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THE INCIDENCE, CLINICAL ASSOCIATIONS AND IN-HOSPITAL MORTALITY OF LOW SERUM ALANINE AMINOTRANSFERASE IN HOSPITALIZED OLDER ADULTS

Medicine

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ABSTRACT

Background: Clinicians are mostly interested in increased activity of aminotransferases. Reduced levels are often overlooked, yet research suggests their consequence. The prevalence and significance of reduced aminotransferases levels was not reported for hospitalized patients and deserves further study.**Setting:** Older adult patients (median 80 years) hospitalized in an academic department of medicine.**Methods:** A retrospective case-control study comparing 200 randomly-selected patients with ≥2 consecutive low alanine aminotransferase (ALT) levels (<18 U/L) to 300 age- and sex-matched controls whose ALT was not reduced.**Results:** Low ALT was prevalent (14.8% of admissions ≥65 years), ~half had ALT <10 U/L. Admission diagnosis, prior morbidity and laboratory tests were not significantly different between patients and controls. Patients' low ALT (median 10 vs. 39 U/L among controls) was significantly associated with strikingly low aspartate aminotransferase (AST, median 17 vs. 39 U/L) (P=0.000), lower lactate dehydrogenase (LDH, median 282 vs. 377 U/L, P=0.001) and markedly decreased gamma-glutamyltransferase (GGT, 27.0 vs. 72.5 U/L, P=0.000), though alkaline phosphatase levels were similar. Low ALT was associated with older age (P=0.0001), more frailty, and greater risk of in-hospital mortality vs. controls (P=0.01).**Conclusion:** Deficient activities of ALT, AST, LDH, and GGT are common in hospitalized older adults and associated with increased in-hospital mortality.

KEYWORDS

Older Adults; Hospitalized Patients; Case-control; Alt (Alanine Aminotransferase); Ast (aspartate Aminotransferase); LDH (lactate Dehydrogenase); Ggt (Gamma-glutamyltransferase); Mortality

Clinicians usually look at liver chemistry test results to identify increased levels which indicate liver cell injury and disease. Serum aminotransferases (previously called transaminases) include alanine aminotransferase (ALT) present predominantly in the liver, and aspartate aminotransferase (AST) which is less specific and may be increased also in extra-hepatic disease such as skeletal muscle or myocardial injury (1). However, low levels of liver enzymes may be of clinical significance as well. Establishing the upper limit of normal (ULN) for ALT/AST has been difficult since "normal" varies with gender, age, body mass index (BMI), the population studied, and even between different laboratories (1). However, several large studies of healthy populations (e.g. blood donors) have determined the ULN for ALT as 29-30 U/L for men and 19-22 U/L, for women, respectively (2-4). Still, the American College of Gastroenterology guideline on abnormal liver tests omits to even mention the clinical significance of low ALT/AST values (1). Previous studies have noted that low serum ALT levels may be associated with several conditions, most recently, increased vulnerability to covid-19 infection (5). Since exceedingly low ALT levels remain an intriguing finding, we have undertaken a retrospective study of its prevalence, associations, and prognostic impact among older adults hospitalized in a department of medicine of an academic general hospital.

Patients and methods

A retrospective case-control study identified a random, computer-selected sample of 200 hospitalized patients ≥65 years of age whose serum ALT levels were <18 U/L on at least two consecutive occasions during the same hospital admission. There is no accurate definition in the literature of low ALT levels, however, this cut-off was chosen to be below the threshold reported in the literature for both men and women (2-4). It was also used in the few studies referenced below, targeting low liver enzyme levels. Patients <65 years and any patient with a history of liver disease have been excluded. The low ALT patients were compared on a 2:3 basis to a random group of age- and sex-matched patients hospitalized over the same time, who had no known liver diseases and whose ALT levels were not reduced. Sample handling was identical for patients and controls. The comparison included demographic, clinical, and laboratory variables, as well as in-hospital mortality. BMI was not done, but Clinical Frailty Scale (CFS) was extracted from the hospital case notes in an arbitrary subset of patients and controls (6). The prevalence of low ALT was also determined, defined as the percentage of low ALT patients among all hospitalized elderly patients over the same time period. This was compared between different age groups. The statistical differences between nominal variables were computed by Chi-Square tests, and parametric variables by T-test. P<0.05 was considered statistically significant. All analyses were done with SPSS-29 (IBM, Armonk, NY, USA). The study was approved by our Institutional Review Board (IRB).

RESULTS

Altogether, 1837 patients ≥65 years of age were admitted during the seven months of the study, and 272 (14.8%) had low serum ALT levels <18 U/L in ≥2 consecutive tests (median 4). In 127/272 (47%) ALT levels were <10 U/L (6.9% of the 1837). Their median age was 80.0 years (mean 75.8±15.6 years), and 56% were women. When admitted patients <65 years were compared with older patients, fewer younger patients had low ALT (54/545 vs. 308/1837, chi square = 14.74, P=0.0001). The baseline characteristics of the patient group (N=200) and control group (N=300) are given in Table 1. Control patients were matched for age and sex. Frailty, based on the Clinical Frailty Scale (CFS) estimation was more severe for the patient group vs. controls. However, ethnicity (not shown), cause of admission, and the distribution of underlying conditions were not significantly different between patients and controls. Laboratory data analysis is presented in Table 2. Mild leukocytosis (neutrophilia) and normal lymphocyte and platelet counts were similar in both groups. Acute-phase reactants C-reactive proteins (CRP) were increased among patients and controls alike (mean 94 mg/dL; N<5). Serum albumin levels were similar (median 3.0 gr/dL), and although hemoglobin was lower among patients, the difference was small and not clinically significant (median 11 vs. 12 g/L). Both groups had increased blood urea nitrogen (BUN) (27 vs. 24 mg/dL, NS) and creatinine (mean 1.68 vs. 1.31, P=0.003).

Patients' low ALT levels (median 10 vs. 39 U/L among controls) were significantly associated with other hepatocellular enzymes. Concurrent low AST levels were particularly significant (median 17 vs. 39 U/L, P=0.000), as was low lactate dehydrogenase (LDH) (median 282 vs. 377 U/L, P=0.001). While alkaline phosphatase (ALP) levels were similar for patients and controls, the other 'cholestatic' enzyme gamma-glutamyltransferase (GGT) was markedly decreased in patients with low ALT (27.0 vs. 72.5 U/L, P=0.000). In a random sample of 10% of either group, 80% of the patients were ranked as CFS ≥6 (moderate to severe frailty) vs. 16.7% of controls (P<0.05). In-hospital mortality of the 'low ALT' patients was significantly increased when compared to matched controls treated in the same department (79/200 vs. 87/300, chi-square = 5.84, P=0.01).

DISCUSSION

Among hospitalized patients ≥65 years of age, ~1:7 patients had low serum ALT levels <18 U/L which were extremely low: <10 U/L in as many as half of the cases (7% of admissions ≥65 years). Thus, low ALT are more common in older adults than reported and was not found to be related to any specific prior morbidity or cause of admission (Table 1). Age was an important risk factor, and older patients were significantly

more likely to exhibit low ALT (P=0.0001). Low ALT was associated with an adverse short-term prognosis since ~40% of low ALT patients died in-hospital (P=0.01 vs. matched controls). Concurrent with ALT, other hepatocellular enzymes were also found to be significantly decreased, including serum AST (median 17 vs. 39 U/L; P=0.000), and LDH (median 282 vs. 377 U/L; P=0.001). ALP levels were similar to the control group, as were most other variables (Table 2), however, in contrast, serum GGT, was also extremely depressed (27.0 in patients vs. 72.5 U/L among controls, P=0.000).

Previous research on low ALT in large populations is relatively scarce. Nevertheless, when 455 70-year-old individuals were prospectively followed for 12 years, ~15% had ALT<10 U/L which was an independent risk factor for mortality in men only (HR 1.5, 95% CI 1.08-2.19) (7). Higher ALT activity was significantly associated with obesity, diabetes, and hyperlipidemia, whereas low ALT was related to lower BMI and hypothesized to be a surrogate marker of enhanced hepatic aging, greater production of free radicals, and noxious oxidative stress (7). Among 1,673 community-dwelling men aged ≥70 and followed ~5 years, low ALT was associated with increasing age, reduced survival (HR 2.1, 95% CI 1.53-2.87), and frailty (HR 9.35) (8). The third National Health and Nutrition Examination Survey (NHANES) reported similar results, and lowest ALT patients also had low AST (15.7-17.6±SD) and low GGT levels (17.5-20.2±SD) (9). This large survey (14,950 participants followed 14.5 years) found increased mortality among people over age 40 years in the lowest deciles of ALT, who also had a decreased lean body mass (9). A more recent study, found low ALT activity <14 in 26.6% of 765 participants (mean 75.3 years), associated with lower BMI, sarcopenia (20.5% vs.1% in the highest quintile), frailty, disability, and 57% long-term mortality (P<0.001) (10). In another study of community-dwelling older adults, either low ALT or low AST were associated with significantly increased overall mortality (aHR 1.76, 95% CI 1.31-2.36, especially when both were decreased aHR 2.39) (11).

Limitations of our study include single center, retrospective design, and the absence of data on BMI, nutritional status, and sarcopenia. Albumin, lymphocytes, and creatinine were similar in both groups, but cannot be considered surrogate markers of nutritional state since they are affected by varied other factors (12). Medications were not compared, however, drugs do not decrease ALT levels. Thus, the significant association of low ALT and increased short-term mortality is a new observation. It could be mediated by the increased frailty of the low ALT group, since frailty in older adults clearly increases mortality risk (13).Long-term population-based studies have already established the clinical significance of low levels of ALT as an independent biomarker of malnutrition, sarcopenia, frailty, functional decline, and all-cause mortality (7-11). In a 5-year study of 2484 elderly individuals, 55% had ALT<20 and 3% had ALT<10, significantly associated with loss of independence and death (14). A smaller study identified an association of low ALT with sarcopenia, disability, and pyridoxine deficiency, noting that subjects in the lowest quintiles of ALT levels showed a sharply increased overall and cardiovascular mortality (10). Low ALT was also associated with increased mortality in specific groups of patients, such as those with nonalcoholic fatty liver disease, coronary artery disease, or atrial fibrillation (15-17).

The mechanisms underlying the association remain incompletely understood, and do not necessarily imply causality. For example, a minority of ALT is derived from skeletal muscle and low ALT could reflect sarcopenia, which has been associated with increased mortality (9). Low ALT had been speculated to represent hepatic aging (7), already demonstrated to involve higher oxidative stress and hepatocyte apoptosis (18, 19). In addition, low ALT levels may imply impaired amino acid metabolism (conversion of L-alanine/α-ketoglutatate to pyruvate and glutamic acid in vital organs), and/or indicate vitamin B6 (pyridoxine) deficiency (15).

CONCLUSION

Rather than being dismissed as a benign finding, clinicians, and gerontologists in particular, need to pay attention to low levels of hepatic enzymes. No previous study to our knowledge examined low activities of liver enzymes in hospitalized older adults. Our findings confirm that hepatic enzyme levels are also significant when their activity is decreased. This was a prevalent condition in this population, and associated with advancing age, frailty, and increased risk of in-hospital mortality. Further research is needed to establish whether early detection and interventions to promote weight gain, correct nutritional deficiencies, and enhance muscle mass may improve health outcomes. Meanwhile, practitioners caring for older adults in any setting should keep an open eye for low aminotransferase levels and be cognizant of these patients' increased risk.

Legend to the Tables:

Table 1. Demographic and clinical characteristics of older adult patients (n=200) and their age-matched and sex-matched controls (n=300).

Variable	**Patients** N=200	**Controls** N=300	**Total** N=500	**Significance**
Age, Years ± SD Median	75.8±15.6 80.0	75.5±15.8 79.0	75.65±15.7 80.0	NS
Gender, Male (%)	88 (44)	150 (50)	238 (47.6)	NS P=0.18
Admission Diagnosis				NS P=0.46
Ac. Infection	112 (56)	160 (53)	272 (54)	
Cancer	16 (8)	18 (41)	34 (7)	
Other	72 (36)	122 (6)	194 (39)	
Major Underlying Condition				NS
CHF	40 (20)	33 (23.7)	73 (21.5)	P=0.41
COPD	32 (16)	15 (10.8)	47 (13.9)	P=0.17
CKD	86 (43)	66 (47.5)	152 (44.8)	P=0.41
Diabetes	76 (38)	62 (44.6)	138 (40.7)	P=0.22
Frailty				
CFS≥6	80%	16.7%	N/A	**P<0.05**

Table 2. Laboratory values (mean±SD, and median) of hospitalized older adult patients with serum ALT<18 U/L (n=200) and their age- and sex-matched controls (n=300).

Variable [Mean ± SD Median]	**Patients N=200**	**Controls N=300**	**All N=500**	**Statistical Significance**
Hemoglobin gr/dL	10.7±2.1 11.0	11.6±2.0 12.0	11.24±2.1 11.0	P=0.000
White Blood Cells x109/L	11.1±10.4 9.0	11.9±13.2 10.0	11.6±12.2 10.0	P=0.48
Neutrophils x109/L	8.6±5.8 7.0	8.9±5.8 8.0	8.8±5.8 7.0	P=0.49
Lymphocytes x109/L	1.85±7.1 1.0	1.97±8.9 1.0	1.92±8.2 1.0	P=0.87
Platelets x109/L	249±130 223.5	246±126 229	247±127 225	P=0.81
Blood Urea Nitrogen mg/dL	36.6±30.1 27.0	33.5±26.6 24.0	34.7±28.1 25.5	P=0.23
Creatinine mg/dL	1.68±1.6 1.1	1.31±1.1 1.0	1.45±1.3 1.0	P=0.003
Albumin gr/dL	3.3±0.7 3.0	3.4±0.7 3.0	3.36±0.7 3.0	P=0.097
Globulin gr/dL	3.05±0.8 3.0	2.98±0.7 3.0	3.01±0.8 3.0	P=0.37
C-reactive Protein mg/L	93.18±91.7 63.0	94.85±106.1 50.0	94.19±100 .5 55.0	P=0.85
Serum Enzymes*:				
ALT U/L	10.16±3.9 10.0	111.94±284. 3 39.0	71.23±225 .7 24.0	P=0.000
AST U/L	19.16±9.9 17.0	112.26±336. 6 39.0	75.02±264 .6 27.0	P=0.000
LDH U/L	349.5±283. 9 282.0	462.6±393.4 377.0	417.4±357 .7 333.5	P=0.001
ALP U/L	127.5±186. 9 83.0	131.3±137.3 101.5	129.8±158 .8 92.0	P=0.78
GGT U/L	61.9±95.5 27.0	128.5±182.7 72.5	101.9±157 .2 48.0	P=0.000

Table 2. * Normal values: ALT<41, AST<40, LDH<225, ALP<130, GGT<61 U/L.

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