Alanine Aminotransferase Level: The Road to Normal in 2021

There have been continuous debates, discussions, and updates on the definition of normal healthy serum alanine aminotransferase (ALT) level over the last few decades. This is important not only to hepatologists but also to all physicians and patients as an abnormal ALT level is often the first trigger for further workup for possible underlying liver diseases, namely viral hepatitis,[1] nonalcoholic fatty liver disease (NAFLD)[2]/metabolic-associated fatty liver disease (MAFLD),[3] as well as many other acute and chronic liver diseases. Nevertheless, the challenge in defining normal ALT is the difficulty of including completely healthy subjects without liver diseases. It is particularly demanding to completely exclude the existence of NAFLD, the most common chronic liver disease worldwide, which may be as frequent as one in every 3 to 4 adults.[4]

In this issue of *Hepatology Communications*, Valenti et al. from Italy report a 2021 updated definition of healthy ranges for ALT, with four different cohorts being included in this meticulous analysis.[5] The study started in a cohort of 21,296 apparently healthy adult blood donors (age capped at 65 years) from which

patients without risk factors for liver diseases were selected; this sets the foundation to define the sex-specific upper reference limits (URLs) for ALT. Such URLs were subsequently tested in an independent cohort of 977 unselected donors ("relatively healthy") and a subset of 745 participants with metabolic risk factors and another cohort of 899 patients with chronic liver disease (both "unhealthy") cohorts to predict liver damage. The updated URLs were 42 U/L in men and 30 U/L in women; these URLs had moderate to high accuracy to discriminate liver conditions (area under the receiver operating characteristic curve, 0.81).

The beauty of this study is its stringent approach by testing the URLs in both healthy and unhealthy cohorts; hence, the validity of these updated URLs is proven in both directions. Yet, only a small subset of patients had undergone more accurate assessments for liver fat, namely transient elastography with controlled attenuation parameter measurement, which is known to be highly sensitive in ruling out significant hepatic steatosis.[6] Another state-of-the-art imaging technique, proton-magnetic resonance spectroscopy, would be an even more accurate tool to exclude fatty liver.[7] It is well understood that such radiologic examinations cannot be carried out in thousands of patients. Instead, laboratory, parameter-based, machine-learning models appear to be an attractive alternative for excluding NAFLD at a population level, with data collected from electronic medical records.[8]

Valenti et al. chose the URL of ALT level by the ninety-fifth percentile in healthy individuals without risk factors for liver disease instead of using the mean + 1.645 SD for a normal distribution. This approach was used due to the right-skewed distribution of ALT with a significant proportion of outliers on the right tail. A logarithmic transformation of ALT level was used in subsequent statistical modeling, so the ALT level was assumed to follow a log-normal distribution, although some outliers were observed (Fig. 1). While outliers on the right tail affect (increase) the value of mean and SD, percentiles would be more robust to outliers for summarizing a specified proportion of the sample. The method of ninety-fifth percentile has previously
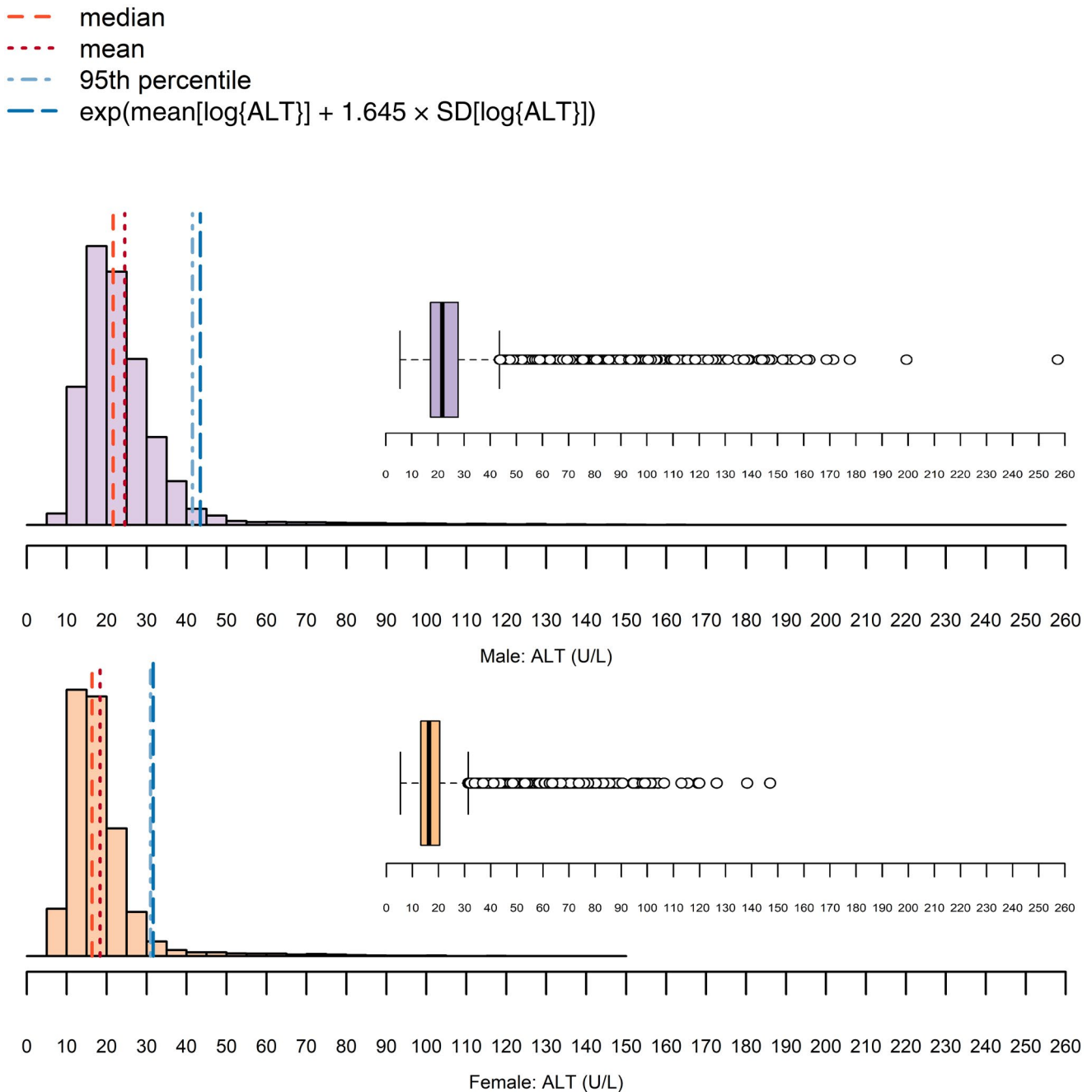
FIG. 1. Simulated log-normal distributions (N = 10,000) with 300 outliers for ALT levels in a healthy population by sex. Percentiles used were adopted from Valenti et al.[5]

been adopted for healthy subjects.[9] Moreover, a linear model after logarithmic transformation of ALT level was fitted to examine factors associated with ALT level. Subjects' age, sex, metabolic risk factors (hypertension, elevated body mass index [BMI], triglycerides, glucose, and total cholesterol), ferritin, recreational drug use,

and significant physical activity were independently associated with ALT level. As ALT levels are correlated with multiple clinical characteristics, a difficulty in determining the URL is the definition of healthy population. Valenti et al. carefully excluded subjects with viral hepatitis, metabolic risk factors (elevated BMI,

total cholesterol, triglycerides, and glucose), regular alcohol intake, and regular/recent recreational drug use. Another potential difficulty in defining the URL is the generalizability in other populations. Thus, Valenti et al. validated the URL in several independent cohorts on its ability to discriminate steatohepatitis and clinically significant fibrosis. It would be helpful for future studies to examine the association of abnormal ALT with the new cutoffs on hard clinical outcomes, such as survival in the general population.

This 2021 updated definition of normal ALT has important diagnostic and therapeutic implications. For examples, in patients with chronic hepatitis B, more patients would have fulfilled the treatment criteria of ALT above 2 times the URL; this would contribute to the hepatitis elimination campaign by bringing down the incidence of deaths secondary to hepatocellular carcinoma and other cirrhotic complications.[10] For NAFLD/MAFLD, this may lower the threshold to proceed to further assessments in order to rule in or out its existence with patients with raised ALT. Prospective studies on the prognostic value of these new URLs of ALT would guide us to further refine its definition.

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