JAMDA 24 (2023) 1594–1599

JAMDA

journal homepage: www.jamda.com

Original Study

Natural Course of Aortic Stenosis in Older Subjects: Effects of COVID-19

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Keywords:
Aortic stenosis
COVID-19
electronic health records
older adults

A B S T R A C T

Objective: Both aortic stenosis (AS) and COVID-19 affect the morbidity and mortality burden among older adults. The aim of the study was to examine whether aortic stenosis (AS) affects the prognosis after SARS-CoV-2 infection and whether COVID-19 affects AS prognosis, in a cohort of older adults hospitalized with and without COVID-19.
Design: Observational study.
Setting and Participants: Patients admitted to 9 geriatric clinics in Stockholm from March 2020 to November 2021.
Methods: AS and COVID-19 diagnoses were identified by electronic health records; the outcomes were mortality at 30 days and any time during a median follow-up of 630 days. The associations between AS, COVID-19, and mortality were assessed by using Royston-Parmar models adjusting for age, sex, comorbidities, and admission waves.
Results: Among 28,974 patients, 85 had concomitant AS and COVID-19, 529 had only AS, and 5033 had only COVID-19. Both at 30 days and at any time, as compared to patients without, concomitant AS and COVID-19 subjects had a higher mortality rate (438.4 per 100 person-years, 95% CI 296.2-648.8, and 72.9, 95% CI 53.7-99.0, respectively) and a higher death risk (adjusted HR 5.5, 95% CI 3.7-8.2; and 2.8, 95% CI 2.1-3.9). AS patients presented increased mortality HR both in the presence and absence of COVID-19 at 30 days (1.6, 95% CI 1.1-2.4; and 1.6, 95% CI 1.2-2.2, respectively) and at any time (1.6, 95% CI 1.1-2.1; 1.4, 95% CI 1.2-1.7, respectively).
Conclusions and Implications: AS was a significant mortality risk factor, independent of concomitant COVID-19. Careful AS management should always be pursued, even in acute and post-acute phases of COVID-19.

The authors declare no conflicts of interest.
Funding: The study did not receive any industrial support. H.X. is supported by the Swedish Research Council (grant 2022-01428), the Center for Innovative Medicine Foundation (CIMED, FoUI-963369), the Strategic Research Area Neuroscience start-up grant, and Åke Wibergs Foundation (M22-0170). M.E. received support from the Swedish Research Council (2020-02014); D.R. received support from the Swedish Research Council (2020-06101).
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https://doi.org/10.1016/j.jamda.2023.07.026

Aortic valve stenosis (AS) is the most common degenerative valvular heart disease among the geriatric population, because its prevalence sharply increases with age.[1,2] AS shows poor prognosis in symptomatic patients[3] and relevant mortality, especially in untreated older patients.[4] Therefore, AS should not be neglected when considering the burden of cardiovascular comorbidities, even in the scenario of the Coronavirus Disease 2019 (COVID-19) pandemic. The geriatric population has been severely affected by COVID-19, with more than 15,000 deaths (out of a total number of more than 17,000) in patients aged ≥70 years in Sweden as of March 9, 2022.[5]

Several risk factors for adverse outcomes have already been described among COVID-19 older adults, such as frailty,[6,7] malnutrition, low body mass index,[8] obesity,[9] and a higher comorbidities burden.[7,8,10,11] Moreover, cardiovascular involvement is a relevant concern in subjects affected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), showing increased mortality among patients with preexisting[12] or concomitant cardiovascular disorders like heart failure,[13] coronary artery disease, and myocardial injury.[14] Increasing interest has been witnessed on concomitant valvular heart disease,[15,16] and mostly on aortic valve stenosis.[17] AS and severe manifestation of COVID-19 share some common risk factors, such as older age, male sex, metabolic syndrome, and kidney function impairment.[17] From a pathophysiological perspective, SARS-CoV-2 may directly lead to aortic valve injury, but it might damage the aortic valve following indirect pathways, including oxidative stress, hyperinflammation, and valve thrombosis.[17] Besides these observations, however, the comprehensive pathophysiological mechanism of valve involvement is yet to be properly understood.[18,19] Recent literature has pointed out the importance of appropriate management of AS[20] in COVID-19 subjects and described the higher mortality among geriatric untreated subjects,[21] but still, less is known about the prevalence and outcome of AS among older patients hospitalized with COVID-19.

The aims of this study were to monitor the prevalence of AS in a wide population of hospitalized geriatric individuals in Sweden and to establish whether AS affects the prognosis of SARS-CoV-2 infection and whether COVID-19 affects the prognosis of AS.

Methods

Design and Sample Eligibility

In the Stockholm region, geriatric inpatient clinics treat and care for patients who are biologically aged and require inpatient geriatric care with specialists in geriatric medicine and multidisciplinary teamwork. Nine of 11 geriatric hospitals in the Stockholm region agreed to participate in this study. During the pandemic, the geriatric clinics in Stockholm were charged with reorganizing to provide care to persons with COVID-19 and supporting the hospital to ensure continued care of other patients.

We identified all hospitalizations of patients who were admitted to 9 geriatric hospitals in Stockholm, Sweden, from March 6, 2020, to November 26, 2021. We excluded 300 patients because of in-hospital staying shorter than 24 hours, or missing diagnosis codes. A total of 28,974 patients were included in the analysis. Among those, 85 individuals had presented with concomitant AS and COVID-19, 529 individuals with AS without COVID-19, and 5033 individuals with COVID-19 without AS, whereas 23,327 patients did not present either AS or COVID-19 (Supplementary Figure 1).

Measures

AS, COVID-19 Diagnosis, and Outcome

The diagnosis of AS was based on the *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes, obtained from electronic health records (I35.0 and I35.2).[22] The diagnosis of COVID-19 was based on a positive reverse transcriptase–polymerase chain reaction (RT-PCR) analysis from nasopharyngeal swabs or a symptomatic patient with a negative RT-PCR but with a typical clinical diagnosis (including a consultation with a specialist in infectious diseases) and a CT scan with typical COVID-19 findings.

The study outcomes were 30-day mortality and anytime mortality from admission. Patients were censored at death or at the end of follow-up (November 26, 2021), whichever came first.

Covariates

We collected information on patient demographics, diagnoses of comorbidities (including hypertension, diabetes mellitus, congestive heart failure, myocardial infarction, atrial fibrillation, stroke, peripheral vascular disease, chronic kidney disease, chronic pulmonary disease, cancer, and dementia), and medications through the electronic health records. Medications were defined as those prescribed within 24 hours after admission.

Data Analysis

Variables were displayed as mean ± SD, median [interquartile range (IQR)], or frequency (percentages). Baseline characteristics were compared across the different diagnoses of AS and COVID-19 by Pearson chi-square for percentages and analysis of variance for continuous variables.

The risk of mortality was assessed by the Kaplan-Meier method, and we also calculated incidence rates with 95% CIs using the exact method. The proportional hazards assumption was checked with the Schoenfeld residuals test. In case of the proportionality assumption for any covariable, we used time-dependent interactions. Flexible parametric survival models (Royston-Parmar models) were used to estimate the adjusted hazard ratio (HR) of death. Models were adjusted for age (continuous), sex, comorbidities (hypertension, diabetes mellitus, congestive heart failure, myocardial infarction, atrial fibrillation, stroke, peripheral vascular disease, chronic kidney disease, chronic pulmonary disease, cancer, and dementia), and admission wave during the COVID-19 pandemic. The main analyses were performed in the overall cohort; the patients were divided into 4 groups, according to the diagnoses of AS and COVID-19. To evaluate whether COVID-19 diagnosis or other comorbidities modified the association between AS and mortality, we performed specific subgroup analyses defined by age (<85, ≥85 years), sex (men vs women), hypertension (yes/no), diabetes (yes/no), congestive heart failure (yes/no), atrial fibrillation (yes/no), chronic kidney disease (yes/no), and COVID-19 infection (COVID-19 vs other diagnosis). Then the patients were divided into AS and non-AS groups; all subgroup analyses were adjusted for age, sex, comorbidities including COVID-19, and admission wave. Finally, in order to illustrate the potential effect of age on the relationship between AS and mortality, we calculated the median survival time among patients with and without AS using adjusted flexible parametric survival model.

According to study design, there were no missing variables reported.

All analyses were performed using R (https://www.r-project.org) and Stata, version 17.0 (StataCorp).

The Swedish Ethical Review Authority approved the study (Dnr 2020-02146, and 2020-03345).

Results

Patients' Characteristics

The study cohort consisted of 28,974 participants, 42% were men, and the median age was 83 years (IQR 77-89 years). Overall, 5118 were

Table 1
Baseline Characteristics of Hospitalized Patients by COVID-19 and Aortic Stenosis Diagnoses in Geriatric Clinics

Characteristics	Overall (N = 28,974)	Non-AS and Non–COVID-19 (n = 23,327)	With AS and Non–COVID-19 (n = 529)	Non-AS and With COVID-19 (n = 5033)	With AS and COVID-19 (n = 85)
Age at admission, y, median (IQR)	83.0 (77.0, 89.0)	83.0 (77.0, 89.0)	88.0 (82.0, 92.0)	83.0 (76.0, 89.0)	87.0 (82.0, 92.0)
Age strata					
<70 y	1816 (6.3)	1452 (6.2)	6 (1.1)	357 (7.1)	1 (1.2)
70-79 y	8203 (28.3)	6603 (28.3)	79 (14.9)	1507 (29.9)	14 (16.5)
80-89 y	12,136 (41.9)	9814 (42.1)	233 (44.0)	2050 (40.7)	39 (45.9)
90+ y	6819 (23.5)	5458 (23.4)	211 (39.9)	1119 (22.2)	31 (36.5)
Sex: female	16,917 (58.4)	13,891 (59.5)	332 (62.8)	2647 (52.6)	47 (55.3)
Comorbidities					
Hypertension	12,406 (42.8)	9985 (42.8)	267 (50.5)	2114 (42.0)	40 (47.1)
Diabetes	8654 (29.9)	6570 (28.2)	109 (20.6)	1941 (38.6)	34 (40.0)
Chronic heart failure	5458 (18.8)	4249 (18.2)	207 (39.1)	963 (19.1)	39 (45.9)
Myocardial Infarction	1315 (4.5)	1009 (4.3)	39 (7.4)	261 (5.2)	6 (7.1)
Chronic kidney disease	4166 (14.4)	3330 (14.3)	103 (19.5)	716 (14.2)	17 (20.0)
Chronical pulmonary disease	4168 (14.4)	3172 (13.6)	58 (11.0)	930 (18.5)	8 (9.4)
Cancer	2611 (9.0)	2158 (9.3)	44 (8.3)	404 (8.0)	5 (5.9)
Stroke	2504 (8.6)	2069 (8.9)	44 (8.3)	385 (7.6)	6 (7.1)
Atrial fibrillation	7993 (27.6)	6352 (27.2)	177 (33.5)	1440 (28.6)	24 (28.2)
Peripheral vascular disease	751 (2.6)	633 (2.7)	16 (3.0)	99 (2.0)	3 (3.5)
Dementia	4042 (14.0)	3217 (13.8)	63 (11.9)	755 (15.0)	7 (8.2)
Time of hospitalization, d, median (IQR)	7.0 (4.0, 9.0)	6.0 (4.0, 8.0)	6.0 (4.0, 8.0)	9.0 (6.0, 13.0)	8.0 (6.0, 13.0)
30-d mortality	2013 (6.9)	1100 (4.7)	51 (9.6)	837 (16.6)	25 (29.4)
Any death	6139 (21.2)	4467 (19.1)	149 (28.2)	1482 (29.4)	41 (48.2)
Waves					
1	8600 (29.7)	6558 (28.1)	175 (33.1)	1831 (36.4)	36 (42.4)
2	5729 (19.8)	4241 (18.2)	86 (16.3)	1385 (27.5)	17 (20.0)
3	14,645 (50.5)	12,528 (53.7)	268 (50.7)	1817 (36.1)	32 (37.6)

Unless otherwise noted, values are n (%).

hospitalized with COVID-19, and 23,586 patients were hospitalized with non–COVID-19 diagnosis at the same time period. AS prevalence was 2.1% in the overall cohort, because it was present in a total of 614 patients, of whom 85 (1.7%) were diagnosed with COVID-19 and 529 (2.2%) hospitalized with other diagnosis.

Age was higher in AS patients, both in COVID-19 and other diagnoses, with the highest median of 88 (IQR 82-92) years in AS patients without COVID-19, followed by 87 (IQR 82-92) years in the concomitant AS and COVID-19 subgroup. AS subgroups also presented significantly ($P < .001$) higher prevalence of chronic heart failure (the highest prevalence of 46% in concomitant COVID-19 followed by 39% in other diagnosis) and chronic kidney disease (20% in AS subgroups vs 14% in groups without AS, $P = .003$). Accordingly, a significantly higher prescription of typical heart failure medications was also observed in the presence of AS: diuretics (highest prescription in concomitant COVID-19 and AS, 77%, followed by 66% in patients with AS and other diagnosis, $P < .001$), beta-blockers (62% in AS vs 50% without AS, $P < .001$), and ACE inhibitors (29% in AS vs 23% without AS, $P = .006$) (Table 1).

AS, COVID-19, and Mortality

During the follow-up time of 630 days, we observed the highest mortality rate among patients with concomitant COVID-19 and AS, both at 30 days and at any time (incidence rate per 100 person-years 438.4, 95% CI 296.2-648.8, and 72.9, 95% CI 53.7-99.0, respectively) (Table 2).

In this subgroup, the mortality rate reached 29.4% at 30 days and 48.2% when considered at any time (Table 1). Thirty days after hospital admission, patients with COVID-19, without AS, showed a higher mortality incidence rate than patients with AS only (225.1 per 100 person-years, 95% CI 210.4-240.9, vs 127.3 per 100 person-years, 95% CI 96.7-167.5); conversely, considering anytime mortality, the

Table 2
Adjusted Hazard Ratios for Mortality in the Overall Population

	Events (Deaths)	Incidence Rate per 100 person-years (95% CI)	HR* (95% CI)
30-d mortality			
Non-AS and non–COVID-19 (n = 23,327)	1100	60.04 (56.60-63.70)	ref
With AS and non–COVID-19 (n = 529)	51	127.33 (96.77-167.54)	1.67† (1.26-2.21)
Non-AS and with COVID-19 (n = 5033)	837	225.138 (210.39-240.92)	3.61† (3.30-3.96)
With AS and COVID-19 (n = 85)	25	438.370 (296.21-648.76)	5.49† (3.68-8.18)
All mortality			
Non-AS and non–COVID-19 (n = 23,327)	4467	27.027 (26.25-27.83)	ref
With AS and non–COVID-19 (n = 529)	149	43.323 (36.90-50.87)	1.40† (1.18-1.65)
Non-AS and with COVID-19 (n = 5033)	1482	37.22 (35.37-39.16)	1.77† (1.67-1.88)
With AS and COVID-19 (n = 85)	41	72.894 (53.67-99.00)	2.83† (2.08-3.86)

*Models were adjusted for age, sex, comorbidities (hypertension, diabetes mellitus, congestive heart failure, myocardial infarction, atrial fibrillation, stroke, peripheral vascular disease, chronic kidney disease, chronic pulmonary disease, cancer, and dementia), and admission wave during COVID-19 pandemic.
†$P < .001$.

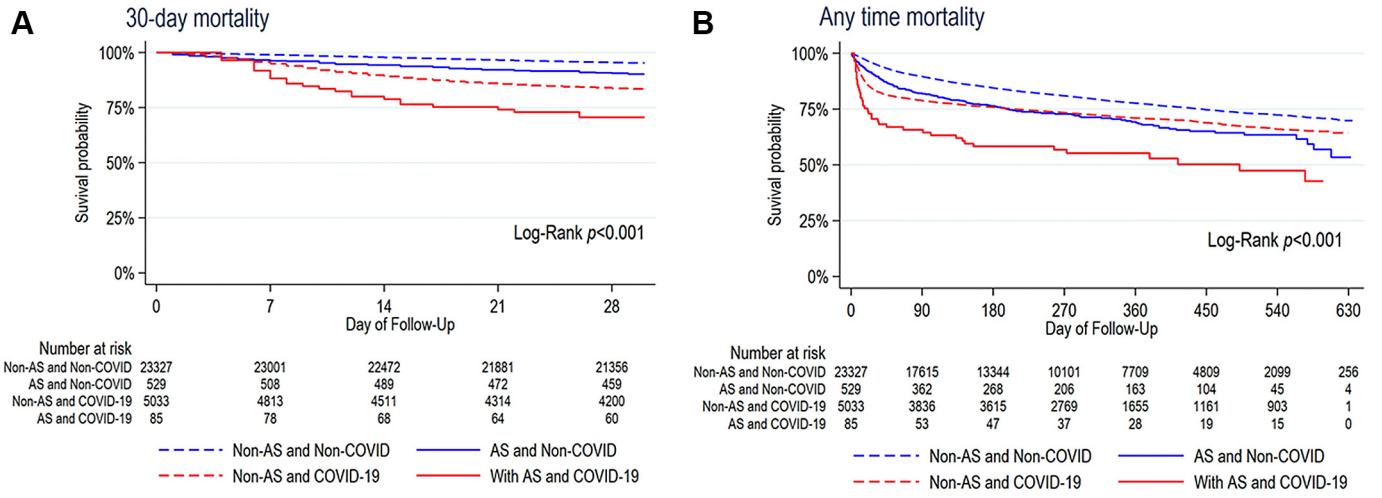

Fig. 1. Kaplan-Meier curve for mortality at (A) 30 days and (B) any time, stratified by AS and COVID-19 diagnoses.

incidence rate was higher for the AS subgroup, compared to COVID-19 patients (43.3 per 100 person-years, 95% CI 36.9-50.9, vs 37.2, 95% CI 35.4-39.2). The lowest mortality incidence rate was registered for patients without AS and neither COVID-19, both at 30 days and at any time (Table 2). These survival trends, obtained by Kaplan Meier curves (Figure 1), considering anytime mortality (Figure 1B), AS curve, and COVID-19 curve crossed about 180 days after hospitalization, outlining, after that point, lower survival in AS patients compared with COVID-19 patients.

In addition to adjusting for multiple variables (Table 2), considering patients without AS or COVID-19 as a reference, both at 30 days and at any time, the highest HR for mortality was confirmed in patients with concomitant AS and COVID-19 (HR 5.5, 95% CI 3.7-8.2, at 30 days and 2.8, 95% CI 2.1-3.9, at any time). As compared to the reference subgroup, AS patients had increased mortality risk (HR 1.7, 95% CI 1.3-2.2, at 30 days and 1.4, 95% CI 1.2-1.7, at any time), which itself was lower than the COVID-19 mortality risk (HR 3.6, 95% CI 3.3-4.0, at 30 days and 1.8, 95% CI 1.7-1.9, at any time).

Subgroup Analyses

Compared to patients without AS, we observed increased HR for 30 days' mortality in AS patients both in the presence and absence of COVID-19 (HR 1.6, 95% CI 1.1-2.4, and HR 1.6, 95% CI 1.2-2.2,

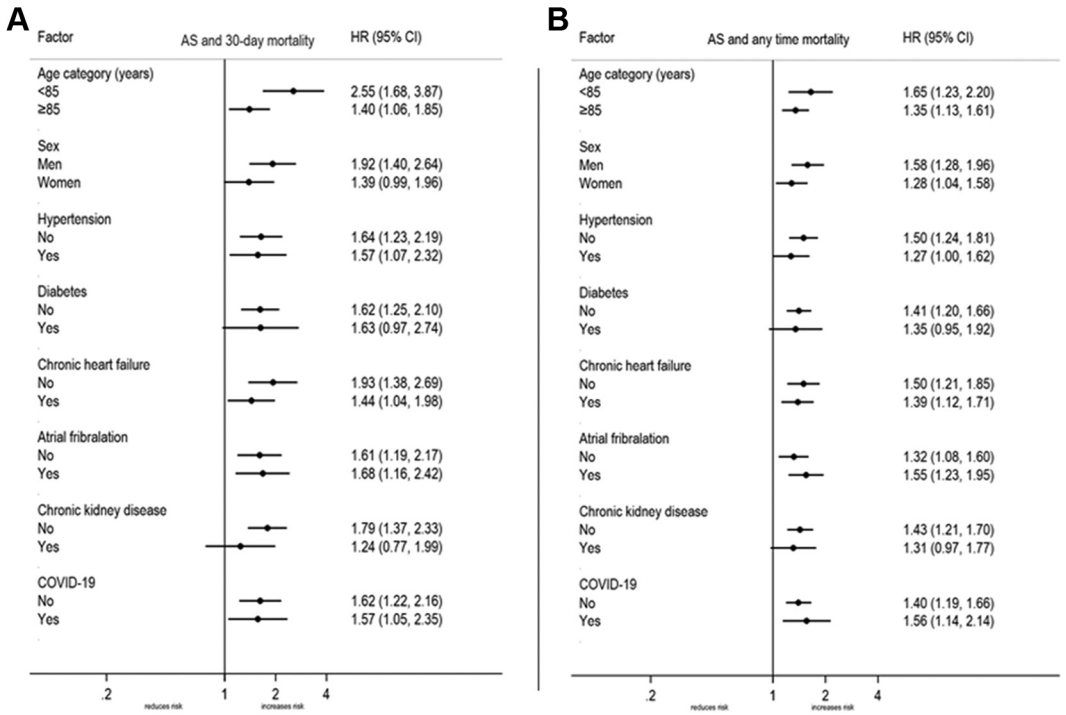

Fig. 2. Subgroup analysis regarding (A) 30-day mortality and (B) all mortality. Models were adjusted for age (continuous), sex, comorbidities (hypertension, diabetes mellitus, congestive heart failure, myocardial infarction, atrial fibrillation, stroke, peripheral vascular disease, chronic kidney disease, chronic pulmonary disease, cancer, and dementia), and admission wave and COVID-19 diagnosis.

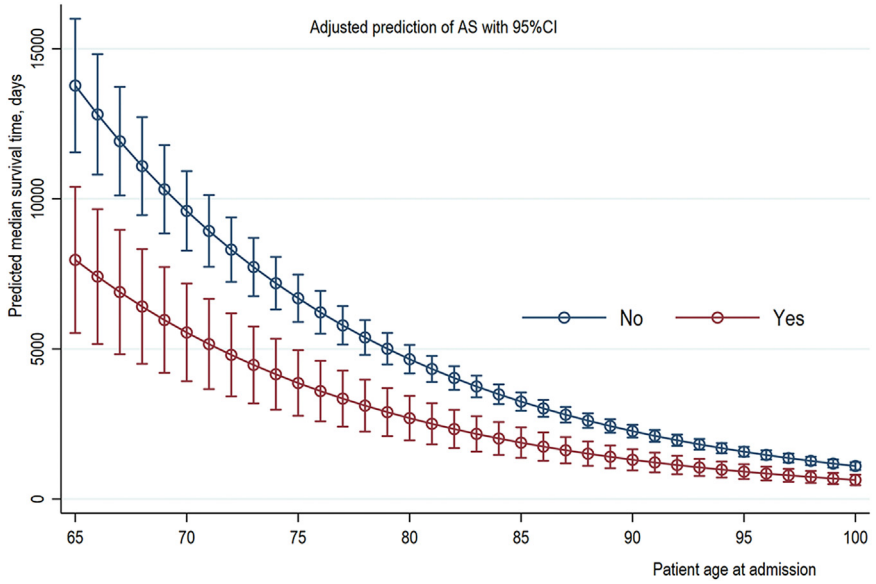

Fig. 3. Median survival time between AS and non-AS. Model was adjusted for age (continuous), sex, comorbidities (hypertension, diabetes mellitus, congestive heart failure, myocardial infarction, atrial fibrillation, stroke, peripheral vascular disease, chronic kidney disease, chronic pulmonary disease, cancer, and dementia), and admission wave and COVID-19 diagnosis.

respectively). This trend was confirmed even considering anytime mortality, showing similar HR risk for AS patients with (HR 1.6, 95% CI 1.1-2.1) and without (HR 1.4, 95% CI 1.2-1.7) COVID-19 (Figure 2).

In multivariable adjusted analyses, patients with AS had a shorter survival time compared with non-AS, confirming statistically significant associations across all age ranges (Figure 3).

Discussion

In this wide population of geriatric patients hospitalized in Stockholm, Sweden, from the outbreak of COVID-19 pandemic, we show that AS was an independent risk factor for mortality in both COVID-19 and non–COVID-19 patients after adjustment for demographics, comorbidities, and pandemic waves. To our knowledge, this is the first study to investigate AS mortality over a fairly long follow-up time (up to 20 months), making comparisons between subjects with and without COVID-19 diagnosis.

The AS prevalence of 2.1% is in line with previous data that outlined AS prevalence in older people ranging from 2% to 3%,[23,24] up to 12.4%,[25] depending on the heterogeneity of the different studies considered. To interpret the relatively low prevalence of AS in our cohort, it should be noted that we included only hospitalized geriatric patients (therefore not comparable with population-based samples[23,24]), with a fairly wide age range (median IQR 83, 77-89 years), whereas some of the previous studies were performed on narrower age subsets (70-79 years, or 80-89 years).[24] Furthermore, cardiac ultrasonography was not available in our patients, which may have led to an underestimation of the actual AS prevalence.

Our principal finding is that the highest mortality was observed in patients with concomitant COVID-19 and AS, that AS was related to increased mortality, both in patients with and without COVID-19 diagnosis, and that AS is an independent risk factor for death. Of note, the AS–COVID-19 subgroup displays increased mortality, as compared to AS subjects without COVID-19, both at 30 days and at any time. Our study agrees with a recent study[21] based on a multicenter registry with collectively 136 patients with severe valvular heart disease that reported a 42.6% 30-day mortality. In our cohort, the 30-day mortality in AS–COVID-19 patients was 29.4%; we speculate that our population included even lower degrees of AS, which may account for the lower 30-day mortality rate. Our finding, however, can still be considered in line with several previous studies. A wide multicenter cohort study, based on more than 16,000 subjects from the CAPACITY-COVID registry and LEOSS study, described an association between valvular heart diseases (including AS) and in-hospital mortality in a crude analysis, which was not observed when adjusting for multiple variables.[15] Neither an Italian multicenter retrospective observational study[26] nor a single-center Brazilian research[16] could actually detect significant difference in AS prevalence between the survived and deceased subgroups of COVID-19–positive hospitalized patients. The first study[26] was based on 226 patients from 7 Italian centers, with confirmed diagnosis of COVID-19, and evaluated by echocardiography. The latter, by Paulino and colleagues,[16] analyzed 120 COVID-19–positive patients, admitted to a quaternary care hospital in Rio de Janeiro, owing to cardiovascular indications due to COVID-19 manifestation. The different size of the samples, the different inclusion criteria, and the dissimilar follow-up time (in-hospital mortality in previous literature whereas ≤20 months of follow-up in our study) might account for the different result.

Lending credibility to our primary observation, we also report a consistent association between AS and mortality on top of several comorbidities including COVID-19, whichever age point was considered. We also noted that in the early stage of COVID-19, a steep drop of survival could be detected in patients with AS and COVID-19, whereas, a few months later, the line assumes a milder slope; we may speculate that in the earliest phase, a possible synergic effect of AS and COVID-19 may give reason of the increased mortality, then, in the late period the mortality may be mostly driven by AS rather than COVID-19. Thus, the well-known post-acute effect of SARS-CoV-2 infection[27] may play a slightly different role in the geriatric population because the burden of other comorbidities might overwhelm COVID-19 effects. As a clinical implication of the present findings is that when considering a COVID-19–positive older adult, each comorbidity, and AS in particular, should be equally managed both in the acute and post-acute phase of infection.

The pathophysiological mechanism underlying a possible synergic effect of AS and COVID-19 is unknown, though, intriguing clues may be derived from angiotensin-converting enzyme 2 (ACE2) receptor as a central player in cardiovascular involvement during COVID-19 infection.[17,18] As a robust knowledge, cardiac complications may arise from SARS-CoV-2 infection, as part of a systemic inflammation process, with consequent endothelial dysfunction,[28] but also by direct viral myocardial damage[29] mediated by viral binding to the ACE2 receptor.[30] Furthermore, the soluble isoform of ACE2 is increased in several cardiovascular disorders, and in AS patients, it can be considered a predictor of mortality.[19] Hence, increased ACE2 might be involved in SARS-CoV-2 susceptibility, and previous studies described increased mortality and worse outcome in patients with COVID-19 and baseline high levels of ACE2.[30] Because of the design of the present study, our data do not allow to provide any certain explanation about this possible mechanism, and further studies are needed to specifically define the involvement of AS during COVID-19 infection. Careful attention should be paid to AS patients during and after SARS-CoV-2 infection, given the relevant mortality affecting this population.

Finally, when considering AS mortality from a health care perspective, it should also be considered that the COVID-19 pandemic consistently affected the AS diagnosis and management system,[20,31] with unavoidable consequences on the clinical outcome.

The strengths and limitations of our research need to be acknowledged for a proper interpretation of our results. The major strength of this study lies in the large size of the population and in the relatively long follow-up time, which allows to enrich previous findings, mostly focused on in-hospital mortality. As a limitation, we need to recognize the possible underestimation of AS prevalence: because the number of AS patients was derived directly from discharge diagnosis codes, both patients with known AS but asymptomatic for aortic valve disease during their hospitalization and those with undiagnosed AS may have been missed. The lack of knowledge regarding AS severity was a limitation to the possibility of analyzing the impact of valve stenosis on hemodynamic status and cardiac failure during the acute illness of COVID-19. We explored the effect of age on survival time in patients with and without COVID-19, yet we acknowledge that this analysis is limited by the lack of information regarding AS severity. Finally, as in all observational studies, causality cannot be inferred, and we acknowledge the possibility of residual and unknown confounding.

Conclusions and Implications

Our study found that AS was an independent pre of mortality, on top of several other concomitant diagnosis and independent of the concomitant COVID-19 infection. Although additional research is needed to further explore the possible involvement of aortic valve during COVID-19 infection, given the remarkable mortality of AS, our results endorse a careful AS evaluation and management, even in the acute and post-acute phases of COVID-19.

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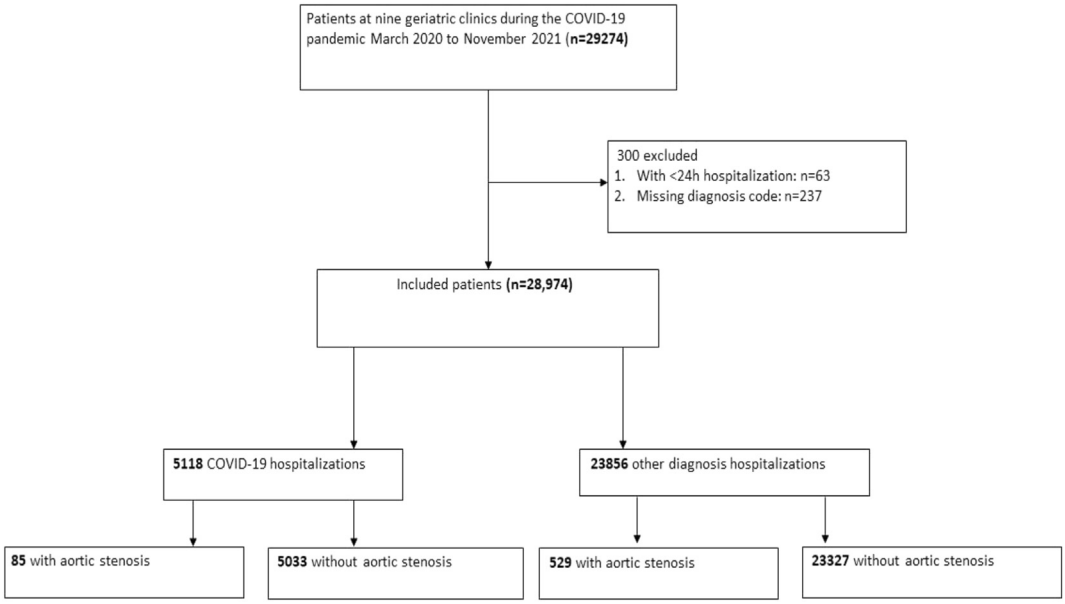

Supplementary Fig. 1. Flowchart of included patients.

Supplementary Table 1
Comprehensive Characterization of the Study Population

Characteristics	Overall (N = 28,974)	Non-AS and Non–COVID-19 (n = 23,327)	With AS and Non–COVID-19 (n = 529)	Non-AS and With COVID-19 (n = 5033)	With AS and COVID-19 (n = 85)
Age at admission, y, median (IQR)	83.0 (77.0, 89.0)	83.0 (77.0, 89.0)	88.0 (82.0, 92.0)	83.0 (76.0, 89.0)	87.0 (82.0, 92.0)
Age strata					
<70 y	1816 (6.3)	1452 (6.2)	6 (1.1)	357 (7.1)	1 (1.2)
70-79 y	8203 (28.3)	6603 (28.3)	79 (14.9)	1507 (29.9)	14 (16.5)
80-89 y	12,136 (41.9)	9814 (42.1)	233 (44.0)	2050 (40.7)	39 (45.9)
90+ y	6819 (23.5)	5458 (23.4)	211 (39.9)	1119 (22.2)	31 (36.5)
Sex: female	16,917 (58.4)	13,891 (59.5)	332 (62.8)	2647 (52.6)	47 (55.3)
Comorbidities					
Hypertension	12,406 (42.8)	9985 (42.8)	267 (50.5)	2114 (42.0)	40 (47.1)
Diabetes	8654 (29.9)	6570 (28.2)	109 (20.6)	1941 (38.6)	34 (40.0)
Chronic heart failure	5458 (18.8)	4249 (18.2)	207 (39.1)	963 (19.1)	39 (45.9)
Myocardial infarction	1315 (4.5)	1009 (4.3)	39 (7.4)	261 (5.2)	6 (7.1)
Chronic kidney disease	4166 (14.4)	3330 (14.3)	103 (19.5)	716 (14.2)	17 (20.0)
Chronical pulmonary disease	4168 (14.4)	3172 (13.6)	58 (11.0)	930 (18.5)	8 (9.4)
Cancer	2611 (9.0)	2158 (9.3)	44 (8.3)	404 (8.0)	5 (5.9)
Stroke	2504 (8.6)	2069 (8.9)	44 (8.3)	385 (7.6)	6 (7.1)
Atrial fibrillation	7993 (27.6)	6352 (27.2)	177 (33.5)	1440 (28.6)	24 (28.2)
Peripheral vascular disease	751 (2.6)	633 (2.7)	16 (3.0)	99 (2.0)	3 (3.5)
Dementia	4042 (14.0)	3217 (13.8)	63 (11.9)	755 (15.0)	7 (8.2)
Medication					
ACE-I	6724 (23.2)	5409 (23.2)	153 (28.9)	1137 (22.6)	25 (29.4)
ARB	8116 (28.0)	6526 (28.0)	175 (33.1)	1390 (27.6)	25 (29.4)
β-blocker	14,538 (50.2)	11,616 (49.8)	330 (62.4)	2539 (50.4)	53 (62.4)
CCB	9055 (31.3)	7340 (31.5)	170 (32.1)	1521 (30.2)	24 (28.2)
Diuretics	14,412 (49.7)	11,405 (48.9)	349 (66.0)	2593 (51.5)	65 (76.5)
Statins	11,509 (39.7)	9174 (39.3)	241 (45.6)	2061 (40.9)	33 (38.8)
Warfarin	1912 (6.6)	1525 (6.5)	37 (7.0)	342 (6.8)	8 (9.4)
Dalteparin (Fragmin)	7454 (25.7)	4630 (19.8)	73 (13.8)	2711 (53.9)	40 (47.1)
DOAC	7742 (26.7)	6020 (25.8)	157 (29.7)	1542 (30.6)	23 (27.1)
Antiplatelet	9182 (31.7)	7300 (31.3)	220 (41.6)	1632 (32.4)	30 (35.3)
NSAID	1896 (6.5)	1615 (6.9)	22 (4.2)	254 (5.0)	5 (5.9)
Glucocorticoids	4999 (17.3)	3474 (14.9)	77 (14.6)	1420 (28.2)	28 (32.9)
Antibiotic	9508 (32.8)	7740 (33.2)	134 (25.3)	1606 (31.9)	28 (32.9)
Time of hospitalization, d, median (IQR)	7.0 (4.0, 9.0)	6.0 (4.0, 8.0)	6.0 (4.0, 8.0)	9.0 (6.0, 13.0)	8.0 (6.0, 13.0)
30-d mortality	2013 (6.9)	1100 (4.7)	51 (9.6)	837 (16.6)	25 (29.4)
Any death	6139 (21.2)	4467 (19.1)	149 (28.2)	1482 (29.4)	41 (48.2)
Waves					
1	8600 (29.7)	6558 (28.1)	175 (33.1)	1831 (36.4)	36 (42.4)
2	5729 (19.8)	4241 (18.2)	86 (16.3)	1385 (27.5)	17 (20.0)
3	14,645 (50.5)	12,528 (53.7)	268 (50.7)	1817 (36.1)	32 (37.6)

ACE-I, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; AS, aortic stenosis; CCB, calcium channel blockers; DOAC, direct oral anticoagulants; NSAID, nonsteroidal antiinflammatory drug.
Unless otherwise noted, values are n (%).

Supplementary Table 2
Adjusted Hazard Ratios for Mortality in the Overall Population the Full Model

	30-d Mortality		All Mortality	
	HR	95% CI	HR	95% CI
Non-AS and non−COVID-19	ref		ref	
With AS and non−COVID-19	1.67‡	1.26-2.21	1.40‡	1.18-1.65
Non-AS and with COVID-19	3.61‡	3.30-3.96	1.77‡	1.67-1.88
With AS and COVID-19	5.49‡	3.68-8.18	2.83‡	2.08-3.86
Age strata				
<70 y	ref		ref	
70-79 y	1.20	0.91-1.57	1.08	0.93-1.25
80-89 y	1.87‡	1.44-2.43	1.49‡	1.29-1.71
≥90 y	2.77‡	2.12-3.61	2.28‡	1.97-2.63
Male	1.29‡	1.18-1.41	1.27‡	1.20-1.34
Comorbidities				
Hypertension	0.70‡	0.64-0.77	0.72‡	0.68-0.76
Diabetes mellitus	1.00	0.90-1.11	1.02	0.96-1.09
Chronic heart failure	1.72‡	1.56-1.91	1.59‡	1.49-1.69
Myocardial Infarction	1.26*	1.05-1.50	1.11	0.99-1.24
Atrial fibrillation	1.12*	1.01-1.23	1.15‡	1.08-1.22
Stroke	1.23†	1.06-1.43	1.17‡	1.09-1.29
Peripheral vascular disease	1.46†	1.15-1.85	1.42‡	1.22-1.63
Chronic kidney disease	1.53‡	1.37-1.70	1.49‡	1.41-1.60
Chronical pulmonary disease	1.39‡	1.24-1.56	1.32‡	1.23-1.42
Dementia	2.01‡	1.80-2.23	1.71‡	1.60-1.83
Cancer	2.24‡	1.99-2.52	2.67‡	2.46-2.85
Waves				
First wave	ref		ref	
Second wave	0.75‡	0.67-0.84	0.86‡	0.83-0.95
Third wave	0.69‡	0.63-0.77	0.77‡	0.70-0.79

AS, aortic stenosis.
*$P < .05$.
†$P < .01$.
‡$P < .001$.