# Elevated Aspartate Aminotransferase to Alanine Aminotransferase Ratio Predicts Poor Outcome in Hepatocellular Carcinoma

## TO THE EDITOR:

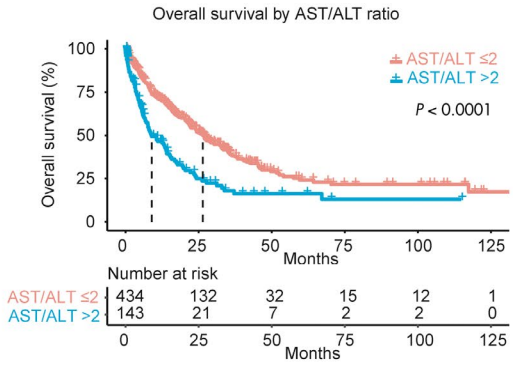
We have read the letter by Lee et al. with great interest. The authors reported a cohort of 376 patients with hepatic neoplasia encountered by the Liver Consult service at University of California, Los Angeles between 2003 and 2019, of whom 12% presented with serum aspartate (AST) to alanine aminotransferase (ALT) ratios >5. The authors suggested that hepatic neoplasia should be considered in the differential diagnosis of patients with elevated AST/ALT ratios, especially when ratios are >5.

We have queried our database, including 982 patients with hepatocellular carcinoma (HCC) who have been treated at the University Medical Center Hamburg-Eppendorf between 2008 and 2017. Among 581 patients with available AST and ALT levels at the time of first presentation with HCC, 3% (n = 15 patients) had AST/ALT ratios >5. This is in contrast to the reported 12% by Lee et al., likely because their

**Characteristics for overall cohort and stratified by AST/ALT ratio.**

| Characteristic | N | Overall, N = 581 | AST/ALT ≤2, N = 437 | AST/ALT >2, N = 144 | *P*-value |
|---|---|---|---|---|---|
| **Age** | 581 | 66 (58, 73) | 66 (58, 73) | 65 (58, 71) | 0.2 |
| **Sex** | 581 | | | | 0.026 |
| Male | | 474 (82%) | 366 (84%) | 108 (75%) | |
| Female | | 107 (18%) | 71 (16%) | 36 (25%) | |
| **AFP** | 296 | 29 (6, 631) | 19 (4, 216) | 193 (9, 13294) | <0.001 |
| **Etiology** | 577 | | | | 0.087 |
| Alcohol-related | | 193 (33%) | 133 (31%) | 60 (42%) | |
| Viral | | 181 (31%) | 142 (33%) | 39 (27%) | |
| NAFLD | | 28 (4.9%) | 24 (5.5%) | 4 (2.8%) | |
| Combination | | 50 (8.7%) | 36 (8.3%) | 14 (9.8%) | |
| Other | | 125 (22%) | 99 (23%) | 26 (18%) | |
| **AST (U/L)** | 581 | 59 (38, 107) | 55 (35, 83) | 104 (53, 188) | <0.001 |
| **ALT (U/L)** | 581 | 44 (29, 67) | 47 (32, 73) | 35 (20, 58) | <0.001 |
| **AST/ALT ratio** | 581 | 1.41 (1.00, 2.00) | 1.16 (0.89, 1.52) | 2.62 (2.27, 3.72) | <0.001 |
| **Platelets** | 572 | 154 (99, 230) | 152 (98, 222) | 160 (102, 280) | 0.13 |
| **CPT** | 426 | | | | <0.001 |
| A | | 218 (51%) | 181 (56%) | 37 (36%) | |
| B | | 102 (24%) | 77 (24%) | 25 (25%) | |
| C | | 49 (12%) | 17 (5.2%) | 32 (31%) | |
| No cirrhosis | | 57 (13%) | 49 (15%) | 8 (7.8%) | |
| **BCLC** | 423 | | | | <0.001 |
| A | | 139 (33%) | 119 (37%) | 20 (20%) | |
| B | | 171 (40%) | 139 (43%) | 32 (32%) | |
| C | | 74 (17%) | 46 (14%) | 28 (28%) | |
| D | | 39 (9.2%) | 19 (5.8%) | 20 (20%) | |
| **PS (ECOG)** | 426 | | | | <0.001 |
| 0 | | 142 (33%) | 124 (38%) | 18 (17%) | |
| 1 | | 196 (46%) | 148 (46%) | 48 (47%) | |
| 2 | | 61 (14%) | 35 (11%) | 26 (25%) | |
| 3 | | 22 (5.2%) | 13 (4.0%) | 9 (8.7%) | |
| 4 | | 5 (1.2%) | 3 (0.9%) | 2 (1.9%) | |

Statistics presented: median (IQR) for continuous variables, n (%) for categorical variables; p-value (AST/ALT ≤2 vs. AST/ALT >2): Wilcoxon rank-sum test; chi-square test of independence; Fisher's exact test. Abbreviations: AFP, alpha fetoprotein; ALT, serum alanine aminotransferase; AST, serum aspartate aminotransferase; BCLC, Barcelona Clinic for Liver Cancer classification; CPT, Child-Pugh-Turcotte score; ECOG, Eastern Cooperative Oncology Group; NAFLD, non-alcoholic fatty liver disease; PS, performance status.




**Multivariate Cox Regression Modeling for Death**

| Characteristic | HR[1] | 95% CI[2] | *P*-value |
|---|---|---|---|
| **AST/ALT ratio >2** | 2.37 | 1.46, 3.86 | <0.001 |
| **Age** | 1.02 | 1.00, 1.05 | 0.050 |
| **Sex** | 1.19 | 0.70, 2.00 | 0.5 |
| **ECOG** | | | |
| 0 (reference) | — | — | |
| 1 | 1.29 | 0.79, 2.12 | 0.3 |
| 2 | 1.45 | 0.75, 2.80 | 0.3 |
| 3 | 3.54 | 1.30, 9.62 | 0.013 |
| **AFP** | 1.00 | 1.00, 1.00 | <0.001 |
| **BCLC** | | | |
| A (reference) | — | — | |
| B | 1.95 | 1.16, 3.26 | 0.011 |
| C | 2.70 | 1.34, 5.43 | 0.006 |
| D | 13.8 | 5.48, 34.8 | <0.001 |
| **Etiology** | | | |
| Alcohol-related | — | — | |
| Viral | 0.93 | 0.44, 1.94 | 0.8 |
| NAFLD | 1.06 | 0.34, 3.32 | >0.9 |
| Combination | 1.17 | 0.64, 2.12 | 0.6 |
| Other | 1.15 | 0.66, 2.00 | 0.6 |
| **Child-Pugh-Turcotte** | | | |
| A (reference) | — | — | |
| B | 1.24 | 0.74, 2.09 | 0.4 |
| C | 0.63 | 0.28, 1.43 | 0.3 |

[1]HR = Hazard Ratio; [2]CI = Confidence Interval

**FIG. 1.** Characteristics of the cohort, Kaplan-Meier survival analysis stratified by AST/ALT ratio, and multivariate Cox regression modeling.

cohort was biased towards patients encountered by the Liver Consult service, e.g., for evaluation of unusual aminotransferases values, as indicated by the authors. In our cohort, 25% of patients had AST/ALT ratios <1, 50% between 1 and 2, and 25% >2. Interestingly and in addition to the reported data by Lee et al., patients with HCC with AST/ALT ratios >5 had a significantly shorter median survival compared to AST/ALT ratios ≤5 (8 vs. 22.1 months; $P < 0.0001$). When stratifying patients by AST/ALT ratios >2 (n = 144 patients, 25%) versus ≤2, an even stronger difference in median survival could be obtained (8.9 vs. 26.4 months, respectively; $P < 0.0001$). Patients with AST/ALT ratios >2 had more advanced tumor disease, worse Child-Pugh-Turcotte class and performance status, and were more frequently women compared to patients with AST/ALT ratios ≤2 (all $P < 0.05$). As expected, alcohol-related HCC trended to be more frequent and viral-related HCC to be less frequent in these patients ($P = 0.087$). Yet, in multivariate Cox regression modeling including these prognostic factors, AST/ALT ratio >2 remained an independent predictor of death with a hazard ratio of 2.37 ($P < 0.001$) (Fig. 1).

Besides the clinical usefulness of high AST/ALT ratios as a surrogate for hepatic neoplasia as indicated by Lee et al., our data underscore the independent prognostic value of elevated AST/ALT ratios in patients with HCC. This seems particularly useful for Consult Services and/or at the time of diagnosis for clinical decision making, especially when considering the broad availability of these simple tests. To our knowledge, the prognostic value of AST/ALT ratios has only been reported in a Taiwanese cohort of patients with hepatitis B virus[1] but never in cohorts with mixed etiologies commonly found in the United States and Europe.

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## REFERENCE

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*Potential conflict of interest: Dr. Schulze advises Bayer and Ipsen. The other authors have nothing to report.*