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Range of Normal Serum Aminotransferase Levels in Liver Transplant Recipients

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Abstract

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are used to monitor liver transplant recipients (LTR) but the reference range and context of its use is not well defined. We aimed to determine the healthy ranges in LTR without chronic liver disease.

Methods—One hundred and three LTR without chronic liver disease based on serology, transient elastography with controlled attenuated parameter, and ultrasound were included. A healthy range of aminotransferases was set to 95th percentile. An updated normal aminotransferase range was used to detect recurrence in post-liver transplantation (LT) with hepatitis C virus (HCV) and nonalcoholic fatty liver disease (NAFLD).

Results—The normal ALT and AST range was 0 to 57 and 0 to 54 IU/L, respectively, in LTR and was not affected by age, sex, obesity, or choice of immunosuppressant. The diagnostic performance of serum ALT and AST to detect recurrence of NAFLD by a controlled attenuated parameter was poor with area under the receiver operating characteristic curve of 0.573 (95% confidence interval 0.493, 0.655; $P = .08$) and 0.537 (0.456, 0.618; $P = .4$), respectively. In contrast, the diagnostic performance of ALT and AST to detect recurrence of HCV after LT was 0.906 (0.868, 0.944; $P < .001$) and 0.925 (0.890, 0.959; $P < .001$), respectively.

Conclusion—The updated aminotransferase range in LTR is higher than the general population and accurate for detecting recurrent HCV, but not NAFLD.

SERUM alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are the most widely ordered liver chemistries and part of the routine surveillance of liver health [1–4]. Abnormalities in serum ALT and AST are nonspecific, but they do suggest potential hepatic injury that must be investigated further with additional more-specific hypothesis-driven testing [5]. The routinely reported normal ALT values by Clinical Laboratory Improvement Amendments certified labs range from 40 to 60 IU/L [6–9]. These thresholds, however, were

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compiled in the 1980s from non-A, non-B hepatitis blood donors that likely included patients with subclinical liver disease [10–13]. Thus, the proposed reference values do not represent truly “normal” values. When patients who are at risk for chronic liver disease are systematically ruled out, the true normal reference range is <30 IU/L for men and 19 IU/L for women [14]. These values have now been confirmed in multiple studies [6,15]. However, failure to change these reference values as reported by commercial laboratories can lead to failure to recognize chronic liver disease, especially in liver disease where liver enzymes may not be significantly elevated [15,16].

Much like the general population, serum ALT and AST are routinely used to follow patients who have received a liver transplantation (LT) [17,18]. After LT, elevation in serum aminotransferase levels are not specific to the etiology of liver injury, but the degree of elevation may provide clues to potential causes of liver injury [19–22]. Similar to the general population, the Clinical Laboratory Improvement Amendments reported a normal serum aminotransferases range from 40 to 60 IU/L, but there is no data to support the use of these reference standards in liver transplant recipients (LTR). Factors such as transplantation, exposure to chronic immunosuppressants, medications (ie, ketoconazole, nonsteroidal anti-inflammatory, etc), thyroid disorders, and bone loss can lead to mild elevations in serum aminotransferases that are not liverspecific and must be accounted for when interpreting liver enzymes in LTR [23–26]. Thus, to fill this major gap in knowledge we conducted a prospective study to define a healthy range for serum aminotransferases (ALT and AST) in LTR without evidence of chronic liver disease.

PATIENTS AND METHODS

The data was prospectively collected at the Virginia Commonwealth University on LTR between August 1, 2016 and March 1, 2018 to define a healthy range of serum aminotransferase. The study was approved by the institutional review board at the Virginia Commonwealth University. All authors reviewed and approved the manuscript before submission.

Patient Population

All adult LTR over the age 18 were screened for participation into the study. Only subjects with no evidence of chronic liver disease were included into the study. Chronic liver disease was ruled out with serologically with an evaluation consisting of viral hepatitis serology (hepatitis B, hepatitis C), anti-smooth muscle antibody, anti-mitochondrial antibody, and iron panel. Those with greater than mild alcohol intake (ie, >20 g/day and 30 g/day in women and men, respectively) were also excluded. Patients with a history of chronic hepatitis C who had achieved sustained viral response with a negative hepatitis C viral load were included if they did not have evidence of fatty liver disease. Because the prevalence of nonalcoholic fatty liver disease (NAFLD) is common after LT among patients transplanted for cirrhosis resulting from nonalcoholic steatohepatitis (NASH), as well as non-NASH etiologies [27], the presence of fatty liver was ruled out via vibration controlled transient elastography (VCTE) using a controlled attenuated parameter threshold of 271 dB/m. Those with no steatosis and fibrosis were included into the study. Finally, patients with acute

cellular rejection, chronic rejection, biliary strictures, heart failure, renal failure, multiviscera transplants, and active malignancy (both hepatic and nonhepatic) were excluded from the analysis.

To assess the diagnostic performance of serum aminotransferases to detect hepatitis C and NAFLD after LT, patients with recurrence of either hepatitis C virus (HCV) or NAFLD were compared with LTR with no evidence of chronic liver disease. In patients with post-LT HCV, those who had achieved sustained virologic response (SVR) or were undergoing treatment for HCV were excluded from the current analysis. Patients with graft cirrhosis were excluded as this may lead to reduction in serum aminotransferase, as well as the ratio of serum AST to ALT [28–30].

Vibration Controlled Transient Elastography

All VCTE examinations were performed using the Fibroscan 502 Touch machines (Echosens, Paris, France) by experienced operators using a standardized protocol [31]. Briefly, after overnight fasting, all subjects were placed in supine position with their right arm in maximal abduction and measurements were taken over the right hepatic lobe through an intercostal space [31]. All examinations were started using the M probe and transitioned to XL probe if prompted by the device's automatic probe selection software. Only cases with 10 valid acquisitions were used.

CLINICAL ASSESSMENT

All patients presented to the liver transplant clinic after an overnight fast and underwent a detailed history and physical examination. After their medical evaluation, routine bloodwork was drawn, which consisted of the following: complete blood count, basic metabolic panel, hepatic panel, prothrombin time, international normalized ratio, immunosuppressant levels (tacrolimus, cyclosporine, or sirolimus), serum lipid profile and hemoglobin A1c.

STATISTICAL ANALYSIS

In descriptive analysis, categorical variables are reported as frequency and percentages (%), while continuous variables are reported as means $\pm$ standard deviation. Normally distributed numerical values were compared using Student *t* test, and Mann-Whitney *U*-test was used for variables with skewed distribution. The χ^2 test and Fisher's exact test were used for qualitative data.

The distribution of serum aminotransferase levels was calculated at 5th, 25th, 50th, 75th, and 95th percentile on empirical distribution of the data. The upper limit of healthy ALT levels was set to 95th percentile. The serum aminotransferase levels were analyzed initially in the entire cohort and subsequently based on sex given the previously reported sex differences [14,32–34]. The impact of types of immunosuppression (cyclosporine, tacrolimus, Rapamune), time from liver transplantation, age, body mass index (BMI), diabetes, hypertension, dyslipidemia, and aminotransferases were evaluated via logistic regression analysis.

The diagnostic performance of serum aminotransferase to differentiate the presence of NAFLD and HCV after LT from LTR with no chronic liver disease was evaluated. The area under the receiver operating characteristics curves, sensitivity, specificity, negative predictive value, and positive predictive value are reported. A 2-sided P value $< .05$ was considered statistically significant. All statistical analysis was conducted using SPSS (IBM, Armonk, New York).

RESULTS

Patient Characteristics

A total of 103 patients met criteria for the study after a negative serologic, radiologic, and VCTE evaluation. The cohort consisted of 50 men (48.5%) with a mean age of 58 ± 15 years (Table 1). The majority of the cohort was non-Hispanic white ($n = 71$ or 71%), followed by black ($n = 26$ or 25%). The mean time from LT to VCTE was 9.4 ± 7.4 years. The mean BMI of the cohort was 27.4 ± 5.7 kg/m², and the distribution of diabetes, hypertension, and dyslipidemia was 32%, 67%, and 34%, respectively. The mean controlled attenuated parameter value of the cohort was 208 ± 48 dB/m.

Healthy Range of Serum Aminotransferase After Liver Transplantation

The mean serum ALT was 27 ± 16 IU/L, and mean serum AST concentrations were 29 ± 11 IU/L. No sex differences between men and women with regard to serum ALT (27 ± 15 vs 26 ± 14 IU/L; $P = .74$) and AST (29 ± 11 vs 29 ± 11 IU/L; $P = .92$) were noted. The serum ALT levels were 11 IU/L, 15 IU/L, 22 IU/L, 38 IU/L, and 57 IU/L, respectively, for the 5th, 25th, 50th, 75th, and 95th percentiles. Similarly, the serum AST levels were 17 IU/L, 21 IU/L, 27 IU/L, 34 IU/L, and 54 IU/L, respectively for the 5th, 25th, 50th, 75th, and 95th percentiles. For men and women, the median ALT value was 23 IU/L and 21 IU/L and the median AST value was 27 IU/L and 27 IU/L, respectively. In men, the 5th, 25th, 75th, and 95th percentiles of serum ALT values were 11 IU/L, 15 IU/L, 37 IU/L, and 60 IU/L, respectively. Similarly, the serum AST values in men were 17 IU/L, 22 IU/L, 35 IU/L, and 52 IU/L for the 5th, 25th, 75th, and 95th percentiles, respectively. In women, the 5th, 25th, 75th, and 95th percentile ALT values, respectively, were 11 IU/L, 14 IU/L, 38 IU/L, and 55 IU/L. The serum AST values in women were 17 IU/L, 21 IU/L, 33 IU/L, and 54 IU/L corresponding to the 5th, 25th, 75th, and 95th percentiles, respectively. In multiple logistic regression analysis, serum ALT and AST levels were not affected by age, BMI, diabetes, hypertension, dyslipidemia, time from LT, and choice of immunosuppression.

Diagnostic Performance of Serum Aminotransferases to Detect Liver Disease after LT

The use of the recommend serum aminotransferase reference range (0–19 and 0–30 IU/L for men and women, respectively) would have resulted in 47% and 63% false positives based on whether serum ALT or AST were used. The ability to distinguish presence of chronic liver disease after LT using normal serum aminotransferase values was determined using the area under the receiver operating characteristic curve (AUROC). LTR with recurrence of NAFLD ($n = 93$) and HCV ($n = 99$) after LT were compared with LTR with no chronic liver disease ($n = 103$) (Table 1). Expectedly the distribution of diabetes, hypertension, and dyslipidemia were higher in the cohort of subjects with NAFLD.

The mean ALT levels were 32 ± 21 IU/L in LTR with NAFLD and 91 ± 62 IU/L in LTR with HCV recurrence (Figs 1A and 1B). Similarly, the mean AST levels were 29 ± 17 IU/L in LTR with NAFLD and 93 ± 57 IU/L in LTR with HCV. The AUROC for detecting NAFLD after LT using serum ALT and AST levels was 0.573 (95% confidence interval 0.493, 0.655; $P = .08$) and 0.537 (0.456, 0.618; $P = .4$), respectively (Figs 2A and 2B). In contrast, the AUROC for detecting HCV recurrence after LT using serum ALT and AST levels was 0.906 (0.868, 0.944; $P < .001$) and 0.925 (0.890, 0.959; $P < .001$), respectively (Figs 2C and 2D). Finally, we attempted to define how many patients with recurrence of either NAFLD or HCV after LT would have serum aminotransferases within the normal range of serum ALT of 0 to 57 IU/L and AST of 0 to 54 IU/L. In patients with recurrence of NAFLD after LT, only 6.9% and 3.7% had serum ALT and AST levels that were higher than the normal range, respectively (Fig 3A). In contrast, in patients with recurrence of HCV, 58.6% and 68.7%, respectively had serum ALT and AST levels that were higher than the reference range (Fig 3B).

DISCUSSION

Serum hepatic aminotransferases are commonly used biomarkers that are an integral part of the routine assessment of all LTR. In alignment with biomarker development guidelines, it is important to define the operating parameters for serum aminotransferases with regards to context of use and reference ranges of serum ALT and AST after LT. The currently utilized reference standard was developed in nonliver transplant patients and thus may not be applicable to LTR. In the current study, using LTR with no evidence of chronic liver disease we defined serum ALT and AST reference range of 0 to 57 IU/L and 0 to 54 IU/L that were independent of sex. The LT specific reference standards are higher than the nontransplant population and this is likely multifactorial resulting from exposure to chronic immunosuppression, insulin resistance, and liver transplantation [24,35–37]. Additionally, the proposed reference standards for serum ALT and AST were independent of age, exposure to immunosuppressants, and comorbid metabolic conditions, underscoring the robustness of this reference range. Because serum aminotransferase are not specific for etiology of underlying liver disease [5,6,8,13], using lower reference range defined in the general population may lead to additional diagnostic work that may not be necessary and contribute to medical waste. In fact, use of non-LT specific reference range for serum aminotransferase would lead to false positives in 47% to 63% of LTR.

Defining the context of use of serum aminotransferase in LTR is important, and in the current study we attempt to define its accuracy in predicting the recurrence of 2 of the most common liver disease after LT [27,38–41]. The accuracy of serum aminotransferase to identify recurrence of NAFLD after LT was low, whereas the accuracy of AST and ALT to identify patients with recurrent HCV after LT was high. These findings likely stem from the different nature of these 2 chronic liver diseases. Histologically, HCV is associated with a higher degree of inflammation and activity when compared with NAFLD [7,42]. In untreated HCV after LT, serum liver enzymes are usually higher in both the general population and LTR [7,43]. In contrast, NAFLD is associated with a relatively mild increase in serum aminotransferases and only a small portion of patients with NAFLD has truly elevated liver enzymes (>60 IU/L) [15]. Additionally, serum aminotransferase levels do not

correlate with disease activity in patients with NAFLD [44]. These observations are also applicable to NAFLD recurrence after LT where serum aminotransferases were unable to differentiate between NAFL vs NASH or severity of liver disease [45]. Thus, it is important to note that while in patients transplanted for HCV, a rise in liver enzyme can suggest recurrence of HCV, normal liver enzymes in patients transplanted for NASH cirrhosis does not exclude recurrence of NAFLD after LT. Thus, in patients transplanted for NASH cirrhosis, alternative means such as VCTE or magnetic resonance proton density fat fraction (MR-PDFF) may be a more apt test for detecting disease recurrence.

In the current study, we defined the absence of chronic liver disease via extensive testing via serologies, medical history, as well as VCTE. However, because of limitations of self-reported bias and limited accuracy of VCTE at the cut-off thresholds, it is possible to misclassify some patients with subclinical alcoholic and nonalcoholic fatty liver disease, respectively. However, we developed standardized protocols for all the implemented measures to minimize misclassifying subclinical liver disease. A liver biopsy would be the gold standard to exclude presence of underlying chronic liver disease; however, performing a liver biopsy in patients who are unlikely to have underlying liver disease is not ethically justifiable and within this limitation our approach was comprehensive. In the present study, we defined the context of use for serum aminotransferases in post-LT NAFLD and HCV, but we did not define it for other chronic liver disease such as hepatitis B, autoimmune hepatitis, alcoholic liver disease, primary biliary cholangitis, and primary sclerosing cholangitis. This is an important limitation; however, these liver diseases contribute to a minority of chronic liver disease after LT and are difficult to diagnose noninvasively. Additionally, because of their relatively small numbers, large multicenter collaborations are necessary to define the context of use of aminotransferases for recurrence of these diseases after LT.

In conclusion, the updated reference standards for serum ALT and AST for LT specific populations are 0 to 57 IU/L and 0 to 54 IU, respectively, and are not sex specific. Serum aminotransferases are useful for detecting presence of HCV recurrence after LT but not NAFLD.

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Fig. 1. Mean serum ALT (**A**) and AST levels (**B**) in liver transplant recipients with no chronic liver disease, NAFLD and hepatitis C. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Fig. 2.

(**A**) Area under the receive operating characteristic curves (AUROC) of serum ALT to detect post-liver transplantation (LT) nonalcoholic fatty liver disease (NAFLD). (**B**) AUROC of serum AST to detect post-LT NAFLD. (**C**) AUROC of serum ALT to detect post-LT hepatitis C virus (HCV) recurrence. (**D**) AUROC of serum AST to detect post-LT HCV recurrence. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Fig. 3.

The proportion of patients with recurrence of NAFLD and HCV after LT with abnormal serum ALT (**A**) and AST (**B**). Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 1.

Clinical Characteristics of the Study Cohort

Patient Characteristics	Post-LT Normal	Post-LT NAFLD	Post-LT HCV	P Value
n	103	87	99	
Demographics				
Age (y)	58 ± 15	63 ± 9.3	56 ± 7	< .001
Sex (% male)	50 (49%)	48 (55%)	73 (74%)	.001
Ethnicity (%)				.003
Non-Hispanic white	73 (71%)	77 (89%)	72 (73%)	
Black (%)	26 (25%)	4 (5%)	24 (24%)	
Other (%)	4 (4%)	6 (6%)	3 (3%)	
Clinical Characteristics				
Body mass index (kg/m ²)	27.4 ± 5.2	32.1 ± 5.9	27.6 ± 5.2	< .001
Diabetes (%)	33 (32%)	63 (72%)	44 (44%)	< .001
Hypertension (%)	69 (67%)	77 (88%)	79 (80%)	.08
Dyslipidemia (%)	35 (34%)	60 (69%)	28 (28%)	< .001
Immunosuppression				
Cyclosporine (%)	27 (26%)	17 (20%)	23 (23%)	.55
Tacrolimus (%)	73 (71%)	68 (78%)	67 (68%)	.27
Rapamune (%)	14 (14%)	14 (16%)	8 (8%)	.23

Abbreviations: HCV, hepatitis C virus; LT, liver transplantation; NAFLD, nonalcoholic fatty liver disease.