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Original Article

Do low levels of alanine aminotransferase, a baseline marker of sarcopenia and frailty, associate with worse clinical outcomes among hospitalized COVID-19 patients? A Retrospective Cohort Study

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Abstract

Objectives: COVID-19 geoperdize lives. Not all the risk factors for negative outcomes are known. Sarcopenia and frailty are common, negatively affecting clinical outcomes. Studies have shown that sarcopenia and frailty are associated with worse outcomes. Our objective was to examine whether low ALT (Alanine-aminotranferase), a surrogate marker for sarcopenia, is associated with worse clinical outcomes among hospitalized COVID-19 patients. **Methods**: We reviewed cases of COVID-19 in a tertiary hospital, during three COVID-19 waves and examined correlations between ALT and mortality using crude, univariate and multivariate analysis for age, gender, hypertension, Chronic obstructive pulmonary disease and Congestive heart failure. **Results**: 357 patients were included in this analysis. Median age was 69, 54% were males. Median ALT was 19 IU/L. During follow-up, 73 (20%) died. Patients with low ALT were more likely to die (HR 1.82, 95% CI 1.06-3.09, P=0.028). Other predictors for mortality were low albumin, background COPD, dyslipidemia, dementia, and malignancy. The multivariate analysis showed that low ALT was still an independent predictor of poor prognosis (HR 1.7, 95% CI 1.0-2.9, P=0.049). **Conclusions**: In our analysis of COVID-19 patients, low ALT levels were independently associated with increased risk of mortality, both as standalone and when incorporated into a multivariate analysis.

Keywords: ALT, Clinical outcomes, Corona virus, Frailty, Sacrcopenia

Introduction

The coronavirus disease 2019 (COVID-19) pandemic originated in China in December 2019 and has since become a global threat[1]. The virus is highly contagious, leading to a rapidly growing number of infections. This large number of infections creates an increased burden on healthcare systems worldwide. COVID-19 causes a broad spectrum of disease varying from asymptomatic to severe[2]. In comparison to Influenza, SARS-CoV-2 causes a higher rate of hospitalization[3] and is characterized by higher transmissibility (R_0), a longer incubation period, and no interval between symptom onset and maximum infectivity, all of which make the virus harder to contain[4]. In recent years as the pandemic progressed, many health care systems throughout the world we and still are, being sometimes stressed beyond their maximum capacity.

A personalized medicine approach could be helpful in wisely allocating resources. This paradigm states that the way to treat one's disease, monitor it, or prevent it, should be individually tailored to the patient's biochemical,

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physiological, environmental exposure, and behavioral profile[5]. The poor prognosis of patients suffering from COVID-19 is already known to be associated with older age, comorbidities such as hypertension, diabetes, cardiovascular disease, respiratory diseases, metabolic syndrome, and suffering from multiple comorbidities[6,7]. Frailty (increased tendency to succumb to morbidities) is associated with old age and other comorbidities[8] and is also strongly related to sarcopenia (decreased muscle mass and function)[9]. Frailty and sarcopenia are two overlapping syndromes related to increased mortality and frequent hospital admissions. Therefore, identifying patients who suffer from sarcopenia and frailty could assist in assessing the patients' gestalt and personalizing their treatment. Circulating biomarkers have been suggested to help diagnose these conditions, track their progress, treat them, and verify treatments' efficacy[10].

Alanine aminotransferase (ALT) is an intracellular transaminase enzyme catalyzing the conversion of α-keto acids into amino acids by transferring amino groups. Hence, it plays a crucial role in essential metabolic pathways, such as glycolysis and gluconeogenesis, mainly in the liver and skeletal muscles[11]. Recent retrospective and prospective clinical studies have shown that low ALT serum levels/ catalytic activity act as a surrogate marker for sarcopenia, frailty, and poor clinical outcomes in multiple clinical settings: the outpatient, in-hospital, and during periods of rehabilitation[12–19]. ALT serum activity levels representing muscle mass tend to change slowly over time unless impacted by severe illness causing hepatocellular injury. Thus, a single measurement could be used as patient baseline levels, excluding higher-than-normal ALT levels (over 40 IU/L). Assessing sarcopenia and frailty is a vital tool to better personalize therapy and may be used to adjust treatment protocols for patients hospitalized in internal medicine departments, as these conditions are related to higher mortality[12]. Thus, we hypothesize that low ALT serum activity baseline levels (under 12 IU/L, based on previous studies which used 10 IU/L [12] or 17 IU/L [19]) could be used in the risk stratification of COVID-19 patients.

In the current study, we retrospectively analyzed a cohort of hospitalized patients and examined whether low baseline ALT serum activity measurement was indeed associated with higher COVID-19 associated mortality. The aim of the study was to strengthen the potential value of low ALT as a biomarker for dismal outcomes in this patients' population.

Materials and Methods

This retrospective cohort study included all patients admitted to the quarantine COVID internal medicine departments in the Sheba medical center, an Israeli university-affiliated tertiary hospital, during the year 2020. Outcome data were collected until March 2021. Patients with severe liver disease, patients with acute myocardial infarction, receiving drugs that might alter the metabolism of ALT, or suffering from hepatitis due to COVID-19 disease as defined by ALT levels above 40 IU/l were excluded from the analysis.

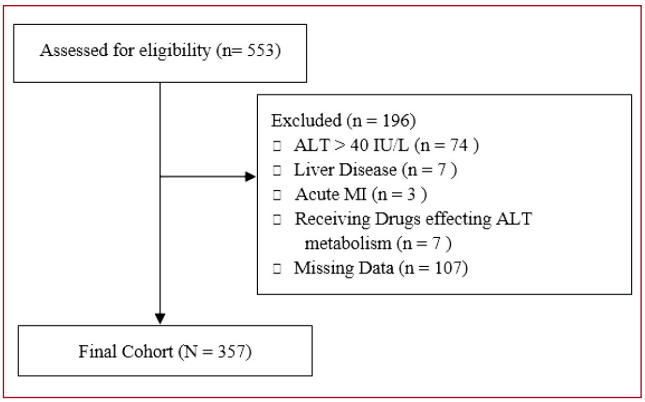

Figure 1. Population flow chart.

The source of clinical data was the patients' electronic medical records (Sheba EMR, the chameleon system). ALT levels were obtained upon patient admission. These medical records are intended for patient care, which increases their reliability. The hospital has strict documentation protocols in accordance with the Joint Commission International (JCI) criteria, all diagnoses are confirmed by attending physicians, and the documentation of the vital signs is done by experienced nurses. All data from patient interactions is promptly entered into the medical record. The Chaim Sheba Institutional Review Board approved access to these medical records (approval # SMC-7705-20). A CONSORT flow chart showing how patients were selected is depicted in Figure 1.

Statistical analysis

Categorical variables are described as frequency and percentage. Continuous variables were evaluated for normal distribution using histogram and Q-Q plots. Normally distributed continuous variables are reported as mean±standard deviation (SD), while other variables are reported as median and interquartile range (IQR). A comparison was performed between patients with and without low ALT serum activity levels. We used both clinically validated cutoffs of ALT levels and the cutoff determined by the Youden index in our analysis. Independent samples t-test and Mann-Whitney test were used to compare continuous variables, while the Chi-square test and Fisher's exact test were used to compare the categorical variables. Variables significantly associated with the dependent variable were included in multivariable logistic regression. All statistical tests were two-sided. $P<0.05$ was considered statistically significant. Statistical analysis was performed using SPSS software.

	Total	ALT ≥ 12 IU/L	ALT < 12 IU/L	p-Value
N	357	298	59	
Age, N (median [IQR])	68.6 (54.2-80.7)	67.9 (55.1-80.1)	71.9 (46.0, 85.4)	0.502
Male, N (%)	193 (54.1)	165 (55.4)	28 (47.5)	0.265
BMI, kg/m^2 (mean sd.)	27.6 5.4	28.0 5.1	25.4 6.4	0.037
LOS, days (median [IQR])	5.0 (2.0-11.0)	5.0 (2.0-11.0)	5.0 (2.0-9.0)	0.527
Laboratory values				
ALT, IU/L (median [IQR])	19.0 (14.0-26.0)	21.0 (16.0-27.0)	10.0 (8.0-11.0)	
LDH, U/L (median [IQR])	276.0 (212.0-374.0)	282.5 (221.5-391.5)	229.0 (182.5-294.0)	<0.001
TSH, mIU/L (median [IQR])	1.4 (0.8-2.6)	1.4 (0.8-2.7)	1.4 (0.8-2.5)	0.979
Saturation – room air, % (median [IQR])	96.0 (93.0-97.0)	96.0 (93.8-97.0)	96.0 (93.0-99.0)	0.190
eGFR-MDRD, mL/min/1.73 m^2 (median [IQR])	80.4 (52.5-110.4)	80.6 (54.7-109.0)	76.9 (39.6-121.9)	0.577
SBP, mmHg (median [IQR])	126.0 (112.0-144.0)	127.0 (114.0-146.0)	117.0 (105.0-136.0)	0.020
Platelets, K/μL (median [IQR])	197.0 (148.5-272.0)	199.0 (150.0-278.0)	180.5 (136.8-263.8)	0.167
WBC, K/μL (median [IQR])	7.2 (5.0-10.3)	7.3 (5.2-10.2)	6.7 (4.5-10.4)	0.500
ALB, g/dL (mean sd.)	3.3 0.6	3.4 0.6	3.2 0.7	0.025
Sodium, mEq/L (mean sd.)	138.1 6.2	138.1 6.2	138.3 6.3	0.828
HGB, g/dL (mean sd.)	12.0 2.1	12.2 2.1	11.0 1.8	<0.001
Background comorbidities				
HTN, N (%)	150 (42.0)	125 (41.9)	25 (42.4)	0.952
DM, N (%)	99 (27.7)	78 (26.2)	21 (35.6)	0.140
Dyslipidemia, N (%)	129 (36.1)	105 (35.2)	24 (40.7)	0.427
IHD, N (%)	58 (16.2)	46 (15.4)	12 (20.3)	0.351
Stroke, N (%)	52 (14.6)	47 (15.8)	5 (8.5)	0.147
Dementia, N (%)	19 (5.3)	17 (5.7)	2 (3.4)	0.751
COPD, N (%)	16 (4.5)	10 (3.4)	6 (10.2)	0.033
Solid malignancy, N (%)	34 (9.5)	28 (9.4)	6 (10.2)	0.853
Hematologic malig. N (%)	16 (4.5)	13 (4.4)	3 (5.1)	0.735
CHF, N (%)	35 (9.8)	26 (8.7)	9 (15.3)	0.123

BMI – Body mass index; ALT - Alanine transaminase; LDH – Lactate dehydrogenase; TSH – Thyroid-stimulating hormone; eGFR-MDRD – Glomerular filtration rate estimated by modification of diet in renal disease; ALB – Albumin; HGB – Hemoglobin; HTN – hypertension; DM – diabetes mellitus; IHD – ischemic heart disease; COPD –chronic obstructive pulmonary disease; CHF – congestive heart failure.

Table 1. Baseline Demographics and clinical data.

Results

The study cohort consisted of 357 patients admitted to Sheba Medical Center with a primary diagnosis of a COVID-19 infection. The median age was 69 (IQR 54-81), and 193 (54%) were males. Table 1 describes patients' characteristics according to their measured ALT serum activity level. The mean body mass index (BMI) was 27.6±5.4. The mean ALT serum activity level was 19 (IQR 14-26). Regarding patients' comorbidities, 150 (42%) suffered from hypertension, 99 (28%) were diagnosed with diabetes mellitus and 129 (36%) with dyslipidemia. 58 (16%) suffered from ischemic heart disease, 52 (15%) suffered from a past stroke, 19 (5.3%) suffered from dementia, 16 (4.5%) suffered from chronic obstructive pulmonary disease (COPD), 35 (9.8%) suffered from congestive heart failure. 34 (9.5%) had a solid malignancy, and 16 (4.5%) had hematologic malignancy. The reverse censoring method was used to evaluate the median length of follow-up – 155 days (IQR 64-236).

Patients with lower ALT levels (Under 12 IU/L) had lower BMI values (25 vs. 28; p=0.037), lower hemoglobin levels

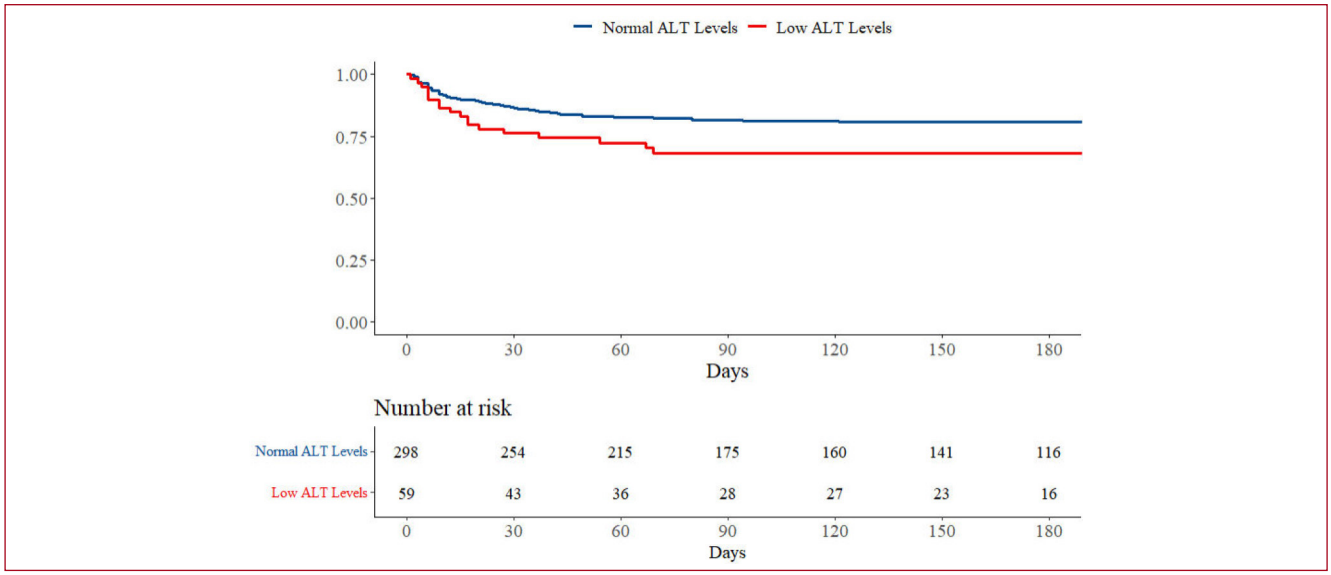

Figure 2. Long-term survival by ALT levels.

(11 vs. 12; p<0.001), lower albumin (3.2 vs. 3.4; p=0.025), lower lactate dehydrogenase (LDH) (229 vs. 283; p<0.001), lower blood pressure (systolic: 117 vs. 127; p=0.020, diastolic: 69 vs. 75; p=0.002), and were more likely to be diagnosed with COPD (10.2% vs. 3.4%; p=0.033). The groups were similar in age (72 vs. 68; p=0.502), and gender (48% vs. 55%, p=0.265). The rates of congestive heart failure, hypertension and diabetes mellitus were not significantly different between lower and normal ALT values (15.3% vs. 8.7%; p=0.123, 42% vs. 42%; p=0.952, and 36% vs. 26%; p=0.140, respectively). Renal functions represented by estimated glomerular filtration rate – modification of diet in renal disease (eGFR-MDRD) formula also similar in both groups (76.9 vs. 80.6; p=0.577).

Long-term outcomes

Univariate analysis

The median follow-up duration was 155 days (IQR 64-236), and 50 patients died (14% of all study patients). 12 in the lower ALT values group (20% of the group patients) and 38 in the higher ALT values group (13% of the group patients). This analysis showed significantly higher mortality in patients with lower ALT values (hazard ratio, 1.8, 95% confidence interval, CI, 1.07-3.09, p=0.028) and is depicted in Figure 2. Using the Youden index, a cutoff of 21 IU/L was used and showed a trend towards reduced long term survival (hazard ratio, 1.55, 95% confidence interval, CI, 0.94-2.6, p=0.085).

Other factors associated with reduced survival are shown in Table 2 and include age (HR 1.05, 95% CI 1.03-1.07, P<0.001), sodium levels (HR 1.06, 95% CI 1.03-1.10, P=0.001), LDH levels (HR 1.00, 95% CI 1.00-1.00, P=0.001), Absolute neutrophil count (HR 1.10, 95% CI 1.07-1.13, P<0.001) and comorbidities: Hypertension (HR 1.91, 95% CI 1.20-3.03, P=0.006), dyslipidemia (HR 1.72, 95% CI 1.08-2.72, P=0.021), dementia (HR 2.290, 95% CI 1.048-5.005, P=0.038), COPD (2.41, 95% CI 1.04-5.55, P=0.040) and more.

Multivariate analysis

A multivariate analysis shown in Table 3 was performed controlling for important predictors of mortality such as age, gender, hypertension, COPD, and Congestive Heart Failure. In this analysis low ALT was an independent predictor of poor prognosis (OR 1.73, 95% CI 1.00-2.99, p=0.049). Age was also a significant risk factor for mortality (OR 1.05, 95% CI 1.03-1.07, p<0.001). Other factors were non-significant in this analysis such as Male gender (OR 1.36, 95% CI 0.84-2.22, P=0.212), hypertension (OR 1.13, 95% CI 0.69-1.84, P=0.631), COPD (OR 1.34, 95% CI 0.56-3.16, P=0.511), congestive heart failure (OR 0.76, 95% CI 0.38-1.53, P=0.447). Using ALT cutoff of 21 IU/L (Based on Youden index) results were not statistically significant.

Discussion

This work investigated whether low ALT levels, a known surrogate marker for frailty, correlate with mortality in COVID-19 patients.Our findings correlate with other cohorts of COVID-19 patients described worldwide[20]. In this cohort, patients with low ALT levels did not differ significantly from patients with normal ALT levels in age, gender, or rates of

Characteristic	Hazard Ratio (95% CI)	P-value
Demographics		
Age. N	1.05 (1.03-1.07)	<0.001
Male, N	1.08 (0.68-1.72)	0.733
BMI, kg/m^2	1.00 (0.93-1.08)	0.945
Laboratory values		
ALT<12, IU/L	1.82 (1.07-3.09)	0.028
AST, U/L	1.01 (1.00-1.02)	0.100
ALB, g/dL	0.30 (0.21-0.43)	<0.001
ALKP, IU/L	1.00 (1.00-1.01)	0.538
GGT, U/L	1.00 (1.00-1.00)	0.291
Sodium, mEq/L	1.06 (1.03-1.10)	0.001
Potassium, mmol/L	1.65 (1.18-2.32)	0.004
LDH, U/L	1.00 (1.00-1.00)	0.001
TSH, mIU/L	0.84 (0.70-1.01)	0.066
Saturation – room air, %	0.89 (0.86-0.92)	<0.001
eGFR-MDRD, mL/min/1.73 m^2	0.99 (0.98-0.99)	<0.001
Systolic blood pressure, mmHg	0.99 (0.98-1.00)	0.112
Diastolic blood pressure, mmHg	0.98 (0.96-1.00(	0.042
EF, %	1.04 (0.96-1.13)	0.347
HGB, g/dL	0.91 (0.81-1.02)	0.104
Absolute lymphocyte count, K/µL	0.91 (0.70-1.19)	0.492
Absolute neutrophil count, K/µL	1.10 (1.07-1.13)	<0.001
Platelets, K/µL	1.00(1.00-1.00)	0.623
White blood cells, K/µL	1.08 (1.06-1.11)	<0.001
Background comorbidities		
HTN, N	1.91 (1.20-3.03)	0.006
DM, N	1.42 (0.88-2.29)	0.155
Dyslipidemia, N	1.72 (1.08-2.72)	0.021
IHD, N	1.55 (0.89-2.71)	0.120
Stroke, N	1.31 (0.72-2.38)	0.380
Dementia, N	2.29 (1.058-5.01)	0.038
COPD, N	2.41 (1.04-5.55)	0.040
Solid malignancy, N	1.46 (0.73-2.94)	0.284
Hematologic malignancy, N	2.47 (1.14-5.39)	0.023
CHF, N	1.50 (0.77-2.92)	0.235
Chronic medications		
Antihypertensives, N	2.26 (1.42-3.61)	0.001
Antiaghregants, N	1.49 (0.92-2.39)	0.102
Antiepileptics, N	0.65 (0.28-1.49)	0.304
Lipid lowering, N	1.48 (0.93-2.37)	0.097
Diuretics, N	2.42 (1.49-3.95)	<0.001
Anticoagulants, N	1.31 (0.57-3.02)	0.528

Table 2. Predictors of mortality in a univariate analysis.

Variable	OR	95% CI		P
		Lower	Upper	
Male	1.36	0.84	2.22	0.212
Age	1.05	1.03	1.07	<0.001
ALT>12	1.73	1.00	2.99	0.049
HTN	1.13	0.69	1.84	0.631
COPD	1.34	0.56	3.16	0.511
CHF	0.76	0.38	1.53	0.447

ALT – Alanine transaminase; HTN = hypertension; COPD – chronic obstructive pulmonary disease; CHF – congestive heart failure.

Table 3. Predictors of mortality in a multivariate analysis.

comorbidities such as ischemic heart disease, dementia, and diabetes mellitus.

A suggested mechanism for the correlation between frailty and death could be further researched, specifically in COVID-19 patients. Frailty causing a worse prognosis in COVID-19 patients could be due to deteriorating function of homeostatic mechanisms and loss of reserve capacities in all body systems, as a whole cascade of catabolic events occurs[21].

Other factors found to be associated with mortality were hypertension, dyslipidemia, dementia, COPD, and hematologic malignancy. These factors are known predictors of mortality in general hospitalization wards. Nevertheless, After performing a multivariate analysis to address such confounders, low ALT levels were still associated with greater mortality among the patient cohort. This finding does not exclude the fact that COVID-19 patients presenting with higher-than-normal ALT values could also be at higher risk of mortality, potentially suffering from COVID 19 associated liver damage. In the current study we excluded such patients because we wanted to concentrate in the ability of using ALT as a marker for sarcopenia and frailty prior to COVID rather than as a marker for COVID 19 associated target organ damage.

Previous studies showed that risk factors for mortality in COVID-19 patients include older age, comorbidities such as hypertension, diabetes, cardiovascular disease, respiratory diseases, metabolic syndrome, and suffering from multiple comorbidities[6,7]. These factors assist in personalizing COVID-19 patients' treatment, as protocols could be adjusted to best fit an individual according to his risk factors. Considering low ALT serum activity levels as another predictor for mortality could benefit in further personalizing COVID-19 patients' treatment.

On a population level, the COVID-19 pandemic causing increased healthcare demand could require difficult decisions in allocating limited resources such as mechanical ventilation. Thus, different algorithms and scoring systems were devised. Frailty has even been proposed as a screening tool in COVID-19 patients to help with triage[23]. According to our findings, low ALT serum activity could be integrated within scoring systems or in addition to them as an available, easy-to-use, reliable measure for frailty with the added benefit of being a simple test that is already routinely incorporated in new patient admission.

Future studies should confirm whether ALT serum activity level could be used in scoring systems for resource allocation regarding patients with COVID-19 and assist in using a more personalized approach in COVID-19 patients; for example, comparing early intervention effects between patients with high and low ALT values.

Limitations

This was a dataset collected from a single tertiary hospital and the first to treat COVID-19 patients in the country. Thus the patient population might not perfectly reflect the global COVID-19 patient population, impeding the study's external validity.

This was a retrospective historical cohort, it is liable to documentation errors and classification bias, and although patients with ALT levels exceeding 40 IU/L were excluded from the study, it is possible that some patients suffered from undiagnosed liver disease and still had an ALT within normal limits and thus were not excluded from the study.The retrospective nature of this study enables us to only suggest an association between low ALT and worse outcomes.

Finally, the COVID-19 pandemic is an ongoing and evolving matter even these days, and changes in treatment protocols and new drugs developed are frequent. Thus some patients in this cohort might have experienced different outcomes if admitted today.

Conclusions

Low ALT levels were found to be associated with a worse prognosis in COVID-19 patients. This is consistent with the surmounting evidence of the importance of ALT as a surrogate marker for sarcopenia and frailty. In face of its accessibility and ease of use, pre-morbid ALT levels should

be incorporated into risk stratification tools for COVID-19 patients. This information is expected to both serve clinicians and researchers in face of next COVID-19 waves of pandemic and we offer this concept to be implemented also in case other viral pandemics will arise.

Ethics approval

This study was approved by the Chaim Sheba Institutional Review Board (Approval # SMC-20-7705).

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. New England Journal of Medicine 2020;382(8):727–33.
2. Garg S, Kim L, Whitaker M, O'Halloran A, Cummings C, Holstein R, et al. Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019 - COVID-NET, 14 States, March 1–30, 2020. MMWR Morb Mortal Wkly Rep 2020; 69(15):458–64.
3. Petersen E, Koopmans M, Go U, et al. Comparing SARS-CoV-2 with SARS-CoV and influenza pandemics. Lancet Infect Dis 2020; 20(9):e238-e244.
4. Goetz LH, Schork NJ. Personalized medicine: motivation, challenges, and progress. Fertil Steril 2018;109(6):952-963.
5. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al. Comorbidity and its impact on 1,590 patients with Covid-19 in China: A nationwide analysis. Eur Respir J 2020; 55(5):2000547.
6. Marhl M, Grubelnik V, Magdič M, Markovič R. Diabetes and metabolic syndrome as risk factors for COVID-19. Diabetes Metab Syndr 2020;14(4):671–7.
7. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: Evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56(3):M146-M156.
8. Marty E, Liu Y, Samuel A, Or O, Lane J. A review of sarcopenia: Enhancing awareness of an increasingly prevalent disease. Bone 2017; 105:276-286.
9. Picca A, Coelho-Junior HJ, Cesari M, et al. The metabolomics side of frailty: Toward personalized medicine for the aged. Exp Gerontol 2019;126:110692.
10. Cox MM, Nelson DL. Lehninger Principles of Biochemistry. Sixth. New York, United States: W.H.Freeman & Co Ltd; 2013. 664–665 p.
11. 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):386.
12. 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. J Gerontol A Biol Sci Med Sci 2018;73(7):925–30.
13. Kashkosh R, Gringauz I, Weissmann J, Segal G, Swartzon M, Adunsky A, et al. Prerehabilitation alanine aminotransferase blood levels and one-year mortality rates in older adults following hip fracture. Int J Rehabil Res 2020;43(3):214–8.
14. le Couteur DG, Blyth FM, Creasey HM, Handelsman DJ, Naganathan V, Sambrook PN, et al. The Association of Alanine Transaminase With Aging, Frailty, and Mortality. J Gerontol A Biol Sci Med Sci 2010;65(7):712–7.
15. Ramaty E, Maor E, Peltz-Sinvani N, Brom A, Grinfeld A, Kivity S, et al. Low ALT blood levels predict long-term all-cause mortality among adults. A historical prospective cohort study. Eur J Intern Med 2014; 25(10):919–21.
16. Ruhl CE, Everhart JE. The Association of Low Serum Alanine Aminotransferase Activity With Mortality in the US Population. Am J Epidemiol 2013;178(12):1702–11.
17. 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.
18. Portal D, Hofstetter L, Eshed I, Dan-Lantsman C, Sella T, Urban D, et al. L3 skeletal muscle index (L3SMI) is a surrogate marker of sarcopenia and frailty in non-small cell lung cancer patients. Cancer Manag Res 2019;11:2579–88.
19. Peltz-Sinvani N, Klempfner R, Ramaty E, Sela BA, Goldenberg I, Segal G. Low ALT Levels Independently Associated with 22-Year All-Cause Mortality Among Coronary Heart Disease Patients. J Gen Intern Med 2016;31(2):209-214.
20. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. JAMA 2020; 324(8):782–93.