Prognostic value of nonalcoholic fatty liver disease in patients with severe aortic stenosis who underwent transcatheter aortic valve implantation

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Prognostic Value of Nonalcoholic Fatty Liver Disease in Patients With Severe Aortic Stenosis Who Underwent Transcatheter Aortic Valve Implantation

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Nonalcoholic fatty liver disease (NAFLD) is associated with an increased risk of cardiovascular events. Although the association between NAFLD and aortic valve sclerosis has been described, the prevalence and prognostic implications of NAFLD among patients with severe aortic stenosis (AS) have not been described. In addition, the effect of the presence of severe tricuspid regurgitation (TR) on the prevalence of NAFLD remains unexplored. Accordingly, we investigated the prognostic implications of NAFLD among patients with severe AS with and without concomitant significant TR. A total of 538 patients (aged 80 ± 7 y, 49.6% men) who underwent noncontrast computed tomography before transcatheter aortic valve implantation (TAVI) between 2007 and 2019 were included. NAFLD was defined as a liver-to-spleen attenuation ratio <1.0 on noncontrast computed tomography. NAFLD was present in 118 patients (21.9%). There were no significant differences in pulmonary arterial pressure, right atrial pressure, or the prevalence of significant TR between patients with and without NAFLD. During a median follow-up of 47 months (interquartile range 20 to 70 months), 224 patients (41.6%) died. Univariate Cox regression analysis demonstrated that NAFLD was not significantly associated with all-cause death among patients treated with TAVI (hazard ratio 1.32, 95% confidential interval 0.97 to 1.79, p = 0.07). In conclusion, among patients with severe AS who underwent TAVI, the prevalence of significant TR and the clinical outcomes were similar in patients with and without NAFLD. **(Am J Cardiol 2023;186:176−180)**

The prevalence of nonalcoholic fatty liver disease (NAFLD), the most common liver disease, increases with the increasing prevalence of obesity and metabolic syndrome.[1,2] NAFLD is associated with increased risk of cardiovascular events; the highest risk is among patients with the most advanced stage of liver fibrosis.[3−5] Previous studies demonstrated that NAFLD is related to aortic valve sclerosis—both in the general population and in patients with type 2 diabetes.[6,7] However, the prevalence and prognostic implications of NAFLD among patients with severe aortic stenosis (AS) are unclear. Furthermore, severe AS may be complicated with right-sided heart failure and tricuspid regurgitation (TR), which are associated with poor prognosis.[8,9] Chronic hepatic congestion is a common feature in patients with right heart failure.[10] The TR severity is also associated with liver fibrosis in patients with heart failure without primary liver disease.[11,12] It can be speculated that patients with degenerative calcific severe AS may have NAFLD and that if severe TR coexists, the prevalence of NAFLD and liver fibrosis may increase. Accordingly, we investigated the prognostic implications of NAFLD in patients with degenerative calcific severe AS with and without concomitant significant TR.

Methods

Patients with severe AS who underwent transcatheter aortic valve implantation (TAVI) and who had noncontrast computed tomography (CT) data that included the liver and spleen were retrospectively included. The noncontrast CT was acquired within a median of 28 days (interquartile range [IQR] 7 to 99 d) before TAVI at the Leiden University Medical Center from 2007 to 2019. Patients with primary liver disease (defined as the liver tumor, cirrhosis, or hepatitis) and patients without noncontrast CT data were excluded. The baseline demographic, clinical, and procedural data were collected from the medical record system of the cardiology department (EPD-Vision, version 12.5.4,

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Leiden, the Netherlands). Because of the retrospective design of the analysis, the institutional review board approved the analysis of clinically acquired data and waived the need for patient written informed consent.

Demographic data and clinical data—including heart failure symptoms (New York Heart Association functional class), co-morbidities, renal function, cardiac rhythm, and medication—were collected from the cardiology departmental information system. Echocardiography was performed using commercially available ultrasound systems within 1 month before the TAVI procedure. Left ventricular volumes and ejection fraction were measured on the apical 4- and 2-chamber views using the biplane Simpson's method and were indexed to body surface area. The maximum left atrial volume was assessed from the apical 4- and 2-chamber views according to the Simpson's method and was indexed for body surface area. The transaortic mean pressure gradient was calculated from spectral Doppler obtained from the apical 3- or 5-chamber views by applying Bernoulli's equation, whereas the aortic valve area was calculated using the continuity equation. Severe AS was defined according to current recommendations.[13] The severities of tricuspid and mitral regurgitation were based on a multiparametric approach, as described in current guidelines.[14] Moderate and severe tricuspid and mitral regurgitation were considered significant valvular disease. Right ventricular systolic function was assessed by measuring the tricuspid annulus plane systolic excursion and right atrial pressure was estimated based on the inferior vena cava diameter and collapse according to current guidelines.[15] The pulmonary arterial systolic pressure was calculated using Bernouilli's equation, measuring the peak TR jet velocity and adding 3, 8, or 15 mm Hg from the right atrial pressure.

Preprocedural noncontrast CT scans were performed using a 64-slice Aquilion 64 or a 320-slice Aquilion One CT scanner (Toshiba Medical Systems, Ōtawara, Japan), as described in detail previously.[16] Assessment of NAFLD was performed as previously described;[17] the regions of interest >100 mm^2 in the area included 2 regions that were aligned with the anterior-posterior dimension of the right liver lobe and 1 that was aligned with the spleen (Figure 1). In the liver, the regions of interest avoided inclusion of large vessels or biliary structures. A liver-to-spleen attenuation ratio <1.0 defined the presence of NAFLD.[3]

We also calculated the NAFLD fibrosis score as −1.675 + (0.037 × age) + (0.094 × body mass index) + (1.13 × hyperglycemia) + (0.99 × aspartate aminotransferase / alanine aminotransferase) − (0.013 × platelet count) − (0.66 × albumin). We have expressed body mass index in kg/m^2, platelet count in 10^9/L, and albmin in g/100 ml.

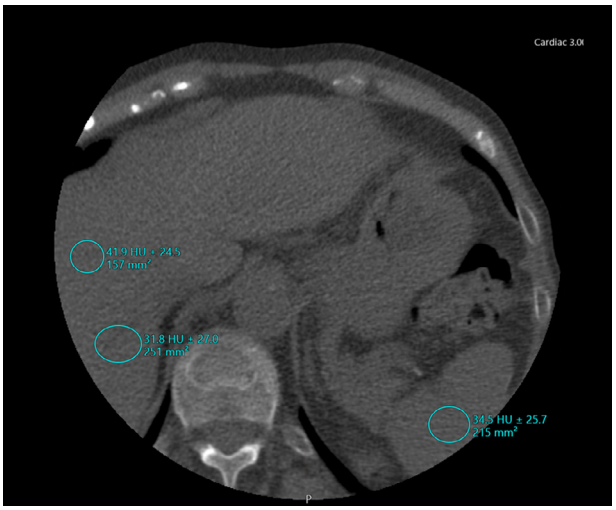

Figure 1. Noncontrast CT to evaluate nonalcoholic fatty liver disease. The regions of interest >100 mm^2 in area included 2 regions that were aligned with the anterior-posterior dimension of the right liver lobe and 1 region that was aligned with the spleen. In the liver, the regions of interest avoided inclusion of any large vessels or biliary structures. A liver-to-spleen attenuation ratio <1.0 was considered the cut-off value for a positive diagnosis of nonalcoholic fatty liver disease.

The NAFLD fibrosis score was further categorized into 3 groups: mild NAFLD fibrosis (≥ −1.455), moderate NAFLD fibrosis (−1.455 to 0.676), and severe NAFLD fibrosis (>0.676).[18]

The primary endpoint was all-cause mortality after TAVI. Mortality data were collected from the individual patient records, which are linked to the governmental death registry. The secondary endpoint was heart failure hospitalization. The occurrence of the secondary endpoint was obtained from the review of medical charts.

Continuous data are presented as mean ± SD or median and interquartile range, as appropriate. To compare the continuous variables, the independent Student *t* test or Mann-Whitney *U* test was used, as appropriate. Categorical variables were expressed as frequency (percentage) and compared using chi-square test. Survival analysis was performed using the Kaplan-Meier approach; log-rank tests

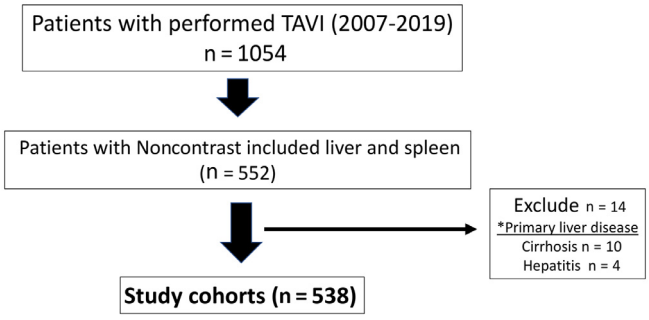

Figure 2. Patient selection flow.

were used to compare the cumulative survival of patients with and without NAFLD (based on noncontrast CT) and to compare survival in patients stratified according to the NAFLD fibrosis score. Univariate Cox regression analysis was used to identify the association between NAFLD and all-cause mortality. Hazard ratios (HRs) with 95% confidence intervals (CIs) were presented. Two-sided p values <0.05 defined statistical significance. The statistical analyses were performed using SPSS Statistics version 25 (IBM Corp., Armonk, New York) and R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Among 1,054 patients who underwent TAVI during the study period, 538 patients were included in the present study (Figure 2). In this cohort, 118 patients (21.9%) had NAFLD (based on noncontrast CT). Patient demographic and clinical characteristics were divided according to the presence of NAFLD (Table 1). Patients with NAFLD were more likely to be male and more likely to have atrial fibrillation. No significant differences were observed between patients with and without NAFLD regarding other clinical and echocardiographic parameters, including pulmonary arterial systolic pressure and the prevalence of significant TR. The NAFLD fibrosis score could be calculated in 253 patients (53%). Among these patients, 32 were classified as having mild NAFLD fibrosis, 138 as having moderate NAFLD fibrosis, and 83 as having severe NAFLD fibrosis.

During a median follow-up of 47 months (IQR 20 to 70 months), 224 patients (41.6%) died. Kaplan-Meier survival analysis showed no significant difference in the primary endpoint of all-cause mortality between patients with and without NAFLD (log-rank p = 0.07, Figure 3). Cox regression analysis also demonstrated that NAFLD was not significantly associated with all-cause mortality (HR 1.32, 95% CI 0.97 to 1.79, p = 0.07). For the patients stratified by the NAFLD fibrosis score, no significant differences in all-cause mortality were observed among the 3 groups (log-rank p = 0.06, Figure 3). Cox regression analysis also demonstrated no significant association between all-cause mortality and NAFLD fibrosis group (mild vs moderate NAFLD fibrosis: HR 0.99, 95% CI 0.53 to 1.84, p = 0.99; mild vs severe NAFLD fibrosis: HR 1.54, 95% CI 0.82 to 2.91, p = 0.18). The secondary endpoint (heart failure hospitalization) was observed in 58 patients (10.8%) during a median follow-up of 12 months (IQR 1 to 24 months). The incidence of heart failure hospitalization was not significantly different between patients with and without NAFLD (log-rank p = 0.69, Figure 3).

Table 1
Baseline clinical and echocardiographic characteristics

Variable	Nonalcoholic fatty liver disease		p Value
	Yes (n=118)	No (n=420)	
Age (years)	80±7	80±7	0.86
Men	68 (58%)	199 (47%)	0.05
BMI (kg/m^2)	26.1±4.4	26.4±4.2	0.49
Hypertension	82 (72%)	320 (77%)	0.25
Hyperlipidemia	69 (61%)	279 (67%)	0.18
Diabetes mellitus	34 (30%)	115 (28%)	0.70
Coronary artery disease	68 (59%)	253 (61%)	0.74
COPD	24 (22%)	90 (23%)	0.78
NYHA functional class ≥3	71 (62%)	252 (61%)	0.78
Atrial fibrillation	41 (35%)	93 (22%)	<0.01
eGFR (ml/min/1.73 m^2)	62±22	64±24	0.42
Platelet count (× 10^9)	229±86	224±74	0.66
Serum albumin (g/100 ml)*	3.9±0.6	3.8±0.6	0.57
AST (U/L)	28±13	27±16	0.91
ALT (U/L)	22±16	20±16	0.40
Total bilirubin (μmol/L)	13±8	11±8	0.33
NT-proBNP (ng/L)	1,837 [552−4,269]	1,422 [683−3,626]	0.84
Echocardiographic parameters			
LVEDVI (ml/mm^2)	54.6±25.7	55.1±24.1	0.86
LVESVI (ml/mm^2)	27.2±19.4	27.2±19.5	0.83
LVEF (%)	53.2±14.0	54.2±13.9	0.47
LAVI (ml/mm^2)	47.8±20.2	44.1±17.5	0.08
Mean aortic valve gradient (mm Hg)	40.3±15.6	40.4±17.1	0.13
Aortic valve area (cm^2)	0.88±0.36	0.88±0.86	0.83
TAPSE (mm)	18.8±4.8	18.7±4.8	0.80
PAP (mm Hg)	37.4±14.2	36.7±13.5	0.65
RAP (mm Hg)	7.2±4.0	6.8±4.2	0.34
Significant MR	6 (5.1%)	16 (3.8%)	0.55
Significant TR	24 (20%)	84 (20%)	0.94
Medical therapy			
Beta blockers	63 (55%)	246 (59%)	0.37
ACEI/ARB	68 (59%)	233 (56%)	0.59
Diuretics	81 (70%)	245 (59%)	0.03
Spironolactone	15 (13%)	62 (15%)	0.60
Statins	71 (62%)	272 (66%)	0.42
Antiplatelet therapy	65 (57%)	241 (58%)	0.73
Anticoagulation therapy	55 (48%)	161 (39%)	0.09

*Serum albumin was obtained for 301 patients.

Values for continuous variables are expressed as mean ± SD or median [interquartile range].

ACEI = angiotensin-converting enzyme inhibitor; ALT = alanine aminotransferase; ARB = angiotensin II receptor blocker; AST = aspartate aminotransferase; BMI = body mass index; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; LAVI = left atrial volume index; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; MR = mitral regurgitation; NT-proBNP = N-terminal pro B-type natriuretic peptide; NYHA = New York Heart Association; PAP = Pulmonary arterial pressure; RAP = Right atrial pressure; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.

Discussion

The main findings of the present study can be summarized as follows: (1) NAFLD (assessed with noncontrast CT and NAFLD fibrosis score) was not associated with all-cause mortality in patients who underwent TAVI, and (2) no association was noted between NAFLD and the presence of significant TR in patients with severe AS.

The prevalence of NAFLD in the general population in Western countries is 20% to 30%, and NAFLD is one of the most frequent causes of chronic liver disease.[2] In addition, NAFLD is associated with increased cardiovascular disease risk, cardiac arrhythmias, chronic kidney disease, and type 2 diabetes.[4] The expanded and inflamed visceral adipose tissue in the liver, which characterizes the NAFLD, releases inflammatory and atherogenic molecules as well as factors

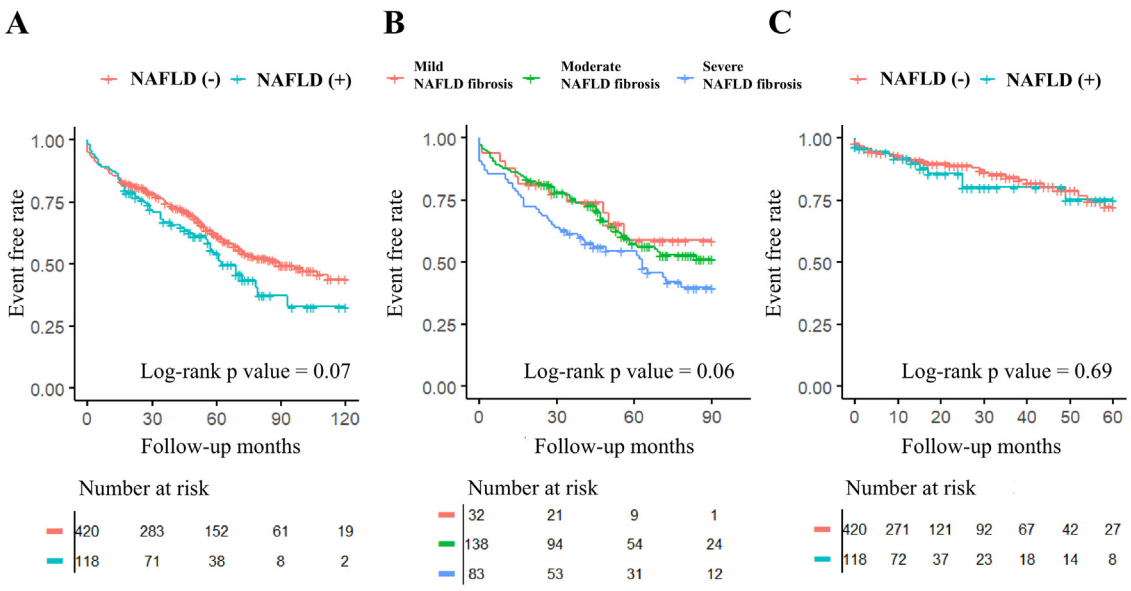

Figure 3. Kaplan-Meier curves for (*A*) all-cause death, comparing patients with versus without NAFLD on noncontrast CT; (*B*) all-cause death, comparing patients stratified based on the NAFLD fibrosis score; and (*C*) heart failure hospitalization, comparing patients with versus without NAFLD on noncontrast CT.

involved in hypercoagulation, hypofibrinolysis, and the development of insulin resistance.[19] The presence of NAFLD is associated with increased coronary atherosclerosis on coronary CT angiography.[20] Furthermore, coronary atherosclerosis and degenerative calcific AS share common pathophysiologic mechanisms.[21] Accordingly, it could be hypothesized that NAFLD may be more frequently observed in patients with AS than in patients without AS. In a study including 247 patients with type 2 diabetes without known heart failure, valvular heart disease, or hepatic disease, the presence of NAFLD as assessed with ultrasonography was independently associated with the presence of aortic valve sclerosis on echocardiography (odds ratio 2.65, 95% CI 1.07 to 6.31, p = 0.04).[22] Noncontrast CT is the reference standard to assess the presence of aortic valve calcification and is an accurate method to identify NAFLD.[14,23] In the present study, the prevalence of NAFLD in patients with severe AS was similar to that reported in the general population. Therefore, these results suggest that NAFLD may not be a risk factor for the development of severe AS. However, the present study was not a longitudinal study to evaluate whether the presence of NAFLD leads to more rapid progression of AS. Moreover, the present study evaluated the association between NAFLD and significant TR, which could enhance the progression of NAFLD to hepatic fibrosis. There was no difference in the frequency of significant TR among patients with versus without NAFLD; therefore, the assessment of NAFLD with noncontrast CT does not appear to be influenced by the congestion caused by significant TR.

Previous studies have shown the independent association between NAFLD and both cardiovascular death and cardiovascular events in the general population.[4] In contrast, the present study demonstrated that NAFLD, assessed by noncontrast CT and by NAFLD fibrosis score, was not associated with increased risk of all-cause death and hospitalization for heart failure in patients with severe AS who were treated with TAVI. This observation is in agreement with other studies that included patients with severe AS who were treated with TAVI and who had advanced stages of NAFLD and liver disease.[24,25] Tirado-Conte et al[25] showed that among patients with severe AS who were treated with TAVI, patients with Child-Pugh class B to C liver disease had impaired survival, whereas patients with an earlier stage of liver disease (Child-Pugh class A) had survival rates similar to those of patients without liver disease. When patients with symptomatic severe AS are considered for TAVI or surgical valve replacement, their risk is systematically discussed within the Heart Team to decide on the optimal therapy. The discussion includes operative risk scores, co-morbidities, and frailty. Liver disease is also discussed as one of the associated co-morbidities that may further increase the operative risk and may negatively impact patient outcomes. However, the present study showed that NAFLD is not associated with increased risk of mortality.

Several limitations of the present study should be acknowledged. First, the study is a single-center, retrospective, observational study with inherent limitations. Noncontrast CT scans were not available in all patients because of changes in the pre-TAVI protocol over the years; therefore, we cannot report on the true prevalence of NAFLD in patients who underwent TAVI. Also, histologic confirmation of hepatic steatosis and fibrosis was not possible, and information on alcohol consumption or hepatitis C infection was not systematically collected. However, considering the low prevalence of alcoholic fatty liver disease relative to NAFLD in the general population and the low prevalence of hepatitis C, the presence of these 2 entities as causes of NAFLD in the present study population is probably minimal. Finally, data for the identification of cardiovascular- or liver-related mortality were not available.

In conclusion, clinical outcomes were not different between patients with and without NAFLD (as assessed with noncontrast CT) with severe AS who underwent TAVI. Moreover, no significant differences were shown in right atrial pressures and in the prevalence of significant TR between patients with and without NAFLD.

Disclosures

The authors have no conflicts of interest to declare.

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