

# Pre-Hospital Low ALT Activity, a Marker of Sarcopenia and Frailty, is Associated with Increased Long-Term Mortality after COPD Exacerbations. Historic Prospective Cohort Study.

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# Abstract

Background COPD exacerbations have negative impact on patients' survival. Several risk factors for grave outcomes of such exacerbations have been described. Muscle dysfunction and mass loss were shown to impact negatively on prognosis and survival. Low activity of the enzyme ALT (Alanine aminotransferase) in the blood is a known indicator for sarcopenia and frailty, however, no previous studies addressed the association of low ALT amongst patients hospitalized due to COPD exacerbation and long-term survival. Methods. This is a historic prospective cohort study of patients hospitalized due to acute COPD exacerbation. Results. Included were 232 consecutive COPD exacerbation patients. The median time of follow-up was 34.9 months (IQR 23.13 – 41.73 months). During this period 104 (44.8%) patients died. All patients were grouped to quartiles according to blood ALT levels (after exclusion of cases considered to have hepatitis (ALT > 40 IU)). The risk of long-term mortality increased, in a statistically significant manner, amongst patients with low ALT values: the median survival of patients with ALT < 11 IU was 18.5 months only while the median survival for the rest of the study group was not reached. For ALT < 11IU; 12-16IU; 17-20IU and >21IU the mortality rates were 69%; 40.9%; 36.3% and 25% respectively ( $p < 0.001$  for comparison of lower quartile with upper three quartiles). The crude hazard ratio for mortality amongst patients with ALT levels lower than 11IU was 2.37 (95% CI; 1.6 – 3.5). This increased risk of mortality remained significant after adjustment for age, weight, creatinine, albumin concentration and cardiovascular diseases (HR = 1.83; 95% CI 1.08 – 3.1,  $p < 0.05$ ). Conclusions. Low ALT values, a biomarker of sarcopenia and frailty, are associated with poor long-term survival amongst patients hospitalized due to COPD exacerbation.

## Background

Chronic obstructive pulmonary disease (COPD) is a highly prevalent disease worldwide. Acute COPD exacerbations have dismal results, both in high patients' mortality (ranging in different publications from over 5% to over 18% in-hospital mortality during exacerbation (1,2)) and in huge health expenses (1–6). Several risk factors for grave outcomes of COPD exacerbations have been described: Sakamoto and co. (6) performed multivariable logistic regression analysis of over 3,000 COPD patients and found that older age and lower body mass index, amongst other patients' characteristics, are significantly associated with increased risk of in-hospital mortality. Serra-Picamal and co., in a big-data analysis of 17,555 COPD patients, identified early re-hospitalizations as another risk factor for mortality after hospitalization due to COPD exacerbation (7).

Survival and COPD mortality are negatively influenced by both dysfunction and impaired muscle mass (sarcopenia) (8,9). Additionally, COPD exacerbations also rapidly induce loss of muscle mass and function through the activation of several biological pathways and systems. Sarcopenia and frailty, two overlapping syndromes, defined as causing increased mortality and frequent hospital admissions, are prime candidates for having a negative impact on COPD exacerbations' outcomes. In a review published back in 2005, Morley and co. (11) stated that COPD is one of the chronic diseases particularly associated with frailty. Vellas and co. (12) relate to COPD as a causative agent for decreased muscle mass, in turn

becoming a risk factor for COPD patients' mortality. In their review regarding "Sarcopenia and frailty in chronic respiratory disease", Bone and co. (13) declare the association between frailty and poor outcomes amongst COPD patients. Maddocks and co. (14) found that frailty affect 25% of all COPD patients and that it is a significant factor for pulmonary rehabilitation failure. Nevertheless, they state that pulmonary rehabilitation programs are beneficial for frail, COPD patients, potentially reversing frailty characteristics even with a short-term rehabilitation program.

Sarcopenia and the resultant frailty, represented by low activity of the enzyme ALT (SGPT) in the peripheral blood, were shown to be associated with shortened survival and other poor clinical outcomes, in various patients' populations and clinical scenarios. It is postulated that this association rise from the fact that low ALT levels are the result of sarcopenia and the resultant frailty is the cause for shortening of life span in low-ALT populations (15–18).

However, there are no previous studies that examined the relationship between low ALT values and mortality amongst hospitalized patients with COPD exacerbation. The aim of the current study was to assess the association between ALT and clinical outcomes.

## **Patients And Methods**

### Patient selection

We executed a historic, prospective cohort study of COPD patients hospitalized to a single department of internal medicine, due to COPD exacerbation as their main diagnosis. The inclusion criteria were: a. age over 18 years, b. diagnosis of COPD exacerbation (ICD code 496) on discharge, c. available ALT blood levels, within the normal limits (lower than 40 IU/L) during the 3 months prior to admission. After study approval by an institutional ethics review board, we excluded patients with ALT levels greater than 40 IU/L, supposed to have hepatitis of any cause. We extracted patients' details from the computerized records, including epidemiologic characteristics, background diagnoses, long-term medications, laboratory parameters, short- and long-term clinical outcomes.

### Statistical methods

In order to assess the association between ALT levels and dichotomous variables we calculated the sample size, as appropriate for medium strength associations. In order to determine such association we needed a sample size greater than 192 patients (for 1% significance and 80% power). The cohort size was determined using G Power software (19).

We assessed the distribution of continuous variables using histograms and Q-Q plots. We described continuous variables with normal distribution by means and standard deviations. Continuous variables that did not have normal distribution were described using median and IQR (Inter-quartile range). We described categorical variables using frequency and percentages. We assessed the association of clinical outcomes with continuous variables using t-tests or Man-Whitney tests. We assessed the association of

categorical variables with clinical outcomes using the chi-square tests or the exact fisher's test. We used logistic regression to assess the association between ALT values while correction of possible confounders. This was a two-block regression: the first block included ALT values and the second block included possible confounders, selected by using the forward stepwise methods and the Wald test. Statistical analysis was done using the SPSS software (IBM Corp., NY USA). All statistical tests were two-sided. We considered as significant only p values lower than 0.05.

## Results

We included in this study 232 consecutive COPD patients, hospitalized due to COPD exacerbation in one internal-medicine department in a large, tertiary hospital, over a period of 38 months. After approval by an IRB, we extracted patients' data from their computerized medical records. The mean age was  $76.06 \pm 10.7$  years, median Norton score was 15.7 (IQR 13-19), median ALT level was 16.5 IU/L (IQR 11-20), median creatinine concentration was 1.15 mg/dL (IQR 0.74-1.35), and the mean albumin concentration was  $3.6 \pm 0.47$  g/dL. Within our cohort, 74.6% had cardio-vascular diseases, 59.9% had metabolic diseases, 35.3% had diabetes, 25.4% had neurological diseases, and 24.1% suffered from hematological or hemato-oncological diseases. Regarding background medical treatments, 19.4% were treated by systemic steroids, 32.8% took anti-diabetic medications, and 84.1% had cardiovascular medications, 26.3% treated by anticoagulants and 67.7% were using inhalers regularly. Patients' characteristics, according to their baseline ALT values (lower quartile ( $< 11$  IU/L) vs. upper three quartiles ( $11$  IU/L  $<$  ALT  $<$  40 IU/L)), are described in table 1. The median time of follow-up was 34.9 months (IQR 23.13 – 41.73). During this period 104 (44.8%) patients died. Table 2 describe patient characteristics found to be associated with increased risk for mortality amongst our study cohort.

**Table 01.** Patients' characteristics according to baseline ALT levels

	ALT < 11 IU/L	11 IU/L ≤ ALT ≤ 40 IU/L	P value
<b>Patients' demographics</b>			
Age (years ± SD)	78.8 ± 9	74.8 ± 11.2	<b>0.008</b>
Gender – males (n (%))	39 (54.9)	77 (47.8)	0.32
Norton score (number, IQR)	14.93 (13-17)	16.06 (13.5-19)	<b>0.002</b>
<b>Background diagnoses (groups)</b>			
Cancer (n (%))	20 (28.2)	36 (22.4)	0.34
Dementia (n (%))	3 (4.2)	7 (4.3)	NS
Diabetes (n (%))	33 (46.5)	49 (30)	<b>0.018</b>
Cardiovascular (n (%))	54 (76.1)	119 (73.9)	0.73
Metabolic (n (%))	47 (66.2)	92 (57.1)	0.19
Neurologic (n (%))	17 (23.9)	42 (26.1)	0.73
Endocrine (n (%))	12 (16.9)	21 (13.0)	0.49
<b>Medications (groups)</b>			
Steroids (n (%))	17 (23.9)	28 (17.4)	0.24
Anticoagulation (n (%))	27 (38)	34 (21.1)	<b>0.007</b>
Inhalers/Inhalation (n (%))	46 (64.8)	111 (68.9)	0.53
Anti-diabetic (n (%))	28 (39.4)	48 (29.8)	0.15
Cardiovascular (n (%))	62 (87.3)	133 (82.6)	0.37
Metabolic (n (%))	17 (23.9)	33 (20.5)	0.56
Neurologic (n (%))	33 (46.5)	62 (36.5)	0.25
<b>Laboratory parameters</b>			
Albumin (g/dL ± SD)	3.4 ± 0.45	3.7 ± 0.45	<b>&lt; 0.001</b>
Creatinine (mg/dL, (IQR))	1.32 (0.93-1.53)	1.07 (0.68-1.29)	<b>&lt; 0.001</b>
<b>Clinical outcomes</b>			
Mortality (n (%))	49 (69.0)	55 (34.2)	<b>&lt; 0.001</b>
Survival time – median (months)	18.5	Median not reached	<b>&lt; 0.001</b>

**Table 02.** Patients' characteristics according to survival – univariate analysis.

patients' characteristics	Alive	Dead	Hazard ratio (95% CI)	P Value
Age (years ± SD)	72.89 ± 10.8	79.96 ± 9.2	1.06 (1.04-1.08)	< 0.001
Norton score (number, (IQR))	16.84 (15-19)	14.33 (11.25-17)	1.14 (1.09-1.19)	< 0.001
Albumin (mg/dL ± SD)	3.69 ± 0.47	3.48 ± 0.45	2.06 (1.43-2.98)	< 0.001
Creatinine (mg/dL, (IQR))	1.03 (0.69-1.21)	1.29 (0.84-1.62)	1.57 (1.23-2)	< 0.001
ALT (IU/L, IQR)	18.71 (13-23.75)	13.77 (9-17)	1.08 (1.05-1.11)	< 0.001
Cardiovascular disease (n (%))	89 (69.5)	84 (80.8)	1.8 (1.1-2.93)	0.019
Cardiovascular medications (n (%))	101 (78.9)	94 (90.4)	2.09 (1.09-4.0)	0.027
Neurologic medications (n (%))	41 (32.0)	54 (51.9)	1.94 (1.31-2.86)	0.001
Anticoagulation medications (n (%))	29 (18.8)	37 (35.6)	1.73 (1.15-2.57)	0.008

We divided all patients to quartiles according to their blood ALT levels (after exclusion of cases considered to have hepatitis (ALT > 40 IU)). The risk of long-term mortality increased, in a statistically significant manner, amongst patients with low ALT values: the median survival for patients with ALT < 11 IU was 18.5 months only while the median survival for the rest of the study group was not reached. For ALT < 11IU; 12-16IU; 17-20IU and >21IU the mortality rates were 69%; 40.9%; 36.3% and 25% respectively (p < 0.001 for comparison of lower quartile with upper three quartiles; figure 1).

The crude hazard ratio for mortality amongst patients with ALT levels lower than 11IU was 2.37 (95% CI; 1.6 – 3.5). This increased risk of mortality remained significant after controlling for age, weight, Norton score, creatinine, albumin concentration and cardiovascular diseases (HR = 1.83; 95% CI 1.08 – 3.1, p = 0.025). Table 3 describe the multivariate logistic regression for mortality in our study cohort.

**Table 03.** Multivariate logistic regression for mortality in our study cohort.

patients' characteristics	Hazard ratio (95% CI)	P value
Lower quartile of ALT	1.83 (1.08-3.1)	<b>0.025</b>
Age	1.02 (0.99-1.05)	0.110
Weight	0.98 (0.97-0.99)	<b>0.02</b>
Low Norton score	1.09 (1.02-1.17)	<b>0.016</b>
High creatinine value	1.79 (1.14-2.81)	<b>0.011</b>
Low albumin concentration	1.34 (0.85-2.42)	0.178
Cardiovascular disease	1.56 (0.83-2.94)	0.167

## Discussion

Current literature promotes personalized medicine. However, most cases of personalized medicine are actually dealing with precise medicine: diagnostic approaches become more focused on disease and pathology rather than on the person / patient as a whole. We believe that thorough evaluation of

sarcopenia and frailty should be considered as true personalized medicine. Appreciation of sarcopenia and frailty enables a summation of patients' characteristics which are associated with his or her risk for subsequent morbidity and mortality. Addressing sarcopenia and frailty in quantitative measures should, therefore, better the prognostication process for many patients' populations. COPD patients should not be an outlier for the aforementioned declaration: these patients should be routinely evaluated for sarcopenia and frailty, and treatment strategies must take into account these patient's characteristics.

In the current study we show that similarly to other patients' groups, COPD patients can also be classified as sarcopenic and frail, according to their baseline ALT values. ALT measurements are a part of routine blood tests and are available worldwide for any hospitalized patient. Acknowledgment of low ALT values during COPD exacerbation could aid the attending physician in taking better clinical / therapeutic decisions (duration and route of administration of steroids, duration and type of antibiotics, promoting physiotherapy sessions and rehabilitation programs prior to patient's discharge to the community etc.).

ALT measurement should not replace other, well established methods for sarcopenia and frailty appreciation. Nevertheless, most such evaluation tools were developed and are being used in the realm of geriatric medicine. The results of this study are applicable to the general population of COPD patients admitted to internal-medicine departments. For these reasons, we suggest that ALT values would be flagged, and diagnoses of sarcopenia and frailty should be highlighted in the discharge documents of COPD patients.

## **Conclusion**

Low ALT values are an independent marker for shortened survival of COPD patients after being hospitalized due to COPD exacerbation. Being a marker for sarcopenia and frailty, low ALT values in these patients should prompt more aggressive therapeutic efforts on behalf of the attending physician. Future, prospective, interventional studies should aim at evaluation of different therapies and rehabilitation programs, concentrated at the sarcopenic and frail COPD patients.

## **Limitations**

This was a retrospective analysis and therefore, not all confounding parameters could be addressed. We demonstrated statistical associations but causality could not be inferred. Also, this study was done in a single department and results might be changed with different patients' demographics.

## **List Of Abbreviations**

ALT; Alanine amino-transferase. SGPT; Serum glutamic pyruvic transaminase. COPD; Chronic, obstructive pulmonary disease. CI; Confidence interval. IU; International units. IQR; Inter-quartile range. Q-Q Plot; Quantile-quantile plot.

## **Declarations**

### Ethics approval and consent to participate

This study was initiated only after approval by the institutional review board at the Chaim Sheba medical center. Approval number 5779-18-SMC. Since this was a retrospective study, consent was not relevant.

### Consent to publish

All authors gave their consent for publication of the completed manuscript.

### Availability of data and materials

All data is available with the authors for further study questions.

### Competing interests

All authors declare they have no competing interests regarding this study and manuscript.

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### Authors' contributions

Study design and planning: LN; SM; TN; GG; LY; LE; BG; ZSG; BA; CD; AC; SG. Data collection: LN; SM; TN; GG; SG. Data analysis: LN; SM; TN; GG; LY; LE; BG; ZSG; BA; CD; AC; SG. Manuscript writing and proofs: LN; SM; TN; GG; LY; LE; BG; ZSG; BA; CD; AC; SG. All authors have read and approved the manuscript.

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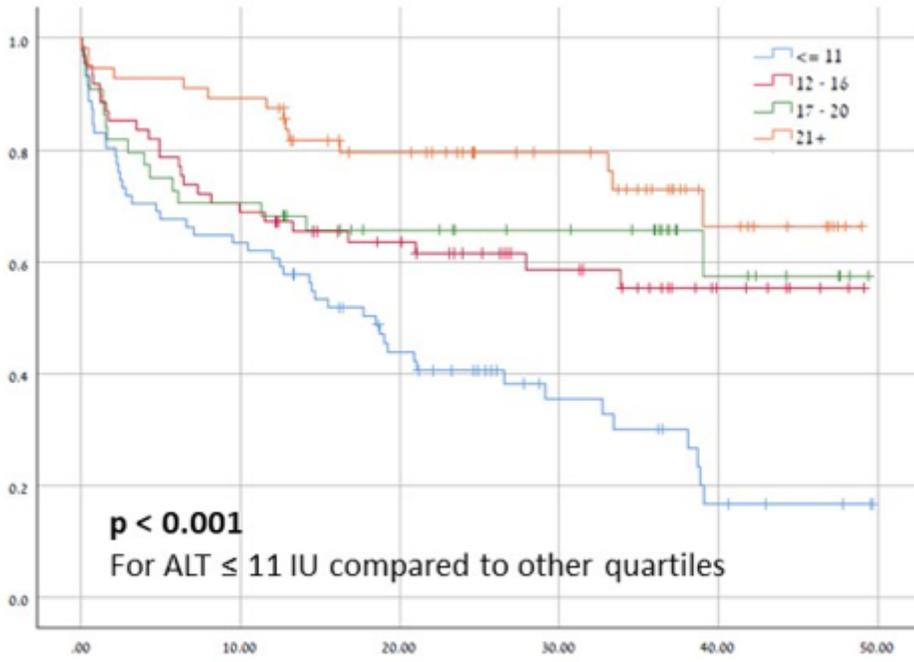
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## Figures



**Figure 1**

Survival (months) of COPD patients according to baseline ALT values