 47.7% (n = 1,630) of 3,416 individuals with severe AS, shown in **Figure 1**.

Table 1 summarizes the clinical characteristics of the entire cohort. Symptoms were common in both groups, representing 915 of 2,213 (41.3%) patients with moderate AS and 1,630 of 3,416 (47.7%) with severe AS. Symptoms were more likely in both moderate and severe AS with increasing age and higher BMI. AV profiling was similar for symptomatic and asymptomatic individuals in both moderate (mean AV gradient 24.0 mm Hg, IQR: 21.0-29.0 mm Hg for asymptomatic and 25.0 mm Hg, 22.0-30.0 mm Hg for symptomatic individuals, $P = 0.003$) and severe AS (37 mm Hg, IQR: 26.0-49.0 mm Hg vs 40.0 mm Hg, IQR: 28.0-49.0 mm Hg respectively, $P = 0.04$). The other echocardiographic characteristics were also similar for those with or without symptoms in both moderate and severe AS. Among symptomatic patients, dyspnea was more likely in severe than moderate AS (n = 1,091 [66.9%] vs n = 523 [57.2%], $P < 0.001$), however angina and syncope were equally represented in both AS groups (49.4% and 26.2% of moderate AS, and 43.6% and 26.3% of severe AS respectively, P = NS). While the presence of symptoms in moderate and severe AS was similar, the echocardiographic profile of men and women presented differently. Men had a larger LV mass, with a median LV mass index of 109 (IQR: 90.0-129.0) compared with women (96.0, IQR: 79.0-119.0, $P < 0.001$). Women had signs of increased LV filling pressure compared with men: E:e′ 16.0 (IQR: 12.0-21.0) vs 13.0 (IQR: 10.0-17.0), respectively ($P < 0.001$).

Comorbidities were common in both moderate and severe AS overall, with hypertension representing over half of all individuals (56.6% moderate AS, 53.1% severe AS), closely followed by coronary heart disease (46.0% and 46.8%, respectively). Atrial fibrillation (AF) was present in almost one-third of all patients (29.6% and 34.8%, respectively). Symptomatic patients in both moderate and severe AS were more likely to have at least one comorbidity, a consistent finding among all diseases except for cancer where no difference was observed. Severe AS patients had a greater proportion of hypertension, heart failure, and AF compared with moderate AS patients but otherwise the comorbidity profile of moderate and severe AS was similar.

SYMPTOMATIC PROFILE IN STUDY COHORT. Of the total cohort (asymptomatic and symptomatic), the overall frequency of symptoms was similar (**Figure 2A**). Dyspnea was the most common symptom in both moderate and severe AS, with a greater proportion of dyspnea in severe AS (67% vs 57% respectively, $P < 0.001$) (**Figure 2B**). Males and females behaved differently, with females displaying a greater proportion of dyspnea than males in moderate AS (females vs males: 64% vs 54%, $P = 0.003$) (**Figure 2B**). Angina and syncope had a similar frequency between moderate and severe AS, and between males and females.

RELATIONSHIP BETWEEN CONFOUNDERS AND SYMPTOMS. In a univariable association, severe AS was associated with dyspnea but not angina or syncope (**Figure 3A**, Supplemental Table 1). In fully adjusted models accounting for age, sex, BMI, LVEF category, dyspnea was the only symptom significantly associated with severe AS (vs moderate AS) OR: 1.73, $P < 0.0001$) (**Figure 3B**). Moderate and severe AS demonstrated almost identical OR for angina (OR: 1.03, 95% CI: 0.82-1.29) and syncope (OR: 1.03, 95% CI: 0.78-1.37) (**Figure 3B**). We saw no association between angina and syncope with increasing AS severity after the addition of patient comorbidities, LVEF, LV mass index, and TR velocity (**Figures 3C to 3E**). In multiple different models shown in **Figure 3** including adjustment for age, sex, body size, echocardiographic variables, and comorbidities, dyspnea remained consistently associated with severe AS (**Figures 3C to 3F**). Amongst individuals with symptomatic dyspnea, diastolic function parameters were similar between moderate and severe AS, with a slightly higher E:e' ratio in severe AS (moderate AS, E:e′ = 14.0, IQR: 10.5-18.5 vs severe AS, E:e′ = 15.0, IQR: 12.0-20.0, $P < 0.001$).

A more granular investigation of individual comorbidities and symptom status in moderate and severe AS is shown in **Figure 4** (Supplemental Tables 2 and 3). The expected association between coronary artery disease (CAD) and angina was observed (OR:

TABLE 1 Baseline Patient Characteristics

	Moderate AS				Severe AS				Overall Moderate vs Severe *P* Value
	Overall (N = 2,213)	**Asymptomatic (n = 1,298)**	**Symptomatic (n = 915)**	***P* Value**	**Overall (N = 3,416)**	**Asymptomatic (n = 1,786)**	**Symptomatic (n = 1,630)**	***P* Value**	
Age in y	75.0 (66.4-81.8) (n = 2,212)	74.6 (65.6-81.3) (n = 1,297)	75.6 (67.4-82.2) (n = 915)	0.006	78.0 (69.2-84.6) (n = 3,416)	77.9 (68.1-84.6) (n = 1,786)	78.2 (70.6-84.7) (n = 1,630)	0.011	<0.001
Male	1,487 (67.2%)	875 (67.4%)	612 (66.9%)	0.80	1,800 (52.7%)	959 (53.7%)	841 (51.6%)	0.22	<0.001
BMI (kg/m^2)	28.4 (25.5-32.3) (n = 1,495)	28.1 (25.0-31.6) (n = 833)	28.7 (25.9-33.2) (n = 662)	0.011	27.4 (24.2-31.2) (n = 2,102)	27.1 (24.1-30.8) (n = 1,022)	27.7 (24.4-31.5) (n = 1,080)	0.014	<0.001
Baseline AV profile									
AV area (cm)	1.3 (1.1-1.5) (n = 2,213)	1.3 (1.1-1.6) (n = 1,298)	1.3 (1.1-1.5) (n = 915)	0.085	0.8 (0.7-1.0) (n = 3,235)	0.8 (0.7-1.0) (n = 1,709)	0.8 (0.7-1.0) (n = 1,526)	0.12	<0.001
Peak AV velocity (m/s)	3.3 (3.1-3.5) (n = 2,213)	3.3 (3.1-3.5) (n = 1,298)	3.3 (3.1-3.6) (n = 915)	0.033	4.1 (3.4-4.5) (n = 3,416)	4.0 (3.3-4.5) (n = 1,786)	4.1 (3.4-4.5) (n = 1,630)	0.043	<0.001
Mean AV gradient (mm Hg)	24.0 (21.0-29.0) (n = 2,195)	24.0 (21.0-29.0) (n = 1,289)	25.0 (22.0-30.0) (n = 906)	0.003	39.0 (27.0-49.0) (n = 3,400)	37.0 (26.0-49.0) (n = 1,774)	40.0 (28.0-49.0) (n = 1,626)	0.042	<0.001
Baseline ventricular dimensions and function									
LVDD (cm)	4.7 (4.3-5.2) (n = 2,190)	4.7 (4.3-5.2) (n = 1,284)	4.7 (4.2-5.2) (n = 906)	0.45	4.6 (4.1-5.1) (n = 3,356)	4.6 (4.1-5.1) (n = 1,757)	4.6 (4.2-5.1) (n = 1,599)	0.69	<0.001
LVEF (Simpson)	64.0 (58.0-68.0) (n = 975)	64.0 (59.0-68.0) (n = 555)	63.0 (58.0-68.0) (n = 420)	0.11	62.0 (55.0-67.0) (n = 1,415)	62.0 (55.0-67.0) (n = 671)	62.0 (55.0-67.0) (n = 744)	0.91	<0.001
TR peak velocity	2.6 (2.4-2.9) (n = 1,370)	2.6 (2.4-2.9) (n = 796)	2.6 (2.4-2.9) (n = 574)	0.20	2.7 (2.5-3.0) (n = 2,284)	2.7 (2.4-3.0) (n = 1,185)	2.7 (2.5-3.1) (n = 1,099)	0.18	<0.001
LV mass/BSA (indexed)	100.0 (83.3-121.0) (n = 607)	99.0 (82.0-121.0) (n = 331)	101.0 (85.0-122.0) (n = 276)	0.32	107.0 (87.0-128.0) (n = 913)	109.0 (88.0-129.0) (n = 420)	105.5 (86.0-128.0) (n = 493)	0.29	<0.001
Septal e' velocity	6.0 (5.0-8.0) (n = 1,632)	6.0 (5.0-8.0) (n = 901)	6.0 (5.0-8.0) (n = 731)	0.051	6.0 (4.0-7.0) (n = 2,292)	6.0 (5.0-7.0) (n = 1,118)	6.0 (4.0-7.0) (n = 1,174)	0.006	<0.001
E/e' ratio	13.0 (10.0-17.0) (n = 1,590)	13.0 (10.0-16.0) (n = 880)	13.0 (10.0-18.0) (n = 710)	0.027	15.0 (11.0-20.0) (n = 2,215)	15.0 (11.0-20.0) (n = 1,088)	15.0 (11.7-20.0) (n = 1,127)	0.012	<0.001
Symptoms									
Any symptoms present			915 (100.0%)				1,630 (100.0%)		<0.001
Dyspnea			523 (57.2%)				1,091 (66.9%)		<0.001
Angina			452 (49.4%)				711 (43.6%)		0.72
Syncope			240 (26.2%)				428 (26.3%)		0.056
Number of symptoms									<0.001
0	1,298 (58.7%)	1,298 (100.0%)			1,786 (52.3%)	1,786 (100.0%)			
1	647 (29.2%)		647 (70.7%)		1,118 (32.7%)		1,118 (68.6%)		
2	236 (10.7%)		236 (25.8%)		424 (12.4%)		424 (26.0%)		
3	32 (1.4%)		32 (3.5%)		88 (2.6%)		88 (5.4%)		
All 3 symptoms present	32 (1.4%)		32 (3.5%)		88 (2.6%)		88 (5.4%)		0.004
Comorbidities									
Diabetes	471 (21.3%)	236 (18.2%)	235 (25.7%)	<0.001	712 (20.8%)	309 (17.3%)	403 (24.7%)	<0.001	0.69
Hypertension	1,252 (56.6%)	668 (51.5%)	584 (63.8%)	<0.001	1,813 (53.1%)	841 (47.1%)	972 (59.6%)	<0.001	0.010
CAD (MI/CABG/angioplasty)[a]	1,018 (46.0%)	490 (37.8%)	528 (57.7%)	<0.001	1,597 (46.8%)	706 (39.5%)	891 (54.7%)	<0.001	0.58
Heart failure	269 (12.2%)	130 (10.0%)	139 (15.2%)	<0.001	516 (15.1%)	227 (12.7%)	289 (17.7%)	<0.001	0.002
Pacemaker	320 (14.5%)	156 (12.0%)	164 (17.9%)	<0.001	503 (14.7%)	213 (11.9%)	290 (17.8%)	<0.001	0.78
AF	655 (29.6%)	356 (27.4%)	299 (32.7%)	0.008	1,188 (34.8%)	552 (30.9%)	636 (39.0%)	<0.001	<0.001
Renal failure	302 (13.6%)	144 (11.1%)	158 (17.3%)	<0.001	440 (12.9%)	190 (10.6%)	250 (15.3%)	<0.001	0.41
Cancer	273 (12.3%)	155 (11.9%)	118 (12.9%)	0.50	404 (11.8%)	183 (10.2%)	221 (13.6%)	0.003	0.57

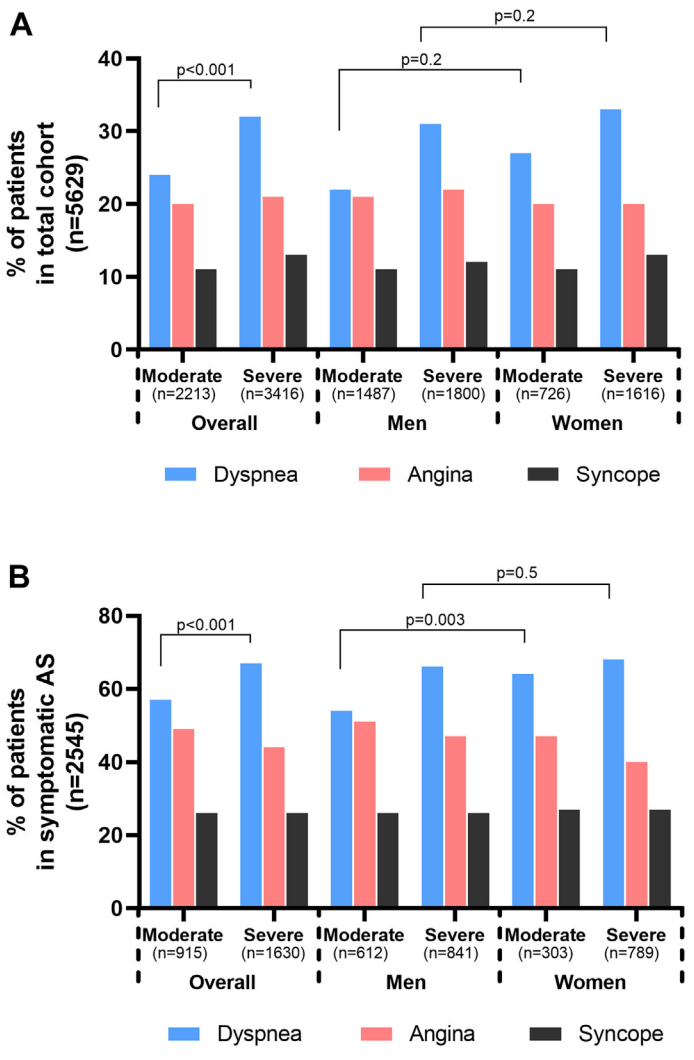
Values are median (IQR) or n (%). [a]Coronary artery disease includes patients who had a myocardial infarction (MI), coronary artery bypass graft (CABG), and angioplasty.

AS = aortic stenosis; AV = aortic valve; CABG = coronary artery bypass graft; CAD = coronary artery disease; LA = left atrial; LVDD = left ventricular diastolic diameter; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic diameter; MI = myocardial infarction; RA = right atrial; TR = tricuspid regurgitation.

2.57, 95% CI: 2.17-3.04, $P < 0.0001$), and between syncope and the presence of a pacemaker (OR: 1.82, 95% CI: 1.40-2.35, $P < 0.0001$) (Figures 4C and 4D). Dyspnea was associated with BMI (OR: 1.05 95% CI: 1.02-1.08, $P < 0.0001$), CAD (OR: 1.49 95% CI: 1.13-1.97, $P = 0.004$), renal failure (OR: 1.80 95% CI: 1.21-2.68, $P = 0.004$), and with the presence of severe AS (OR: 1.71 95% CI: 1.29-2.27, $P < 0.0001$) (Figure 4B). Angina and syncope did not demonstrate significant associations with severe AS (Figures 4C and 4D). As a sensitivity analysis, patients with specific comments on all 3 symptoms were substituted into the models and revealed parallel results (Figures 5A and 5F, Supplemental Table 4).

RELATIONSHIP BETWEEN CARDIAC DAMAGE STAGE AND SYMPTOMS. The cardiac damage stage[13] could be assessed in all 5,629 patients with moderate or severe AS. 926 patients (41.8% of the moderate AS cohort) with moderate AS had no cardiac damage, compared with 1,106 (32.4% of the severe AS cohort) with severe AS ($P < 0.001$). Stage 1 (LV damage) was present in 430 (19.4%) with moderate vs 768 (22.5%) with severe AS, $P = 0.01$; stage 2 (LA or mitral damage) in 727 (32.9%) vs 1,112 (32.6%), $P = 0.01$; stage 3 (pulmonary hypertension or TR damage) in 129 (5.8%) vs 415 (12.3%), $P < 0.001$; and stage 4 (right ventricular [RV] damage) in 1 (0.05%) vs 15 (0.4%), $P = 0.01$. After adjustment for age, sex and comorbidities, symptoms were not associated with the degree of cardiac damage for moderate or severe AS (OR: 0.96, 95% CI 0.91-1.02, $P = 0.16$) (Table 2). Compared with moderate AS, severe AS was strongly associated with cardiac damage. Unadjusted comparison of severe vs moderate AS, for each stage increase in cardiac damage the OR was 1.24 (95% CI: 1.18-1.31, $P < 0.001$). After full adjustment for age, sex, and the presence of all measured comorbidities the OR was 1.19 (95% CI: 1.12-1.25, $P < 0.001$) (Table 2).

FIGURE 2 Presence of Symptoms by AS Severity and Sex



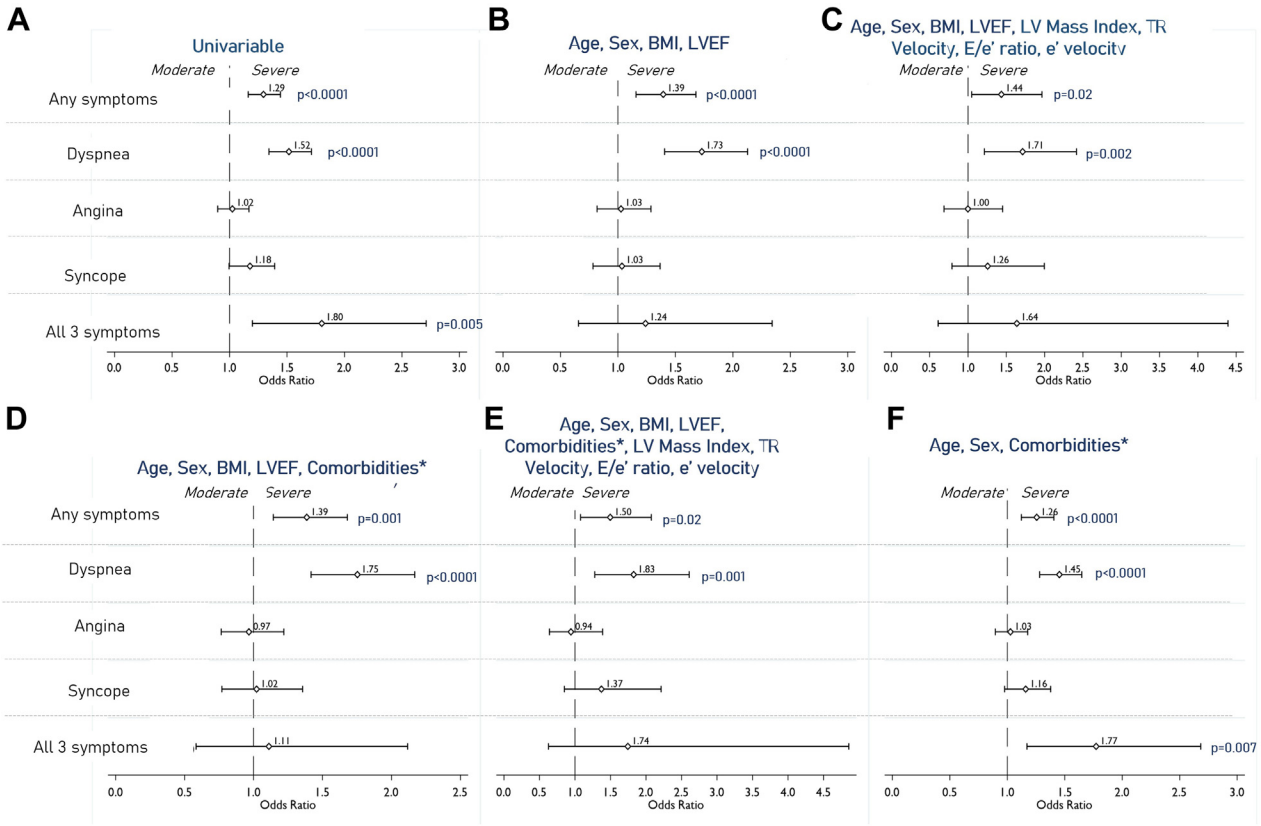
Frequency of symptoms (dyspnea, angina, or syncope) in the **(A)** total (n = 5,629) and **(B)** symptomatic (n = 2,545) population.

DISCUSSION

To our knowledge, this is the largest cohort study examining frequency of symptoms in predominantly outpatients receiving echocardiography for clinical indications. Symptoms were present in 915 (41.3%) of patients with moderate AS and 1,630 (47.7%) of those with severe AS. Dyspnea is more common in severe than in moderate AS but is a poor discriminator of hemodynamic severity of AS, including after adjustments for multiple comorbidities. In addition, all stages of cardiac damage were more common in severe than in moderate AS and remained associated with severe AS after adjustment for age, sex, and comorbidities. However, after adjustment, symptoms were not associated with the degree of cardiac damage for moderate or severe AS. Traditional "red flag" symptoms of angina and syncope do not assist in discriminating between moderate and severe AS, with these symptoms being most associated with coronary heart disease and pacemaker insertion, respectively.

Current clinical practice guidelines note a low mortality in patients with asymptomatic severe aortic stenosis, recommending a conservative approach until symptoms develop. The presence of symptoms in moderate AS is not currently addressed in these guidelines, nor the overall frequency of symptoms in

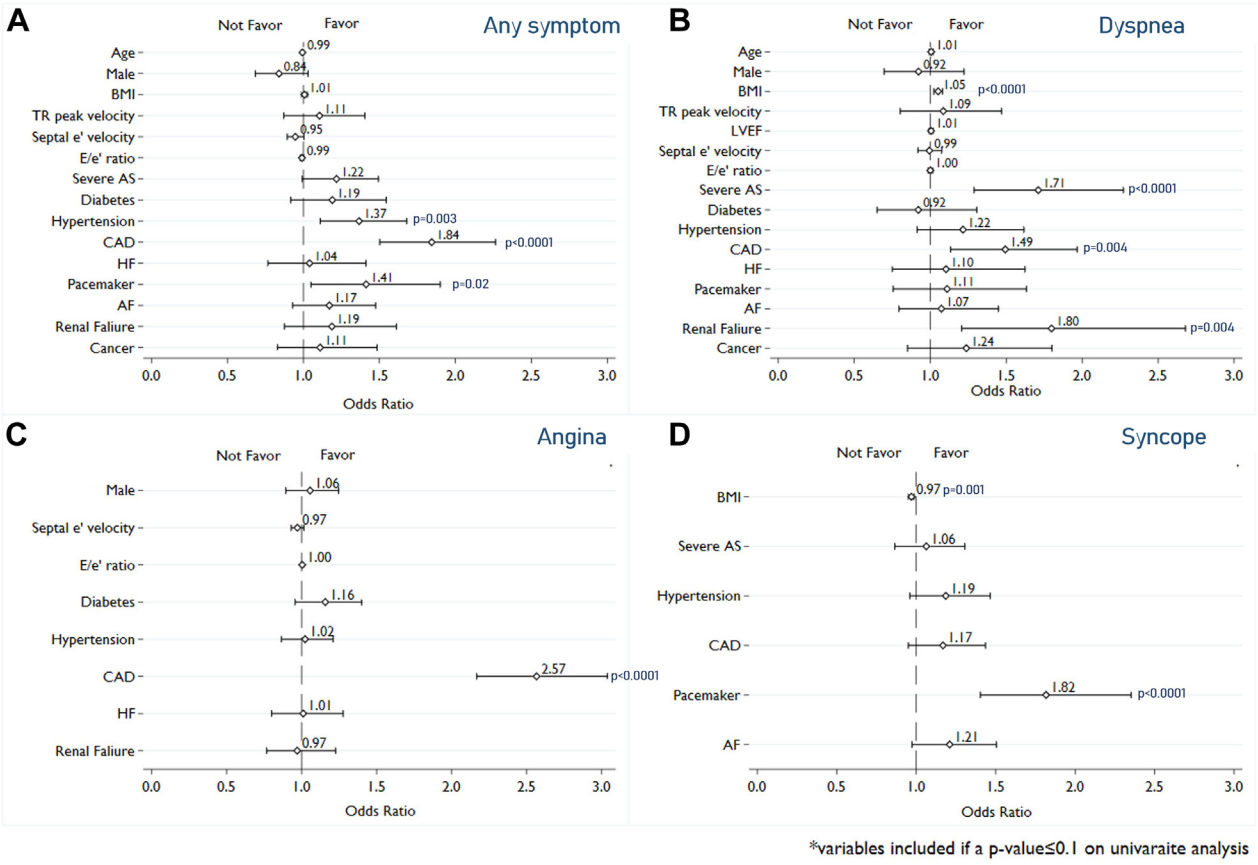
FIGURE 3 Association Between Symptoms and AS Severity



Results are given for **(A)** univariable analyze of symptoms and **(B to F)** multivariable model to analyze symptoms in the same model. Multivariable models are adjusted for **(B to E)** age, sex, BMI and LVEF, plus/minus comorbidities and echocardiographic parameters and **(F)** Age, sex, and presence of comorbidities. *Comorbidities include diabetes, hypertension, coronary disease (MI/CABG/angioplasty/CAD), pacemaker, AF, heart failure, renal failure, and cancer. AF = atrial fibrillation; BMI = body mass index; CABG = coronary artery bypass graft; LV = left ventricular; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

AS. Previous data from the National Echo Database of Australia across 12 contributing centers in Australia demonstrated poor survival in untreated moderate AS, with 56% 5-year mortality compared with 65% in untreated severe AS,[5] but symptomatic status was not addressed in that report. In a separate more recent report, parallel groups from U.S. and Australia were studied with similar mortality shown in both countries-including after correction for >30 potential clinical, laboratory and medication confounders.[14] A recent study of symptoms in moderate AS[6] demonstrated 43% of patients had NYHA functional class II-IV symptoms, remarkably consistent with our findings of symptoms in 41.3% of moderate AS patients. Also consistent with our findings, they found similar AV parameters across the NYHA spectrum, although they reported a lower LVEF, larger LV volumes and LV mass, and more diastolic dysfunction with increasing symptom severity. Recent data from the same group reported that the degree of cardiac damage strongly influenced outcome even in moderate AS.[15] A multicenter retrospective study in 2017 demonstrated most patients with moderate AS and LVEF <50% were symptomatic (74% had symptomatic NYHA functional class II-IV) and a high risk of clinical events,[16] and a later publication from the same group showed with AVR (and especially transcatheter AVR) improved survival in these patients.[17] A poor outcome of moderate AS patients with impaired global longitudinal strain rather than LVEF has also been reported.[18] In severe AS, worsening cardiac damage was strongly associated with mortality in

FIGURE 4 **Predictors of Symptoms in Moderate vs Severe AS and Comorbidities**



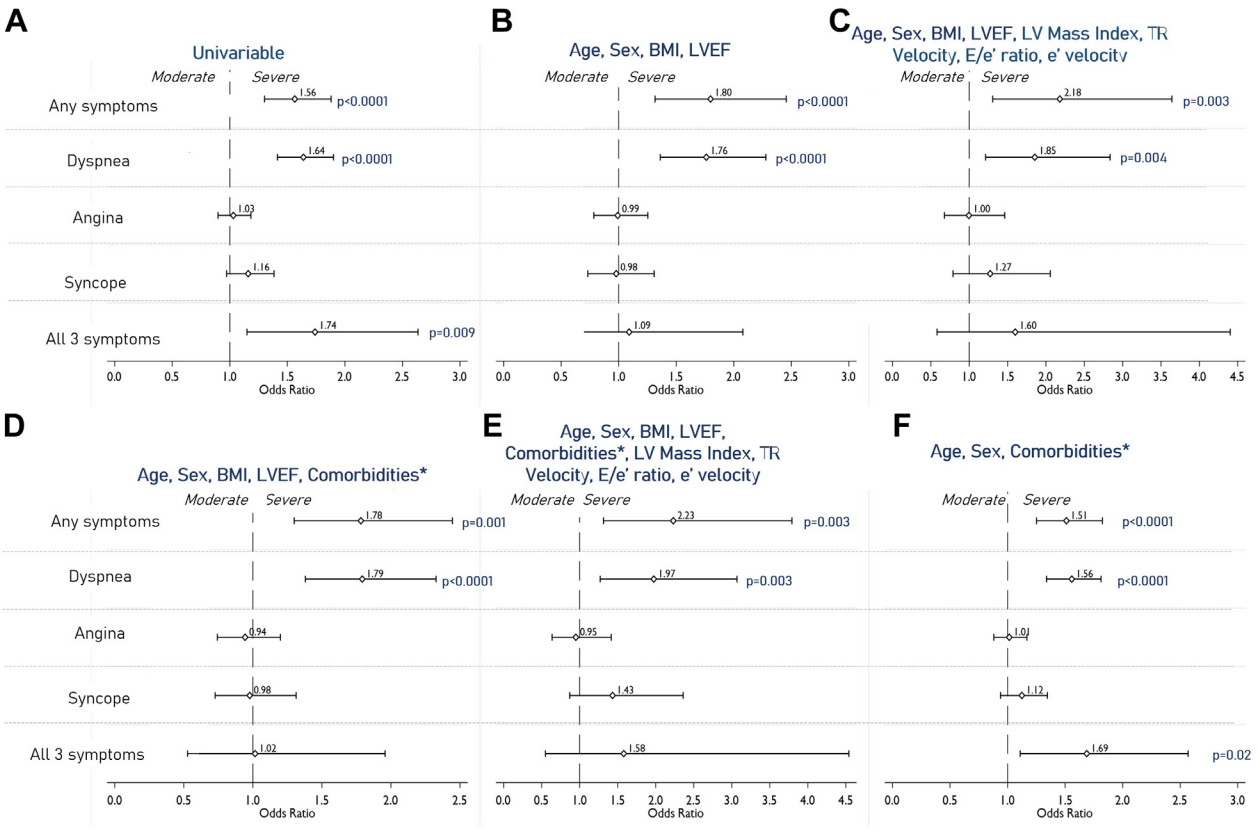
Forest plots of multivariable logistic regression comparing the association of patient characteristics with **(A)** any symptoms, **(B)** dyspnea, **(C)** angina, and **(D)** syncope. Variables have only been included if $P \leq 0.10$ on univariable analysis. AF = atrial fibrillation; BMI = body mass index; CAD = coronary artery disease; HF = heart Failure; LV = left ventricular; LVEF = left ventricular ejection fraction; TR = tricuspid regurgitation.

both symptomatic[11,13] and asymptomatic[19] individuals.

Concomitant CAD, hypertension, and chronic kidney disease are important additional causes of dyspnea in moderate and severe AS. We found coronary heart disease independently associated with the presence of dyspnea and chest pain, consistent with the previous findings of a large stress echocardiography study.[20] Hypertension and AS share a common pressure-loading pathophysiology on the LV that may result in left ventricular hypertrophy (LVH),[21] and recently the AS cardiac damage stage has also been proposed for hypertension and found to be strongly associated with mortality outcomes and major adverse cardiac events.[22] Despite over half of the patients in our cohort having a history of hypertension, the observed LV mass was normal for most patients and there was no association between a history of hypertension and symptom status. Chronic kidney disease (CKD) has been associated with dyspnea in a large community study,[23] independent of the degree of cardiac dysfunction. Our findings are consistent with this observation, with dyspnea almost twice as likely in patients with renal failure, however the proportion of patients with CKD was similar for moderate and severe AS ($P = 0.41$).

AS is a chronic disease, more common in older individuals[24] and associated with progressive structural changes.[25] Symptom status has a complex interaction with AS, since physical frailty increases with age along with a tendency to under-report symptoms[26] and health events.[27] In AS, exertional dyspnea is most likely due to pulmonary capillary engorgement and transitory pulmonary edema resulting from increased LA pressure, due in turn to elevated LV filling pressure, a consequence of the combined

FIGURE 5 Association of Definitive[#] Symptoms in Moderate and Severe AS



[#]Definitive symptoms based on patients with data on all 3 symptoms. Results are given for **(A)** univariable and **(B to F)** multivariable models to analyze symptoms in the same model. Multivariable models are adjusted for **(B to E)** age, sex, BMI and LVEF, plus/minus comorbidities and echocardiographic parameters and **(F)** age, sex, and presence of comorbidities. *Comorbidities include diabetes, hypertension, coronary disease (MI/CABG/Angioplasty/CAD), pacemaker, AF, heart failure, renal failure, and cancer. AF = atrial fibrillation; BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease (including prior AMI/angioplasty); LV = left ventricular; LVEF = left ventricular ejection fraction; MI = myocardial infarction; TR = tricuspid regurgitation.

effects of chronic outflow obstruction from AS and development of LV hypertrophy, fibrosis and adverse LV remodeling.[10,13] These cardiac pathophysiological changes, often termed cardiac "damage", begin during the period when valve obstruction is not yet severe, and at different rates across individuals[15] and consistent with the findings of our study. Although AF is more likely to occur in the setting of chronically elevated filling pressures, we did not observe an association between the presence of AF and AS severity. Myocardial ischemia due to LV hypertrophy and pathologically increased LV wall stress develop late in the AS disease process, and may explain the lack of association of chest pain with AS severity since AVR may have been undertaken prior to the development of chest pain due to AS. Similarly, syncope is a late stage symptom, thought to be due to impaired cerebral blood flow due to hypotension from impaired cardiac output with exercise. The association of chest pain with CAD and syncope with the need for a pacemaker insertion, similar in both moderate and

TABLE 2 The Association of Symptoms with Cardiac Damage and AS Severity

OR for Any Symptom With Cardiac Damage Stage and AS Severity Adjusted for Age, Sex and Comorbidities			
Any Symptom (vs No Symptom)	**OR**	**95% CI**	***P* Value**
Stage of cardiac damage (by each stage increase)	0.96	0.91-1.02	0.16
Severe AS (vs moderate)	1.26	1.13-1.41	<0.001
OR for AS Severity With Symptoms and Cardiac Damage Stage Adjusted for Age, Sex, and Comorbidities			
Severe AS (vs Moderate)	**OR**	**95% CI**	***P* Value**
Presence of any symptom (vs no symptom)	1.26	1.13-1.41	<0.001
Stage of cardiac damage (by each stage increase)	1.19	1.12-1.25	<0.001

severe AS, is consistent with background levels of these cardiac diseases and may not be directly related to AS.

The long-held notion since Ross and Braunwald's publication in 1968[28] that symptom onset in AS is discrete, easily identifiable and inexorably linked to AS severity must now be questioned for 3 reasons: 1) while dyspnea is more common in severe AS than moderate AS, it is common in moderate AS and the hemodynamic severity of AS does not accurately predict dyspnea; 2) that chest pain and syncope were strongly associated with coronary disease and pacemaker requirement, respectively, but not related to AS severity; and 3) the degree of valve obstruction is not the only pathophysiological mechanism involved in most patients, considering that ventricular fibrosis, diastolic dysfunction, and pulmonary hypertension are strong predictors of symptom development which in turn may be due to aortic stenosis and/or the interaction of multiple comorbidities.[13] Although outcomes following AVR relate to the degree of cardiac damage at baseline,[29] it remains unproven whether earlier AVR in symptomatic individuals with moderate AS would improve symptomatic status, heart failure progression or mortality. What is clear, however, is that traditional management decisions in AS based on a simple dichotomous threshold may be overly simplistic, and may lead to under-treatment of patients with a poor prognosis.[30]

STUDY LIMITATIONS. Symptoms were extracted from cardiologist's clinical letters and based on clinical history taking rather than objective stress testing and observation of the degree of exercise impairment. However, reliability of cardiac symptoms extracted during a medical interview have been previously validated[26] and are recommended in current guidelines to guide treatment decisions.[4] In addition, we did not use stress testing in symptomatic patients since current guidelines recommendations include stress testing only in the absence of reported symptoms.[4]

The echocardiograms used in this study were undertaken for clinical indications for known or suspected cardiac disease and reported by cardiologists with expertise in echocardiography. No core laboratory was used, or retrospective image review undertaken. However, similar methodology has been utilized by our group and others with robust mortality outcomes.[24,31-36] Individuals with AS that have not yet undergone echocardiography will not have been captured in this study, and therefore our results should not be taken to reflect the population prevalence of moderate and severe AS.

It is possible some patients may have had additional heart diseases not yet identified by the treating cardiologist. For example transthyretin amyloid (aTTR) may be found in 12% of patients with severe AS.[37] This could have impacted the prevalence of dyspnea identified. It is important to note however, that every patient in this report has been reviewed by a board-certified cardiologist with expertise in clinical cardiology.

CONCLUSIONS

Symptoms are common in both moderate and severe AS, with dyspnea more common in severe AS. Dyspnea is also associated with the presence of comorbidities such as obesity, coronary disease and CKD. Angina and syncope do not relate to AS severity in our study and appear more associated with underlying coronary artery disease and conducting system disease (with concomitant pacemaker utilization). In addition, although there was more evidence of cardiac damage in severe AS, symptom status was not associated with the degree of cardiac damage. These data challenge the notion that symptoms only occur in severe AS or in AS with LV dysfunction, and more accurately reflects the complex interaction of comorbidities, unique patient related factors, and the pathophysiological effects of AS on ventricular structure and function. Patients with symptomatic moderate and severe AS should therefore undergo thorough clinical review to decide on optimal timing of AV intervention with the goal of preventing death and/or long-term disability from heart failure.[38-40] Ongoing clinical trials such as the PROGRESS trial (NCT04889872) will assist in future decision-making in moderate AS.

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ADDRESS FOR CORRESPONDENCE: Prof David Playford, School of Medicine, The University of Notre Dame, Australia, Henry Street, Fremantle, Australia. E-mail: David.playford@nd.edu.au.

PERSPECTIVES

COMPETENCY IN PATIENT CARE: Symptoms are common in moderate and severe aortic stenosis (41.3% and 47.7% respectively) and associated with the presence of comorbidities. Dyspnea is more common in severe (than moderate) AS, whereas syncope and chest pain are more associated with comorbidities than with AS. No symptoms are associated with the degree of cardiac damage.

TRANSLATIONAL OUTLOOK: The long-held view that symptoms only occur in severe AS needs to be re-examined in the light of these data. Clinical trials are required to examine whether the imaging severity of AS (including phenotypic cardiac changes such as cardiac damage) rather than symptoms should guide decisions on aortic valve intervention.

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KEY WORDS **aortic stenosis, cardiac damage, dyspnea, Natural Language Processing, symptoms, syncope**

APPENDIX **For supplemental tables and figure, please see the online version of this paper.**