

# Brief Communication: Clinical Implications of Short-Term Variability in Liver Function Test Results

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**Background:** Clinicians sometimes order liver tests as part of a screening examination or general work-up. Current guidelines do not recommend routine retesting of abnormal results in asymptomatic patients.

**Objective:** To characterize the magnitude of intraindividual variability of liver test results and determine the proportion of adults with persistently elevated levels after 1 positive test.

**Design:** Reliability study.

**Setting:** The NHANES (National Health and Nutrition Examination Survey) III First and Second Examinations (1988 to 1994).

**Participants:** 1864 men and women age 18 years or older living in the United States.

**Measurements:** Repeated measurements (mean, 17.5 days apart) of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase,  $\gamma$ -glutamyltransferase, and bilirubin.

**Results:** Using NHANES III cutoffs for normal levels, 38% of adults with initially elevated bilirubin levels had normal levels at the second examination. These proportions were 36%, 31%, 17%, and

12% for AST, ALT, alkaline phosphatase, and  $\gamma$ -glutamyltransferase, respectively. More than 95% of initially normal results remained normal. The results did not differ by alcohol consumption; hepatitis A, B, or C serologic status; recent infection; body mass index; or sociodemographic characteristics. Intraindividual variability was significantly higher for bilirubin (coefficient of variation, 23.4%) and ALT (coefficient of variation, 20.4%) than for AST (coefficient of variation, 13.9%),  $\gamma$ -glutamyltransferase (coefficient of variation, 13.8%), and alkaline phosphatase (coefficient of variation, 6.7%).

**Limitations:** Only 2 measurements were available. Complete liver disease history was lacking.

**Conclusion:** If retested, more than 30% of adults with elevated AST, ALT, or bilirubin levels would be reclassified as normal. Clinicians should be aware of the high intraindividual variability in common liver tests, and practice guidelines should explicitly recommend retesting of asymptomatic individuals with abnormal liver test results.

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Clinicians sometimes order liver tests as part of a screening examination or general work-up (1–4). However, how they manage asymptomatic patients with elevated liver tests is unclear (5–7). Although many clinicians may repeat the test, the American Gastroenterological Association guideline “American Gastroenterological Association Medical Position Statement: Evaluation of Liver Chemistry Tests” recommends repeating tests before more extensive work-up only if there is “suspicion of laboratory error” (8).

Liver tests, however, are highly variable, and thus many asymptomatic patients may undergo intensive liver work-up on the basis of the result of a single screening test. The cost of the tests to identify some common causes of elevated liver enzymes, such as serologic tests for hepatitis B and C infection and ultrasonography for nonalcoholic fatty liver disease, is approximately \$400. In contrast, re-

peating the liver tests costs about \$30 (9). Furthermore, false-positive results may cause unnecessary patient anxiety.

We analyzed data from the NHANES (National Health and Nutrition Examination Survey) III First and Second Examinations to characterize the magnitude of the intraindividual variability of liver tests and determine the proportion of adults with persistent elevations of liver test results after a single positive test. This information should be useful to practicing physicians and to experts developing guidelines for the management of asymptomatic patients with elevated liver test results.

## METHODS

### Participants

The NHANES III was a large cross-sectional study of the civilian noninstitutionalized U.S. population. The NHANES III First and Second Examinations were conducted from 1988 to 1994. The NHANES III Second Examination was a substudy of NHANES III in which a nonrandom sample of 2209 of the original NHANES III participants repeated the complete study visit by following identical protocols a mean of 17.5 days after the first examination. The sample for the second examination was obtained by selecting participants from each survey location according to the following general guidelines: 1) mainly adults, 2) equally split between age 20 to 39 years and age 40 years or older, and 3) equal sex distribution

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Appendix Table

Conversion of graphics into slides

**Context**

Should clinicians work up or repeat liver tests when abnormal values are found in asymptomatic individuals?

**Contribution**

This analysis examined repeated liver tests (for aminotransferases, alkaline phosphatase,  $\gamma$ -glutamyltransferase, and bilirubin), obtained about 17 days apart, from 1864 men and women who participated in NHANES (National Health and Nutrition Examination Survey) III. More than 95% of the initially normal results remained normal, whereas 12% to 38% of the elevated values were normal at the second examination.

**Implication**

Intraindividual variability of liver tests is high: Many "abnormal" values in asymptomatic individuals are normal on retesting.

—The Editors

(10, 11). We restricted our analyses to the 1864 men and women age 18 years or older who had liver tests at both examinations (Figure).

**Measurements**

Serum biochemistries were performed by using the Hitachi 737 automated multichannel chemistry analyzer (Boehringer Mannheim Diagnostics, Indianapolis, Indiana) at a central laboratory (White Sands Research Center, Alamogordo, New Mexico). Alanine aminotransferase (ALT), aspartate aminotransferase (AST),  $\gamma$ -glutamyltransferase, alkaline phosphatase, and total bilirubin were assayed. A detailed description of the laboratory assays and quality control procedures is available elsewhere (12).

On the basis of the NHANES III laboratory cutoff values for normal levels, we defined elevated liver test results as AST levels higher than 37 U/L for men and 31 U/L for women, ALT levels higher than 40 U/L for men and 31 U/L for women,  $\gamma$ -glutamyltransferase levels higher than 51 U/L for men and 33 U/L for women, alkaline phosphatase levels higher than 177 U/L, and total bilirubin levels higher than 17.1  $\mu$ mol/L (>1 mg/dL) (12). We considered test results to be persistently elevated if the levels were above the normal limit on both examinations.

Participants were interviewed to obtain information on alcohol use and binge drinking; medication use, including acetaminophen, aspirin, or ibuprofen; and infections in the past month. The presence of antibodies to hepatitis C was tested by using a second-generation enzyme immunoassay test (Abbott Laboratories, Chicago, Illinois) and confirmed with the MATRIX assay (Abbott Laboratories), a third-generation hepatitis C virus antibody test. The presence of antibodies to hepatitis B core antigen was tested by using a solid-phase competitive immunoassay (Abbott Laboratories). Finally, the presence of antibodies to hepatitis A

virus was tested by using solid-phase competitive enzyme immunoassay (Abbott Laboratories) (12).

**Statistical Analysis**

We examined the proportion of participants with persistently elevated values and the intraindividual variability of the tests. We assessed intraindividual variability by using the within-person coefficient of variation calculated with the root-mean-square method (13, 14). We compared the within-person coefficient of variation of each liver test by using multiple paired *t* tests. We also report the intraclass correlation for the paired liver test measurements (15).

All analyses were unweighted because sample weights were not provided for the NHANES III Second Examination (11). We conducted statistical analyses by using Stata, version 9 (Stata, College Station, Texas).

**Role of the Funding Source**

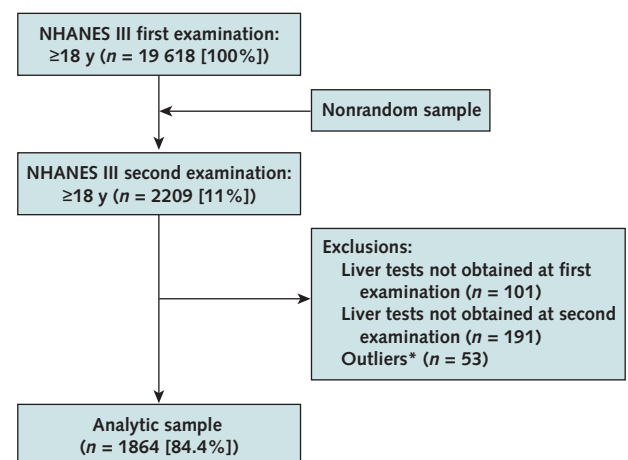
The study did not receive funding.

**RESULTS**

The Figure shows the number of participants who were included in the analyses. The study population was 45% male, had a mean age of 49 years (SD, 18.8), and was racially or ethnically diverse (Table 1). The prevalence of antibodies to hepatitis A, hepatitis B core, and hepatitis C was 54%, 8%, and 3%, respectively. With regard to alcohol use, 53% reported consuming at least 12 drinks in the past 12 months.

The proportions of participants with abnormal liver test results in the first examination were 6.2%, 5.9%, 17.9%, 11.7%, and 9.3% for AST, ALT,  $\gamma$ -glutamyltransferase, alkaline phosphatase, and total bilirubin, respec-

Figure. Study flow diagram.



NHANES = National Health and Nutrition Examination Survey.  
\*Values with a difference (examination 2 minus examination 1) >4 SDs from the mean difference. These values are likely to have arisen from non-method-related error processes (inadequate mixing, evaporation, or mislabeling).

tively (Table 2). Of those with an initially elevated AST level, the proportion with a persistently elevated level was 64.4% (95% CI, 54.8% to 73.0%). The corresponding proportions were 68.8% (CI, 59.2% to 77.3%) for ALT, 87.9% (CI, 83.4% to 91.6%) for  $\gamma$ -glutamyltransferase, 83.5% (CI, 77.9% to 88.2%) for alkaline phosphatase, and 62.4% (CI, 54.8% to 69.7%) for total bilirubin.

Compared with participants who returned to a normal result, participants who had persistently elevated test results tended to have higher median levels at the first examination. For each test, most people who returned to normal levels had had elevated levels within 1.1 to 2.0 times the normal range (Appendix Table, available at [www.annals.org](http://www.annals.org)). Few people (<5% for all tests) were reclassified as having elevated levels on the second examination after a normal result on the first examination.

On the basis of the within-person coefficient of variation, ALT and total bilirubin levels had significantly higher variability than AST,  $\gamma$ -glutamyltransferase, and alkaline

phosphatase levels ( $P < 0.050$  for all comparisons). In contrast, alkaline phosphatase levels had significantly lower variability compared with all the other tests ( $P < 0.050$  for all comparisons).

These results were essentially identical when we restricted the analyses to persons who reported no lifetime alcohol consumption ( $n = 324$ ), those who were negative for hepatitis B core and hepatitis C virus antibodies ( $n = 1678$ ), and those who reported no infection or illness in the past 4 weeks ( $n = 1361$ ). Additional analyses stratified by sex, race, body mass index, and number of days between examinations yielded similar results.

## DISCUSSION

Elevated AST, ALT, or bilirubin levels would be reclassified as normal in more than 30% of retested individuals.  $\gamma$ -Glutamyltransferase and alkaline phosphatase were more reliable, with approximately 15% of adults being reclassified as having normal levels after initially abnormal test results. The results were unchanged, even after alcohol use, hepatitis infection status, and use of medications known to be hepatotoxic were taken into account. Our results suggest that routinely repeating liver tests when the results are elevated may reduce uncertainty in the clinical assessment of individuals with abnormal test results and substantially decrease further unnecessary tests.

In other clinical contexts, information on the biological short-term variability of commonly used measurements, such as fasting glucose level (coefficient of variation, 5.7%) (16), systolic blood pressure (coefficient of variation, 4.1% to 4.3%), and diastolic blood pressure (coefficient of variation, 6.1% to 6.7%) (17, 18), was key for providing the rationale for routine repeated testing in confirming the diagnoses of diabetes (19) and high blood pressure (18). Our results, which indicate even higher short-term variability in all of the liver tests except alkaline phosphatase, are important for the management of asymptomatic patients with elevated liver test results in screening examinations and support the need to obtain 2 or more liver test results rather than rely on a single measurement.

Our study has limitations. Only 2 measurements were obtained within a short interval; intraindividual variability may differ over a longer period. However, the period assessed here reflects the common clinical situation in which abnormal liver tests are usually flagged and repeated within 1 month. Alcohol use was self-reported and therefore subject to the limitations inherent to such data.

Participants in the NHANES III Second Examination were a convenience sample of the original NHANES. Compared with nonparticipants, participants were more likely to be non-Hispanic white (44.3% vs. 42.5%) and less likely to be Mexican American (25.1% vs. 26.4%) or men (45.6% vs. 47%). However, our estimates of intraindividual variability did not differ by sociodemographic characteristics. In addition, the results of the first examina-

**Table 1. Selected First Examination Characteristics of the Study Population, National Health and Nutrition Examination Survey III\***

Characteristic	Value
Mean age (SD), y	48.7 (18.8)
Mean BMI (SD), kg/m <sup>2</sup>	27.8 (6.1)
Race/ethnicity, n (%)	
Non-Hispanic white	872 (47)
Non-Hispanic black	489 (26)
Mexican American	449 (24)
Other	54 (3)
Male, n (%)	838 (45)
Diabetes, n (%)	166 (9)
Hypertension, n (%)	445 (24)
Transferrin saturation >50%, n (%)	40 (2)
Hepatitis A antibody (positive), n (%)	1015 (54)
Hepatitis B core antibody (positive), n (%)	154 (8)
Hepatitis B surface antigen (positive)†, n (%)	9 (0.5)
Hepatitis B surface antibody (positive)‡, n (%)	76 (4)
Serum hepatitis C antibody (positive), n (%)	48 (3)
Alcohol use	
Had $\geq 12$ drinks in life, n (%)	1513 (82)
Had $\geq 12$ drinks in past 12 mo‡, n (%)	808 (53)
Median days that alcohol was consumed in past 12 mo (IQR)§	52 (24–156)
Median average drinks per day on drinking day (IQR)§	3 (2–4)
Median days had $\geq 9$ drinks in past 12 mo (IQR)§	0 (0–1)
Median days had $\geq 5$ drinks in past 12 mo (IQR)§	1 (0–24)
Mean time between examinations	
Overall (SD), d	17.5 (7.9)
$\leq 7$ d, n (%)	127 (11)
8–14 d, n (%)	382 (31)
15–30 d, n (%)	644 (53)
>30 d, n (%)	67 (5)

\* BMI = body mass index; IQR = interquartile range.

† Percentage among those who tested positive for hepatitis B core antibody.

‡ Percentage among those who reported consuming  $\geq 12$  alcoholic drinks in the past 12 months.

§ Percentage among those who reported consuming  $\geq 12$  drinks in the past 12 months.

|| For 1220 participants out of the previously selected 1864.

**Table 2. Characteristics of Liver Tests in the National Health and Nutrition Examination Survey III First and Second Examination Samples\***

Characteristic	AST Level	ALT Level	$\gamma$ -Glutamyltransferase Level	Alkaline Phosphatase Level	Total Bilirubin Level
Elevated at examination 1, <i>n</i> (%)	115 (6.2)	109 (5.9)	265 (18.0)	218 (11.7)	173 (9.3)
Returned to normal at examination 2, <i>n</i> (%)	41 (35.7)	34 (31.2)	32 (12.1)	36 (16.5)	65 (37.6)
Median at examination 1 (range), <i>n</i>	38 (32–69)	43 (32–66)	36 (34–70)	126 (118–140)	17 (19–29)
Median at examination 2 (range), <i>n</i>	27 (16–34)	27 (10–40)	32 (8–48)	112.5 (96–117)	14 (7–15)
Persistently elevated at examination 2, <i>n</i> (%)	74 (64.4)	75 (68.8)	233 (87.9)	182 (83.5)	108 (62.4)
Median at examination 1 (range), <i>n</i>	51 (32–257)	55 (33–395)	67 (34–805)	138 (118–297)	21 (17–53)
Median at examination 2 (range), <i>n</i>	51 (32–234)	53 (32–367)	67 (34–790)	138 (118–297)	21 (17–51)
Mean within-person coefficient of variation (95% CI)	13.9 (13.2–14.5)	20.4 (19.5–21.2)†	13.8 (12.6–148)	6.7 (6.4–6.9)‡	23.4 (22.4–24.3)†
Mean intraclass correlation (reliability) (95% CI)	0.912 (0.904–0.919)	0.929 (0.923–0.935)	0.981 (0.979–0.983)	0.950 (0.945–0.954)	0.775 (0.756–0.792)

\* Elevated levels were defined as AST >37 U/L for men and >31 U/L for women; ALT >40 U/L for men and >31 U/L for women;  $\gamma$ -glutamyltransferase >51 U/L for men and >33 U/L for women; alkaline phosphatase >177 U/L; and total bilirubin >17.1  $\mu$ mol/L (>1 mg/dL). ALT = alanine aminotransferase; AST = aspartate aminotransferase.

† *P* values were calculated by using the *t* test. *P* < 0.050 compared with AST,  $\gamma$ -glutamyltransferase, and alkaline phosphatase.

‡ *P* values were calculated by using the *t* test. *P* < 0.050 compared with ALT, AST,  $\gamma$ -glutamyltransferase, and total bilirubin.

tion were not reported to participants before the second examination, so examination results could not have affected participation (20). Finally, the NHANES III questionnaire and examination were not specifically designed to assess liver disease and thus lacked additional information that would typically be used in clinical decision making.

Despite these limitations, the NHANES III First and Second Examinations represent, to our knowledge, the largest multiracial study of short-term repeated laboratory and physical examination measurements in a general population. All data collection was conducted by trained personnel following rigorous standardized protocols.

In conclusion, clinicians should be aware of the relatively high intraindividual variability in common liver tests in the general population, and practice guidelines should explicitly incorporate retesting of asymptomatic individuals with abnormal liver test results.

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**Potential Financial Conflicts of Interest:** None disclosed.

**Reproducible Research Statement:** The protocol for this study is not available. The statistical code is available to interested readers by contacting Dr. Lazo at mlazo@jhsph.edu. The data, which came from the NHANES III First and Second Examinations, are publicly available at [www.cdc.gov/nchs/about/major/nhanes/nh3data.htm](http://www.cdc.gov/nchs/about/major/nhanes/nh3data.htm).

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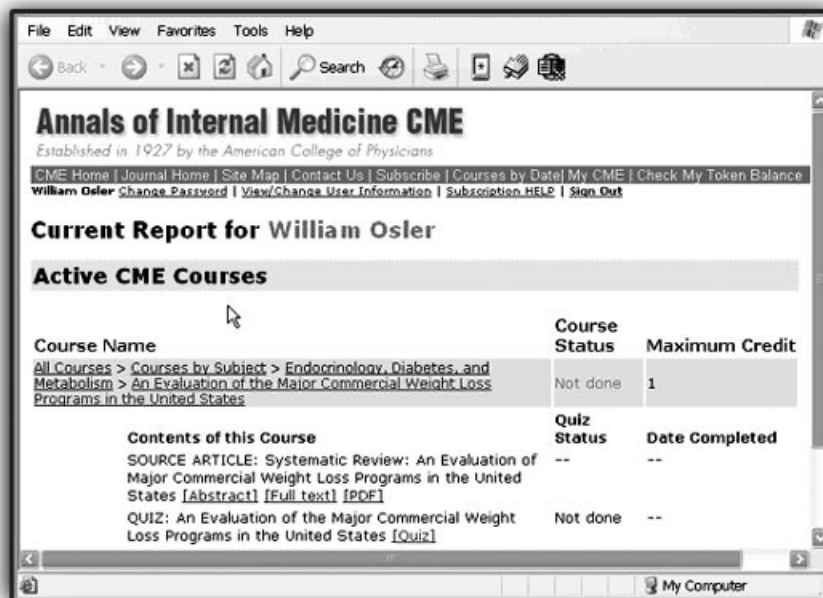
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Collection and assembly of data: M. Lazo.

**Appendix Table. Liver Test Results in the National Health and Nutrition Examination Survey III First and Second Examinations\***

Examination 1 Result	Participants, n (%)	Examination 2 Result	Participants, n (%)	Median Level at Examination 1 (Range)	Median Change (Range)
<b>ALT</b>					
Normal	1755 (94.2)	Normal	1731 (98.6)	13 U/L (3 to 40 U/L)	-26 U/L (0 to 20 U/L)
		1.1 to 2 times ULN	24 (1.4)	30 U/L (12 to 40 U/L)	14.5 U/L (6 to 39 U/L)
		>2 times ULN	0 (0)	-	-
1.1 to 2 times ULN	89 (4.8)	Normal	34 (38.2)	43 U/L (32 to 66 U/L)	-15.5 U/L (-38 to -4 U/L)
		1.1 to 2 times ULN	51 (57.3)	48 U/L (33 to 75 U/L)	-1 U/L (-31 to 23 U/L)
		>2 times ULN	4 (4.5)	60 U/L (48 to 77 U/L)	15.5 U/L (14 to 19 U/L)
>2 times ULN	20 (1.1)	Normal	0 (0)	-	-
		1.1 to 2 times ULN	6 (30)	82 U/L (65 to 94 U/L)	-31 U/L (-35 to 4 U/L)
		>2 times ULN	14 (70)	99 U/L (66 to 395 U/L)	-7 U/L (-31 to 22 U/L)
<b>AST</b>					
Normal	1749 (93.8)	Normal	1703 (97.4)	19 U/L (8 to 37 U/L)	0 U/L (-15 to 15 U/L)
		1.1 to 2 times ULN	45 (2.6)	29 U/L (17 to 37 U/L)	10 U/L (1 to 39 U/L)
		>2 times ULN	1 (4.2)	31 U/L	48 U/L
1.1 to 2 times ULN	94 (5.0)	Normal	41 (43.6)	38 U/L (32 to 69 U/L)	-11 U/L (-44 to -1 U/L)
		1.1 to 2 times ULN	49 (52.1)	44 U/L (32 to 74 U/L)	0 U/L (-19 to 16 U/L)
		>2 times ULN	4 (4.3)	49 U/L (48 to 64 U/L)	24.5 U/L (12 to 34 U/L)
>2 times ULN	21 (1.1)	Normal	0 (0)	-	-
		1.1 to 2 times ULN	2 (9.5)	99 U/L (85 to 113 U/L)	-31 U/L (-42 to -20 U/L)
		>2 times ULN	19 (90.5)	105 U/L (68 to 257 U/L)	1 U/L (-45 to 34 U/L)
<b><math>\gamma</math>-Glutamyltransferase</b>					
Normal	1210 (82.0)	Normal	1179 (97.4)	19 U/L (3 to 51 U/L)	0 U/L (-19 to 34 U/L)
		1.1 to 2 times ULN	31 (2.6)	33 U/L (19 to 50 U/L)	12 U/L (1 to 33 U/L)
		>2 times ULN	0 (0)	-	-
1.1 to 2 times ULN	185 (12.5)	Normal	32 (17.3)	36 U/L (34 to 70 U/L)	-6.5 U/L (-48 to -1 U/L)
		1.1 to 2 times ULN	141 (76.2)	54 U/L (34 to 102 U/L)	0 U/L (-36 to 26 U/L)
		>2 times ULN	12 (6.5)	64 U/L (42 to 100 U/L)	18.5 U/L (6 to 51 U/L)
>2 times ULN	80 (5.4)	Normal	0 (0)	-	-
		1.1 to 2 times ULN	11 (13.8)	73 U/L (67 to 122 U/L)	-19 U/L (-38 to -6 U/L)
		>2 times ULN	69 (86.3)	128 U/L (67 to 805 U/L)	-2 U/L (-53 to 51 U/L)
<b>Alkaline phosphatase</b>					
Normal	1846 (99)	Normal	1844 (99.9)	82 U/L (17 to 174 U/L)	0 U/L (-41 to 35 U/L)
		1.1 to 2 times ULN	2 (0.1)	153 U/L (149 to 156 U/L)	27 U/L (23 to 31 U/L)
		>2 times ULN	0 (0)	-	-
1.1 to 2 times ULN	18 (1)	Normal	6 (33.3)	186 U/L (179 to 207 U/L)	-26.5 U/L (-47 to -5 U/L)
		1.1 to 2 times ULN	12 (66.7)	200 U/L (181 to 297 U/L)	-6.5 U/L (-43 to 26 U/L)
		>2 times ULN	0 (0)	-	-
>2 times ULN	0 (0)	Normal	0 (0)	-	-
		1.1 to 2 times ULN	0 (0)	-	-
		>2 times ULN	0 (0)	-	-
<b>Total bilirubin†</b>					
Normal	1746 (93.7)	Normal	1697 (97.2)	9 $\mu$ mol/L (1.7 to 17.1 $\mu$ mol/L)	0 $\mu$ mol/L (-10.3 to 11.9 $\mu$ mol/L)
		1.1 to 2 times ULN	49 (2.8)	15 $\mu$ mol/L (6.8 to 17.1 $\mu$ mol/L)	9 $\mu$ mol/L (1.7 to 13.7 $\mu$ mol/L)
		>2 times ULN	0 (0)	-	-
1.1 to 2 times ULN	112 (6)	Normal	49 (43.8)	21 $\mu$ mol/L (18.8 to 29.1 $\mu$ mol/L)	-6.8 $\mu$ mol/L (-13.7 to -1.7 $\mu$ mol/L)
		1.1 to 2 times ULN	62 (55.4)	21 $\mu$ mol/L (18.8 to 34.2 $\mu$ mol/L)	0 $\mu$ mol/L (-11.9 to 13.7 $\mu$ mol/L)
		>2 times ULN	1 (1)	32 $\mu$ mol/L	15 $\mu$ mol/L
>2 times ULN	6 (0.3)	Normal	0 (0)	-	-
		1.1 to 2 times ULN	0 (0)	-	-
		>2 times ULN	6 (100)	43 $\mu$ mol/L (37.6 to 53.0 $\mu$ mol/L)	-0.9 $\mu$ mol/L (-3.4 to 6.8 $\mu$ mol/L)

\*ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

† To convert bilirubin values to mg/dL, divide by 17.104.