Invited critical review

Upper limit of normal for alanine aminotransferase: Quo vadis?

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Abstract

Several studies suggest that a substantial number of patients with normal serum alanine aminotransferase (ALT) levels, defined by current thresholds, have ongoing hepatic necro-inflammation and fibrosis, and are at risk of liver disease progression. A major problem lies in the definition of normality. The current upper limit of normal (ULN) for ALT was established in the 1980s when reference populations were likely to include many persons with hepatitis C virus infection and nonalcoholic fatty liver disease. Because ALT may be influenced, not only by liver disease, but also by other medical conditions, changing lifestyle factors and demographic determinants, the current ALT ULN threshold has recently been challenged. This review not only highlights current evidence on why and how ALT ULN should be redefined, but also discusses the current concerns about updating the ULN threshold for ALT.

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1. Introduction

The cutoff serum alanine aminotransferase (ALT) value to be used to discriminate between healthy and diseased livers has not been clearly defined. Several studies have recently questioned whether previously established values defining the upper limit of normal (ULN) for ALT are sufficiently sensitive, and have suggested that the ULN should be revised. This review highlights the evidence for a redefinition of ALT ULN, and also discusses the current skepticism.

2. Point: why and how ALT ULN should be redefined

The serum ALT value has long been used as a surrogate marker of liver injury [1]. Thus it is the most widely used laboratory parameter...
for the evaluation of liver disease in daily clinical practice. However, the available literature indicates that the ALT values do not correlate well with the severity of liver disease as found by liver biopsy in subjects with chronic liver diseases of different etiologies [1–11]. This is particularly true when the stage of fibrosis present in an individual patient is considered. A major problem lies in the definition of normality [2]. Several studies suggest that many patients with normal serum ALT levels by current thresholds, have ongoing hepatic necro-inflammation and fibrosis, and are not truly healthy [1–11].

The current ULN threshold for ALT is usually set at around 40 IU/L, although there may be slight variations among different laboratories [12]. Most of the ULN thresholds were computed in the 1980s when ALT testing was introduced as a surrogate marker for the screening of non-A, non-B hepatitis among blood donors. However, they were established before anti-hepatitis C virus (HCV) testing and before the introduction of restrictive behavior for blood donors [12,13], and were set at the 97.5th percentile of the “healthy reference population” [14]. Furthermore, the “reference” populations were likely to include many persons with nonalcoholic fatty liver disease (NAFLD), now recognized as the most prevalent cause of chronic liver disease in developed countries [15–17]. Because ALT may be influenced, not only by liver disease, but also by demographic, anthropometric and metabolic characteristics [12,18], the ALT threshold that discriminates between healthy and diseased livers has recently been challenged [8,12,19–21]. Compounding this problem is the fact that the laboratories, in general, do not have a well-defined healthy group prescreened by physicians from which to compute reference intervals [22]. In contrast, the National Health and Nutrition Examination Survey (NHANES) data, with extensive subject compute reference intervals [22]. In fact, there is poor correlation between the degree of liver-cell damage and the level of aminotransferases [14]. Accordingly, their absolute elevations are of little prognostic value [32].

The half-life of total AST released in the blood is 17 ± 5 h, whereas that of ALT is 47 ± 10 h [31]. Typically AST is increased to a greater degree than ALT in the very acute stages of hepatocellular injury, as with acetaminophen or ischemic liver injury [33]. Recognition of this ratio often provides a clue to the presence of one of these two etiologies. Within 24 to 48 h, particularly if ongoing damage occurs, ALT will become higher than AST, because of its longer plasma half-life. In chronic hepatocellular injury, ALT is usually more elevated than AST. However, as fibrosis progresses, ALT activities typically decline, and the ratio of AST to ALT gradually increases, so that by the time cirrhosis is present, AST is often higher than ALT [34,35]. Of note, an increasing AST/ALT ratio is relatively specific for the development of cirrhosis in patients with HCV infection, and may be present long before clinical symptoms of decomposition develop. The reason for the increase in the AST/ALT ratio with increasing fibrosis and cirrhosis is not known. It has been suggested that sinusoidal liver cells have a role in the clearance of AST from the serum [36]. Therefore, it is possible that with progressive fibrosis and cirrhosis, the sinusoidal function is progressively impaired, resulting in a relative increase in the serum AST levels. One notable exception to the predominance of serum ALT activity in chronic liver disease is alcoholic hepatitis. The high AST/ALT ratio seen in alcohols is partly attributable to low P-5′-P, which in animal models is associated with decreased ALT activities [37]. It may be that modern AST and ALT assays, being preincubated with P-5′-P, do not show this increased AST/ALT ratio. However, Matloff et al. [38] showed that the correction of plasma P-5′-P does not eliminate the high AST/ALT ratio in alcoholic hepatitis. Yet, alcohol increases mitochondrial AST activity in plasma, whereas other causes of hepatitis do not [39]. While most forms of liver injury decrease the hepatocyte activity of both cytosolic and mitochondrial AST, alcohol produces a decrease only in cytosolic AST activity [40].

3. Physiology of aminotransferases

Injury to the liver, whether acute or chronic, eventually results in an increase in serum concentrations of aminotransferases. The aspartate aminotransferase (AST) and ALT are abundant hepatic enzymes that catalyze the transfer of alpha-amino groups from aspartate and alanine to the alpha-keto group of ketoglutaric acid to generate oxaloctic and pyruvic acids, which are important contributors to the citric acid cycle [23]. Both enzymes require pyridoxal-5′-phosphate (P-5′-P) for maximum activity, though the effect of deficient P-5′-P on ALT is greater than the effect on AST [24].

AST is found, in decreasing order of concentration, in the liver, cardiac muscle, skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes, and erythrocytes [14]. The highest level of ALT is in the liver, and levels of this enzyme are generally considered specific for hepatocellular injury [14]. However, serum ALT elevation can occur in nonhepatic conditions such as myopathic diseases including dermatomyositis, polymyositis, and muscular dystrophy [25,26]. In addition, serum ALT values have diurnal variation, and may be decreased by exercise [27]. Under physiologic circumstances, serum ALT has 45% variation during the day, with higher values during the day than at night and a peak time in the afternoon [28,29]. Circadian variation may be especially important when ALT values are compared in a patient with chronic liver disease who has had blood sampled at different times during the day. Serum ALT values are 20% lower in those who exercise at usual levels than in those who do not exercise or exercise more strenuously than usual [28]. Other factors known to affect ALT levels include medications and herbal supplements [30].

ALT is exclusively cytoplasmic, whereas both mitochondrial and cytoplasmic forms of AST are found in all cells [28]. The AST and ALT activities in the liver are about 7000- and 3000-fold higher than serum activities, respectively [31]. Both enzymes are released into the blood in increasing amounts when the liver cell membrane is damaged. Necrosis of liver cells is not required for the release of the aminotransferases. In fact, there is poor correlation between the degree of liver-cell damage and the level of aminotransferases [14]. Accordingly, their absolute elevations are of little prognostic value [32].

Studies of the ULN for ALT have been concerned with the interlaboratory variability [41,42]. It is important to stress that there is more variation between laboratories than between analyzers, and that the reference populations from which ULN is defined have often been poorly characterized and may have included persons with liver disease [43]. Although greater variation across analyzers is to be expected from enzyme activities than from chemical analytes, the increasing availability of commercial assays (traceable to the International Federation of Clinical Chemistry reference procedures) is eliminating, or at least greatly reducing, the dependency of test results on the method used for measurement and thus the need for separate reference intervals, unless regional population differences are present [44]. A multinational evaluation found very minor differences between three models of autoanalyzers for a reference sample with an ALT activity of 39.7 IU/L.
which is within the range of activity that is of greatest interest for determining interlaboratory agreement [45]. Thus differences in laboratory procedures explain only part of the difference in reference limits between laboratories.

Why is ULN for ALT so different between laboratories? In a brief report [41] on 11 tertiary academic laboratories looking at results on samples sent out by the College of American Pathologists (CAP) as part of proficiency testing, the primary factor contributing to the widely divergent ALT ULN values was not variability within a laboratory or variability caused by the analyzers provided by different manufacturers, but was attributed to differences in the characteristics of the cohorts used by individual laboratories to define their own reference ranges. This was also the case in a survey of 43 freestanding acute care children's hospitals in the United States [46]. Again, the wide variability in ALT ULN at children's hospitals was not attributable to the equipment or laboratory used to measure ALT activity but was most likely related to the characteristics of the populations used by individual laboratories to define their own reference ranges. However, the study by Dutta et al. [42] does not support the notion that suboptimal healthy volunteer testing is the major reason why ALT ULN is highly variable among different clinical laboratories. Their survey investigated the variability in the ULN for ALT across different community laboratories in the state of Indiana, and made several clinically important observations. First, it confirmed there was wide variability for ALT ULN across different clinical laboratories, with values ranging from 31 to 72 IU/L. Second, for a given CAP sample, there was a statistically significant analyzer-to-analyzer variability, but these differences were not clinically significant. Third, the majority of laboratories based their ULN on the manufacturers' recommendations for different analyzers, rather than on healthy volunteers (only 17%). Fourth, there was no statistically significant relationship between the method used to establish ULN and the ALT ULN values, after taking account of the type of chemical analyzer used. Thus, the findings by Dutta et al. [42] suggest that the widely variable ALT ULN could be due to variable reference intervals established by different manufacturers, and that the problem could be related to the methodology used by different manufacturers to establish their reference intervals.

4.2. Demographic characteristics

In adults, several studies have investigated the effect of age and gender on serum ALT activity [12,18,20,47–51]. In a cross-sectional study, Elinav et al. [47] collected laboratory data of 128 subjects from a home for the aged (“older subgroup”; mean age ± SD, 84 ± 8 years) and of 207 subjects from three family practices (“younger subgroup”; mean age ± SD, 52 ± 19 years). Individuals with known or suspected (according to their primary-care physician) liver disease and those taking hepatotoxic medications were excluded. The mean ALT activity level was significantly lower in the older subgroup than the younger subgroup. ALT activity linearly regressed with age. However, polynomial regression produced a better fit, creating an inverted U curve with a peak at 40–55 years. Gender was also associated with ALT (22 ± 15 IU/L in men, and 17 ± 11 IU/L in women). Data from Grossi et al. [48] showed, in part, similar results. In a subset of subjects (19,601 women and 24,945 men, 5– to 85-year old) recognized as healthy, the Authors showed an inverted U-curve pattern for the observed and predicted ALT concentrations than other anthropometric (including BMI) or metabolic variables in both genders. The risk of elevated ALT concentration increased according to the category of BMI. Compared with men of normal weight, the odds ratio (OR) for overweight men was 1.9 [95% confidence interval (CI), 1.25–2.93; P < 0.0001] and for obese men was 5.01 (95% CI, 3.49–7.21; P < 0.0001). Similarly, for women the OR were 2.44 (95% CI, 1.24–4.82; P < 0.0001) and 3.94 (95% CI, 2.18–7.13; P < 0.001). This trend did not differ after adjustment for putative risk factors including alcohol intake in men and women. These results suggested that overall obesity measured by BMI is an independent indicator of elevated ALT concentration. Nonetheless, growing evidence suggests that body fat distribution may be even more important than the grade of obesity as determined by the BMI in the relationship between body weight and potential liver damage [66–71]. It is clear that central body fat distribution [as measured by abdominal height, waist circumference (WC), or waist-to-hip circumference ratio] is different to obesity associated with increased peripheral adipose tissue. Central obesity is associated with excessive visceral adipose tissue which increases the portal free fatty acids load flowing to the liver. This provides an impetus for hepatic fat accumulation [72], which has been postulated as the most likely cause of abnormal biochemical liver tests in overweight and obese individuals [57]. In particular, measures of central obesity have been more closely associated with ALT levels and cirrhosis-related death or hospitalization than BMI [73–75]. A cross-sectional study [76] found that abdominal visceral adipose tissue (as measured by computed tomographic scanning) had a greater effect on ALT concentrations than other anthropometric (including BMI) or cardiometabolic variables among non-diabetic overweight women. In a random sample of 2704 residents in New York State (35–80 years of age, and free from known hepatic diseases), abdominal adiposity,
simply measured by anthropometry, appeared to be a slightly but consistently stronger predictor of ALT and, consequently, potential liver injury, than BMI in both genders [73].

4.4. Metabolic variables

To confirm the clinical significance of the healthy range of serum ALT levels, the characteristics of unhealthy patients with normal ALT levels need to be evaluated. These patients with ALT within the currently accepted normal range may display dyslipidemia, obesity, excess alcohol consumption, or diabetes type 2. All of these conditions are associated with the development of fatty liver disease, suggesting that an “unhealthy” normal ALT level is also indicative of hepatic inflammation due to hepatic steatosis.

In developed countries, the most common cause of elevated ALT activity, in the absence of excess alcohol consumption and viral hepatitis is NAFLD, which is now considered to be an additional component of metabolic syndrome (MetS) but also as one of the most common causes of chronic liver diseases [15–17]. In a cross-sectional study [77] in the United States aimed at determining the prevalence and possible etiology of elevated aminotransferase levels in the general population, gathered during the NHANES III 1988–1994 on individuals aged 17 years or more (N = 15,676), the prevalence of aminotransferase elevation (for men, ALT > 40 IU/L and AST > 37 IU/L; for women, both ALT and AST > 31 IU/L) was 7.9%. Aminotransferase elevation was more common in men than women (9.3% vs 6.6%), in Mexican Americans (14.9%) and non-Hispanic blacks (8.1%) compared to non-Hispanic whites (7.1%). High alcohol consumption, hepatitis B virus (HBV) or HCV infection and high (>50%) transferrin saturation were found in only 31.0% of cases. Aminotransferase elevation was unexplained in the majority (69.0%). In both men and women, unexplained aminotransferase elevation was significantly associated with total and central adiposity and other features of MetS [higher triglycerides and fasting insulin, and lower high-density lipoprotein cholesterol (HDL-C)]. It was also associated with type 2 diabetes and hypertension in women. These findings remained in subgroups who consumed no alcohol and who took no prescription medication or acetaminophen in the past month. This may imply a large reservoir of NAFLD in the general population. Subsequent results from the United States NHANES 1999–2002 [78], obtained from 6823 participants aged 20 years or older, showed that the prevalences of elevated ALT (>43 IU/L) and AST (>40 IU/L), or either ALT or AST were 8.9%, 4.9%, and 9.8%, respectively, in the entire population. The prevalence of elevated ALT and AST remained high (7.3%) even among participants without HCV antibodies or excess alcohol consumption and was strongly associated with risk factors for NAFLD.

Most subjects with NAFLD are asymptomatic, and elevated ALT levels are frequently found incidentally during routine laboratory examination or after screening for obesity-related comorbidities. Although in cross-sectional studies participants with NAFLD often have increased circulating concentrations of ALT [74,77,78], paradoxically, the full histopathological spectrum of NAFLD has been reported in patients with normal ALT activity, even after the cutoff value was decreased to ≤19 IU/L [79]. Moreover, although liver ultrasonography is widely used for diagnosing NAFLD, this method has good sensitivity and specificity only for the detection of moderate and severe hepatic steatosis, and its sensitivity is reduced when hepatic fat infiltration on liver biopsy is reduced to less than 33% [80]. Only liver biopsy can be used for diagnosing NAFLD and accurately determining the histological severity and prognosis of liver damage. Thus, some nondifferential misclassification of NAFLD on the basis of ALT and ultrasonography is likely [81]. That is, some of the study participants may not have NAFLD despite ultrasound detection of fatty liver and some may have underlying NAFLD with normal liver enzymes and negative ultrasound findings. As such, an accurate selection of reference subjects free of NAFLD is a challenge.

In addition, ALT activity is related to lipid and carbohydrate metabolism, and therefore serum ALT has been also suggested as an indicator for metabolic derangement. Studies have suggested that even high-normal ALT levels are associated with insulin resistance [21,82]. The prospective cohort study by Vozarova et al. [83] showed that ALT appears to have associations with both hepatic insulin resistance and later decline in hepatic insulin sensitivity. Moreover, the study by Burgert et al. [84] demonstrated that subtle alterations in glucose tolerance and lipid metabolism exist in those patients with higher ALT, and this is not necessarily accompanied by hepatic steatosis. Another prospective study [85] suggested that serum ALT level may be more than an indicator of liver injury due to hepatic steatosis; it might also be an early indicator of impaired insulin signaling.

Various studies have also shown that elevations in ALT, including levels lower than the ULN for ALT, are associated with MetS [21,82,86–89]. In particular, in the Korean 1998–2001 [89], 2005 [82], and 2005–2007 [21] NHANES, an increase in serum ALT level, even within the normal range, was associated with the presence of MetS. It has also been suggested that each component of MetS may have different weighting in relationship with abnormal liver enzymes in each gender. In a prospective cross-sectional study, Pan et al. [80] investigated the prevalence of MetS and risk factors for ALT as markers of hepatic injury in a large Hispanic health disparity cohort with high rates of obesity. While obesity was a strong risk for elevated ALT in both genders, hypertriglyceridemia and hypercholesterolemia were significant risk factors for males but not for females. On the other hand, high fasting glucose increased the risk of abnormal ALT in females but not in males. A number of mechanisms may explain the association of ALT with MetS. ALT activity is known to be significantly correlated with increased hepatic fat content, which worsens hepatic insulin resistance [91]. This association most likely reflects a more generalized insulin resistance. Some investigators [92] have shown a direct association between elevated ALT levels and serum C-reactive protein concentrations, raising the possibility that hepatic inflammation contributes to the low-grade systemic inflammation observed in subjects with MetS.

In children and adolescents a healthy population should also take into account any abnormality, not only of clinical variables, but also of metabolic factors independently and significantly associated with serum ALT levels.

In a cross-sectional study involving a civilian non-institutionalized population of 5586 adolescents (aged 12–19 years) in the United States NHANES 1999–2004, Fraser et al. [74] found that the strongest associations with elevated ALT (>30 IU/L) were gender (OR male vs female, 7.7), ethnicity (OR black vs white, 0.6; OR Mexican American vs white adolescents, 1.6), WC (OR per 1 SD change, 1.4; SD, 14.5 cm), and fasting insulin (OR per 1 SD change, 1.6; SD, 2.0 µIU/L). Age (OR per 1 SD change, 1.7; SD, 2.3 years), C-reactive protein (OR per 1 SD change, 1.3; SD, 4.2 mg/dL) and triglycerides (OR per 1 SD change, 1.2; SD, 1.6 mmol/L) were also positively associated with elevated ALT. These associations were similar in all ethnic groups. These findings highlight the importance of metabolic risk factors for potential liver damage even at a young age. In a cohort of 925 school children (aged 7–18 years), Poutschi et al. [93] found that independent predictors of an elevated ALT included BMI, visceral obesity (as measured by waist-to-hip circumference ratio) and levels of serum total cholesterol. In females, age was an additional inverse predictor. Visceral obesity was a stronger predictor of elevations in ALT (OR, 2.25; 95% CI, 1.4–3.56 in boys and 1.8; 95% CI, 1.16–2.8 in girls) than the BMI (OR, 2; 95% CI, 1.68–2.37 in boys and 1.61; 95% CI, 1.34–1.94 in girls). Finally, Di Bonito et al. [94] analyzed the association between ALT levels and metabolic factors in a cohort of 358 obese (BMI ≥ 95th percentile for age and gender) children (168 boys and 190 girls; mean age, 10.0 ± 3 years). Linear regression analysis showed that in obese boys WC was the only independent factor associated with ALT level. In obese girls, ALT levels were independently associated only with triglycerides.
4.5. Genetic component

As pointed out by Das [95], race has never been used to select the reference class for ALT. The significant genetic component in ALT variability among twins, even after adjustments for age, gender, BMI, and alcohol consumption [96], hints to the possibility that normal values of ALT will vary according to race and this may be an explanation for the differences in the prevalence of elevated ALT activity by ethnic group [74,77,78].

5. Proposals to redefine ALT ULN

Several authors have proposed the updating of ULN for serum ALT levels (Table 1). In 1998, in a prospective study from France investigating factors associated with ALT variability in a cohort of 1033 blood donors (mean age, 30 years), Pitton et al. [18] suggested that definitions of normal ALT values should be adjusted for gender and BMI to reduce artificial heterogeneity in blood donor selection and in hepatitis C clinical studies. They found that ALT was independently and highly associated with male gender and BMI, which explained 22% of the ALT variability.

Therefore they recommended the following limits of upper normal value: 31 IU/L for females with BMI ≤ 23 kg/m², 42 IU/L for males with BMI ≤ 23 kg/m²; 44 IU/L for females with BMI > 23 kg/m², and 66 IU/L for males with BMI > 23 kg/m².

In 2002, the study by Prati et al. [12] in a blood-bank setting from Italy extended the previously reported data by Pitton et al. [18] recommending that persons with body fat accumulation or dysmetabolic state should not be included in a reference population for calculations of healthy ALT values. In a multivariate analysis of 6835 blood-donors (mean age ± SD, 29.8 ± 9.5 years) presenting for donation for the first time and undergoing clinical and laboratory examinations, ALT levels correlated strongly with BMI and correlated less robustly with serum triglyceride levels in both men and women. ALT levels correlated directly with cholesterol levels in men and glucose level and the use of contraceptive drugs among women. They then calculated “healthy” ranges for serum ALT levels in a population at lowest risk for subclinical liver disease by retrospectively considering blood donors who satisfied the following criteria: normal BMI (<25 kg/m²); normal serum triglyceride (<200 mg/dL); cholesterol (<220 mg/dL), and glucose (<105 mg/dL) levels; and absence of concurrent medication use. Among the 3927 persons (1995 men and 1932 women) at lowest risk for liver disease, the values of the 95th percentiles were 30 IU/L for men and 19 IU/L for women. These revised ALT ULN values were lower than those previously established at their clinical center over the past 15 years in men (40 IU/L) and women (30 IU/L).

To validate their updated definition of normal ALT values, an additional 131 HCV RNA-positive donors and 78 HCV RNA-negative donors were considered. Using the newly calculated normal values, the authors found that the sensitivity for the detection of HCV RNA-positive donors increased from 55% (95% CI, 46.4%–63.5%) to 76.3% (95% CI, 69.1%–83.6%). The gain of sensitivity mainly targeted patients with minimal to mild histologic lesions. Among the 103 patients with HCV who had liver biopsies, the number with abnormal ALT values increased from 63 (sensitivity, 61.1%) to 80 (sensitivity, 77.7%). Of the 17 patients whose ALT levels are now considered abnormal but had been previously considered normal according to the currently used standards, 2 patients had normal or nonspecific changes on liver biopsy, 9 had minimal histologic abnormalities, and 5 had mild abnormalities of the liver. On the other hand, the new normal ranges decreased the specificity from 97.4% (95% CI, 91%–99.7%) to 88.5% (95% CI, 79.2%–94.6%). However, most nonviremic donors with abnormal ALT values had hepatic steatosis diagnosed by ultrasound because the mildness of laboratory abnormalities rendered liver biopsy analyses unjustifiable for ethical reasons.

Thus, the study by Prati et al. [12] suggested that the adoption of lower limits for ALT values would increase the effectiveness of case finding for active HCV infection and also the detection of persons with minimal to mild histologic lesions, in particular patients with fatty liver. In conclusion, while Pitton et al. [18] suggested that ALT levels should be interpreted with reference to BMI, Prati et al. [12] suggested that ALT should be determined in healthy subjects at low risk for NAFLD, to minimize the influence of NAFLD.

While the two previous studies suggested new ULN for ALT in a very selected population such as blood donors, in 2006 the retrospective study by Kariv et al. [20] aimed to show the “healthy” ULN for serum ALT in a very large community-based population from Israel. The authors reviewed medical records of subjects aged 15–90 years, who underwent standard panels of laboratory tests, including serum ALT, over 6 months at a central laboratory. Three groups were defined. Group 1 consisted of the total population of 272,273 subjects. Group 2 (87,020 subjects) comprised the total population after exclusion of subjects with abnormal values of one or more of the laboratory parameters, medical diagnoses that may affect liver function tests, or a medication profile consisting of potentially hepatotoxic drugs. Not excluded from this group were subjects with abnormal levels of serum triglycerides, cholesterol, glucose, or HbA1C. Group 3 (17,496 subjects) comprised only those subjects from group 2 whose values of triglycerides, cholesterol, glucose, and HbA1c were normal, and thus included a ‘healthy’ population. The 95th percentile ALT values in groups 1, 2 and 3 were, respectively, 50.1 IU/L (for females, 40.6; for males, 60.8), 40 IU/L (for females, 32.4; for males, 48), and 37.5 IU/L (for females, 31.8; for males, 44.9). In this first large-scale study of “healthy” population [20], the new ALT ULN (37.5 IU/L) was lower than the current ALT threshold of manufacturers (52 IU/L), but higher than the ALT ULN suggested by Prati et al. [12]. This discrepancy in the healthy range might be attributable to potential limitations of the study by Kariv et al. [20], which included the collection of retrospective data, lack of several blood test results such as anti-HCV antibody or hepatitis B surface antigen (HBsAg) for many subjects, and no BMI data. Therefore, their “healthy” population might have been “contaminated” with patients with viral liver disease or NAFLD. Nonetheless, in agreement with Prati et al. [12], the retrospective study by Kariv et al. [20] evaluating, through linear and logistic-regression analyses, factors modulating serum ALT in the “healthy” subjects, showed that ALT levels were significantly modified by gender, age, glucose, cholesterol, triglycerides, and overweight/obesity diagnosis. Significant interaction was found between gender, glucose and cholesterol levels. The interaction of cholesterol and ALT levels was significantly stronger in males than in females, whereas the interaction of glucose and ALT levels was significantly weaker in males than in females. No significant interaction was detected between triglyceride values and gender.

The 2010 histologic data obtained by Lee et al. [97] in a Korean cohort of 1105 potential liver donors with biopsy-proven normal livers emphasized the considerable influence of clinical (i.e. age and BMI) and metabolic factors when interpreting ALT values even in populations with normal livers. Normal histology on liver biopsy was defined as fatty changes in less than 5% of hepatocytes, including both macro- and microvesicular steatosis, and absence of significant fibrosis or inflammatory cell infiltration. The calculated thresholds for ALT values (set at the 95th percentiles) in these subjects (643 men with a median age of 25 years, and 462 women with a median age of 30 years) were 31 IU/L for men and 24 IU/L for women. Among the 1105 potential liver donors, Lee et al. [97] selected a subgroup of 665 subjects [mean age ± SD, 26.0 ± 7.6 years for the 346 men and 30.0 ± 8.2 years for the 319 women] as being at clinically low risk for NAFLD using the criteria of Prati et al. [12], modified by the BMI cutoff points (≤ 23 kg/m²) for Asian populations. The 95th ALT percentiles for Korean subjects within the modified Prati criteria were 29 IU/L and 22 IU/L, respectively, in men and women. Thus, serum ALT upper limits in healthy Asian populations with normal liver histology were consistent with those suggested by Prati et al. [12].

In 2011, Volzke et al. [19] sought to establish ALT ULN for North-East Germany using data from 4242 adult subjects (2154 women) recruited...
Table 1

<table>
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<tr>
<th>Authors, country/year [reference]</th>
<th>Study design and population</th>
<th>Exclusion criteria</th>
<th>Factors modulating ALT activity</th>
<th>Updated ULN for ALT</th>
<th>Methods</th>
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<tr>
<td>Pston et al., France/2011 [18]</td>
<td>Prospective cohort of 1033 blood donors</td>
<td>Of the initial 1085 donors, 52 were excluded because of the presence of HBsAg, anti-HBc, anti-HCV, anti-HIV and anti-HTLV antibodies; and a positive test for syphilis</td>
<td>Gender and BMI</td>
<td>BMI ≤ 23 kg/m²: 42 IU/L for males and 31 IU/L for females; BMI &gt; 23 kg/m²: 66 IU/L for males and 44 IU/L for females</td>
<td>95th percentile according to BMI and gender</td>
<td>The influence of NAFLD and other metabolic risk factors was not evaluated</td>
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<tr>
<td>Prati et al., Italy/2002 [12]</td>
<td>Retrospective cohort of 3927 first-time blood donors</td>
<td>Of the initial 9221 donors, 2924 were excluded because of the presence of HBsAg, anti-HCV, anti-HIV1 and HIV2 antibodies; a positive test for syphilis; dysmetabolic state (BMI &gt; 25 kg/m²); elevated serum triglyceride, cholesterol and glucose levels; and concurrent medication use</td>
<td>Age, gender, and BMI; physical exercise; total cholesterol, triglyceride, and glucose levels; alcohol consumption; use of medications</td>
<td>44.9 IU/L for males and 31.8 IU/L for females</td>
<td>95th percentile according to gender</td>
<td>ULN for ALT was computed from a population at low risk for liver disease</td>
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<td>Kariv et al., Israel/2006 [20]</td>
<td>Retrospective cohort of 17,496 pediatric and adult subjects undergoing standard panels of laboratory tests, including ALT, at a central laboratory</td>
<td>Of the initial 273,273 subjects, 255,777 were excluded because of abnormal values of one or more laboratory parameters (including triglycerides, cholesterol, glucose and HbA1c); use of hepatotoxic drugs; and medical diagnosis affecting liver function tests (i.e. chronic liver disease, overweight/obesity, ethanolism)</td>
<td>Age and gender; total cholesterol, triglyceride, and glucose levels; and overweight/obesity</td>
<td>28 IU/L</td>
<td>95th percentile according to sex and BMI</td>
<td>Only 1.5% and 5.4% of the study population was tested for HCV and HBV, respectively</td>
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<tr>
<td>Van Der Poorten et al., Australia/2007 [99]</td>
<td>Prospective cohort of 206 adolescent male offenders participating in a health survey and laboratory assessment</td>
<td>Of the initial 439 young male offenders, 233 were excluded because of overweight/obesity; high systolic blood pressure; elevated triglycerides and LDL-C; HBV and HCV infection; and high alcohol consumption</td>
<td>Overweight/obesity; triglycerides, total cholesterol and LDL-C; and anti-HCV antibodies</td>
<td>35 IU/L for males and 26 IU/L for females</td>
<td>95th percentile according to gender</td>
<td>In Asian subjects with normal liver histology, ALT ULN was consistent with that reported by Prati et al. in Italian blood donors [12]</td>
</tr>
<tr>
<td>Lee et al., Korea/2010 [97]</td>
<td>Prospective cohort of 1105 potential living liver donors with biopsy-proven normal livers</td>
<td>Of the initial 2054 potential living liver donors, 949 were excluded because of the presence of histologic steatosis in &gt;5% of hepatocytes and/or inflammation and/or fibrosis</td>
<td>Age and gender; total cholesterol, and glucose levels</td>
<td>25.8 IU/L for boys and 22.1 IU/L for girls</td>
<td>95th percentile according to gender</td>
<td>Exclusion criteria did not include metabolic risk factors, use of hepatotoxic drugs, and autoimmune hepatitis</td>
</tr>
<tr>
<td>Völzke et al., Germany/2010 [19]</td>
<td>Cross-sectional study of Health including 1953 adult participants</td>
<td>Of the initial 4242 subjects, 2289 were excluded because of chronic liver disease; malignant diseases; high alcohol consumption; seropositivity for HBsAg or anti-HCV; increased levels of ferritin; sonographic evidence of hepatic steatosis</td>
<td>Age and gender</td>
<td>Age, 20–49 years: 65 IU/L for males and 33 IU/L for females; age, 50–79 years: 42 IU/L for males and 35 IU/L for females</td>
<td>95th percentile according to age and gender</td>
<td>Exclusion criteria did not include metabolic risk factors, use of hepatotoxic drugs, and autoimmune hepatitis</td>
</tr>
<tr>
<td>Schwimmer et al., United States/2010 [46]</td>
<td>Prospective cohort of 982 pediatric participants of the National Health and Nutrition Examination Survey</td>
<td>Of the initial 7180 participants, 6198 were excluded because of the presence of viral hepatitis, HIV infection, and iron overload; use of hepatotoxic medications; overweight/obesity; metabolic risk factors for NAFLD; and missing ALT values</td>
<td>Not available</td>
<td>25.8 IU/L for boys and 22.1 IU/L for girls</td>
<td>95th percentile according to gender</td>
<td>ULN for ALT was established in a healthy weight, metabolically normal, liver disease-free, pediatric population</td>
</tr>
<tr>
<td>Kang et al., Korea/2011 [21]</td>
<td>Retrospective cohort of 1745 adult participants who had undergone a routine health examination</td>
<td>Of the initial 9616 subjects, 7870 were excluded because of the presence of HBsAg, anti-HCV, and anti-HIV antibodies; use of hepatotoxic drugs; high alcohol consumption; treatment for chronic liver disease; malignancy and other chronic conditions; sonographic evidence of hepatic steatosis; abnormal WC; elevated total cholesterol and glucose levels, and low HDL-C</td>
<td>Age, gender, WC; total cholesterol, HDL-C, and glucose levels; alcohol consumption; and fatty liver</td>
<td>31 IU/L for males and 23 IU/L for females</td>
<td>95th percentile according to gender</td>
<td>ALT ULN was quite similar to that reported by Prati et al. [12]</td>
</tr>
<tr>
<td>Poustchi et al., Iran/2011 [93]</td>
<td>Prospective cohort of 371 school aged children and adolescents</td>
<td>Of the initial 1000 participants, 629 were excluded because of the presence of HBsAg and anti-HCV antibodies; and abnormal values for factors that correlated with ALT</td>
<td>Gender, BMI, blood pressure; total cholesterol, insulin, triglycerides, and HOMA-IR values. Age only in females</td>
<td>30 IU/L for boys and 21 IU/L for girls</td>
<td>95th percentile according to gender</td>
<td>The influence of fatty liver on the threshold values for ALT was not determined</td>
</tr>
</tbody>
</table>
for the population-based Study of Health in Pomerania. A reference population (1953 subjects, of whom 1129 women) was created from a population at low risk for liver disease. The study provided no detailed information on alcohol status. Exclusion criteria did not include autoimmune hepatitis.

Table 1 (continued)

<table>
<thead>
<tr>
<th>Authors, country/year [reference]</th>
<th>Study design and population</th>
<th>Exclusion criteria</th>
<th>Factors moderating ALT activity</th>
<th>Updated ULN for ALT</th>
<th>Methods</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu et al., Taiwan/2012 [50]</td>
<td>Retrospective cohort of 2894 adult subjects who had undergone health check-up</td>
<td>Of the initial 21,282 subjects, 18,388 were excluded because of the presence of abnormal values for factors associated with serum ALT levels &gt; 40 IU/L by multivariate analysis</td>
<td>Age, gender, BMI, WC; total cholesterol, HDL-C, triglyceride, and glucose levels; HBSAg, anti-HCV antibodies; and fatty liver on ultrasound</td>
<td>Not available</td>
<td>95th percentile according to gender</td>
<td>The study provided no detailed information on alcohol status. Exclusion criteria did not include autoimmune hepatitis</td>
</tr>
<tr>
<td>Zheng et al., China/2012 [98]</td>
<td>Cross-sectional study of Health including 13,637 adult participants</td>
<td>Of the initial 53,037 participants, 39,400 were excluded because of alcohol consumption; concurrent use of hepatotoxic medications or herbs; HBV, HCV or HIV infection; NAFLD at ultrasound; metabolic risk factors; and ALT missing values</td>
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</tr>
<tr>
<td>Park et al., Korea/2012 [51]</td>
<td>Cross-sectional study of 3316 adult participants of the National Health and Nutrition Examination Survey</td>
<td>Of the initial 16,608 participants, 13,292 were excluded because of seropositivity for HBSAg; alcohol consumption; use of hepatotoxic drugs; medical diagnosis of chronic hepatitis and liver cirrhosis; malignancy and other chronic conditions; and any abnormality among metabolic syndrome components</td>
<td>Age, gender, BMI, and WC; glucose, total cholesterol, HDL-C, and triglycerides; and HBSAg</td>
<td>53 IU/L for males and 30 IU/L for females</td>
<td>95th percentile according to gender</td>
<td>Autoimmune hepatitis, HCV, and iron overload were not excluded. No ultrasound evaluation was made to exclude fatty liver</td>
</tr>
<tr>
<td>Park et al., Korea, 2013 [100]</td>
<td>Cross-sectional study of 1717 adolescent participants of the National Health and Nutrition Examination Survey</td>
<td>Of the initial 2746 participants, 1029 were excluded because of seropositivity for HBSAg; alcohol consumption; overweight/obesity; blood lipid abnormality and elevated fasting glucose; and missing data</td>
<td>Age, gender, and BMI; triglycerides and LDL-C</td>
<td>33 IU/L for boys and 25 IU/L for girls</td>
<td>95th percentile according to gender</td>
<td>Autoimmune hepatitis, HCV, iron overload, and NAFLD were not excluded</td>
</tr>
</tbody>
</table>

BMI, body mass index; HBSAg, hepatitis B surface antigen; HBC, hepatitis B core; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HTLV, human T leukemia lymphoma virus; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; NAFLD, nonalcoholic fatty liver disease; WC, waist circumference

da daily alcohol intake ≥ 60 g, treatment with potentially hepatotoxic drugs for medical reasons, treatment for chronic liver disease or malignancy, or a newly diagnosed specific disease during routine health examinations (i.e. hepatic or biliary disease, malignancy, infectious disease, hyperthyroidism, cardiovascular disease, renal disease, rheumatologic disease, or Parkinson’s disease). More important, to establish a truly healthy population, subjects who showed abnormal values of those variables significantly associated (after adjustment for age and gender) with serum ALT level in multivariate analysis (i.e. the group with “unhealthy” ALT levels) were also excluded [21]. The limits of these variables were as follows: WC ≥ 90 cm in males and ≥ 80 cm in females, daily alcohol consumption ≥ 20 g in males and ≥ 10 g in females, fatty liver upon ultrasound, serum AST level ≥ 45 IU/L, GGT ≥ 50 IU/L, cholesterol ≥ 200 mg/dL, HDL-C < 40 mg/dL in males and < 50 mg/dL in females, and glucose ≥ 100 mg/dL. Thus, the “unhealthy normal” ALT group with a serum ALT level of 31–40 IU/L (males) or 23–40 IU/L (females) comprised patients with dyslipidemia, obesity, diabetes, insulin resistance, or MetS. After meticulous exclusion of such patients, the healthy ALT group comprised 1745 subjects whose gender-specific 95th percentiles for the serum ALT levels were 31 IU/L in males and 23 IU/L in females. These are similar to those previously found by Prati et al. [12], but consistently lower than those more recently reported by Park et al. [51] using data from the 2007–2009 Korean NHANES. In these Korean adults at low risk for liver disease (N = 3316; negative HBSAg, low alcohol intake, normal WC, normal lipid or carbohydrate metabolism, and absence of medication use), the 95th percentiles for ALT were 53 IU/L for men and 30 IU/L for women. There are a number of reasons for this discrepancy. First, in the study of Park et al. [51], the ULN for ALT activity was
derived. Using the 97.5th percentile cutoff rather than the 95th percentile cutoff. Second, causes of elevated ALT, such as autoimmune hepatitis, HCV, and iron overload were not excluded. Third, no ultrasound evaluation of fatty liver was made to exclude NAFLD.

In 2012, a revision of serum ALT ULN values was also performed in Taiwan by Wu et al. [50] and in China by Zheng et al. [98]. In the large-scale cohort study from Taiwan [50] involving 21,282 persons who underwent physical check-up over a 4-year period, a reference healthy population (N = 2894) was selected after excluding all subjects with any abnormality in independent risk factors associated with the current ALT threshold of manufacturers (>40 IU/L). Using multivariate analysis independent risk factors were BMI (>24 kg/m²), WC (≥ 90 cm for men and ≥ 80 cm for women), glucose (≥ 100 mg/dL), cholesterol (>200 mg/dL), HDL-C (<40 mg/dL for men and <50 mg/dL for women), triglycerides (≥ 150 mg/dL), presence of HBsAg, anti-HCV antibody and ultrasound-diagnosed fatty liver. The major finding of this study was that most subjects with normal serum ALT levels according to the current threshold, still had unhealthy status, including viral hepatitis, MetS and fatty liver, and therefore the ULN of serum ALT levels needed to be revised. Accordingly, the optimal threshold of ULN for ALT level (set at the 95th percentiles), for better discrimination between healthy and unhealthy status, was 21 IU/L for men and 17 IU/L for women.

In a large population-based study from China [98], 53,037 healthy participants were registered and the 95th percentile for ALT was 67.0 IU/L in men and 46.6 IU/L in women. However, exclusion of 39,400 subjects because of confounding variables [512 due to missing ALT values; 15,154 because of excess alcohol drinking; 3523 because of ultrasound-diagnosed NAFLD; 2198 because of the current use of hepatitis C virus, HCV, and iron overload were not excluded. No ultrasound evaluation of fatty liver was made to exclude NAFLD. The ULN (set at the 97.5th percentile) for ALT was 33 IU/L in boys and 22.1 IU/L in girls.

In the liver SAFETY study [46], the new normal ranges increased the sensitivity for detection of children with HBV, HCV, and NAFLD. When the ALT thresholds in current use by children’s hospitals in the United States were applied, sensitivity was low for HBV, HCV, and NAFLD (defined as hepatic fat fraction ≥ 5% by magnetic resonance imaging) in boys and girls, with median sensitivities ranging from 32% to 48%. By comparison, the median specificities were high: 92% in boys and 96% in girls. In contrast, for boys, using the NHANES-derived threshold the sensitivity increased to 72% for HBV, 85% for HCV, and 80% for NAFLD. The specificity decreased to 79%. For girls, using the NHANES-derived ALT threshold the sensitivity increased to 74% for HBV, 79% for HCV, and 92% for NAFLD. The specificity decreased to 85%. Thus, the analysis of diagnostic performance in children with and without liver disease showed that ALT thresholds in current use have low sensitivity for detection of liver disease. Conversely, the gender-specific NHANES-derived ALT thresholds doubled the sensitivity with a small reduction in specificity. Thus, using these new thresholds, ALT has utility as an important component in screening for liver disease.

Poutschi et al. [93] sought to establish age- and gender-specific ULN for ALT in 1000 school aged children and adolescents from Iran. They selected their healthy population by excluding in a first step those who were unable to fast overnight (N = 74) or those who tested positive for HBsAg (N = 1). None of the students were positive for anti-HCV antibody, and all subjects denied cigarette smoking or alcohol consumption. In a second step, they assessed factors associated with serum ALT in univariate analysis. BMI, systolic and diastolic blood pressure, insulin levels, HOMA-IR values, and total cholesterol and triglyceride concentrations correlated with the serum ALT. Participants who had abnormal results for these components based on age-specific values were excluded. Among the 371 healthy students (186 boys, and 185 girls), the 95th percentile for ALT was 30.0 IU/L in boys (mean age ± SD, 12.5 ± 3 years) and 20.7 IU/L in girls (mean age ± SD, 13.1 ± 3.4 years) [93]. Despite the rigorous criteria to define normal values for ALT in children and adolescents, a major limitation of that study was that the possible influence of (ultrasound-diagnosed) fatty liver on the threshold values for ALT was not determined.

More recently, among the 2746 adolescent participants in the 2007−2009 Korean NHANES, Park et al. [100] selected a reference healthy population (N = 1717 adolescents; mean age, 14.4 years) as being at clinically low risk for liver disease using the following exclusion criteria: presence of HBsAg (N = 20), history of excess alcohol intake (N = 58), a BMI ≥ 85th percentile (N = 577), any blood lipid abnormality such as LDL-C ≥ 130 mg/dL, triglycerides ≥ 150 mg/dL, or HDL-C < 35 mg/dL (N = 277), fasting serum glucose ≥ 100 mg/dL (N = 73), and missing data (N = 24). However, in that reference population [100], causes of elevated ALT, such as autoimmune hepatitis, HCV, and iron overload were not excluded. No ultrasound evaluation of fatty liver was made to exclude NAFLD. The ULN (set at the 97.5th percentile) for ALT was 33 IU/L in boys and 25 IU/L in girls.

6. Counterpoint: why the current ALT ULN should not be redefined

Several studies have shown that subjects with elevated ALT levels as defined by the Prati criteria [12] but within the normal ranges according to the older criteria, have increased liver-related mortality or may show
active hepatic inflammation or be cases of chronic HBV or HCV infection [101–104]. Likewise, studies have reported cirrhosis in 8–12% of adult patients with NAFLD who had elevated ALT levels by using the new criteria but within the current normal range according to the old criteria [6,10,105]. Therefore, the current ALT range of “normal” may underestimate the presence of these common forms of chronic liver disease. However, skepticism concerning the need to update the current normal range of serum ALT activities is due to variety of concerns. Population-based studies have suggested that the application of the new ALT standards may not be cost-beneficial [79,106]. A population-based study performed in the United States showed that approximately 40% of the general population has abnormal ALT activities using the updated Prati criteria, suggesting that application of these new definitions could result in a dramatic increase in the healthcare expenditures [106]. Ruhi and Everhart [71], in a large epidemiologic study, noted that 2.8% of the adult population had elevated ALT levels according to the old reference range (≥43 IU/L). In subjects with class II/III obesity, this prevalence increased to 6.6%. The authors also demonstrated that the application of the new criteria (≥19 IU/L) would result in a fivefold increase in the prevalence of an elevated ALT level in the general population (men, 12.8%; women, 13.9%). Using an old ALT cutoff (≥43 IU/L) as in the study by Ruhi and Everhart [71], Kunde et al. [79] showed that 8.6% of their study cohort comprising 233 women with class II/III obesity undergoing gastric bypass surgery, had an elevated ALT level. Their study also showed that 63.1% of the 233 obese would have been classified as having abnormal ALT using the new standard (≥19 IU/L). As pointed out by Park et al. [51], if the Prati [12] or Lee [97] cutoffs were applied across the entire 2007–2009 Korean NHANES population, then nearly a third of the adult Korean population would have an abnormal activity by Prati criteria, and a fifth of the population would be classified as having an abnormal ALT activity by Lee criteria.

The diagnostic implications of the new ALT reference range for the complete spectrum of NAFLD need also to be considered. Kunde et al. [79] showed that patients identified by the new criteria as having an elevated ALT value primarily demonstrated minor liver injury on biopsy. In fact, applying the new standard for elevated ALT value (≥19 IU/L), the number of individuals with minimal steatosis (hepatocyte fat content ≤5%) and mild steatosis (hepatocyte fat content between 6% and 33%) on biopsy increased by 48.1% and 48.4%, respectively. Thus the adoption of the new ALT standard would significantly increase the diagnosis of early stages of NAFLD and would be useful in counseling patients but would result in questionable benefit. Kunde et al. [79] also demonstrated that in patients with normal ALT activity [new (≥19 IU/L)] vs old (≤30 IU/L) standard], the prevalence of fatty liver (39.5% vs 40.2%), portal-only fibrosis, without perisinusoidal fibrosis (37.2% vs 33.7%) and nonalcoholic steatohepatitis (23.3% vs 26%) were similar [79]. Importantly, despite the significant decrease in the new cutoff level for ALT, 18.2% of patients with advanced fibrosis had normal ALT levels. Although the application of the newly calculated healthy limits to patients with chronic viral hepatitis would identify more patients with active inflammation, this approach would result in the unnecessary use of antiviral agents [97], in that an elevated ALT level might be a consequence of patient age, anthropometric and metabolic characteristics, and/or combined with NAFLD. Moreover, there are numerous other factors which should impact on this decision, including genotype, histology, and comorbid condition or illness [107].

Another concern is that decreasing the ULN for ALT would also deleteriously affect blood donations. Potential blood donors might be rejected solely because of minimally-elevated ALT values. However, the donor candidates who would become ineligible for donation applying the new ALT guideline, would be mostly persons with hepatic steatosis, who would otherwise be acceptable as blood donors. Furthermore, blood banks screen all prospective donors for HCV infection. Thus, lowering the ULN for ALT would not increase the safety of blood transfusions.

Finally, a lowered ULN might cause patient anxiety about liver disease and may cause medicolegal concerns.

7. Conclusions

Physicians should be cautious in interpreting the normal range of serum ALT levels, while laboratories should think very carefully how to ascertain an “optimal” upper limit of normal for ALT. Laboratories should consider the scientific difficulties and problems that we have highlighted and, if possible, participate in discussions with clinicians to reach consensus on the best way ahead. An abnormal, as well as normal, ALT result after the application of the proposed lower ALT standards must trigger a complete clinical evaluation, education and follow-up of patients. To assess the risk-benefit and cost-effectiveness of the new vs the old ALT reference standard, formal well-designed prospective outcome-based studies remain to be done.

Conflict of interest

The authors have nothing to disclose and declare no potential conflict of interest.

Abbreviations

ALT alanine aminotransferase
AST aspartate aminotransferase
BMI body mass index
CAP College of American Pathologists
CL confidence interval
HBSAg hepatitis B surface antigen
HBV hepatitis B virus
HCV hepatitis C virus
HIV human immunodeficiency virus
HDL-C high-density lipoprotein cholesterol
LDL-C low-density lipoprotein cholesterol
MetS metabolic syndrome
NAFLD nonalcoholic fatty liver disease
NHANES National Health and Nutrition Examination Survey
OR odds ratio
P-5′-P pyridoxal-5′-phosphate
SAFETY screening ALT for elevation in today’s youth
ULN upper limit of normal
WC waist circumference

References


