Original research

Prevalence of pulmonary hypertension in aortic stenosis and its influence on outcomes

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ABSTRACT

Objective The significance of pulmonary hypertension (PHT) complicating aortic stenosis (AS) is poorly characterised. In a large cohort of adults with at least moderate AS, we aimed to describe the prevalence and prognostic importance of PHT in such patients.

Methods In this retrospective study, we analysed the National Echocardiography Database of Australia (data from 2000 to 2019). Adults with an estimated right ventricular systolic pressure (eRVSP), left ventricular ejection fraction (LVEF) >50% and with moderate or greater AS were included (n=14 980). These subjects were then categorised according to their eRVSP. The relationship between PHT severity and mortality outcomes were evaluated (median follow-up of 2.6 years, IQR 1.0–4.6 years).

Results Subjects were aged 77±13 years and 57.4% were female. Overall, 2049 (13.7%), 5085 (33.9%), 4380 (29.3%), 1956 (13.1%) and 1510 (10.1%) patients had no (eRVSP<30.00 mm Hg), borderline (30.00–39.99 mm Hg), mild (40.00–49.99 mm Hg), moderate (50.00–59.99 mm Hg) and severe PHT (>60.00 mm Hg), respectively. An echocardiographic phenotype was evident with worsening PHT, showing rising E:e' ratio and right and left atrial sizes(p<0.0001, for all). Adjusted analyses showed that the risk of long-term mortality progressively rose as eRVSP level increased (HR 1.14–2.94, borderline to severe PHT, p<0.0001 for all). A mortality threshold was identified in the 4th decile of eRVSP categories (35.01–38.00 mm Hg; HR 1.19, 95% CI 1.04 to 1.35), with risk progressively increasing through to the 10th decile (HR 2.86, 95% CI 2.54 to 3.21).

Conclusions In this large cohort study, we find that PHT is common in ≥moderate AS and mortality increases as PHT becomes more severe. A threshold for higher mortality lies within the range of 'borderline-mild' PHT.

Trial registration number ACTRN12617001387314.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Individually aortic stenosis (AS) and pulmonary hypertension (PHT) both confer an increased risk of mortality as they progress. However, the significance of PHT complicating AS remains poorly characterised.

WHAT THIS STUDY ADDS

⇒ Within a large cohort of adults (n=14 980) with ≥moderate AS PHT is common, and mortality increases as PHT becomes more severe.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ A greater understanding of the phenotype of PHT complicating AS provides clinicians with clear parameters to monitor with the knowledge that even mildly raised pulmonary pressures have negative prognostic implications in these patients.

INTRODUCTION

Aortic stenosis (AS) is the the most common valve abnormality in developed countries with an increasing prevalence and a long pre-symptomatic phase.[1] Measurable demographic, baseline and imaging characteristics are likely important in stratifying risk and potentially guiding treatment decisions. A cardiac damage score has been proposed and validated in AS; this includes extra variables related to left and right heart structure and function.[2 3] The prevalence and prognostic importance of pulmonary hypertension (PHT) in patients with AS, however, has been poorly characterised.[4–8]

PHT secondary to left heart disease (LHD), also known as post-capillary PHT, is the the most common type of PHT (65%–80% of all PHT cases), in most reported series.[9–11] It refers to patients who develop PHT secondary to LHD, such as left ventricular systolic or diastolic dysfunction or left-sided valvular pathologies. In these patients, PHT is thought due to 'back pressure' from an elevated left atrial (LA) pressure. In AS specifically, PHT likely arises from left ventricular hypertrophy and diastolic dysfunction, thence an increase in LA pressure.[12] PHT has been previously documented as an important prognostic factor in other LHD, such as left ventricular failure.[9 10]

In AS, however, a clear picture of the prevalence of PHT and its prognostic importance has not yet emerged. In relatively small series, there have been inconsistent data concerning PHT prevalence, phenotype and mortality trends in these patients.[4–8] Utilising data from the National Echo Database of Australia (NEDA), we aimed to clearly describe the prevalence of PHT, of varying severities, and then, assess the independent prognostic value of pulmonary pressure in patients with ≥moderate AS.

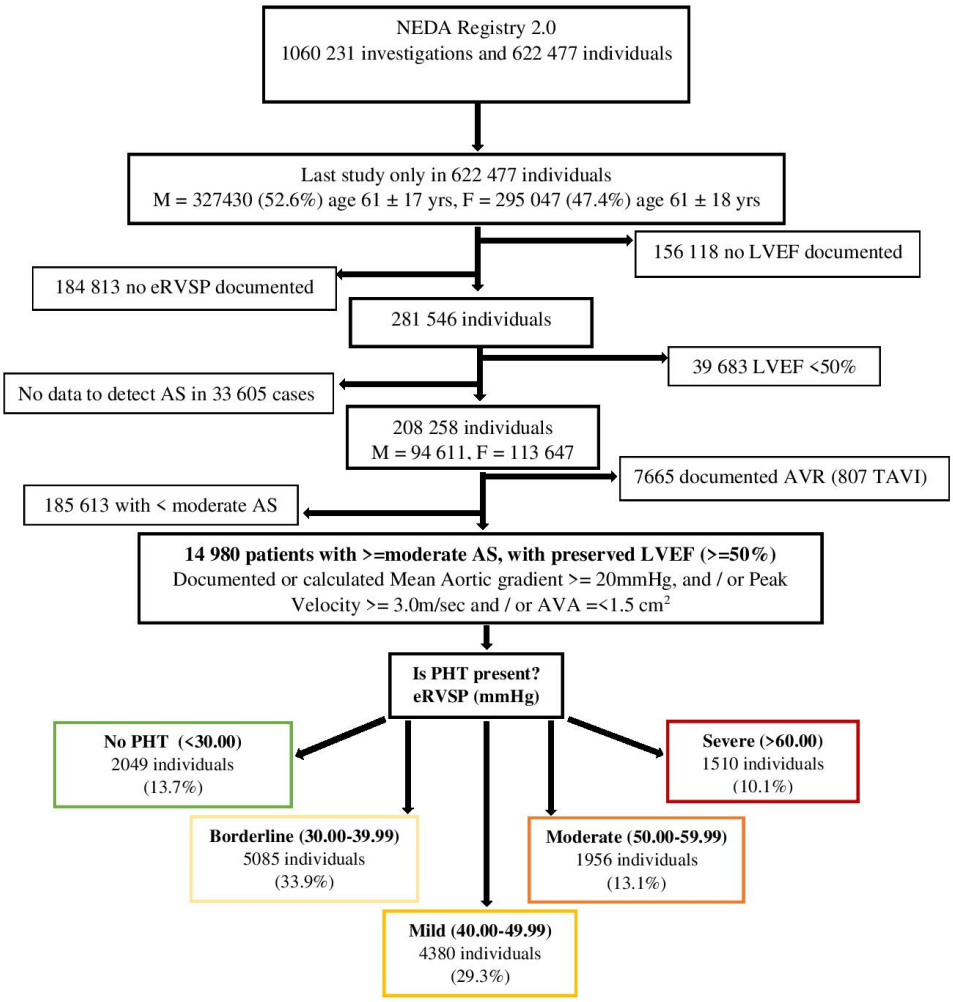


Figure 1 Study flow chart. This figure shows the analysis flowchart performed in this study. AS, aortic stenosis; AVA, aortic valve area; AVR, aortic valve replacement; eRVSP, estimated right ventricular systolic pressure; LVEF, left ventricular ejection fraction; NEDA, National Echo Database Australia; PHT, pulmonary hypertension; TAVI, transcatheter aortic valve implantation.

METHODS

NEDA database and study design

The NEDA is a multi-centre registry, previously described, in detail.[13–15] NEDA contains basic demographic and detailed echocardiographic data of adults from >25 centres across Australia. The database is linked with the comprehensive National Death Index (NDI). The study period included >1 million echo reports from >6 00 000 individuals, studied between January 2000 and June 2019. Vital status was determined as of 21 May 2019 (median follow-up 6.2 years, IQR 3.8–9.8 years); patients alive at this date were censored alive.

Study cohort

Figure 1 shows our study flow diagram; baseline for our study was the date of each person's last echo in the database. Survival data at study census were used to identify patients with significant AS and thence to characterise the prevalence and prognostic impact of PHT. Included subjects were (1) adults ≥18 years of age, (2) with at least one echocardiogram recorded (where patients had multiple studies, only the last study was analysed), (3) with a recorded left ventricular ejection fraction (LVEF), estimated right ventricular systolic pressure (eRVSP) and sufficient data to determine AS severity (aortic valve (AV) mean gradient and/AV peak velocity and/or aortic valve area (AVA) via velocity time integral (VTI)). Moderate or severe AS was defined using current diagnostic guidelines,[16] with AV mean gradient ≥20 mm Hg and/or AV peak velocity ≥3.0 m/sec and/or AVA (by VTI) ≤1.5 cm^2. Patients with AV replacements were excluded from these analyses, as were patients with LVEF<50%. eRVSP was derived using the Bernoulli equation (4×[(tricuspid regurgitation velocity) TRV]^2 + assumed RA pressure of 5 mm Hg).[17] As noted in previous NEDA literature,[14] a consistent RA pressure of 5 mm Hg removes variation between laboratories by approximating the average value recorded overall. RV size and function were described qualitatively using text extraction from echo reports.[14]

Study methods

Once the cohort of patients with moderate or greater AS was identified, subjects were categorised by their eRVSP, according to clinical guidelines, to document the distribution of PHT severity.[18] A 'borderline PHT' group which has previously been determined as potentially significant in both NEDA papers and in other recent publications was also included.[14 19 20] Prospectively defined categories of PHT were: (1) normal (eRVSP<30 mm Hg), (2) borderline (30.00–39.99 mm Hg), (3) mildly elevated (40.00–49.99 mm Hg), (4) moderately elevated (50.00–59.99 mm Hg) and (5) severely elevated (eRVSP≥60 mm Hg).[14]

All-cause mortality was determined, during a median follow-up of 2.6 years (IQR 1.0–4.6 years). We explored the relationship between eRVSP level and survival, looking at both the five clinically defined groups (as above) and the eRVSP deciles.

Statistical analysis

All continuous variables are expressed as mean±SD, unless otherwise stated, and categorical data as frequency and percentages. For continuous variables, linear regression analysis using ANOVA was used to test whether the trend of the mean across the categorical groups of eRVSP levels was linear. For binary variables, the χ^2 test was used to determine if there was a trend in the change in proportions across the groups.

Actuarial 1-year and 5-year survival rates for all-cause mortality were calculated from the 14 173 (94.6%) and 9838 (65.7%) subjects with complete follow-up for those time points.[14] Multiple logistic regression models (entry at univariate p value<0.05) were used to derive adjusted ORs for mortality models at these fixed time points. Cox regression hazard models were used to derive adjusted HRs for mortality outcomes during follow-up (entry model at a univariate p value<0.05). Adjusted analyses included age and sex, as well as mean AV gradient. Mortality was also assessed when the cohort was divided into two groups, based on AS severity (moderate AS—10 085 patients, severe AS—4895 patients).

Sensitivity analyses were performed excluding patients with concurrent moderate or greater concurrent mitral regurgitation and/or moderate or greater aortic regurgitation. Patients with moderate or severe AS were also assessed separately to determine if there were differences between these two groups. Severe AS was defined as AV mean gradient ≥40 mm Hg, and/or AV peak velocity ≥4.0 m/sec and/or AVA (by VTI) ≤1.0 cm^2 [16].

We then examined the pattern of mortality according to the decile distribution of eRVSP[14]: first decile—5.00–28.00 mm Hg, second— 28.01–32.00 mm Hg, third—32.01–35.00 mm Hg, fourth—35.01–38.00 mm Hg, fifth—38.01–40.69 mm Hg, sixth—40.70–43.64 mm Hg, seventh—43.65–46.48 mm Hg, eighth—46.49–50.96 mm Hg, ninth—50.97–60.00 mm Hg and tenth—>60.00 mmHg.

All analyses were performed with SPSS software V.25.0 (IBM Corp), and statistical significance was accepted at a two-tailed p value of<0.05.

RESULTS

Prevalence of PHT and distribution of eRVSP

A total of 14 980 patients with moderate or greater AS were identified (figure 1), with 57.4% being female. Figure 2 shows the frequency distribution of eRVSP levels (median 40.69 mm Hg, IQR 33.23–48.44 mm Hg). The number of patients in each subgroup were: No PHT (eRVSP<30 mm Hg)—2049 individuals (13.7%), borderline PHT (eRVSP 30.00–39.99 mm Hg)—5085 individuals (33.9%), mild (eRVSP 40.00–49.99 mm Hg)—4380 (29.3%), moderate (eRVSP 50.00–59.99 mm Hg)—1956 (13.1%) and severe (eRVSP>60 mm Hg)—1510 (10.1%).

Subject profiles

Table 1 summarises the demographic and echocardiographic characteristics of the study cohort divided into subgroups based on eRVSP levels. Age was greater in those with higher eRVSP levels, from a mean of 70±17 years in patients with no PHT to 81±10 years in patients with severe PHT (p<0.0001 for all).

A typical pattern of phenotypic response was evident along with worsening PHT. E:e' increased progressively with worsening PHT (13.18±5.67 vs 21.2±9.5, no PHT vs severe PHT, respectively, p<0.0001 for all). There was also a progressive increase in right atrial area and indexed LA volume, along with increasing frequency of aortic and mitral regurgitation with worsening PHT. The proportion of patients with RV dilation and impaired RV function increased from 3.9% to 36.8% and 1.0% to 7.8%, respectively, in those with no PHT compared with those with severe PHT. Atrial fibrillation was more common with worsening PHT (12.7% vs 42.1%, no PHT vs severe PHT, p<0.0001 for all).

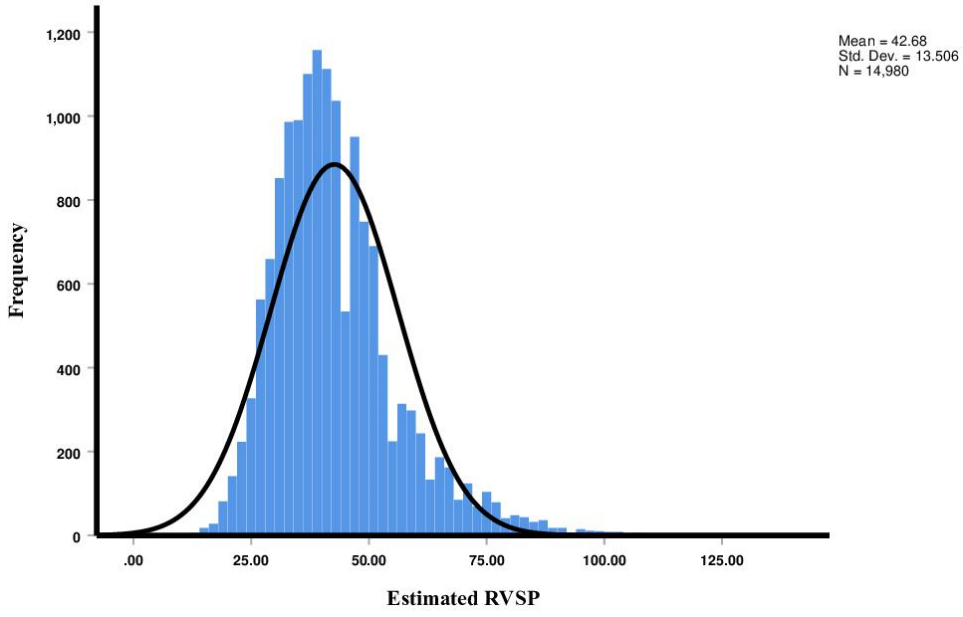


Figure 2 Frequency distribution of eRVSP within the cohort. These data show the statistical distribution of estimated right ventricular systolic pressure (eRVSP) levels.

Table 1 Baseline characteristics of study cohort (n=14 980)

	eRVSP 0.00–29.99 n=2049	eRVSP 30.00–39.99 n=5085	eRVSP 40.00–49.99 n=4380	eRVSP 50.00–59.99 n=1956	eRVSP >60.00 n=1510	P value
Demographics						
Age, years	70±17	76±14	79±11	81±10	81±11	<0.0001
Female (%)	1243 (60.7)	2854 (56.1)	2380 (54.3)	1136 (58.1)	992 (65.7)	<0.0001
Anthropometrics						
BMI	26.77±5.55	26.9±5.67	27.76±6.08	27.55±6.52	26.57±6.18	0.02
BSA	1.81±0.25	1.81±0.24	1.84±0.25	1.82±0.26	1.78±0.25	0.27
Rhythm						
Atrial fibrillation/arrhythmia	260 (12.7)	979 (19.3)	1115 (25.5)	701 (35.8)	635 (42.1)	<0.0001
LV dimensions and function						
LVEF %	64.28±7.44	65.59±8.50	68.44±10.25	67.26±10.16	65.53±9.5	<0.0001
E:e' ratio	13.18±5.67	14.19±6.52	15.01±5.97	16.84±7.15	21.2±9.5	<0.0001
LVEDD	4.31±0.63	4.45±0.65	4.66±0.72	4.65±0.77	4.45±0.75	<0.0001
LVESD	2.74±0.53	2.76±0.60	2.73±0.66	2.78±0.70	2.76±0.67	<0.0001
Atrial dimensions						
LA volume index, mL/m^2	34.36±14.92	46.73±27.52	76.05±40.32	81.78±45.62	82.98±49.16	<0.0001
RA area, cm^2	16.91±7.24	21.59±7.37	27.93±7.53	29.67±8.92	29.78±9.7	<0.0001
Right heart dimensions and function						
eRVSP, mm Hg	25.61±3.41	35.12±2.89	44.39±2.75	53.91±2.93	71.8±11.19	<0.0001
TR peak velocity, m/s	2.2±0.2	2.5±0.2	2.9±0.1	3.3±0.2	3.9±0.3	<0.0001
RV basal diameter	3.44±0.54	3.25±0.44	3.27±0.34	3.4±0.4	3.6±0.5	<0.0001
Dilated RV	80 (3.9)	303 (4.3)	952 (21.7)	549 (28.1)	556 (36.8)	<0.0001
Impaired RV function	20 (1.0)	47 (0.7)	68 (1.5)	71 (3.6)	118 (7.8)	<0.0001
AV dimensions and function						
Peak aortic velocity, m/s	2.8±1.0	3.1±0.9	3.2±0.9	3.3±0.9	3.6±0.8	<0.0001
Mean aortic gradient, mm Hg	20.00±14.8	23.28±15.09	26.8±16.0	27.6±17.1	31.5±16.5	<0.0001
AV area (VTI), cm^2	1.2±0.4	1.2±0.3	1.1±0.3	1.1±0.3	0.9±0.4	<0.0001
Concomitant valvular pathology						
≥moderate mitral regurgitation	126 (6.1)	404 (5.7)	594 (30.4)	444 (22.7)	377 (24.9)	<0.0001
≥moderate aortic regurgitation	162 (7.9)	423 (5.9)	461 (10.6)	226 (11.5)	193 (12.8)	<0.0001

Values are n (%) unless otherwise indicated.
AV, aortic valve; BMI, body mass index; BSA, body surface area; eRVSP, estimated right ventricular systolic pressure (mm Hg); LA, left atrial; LV, left ventricle; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic pressure; RA, right atrial; RV, right ventricle; TR, tricuspid regurgitant; VTI, velocity time integral.

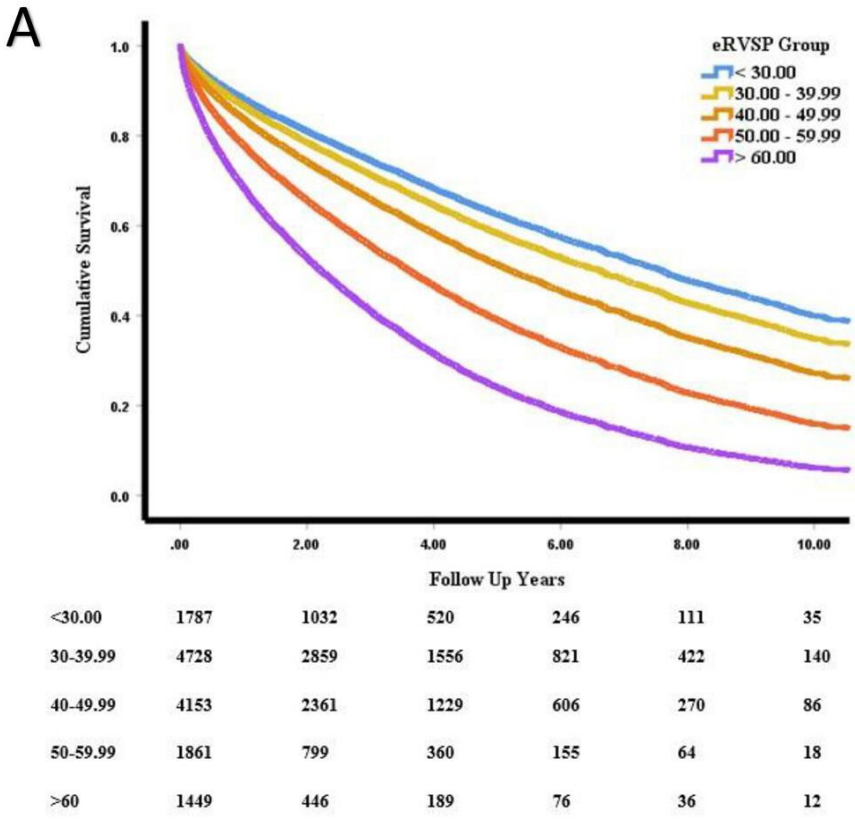
Survival data

All-cause long-term survival (table 2, figure 3A) and actuarial mortality at 1 and 5 years (figure 4) (all adjusted for age, sex and mean AV gradient) are shown for those with eRVSPs <30.00 mm Hg and the four categories of progressively higher eRVSP. Median follow-up was 2.6 years (IQR 1.0–4.6 years). The risk of mortality progressively increased as eRVSP level increased, as evidenced in adjusted long-term mortality results which showed a 1.14-fold increase in risk in those with borderline PHT and a 2.94-fold increase in those with severe PHT compared with those with normal eRVSP (p<0.0001 for all) (table 2, figure 3A). These trends were less pronounced when assessing cardiovascular mortality, although those with moderate and severe PHT still had significantly higher risk of dying (table 2). Trends were less clear for milder elevations of eRVSP with smaller numbers and possible inaccurate coding for causes of death documented on death certificates, as possible contributing factors. When we excluded patients where the severity was solely based on an

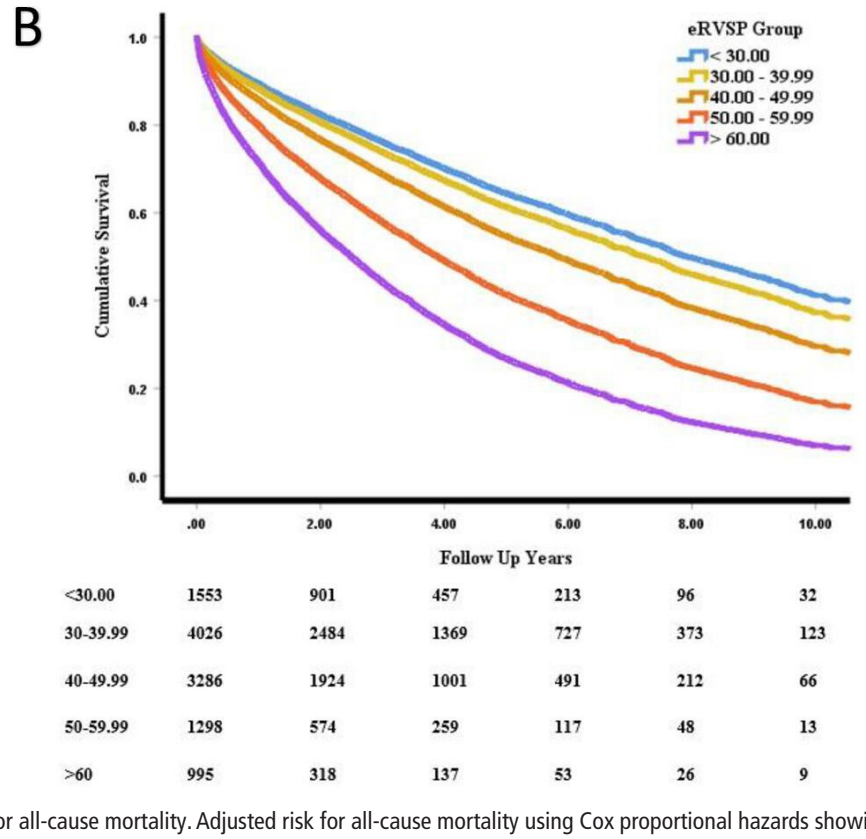
Table 2 Survival profile and adjusted risk for mortality according to eRVSP levels (n=14 980)

	Normal eRVSP (<30 mm Hg) n=2049	Borderline PHT (eRVSP 30.00–39.99) n=5085	Mild PHT (eRVSP 40.00–49.99) n=4380	Moderate PHT (eRVSP 50.00–59.99) n=1956	Severe PHT (eRVSP>60) n=1510
All-cause mortality N (%) HR (95% CI)	544 (26.5) Reference	2101 (41.3) HR 1.14 (1.03 to 1.25)	2371 (54.1) HR 1.38 (1.26 to 1.52)	1282 (65.5) HR 1.96 (1.77 to 2.18)	1148 (76.0) HR 2.94 (2.65 to 3.27)
Cardiovascular mortality N (%) HR (95% CI)	186 (9.1) Reference	757 (14.8) HR 0.83 (0.71 to 0.99)	915 (20.8) HR 0.93 (0.79 to 1.09)	538 (27.5) HR 1.31 (1.11 to 1.55)	542 (40.7) HR 2.00 (1.69 to 2.37)

Cox regression analyses for total cohort adjusted for age, sex and mean aortic valve gradient. Values are n (%) or n/M (%), unless otherwise indicated.
eRVSP, estimated right ventricular systolic pressure (mm Hg); PHT, pulmonary hypertension.



<30.00	1787	1032	520	246	111	35
30-39.99	4728	2859	1556	821	422	140
40-49.99	4153	2361	1229	606	270	86
50-59.99	1861	799	360	155	64	18
>60	1449	446	189	76	36	12



<30.00	1553	901	457	213	96	32
30-39.99	4026	2484	1369	727	373	123
40-49.99	3286	1924	1001	491	212	66
50-59.99	1298	574	259	117	48	13
>60	995	318	137	53	26	9

Figure 3 Adjusted risk for all-cause mortality. Adjusted risk for all-cause mortality using Cox proportional hazards showing as eRVSP level increases based on clinical severity, risk of mortality increases in (A) the total cohort (adjusted for age HR 1.06, 95% CI 1.05 to 1.06, sex HR 0.85, 95% CI 0.81 to 0.89 and mean aortic valve gradient HR 1.01, 95% CI 1.004 to 1.007) and (B) the cohort excluding patients with ≥moderate mitral regurgitation and/or ≥moderate aortic regurgitation (adjusted for age HR 1.06, 95% CI 1.05 to 1.06, sex HR 0.83, 95% CI 0.79 to 0.88 and mean aortic valve gradient HR 1.01, 95% CI 1.003 to 1.007). eRVSP, estimated right ventricular systolic pressure.

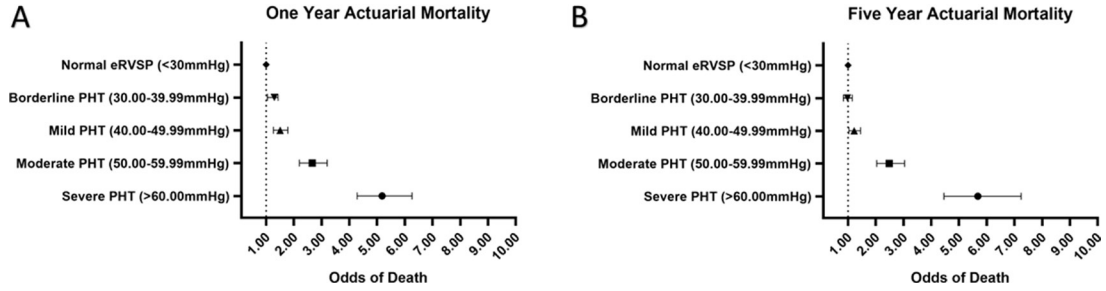


Figure 4 One-year and 5-year actuarial mortality for the total cohort. Actuarial all-cause mortality using logistic regression, adjusted for age, sex and mean aortic valve gradient, for the total cohort showing increased odds of death as pulmonary pressures increase. eRVSP, estimated right ventricular systolic pressure; PHT, pulmonary hypertension.

AVA<1.5 cm^2, mortality trends of the total cohort were maintained (online supplemental table 1 and figure 1). These trends were maintained in sensitivity analyses performed excluding patients with ≥moderate MR and/or ≥moderate AR, though significance was not reached at milder elevations of pulmonary pressures in 1-year or 5-year actuarial mortality (table 3, figure 3B, online supplemental figure 2). These inconsistencies may be due to lower numbers and a loss of study power as well as potential confounding from unknown cardiovascular comorbidities. In all models, increasing age and male sex were also associated with increased mortality (p<0.0001, for all).

Mortality was also assessed when the cohort was divided into two groups, based on AS severity (moderate AS—10 085 patients, severe AS—4895 patients). In the moderate AS cohort, which had comparatively larger numbers, results mirrored those of the total cohort, with adjusted long-term mortality increasing progressively as eRVSP increased (HR 1.13, 95% CI 1.01 to 1.27 for borderline PHT vs HR 3.28, 95% CI 2.87 to 3.73 for severe PHT) (online supplemental table 2 and figure 3). Patients with severe AS had similar trends, although statistical significance was not reached at milder elevations of eRVSP, most likely a consequence of the smaller subject numbers (online supplemental table 3 and figure 4).

Threshold for mortality

The regression model for the decile distribution of eRVSP, adjusted for age, sex and mean AV gradient, confirmed a threshold of increased risk from eRVSP 35.01–38.00 mm Hg relative to the lowest decile (<28.00 mm Hg) (p=0.009). No significantly increased risk in the second (eRVSP 28.01–32.00) or third (eRVSP 32.01–35.00) deciles was observed. Increased risk was noted from the fourth decile (eRVSP 35.01–38.00; HR 1.19, 95% CI 1.04 to 1.35) and became progressively higher through to the 10th decile (eRVSP 60.01–136.97; HR 2.86, 95% CI 2.54 to 3.21) (online supplemental table 4). Hence, the adjusted risk for mortality is markedly higher in those with borderline-mild PHT and above regardless of age, sex or mean AV gradient.

DISCUSSION

In this 'real-world' cohort study, including over 14 000 adults with ≥moderate AS and normal LVEF, we have documented the prevalence of mild, moderate and severe PHT in these subjects and demonstrated the independent prognostic importance of PHT in the context of AS.

The use of 'big data' from the NEDA, which includes over 1 million ultrasounds from over 600 000 unique adults, has yielded a more comprehensive, contemporary description of the prevalence and phenotype of patients with ≥moderate AS compared with smaller previous studies,[4–7] the largest of which included 2435[21] such patients. We confirmed the adverse prognostic impact of PHT in AS and have now documented that the threshold for excess mortality lies at a relatively modest elevation of eRVSP.

PHT most likely develops in those with AS via the following mechanism: As the severity of AS worsens, LV pressure overload increases, leading to compensatory concentric hypertrophy (and progressive myocardial fibrosis), subsequent LV diastolic dysfunction and eventually elevated LV end-diastolic pressure, increased LA pressure[12] and post-capillary PHT.

Prevalence and phenotype of PHT with AS

We confirm a high prevalence of PHT in patients with AS, especially as age increases, but rates have varied considerably in previously published studies, dependent on their selection criteria.[4–6 12] In prior echo studies, PHT was noted in 15%–30%

Table 3 Sensitivity analysis—survival profile and adjusted risk for mortality according to eRVSP levels (excluding patients with significant aortic and/or mitral regurgitation, n=12 005)

	Normal eRVSP (<30 mm Hg) n=1793	Borderline PHT (eRVSP 30.00–39.99) n=4337	Mild PHT (eRVSP 40.00–49.99) n=3464	Moderate PHT (eRVSP 50.00–59.99) n=1367	Severe PHT (eRVSP>60) n=1044
All-cause mortality N (%) HR (95% CI)	446 (24.9) Reference	1710 (39.4) HR 1.10 (1.002 to 1.21)	1809 (52.2) HR 1.33 (1.20 to 1.48)	875 (64.0) HR 1.98 (1.76 to 2.22)	760 (72.8) HR 2.92 (2.59 to 3.2)
Cardiovascular mortality N (%) HR (95% CI)	153 (8.5) Reference	592 (13.6) HR 0.77 (0.64 to 0.92)	682 (19.7) HR 0.88 (0.74 to 1.05)	338 (24.7) HR 1.20 (0.99 to 1.45)	338 (32.4) HR 1.96 (1.61 to 2.38)

Cox regression analyses for excluding patients with ≥moderate aortic regurgitation and/or ≥moderate mitral regurgitation adjusted for age, sex and mean aortic valve gradient.
Values are n (%) or n/M (%), unless otherwise indicated.
eRVSP, estimated right ventricular systolic pressure; PHT, pulmonary hypertension.

of patients with symptomatic AS (>19% mild, >10%–45% moderate, 15%–30% severe).[4–6 12 22] Our study from community and hospital-based echo laboratories around Australia showed that >50% of studied patients with significant AS and normal LVEF had at least some degree of PHT, as defined by clinical guidelines (mild PHT—29.3%, moderate—13.1%, severe—10.1%). Significantly, the subgroup with the highest proportion of patients was those with 'borderline PHT', with eRVSP 30–39 mm Hg (33.9%).

Previous studies report that the most frequent features of PHT in patients with AS are reduced LVEF, concomitant MR and, as confirmed in our study, more severe AS.[21 23] Our cohort confirms the impact of PHT in patients with significant AS with normal ejection fraction.[24] The resultant echocardiographic phenotype is that of progressively increased E:e' ratio and indexed LA volume, and progressively higher proportions of RV dilation and dysfunction. Better identification of this phenotype provides clinicians with clear parameters to monitor and allows for further understanding of the remodelling associated with worsening PHT. This has been recently described by us and others, in a cardiac damage score, which has now been validated in both high-gradient, low-flow low-gradient, symptomatic and asymptomatic severe AS patients.[2 3 25 26]

Outcomes of PHT in patients with AS

This large study has confirmed the serious impact of worsening PHT in patients with significant AS, even in the absence of LV systolic dysfunction, with 52.4% of patients with eRVSP >40.00 mm Hg having a 1.4-fold to 2.9-fold adjusted increased risk of long-term all-cause mortality, dependent on PHT severity, compared with those without PHT. Similar to our previous studies,[14 27] we find that there is even an increased risk associated with borderline PHT (eRVSP 30.00–39.99) compared with normal estimated eRVSP. This observation was evident even at 12 months, with 1-year actuarial mortality increased 1.29-fold, and long-term all-cause mortality increased 1.14-fold, in borderline PHT subjects. Furthermore, the high numbers provided by the NEDA allowed us to identify a clear threshold for excess mortality risk at eRVSP>35.00 mm Hg. These results were independent of age, sex and mean AV gradient and our sensitivity analysis showed that they did not appear to be confounded by the presence of concomitant left-sided valvular pathology. Furthermore, the severity of AS did not impact on result, suggesting that PHT independently predicts mortality in the setting of moderate and severe AS.

Clinical implications

The presence of PHT is only acknowledged as an indication for 'early' intervention in asymptomatic patients with severe AS when pulmonary pressures exceed 60 mm Hg.[28] PHT increases mortality in patients who undergo AV intervention,[7 12 23 29 30] with only modest reductions in eRVSP following intervention.[7 16 18] Our recent publication[15] showed that patients with moderate AS had a similarly high risk of mortality as those with severe AS, raising the question on the optimal timing of intervention. In the absence of clinical trials showing the effect of earlier valve intervention in AS, it is unclear whether earlier AVR would improve the outcome of these individuals or whether the cardiac structural changes will reverse after valve intervention.

Limitations

NEDA provides detailed echocardiographic data and linkage to mortality; NEDA is, however, a retrospective de-identified electronic record interface, which means that we were unable to directly review echocardiographic images with regard to pressure estimates or other parameters. Furthermore, NEDA does not (yet) provide granular clinical data such as symptoms, co-morbidities or pharmacological treatments. This is important in this study as we do not have information regarding key cardiovascular co-morbidities such as hypertension or coronary artery disease which may contribute to the mortality trends noted. Most patients included in the database have undergone an echocardiogram for investigation of confirmed or suspected cardiac disease and should not be taken to reflect the population prevalence. A small proportion of patients in this study were included based on the AVA alone. We believe that a significant portion of these patients are likely to have normal-flow, low-gradient AS or paradoxical-flow, low-gradient AS. We acknowledge that this cannot be confirmed in the present study. Importantly, a subgroup analysis excluding these 'AVA only' AS patients showed that mortality trends mirrored that of the total cohort, suggesting that their inclusion did not introduce significant bias.

These studies were primarily derived from specialist centres or clinics across Australia, so some caution should be applied when applying these findings to other populations. However, Australia is a multi-ethnic population with universal health coverage, aspects captured within the NEDA database. Our data is lacking in quantitative RV measurements, so we are unable to fully assess the impact of PHT on the right heart, nor can we determine the impact of RV abnormalities on mortality, in this cohort. This is an important question when assessing PHT and outcomes and thus is a limitation of this current study. Future studies should address the role of RV size and function in the relationship between AS and PHT.

As noted in our previous studies,[14] the data concerning PHT in NEDA is based on echocardiography-based measures rather than haemodynamic assessment at right heart catheterisation. Prior studies have correlated eRVSP with invasive pulmonary artery systolic pressure,[17 31] supporting the broad validity of our approach. Furthermore, echocardiography remains the the most common screening tool to detect PHT and is the guideline-recommended diagnostic method of choice, to allow for monitoring and follow-up. We acknowledge that diagnosis of PHT should generally be confirmed on right heart catheterisation, after initial screening is suggestive of PHT. We also note that the absence of a tricuspid regurgitation jet does not exclude PHT and there may be a number of patients with AS and PHT who were not included in the study due to lack of correct TR sampling or no quantifiable TR. Thus, although our data indicate a threshold for mortality somewhere in the 'borderline/mild' PHT range, we must acknowledge some uncertainties about where this prognostic threshold actually lies. Uncertainties in this regard relate to (1) exclusion of those with no TR, (2) inclusion of those where TR may have been incorrectly sampled, (3) the use of an assumed RA pressure for sound methodological reasons.

CONCLUSIONS

Both AS and PHT confer an increased risk of mortality as they progress. This very large cohort study confirms that patients with ≥moderate AS have higher mortality as PHT becomes more severe. The threshold for mortality lies within the range of borderline to mild PHT.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval NEDA is registered with the Australian New Zealand Clinical Trials Registry and human ethics approval was obtained, protocol SLHD X15-0387 and 2019/ETH069899, with retrospective waiver of consent authorised.

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