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BRIEF REPORT

Association of Low Alanine Aminotransferase Levels and Outcomes in Patients Undergoing Tricuspid Valve Edge-to-Edge Repair

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Patients undergoing tricuspid valve transcatheter edge-to-edge repair (T-TEER) for relevant tricuspid regurgitation (TR) represent a heterogeneous cohort. Frailty and sarcopenia are commonly observed among TR patients and might influence outcomes.[1] Low alanine aminotransferase (ALT) levels have bene proposed as an easily available surrogate marker of frailty and sarcopenia and reduced physiological reserve. In patients undergoing transcatheter aortic valve replacement, ALT levels <12 U/L have been independently associated with adverse outcomes.[2] The aim of the present study was to assess the prognostic value of low ALT levels as a surrogate parameter of frailty and sarcopenia in patients undergoing T-TEER for significant TR in a real-world setting.

The study included patients from the EuroTR (European Registry of Transcatheter Repair for Tricuspid Regurgitation) registry (NCT06307262) who underwent T-TEER at 30 European centers between 2016 and 2024 . Patients with ALT levels >40 U/L were excluded to reduce the likelihood of including patients with predominant hepatocellular injury (n = 160). The study cohort was divided into patients with low (<12 U/L) and normal (≥12 U/L) ALT levels.[2-4] Study endpoints were 2-year survival free from heart failure hospitalization (HFH) and symptomatic alleviation at 1-year follow-up as expressed by NYHA functional class. A multivariable Cox regression model was used to adjust for potential confounders. Cardiohepatic syndrome (CHS) was defined by elevations of 2 of 3 laboratory parameters of hepatic cholestasis, as previously described. The study conformed with the principles outlined in the Declaration of Helsinki and received appropriate ethical oversight.

A total of 2,434 patients at a mean age of 78.8 ± 7.5 years (53.8% women) were included. TR was graded

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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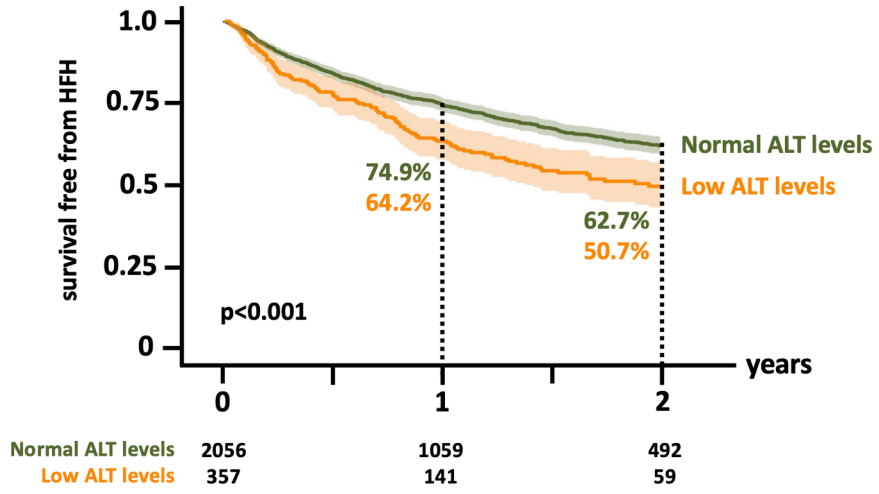
FIGURE 1 **Low ALT Level as a Surrogate Parameter of Frailty and Sarcopenia Is Associated With Reduced Heart Failure–Free Survival After Tricuspid Valve Transcatheter Edge-to-Edge Repair**



One- and 2-year survival rates free from heart failure hospitalization (HFH) were significantly lower in patients with low alanine aminotransferase (ALT) levels.

as severe in 45.9%, massive in 32.1%, and torrential in 20.1% of patients. The mean ALT level was 19.1 ± 7.5 U/L, with 359 patients (14.7%) presenting with ALT levels <12 U/L. Beyond that, 6-minute walking distance was significantly shorter in patients with low ALT levels (198 ± 115 m vs 251 ± 111 m; $P < 0.001$).

Patients with low ALT levels presented with more advanced heart failure symptoms (NYHA functional class IV in 20.0% vs 10.7%; $P < 0.001$), lower hemoglobin (11.0 ± 1.9 g/dL vs 12.1 ± 1.9 g/dL; $P < 0.001$) and albumin (.8 ± 0.6 g/dL vs 4.0 ± 0.6 g/dL; $P < 0.011$) levels, more severe TR (torrential in 25.7% vs 19.2%; $P < 0.001$), pronounced right ventricular remodeling (midventricular RV diameter 50 ± 9 mm vs 40 ± 9 mm; $P = 0.018$), and worse renal function (estimated glomerular filtration rate 42 ± 20 mL/min vs 48 ± 21 mL/min; $P < 0.001$).

One- and 2-year survival rates free from HFH were significantly lower in patients with low ALT levels (1 year, 64.2% vs 74.9%; 2 years, 50.7% vs 62.7%; $P < 0.001$ for both). After multivariable adjustment for sex, tricuspid annular plane systolic excursion, NYHA functional class, TR severity, midventricular RV diameter, estimated glomerular filtration rate, and left ventricular ejection fraction, low ALT level remained an independent predictor of 2-year survival free from HFH (adjusted HR: 1.31; 95% CI: 1.02-1.68; $P = 0.034$) (Figure 1).

Heart failure symptoms as defined by NYHA functional class were more severe in patients with low ALT levels at both baseline (NYHA functional class IV in 20.0% vs 10.7%; $P < 0.001$) and follow-up (NYHA functional class ≤ II in 51.5% vs 61.1%; $P < 0.001$). The degree of NYHA functional class improvement was comparable in patients with low vs high ALT levels (≥1-class NYHA functional class improvement in 54.2% vs 57.3%; $P = 0.930$).

Low aspartate aminotransferase (AST) levels were uncommon (0.7% of patients) and were not associated with outcomes. In the cohort with ALT levels <40 U/L, CHS was highly prevalent (81.7%) and was associated with worse 2-year survival free from HFH (CHS vs no CHS, 60.9% vs 77.9%; $P < 0.001$).

The present study showed that low ALT levels as a surrogate parameter for frailty and sarcopenia: 1) are observed in 14.7% of patients undergoing T-TEER; 2) are independently associated with worse 2-year survival rates free from HFH; but 3) are associated with comparable symptomatic alleviation.

The present findings are in line with those of previous studies that identified low ALT level as an outcome predictor in transcatheter aortic valve replacement, acute coronary syndrome, and other disease entities.[1,2] Therefore, ALT could serve as a broadly available and potential easy marker of frailty and sarcopenia and might be of additional value for patient selection and treatment decision within the

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heart team. This interpretation is supported by consistent baseline differences such as lower hemoglobin, albumin, and worse 6-minute walking test performances in patients with low ALT levels.

In contrast, low AST levels were significantly less frequent in our cohort, presumably because of their lack of liver specificity compared with ALT. As a consequence, low AST levels did not predict outcomes in this large real-world registry. Even within a preselected study cohort of patients with normal ALT levels, CHS was very common among T-TEER patients and showed association with worse 2-year outcomes. This mirrors the fact that irrespective of nutritional status and ALT levels, CHS due to congestion in the setting of right heart failure is an important outcome predictor for T-TEER patients.

Although subject to the typical limitations of a retrospective cohort study (no control group, no clinical event committee, no central laboratory), the present analysis is the largest evaluating the prognostic value of ALT levels in T-TEER patients. In summary, low ALT levels may reflect frailty and sarcopenia and provide incremental prognostic information in T-TEER patients and might serve as an additional tool for clinical decision-making.

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APPENDIX For PubMed-indexed investigator list (EuroTR investigators), please see the online version of this paper.