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LETTER TO THE EDITOR

ROC Curves Can be Used to Determine the Optimal Criterion of ALT for Reflex-to-AST Testing

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In recent years, there have been many research topics [1-3] aimed at reducing AST measurements rather than stopping AST testing. Some studies [1,2] have shown the proportion of missed AST measurements (ASTs that are above the upper limit of the reference interval and should be tested but are not) is approximately 3% - 7%. Our optimized protocol achieves markedly lower missed AST measurement rates (0.3 - 3.6%) through threshold derivation methodology innovations [3,4]. There are significant differences in the comparison of missed AST measurement rates, which may be related to the research methods used. Conventional Practice: Triggering AST testing at ALT upper reference limits (URLs) without diagnostic accuracy validation [1,2], whereas our study [3,4] used the ROC curve to determine the ALT cutoff value and initiated AST testing when the ALT cutoff value was greater than the cutoff value (the point on the ROC curve corresponding to maximizing Youden's index). This type of research strategy is mainly based on the following: 1. AST has poor specificity and is not as specific as ALT in assessing liver function; 2. AST is positively correlated with ALT [1,3]. To further investigate the above issues, we used data from NHANES 2017 - 2020 to conduct a study to reduce AST measurements.

We retrieved paired data on ALT, AST, age, gender, and liver ultrasound transient elastography from NHANES 2017 - 2020. The upper limit of the reference

Table 1. ROC curve of ALT for the prediction of elevated AST with and without liver fibrosis in the NHANES 2017 - 2020 population.

Parameter	Liver Ultrasound Transient Elastography					
	ALL	F1	F2	F3	F4	F2-4
n	15,317	13,403	1,112	523	279	1,914
Associated criterion (U/L)	32	30	36	25	35	32
AUC	0.962 95% CI: 0.959 - 0.965	0.960 95% CI: 0.957 - 0.964	0.976 95% CI: 0.965 - 0.984	0.964 95% CI: 0.945 - 0.979	0.995 95% CI: 0.978 - 1.000	0.975 95% CI: 0.968 - 0.982
Youden index	0.779	0.7703	0.864	0.8177	0.9813	0.8447
Sensitivity (%)	88.0 95% CI: 85.1 - 90.5	89.9 95% CI: 87.0 - 92.3	91.9 95% CI: 78.1 - 98.3	94.4 95% CI: 72.7 - 99.9	100.0 95% CI: 71.5 - 100	90.9 95% CI: 81.3 - 96.6
Specificity (%)	89.9 95% CI: 89.4 - 90.4	87.2 95% CI: 86.6 - 87.8	94.5 95% CI: 93.0 - 95.8	87.3 95% CI: 84.1 - 90.1	98.1 95.7 - 99.4	93.6 95% CI: 92.3 - 94.6
Positive predictive value (%)	26.5 95% CI: 25.4 - 27.6	22.8 95% CI: 21.9 - 23.7	36.6 95% CI: 30.6 - 42.9	21.0 95% CI: 17.1 - 25.5	68.7 95% CI: 48.0 - 84.0	33.5 95% CI: 29.4 - 37.9
Negative predictive value (%)	99.5 95% CI: 99.3 - 99.6	99.5 95% CI: 99.4 - 99.6	99.7 95% CI: 99.1 - 99.9	99.8 95% CI: 98.5 - 100.0	100.0 95% CI: 100.0 - 100.0	99.7 95% CI: 99.3 - 99.8
AST not measured	86.8% (13,297/15,317)	84.1% (11,267/13,403)	91.6% (1,019/1,112)	84.5% (442/523)	94.3% (263/279)	90.6% (1,735/1,914)
The percentage of elevated AST (> 40 U/L) missed	0.55% (73/13,297)	0.49% (55/11,267)	0.29% (3/1,019)	0.22% (1/442)	0% (0/263)	0.35% (6/1,735)
Range of 95% right-side (U/L)	41.0 - 73.3	41.0 - 73.0	41.0 - 45.0	46	NA	41.0 - 46.0

F: represents the fibrosis stage (F1: mild; F2: moderate; F3: severe; F4: cirrhosis), as assessed by liver elastography.

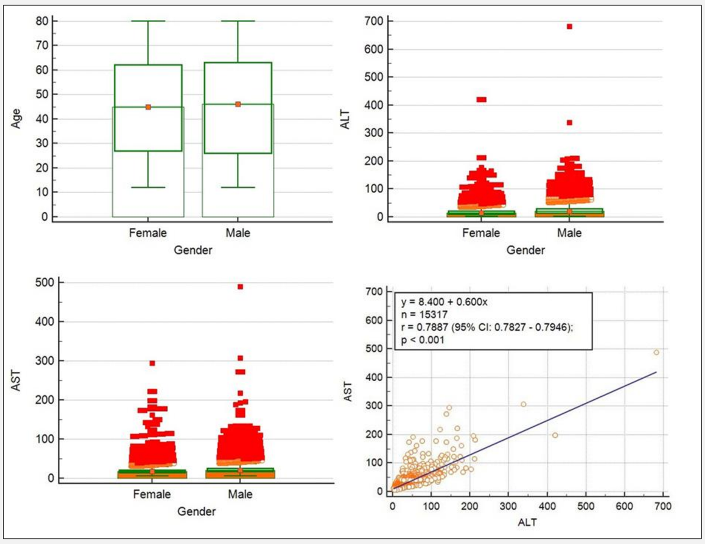

Figure 1. Basic characteristics of NHANES 2017 - 2020.

The unit of age is years; the units of ALT and AST are U/L; and Pearson's correlation is used.

interval (ULR) for AST was 40 U/L. Please refer to the official website of the NHANES for information on laboratory testing methods, instruments, reagents, quality control procedures, etc. ROC curve analysis was conducted to identify the optimal criterion for predicting elevated AST. All the statistical analyses were performed via MedCalc (version 19.4.0 - 64-bit) to determine the AUC, Youden index, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and optimal ALT criterion (the corresponding point is the maximal Youden index) [5]. The basic characteristics of the 15,317 subjects are shown in Figure 1, including age, gender, ALT, AST, and the correlation between ALT and AST ($r = 0.79$; 95% CI: 0.78 - 0.79; $p < 0.0001$). Overall, 86.8% of the ASTs were saved. Moreover, only 0.55% of the ASTs were missed, and the range of the 95% right-sided missed ASTs was 41.0 - 73.3 U/L (Table 1). The missed detection rate and savings rate are similar to those reported in our previous studies [3,4]. Some studies [1,3] have shown that as the ALT cutoff value increases, the proportion of missed ASTs increases. Therefore, the optimal criterion of the ALT is not defined artificially (such as using the ULR of the ALT [1,2].) but requires statistics or AI to define. Our research revealed that regardless of the presence of liver fibrosis, the NPV was as high as 99%, which means that the proportion of AST leakage was less than 1%. Assuming that there are 8 billion liver function tests performed annually and that the cost of AST testing is approximately $3, if the reflex strategy of this study is applied, 6.94 billion AST tests can be reduced, saving $20.8 billion in testing costs.

In summary, defining optimal criteria for the reflex-to-AST testing method via the ROC curve of ALT is suitable for NHANES. Our study demonstrated that the method can be applied to the US population.

Data Accessibility:

The datasets analyzed in this study are available through two primary channels: 1) Researchers may contact the corresponding author via email to request access to the study data; 2) Publicly available data can be downloaded directly from the official NHANES website at [https://wwwn.cdc.gov/nchs/nhanes/default.aspx].

Declaration of Interest:

The authors of this letter have no relevant financial or other relationships to disclose.

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