

Elevation of Alanine Amino-Transferase Blood Activity Within Normal Values, is Associated with Negative Clinical Outcomes in Anorexia Nervosa Patients. A Retrospective Analysis of 907 Patients

Qamar Daher

Sheba Medical Center

Adva Weissman

Sheba Medical Center

Gad Segal

`segal@sheba.health.gov.il`

Sheba Medical Center

Ziv Sussman

Sheba Medical Center

Rona Rabinovich

Begin High

Guy Dumanis

Sheba Medical Center

Yehonatan Shefer

Sheba Medical Center

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Abstract

Background. Alanine aminotransferase blood activity is a biomarker for sarcopenia and frailty when lower than anticipated. Anorexia Nervosa patients are prone to both pathologies. variations of ALT activity within the normal range and their prognostic implications are uncertain.

Methods. This was a retrospective analysis of AN patients hospitalized in a psychiatric department within a general hospital.

Results. A cohort of 907 AN patients was divided into two groups according to their ALT blood level: High-Normal (HN) ($17 \leq \text{ALT} < 40$ IU/L; N = 335) and Low-Normal (LN) ($\text{ALT} < 17$ IU/L; N = 572). Amongst HN ALT group of patients, there was also a higher blood albumin (median 4.6 IQR [4.2-4.9] vs. 4.5 [4.2 – 4.7]; $p = 0.005$). CPK levels were also higher in the HN group (median 68 [IQR 47.5-103] vs. 57 [43 – 82.75]; $p < 0.001$). HN ALT patients had longer in-hospital stay (median 65 days, IQR [26.5 – 86] vs. 56 [16.5 – 84]; $p = 0.007$) and higher rate of mortality (5.7% vs. 2.1%; $p = 0.008$). In a multivariate analysis, HN ALT values remained an independent risk factor for mortality (HR = 2.69, 95% CI 1.02 – 7.36; $p = 0.047$). Increased rate of hospital readmissions was independently associated with increased risk of mortality (HR = 6.75, 95% CI 2.8 – 17.7; $p < 0.001$).

Conclusions. Within the normal range, higher ALT blood levels are associated with increased risk of mortality and longer in-hospital length of stay in Anorexia Nervosa patients.

Background

Low Alanine aminotransferase blood activity and its potential association with Sarcopenia and frailty in Anorexia Nervosa patients.

Patients suffering from Anorexia Nervosa (AN) experience a myriad of metabolic derangements such as severe osteoporosis (1–3) and sarcopenia, as potentially demonstrated by both dual X-ray absorptiometry (DXA) and Three-dimensional optical imaging (3DO) (4). Garrido et al. showed that AN affects both muscular mass but also muscular function when they demonstrated lowered Peak Expiratory Flow (PEF) values amongst AN patients (5).

Low Alanine aminotransferase (ALT) blood activity serves as a biomarker for sarcopenia and frailty, as demonstrated by its association with low muscle mass and handgrip strength (6–8). ALT was found to be a practical tool for assessing frailty in hospitalized patients (7–9). Low ALT was shown to be an independent indicator of poor prognosis in multiple medical conditions (10–13) such as myelodysplastic syndrome, renal and bladder cancers. Further studies proved low ALT to be an indicator of poor rehabilitation outcomes in patients with hip fractures and in those in need of cardiac rehabilitation (14, 15).

Higher values of Alanine aminotransferase blood activity and their potential association with liver tissue damage in Anorexia Nervosa patients.

Disrupted Liver Function Tests (LFTs) are a common phenomenon in severely malnourished patients, reaching up to 43% in a retrospective study published by Hanachi et al. (16). Often addressed as anorexia nervosa–related hepatitis, it can be roughly divided as arising from two different pathophysiologies: starvation and refeeding hepatitis (17).

In starvation hepatitis, the suggested mechanism involves a process called autophagy, which translates to ‘eating of self,’ where cytosolic proteins are degraded inside lysosomes to supply energy for the cell. While thought to be initially beneficial, after prolonged starvation, such as that seen in anorexia nervosa, autophagy results in increased hepatocyte membrane permeability and increased levels of transaminase enzymes in the peripheral blood (18, 19).

In the case of refeeding hepatitis, sometimes referred to as ‘refeeding steatosis,’ rapid introduction of calories in anorexic patients can lead to paradoxical fat deposition in the liver. As a result, these patients may exhibit elevated levels of transaminase enzymes, either AST or ALT, requiring close monitoring and a more gradual refeeding process (20).

In both cases, either low-normal ALT blood activity and high-normal ALT blood activity could serve as biomarkers for pathologies in AN patients: anorexia-associated sarcopenia and starvation / refeeding hepatitis.

Aim of the current study.

In a retrospective analysis, we aimed at assessing the potential prognostic value of ALT measurements in AN patients. We sought to find which of the two phenomenon, either low-normal or high-normal ALT levels would prevail.

Methods

Patients’ data.

This study utilized data retrieved from the electronic medical records (EMRs) of the Chaim Sheba Medical Centre, the largest tertiary care medical centre in Israel. Following approval by our Institutional Review Board (IRB), in accord with the Helsinki declaration (approval # 1741-24-D), and waiver of informed consent due to the retrospective nature of this study, we collected relevant clinical data of all females AN patients admitted to the psychiatric ward between the years 2013 and 2023.

Clinical, demographic, and laboratory information was extracted directly from the EMR database using standardized queries. Each record was subsequently reviewed for data completeness. Exclusion criteria (male AN patients and patients with ALT activity blood levels above the upper normal limit (40IU/L) were applied prior to analysis to ensure data validity and minimize bias related to hepatic disease.

Variables.

Patients were divided into two groups according to their first alanine aminotransferase (ALT) measurement during hospitalization in the psychiatric ward: those with ALT values ≥ 17 IU/L and those with ALT values < 17 IU/L. Patients with ALT levels exceeding 40 IU/L were excluded to minimize bias associated with underlying hepatic disease or other liver-related conditions. The analysis was restricted to female patients, reflecting the higher prevalence of eating disorders in this population.

Variables included demographic factors (age, body mass index [BMI], smoking status), and psychiatric comorbidities including bulimia, depression, bipolar disorder, anxiety, trauma-related disorders, substance abuse, personality disorders, psychotic disorders, obsessive-compulsive disorder (OCD), suicidal ideation, and past suicide attempts. Chronic psychiatric medications use was also recorded, including sedatives, antidepressants, antipsychotics, hormonal therapy, and thyroid medications. Relevant laboratory results during hospitalization were included: albumin, creatine phosphokinase (CPK), creatinine, urea, potassium, and hemoglobin.

The primary outcome was all-cause mortality. Secondary outcomes included length of hospital stay (LOS) and events of readmission to the psychiatric ward.

Statistical Analysis

Continuous variables were presented as mean $\pm$ standard deviation (SD) or median with interquartile range (IQR), depending on data distribution assessed by the Shapiro-Wilk test. Categorical variables were presented as absolute numbers and percentages. Kaplan-Meier function was used for crude mortality assessment.

Between-group comparisons were conducted using the t-test or Mann-Whitney U test for continuous variables, and the χ^2 or Fisher's exact test for categorical variables, as appropriate.

Associations between ALT category and the study outcomes were examined using logistic regression models. Separate models were built for each outcome, including all-cause mortality and LOS. For each outcome, both univariate and multivariable logistic regression models were constructed. Variables demonstrating significant associations ($p < 0.05$) in univariate analyses or deemed clinically relevant were included in the multivariable models. Results of these models include the odds ratio (OR) and confidence interval (CI) of 95%. A two-sided p value < 0.05 was considered statistically significant. All analyses were performed using R software version 4.4.2 (R Foundation for Statistical Computing).

Results

After approval of an Institutional Review Board as mentioned above, relevant patients' electronic medical records were addressed according to our inclusion criteria. Patients' flow in the study algorithm is presented as a CONSORT flow diagram in Fig. 01.

Out of an initial cohort of 1,083 AN patients we excluded 60 males (in order to remain with a gender – homogenous cohort) and another 116 patients were excluded due to insufficient data and those with apparent hepatitis (ALT levels over the upper normal limit in our institution, 40 IU/L). The remaining 907 eligible patients were divided according to their first ALT levels' measurement during hospital stay: 572 patients had ALT < 17 IU/L (low-normal group) while 335 patients had their ALT values above 17 IU/L and still within the normal limit (< 40 IU/L), (high-normal group). The rate of survival within these two patients' groups was different in a statistically significant manner (as presented in both Fig. 01 and Table 01): the rate of death during a 12-years follow-up period from the first patient's admission was higher in the high-normal ALT group (5.7% vs. 2.1%, $p = 0.008$).

Patients' characteristics in both study groups are presented in Table 01. The median ALT blood level in the low-normal ALT group was 12 [IQR 10–14] while in the high normal ALT group it was 21 [19–26]; $p < 0.001$. There was no significant difference between both study groups in age (the whole cohort median age was 22.4 years [IQR 19.6–28.6]). The median BMI, Body Mass Index, in the low-normal ALT group was 16.3 [IQR 14.9–17.5] compared with 15.9 [IQR 14–17.4] in the high-normal ALT group; $p = 0.004$. The smoking rate in the low-normal ALT group was 43.6% while in the high-normal ALT group it was 33.6%; $p = 0.008$.

The prevalence of psychiatric comorbidities was comparable between the two groups, with no significant differences observed in the rates of bulimia disorder, depression disorder, bipolar disorder, anxiety disorder, trauma stress disorder, substance use disorder, personality disorder, psychotic disorder, obsessive-compulsive disorder (OCD), or suicidal ideation. Likewise, the frequency of suicide attempts prior and during hospital stay did not differ significantly between the two groups.

Regarding psychiatric medications, the use of sedatives in the low-normal ALT group was 18.9% while in the high-normal ALT group it was 13.4%; $p = 0.043$. Antipsychotics use in the low-normal ALT group was 19.1% compared with 26.3% in the high-normal ALT group; $p = 0.014$. No significant differences were observed between the groups in the use of antidepressants, hormone therapy, or thyroid medications.

Regarding laboratory parameters, the median albumin level in the low-normal ALT group was 4.5 [IQR 4.2–4.7], compared with 4.6 [IQR 4.2–4.9] in the high-normal ALT group; $p = 0.005$. The median CPK levels were 57 [IQR 43–82.7] in the low-normal group while in the high-normal ALT group it was 68 [IQR 47.5–103]; $p < 0.001$. The median urea level in the low-normal group was 24 [IQR 18–30] compared to 26 [IQR 19.2–33] in the high normal ALT group; $p = 0.002$. Creatinine, potassium and hemoglobin levels did not differ significantly between the two groups.

Regarding clinical endpoints, the median length of stay (LOS) in the low-normal ALT group was 56 days [IQR 16.5–84], compared with 65 days [IQR 26.5–86] in the high-normal ALT group; $p = 0.007$. The mortality rate in the low-normal ALT group was 2.1% compared with 5.7% in the high-normal ALT group; $p = 0.008$. The readmission rate did not differ significantly between the two study groups.

Figure 2 present the Kaplan-Meier crude mortality curve for accumulated death events in our study cohort. The death rate in the high-normal ALT group was higher in a statistically significant manner ($p = 0.011$).

Table 01
Cohort patients' characteristics according to ALT levels

Patients' characteristics	Overall [n = 907]	ALT < 17 [n = 572]	17 ≤ ALT < 40 IU/L [n = 335]	P- value
ALT; IU/L, median [IQR]	14 [11, 20]	12 [10, 14]	21 [19, 26]	< 0.001
Patients' demographics				
Age; years, median [IQR]	22.4 [19.6, 28.6]	22 [19.5, 28.3]	23 [19.6, 29]	0.118
BMI, median [IQR]	16.2 [14.7, 17.5]	16.3 [14.9, 17.5]	15.9 [14.0, 17.4]	0.004
Smoker; N (%)	309 (39.9)	213 (43.6)	96 (33.6)	0.008
Psychiatric comorbidities				
Bulimia disorder; N (%)	41 (4.5)	27 (4.7)	14 (4.2)	0.83
Depression disorder; N (%)	98 (10.8)	71 (12.4)	27 (8.1)	0.054
Bipolar disorder; N (%)	4 (0.4)	2 (0.3)	2 (0.6)	0.63
Anxiety disorder; N (%)	36 (4)	27 (4.7)	9 (2.7)	0.18
Trauma stress disorder; N (%)	20 (2.2)	17 (3)	3 (0.9)	0.07
Substance use disorder; N (%)	26 (2.9)	15 (2.6)	11 (3.3)	0.71
Personality disorder; N (%)	71 (7.8)	52 (9.1)	19 (5.7)	0.08
Psychotic disorder; N (%)	6 (0.7)	6 (1)	0 (0)	0.09
OCD; N (%)	40 (4.4)	24 (4.2)	16 (4.8)	0.81
Suicidal ideation; N (%)	17 (1.9)	11 (1.9)	6 (1.8)	1
Suicidal attempt; N (%)	84 (9.3)	48 (8.5)	36 (10.8)	0.3
Psychiatric medications				
Sedatives; N (%)	153 (16.9)	108 (18.9)	45 (13.4)	0.043
Antidepressants; N (%)	316 (34.8)	200 (35)	116 (34.6)	0.975
Antipsychotics; N (%)	197 (21.7)	109 (19.1)	88 (26.3)	0.014
Hormone therapy; N (%)	32 (3.5)	22 (3.8)	10 (3)	0.62
Thyroid med; N (%)	22 (2.4)	12 (2.1)	10 (3)	0.54
Laboratory parameters				

Patients' characteristics	Overall [n = 907]	ALT < 17 [n = 572]	17 ≤ ALT < 40 IU/L [n = 335]	P-value
Albumin, median [IQR]	4.5 [4.2, 4.8]	4.5 [4.2, 4.7]	4.6 [4.2, 4.9]	0.005
CPK, median [IQR]	60 [44, 91]	57 [43, 82.7]	68 [47.50, 103]	< 0.001
Creatinine, median [IQR]	0.7 [0.6, 0.8]	0.7 [0.6, 0.8]	0.7 [0.6, 0.9]	0.12
Urea, median [IQR]	25 [18, 31]	24 [18, 30]	26 [19.2, 33]	0.002
Potassium, meq/L, median [IQR]	4.1 [3.8, 4.4]	4.1 [3.8, 4.4]	4.1 [3.8, 4.4]	0.03
Hb, gr/dL, median [IQR]	13.0 [12.2, 13.7]	12.9 [12.2, 13.7]	13.1 [12.3, 13.8]	0.07
Clinical endpoints				
Re admissions; N (%)	83 (9.2)	56 (9.8)	27 (8.1)	0.45
LOS (days), median [IQR]	61 [21, 85]	56 [16.50, 84]	65 [26.50, 86]	0.007
Mortality; N (%)	31 (3.4)	12 (2.1)	19 (5.7)	0.008

Univariate and multivariate analysis for LOS

As presented in Table 2, In univariate analyses examining factors associated with prolonged length of stay (LOS) in the inpatient setting (Table 2), ALT values ≥ 17 IU/L (the high-normal group) were associated with increased odds of extended hospitalization (OR = 1.41; 95% CI 1.05–1.90; p = 0.024).

Table 02
Uni- and Multivariate analyses for length of hospital stay.

Variable	Univariate models		Multivariate model	
	OR [95% CI]	P value	OR [95% CI]	P value
High - Normal ALT group	1.41 [1.05, 1.9]	0.024	1.34 [0.85, 2.13]	0.207
Albumin (g/dL)	1.65 [1.25, 2.2]	< 0.001	0.86 [0.47, 1.57]	0.625
Antidepressants use	1.36 [1.01, 1.85]	0.045	1.3 [0.83, 2.06]	0.248
BMI	1.85 [1.69, 2.03]	< 0.001	1.94 [1.73, 2.2]	< 0.001
Calium (meq/L)	1.6 [1.24, 2.07]	< 0.001	1.79 [1.04, 3.1]	0.036
Recurrent ER visits	0.72 [0.53, 0.97]	0.028	0.6 [0.38, 0.93]	0.023
Personality disorder	0.58 [0.36, 0.96]	0.033	0.46 [0.22, 0.96]	0.037
Smoker	0.53 [0.39, 0.72]	< 0.001	0.49 [0.32, 0.75]	0.001
Urea (meq/L)	1.02 [1.01, 1.04]	0.007	1.02 [1, 1.04]	0.114

Additional variables associated with longer LOS included lower serum albumin (OR = 1.65; 95% CI 1.25–2.20; $p < 0.001$), higher BMI (OR = 1.85; 95% CI 1.69–2.03; $p < 0.001$), higher calcium levels (OR = 1.61; 95% CI 1.24–2.07; $p < 0.001$), and higher urea levels (OR = 1.02; 95% CI 1.01–1.04; $p = 0.007$).

Antidepressant treatment was also associated with prolonged hospitalization (OR = 1.36; 95% CI 1.01–1.85; $p = 0.045$). Conversely, fewer emergency department visits prior to admission (OR = 0.72; 95% CI 0.53–0.97; $p = 0.028$), a diagnosis of personality disorder (OR = 0.58; 95% CI 0.36–0.96; $p = 0.033$), and smoking status (OR = 0.53; 95% CI 0.39–0.72; $p < 0.001$) were associated with reduced odds of prolonged LOS.

In multivariate analyses evaluating independent predictors of prolonged LOS, high-normal ALT values were not independently associated with LOS (OR = 1.34; 95% CI 0.85–2.13; $p = 0.207$). Higher BMI remained significantly associated with longer hospitalization (OR = 1.94; 95% CI 1.73–2.20; $p < 0.001$), as did elevated calcium levels (OR = 1.79; 95% CI 1.04–3.10; $p = 0.036$). Fewer emergency department visits continued to be associated with shorter hospitalization duration (OR = 0.60; 95% CI 0.38–0.93; $p = 0.023$), and both personality disorder (OR = 0.46; 95% CI 0.22–0.96; $p = 0.037$) and smoking status (OR = 0.49; 95% CI 0.32–0.75; $p = 0.001$) remained independently protective. Serum albumin, antidepressant treatment, sodium concentration, hypothyroidism, and urea were not significantly associated with LOS in the adjusted model (all $p > .05$).

Univariate and multivariate analysis for mortality.

As presented in Table 3, In univariate analyses assessing factors associated with mortality during or following hospitalization, high-normal ALT values were significantly associated with an increased odds

of death (OR = 2.81; 95% CI 1.36–6.02; $p = 0.006$). Older age at diagnosis was also associated with higher mortality (OR = 1.09; 95% CI 1.05–1.12; $p < 0.001$). Lower serum albumin (OR = 0.33; 95% CI 0.19–0.58; $p < 0.001$) and lower haemoglobin (OR = 0.66; 95% CI 0.52–0.83; $p < 0.001$) were associated with reduced odds of survival. Additional significant laboratory associations included higher AST (OR = 1.03; 95% CI 1.01–1.06; $p = 0.008$), creatinine (OR = 3.6; 95% CI 1.57–10.98; $p = 0.007$), urea levels (OR = 1.02; 95% CI 1–1.05; $p = 0.02$), and lower sodium levels (OR = 0.33; 95% CI 0.19–0.58; $p = 0.001$). Lower BMI was associated with mortality (OR = 0.88; 95% CI 0.81–0.95; $p < 0.001$). Bipolar disorder (OR = 30.14; 95% CI 3.52–258.42; $p < 0.001$), hypothyroidism (OR = 8.61; 95% CI 1.25–37.60; $p = 0.009$), and more hospital readmissions (OR = 6.14; 95% CI 2.75–13.11; $p < 0.001$) also showed significant associations.

In multivariate analyses identifying independent predictors of mortality, high-normal ALT values remained significantly associated with increased odds of death (OR = 2.69; 95% CI 1.02–7.36; $p = 0.047$). Older age at diagnosis continued to be associated with mortality (OR = 1.08; 95% CI, 1.04–1.12; $p < 0.001$). Bipolar disorder showed a strong and independent association with death (OR = 85.77; 95% CI 4.16–1,198.01; $p = 0.001$), and greater readmission frequency remained associated with mortality (OR = 6.75; 95% CI 2.50–17.70; $p < 0.001$). BMI demonstrated a borderline association (OR = 0.83; 95% CI 0.69–1.00; $p = 0.05$). Albumin, AST, creatinine, haemoglobin, hypothyroidism, sodium, and urea concentrations were not independently associated with mortality (all $p > 0.05$).

Table 03
Uni- and Multivariate analyses for mortality.

Variable	Univariate models		Multivariate model	
	OR [95% CI]	P value	OR [95% CI]	P value
Age (each added year)	1.09 [1.05, 1.12]	< 0.001	1.08 [1.04, 1.12]	< 0.001
High - Normal ALT group	2.81 [1.36, 6.02]	0.006	2.69 [1.02, 7.36]	0.047
Albumin (g/dL)	0.33 [0.19, 0.58]	< 0.001	1 [0.47, 2.18]	0.991
AST (IU/L)	1.03 [1.01, 1.06]	0.008	1.02 [0.97, 1.05]	0.368
Bipolar disorder	30.14 [3.52, 258.42]	< 0.001	85.77 [4.16, 1198.01]	0.001
BMI	0.77 [0.67, 0.89]	< 0.001	0.83 [0.69, 1]	0.05
Creatinine (meq/L)	3.6 [1.57, 10.98]	0.007	2.23 [0.8, 10.26]	0.217
Haemoglobin (g/dL)	0.66 [0.52, 0.83]	< 0.001	0.78 [0.58, 1.06]	0.108
Hypothyroidism	8.61 [1.25, 37.6]	0.009	1.9 [0.18, 13.65]	0.55
Sodium (meq/L)	0.88 [0.81, 0.95]	0.001	1 [0.91, 1.11]	0.992
Readmissions	6.14 [2.75, 13.11]	< 0.001	6.75 [2.5, 17.7]	< 0.001
Urea (meq/L)	1.02 [1, 1.05]	0.02	1.01 [0.98, 1.04]	0.394

Discussion

In this large retrospective cohort of hospitalized female patients with anorexia nervosa (AN), we demonstrate that alanine aminotransferase (ALT) activity within the traditionally normal range carries significant prognostic information. Specifically, patients with high-normal ALT values (17–40 IU/L) experienced higher all-cause mortality and longer hospitalizations compared with those whose ALT values were in the low-normal range. Importantly, this association persisted after multivariable adjustment for demographic, clinical, psychiatric, and laboratory confounders, underscoring the robustness of ALT as an independent prognostic marker in this population.

These findings contrast sharply with the prevailing body of literature in non-AN populations, where low-normal ALT activity has been consistently associated with sarcopenia, frailty, functional decline, and adverse clinical outcomes [7–13]. In elderly individuals, low ALT correlates with reduced skeletal muscle mass, diminished grip strength, impaired mobility, and increased mortality, supporting its interpretation as a surrogate marker of reduced physiological reserve and biological aging [7–13]. Similar associations have been reported in hospitalized medical patients, community-dwelling cohorts, and in diverse oncological populations, including both solid tumors and hematologic malignancies [10–12]. Collectively, these studies have positioned low ALT as a biomarker of vulnerability rather than resilience.

Based on this framework, one might have expected patients with AN, who universally suffer from severe malnutrition and muscle wasting, to demonstrate worse outcomes at lower ALT levels. However, our data reveal the opposite pattern: higher, not lower, ALT values within the normal range identified patients at increased risk of mortality and prolonged hospitalization. This paradox suggests that the biological meaning of ALT variation in AN differs fundamentally from that observed in other clinical contexts.

A plausible explanation lies in the dual origin of circulating ALT, which reflects not only skeletal muscle mass but also hepatocellular integrity. In most populations, ALT variation within the normal range is driven predominantly by muscle mass and metabolic reserve. In contrast, in patients with AN, particularly those with severe and prolonged malnutrition, muscle mass is uniformly reduced, limiting the contribution of skeletal muscle to circulating ALT levels. Under these circumstances, we hypothesize that even modest increases in ALT may predominantly reflect ongoing hepatocellular injury rather than preserved muscle mass, thereby reversing the prognostic interpretation of ALT within its normal limits.

Liver involvement is a well-recognized, yet often underappreciated complication of AN. Abnormal liver function tests were been reported in up to 43% of severely malnourished patients [16], frequently in the absence of overt clinical liver disease. Two main pathophysiological mechanisms have been described. First, starvation-related hepatitis arises during prolonged caloric deprivation and is characterized by hepatocyte injury mediated by excessive autophagy, oxidative stress, mitochondrial dysfunction, and increased membrane permeability. While autophagy may initially serve as an adaptive mechanism, sustained activation ultimately leads to cellular injury and leakage of aminotransferases into the circulation [17]. Second, refeeding-associated liver injury, including hepatic steatosis and cholestasis, may occur during nutritional rehabilitation, particularly when caloric intake is advanced rapidly. Both

mechanisms can result in ALT elevations that may remain within conventional laboratory reference ranges yet reflect clinically meaningful liver parenchymal damage [17].

Our findings suggest that, in AN, hi-normal ALT values may represent a subclinical manifestation of these hepatic processes, identifying patients with ongoing metabolic or hepatocellular vulnerability. This interpretation is supported by studies in other liver-related conditions demonstrating that ALT values within the upper normal range can be associated with histological liver injury. In HBeAg-negative chronic hepatitis B patients, high-normal ALT has been linked to fibrosis, steatosis, and adverse hepatic outcomes, challenging the traditional dichotomy between “normal” and “abnormal” ALT [21–23].

The association between high-normal ALT and mortality observed in our cohort may therefore reflect a broader syndrome of metabolic instability, impaired hepatic adaptation to starvation and refeeding, and reduced capacity to tolerate physiological stress. Notably, patients in the high-normal ALT group also exhibited higher creatine phosphokinase and albumin levels, suggesting that ALT elevation is not merely a marker of generalized catabolism but may reflect organ-specific injury occurring despite relatively preserved synthetic parameters.

An additional strength of this study lies in the demonstration that the prognostic value of ALT remained significant even after adjustment for BMI, albumin, renal indices, psychiatric comorbidities, and readmission burden. This suggests that ALT captures risk information not fully explained by traditional markers of nutritional status or disease severity. The strong association between readmission frequency and mortality further emphasizes the importance of chronic disease burden and recurrent decompensation in shaping long-term outcomes in AN.

From a clinical perspective, these findings carry important implications. ALT is an inexpensive, routinely measured laboratory parameter that is readily available at the time of hospital admission. Our data suggest that clinicians should exercise caution in dismissing high-normal ALT values as benign in patients with AN. Instead, such values may warrant closer monitoring, careful nutritional advancement, and heightened awareness of potential hepatic and metabolic complications.

Conclusions

In summary, this study demonstrates that, contrary to patterns observed in other populations, high-normal ALT activity is associated with worse clinical outcomes in patients with anorexia nervosa. These findings highlight the context-dependent interpretation of ALT and suggest that, in AN, ALT may serve primarily as a marker of subclinical liver injury rather than preserved muscle mass. Future prospective studies incorporating longitudinal ALT measurements, imaging, and nutritional data are needed to clarify the mechanisms underlying this association and to determine whether ALT-guided risk stratification can inform clinical management in this vulnerable population.

Limitations

Several limitations should be acknowledged. The retrospective, single-center design limits causal inference and may reduce generalizability. ALT measurements were based on a single early hospitalization value, precluding assessment of dynamic changes over time or differentiation between starvation- and refeeding-related injury. Additionally, imaging and histological data were unavailable, preventing direct confirmation of liver pathology. Nevertheless, the large sample size, long follow-up duration, and comprehensive adjustment for confounders strengthen the validity of our conclusions.

Abbreviations

ALT – Alanine amino transferase

LOS – Length of stay

HR – Hazard ration

IQR – Inter quartile range

HN – High Normal

LN – Low normal

CI – Confidence Interval

AN – Anorexia Nervosa

PEF – Peak Expiratory Flow

DXA – Dual X-ray absorptiometry

3DO - Three-dimensional optical imaging

LFT – Liver function test

EMR – Electronic medical record

IRB – Institutional review board

OCD – Obsessive compulsive disorder

CPK – Creatine phosphor-kinase

SD – Standard deviation

OR – Odds Ratio

AST – Aspartate aminotransferase

IU – International unit

BMI – Body mass index

Declarations

Human Ethics

This study was approved by the Chaim Sheba Institutional Review Board under the Helsinki declaration (approval #). Informed consent was waived by the IRB due to the retrospective nature of this study.

Consent to Participate

NA

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This study had no external funding.

Author Contribution

Q.D., A.W., G.S., Z.S.N., R.R., G.D., AND Y.S. ALL participated in establishing the research question, study design, data mining, data analysis, writing of manuscript drafts and the final submission.

Acknowledgement

NA

Data Availability

Original research data of the current study are available with the corresponding author under the terms and conditions of the IRB.

References

1. Fujimoto K, Maki N, Hashiba D, Maeyama T, Nakagawa R, Arai H et al. Effect of romosozumab in premenopausal women with severe osteoporosis and anorexia nervosa. Osteoporos Sarcopenia [Internet]. 2023 Dec [cited 2024 Oct 13];9(4):137–41. Available from: <https://pubmed.ncbi.nlm.nih.gov/38374824/>
2. Gielen E, Bergmann P, Bruyère O, Cavalier E, Delanaye P, Goemaere S et al. Osteoporosis in Frail Patients: A Consensus Paper of the Belgian Bone Club. Calcif Tissue Int [Internet]. 2017 Aug 1 [cited

- 2024 Oct 13];101(2):111–31. Available from: <https://pubmed.ncbi.nlm.nih.gov/28324124/>
3. Fazeli PK, Klibanski A. Effects of Anorexia Nervosa on Bone Metabolism. *Endocr Rev* [Internet]. 2018 Dec 1 [cited 2024 Nov 4];39(6):895–910. Available from: <https://pubmed.ncbi.nlm.nih.gov/30165608/>
 4. Garber AK, Bennett JP, Wong MC, Tian IY, Maskarinec G, Kennedy SF et al. Cross-sectional assessment of body composition and detection of malnutrition risk in participants with low body mass index and eating disorders using 3D optical surface scans. *Am J Clin Nutr* [Internet]. 2023 Oct 1 [cited 2024 Oct 13];118(4):812–21. Available from: <https://pubmed.ncbi.nlm.nih.gov/37598747/>
 5. Minano Garrido E, Di Lodovico L, Dicembre M, Duquesnoy M, Ohanyan H, Melchior JC, et al. Evaluation of muscle-skeletal strength and peak expiratory flow in severely malnourished inpatients with anorexia nervosa: A pilot study. *Nutrition*. 2021;85:111133.
 6. Luo L, Li J, Song J, Li Y. Association between low alanine aminotransferase levels and sarcopenia in older adults: A cross-sectional study [Internet]. 2022. Available from: <https://www.researchsquare.com/article/rs-2263366/v1>
 7. Vespasiani-Gentilucci U, De Vincentis A, Ferrucci L, Bandinelli S, Antonelli Incalzi R, Picardi A. Low Alanine Aminotransferase Levels in the Elderly Population: Frailty, Disability, Sarcopenia, and Reduced Survival. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*. 2018;73(7):925–30.
 8. Anani S, Goldhaber G, Brom A, Lasman N, Turpashvili N, Shenhav-Saltzman G, et al. Frailty and sarcopenia assessment upon hospital admission to internal medicine predicts length of hospital stay and re-admission: A prospective study of 980 patients. *J Clin Med*. 2020;9(8):1–12.
 9. Irina G, Refaela C, Adi B, Avia D, Liron H, Chen A et al. Low blood ALT activity and high FRAIL questionnaire scores correlate with increased mortality and with each other. A prospective study in the internal medicine department. *J Clin Med*. 2018;7(11).
 10. Laufer M, Perelman M, Segal G, Sarfaty M, Itelman E. Low Alanine Aminotransferase as a Marker for Sarcopenia and Frailty, Is Associated with Decreased Survival of Bladder Cancer Patients and Survivors—A Retrospective Data Analysis of 3075 Patients. *Cancers (Basel)*. 2024;16(1).
 11. Uliel N, Segal G, Perri A, Turpashvili N, Kassif Lerner R, Itelman E. Low ALT, a marker of sarcopenia and frailty, is associated with shortened survival amongst myelodysplastic syndrome patients: A retrospective study. *Med (United States)*. 2023;102(17):E33659.
 12. Laufer M, Sarfaty M, Jacobi E, Itelman E, Segal G, Perelman M. Low Serum Alanine Aminotransferase Blood Activity Is Associated with Shortened Survival of Renal Cell Cancer Patients and Survivors: Retrospective Analysis of 1830 Patients. *J Clin Med*. 2024;13:19.
 13. Itelman E, Segev A, Ahmead L, Leibowitz E, Agbaria M, Avaky C, et al. Low ALT values amongst hospitalized patients are associated with increased risk of hypoglycemia and overall mortality: A retrospective, big-data analysis of 51 831 patients. *QJM: Int J Med*. 2021;114(12):843–7.
 14. Gringauz I, Weismann J, Justo D, Adunsky A, Segal G. Alanine aminotransferase blood levels and rehabilitation outcome in older adults following hip fracture surgery. *Int J Rehabil Res*.

2018;41(1):41–6.

15. Kogan M, Klempfner R, Lotan D, Wasserstrum Y, Goldenberg I, Segal G. Low ALT blood levels are associated with lower baseline fitness amongst participants of a cardiac rehabilitation program. *J Exerc Sci Fit*. 2018;16(1):1–4.
16. Hanachi M, Melchior JC, Crenn P. Hypertransaminasemia in severely malnourished adult anorexia nervosa patients: Risk factors and evolution under enteral nutrition. *Clin Nutr*. 2013;32(3):391–5.
17. Sakata M, Takaki A, Oyama A, Adachi T, Wada N, Takeuchi Y et al. Pathogenesis of Severe Liver Injury in Patients with Anorexia Nervosa: A Report of Two Cases and a Literature Review. *Kurume Med J [Internet]*. 2022 [cited 2025 Sep 29];67(2.3):121–9. Available from: <https://pubmed.ncbi.nlm.nih.gov/36130885/>
18. Rautou PE, Cazals-Hatem D, Moreau R, Francoz C, Feldmann G, Lebrech D et al. Acute Liver Cell Damage in Patients With Anorexia Nervosa: A Possible Role of Starvation-Induced Hepatocyte Autophagy. *Gastroenterology*. 2008;135(3).
19. Rosen E, Bakshi N, Watters A, Rosen HR, Mehler PS. Hepatic Complications of Anorexia Nervosa. *Dig Dis Sci [Internet]*. 2017 Nov 1 [cited 2025 Sep 29];62(11):2977–81. Available from: <https://pubmed.ncbi.nlm.nih.gov/28932925/>
20. Narayanan V, Gaudiani JL, Harris RH, Mehler PS. Liver function test abnormalities in anorexia nervosa - Cause or effect. *Int J Eat Disord*. 2010;43(4):378–81.
21. Duan M, Chi X, Xiao H, Liu X, Zhuang H. High-normal alanine aminotransferase is an indicator for liver histopathology in HBeAg-negative chronic hepatitis B. *Hep Intl*. 2021;15(2):318–27. <https://doi.org/10.1007/s12072-021-10153-2>.
22. Chen JF, Wu ZQ, Liu HS, Yan S, Wang YX, Xing M, Song XQ, Ding SY. Cumulative effects of excess high-normal alanine aminotransferase levels in relation to new-onset metabolic dysfunction-associated fatty liver disease in China. *World J Gastroenterol*. 2024;30(10):1346–57. <https://doi.org/10.3748/wjg.v30.i10.1346>.
23. Zheng MH, Shi KQ, Fan YC, Liu WY, Lin XF, et al. Upper Limits of Normal for Serum Alanine Aminotransferase Levels in Chinese Han Population. *PLoS ONE*. 2012;7(9):e43736. <https://doi.org/10.1371/journal.pone.0043736>.

Figures

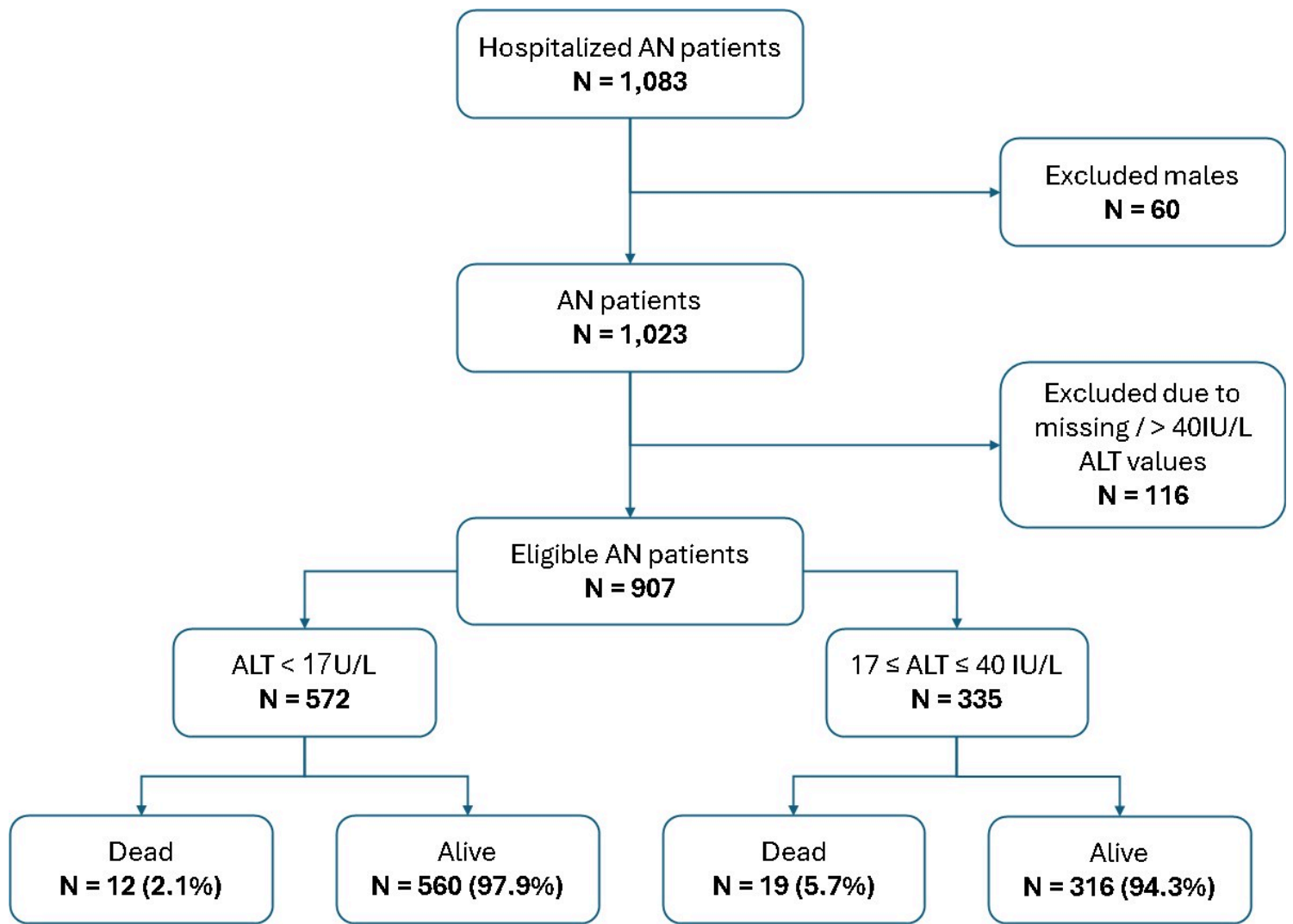


Figure 1

CONSORT flow of study patients.

— ALT < 17 · · ALT ≥ 17

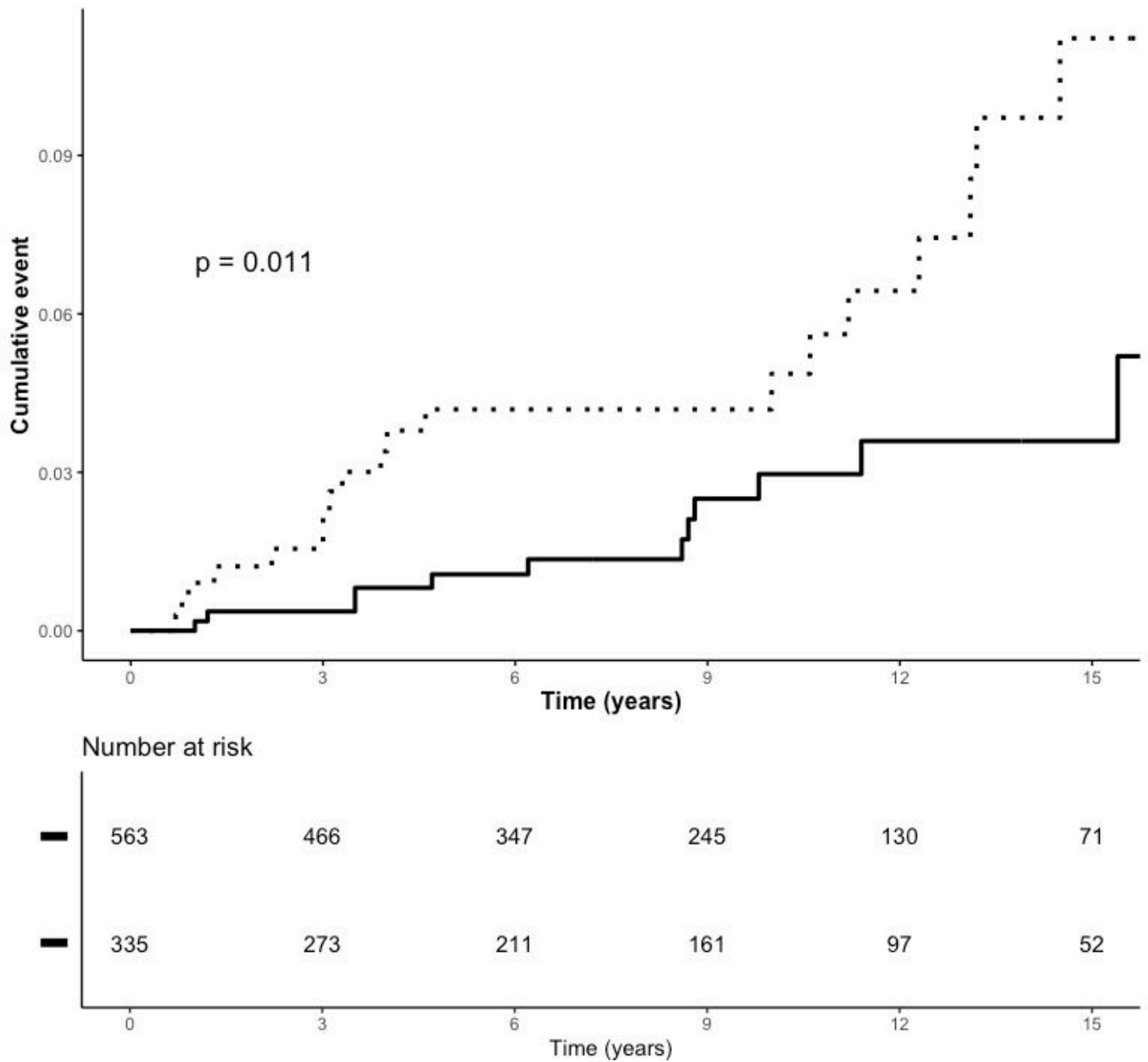


Figure 2

Crude Mortality, Kaplan-Meier Curve.