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Upper Normal Limits of Serum Alanine Aminotransferase in Healthy Population: A Systematic Review

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ABSTRACT

BACKGROUND

Measuring serum alanine aminotransferase (ALT) enzyme is a routine clinical test commonly used to evaluate abnormalities in the body in general, and in the liver function in particular. Higher ALT levels are associated with some metabolic disorders. The upper limit normal (ULN) is considered as a reliable threshold for the definition of high ALT.

OBJECTIVES:

To assess the existing evidence on the ULN for ALT in the general population.

DATA SOURCE:

PubMed (Medline), EMBASE, Scopus, and Web of Science (ISI) were searched using a specified search strategy.

ELIGIBILITY CRITERIA:

We collected documents published from 1980 to 2018 in the English language, focusing on human samples at the population level and extracted the data after qualitative evaluation.

METHODS

We conducted this study in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement. We used specific search terms and their combinations to find documents from relevant databases. We used a snowballing approach to find documents not captured in the main phase of the search. Two authors separately conducted the search, screened the articles, and selected documents that were qualified for data extraction based on the defined inclusion criteria. Finally, data extraction was conducted by two authors using PRISMA checklist. Reported ULNs for ALT and 95% confidence intervals (CIs) were documented in previously developed datasheets.

RESULTS

Out of 15242 studies, 47 articles were included for data extraction and analysis. Data were sparse and lacked the consistency to precisely estimate ULN for serum ALT. The ULN of ALT was significantly diverse across various geographical locations and sexes. The lowest value of ULN for ALT was 19 IU/L in Chinese children (age range: 7 to < 10 years), and the highest value of ULN for ALT was 55 IU/L in children from Ghana aged < 5 years.

LIMITATIONS:

The main limitation of the current systematic review was the scarcity of the reported measures for ULN of ALT.

CONCLUSION

Based on the results of the current systematic review, it is suggested that the normal range of ALT be redefined, but this redefinition should be done according to the localized data. In order to redefine the ULN for ALT, regional differences, methods used in ALT measurements, and ULN determination should be considered.

KEYWORDS:
Alanine Transaminase, Alanine Aminotransferase, SGPT, ALT, Liver Enzymes

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INTRODUCTION

Measuring liver aminotransferase enzymes levels is an integral part of the screening and diagnosis of liver disease. Liver injury, in any form and duration, finally results in an increase in the plasma level of liver aminotransferases. The aspartate aminotransferase (AST) is found in the liver, cardiac and skeletal muscles, kidneys, brain, and pancreas, in descending order. The highest level of alanine aminotransferase (ALT) enzyme is found in the liver, although non-hepatic causes of ALT elevation may also occur during myopathies.[1]

ALT enzyme is commonly used to diagnose liver injuries and evaluate overall health. Among different liver-related enzymes, ALT is probably the most specific predictor of liver damage, due to its exclusive production site, which is the liver. Therefore, it is necessary to define a clear-cut uniform upper normal range for ALT. Liver cell injuries are responsible for most, but not all the cases of increased ALT levels.[2-5] Studies show a possible association between ALT and the components of metabolic syndrome, i e, fasting blood glucose, and serum lipoproteins. People with persistently elevated ALT are at higher risk of metabolic syndrome.[6] Elevated ALT is assumed as a predictor of metabolic syndrome or type 2 diabetes.[2,4,5] In addition, previous evidence showed a positive relationship between ALT and overall mortality. Strong population-based studies suggest ALT as a measure of overall survival and mortality risk.[7,8]

There are controversies regarding the upper limit of normal (ULN) definition and measurement of ALT across insurance companies, health-care providers, and internists, and thus, there is no unique consensus on the ULN of ALT. A 2-fold variation is reported in different reference values.[9,10]

The ULN for ALT was estimated to be 40 IU/mL based on older population-based studies in which liver biopsy was not performed, and liver inflammation due to viral hepatitis infection and fatty liver disease were not considered.[8,11] Further studies suggested lower healthy ALT levels.[12] Clinical studies suggested that the current thresholds for ALT were not adequately effective to distinguish liver abnormalities and to evaluate disease progression in patients with chronic liver conditions such as fatty liver disease.[13] Several studies investigated the distribution of ALT in different populations to define reference values and variations at individual level.[12] The exact level of ALT to be considered clinically normal is still doubted, and lab techniques could also affect the reported level of ALT.[14]

In this systematic review, we aimed at gathering data from studies that investigated the reference ranges of ALT in human samples and updating the definition of ULN for ALT based on these studies.

MATERIALS AND METHODS

Protocol

Prospective, retrospective cohorts studies with population-based controls, and cross-sectional population-based studies were evaluated. Reviews and animal studies were excluded. In order to collect all eligible documents that might have been missed by the search strategy, the reference lists in the retrieved articles, reviews, and textbooks were searched and evaluated in this systematic review.

Eligibility criteria

All population-based studies assessing ALT level in the general adult population through any diagnostic blood tests were examined in this review. Adult general population refers to individuals older than 18 years old without reference to any specific characteristic and with the same male to female ratio.

Information sources

PubMed (Medline), EMBASE, Scopus, and Web of Science databases were searched using the search strategy considering Cochrane and PubMed subject filtering guidelines.[15,16] In addition to the above-mentioned databases, the grey literature; i e, thesis databases, and Google Scholar were also searched.

Study selection

The search results from all databases were combined in an EndNote file, and duplicates were excluded. Two separate reviewers evaluated the documents to be included based on their titles/abstracts. The kappa statistics was used to calculate the degree of agreement between the two reviewers (kappa = 67%). The quality of included studies was assessed by two review authors

using a modified STROBE checklist. Any disagreement was resolved by consensus.

Data extraction

Data extraction forms were designed according to the PRISMA guideline 17 to extract the following data from the selected articles: study design, publication date, sample size, demographic and anthropometric characteristics of participants, mean values or ULN for ALT, and 95% confidence intervals (CIs) (if available).

RESULTS

Following the defined search strategy, 15282 articles were collected for review. After removing duplicates, by screening titles and abstracts, out of 123 remaining documents, 50 studies were selected for full-text appraisal. After quality assessment, 47 qualified articles reporting either mean or ULN for ALT level, were evaluated at the final step (Table 1).[7, 12-14, 18-58] This process was summarized in a flowchart (Figure 1).

Overall, 14 studies reported mean ALT and 41 reported ULN (Table 1). The study participants were selected from the general population only in four studies.[7, 25, 33, 44] The study participants were among healthy blood donors or liver donors in 15 studies.[13, 19-21, 23, 24, 31, 32, 34, 35, 37-39, 46, 59]

The lowest ULN in the overall population, males and females, was 19 in children (age range: 7 to < 10 years from China,[59] followed by 17.1 in the subjects aged 9-18 years from Sweden,[43] and 17.0 in people with the mean age of 52 ± 13.1 years from Taiwan.[49] Moreover, the highest ULN was 55.0 in a population aged < 5 years from Ghana,[60] followed by 65.0 in children < 1 year old from Pakistan in both male and female participants.[30, 49]

Measures of dispersion were not adequately reported in selected studies; therefore, a meta-analysis could not be performed.

DISCUSSION

Overall, the current systematic review found 47 articles reporting either upper normal limit or mean ALT level. Almost in all studies, female participants had lower ULN than male participants. Although there were diversities in the reported ALT levels, in most studies, the ULNs were lower than the current standard limits both in male and female participants. Most studies suggested some adjustments to the current thresholds of ALT to provide a more effective tool to screen liver cell injuries, particularly non-alcoholic fatty liver disease (NAFLD).

The ALT activity depends on demographic variables such as sex, age, height, weight (mainly in men), and the use of specific medications.[8, 30, 49] The variations in the reported ULNs might not be totally due to regional differences. In other words, since some of the studies selected their participants from specific groups such as hospital inpatients or blood/liver donors, their results cannot be generalized to the total population. As mentioned by Neuschwander-Tetri and colleagues,[10] utilization of blood samples obtained from frequent blood donors to calculate ALT normal thresholds might result in misleading thresholds.

Some studies excluded participants with particular characteristics; i e, people with very high or very low body mass index (BMI) or the ones with any kind of chronic conditions. Prati and others, [13] in a study on blood-bank records recommended that people with an elevated BMI, waist-to-hip ratio, or any components of metabolic syndrome should not be included in the reference population when defining the healthy ALT range.

The need for redefining ULN for ALT originates from the need to reassess the sensitivity and specificity of liver enzymes in screening patients with hepatitis B virus (HBV) or hepatitis C virus (HCV) infections, or NAFLD. The current "normal" range of ALT may underestimate the presence of these common causes of liver inflammation and chronic liver disease.[61]

Different definitions of "normal" persons to be included in the study population are one of the key parts that cause variations in ULN for ALT in different studies. For example, in a large population-based retrospective study by Kariv and co-workers, [12] the objective was to show the "healthy" ULN for ALT in Israel. The study information was gathered from medical records of about 272.000 participants. Three groups were defined. Group 1 consisted of the total population of 272.273 subjects. Group 2, which included 87.020 subjects, comprised the total population after exclusion of subjects with abnormal values in at least one laboratory parameter, medical diagnoses that might affect liver function tests, or a medication profile consisting of potentially hepatotoxic drugs. Subjects with abnormal levels of serum triglycerides, cholesterol, glucose, or

Table 1: Characteristics of studies that had reported mean ALT (ALT level IU/L)

Country	Author	Year	ULN definition method	Samples and inclusion criteria	Analyzer/ Kit	Samples			Age	Mean			ULN		
						overall	Male	Female	Range/ Mean	overall	Male	Female	Overall	Male	Female
USA	Ruhl, C.E.[44]	2012	ROC curve	General population	Hitachi model 917 multi-channel analyzer	18,518	-	-	46.5 ± 6.4	-	-	-	-	29.0	22.0
Korea	Kang, H.S.[53]	2011	95th percentile	Healthy cohort	-	7,403	-	-	48.0 ± 12. 3	-	-	-	-	31.0	23.0
	Park, H.N.[40]	2012	95th percentile	Healthy subjects with normal weight	ADI-VIA1650 analyzer	27,913	-	-	20-69	-	34.0	25.0	-	-	-
	Kim, H. C.[7]	2004	ROC curve	Prospective cohort study (Health insurance data)	-	142,055	-	-	35-59	-	-	-	-	30.0	< 30
	Sohn, W.[46]	2013	95th percentile	Healthy blood donors	-	411,240	-	-	24.6 ± 6.4	-	-	-	-	34.0	24.0
	Park, S.H.[41]	2012	95th percentile	Cross-sectional	-	3,316	-	-	10 - 19	-	53.0	30.0	-	33.0	25.0
	Lee, J.K.[35]	2010	97.5th percentile	Healthy liver donors	TBA 200FR NEO auto analyzer (Toshiba, Tokyo, Japan)	1,105	643	462	29.1 ± 9.0	-	-	-	-	35.0	26.0
Taiwan	Wu, W.C.[49]	2012	95th percentile	Cross-sectional (large-scale population based)	-	34,346	-	-	52.4±13.1	-	-	-	-	21.0	17.0
	Lai DS.[1]	2009	97.5th percentile	students and their teachers	-	4,326	2138	2188	-	-	-	-	38.0	41.0	36.0
				Teachers	-	348	-	-	20 ≤	-	-	-	49.1	-	-
				Healthy students/ children	-	325	-	-	13 - 15	-	-	-	29.7	-	-
						1,624	-	-	9 - 12	-	-	-	29.6	-	-
						2,029	-	-	3 - 6	-	-	-	24.0	-	-
China	Zheng, M.H.[52]	2012	95th percentile	Cross-sectional	Hitachi 7600 automatic Analyzer (Hitachi, Japan)	53,037	-	-	19 - 44	-	35.0	23.0	-	-	-
	Zhang, G.M.[50]	2014	97.5th percentile	Healthy population	-	54,912	-	-	65 – 104	-	-	-	-	47.3	45.2
	Zhang, P.[51]	2015	ROC curve	Non-random samples	-	37,69	-	-	45.0± 19.0	-	-	-	-	22.15	22.40
UK	Mijovic V.[2]	1987	Not reported	Frequent blood donors	Epos automated clinical analyzer at 37°C	2023									

Country	Author	Year	ULN definition method	Samples and inclusion criteria	Analyzer/ Kit	Samples			Age		Mean			ULN		
						overall	Male	Female	Range/ Mean	over-all	Male	Female	Overall	Male	Female
UK	Mijovic V.[2]	1987	Not reported	Frequent blood donors	Epos automated clinical analyzer at 37°C	2023	1088	935	18-65	18.0 ± 12.8	22.3 ± 14.7	13.4 ± 7.7	-	-	-
							200	247	18-25	-	20.0 ± 13.3	12.4 ± 6.8	-	-	-
							292	240	26-35	-	22.5 ± 9.5	13.2 ± 7.1	-	-	-
							317	235	36-45	-	24.1 ± 17.2	13.7 ± 9.0	-	-	-
							191	126	46-55	-	20.6 ± 9.9	14.5 ± 8.9	-	-	-
							88	74	56-65	-	20.3 ± 9.7	14.9 ± 5.9	-	-	-
	Goldie D.J.[3]	1990	97.5th percentile	Blood donors	Technicon SMAC 1 analyzer at 37°C	-	209	155	Mean =31	-	20.1	14.1	-	65.0	32.0
				Plasma-pheresis donors		-	374	193	Mean =33	-	23.4	15.2	-	62	46.0
Italy	Prati, D.[13]	2002	95th per-centile	Blood donors with low risk of liver disease	Olympus AU510 Analyzer	6,835	3865	2970	29.8 ± 9.5	-	17.6 (17.4-17.9)	11.0 (10.7-11.3)	-	30.0	19.0
	Vespa-siani-Gentiluc-ci, U.[48]	2014	Not reported	Large-scale study	-	44,232	-	-	18 ≤	-	28.0	20.0	-	-	-
	Dorizzi, R. M.[4]	1991	97.5th percen-tile	Blood donors		314	209	105	-	-	21.4	14.7	-	42.0	28.0
						311	206	105	-	-	20.0	12.1	-	43.0	23.0
Morocco	Laouina, A.[34]	2012	Not reported	Healthy blood donors	Kinetic method using flat-bottomed micro-plate tech-niques	14,071	-	-	18-60	-	-	-	-	64.0	52.0
Germany	Grunen-berg, R.[24]	1995	Not reported	Healthy blood donors	-	5,706	-	-	Adults	-	-	-	-	45.0	45.0
	Brink-mann, T.[19]	2003	Linear regres-sion model	Healthy blood donors	-	333	-	-	-	-	-	-	-	43.9	34.4
Spain	Lozano, M.[37]	1998	97.5th percen-tile	Healthy blood donors	-	1,036	579	457	18 - 65	-	-	-	-	56.0	34.0
Milan, Beijing, Bursa, Nordic Countries	Ceriotti, F.[14]	2010	97.5th percen-tile	Non-random laboratory samples	-	765	-	-	18 - 85	-	-	-	-	59.0	41.0
Finland	Leino, L.[36]	1995	Trans-formed 97.5th percentile	General popula-tion	-	954	-	-	27-67	-	-	-	-	50.0	38.0
Sweden	Rodoo P.[5]	2013	97.5th percen-tile	Healthy individu-als	-	157	-	157	8≤	-	-	-	-	-	22.9
						173	173	-	9-18	-	-	-	-	17.1	-
						356	-	-	-	-	-	-	30	-	-

Country	Author	Year	ULN definition method	Samples and inclusion criteria	Analyzer/ Kit	Samples			Age		Mean			ULN		
						overall	Male	Female	Range/ Mean	over-all	Male	Female	Overall	Male	Female
Sweden	Helmersson-Karlqvist, J.[25]	2016	97.5th percentile	General population	-	531	265	266	80	-	-	-	-	35.9	34.12
Denmark	Hilsted L.[6]	2013	97.5th percentile	Healthy individuals	-	84	36	48	5 - 6	-	-	-	24	24.0	24.0
						228	93	135	7 - 8	-	-	-	28	28.0	35.0
						362	158	204	9 - 10	-	-	-	35	37.0	32.0
						391	164	227	11 - 13	-	-	-	32	37.0	33.0
						198	83	106	14-16	-	-	-	31	31.0	32.0
						167	62	105	17-19	-	-	-	43	64.0	31.0
Palestine	Kariv, R.[12]	2006	95th percentile	Lab-based study	-	17,496	-	-	15-90	-	22.7	16.7	-	44.9	31.8
Saudi Arabia	Alhamoudi, W.[18]	2013	ROC curve	Healthy Liver donors	-	175	-	-	29.9 ± 7.3	-	25.4	17.7	-	33.0	22.0
Ghana	Dosoo DK.[7]	2014	97.5th percentile	General population	-	491	-	-	< 5	-	-	-	55.0	-	-
						473	-	-	5 - 12	-	-	-	53.0	-	-
						281	-	-	13 - 17	-	-	-		61.0	48.0
						57	31	26	Infants	-	-	-	24.8	22.1	27.3
Iran	Jamali, R.[28]	2008	95th percentile	Case-control (normal weight & non- diabetic)	-	859	-	-	18 - 75	-	-	-	-	37.5	36.0
	Khedmat, H.[31]	2007	33.33 and 66.66 Tertiles	Healthy blood donors	-	934	-	-	18 - 68	-	33.1	-	-	35.0	-
	Mohamad nejad, M.[39]	2003	95th percentile	Healthy blood donors, normal weight	-	1,939	-	-	-	-	21.0	16.4	-	40.0	34.0
	Kabir, A.[29]	2013	95th percentile	Healthy populations	Hitachi 704 auto analyzer, (To¯kyo, Japan) with Pars Azmoon Reagents kit (Tehran, Iran).	1,309	-	-	50 <	-	-	-	-	21.4	18.8
	Poustchi, H.[42]	2011	95th percentile	Healthy school children	-	975	-	-	7 - 18	-	-	-	-	30.0	21.0
Pakistan	Khan, F. A.[8]	1997	97.5th percentile	Healthy individuals	-	90	-	-	< 1	-	-	-	-	65.0	65.0
						370	-	-	1 - 10	-	-	-	-	52.0	49.0
						-	-	-	11 - 14	-	-	-	-	45.0	43.0
						1,452	-	-	15-40	-	-	-	-	42.0	41.0
						-	-	-	41 - 60	-	-	-	-	41.0	40.0
						203	-	-	61 - 80	-	-	-	-	40.0	40.0
	Ibrahim K.[9]	1988	97.5th percentile	Healthy individuals	Hyland Kit	202	114	88	15 ≤	-	-	-	-	48.0	50.0
						137	74	63	< 15	-	-	-	-	41.0	44.0

Country	Author	Year	ULN definition method	Samples and inclusion criteria	Analyzer/ Kit	Samples			Age	Mean			ULN		
						overall	Male	Female	Range/ Mean	overall	Male	Female	Overall	Male	Female
India	Choudhary, N.S.[20]	2014	Linear regression	Healthy donors	pyrodoxal [5] phosphate (lactate dehydrogenase/ nicotinamide adenine dinucleotide) reflectance spectrophotometry method on Vitros instrument (Johnson and Johnson USA)	331	147	184	35.7± 10.2	-	-	-	-	35.0	28.0
	Kumar, S.[32]	2013	Not reported	Healthy blood donors	Olympus AU400 auto-analyzer (Mishima Olympus Co. Ltd., Shizuoka-ken, Japan	5,077	-	-	18-60	-	-	-	-	30.0	19.0
	Mohan P.[10]	2016	97.5th percentile	Healthy population	Sysmex XN 3120 7 Part cell Counter (Kobe, Japan)	2600	132	104	20-35	-	-	-	-	22.23± 2.83	19.22± 3.30
							30	34	36-50	-	-	-	-	21.10± 2.68	19.76± 3.22
							21	23	>50	-	-	-	-	20.71± 3.33	19.30± 3.66
Australia	George, J.[22]	2008	95th percentile	Healthy students	-	496	292	204	15y	-	-	-	-	59.0	54.0
	Van Der Poorten, D.[47]	2007	95th percentile	Healthy adolescents	Beckman Synchron LX 20	209	-	-	12 -19	-	-	-	-	28.0	-
Eritrea	Achila, O.O.[55]	2017		Healthy elderly subjects	Beckman Coulter: AU 480 Chemistry System	249	116	133		16.6 (16-17.7)	17 (15.8-18.2)	16.7 (15.5-18)			
Ethiopia	Abebe, M.[54]	2018		Healthy Young, adult, blood donors	Mindray BS-200E (Shenzhen Mindray Bio-medical electronics co.ltd, China)	1175	644	531	20 (18-22)	15.71 (15.22-16.24)	17.15 (16.5-17.88)	13.97 (13.34-14.74)			
China	Li X*	2018	nonparametric method	healthy children aged from 2 to 14 years	Hitachi 7600-210 automatic biochemical analyzer	196			2				24 (22-26)		
						663			3 to < 6				23 (21-24)		
						275			7 to < 10				19 (16-22)		
						113			11 to < 14				25 (15-33)		
	Li, Y.[58]	2018	97.5th percentile	Children aged 12–18 years old at the Health Management Center	Architect C-8000 (Abbott laboratories, USA) automated chemistry analyzer	1682			12-18				41.5	42.8	32.8

Country	Author	Year	ULN definition method	Samples and inclusion criteria	Analyzer/ Kit	Samples			Age	Mean			ULN		
						overall	Male	Female	Range/ Mean	overall	Male	Female	Overall	Male	Female
Germany	Bussler, S.[56]	2018	97th percentile	Primarily healthy children and adolescent	cobasR analyzer series (photometric measuring unit, c-module, Roche Diagnostics GmbH, Mannheim, Germany).	3131	1663	1468	11 months to 16 years					29.9-38	24.2-31.7

hemoglobin A1c (HbA1c) were not excluded from this group. Group 3, with 17.496 subjects, comprised only the subjects from group 2 with normal values of triglycerides, cholesterol, glucose, and HbA1c, and thus it included a 'healthy' population. The 95th percentile ALT values in the groups 1, 2, and 3 were respectively 50.1 IU/L (40.6 for females; 60.8 for males), 40 IU/L (32.4 for females; 48 for males), and 37.5 IU/L (31.8 for females; 44.9 for males).

In addition to the known variables such as sex, age, weight, socioeconomic status, and nutritional habits, [13, 44, 62] there were other probable confounding factors that would make the results inconsistent. In this regard, Dutta and colleagues mentioned the variety of commercial kits used to evaluate ALT levels as a possible influential factor in the variation of reported ALT normal limits.[63] Table 1 shows similar diversities in laboratory kits used in different studies enrolled in the current systematic review.

On the other hand, the methodologies used to compute these thresholds were also debatable. Most studies either used the receiver operating characteristic (ROC) curve method or considered 97.5th or 95th percentile to define ULNs (Table 1).

Different studies listed a variety of factors that could modulate the ALT activity and proposed to consider the variables in defining the normal range of ALT. The mentioned variables that may influence the ALT level were age, sex, waist circumference, and BMI. Some authors suggested that factors such as lipid profile; i e, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglyceride, fasting glucose and insulin level, viral profile; i e hepatitis B surface antigen (HBsAg) and anti-HCV Ab, alcohol consumption, and the use of potentially hepatotoxic medications should be considered in defining the healthy reference population participating in the calculation of the ULN for ALT.[13, 47, 49]

Besides the observed differences between reported ULNs for ALT and its current standard limits in most studies, there were variations in the results of studies from the same country, as well. Some evidence peculated the influence of ethnicity on ALT levels in a healthy population, although there were some contradictory discussions regarding this issue. [63, 64] As mentioned before, these diversities might be related to the source cohorts of studies samples.[64] Due to the growing prevalence of obesity and metabolic syndrome, in which the hepatic component presents as NAFLD and may cause an asymptomatic rise in ALT, it is worthwhile to consider the association between BMI and ALT levels in calculating the normal range for ALT. As an example, among the studies conducted in Iran, one study recruited its participants from a general population with BMI ranging from low to high, while the others restricted their participants only to individuals with normal BMI levels. [28, 29, 31, 39, 42]

Many authors suggested that the currently used ULN for ALT does not make an exact clear-cut and true discrimination between the presence and absence of liver disease. Many patients with mild chronic liver disease are not detected using the current ULN for ALT test. More than half of patients with NAFLD, which is now recognized as one of the most common causes of chronic liver disease and cirrhosis in many parts of the world, have serum ALT levels within the current normal limit. Moreover, various population-based studies showed that increased serum ALT levels might be independently

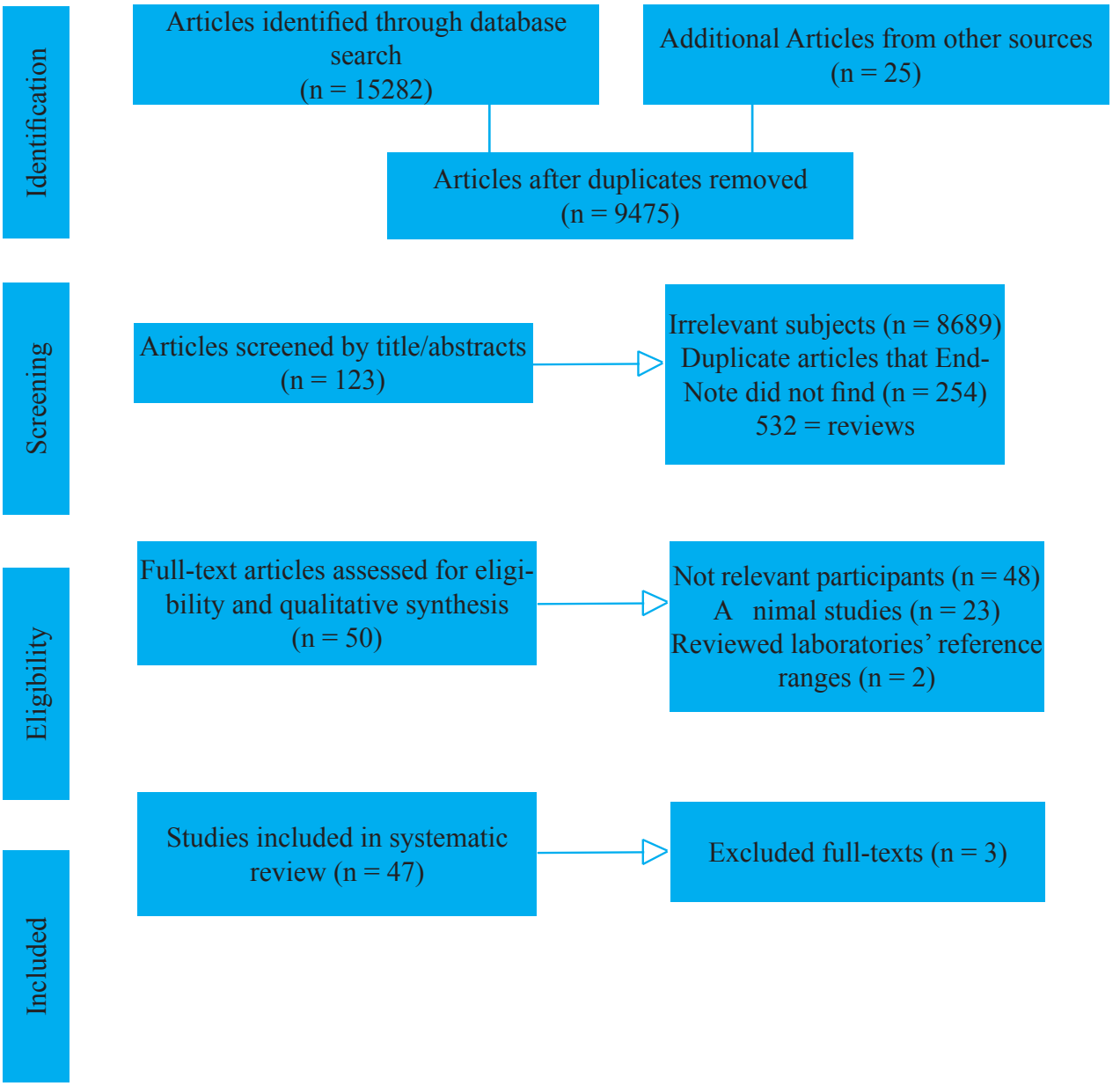

Fig.1: **The process of selection eligible studies**

related to increased risk of mortality, even within the normal range of ALT level.[53, 65] One recent study showed that people with no liver disease and a slightly elevated, but still normal ALT level, seemed to have an increased all-cause mortality rate.[66] However, some other studies showed that normal ALT levels were protective. It is important to have a clear definition of normal and abnormal ALT tests to better interpret the results of such studies.

Strengths and limitations

To the best of the authors knowledge, the current study was the first systematic review in this field.

One limitation of the current review was the number of studies reporting CIs for the estimated ULN in healthy individuals. This withheld authors to perform a meta-analysis to determine a combined weighted value for ULN. Another limitation of the current systematic review was the restriction of this review to studies with healthy samples. This might cause incomplete retrieval of relevant

studies. Defining criteria for a healthy individual might be different from one study to another.

CONCLUSION

Since several factors affect ALT level among apparently healthy individuals and even in the tested healthy people, it seems impossible to internationally determine a reliable ULN for serum ALT to be used in all laboratories. There is a need for designing and conducting nationwide studies with identical inclusion criteria to provide reliable and large domestic datasets and estimate a reliable ULN for ALT.

ETHICAL APPROVAL

There is nothing to be declared.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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