Original Article

Age-dependent clinical and echocardiographic manifestations of aortic stenosis in an unselected, non-biased cohort

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Background: Age, clinical presentation and echocardiographic parameters are important factors in the decision on an individualized therapeutic strategy for patients with aortic stenosis (AS). Less is known about this information in a non-selected non-biased cohort.

Methods: We performed a retrospective, systematic analysis of patients admitted to our hospital from 1/1/2014 to 1/6/2018 with the diagnosis of AS. We collected demographic, clinical and echocardiographic parameters. All patients were evaluated and treated in one single institution by experienced cardiologists. We classified patients into 4 age groups to compare the above-mentioned variables. Category A: patients younger than 65 years, category B age between 65–74, category C age between 75–84, and category D patients older 85.

Results: We included 321 adults with AS in our study. There was a significant correlation between the aortic valve area, aortic velocity (Vmax), aortic pressure gradients (PMax) and age. The AVA decreased, Vmax and PMax increased with age (P=0.001, P=0.042 and P=0.017, respectively). 74.1% of all patients were symptomatic, but there were no differences between the age categories (P=0.406). The incidence of cardiovascular comorbidities was high throughout all age categories. Forty-four point five percent of all patients had a coronary artery disease, but there were no differences between the age categories (P=0.221). Echocardiographic aspect of AS was similar in all age groups except the right ventricular pressure (RVP): RVP was significantly higher in patients younger than 65 years.

Conclusions: Based on our results, we conclude that age is a weak parameter for making decisions about the optimal AS therapy. AVAs in AS decreases moderately with age. Age does not impact any clinical or echocardiographic parameters. Cardiovascular diseases and symptomatic AS are found in all age categories.

Keywords: Aortic stenosis (AS); echocardiography; acquired valve disease

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Introduction

Aortic stenosis (AS) is the most common acquired aortic valve disease in western countries, with a prevalence of 1–2% (1). Both the prevalence and the incidence increase up to 12% with age (2). Clinical symptoms diverge broadly: heart failure, angina, syncope, and sudden death are common; however, some patients remain asymptomatic (3). Curative therapy options include replacing the aortic valve, either with conventional surgical aortic valve replacement (SAVR), which requires a thoracotomy, or with transcatheter aortic valve replacement (TAVR). In some cases, balloon angioplasty is an option for treating AS. Treatment decision pathways are predominantly established based on age: SAVR is recommended for younger patients, and TAVR is an option for older patients that are at high risk (4,5).

However, the management of AS is a controversial issue. The first TAVR was performed in 2002. Since then, the method has improved with the production of smaller devices and the introduction of a sheath, which was less harmful (6). Currently, an increasing number of patients are being treated with TAVR. In Germany, 15 964 patients received TAVR during 2011–2013 (7).

Surprisingly, very few studies have scrutinized whether the echocardiographic clinical manifestations and comorbidities of AS might depend on patient age. Available data are largely from tertiary heart centers and carry a significant referral bias. Unbiased data are lacking, and it remains unclear whether the severity of aortic valve disease and the presence of comorbidities might be correlated with patient age.

In this retrospective, observational cohort study (8), we analyzed the clinical and echocardiographic manifestations of AS according to age. This study included 321 adults with AS that were admitted to Reinbek hospital.

Methods

We performed a retrospective, systematic analysis of all patient records admitted to our hospital from 1/1/2014 to 1/6/2018. To identify patients with AS, we defined AS with echocardiographic parameters, according current guidelines (9). All data were derived from a primary care hospital (Reinbek Hospital). All patients were investigated in this hospital.

We collected detailed data on the medical history and physical examination for all patients. In all patients with AS, we performed and evaluated a complete set of echocardiographic measurements. We used the aortic valve area (AVA) to characterize the disease stage. We defined the stages, based on the aortic orifice, as follows: mild AS: 1.5–2 cm^2; moderate AS: 1.0–1.5 cm^2, and severe AS: <1.0 cm^2. All clinical and echocardiographic data were extracted from electronic data records (IMED One©, Deutsche Telekom Clinical Solutions GmbH, Köln, Germany) in pseudonymized manner. We classified the patients into 4 age categories, according to earlier recommendations: <65, 65–74, 75–84, and >85 years (4).

All echocardiographic investigations were performed by experienced investigators. The GE Vivid E9© Ultrasound machine was used with GE EchoPac© software tools for analyzing raw data (both products from General Electronics Healthcare).

Statistics

We described quantitative data as the mean ± standard deviation, and qualitative data as the number and proportion (%), unless otherwise specified. We compared continuous data with one-way Analysis of Variance (ANOVA) and the post-hoc Tukey Test for comparing multiple variables. We compared categorical data with Pearson's chi squared test and contingency tables. The Pearson correlation analysis and scatter plots were calculated to determine relationships between continuous variables.

We considered P values $P<0.05$ as an indicator of significance between patient groups. We performed all statistical analyses with SPSS software (SPSS for Windows, Release 25.0, SPSS Inc., 1993 to 2007, Chicago, Illinois, USA).

The authors of this manuscript certify that they have complied with the principles of ethical publishing. The study and analyses were performed according to the guidelines of the local Ethics Committee (Ärztekammer Schleswig-Holstein). All information in the data bank was encoded in a pseudonymized manner.

Results

We identified 321 patients with AS in our records. Of these patients, 2 had bicuspid valves and 15 had massive calcifications. Consequently, it was not possible to classify the aortic valve type as uni-, bi-, or tricuspid types.

Of all 321 patients, 74.1% had symptoms of angina and dyspnea, with no differences between age categories

Table 1 Patient demographics and clinical parameters for aortic stenosis

Parameter	Total	<65 years	66–74 years	75–85 years	>85 years	P
Number of patients, n (%)	321	8 (2.5)	24 (7.5)	137 (42.7)	152 (47.4)	
Age (years)	83.8±7.7	63.6±1.1	70.6±2.7	80.1±2.8	90.2±4.4	<0.001
Male, n (%)	159 (49.5)	2 (25.0)	10 (41.6)	57 (41.6)	90 (59.2)	0.009
Systolic blood pressure (mmHg)	138±28	144±25	138±25	139±27	138±29	0.990
Diastolic blood pressure (mmHg)	77±14	84±16	83±16	78±13	76±14	0.086
Heart rate (beats per minute)	83±20	91±20	89±22	83±20	83±20	0.131
Symptoms, n (%)	238 (74.1)	7 (87.5)	15 (62.5)	100 (72.9)	116 (76.3)	0.406
NYHA classification (range, 1–4)	1.5±1.4	1.8±1.3	1.3±1.5	1.4±1.3	1.6±1.7	0.435
Syncope, n (%)	37 (11.5)	1 (12.5)	1 (4.2)	16 (11.7)	19 (12.5)	0.699
Coronary artery disease, n (%)	143 (44.5)	5 (62.5)	12 (50.0)	67 (48.9)	59 (38.8)	0.221
Myocardial infarction, n (%)	48 (14.9)	1 (12.5)	2 (8.3)	16 (11.7)	29 (19.1)	0.256
Coronary intervention, n (%)	65 (20.6)	3 (37.5)	5 (20.8)	34 (24.8)	23 (15.1)	0.121
Coronary bypass surgery, n (%)	33 (10.4)	1 (12.5)	3 (12.5)	15 (10.9)	14 (9.2)	0.930
Peripheral arteriosclerosis, n (%)	54 (16.8)	0 (0.0)	5 (20.8)	24 (17.5)	25 (16.4)	0.581
COPD, n (%)	53 (16.5)	3 (37.5)	3 (12.5)	32* (23.3)	15* (9.9)	0.006
Stroke, n (%)	43 (13.4)	0 (0.0)	1 (4.2)	20 (14.6)	22 (14.5)	0.345
Atrial fibrillation, n (%)	128 (39.9)	1 (12.5)	8 (33.3)	57 (41.6)	62 (40.8)	0.369
Aortic surgery, n (%)	8 (2.5)	0 (0.0)	0 (0.0)	5 (3.6)	3 (1.9)	0.629
Aortic aneurysm, n (%)	15 (4.7)	0 (0.0)	0 (0.0)	8 (5.8)	7 (4.6)	0.575
Aortic dissection, n (%)	0					
Arterial hypertension, n (%)	262 (81.5)	7 (87.5)	17 (70.8)	116 (84.7)	122 (80.3)	0.379
Hyperlipidemia, n (%)	104 (32.4)	3 (37.5)	8 (33.3)	49 (35.7)	44 (28.9)	0.650
Diabetes, n (%)	99 (30.8)	3 (37.5)	6 (25.0)	51 (37.2)	39 (25.7)	0.166
Hyperuricemia, n (%)	31 (9.7)	0 (0.0)	3 (12.5)	15 (10.9)	13 (8.6)	0.670
Smoker, n (%)						<0.001
Never	153 (53.3)	1 (12.5)	11 (45.8)	54 (39.4)	87 (57.2)	
Current	30 (10.5)	4* (50.0)	3 (12.5)	15 (10.9)	8 (5.3)	
Ex	104 (36.2)	2 (25.0)	9 (37.5)	57 (41.6)	36 (23.7)	
Obesity, n (%)	136 (42.4)	5 (62.5)	12 (50.0)	63 (45.9)	56 (36.8)	0.209

Values are presented as the mean ± standard deviation or the number and percentage (%). COPD, chronic obstructive pulmonary disease. *, statistically significant.

(*Table 1*). The mean New York Heart Association (NYHA) class was 1.5. Only 11.5% of patients experienced syncope. Coronary heart disease and atrial fibrillation were the most common comorbidities. We found no differences between age categories regarding the incidences of coronary heart disease (CAD), myocardial infarction, peripheral artery disease, cerebral insults, or atrial fibrillation. The prevalence of cardiovascular risk factors was the same in all groups (*Table 1*).

The AVAs were 1.2±0.15 cm^2 in patients under 65 years, 1.1±0.3 cm^2 in patients 65–74 years, 1.1±0.35 cm^2 in patients

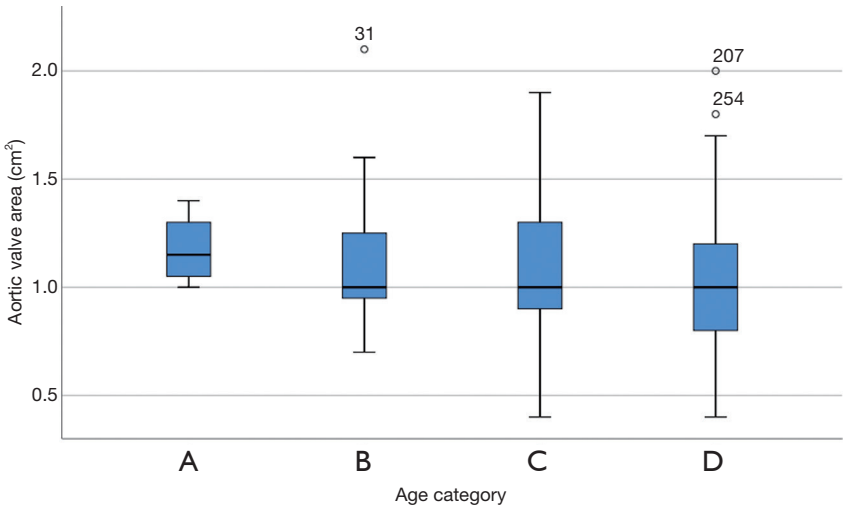

Figure 1 Distribution of aortic valve areas across different age categories. Patients were classified into 4 age categories, according to earlier recommendations: (A) age <65 years; (B) age 65–74 years; (C) age 75–84 years; (D) age >85 years.

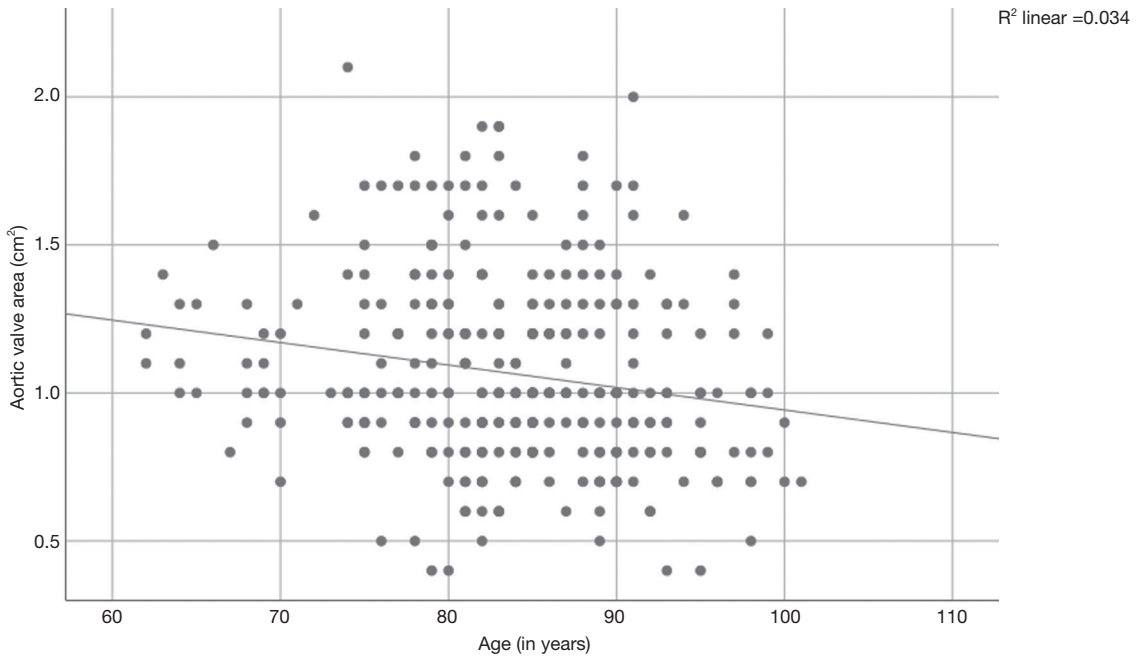

Figure 2 Relationship between aortic valve area and age. Pearson correlation analysis shows a significant negative correlation between age and aortic valve area (P=0.001, correlation coefficient r=1).

75–84 years, and 1.0±0.3 cm^2 in patients 85 years and older (P=0.061; *Figure 1*).

A Pearson product-moment correlation coefficient was computed to assess the relationships between AVA, aortic velocity, pressure gradients, and age. We found a correlation between the AVA and age (r=–0.185, P=0.001; *Figure 2*) and between aortic velocity and age (r=0.114, P=0.042; *Figure 3*). Furthermore, there was a correlation between peak pressure and age (r=0.134, P=0.017), but there was no correlation between mean pressure and age (r=0.108, P=0.054).

Patient echocardiographic results are presented in *Table 2*. No differences were found in the peak aortic

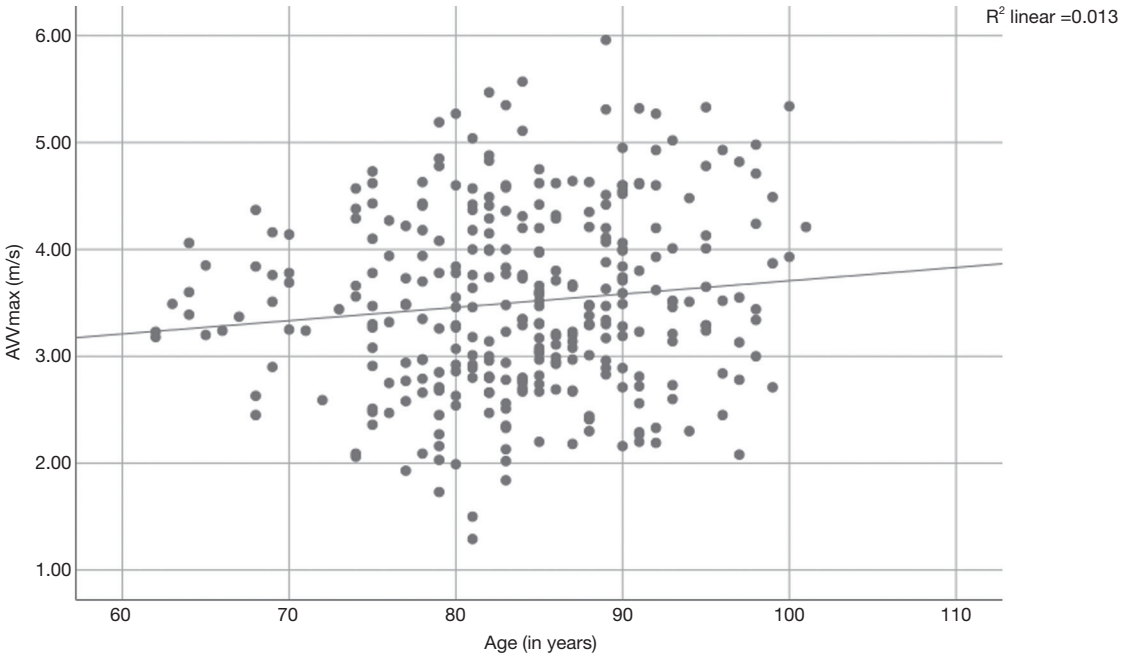

Figure 3 Relationship between peak aortic valve velocity (AVVmax) and age. Pearson correlation analysis shows a significant correlation between age and peak aortic valve velocity (P=0.042, correlation coefficient r=1).

velocity or aortic pressure gradients among the different age categories. Other echocardiographic criteria, like left ventricular function, were similar in all age categories (*Figure 4*). Interestingly, right ventricular pressure (RVP) was elevated in the youngest age category (age <65 years); in that category, the mean pressure was 49±18.6 mmHg, compared to 38±11.9 mmHg among patients 65–74 years, 36±13.4 mmHg among patients 75–84 years, and 39±14.1 mmHg in patients 85 years and older. We did not detect any other echocardiographic differences between these age groups.

Discussion

The main findings of our study were: (I) with increasing age, the AVA declined and the aortic velocity increased; (II) the symptoms of aortic valve dysfunction were common across all age groups, and (III) the incidences of cardiovascular comorbidities and risk factors were similar in all age groups.

Severity of AS and age

Our data were consistent with the traditional ideas that severe AS is a disease of older individuals, and that the severity of AS increases with age. Interestingly, other cardiac disorders or risk factors did not correlate with severe AS. Older patients had smaller AVAs, higher aortic velocities, and greater pressure gradients. The decision of whether to treat with conservative observation or a palliative, surgical, or interventional procedure often depends on the patient's age (5). Most TAVR trials included patients older than 75 or 80 years. However, recent trials have shown that patient characteristics and outcomes were independent of age. Interestingly, older patients had a better outcome than younger patients in the PARTNER Trial (10). Of note, in the present study, we included only 8 patients under 65 years old.

Clinical manifestation of AS

In our cohort, the patients had the same clinical presentation and symptoms, independent of age. Of all 321 patients included, 74% had symptoms. The NYHA classifications were low in all categories. The syncope frequency was about 11%. However, in contrast to earlier observations, our frequency of symptomatic AS was high. In a recent meta-analysis, 50% of patients with AS were reported to be asymptomatic (11). In many patients, it is difficult to define symptoms—particularly in patients

Table 2 Echocardiographic results in patients with aortic stenosis

Parameters	Total	<65 years	66–74 years	75–85 years	>85 years	P
Number of patients, n (%)	321	8 (2.5)	24 (7.5)	137 (42.7)	152 (47.4)	
Aortic valve area (cm^2)	1.1±0.32	1.2±0.15	1.1±0.30	1.1±0.35	1.0±0.30	0.061
Peak aortic velocity (m/s)	3.5±0.85	3.5±0,32	3.5±0.71	3.4±0.92	3.6±0.82	0.399
Peak aortic pressure gradient (mmHg)	52±24.5	49±9.2	50±18.8	49±25.7	54±24.7	0.279
Mean aortic pressure gradient (mmHg)	32±16.2	30±5.6	32±13.5	31±17.3	34±16	0.353
Aortic velocity time interval (ms)	80±38.8	75±15.3	75±21.3	80±53.1	81±24.6	0.384
Aortic insufficiency, n (%)						0.431
No	153 (47.8)	4 (50.0)	16 (66.6)	70 (51.1)	63 (41.4)	
Mild	152 (47.5)	4 (50.0)	8 (33.3)	59 (43.1)	81 (53.3)	
Moderate	14 (4.4)	0 (0.0)	0 (0.0)	6 (4.4)	8 (5.3)	
High	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	
Interventricular septum (cm)	1.19±0.19	1.16±0.21	1.13±0.15	1.18±0.22	1.2±0.16	0.330
Left ventricular function, n (%)						0.080
Good	229 (71.3)	6 (75.0)	18 (75.0)	106 (77.4)	99 (65.1)	
Mild dysfunction	43 (13.4)	0 (0.0)	0 (0.0)	13 (9.5)	30 (19.7)	
Moderate dysfunction	35 (10.9)	1 (12.5)	4 (16.7)	14 (10.2)	16 (10.5)	
Severe dysfunction	14 (4.4)	1 (12.5)	2 (8.3)	4 (2.9)	7 (4.6)	
Left atrial diameter (mm)	44±6.6	45±7.6	42±5.6	43±6.7	45±6.6	0.125
Left ventricular end diastolic diameter (mm)	46±8.0	51±13.6	49±8.7	47±8.3	45±7.2	0.125
Left ventricular end systolic diameter (mm)	34±8.5	39±10.3	36±9.9	34±8.8	33±7.9	0.192
Aortic root (mm)	31±4.4	32±4.4	32±3.6	32±5.0	31±3.9	0.356
Aortic aneurysm , n (%)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0.715
Aortic ectasia, n (%)	2 (0.6)	0 (0.0)	0 (0.0)	2 (1.5)	0 (0.0)	0.425
Mitral regurgitation, n (%)						0.421
No	8 (2.5)	0 (0.0)	2 (8.3)	4 (2.9)	2 (1.3)	
Mild	207 (64.7)	7 (87.5)	17 (70.8)	85 (62)	98 (64.5)	
Moderate	91 (28.4)	1 (12.5)	5 (20.8)	42 (30.7)	43 (28.3)	
High	14 (4.4)	0 (0.0)	0 (0.0)	5 (3.6)	9 (5.9)	
Mitral stenosis, n (%)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0.716
Tricuspidal regurgitation, n (%)						0.413
No	64 (19.9)	1 (12.5)	6 (25.0)	27 (19.7)	30 (19.7)	
Mild	180 (56.3)	4 (50.0)	14 (58.3)	85 (62.0)	77 (50.6)	
Moderate	65 (20.3)	2 (25.0)	4 (16.7)	19 (13.9)	40 (26.3)	
High	11 (3.4)	1 (12.5)	0 (0.0)	5 (3.6)	5 (3.3)	
Right ventricular pressure (mmHg)	38±13.9	49*±18.6	38±11.9	36±13.4	39±14.1	0.045

Values are presented as the mean ± standard deviation or the number and percentage (%), unless otherwise indicated. *, statistically significant.

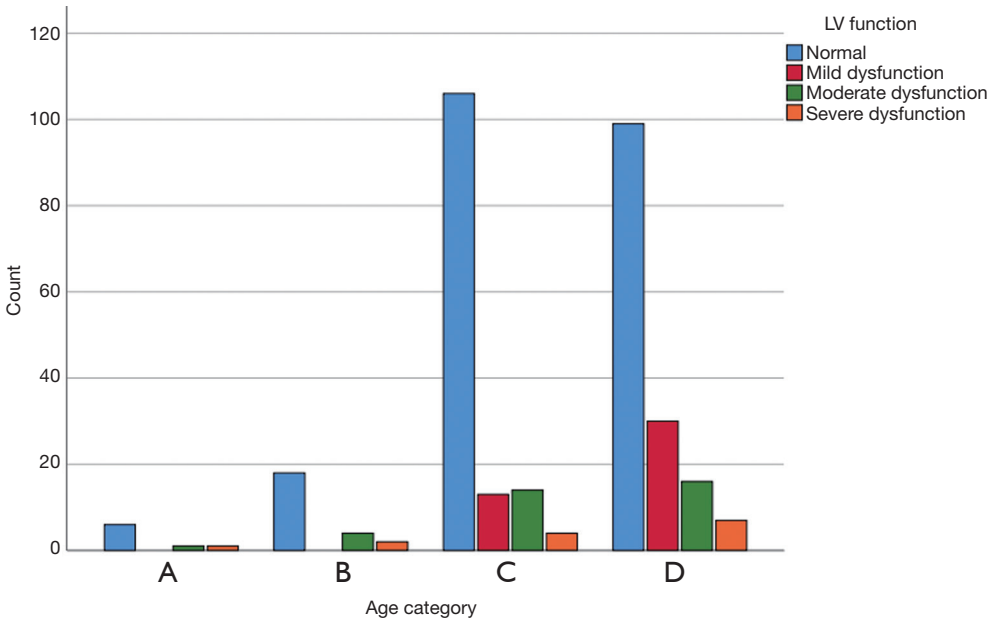

Figure 4 Left ventricular function within different age categories. Color coding shows different grades of left ventricular function. Patients were classified into 4 age groups: (A) age <65 years; (B) age 65–74 years; (C) age 75–84 years; (D) age >85 years.

that are older or with multimorbidities. Nevertheless, the indication and timing for interventional or surgical valve replacement is based on clinical symptoms (5). Symptomatic patients are referred for interventional or surgical treatment earlier than asymptomatic patients; in the latter group, a "watchful waiting" strategy is possible (5).

A recent trial (FRAILTY-AVR-Trial) investigated different frailty scores for patients before TAVR or SAVR. They showed that frailty was correlated with outcome after the procedure (12). In that study, the prevalence of frailty varied broadly in the cohort, depending on the scoring method used: frailty was diagnosed in 12% to 56% among patients that received SAVR and from 35% to 74% among patients that received TAVR (12). Further investigations are needed to unravel the complex clinical characteristics of patients with AS.

Cardiovascular comorbidities

The incidence of cardiovascular comorbidities and risk factors was high in all age categories. In our cohort, at the time of the AS diagnosis, 143 patients (44.5%) had CAD; 48 patients (14.9%) had prior myocardial infarctions; 65 patients (20.6%) had percutaneous coronary interventions; and 33 patients (10.4%) had undergone coronary artery bypass surgery. Interestingly, the incidence of CAD was the same in all age categories; i.e., it did not significantly increase with age. This observation was novel, because in previous studies, CAD severity was correlated with age.

Cardiovascular comorbidities have a crucial impact on AS. Among patients with AS, those with concomitant CAD have a worse outcome than those without CAD (13). Many patients with AS had CAD and/or myocardial infarctions, and they had previously received coronary interventions or aorto-coronary bypass surgery (13).

Clinical variables that influence mortality

The prognosis of patients with AS depends on several clinical factors. A previous study evaluated 241 patients with severe AS and preserved left ventricular (LV) ejection fraction that did not undergo valve replacement. They showed that older age, a history of hypertension, and LV diastolic dysfunction were independent predictors of mortality (14). Interestingly, in our analysis, these factors were equally distributed throughout our predefined age categories. Nevertheless, these predictors of death should be considered, when deciding on the mode and timing of therapy. We confirmed that LV function and arterial hypertension were not correlated with age.

A large analysis of patients with AS that were treated with aortic valve surgery showed that patients with

isolated AS, with none or with only a few comorbidities, had better postprocedural and long-term outcomes than patients with AS and CAD (13). A complete evaluation of clinical characteristics is essential in the treatment decision process. For example, metabolic syndrome was associated with accelerated progression and calcification in AS (15). In our analysis, we did not find any differences in clinical characteristics, particularly metabolic syndrome, between our predefined age groups.

Study limitations

We could not completely exclude biases in our study, due to the inclusion of patients that received both outpatient and in-hospital treatments. Patients that were treated in the hospital had a different clinical presentation and probably had more severe symptoms. Additionally, we did not perform a systematic analysis or screening of a healthy population. Finally, although symptomatic complaints are perceived very subjectively and variably, by both patients and physicians, we did not perform "objective" stress tests or pro-BNP tests to ascertain the level of symptomatic AS.

Conclusions

Based on our results, we conclude that age is a weak parameter for making decisions about the optimal AS therapy. AVAs in AS decreases moderately with age. Age does not impact any clinical or echocardiographic parameters. Cardiovascular diseases and symptomatic AS are found in all age categories.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The research was performed according to the guidelines of the local ethics committee (Ärztekammer Schleswig Holstein) as a retrospective, pseudonymized research and is listed as a research project at the University Hospital Hamburg-Eppendorf. All patients have given written consent accepting the data processing and analysis before beginning of the treatment.

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