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Age Dependence of Liver Enzymes: An Analysis of Over 1,300,000 Consecutive Blood Samples

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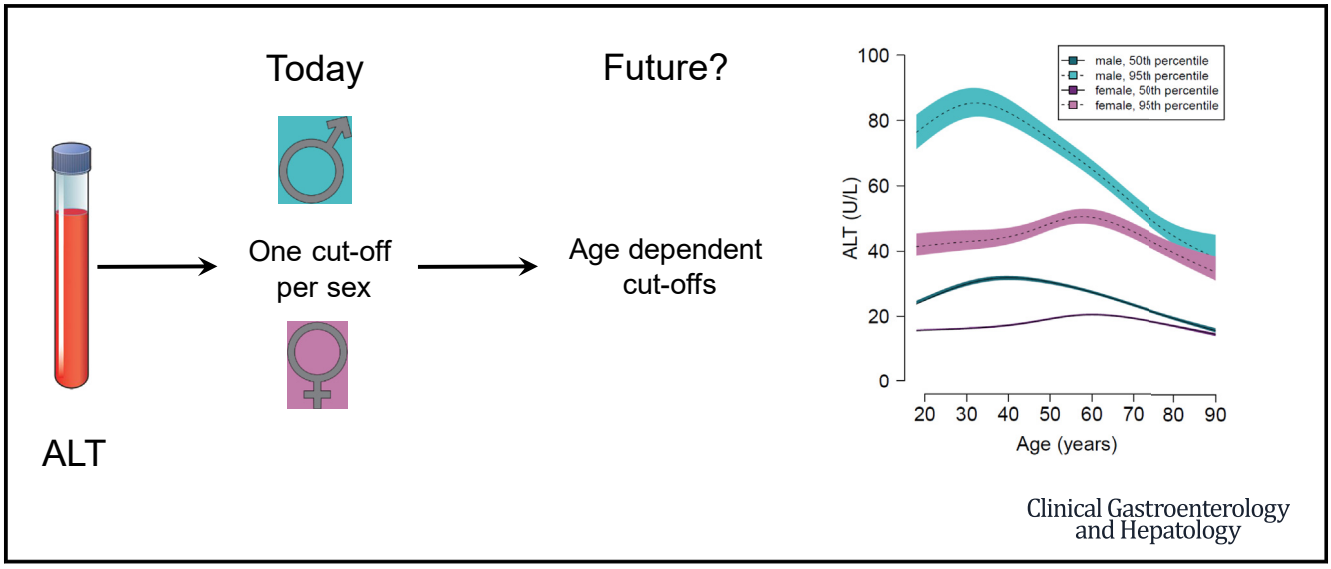

BACKGROUND & AIMS: **Upper levels of normal for alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyltransferase (GGT) generally take sex into account, but not age. This simplification may lead to misclassification and burden the patient and health system unnecessarily.**

METHODS: **Consecutive blood samples were analyzed from a German laboratory. Subcohorts included samples from a prescribed routine check-up and a healthy cohort, defined as patients without increased GGT, triglyceride, cholesterol, glycated hemoglobin, or glucose levels, and without known hepatitis B.**

RESULTS: **A total of 1,369,180 blood samples were analyzed from 601,779 participants (50.8% female; mean age, 58.5 y; SD, 18.0 y). There is an extreme age dependence in ALT values for men: increased values were seen in 20.0% (95% CI, 19.5%–20.4%) of patients in the age group of 25 to 34 years, but only 6.7% (95% CI, 6.4%–7.0%) for the ages of 65 to 74 years. The 95th percentile reaches values greater than 80 U/L instead of 50 U/L at the age of 35, and decrease to less than 50 U/L by the age of 75. Similar qualitative results were found in the healthy and prescribed routine check-up subcohorts. The age dependence is much weaker for ALT in women. The proportion of women with an increased AST level increases from approximately 6% to 12% at approximately age 50. The 95th percentile for GGT increases up to the age of 60 in men, and throughout life in women.**

Abbreviations used in this paper: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; ULN, upper limit of normal.

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CONCLUSIONS: **Current guidelines and reference values for ALT imply that subsequent diagnostics are needed for a large proportion of young men. Our data strongly suggest that age adaptation should be considered.**

Keywords: Alanine Aminotransferase; Aspartate Aminotransferase; γ-Glutamyltransferase; Percentile; Normal Liver Function; Abnormal Liver Chemistries; Normal Liver Blood Tests.

Alanine aminotransferase (ALT) is the most widely used laboratory parameter when screening, diagnosing, or monitoring liver disease.[1] Despite the loss of relevant information, values often are dichotomized because physicians are interested primarily in whether or not the value is increased. The definition of the upper limit of normal (ULN) typically relies on an estimate of the 95th or some other percentile in a healthy population, usually stratified by sex.[1] "Healthy" is not uniquely defined, but a basic philosophy involves inclusion of a low-risk group and subsequent exclusion of those with abnormal values for a predefined set of blood parameters.[2,3] Because these parameters may be correlated with ALT even in a healthy population, this process can lead to an underestimate of the 95th percentile. Changes in the populations used to define the ULN may explain the decrease over time from, for example, 40 U/L to 30 U/L in men and from 30 U/L to 19 U/L in women.[2,3] However, when interpreting ALT values, it should be noted that increases within the normal range are associated with liver-related and non–liver-related morbidity (ie, diabetes mellitus, cardiovascular disease) and mortality.[4–7]

Although several studies have noted age dependence for ALT, particularly in men,[2,8–14] age-adjusted cut-off values are not currently a broad topic of discussion. Few studies, however, have had the sample size to resolve age dependence adequately. Moreover, ethnicity and selection criteria influence results and have to be verified in large and disparate populations. Hence, we analyzed ALT along with aspartate aminotransferase (AST) and γ-glutamyltransferase (GGT) in more than 1,300,000 consecutive blood samples from a large laboratory serving medical practices and hospitals in Germany.

Methods

Consecutive blood samples from 2015 to 2017 were analyzed retrospectively from a laboratory (LADR Centrallab Dr. Kramer & Colleagues, Geesthacht) servicing a broad spectrum of medical practices (general practitioners and specialists) and hospitals in northern Germany. All blood samples were considered in which ALT, AST, or GGT were measured and were analyzed on Beckman Coulter autoanalyzers according to International Federation for Clinical Chemistry criteria (Beckman Coulter Ireland, Inc, Lismeehan, Ireland; O'Callaghan's Mills, Co, Clare, Ireland). The ULN for ALT and AST is 35 U/L for women and 50 U/L for men, based on a consensus report.[15] For GGT the respective ULNs are 40 U/L and 60 U/L for women and men. Cut-off values for increased values of the De Ritis ratio (AST/ALT) were 1.3 for women and 1.7 for men.[16] Age was categorized in decades (18–24, 25–34, and so forth).

The data were available only in anonymized form, meaning that it was not possible to acquire further clinical information. In particular, parameters such as body mass index or alcohol consumption were not available, and the clinical indication for the blood sample also was not available. However, because of the known association between iron stores and alcohol intake,[17,18] ferritin was analyzed using a cut-off value of 400 ng/mL in men and women older than 60 years of age, and 150 ng/mL in women younger than age 60.

Analyses were performed for (1) the whole cohort; (2) subjects at a check-up because of occupational regulations and not for health reasons, which we refer to in this article as a *prescribed routine check-up*; and (3) a healthy cohort defined to be patients without increased GGT, triglyceride, cholesterol, glycated hemoglobin, or glucose (according to Prati et al[2]) levels, and without known hepatitis B (hepatitis B surface antigen or anti–hepatitis B core positive) in any of the blood samples, but without any restriction on ALT or body mass index. Analyses also were performed using 1 random sample per patient, that is, each patient was considered in the analysis with exactly 1 blood sample, and for those patients who provided multiple samples the choice was made randomly. Such an analysis is equivalent to using a mean value for each patient. Finally, the maximal and minimal influence of multiple samples on percentiles was explored in a sensitivity analysis taking the maximal or minimal value per patient.

The anonymous transfer of data and their analysis were approved by the local ethics committee of the University of Leipzig (199/18-ek).

Statistical Analysis

For proportions, the Wilson CI was used. Because of the huge number of blood samples, it was possible to forgo model-based methods such as quantile regression to estimate age dependence. Instead, estimates with CIs were found for each age or age category and combined using smoothing splines. Problems of estimating high percentiles, especially in skewed distributions, thus are minimal.[19] For analyses considering the Pearson

correlations between ALT, AST, and GGT, 1 random blood sample per patient was used, values were treated on a logarithmic scale, and the Fisher transformation was used for the CI. Multiple blood samples from prescribed routine check-ups were analyzed regarding changes in time with a mixed model containing log(ALT) as the independent variable; time since first measurement; and sex, age category, and their interaction as fixed effects with patient identification as a random term. Multiple blood samples from other sources were not analyzed regarding time variation because information on the underlying disease and interventions were lacking.

What You Need to Know

Background

Upper levels of normal for alanine aminotransferase (ALT) generally take sex into account, but not age. This simplification may lead to misclassification and burden the patient and health system unnecessarily.

Findings

There is an extreme age dependence in ALT values for men: increased values were seen in 20.0% (95% CI, 19.5%–20.4%) of patients in the age group of 25 to 34 years, but in only 6.7% (95% CI, 6.4%–7.0%) for the ages of 65 to 74 years.

Implications for patient care

Current guidelines and reference values for ALT imply that subsequent diagnostics are needed for a large proportion of young men. Our data strongly suggest that age adaptation should be considered.

Results

Participant Characteristics

A description of the participants and their blood samples is provided in Table 1. There were almost no blood samples from the prescribed routine check-up for participants older than the age of approximately 65 (age of retirement), leading to a younger average age. Moreover, although 50.8% of all blood samples were from female participants, this was true for only 29.9% from the prescribed routine check-up. A total of 310,905 (22.7%) of the blood samples were deemed to

Table 1. Blood Sample and Patient Characteristics According to Cohort

	All patients	Patients from prescribed routine check-ups	Healthy patients according to laboratory values
Number of blood samples			
ALT only	33,884 (2.5%)	666 (0.6%)	7585 (2.4%)
AST only	24,350 (1.8%)	0 (0%)	5985 (1.9%)
GGT only	303,337 (22.2%)	3091 (2.7%)	54,911 (17.7%)
ALT and AST only	33,297 (2.4%)	272 (0.2%)	9399 (3.0%)
ALT and GGT only	237,040 (17.3%)	54,432 (47.5%)	58,356 (18.8%)
AST and GGT only	41,442 (3.0%)	4070 (3.6%)	13,907 (4.5%)
ALT, AST, and GGT	695,830 (50.8%)	52,132 (45.5%)	160,762 (51.7%)
Total	1,369,180	114,700	310,905
Number of patients			
1 blood sample	350,865 (58.3%)	102,976 (95.2%)	160,275 (77.3%)
2 blood samples	107,438 (17.9%)	4394 (4.1%)	27,203 (13.1%)
3 blood samples	54,537 (9.1%)	587 (0.5%)	9584 (4.6%)
4–10 blood samples	75,731 (12.6%)	199 (0.2%)	9196 (4.4%)
>10 blood samples	13,208 (2.2%)	10 (< 0.1%)	1131 (0.5%)
Total	601,779	108,166	207,389
Number of females	305,620 (50.8%)	31,833 (29.9%)	111,970 (54.0%)
Age, *y*			
18–24	41,016 (6.8%)	12,652 (11.9%)	31,111 (15.0%)
25–34	72,167 (12.0%)	24,168 (22.7%)	45,322 (21.9%)
35–44	86,260 (14.3%)	22,454 (21.1%)	38,394 (18.5%)
45–54	130,561 (21.7%)	29,437 (27.7%)	38,532 (18.6%)
55–64	109,266 (18.2%)	16,434 (15.5%)	22,954 (11.1%)
65–74	77,411 (12.9%)	920 (0.9%)	14,555 (7.0%)
75–84	65,901 (11.0%)	181 (0.2%)	12,696 (6.1%)
85–94	18,302 (3.0%)	41 (< 0.1%)	3629 (1.7%)
95–104	895 (0.1%)	16 (< 0.1%)	196 (0.1%)
Means (SD)	58.5 (18.0)	41.4 (12.7)	46.8 (19.0)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; SD, standard deviation.

come from healthy participants, 54,762 (17.6%) of whom were derived from the prescribed routine check-up.

Alanine Aminotransferase

There is an extreme age dependence in ALT values for men, in which the 95th percentile reached values of approximately 80 U/L at the age of 35 and decreased to less than 50 U/L by the age of 75 (Figure 1). By using the age-independent, cut-off value of 50 U/L for men, this implies increased values for 20.0% (95% CI, 19.5%–20.4%) of men between the ages of 25 and 34, but in only 3.5% (95% CI, 3.3%–3.8%) between the ages of 75 and 84 (Figure 2). This qualitative behavior also holds for the prescribed routine check-up patients and the healthy cohort. Taking the maximal or minimal ALT value per patient had little effect on the percentiles (Supplementary Figure 1).

Aspartate Aminotransferase

In contrast to ALT, there was little age dependence for AST (Supplementary Figure 2). The 95th percentile was approximately 55 U/L up to the age of 60, before decreased to approximately 45 U/L by the age of 80. The 95th percentile for women younger than the age of 50 was approximately 40 U/L, before reaching 45 U/L by the age of 60. This small change around the time of menopause has a large effect on the percentage higher than the ULN, however, which increased from less than 7% in women younger than the age of 45 to more than 12% in women older than the age of 55 (Supplementary Figure 3).

γ-Glutamyltransferase

Although median GGT does not change much with age, the 95th percentile increases quickly in men from 50 to 140 U/L from the ages of 20 to 60, and in women from 35 U/L steadily throughout life, reaching 100 U/L by the age of 70 (Supplementary Figure 4). This corresponds to more than 20% of men and women alike who have GGT values greater than 1 ULN from the age of 55 onward (Supplementary Figure 5). The definition of the healthy cohort requires a GGT less than the ULN, meaning that analyses were not sensible for this cohort.

Sensitivity Analysis With One Blood Sample per Patient

The earlier-described analyses were repeated, taking 1 random blood sample per patient. This resulted in almost identical results (see Supplementary Table 1, Supplementary Figure 6 and Supplementary Figure 7).

Correlation Between Alanine Aminotransferase, Aspartate Aminotransferase, and γ-Glutamyltransferase, and the De Ritis Ratio: Aspartate Aminotransferase/Alanine Aminotransferase

The Pearson correlation coefficient was 0.752 (95% CI, 0.751–0.754) between the logarithms of ALT and AST, 0.552 (95% CI, 0.550–0.554) between those of ALT and GGT, and 0.514 (95% CI, 0.512–0.517) between those of AST and GGT.

Table 2 shows how increased levels of ALT, AST, and GGT are inter-related. There are large differences between those with or without increased GGT. For example ALT and/or AST were increased in 8.8% of the population with normal GGT levels compared with 43.1% when GGT was increased. Moreover, one expects by definition that approximately 5% of a healthy population would have increased ALT values. When GGT was normal, this expectation was met very well in the women in our study (4.7% $<$55 y, 6.0% of women age $\geq$55 y), and for the older men (4.3% for men age $\geq$55 y). However, in men younger than age 55 with normal GGT levels, 11.7% of them had increased ALT levels.

Supplementary Table 2 provides the median values for the De Ritis quotient (AST/ALT) by age and sex along with the percentage of samples with increased values. Young women had median values of approximately 1.3, that decreased to approximately 1.1 around the age of 60 years before increasing again. Men had lower values that began around 1.1 in the youngest age group, and decreased to less than 0.9 by the age of 45 before increasing again. Approximately 5% of men and women in the youngest age group had increased values, a percentage that increased to more than 20% in older men.

Association Between Alanine Aminotransferase and Ferritin

Ferritin and ALT values were available in 64,075 samples, making up 6.5% of the samples with normal ALT and 5.5% of those with increased ALT levels. In men aged 25 to 34, 3.2% of those with normal ALT levels had increased ferritin compared with 21.1% with increased ALT. In women of the same age group, the corresponding numbers were 4.1% and 19.5%.

Changes in Alanine Aminotransferase Level Over Time for Patients From Prescribed Routine Check-Ups

There were 11,212 blood probes from 4950 patients at prescribed routine check-ups with ALT values available. Values decreased by a factor of 0.991 (95% CI, 0.983–0.999) per year within this 3-year observation time according to a mixed model correcting for sex, age category, and their interaction. The SD for a given patient

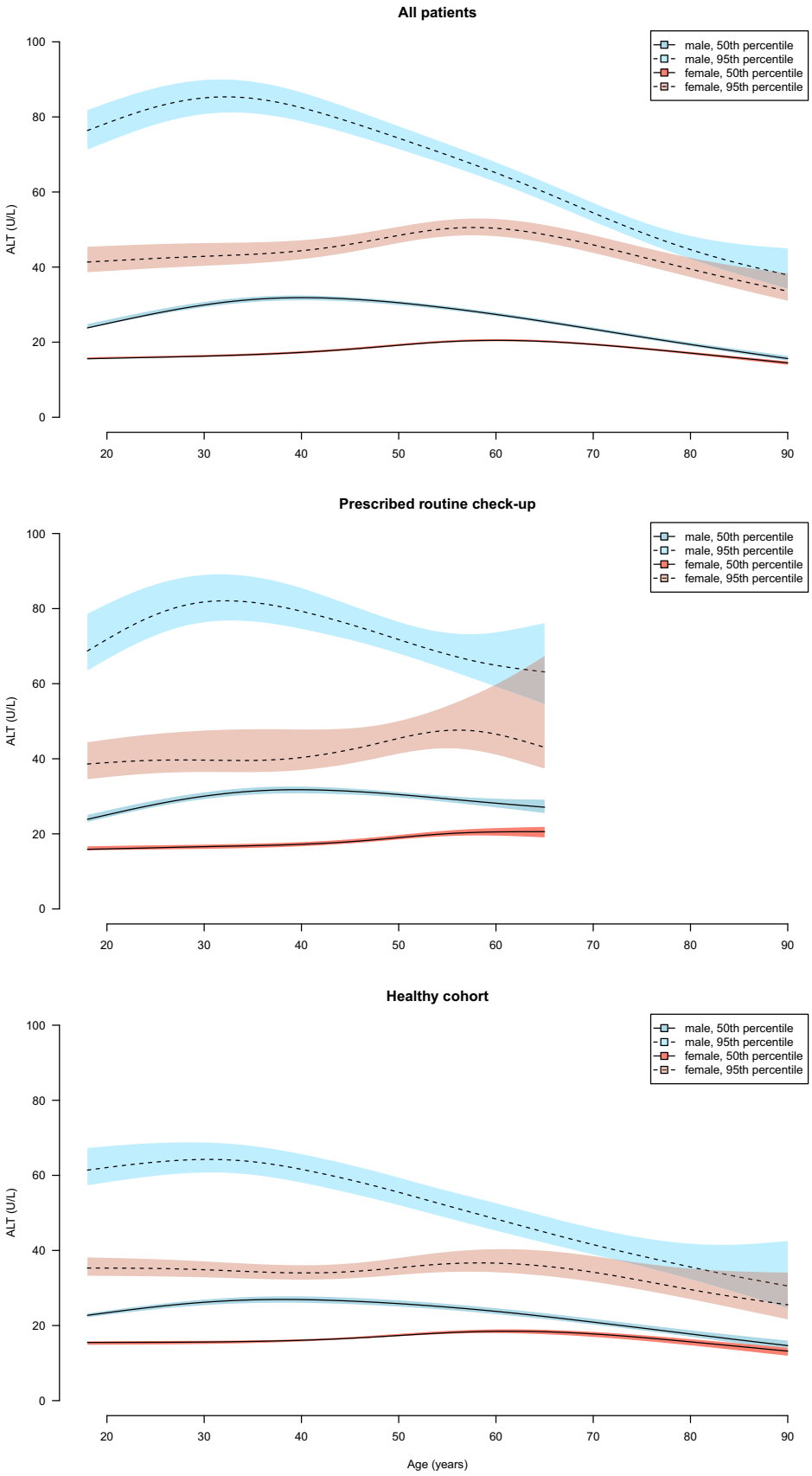

Figure 1. The concentration of alanine aminotransferase (ALT) for males and females is shown for the 50th and 95th percentiles as a function of age. The shaded regions depict 95% confidence bands. For prescribed routine check-ups, it is only sensible to provide estimates up to the typical age of retirement, here taken to be 65.

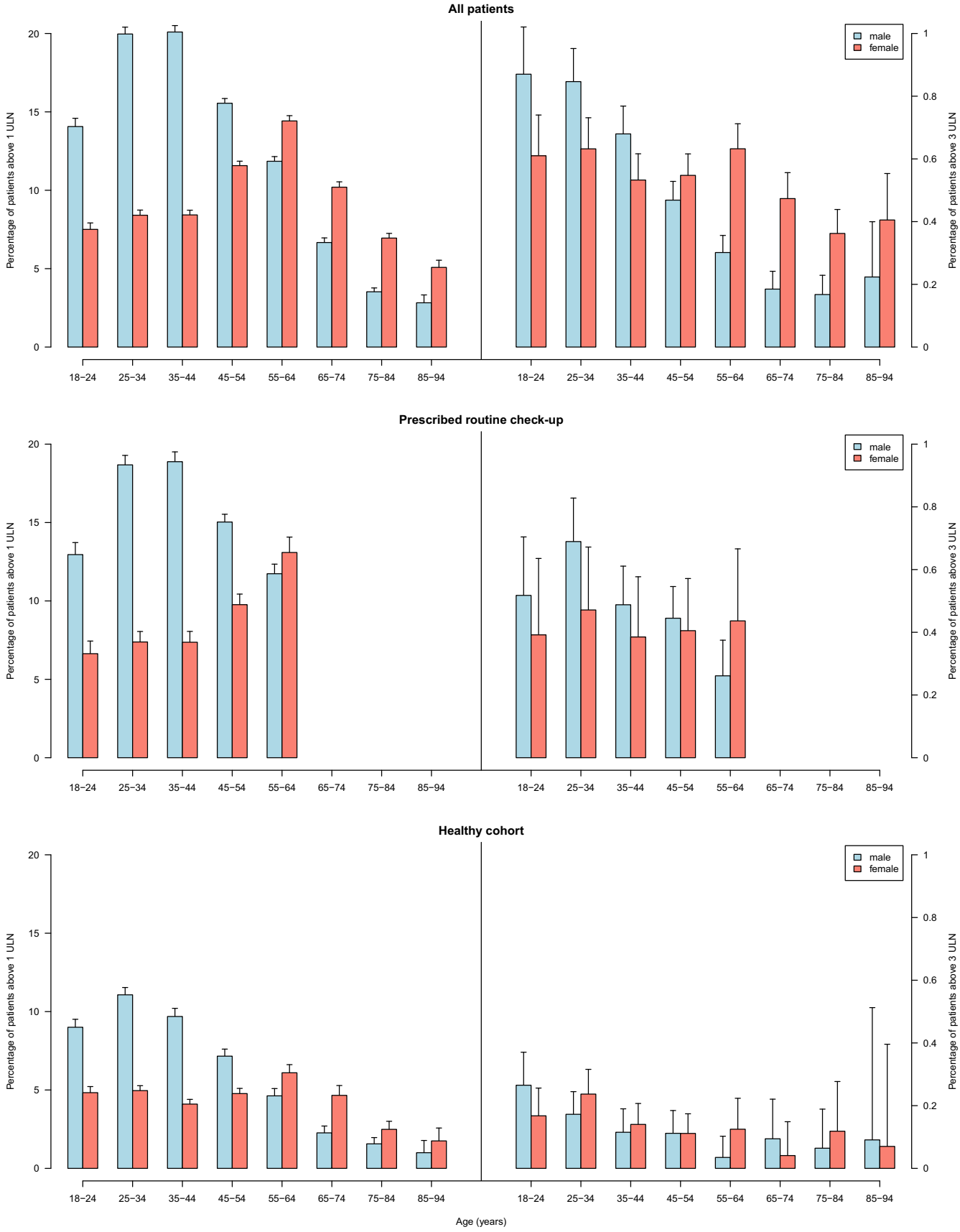

Figure 2. The percentage of patients with alanine aminotransferase (ALT) levels greater than the upper level of normal (ULN) (*left panels*) or 3 times the ULN (*right panels*) is depicted for males and females. *Whiskers* represent a 95% CI.

Table 2. Dependence Between ALT, AST, and GGT, Including Age and Sex

	Normal AST level	Increased AST level
Normal GGT, whole population		
Normal ALT	240,200 (91.2%)	4605 (1.7%)
Increased ALT	12,679 (4.8%)	6024 (2.3%)
Increased GGT, whole population		
Normal ALT	36,915 (56.9%)	3757 (5.8%)
Increased ALT	10,644 (16.4%)	13,566 (20.9%)
Normal GGT, men <55 y		
Normal ALT	63,012 (87.3%)	732 (1.0%)
Increased ALT	6733 (9.3%)	1718 (2.4%)
Elevated GGT, men <55 y		
Normal ALT	7661 (47.2%)	403 (2.5%)
Increased ALT	4840 (29.8%)	3340 (20.6%)
Normal GGT, men ≥55 y		
Normal ALT	50,544 (94.7%)	529 (1.0%)
Increased ALT	1751 (3.3%)	556 (1.0%)
Increased GGT, men ≥55 y		
Normal ALT	11,339 (67.8%)	945 (5.7%)
Increased ALT	1967 (11.8%)	2465 (14.7%)
Normal GGT, women <55 y		
Normal ALT	73,095 (92.0%)	1511 (1.9%)
Increased ALT	2632 (3.3%)	2188 (2.8%)
Increased GGT, women <55 y		
Normal ALT	5356 (49.8%)	498 (4.6%)
Increased ALT	1878 (17.5%)	3027 (28.1%)
Normal GGT, women ≥55 y		
Normal ALT	53,549 (91.5%)	1833 (3.1%)
Increased ALT	1563 (2.7%)	1562 (2.7%)
Increased GGT, women ≥55 y		
Normal ALT	12,559 (59.3%)	1911 (9.0%)
Increased ALT	1959 (9.3%)	4734 (22.4%)

NOTE. One random blood sample per participant was chosen.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase.

was a factor of 1.5. There were 4164 patients with 2 measurements, 3275 (78.7%) of whom had values less than the ULN on both occasions, 236 (5.7%) had values greater than the ULN only on the first occasion, 294 (7.1%) only on the second occasion, and 358 (8.6%) on both occasions. The subgroup of men younger than the age of 45 comprised 1500 of these patients, 1096 (73.1%) of whom had values less than the ULN on both occasions, 105 had values greater than the ULN (7.0%) only on the first occasion, 117 (7.8%) only on the second occasion, and 182 (12.1%) on both occasions.

Discussion

Our analyses clearly show that there is a strong age dependence for ALT in men. Indeed, 10.1% of a healthy male population younger than age 45 had increased ALT values despite the fact that most definitions of ULN imply that it be 5% or lower. The age dependence is much weaker for ALT in women. The proportion of men with increased AST values did not depend strongly on age, whereas an increase was seen in women around the time of menopause. The proportion of men and women with increased GGT values increased steadily up to the age of approximately 65. These statements apply qualitatively to all 3 cohorts studied here and to the subset of 1 blood sample per patient.

Other studies that considered sex-specific age dependence in ALT also found a strong effect in men. Völzke et al[10] found that the odds ratio for increased ALT was 10 in males age 20 to 49 compared with age 50 to 79, and Ruhl and Everhart,[3] using lower cut-off values, reported 40% increased ALT in males age 20 to 39 compared with 20% older than the age of 60. Failure to distinguish between sex can lead to a masking of age dependence (see Table 3 from Park et al[12]). Age and sex dependence in AST and GGT was analyzed by Völzke et al,[10] who found very similar results to ours. A large study for the National Institute for Health Research in

the United Kingdom, used age- and sex-adapted cut-off values for ALT, AST, and GGT.[20] One study examined the age and sex dependence of the De Ritis ratio and found values between 0.86 and 1.04 for women and between 0.72 and 1.07 for men.[21] For women, the median values we found tended to be higher, but were similar for men except in the oldest age groups. Our values agree well with a healthy subcohort of 2700 participants, although age was not taken into account.[22] In addition to the De Ritis ratio, we previously analyzed Fibrosis-4 data from the same database used in this project and showed that more than 95% of males and females younger than age 45 years present with low Fibrosis-4 results, indicating the absence of advanced liver fibrosis.[23]

The clinical relevance of abnormal liver blood tests has been questioned.[10,24] Although evidence has suggested that increases in ALT values even within the ULN are associated with metabolic disorders, diabetes, and cardiovascular disease, there is little evidence that the ULN per se plays a particular role.[7,20,25] Moreover, it is known from a National Health and Nutrition Examination Survey analysis that approximately one third of increased AST or ALT values are found to be normal if retested within 3 weeks.[26] Our data from prescribed routine check-ups corroborate that a large proportion of increased values normalize a short time later. Without taking clinical context into account, laboratory results alone are not always meaningful and correlated with prognosis. For example, even an ALT value greater than 3 ULN may have no relevance for a self-limiting acute hepatitis A patient.

The 95th percentile for GGT increases with age, which is likely to reflect the increased prevalence of obesity and diabetes[27] and increased GGT predicts morbidity and mortality.[6] The question our data on ALT beg is if the high prevalence of increased values among men between the ages of 25 and 45 represents a clinical problem. We note that, if so, it resolves itself by the age of 60, before a relevant number has died. A biopsy-controlled study of patients with chronically increased ALT or AST values found that patients were younger than the age of 45 on average and only 6 of 81 (7%) had fibrosis or cirrhosis.[28] One might hypothesize that risky alcohol consumption is at the root of it. However, a variety of arguments have shown that this cannot go far in explaining increased ALT values in younger men. For one, the German alcohol atlas shows that 14% of men aged 25 to 34 drink more than 20 g of alcohol per day compared with 24% of men aged 55 to 64.[29] Two articles addressing age and ALT values found that alcohol consumption was associated with only a 1.1-U/L increase in ALT level[11] or that consumers vs abstainers had mean values that were 1.3 U/L higher in men and 0.0 U/L in women.[2] Ferritin, which is associated with alcohol intake[17] and fatty liver disease,[30,31] also fails to indicate a higher proportion of increased values in young men compared with young women. Finally, if alcohol were the explanation for the observed ALT values in younger men, then one would expect AST values to parallel these changes, but the De Ritis ratio was lower in men at the age of 30 compared with 70.

Recent articles have suggested adopting a lower ULN for ALT,[3,8–10,13,24] but acknowledge that the "utility of labelling a large minority of the population as having liver injury [is]… uncertain."[3] If one considers ULNs to be epidemiologic descriptions of healthy populations, then ignoring age dependence for ALT in males leads to poor estimates. If one considers ULN to be a clinical tool for diagnosis and prognosis, then studies extending over decades would be necessary to establish optimal cut-off values.

A limitation of our study was the lack of data on obesity status and we are not in a position to be able to propose specific cut-off values for liver enzyme levels. One must bear in mind that obesity and diabetes prevalence increase substantially with age and that invoking these as the explanation for increased ALT values in young men is particularly challenging, especially considering the opposite observations in GGT. Our hypothesis is that the distribution of ALT in young men includes a large proportion of high values that may not indicate any physiological problem whatsoever.

Because GGT and ALT are correlated, including normal GGT as part of the definition of healthy may mean that the prevalence of increased ALT is underestimated, especially in older patients, but not differentially between men and women. This correlation may account for the quantitative difference seen in the lower 2 panels of Figure 2, although the same qualitative message is seen in both. A further minor limitation was the lack of data regarding hepatitis C, which has a prevalence of 0.3% in Germany[32] and therefore cannot affect the results meaningfully. Despite the very large number of blood samples arising from different clinical disciplines, the blood tests were performed by a single laboratory, thus limiting generalizability.

In conclusion, although current guidelines recommend flexible interpretation of increased liver enzyme levels after review of previous results, past medical history, and current medical condition, the analyzed reference values for ALT imply that subsequent diagnostics are needed for a large proportion of young men. This is not true for AST or GGT. Because increasing ALT values are associated with liver-related and non–liver-related morbidity and mortality, further diagnostics should be initiated if ALT values are at the 95th percentile (80 IU/L in young men), although other factors such as the presence of metabolic syndrome also must be accounted for when deciding to pursue additional diagnostics, regardless of ALT levels. However, our data strongly suggest that age adaptation for ALT reference ranges should be considered.

Data Sharing Statement

Data will be shared upon reasonable individual request and consultation of the ethics committee and the data protection officer if indicated.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2021.01.039.

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