

Differences in Sensitivity to Alcohol Exposure Among Liver Function Indicators and Their Methodological Impact on Dose-Response Research in ALD

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摘要 | Dose-response studies in alcohol-related liver disease (ALD) vary widely in their choice of effect indicators, making low-risk drinking thresholds difficult to compare across studies. This narrative review examines recent literature to compare the sensitivity of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), the AST/ALT ratio, the AST-to-platelet ratio index (APRI), and the fibrosis-4 index (FIB-4) in reflecting alcoholic liver injury. We searched PubMed, CNKI, Wanfang, and other databases from inception to September 13, 2026, focusing on ALD liver function indicators and non-invasive tests. The available evidence suggests that GGT and the AST/ALT ratio appear to be more sensitive to alcohol intake than ALT. GGT can rise even in light-to-moderate drinkers and often becomes abnormal earlier than ALT or AST. The AST/ALT ratio rises more steeply with increasing alcohol consumption. When ALT is used as the sole effect indicator, the dose-response curve tends to be flattened, which may lead to a higher estimated threshold. When GGT or the AST/ALT ratio is used as the effect indicator, the curve is steeper, and significant liver injury may detect biochemical abnormalities at lower doses. However, because this is a narrative review, most existing evidence is indirect, and few studies have directly compared the slopes of these indicators within the same cohort. We recommend that future studies combine multiple indicators in a comprehensive assessment model and use objective alcohol markers to calibrate dose assessment.

关键词 | Alcohol-related liver disease; Alcohol consumption; Liver function indicators; Gamma-glutamyl transferase; AST/ALT ratio

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1 Introduction

Alcohol-related liver disease (ALD) is one of the leading causes of chronic liver disease and cirrhosis worldwide. According to World Health Organization reports, harmful alcohol use caused approximately 3 million deaths globally in 2016, accounting for 5.3% of all deaths. In Europe, alcohol is estimated to cause

about 40% of premature liver-related deaths each year. ALD accounts for at least half of cirrhosis cases and is the most common indication for liver transplantation ^[1]. Its disease burden is expected to continue rising between 2015 and 2030 ^[2]. The disease spectrum of ALD covers a continuum from simple steatosis and alcoholic steatohepatitis to progressive fibrosis, cirrhosis, and even hepatocellular carcinoma ^[3,4]. Early stages are usually asymptomatic, and patients are often

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<https://doi.org/10.68070/hrq3m447>

identified only when decompensated cirrhosis complications appear [5]. A global survey by Shah et al. showed that, compared with liver disease of other etiologies, ALD is diagnosed at the latest stage [5]. In this context, clarifying the dose-response relationship between alcohol consumption and liver injury—that is, how much and for how long drinking harms the liver—is fundamental to ALD clinical management, public health policy, and clinical research design. It directly affects the scope of health education, the starting point for early screening, and the timing of intervention [6].

To ensure conceptual clarity, in this review, “effect indicator” refers to a biochemical measurement used to reflect the state of liver injury (e.g., ALT and GGT); “slope of the dose-response curve” refers to the rate at which the effect indicator increases as alcohol intake increases. The steeper the slope, the more sensitive the indicator is to alcohol exposure. With respect to exposure assessment, commonly used international indicators include average daily ethanol intake (g/d), drinking years, and cumulative ethanol exposure (g·years), but each has limitations. Average daily intake masks differences in drinking patterns. Drinking years cannot reflect actual cumulative dose. Cumulative exposure depends on patients’ recall of drinking behavior from decades ago [6,7]. Mellinger et al. noted that accurate quantification of alcohol exposure is a core challenge in ALD clinical research. Self-reported drinking is subject to recall bias and social desirability bias, which may lead to erroneous estimation of dose-response relationships [7]. In addition, existing ALD dose-response studies vary in their choice of effect indicators. ALT, AST, GGT, the AST/ALT ratio, APRI, and FIB-4 differ in sensitivity to alcohol exposure, making thresholds from different studies difficult to compare [8]. When comparing indicators, three dimensions must be clearly distinguished: (1) sensitivity/responsiveness to alcohol intake (e.g., GGT); (2) specificity for alcohol-related injury (e.g., AST/ALT); and (3) predictive ability for clinical outcomes (e.g., APRI/FIB-4). Existing reviews have mostly focused on non-invasive fibrosis scores or alcohol biomarkers in ALD. We include APRI and FIB-4 in the discussion because they often appear alongside liver enzymes in routine tests; however, in this article, we explicitly position them as supplementary indicators of fibrosis severity rather than primary indicators of recent alcohol exposure.

Unlike previous reviews focused on non-invasive tests, this review specifically addresses how the choice of effect indicator affects the slope and threshold of the dose-response curve. For example, Johansen et al. and Israelsen et al. reviewed non-invasive tests separately, but they did not focus on how effect indicator selection affects the slope of dose-response curves. Therefore, this review aims to: (1) compare the responsiveness of commonly used liver function indicators to alcohol exposure; (2) examine how indicator selection affects the shape of the dose-response curve and estimates of low-risk thresholds; and (3) propose methodological recommendations for future same-cohort studies.

2 Methods

This article is a narrative review. This review searched only PubMed, CNKI, and Wanfang, from database inception to September 13, 2026. Other databases such as Embase and grey literature were not searched. As a narrative review, it was not registered in PROSPERO, and no formal bias assessment or quantitative synthesis was performed. The Chinese search string was as follows (translated): (“alcoholic liver disease” OR “ALD”) AND (“dose-response” OR “alcohol intake” OR “drinking years”) AND (“liver function” OR “ALT” OR “GGT” OR “AST/ALT”). The English search string was: (“alcohol-related liver disease” OR “alcoholic liver disease” OR “ALD”) AND (“dose-response” OR “dose-response relationship” OR “alcohol intake” OR “drinking amount”) AND (“ALT” OR “AST” OR “GGT” OR “AST/ALT ratio” OR “APRI” OR “FIB-4” OR “liver function”). Inclusion criteria were: the study population was an ALD or alcohol-exposed population; the study reported an association between alcohol consumption and at least one liver function indicator; and the study provided effect size or threshold information. Exclusion criteria were: case reports or conference abstracts only; no quantitative alcohol consumption data; and a focus only on non-alcoholic liver disease. The initial search yielded 130 records. After removing duplicates and screening titles and abstracts, 61 full texts were obtained after excluding irrelevant records, and 58 studies were finally included. This article first outlines commonly used indicators, then compares their sensitivity, analyzes influencing factors, and finally proposes optimization strategies.

3 Common Liver Function Indicators in ALD and Their Pathophysiological Significance

To avoid conceptual confusion, four types of markers in ALD research must be strictly distinguished: (1) Exposure markers: e.g., self-reported alcohol intake, PEth, and EtG; these answer “how much alcohol was consumed” and do not directly reflect pathological changes. (2) Biochemical response/induction markers: e.g., GGT and ALP; these reflect alcohol-induced enzyme induction and a cholestatic tendency, representing physiological adaptation or early stress rather than hepatocyte necrosis. (3) Hepatocyte injury markers: e.g., ALT and AST; these reflect increased cell membrane permeability or parenchymal necrosis. (4) Fibrosis/staging markers: e.g., APRI, FIB-4, and ELF; these reflect long-term cumulative matrix remodeling and disease stage and cannot serve as acute injury indicators.

3.1 Hepatocyte injury markers

ALT is mainly present in the cytoplasm of hepatocytes and is highly sensitive to changes in hepatocyte membrane permeability and hepatocyte necrosis [9]. AST is present in both the cytoplasm and mitochondria of hepatocytes, and mitochondrial AST (mAST) accounts for about 80% of total AST in hepatocytes [10]. When hepatocytes are damaged, cytoplasmic ALT and AST are released into the blood, leading to elevated serum enzyme activity.

In ALD, AST elevation typically exceeds ALT elevation, and the AST/ALT ratio is often greater than 1.5 or even 2 [11,12]. This is opposite to the common ALT > AST pattern in viral hepatitis and non-alcoholic fatty liver disease (NAFLD). Rasmussen et al. studied 462 patients with early ALD and showed that the AST/ALT ratio was positively correlated with liver biopsy-confirmed fibrosis stage and risk of liver-related events [13].

3.2 Cholestasis and alcohol-induced enzymes

GGT is a membrane-bound enzyme found mainly on biliary epithelial cells and hepatocyte membranes [14]. Alcohol intake can induce GGT synthesis in hepatocyte microsomes [15,16]. GGT elevation is mainly caused by alcohol-induced increases in hepatic microsomal enzyme activity (such as cytochrome P450 2E1) and oxidative stress. GGT

shows a dose-dependent induction response to alcohol exposure, but it is also regulated by inflammatory cytokines secreted by adipose tissue; therefore, false positives are likely in obese individuals. The high sensitivity of GGT to alcohol exposure makes it an important tool for alcohol misuse screening and early identification of ALD.

Alkaline phosphatase (ALP) is markedly elevated in cholestatic liver injury [17]. However, in ALD, ALP elevation is usually less prominent than GGT elevation and is more often seen in alcoholic hepatitis with cholestasis or decompensated cirrhosis [18]. The sensitivity of ALP to alcohol exposure is far lower than that of GGT, so it is rarely used as a primary effect indicator in ALD dose-response studies.

3.3 Liver synthetic function and composite scores

Albumin (ALB), total bilirubin (TBil), and prothrombin time/international normalized ratio (PT/INR) reflect liver synthetic function and disease severity and are mostly used for assessment in intermediate and advanced stages [13]. These indicators usually do not change significantly in early ALD, so they are not suitable as effect indicators in dose-response studies.

APRI and FIB-4 are commonly used non-invasive fibrosis scores, and both depend on AST and platelet count [19,20]. In ALD, their elevation reflects the dual effect of increased AST and decreased platelets [13]. Garg et al. showed that APRI ≥ 1 had a sensitivity of 80.2% and specificity of 88.9%, while FIB-4 ≥ 3.24 had a sensitivity of 44% and specificity of 100% [21]. Thus, if APRI or FIB-4 is used as the effect indicator, a high threshold may miss many light-to-moderate drinkers, while a low threshold may include many patients with non-alcoholic liver injury. APRI and FIB-4 are essentially fibrosis scores that reflect cumulative fibrotic effects. They are not suitable for assessing recent alcohol exposure alone, but can serve as supplementary indicators of injury severity.

4 Differences in Sensitivity to Alcohol Exposure Among Different Indicators

Common liver function indicators in ALD reflect different pathological processes, and differences in their sensitivity underlie discrepancies in dose-response curves.

4.1 High sensitivity of GGT to alcohol exposure

Among ALD-related liver function indicators, GGT is the most sensitive to alcohol exposure. In heavy drinkers, the increase in GGT is significantly greater than that of other liver enzymes [8,15]. GGT can increase early after alcohol intake, even before obvious histological changes are detected [22]. However, this view is largely based on early observational studies and has not yet been confirmed by large-scale prospective cohorts; it should therefore be regarded as a hypothesis. There is a dose-dependent association between GGT levels and alcohol consumption, making it a potential quantitative indicator for assessing alcohol exposure [23].

Israelson et al. noted that GGT elevation in ALD patients is usually 3–8 times that of ALT, and its correlation with alcohol consumption is significantly stronger than that of ALT and AST [15]. Tavaglione et al. used phosphatidylethanol (PEth) as an objective marker of alcohol exposure and showed that 16% of patients with steatotic liver disease (SLD) underreported alcohol intake. If only self-report and traditional indicators such as ALT are used, their alcohol-related liver injury would be severely underestimated [24]. Consequently, dose-response studies using GGT as the effect indicator may have much higher statistical power than those using ALT or AST.

However, high sensitivity of GGT to alcohol exposure does not mean high specificity. GGT is also affected by obesity, metabolic syndrome, drugs (such as phenytoin and barbiturates), biliary tract diseases, and drinking patterns. Therefore, using GGT alone as the effect indicator may misclassify GGT elevation caused by non-alcoholic factors as alcoholic liver injury, especially in populations such as MetALD (metabolic dysfunction and alcohol-related liver disease) where metabolic and alcohol factors coexist. It is recommended to combine PEth, EtG (urinary ethyl glucuronide), or the AST/ALT ratio to improve alcohol attribution.

4.2 Limitations of ALT as an indicator of alcoholic liver injury

ALT is the most commonly used marker of liver injury in clinical practice, but it has significant limitations as an effect indicator in ALD. Neuman et al. studied 114 heavy drinkers (average alcohol intake 204 ± 148 g/d) and showed that ALT was only mildly

elevated (74 ± 67 U/L), and about half of the patients had ALT levels within the normal range [25]. Multiple studies have shown that the correlation between ALT and average daily alcohol intake is usually weaker than that of GGT and the AST/ALT ratio [23,26].

The mechanisms underlying the low sensitivity of ALT in ALD mainly include pyridoxal-5'-phosphate deficiency, which inhibits ALT activity [12]; alcohol-induced mitochondrial injury, which preferentially releases mAST rather than ALT [27]; and direct effects of alcohol on ALT gene expression that may differ from those on GGT [28]. Although the biochemical mechanisms are plausible, evidence from human studies on their absolute contribution to the low sensitivity of ALT remains limited. Using ALT as the effect indicator in dose-response studies may lead to severe underestimation of alcohol hepatotoxicity. If $ALT > 40$ U/L is used as the criterion for liver injury, many heavy drinkers will be incorrectly classified as having no liver injury [8]. Rasmussen et al. found that a considerable proportion of patients with significant liver injury confirmed by biopsy still had ALT levels within the normal reference range [13]. This may explain why some studies using ALT as the indicator concluded that moderate drinking is harmless to the liver [29].

It should be noted that the above inferences are mostly based on indirect comparisons across different studies. Few studies have directly fitted dose-response curves for ALT, GGT, and the AST/ALT ratio within the same cohort and compared their slopes and thresholds. Future studies should use PEth/EtG to calibrate alcohol exposure in prospective cohorts, fit dose-response curves with each indicator as the effect variable, and directly compare slopes and thresholds.

4.3 Characteristic changes in AST/ALT ratio

An AST/ALT ratio greater than 1.5, or even greater than 2, is one of the most characteristic laboratory findings in ALD. It reflects two mechanisms: increased AST release due to mitochondrial injury and relative suppression of ALT activity due to pyridoxal-5'-phosphate deficiency [11,12].

In ALD dose-response studies, the AST/ALT ratio has unique advantages as an effect indicator. It has high specificity for ALD [11], is associated with alcohol consumption and drinking years [30], and is associated with the degree of liver fibrosis and risk of liver-related events [13].

Ignat and Stefanescu noted that the AST/ALT ratio is valuable for distinguishing alcoholic hepatitis from decompensated cirrhosis, and its diagnostic specificity is superior to that of AST or ALT alone [31]. However, the AST/ALT ratio may lose specificity in cirrhosis because both AST and ALT can decrease in advanced cirrhosis, and the ratio may fall [32]. In addition, the AST/ALT ratio can increase in non-alcoholic steatohepatitis and some drug-induced liver injuries, but it usually does not exceed 1.5 [33]. Garg et al. found that the AST/ALT ratio had low diagnostic accuracy in the intermediate fibrosis stage, and the sensitivity of its optimal threshold (>1) was only 73.6%, with a specificity of 100% [21]. This suggests that the AST/ALT ratio may be more suitable for excluding advanced fibrosis than for early screening.

Taken together, these differences in sensitivity mean that defining liver injury by different indicators may produce different dose-response curves. A conceptual synthesis of the literature suggests: that the differences in response patterns and slopes among indicators become more evident. In the low-dose stratum (daily alcohol intake <20 g), ALT often remains within the normal reference range and shows almost no measurable response. In contrast, the GGT curve has already begun to rise at this stage, and the AST/ALT ratio may also show mild abnormalities. In the moderate-dose stratum (20–40 g/d), the slopes of the dose-response curves for GGT and the AST/ALT ratio increase markedly and show a steep upward trend. ALT may be only mildly elevated, with large inter-individual variability and a relatively flat curve. In the high-dose stratum (>40 g/d), although all three indicators increase significantly, the absolute change in GGT and its correlation with alcohol intake (r value) remain greater than those of ALT. This difference in curve shape, a flat ALT curve and a steep GGT curve, directly leads to a rightward shift of the threshold when ALT is used as the effect indicator (overestimating the low-risk threshold). In contrast, when GGT or AST/ALT is used, a significant inflection point can be captured at a lower dose. The above stratified pattern is only illustrative and must be validated in head-to-head analyses within the same cohort; it should not be interpreted as a pooled effect estimate.

It should be noted in advance that this review itself has unavoidable limitations, including limited database coverage (Embase and other databases were

not searched), possible language bias (English and Chinese only), and publication bias. In addition, because threshold definitions differed across studies and original individual-level data were lacking, we did not perform quantitative meta-synthesis. These limitations not only reduce the certainty of the evidence but also require restraint when interpreting conclusions drawn from the above indirect comparisons.

5 Effect Indicator Selection and Divergence in Dose-Response Conclusions

Differences among these indicators in sensitivity, specificity, and applicable stage directly lead to divergence in effect indicator selection across studies. This divergence affects not only the slope of dose-response curves but also the determination of low-risk drinking thresholds. For example, some studies using ALT as the effect indicator concluded that liver injury risk does not increase when daily alcohol intake is below 30 g in men or 20 g in women [34]. However, studies using GGT or the AST/ALT ratio as the effect indicator showed that even at daily alcohol intake as low as 20–30 g, GGT and the AST/ALT ratio already increased significantly [35,36].

This divergence is particularly prominent in discussions about whether moderate drinking benefits the liver. Some observational studies reported that light-to-moderate drinking was associated with lower NAFLD prevalence and better liver function indicators, but these studies mostly used ALT as the main effect indicator of liver injury [37]. However, when GGT or the AST/ALT ratio was used, the protective effect of light drinking often disappeared, and dose-dependent elevation even appeared [38]. Tavaglione et al. used PEth as an objective marker of alcohol exposure and found that 16% of SLD patients underreported alcohol intake. If only self-reported alcohol intake and traditional indicators such as ALT are used, these patients' alcohol-related liver injury would be severely underestimated [24]. Vanlerberghe et al. further confirmed that in patients with alcoholic cirrhosis, PEth had excellent accuracy for detecting any drinking and excluding increased/excessive drinking, with AUROC values of 0.986 and 0.936, respectively [39].

Neuman et al. studied 45 heavy drinkers before and after abstinence and showed that after about 1 week of abstinence, liver stiffness decreased from 32.9

± 29.7 kPa to 24.8 ± 27.1 kPa, and AST, GGT, and ALP decreased significantly, but ALT and bilirubin did not change significantly [25]. This suggests that GGT and AST recover faster, which reflects their closer association with recent alcohol exposure. ALT recovers more slowly, which suggests that it may be affected by other factors.

Garg et al. showed that $\text{APRI} \geq 1$ had a sensitivity of 80.2% and specificity of 88.9%, while $\text{FIB-4} \geq 3.24$ had a sensitivity of 44% and specificity of 100% [21]. If $\text{APRI} \geq 1$ or $\text{FIB-4} \geq 3.24$ is used as the criterion for liver injury, many light-to-moderate drinkers will be classified as having no liver injury, which underestimates the true harm of alcohol. If the threshold is lowered to $\text{APRI} > 0.5$ or $\text{FIB-4} > 1$, sensitivity can rise to 95.6% and 98.9%, but specificity falls to 0 and 88.9%, respectively [21], and the risk of misdiagnosis increases markedly. This sensitivity–specificity trade-off is particularly critical in dose-response studies. Low thresholds are suitable for screening to avoid missed diagnosis, while high thresholds are suitable for confirmation to avoid misdiagnosis. However, the two may yield entirely different shapes of dose-response relationships.

A recent systematic review and meta-analysis by

Tampaki et al. (including 33 studies and 7,504,674 individuals) provides the most comprehensive quantitative evidence to date for divergence in indicator selection. The results are shown in Table 1. The mean difference in GGT between metabolic dysfunction and alcohol-related liver disease (MetALD) and metabolic dysfunction-associated steatotic liver disease (MASLD) was 24.15 IU/L, much larger than that for AST (3.56 IU/L) and ALT (3.09 IU/L). Heterogeneity for GGT ($\tau^2 = 225.70$) was also much greater than that for AST ($\tau^2 = 6.74$) and ALT ($\tau^2 = 9.73$) [40]. This means that when alcohol intake increases from the MASLD level to the MetALD level, the change in GGT is about seven times that of AST and ALT. If ALT is used as the effect indicator, the dose-response difference between MetALD and MASLD may be severely underestimated and may even fail to reach statistical significance because of insufficient sample size. It should be emphasized that this is a cross-sectional between-group difference and cannot be equated with a longitudinal dose-response slope difference. In addition, the extremely high heterogeneity of GGT ($\tau^2 = 225.70$) indicates that this result should be interpreted with great caution.

Table 1: Meta-analysis results of differences in liver function indicators between MetALD and MASLD patients

Indicator	Mean difference	95% CI	P value	Heterogeneity τ^2	Number of studies	Number of participants
GGT	24.15 IU/L	17.51–30.79	<0.0001	225.70	33	7504674
AST	3.56 IU/L	2.55–4.58	<0.0001	6.74	33	7504674
ALT	3.09 IU/L	1.84–4.33	<0.0001	9.73	33	7504674

Note: Data are from Tampaki et al. [40]. MetALD, metabolic dysfunction and alcohol-related liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; CI, confidence interval; τ^2 , heterogeneity parameter (Tau-squared). This table shows cross-sectional mean differences between the MetALD and MASLD groups and is not equivalent to longitudinal dose-response curve slopes. The extremely high heterogeneity of GGT ($\tau^2 = 225.70$) substantially limits interpretation of the results and suggests unmeasured between-study variation. The “approximately seven-fold” mentioned in the main text is calculated from the ratio of mean differences ($24.15 / 3.56 \approx 6.8$) and is only a rough estimate for indirect comparison; it does not have statistical significance for slope differences.

The above divergence suggests that effect indicator selection affects not only threshold determination but is also influenced by drinking

patterns, metabolic comorbidities, and timing of detection. The next section analyzes these factors. In addition, it must be noted that the divergence in the

above dose-response curves mostly arises from indirect comparisons across studies. Such indirect comparisons have two main types of bias. The first is ecological fallacy: differences in baseline characteristics among cohorts (such as age, sex ratio, and BMI distribution) may mask or exaggerate the true differences among effect indicators. The second is measurement heterogeneity bias: different studies use different alcohol intake assessment tools (self-reported questionnaires versus PEth calibration), different blood collection timing (immediately on admission versus after abstinence), and different liver function testing platforms, all of which can lead to systematic shifts in effect sizes. Therefore, direct cross-study comparison of the slopes and thresholds of different indicators carries a high risk of false positives or false negatives. The current conclusions can only serve as a basis for generating hypotheses and urgently require head-to-head comparison within the same cohort. These indirect comparisons generate a testable hypothesis but cannot establish slope differences; therefore, the next section examines factors that alter indicator sensitivity.

6 Factors Affecting the Sensitivity of Liver Function Indicators

This section systematically analyzes the effects of drinking patterns, metabolic comorbidities, timing of detection, and abstinence status on the sensitivity of liver function indicators.

6.1 Effects of drinking patterns

Binge drinking and spread-out intake may have different effects on liver injury even when total alcohol intake is the same. In a Finnish population cohort study, Aberg et al. showed that binge drinking patterns were associated with increased risk of liver events, and this association remained significant after adjustment for total alcohol intake [41]. Binge drinking causes a sharp rise in blood alcohol concentration, which may exacerbate oxidative stress and mitochondrial injury, thereby more significantly increasing AST and GGT [42].

Kann et al. recently conducted a clinical cohort study of 104 patients with newly diagnosed ALD. They showed that within 90 days after diagnosis, 37% of initially abstinent patients resumed drinking. The abstinence rate indicated by PEth detection (37%) was

far lower than the self-reported abstinence rate (56%) [43]. Therefore, dose-response studies should record drinking patterns whenever possible and adjust for them in the analysis.

6.2 Effects of metabolic comorbidities

Obesity and metabolic syndrome alone can cause mild elevation of ALT and GGT, and this elevation is unrelated to alcohol exposure [44]. In ALD patients, those with metabolic syndrome usually have higher GGT and ALT levels than those without metabolic comorbidities, which may reflect a synergistic effect of metabolic dysfunction and alcohol hepatotoxicity [45].

Díaz et al. noted that ALD and non-alcoholic fatty liver disease (NAFLD) overlap extensively in pathophysiological mechanisms, and the two can synergistically promote liver fibrosis progression [4]. Tampaki et al.'s meta-analysis showed that BMI and HbA1c in MetALD patients were significantly lower than in MASLD patients (BMI mean difference -0.49 kg/m², HbA1c mean difference -0.14% , both $P < 0.05$), but triglycerides and high-density lipoprotein cholesterol were significantly higher than in MASLD patients [40]. This metabolic paradox suggests that MetALD patients may have a metabolic phenotype different from that of MASLD. If ALT is used as the effect indicator, this difference in metabolic phenotype may be underestimated.

6.3 Effects of timing of detection and abstinence status

Liver function indicators reflect alcohol exposure in a time-dependent manner. The half-life of GGT is about 14–26 days. After abstinence, GGT levels usually decrease significantly within 2–3 weeks, but complete normalization requires 4–6 weeks [46]. The half-lives of AST and ALT are shorter (about 17 and 47 hours, respectively), and they decrease faster after abstinence, but the AST/ALT ratio may remain elevated during early abstinence [47].

Neuman et al.'s study showed that after about 1 week of abstinence, AST, GGT, and ALP decreased significantly, but ALT and bilirubin did not change significantly [25]. This means that if studies include patients at different abstinence stages, their liver function indicators may reflect recent drinking rather than long-term cumulative alcohol effects, which may dilute or distort the dose-response relationship [48]. Therefore, dose-response studies should standardize the timing of blood collection as much as possible (for

example, within 24 hours after admission) and record abstinence time.

The preceding sections show that indicator selection, exposure measurement, and confounders jointly affect dose-response estimates; the next section translates these issues into a prioritized research agenda.

6.4 Bias and Reverse Causation

When examining the “protective effect” of moderate drinking, reverse causation and “sick-quitter bias” must be considered. People with health problems (such as early liver disease or other diseases) often voluntarily stop drinking; if studies incorrectly assign these individuals to the “non-drinking” or “abstinent” reference group, the “moderate drinking group” may appear relatively healthier. This bias, together with healthy drinker bias, may be an important source of erroneous conclusions in some observational studies that moderate drinking is beneficial.

7 Optimization Strategies and Future Roadmap

This section proposes strategies to optimize ALD dose-response research, including core indicator selection, multi-indicator combination, calibration with objective alcohol markers, and stratified modeling.

7.1 Current challenges

ALD dose-response research faces five main challenges. The specific molecular mechanisms are described in Sections 2 and 3. First, exposure measurement is inaccurate because self-reported drinking is affected by recall bias and social desirability bias, and PEth/EtG are not yet widely available. Second, effect indicators are non-specific: GGT is affected by metabolic and drug factors, ALT has low sensitivity, and the AST/ALT ratio may fall in advanced cirrhosis. These differences in non-specificity and sensitivity have profound molecular and pathological bases. Third, direct comparative evidence is lacking; no study has directly fitted dose-response curves for each indicator within the same cohort and compared slopes and thresholds. Fourth, confounding factors are complex, and interactions among drinking patterns, metabolic comorbidities, and abstinence status are difficult to fully adjust for. Fifth, ethical, regulatory, and cost accessibility issues exist, including alcohol information

privacy, PEth/EtG informed consent, genetic discrimination risk, and testing costs that limit grassroots promotion. These challenges are the starting point for subsequent optimization strategies. Based on the above methodological challenges, Section 7.2 identifies GGT and the AST/ALT ratio as core effect indicators.

7.2 Priority recommendation of GGT and AST/ALT ratio as core effect indicators

When constructing a dose-response model of alcohol consumption and liver injury, GGT and the AST/ALT ratio should be preferred effect indicators. GGT is highly sensitive to alcohol exposure and is suitable for early screening and effect assessment of low-dose alcohol exposure [15,16]. The AST/ALT ratio provides relatively specific information on the injury pattern of ALD, and its association with alcohol consumption and liver fibrosis makes it an important supplement for assessing injury severity [11,12].

Specifically, for studies aimed at detecting alcohol exposure, GGT should be the main effect indicator, supplemented by the AST/ALT ratio. In terms of operational details, we recommend prespecifying categorical or continuous variable analyses rather than relying only on a single clinical cutoff (such as >50 U/L in men). Comparing slopes for continuous variables can more sensitively capture subtle changes at low doses. For studies aimed at assessing the severity of liver injury, the AST/ALT ratio and AST-based composite scores (such as APRI and FIB-4) should be the main effect indicators, supplemented by GGT. Specifically, when building multivariable regression models, stratified analysis by fibrosis stage should be considered to avoid reverse causation bias caused by a falling ratio in patients with advanced cirrhosis. In addition, GGT and the AST/ALT ratio should be regarded as complementary “dual effect endpoints”: the former captures “whether exposure occurred,” and the latter assesses “how severe the injury is.” They should be fitted independently for dose-response in statistical analysis to avoid mutual dilution when combined into a single composite indicator. ALT can still be included in the detection panel as a routine liver injury marker, but it should not be used as the sole or primary effect indicator in ALD dose-response studies [13,15].

7.3 Combining multiple indicators to build a comprehensive assessment model

A single indicator cannot fully reflect the complexity of alcoholic liver injury. Combining multiple indicators in a comprehensive assessment model can improve assessment accuracy and robustness. The recommended comprehensive model should include GGT (reflecting alcohol exposure and cholestasis), the AST/ALT ratio (reflecting the pattern of alcoholic injury), ALT (a general marker of hepatocyte injury), platelet count (reflecting portal hypertension and fibrosis), and ALP (reflecting the cholestatic component).

In intermediate and advanced patients, non-invasive scoring systems such as APRI and FIB-4 can be added to account for both inflammatory activity and fibrosis [21,19,20]. Johansen et al. showed that FIB-4 and the ELF(Enhanced Liver Fibrosis Score) test perform well in ALD prognosis assessment, but their sensitivity in reflecting the dose-response relationship of alcohol exposure has not been systematically evaluated [49]. A 2026 study by Johansen et al. further noted that fibrotic activity and disease stage are complementary and independent predictors of ALD outcomes [50].

7.4 Introducing objective alcohol markers to calibrate dose assessment

One of the core challenges in dose-response research is accurate quantification of alcohol exposure. Self-reported alcohol intake is susceptible to recall bias and social desirability bias, which may lead to erroneous estimates of dose-response relationships [7]. Specifically, non-differential misclassification (e.g., all participants randomly underreport alcohol intake) usually biases the dose-response curve toward the null (i.e., the curve slope tends to flatten). However, differential misclassification (e.g., heavy drinkers underreport more severely than light drinkers) may bias the curve in either direction, thereby greatly distorting the true slope.

We recommend introducing objective alcohol markers such as PEth or urinary ethyl glucuronide (EtG) in dose-response studies to calibrate self-reported alcohol intake. PEth reflects alcohol intake over the past 2–4 weeks, and EtG reflects alcohol intake over the past 3–4 days. Combining the two can provide alcohol exposure information at different time scales [39,51]. PEth detection requires equipment such as liquid

chromatography-tandem mass spectrometry, which is still difficult to implement in primary healthcare institutions. However, in qualified medical institutions or clinical research, introducing PEth to calibrate dose assessment is valuable [24,39].

7.5 Establishing stratified and typed dose-response models

Because ALD is heterogeneous, dose-response models should fully consider stratification factors. We recommend stratification by metabolic phenotype (simple ALD vs MetALD), drinking pattern (daily spread-out vs intermittent binge), liver fibrosis stage (early vs advanced), sex, and genetic background [4,40].

Tampaki et al.'s meta-analysis showed that liver function indicators (AST, ALT, GGT) in MetALD patients were significantly higher than in MASLD patients, but significantly lower than in ALD patients, supporting MetALD as an independent disease entity [40]. However, the study also found no significant differences in most metabolic parameters between MetALD and ALD, suggesting that when alcohol intake reaches the MetALD level, the synergistic effect of metabolic dysfunction and alcohol hepatotoxicity may be close to saturation [40]. Therefore, dose-response studies should treat MetALD as an independent stratum and separately analyze its dose-response relationship relative to MASLD and ALD.

7.6 Priority should be given to head-to-head fitting of multiple indicators in the same cohort

To overcome the limitations of indirect evidence, future studies should prioritize multicenter prospective cohorts. The proposed research plan is as follows: ① Inclusion criteria: include light-to-moderate drinkers (average daily <40 g/d) and heavy drinkers, covering simple ALD, MetALD, and MASLD populations, to fully capture changes across different dose strata; ② Harmonized exposure and effect measurement: use self-reported diaries combined with PEth/EtG to calibrate exposure, collect blood within 24 hours after admission, and simultaneously measure ALT, AST, and GGT. Before statistical fitting, sample size and power for the low-dose stratum must be rigorously estimated in advance. For data analysis, restricted cubic splines (RCS) are recommended for nonlinear relationships; a two-part model can be used to address zero inflation caused by the completely non-drinking population; and mixed-effects models should be used

for repeated-measures data. ③ Statistical fitting: use restricted cubic splines (RCS) or piecewise linear regression models. After adjusting for the same covariates (age, sex, BMI, and metabolic indicators), fit dose-response curves with ALT, GGT, and AST/ALT as dependent variables, respectively; ④ Slope comparison: use the likelihood ratio test or Z test to directly compare slope differences among indicator curves in low-dose strata (<20 g/d and 20–30 g/d), and calculate the threshold dose at which each curve shows a significant inflection point. Only through such same-cohort head-to-head fitting can the hypothesis that “the ALT curve is flatter” be directly confirmed.

In addition, to strengthen causal inference, future studies may consider incorporating negative control outcomes or conducting Mendelian randomization (MR) analyses. However, appropriate caveats are required: MR analyses must exclude the interference of pleiotropy, and their conclusions reflect the effects of lifetime exposure, which may not be directly equivalent to the clinical effects of short-term interventions. Given limited resources, the three most essential and core steps for the next generation of studies are: (1) objective markers such as PEth/EtG must be introduced to calibrate self-reported alcohol intake; (2) blood collection timing must be standardized (e.g., within 24 hours after admission),

and the exact number of abstinence days must be recorded; and (3) head-to-head dose-response curve fitting for ALT, GGT, and AST/ALT using continuous variables must be performed within the same cohort.

7.7 Ethical, regulatory, and implementation considerations

When introducing PEth/EtG, research ethics and regulatory issues must be addressed in advance. Alcohol use information is sensitive personal health information and should be collected minimally, de-identified, stored encrypted, and access-restricted. PEth/EtG testing requires separate informed consent that explains the detection window, significance, possible false-positive and false-negative results, and how results will be returned. If genes such as ALDH2 and ADH1B are tested, the risk of genetic discrimination should be disclosed, and regulations on non-discrimination based on genetic information should be followed. Cost and accessibility should be graded. Primary care can use self-report combined with GGT, AST, and ALT. Qualified institutions can use urinary EtG or dried blood spot PEth [52–55]. PEth requires liquid chromatography-tandem mass spectrometry, so its accessibility at the primary level is limited. EtG can be tested in urine, but its window is short, so graded implementation is recommended.

Table 2: Proposed implementation framework for future ALD dose-response research

Step	Executable points	Corresponding challenge	Priority
Core indicator set	Exposure: g/d, drinking years, g·years, binge frequency, PEth/EtG; Effect: GGT, AST/ALT ratio, ALT, AST, PLT, APRI, FIB-4	Inaccurate measurement Non-specific indicators	Essential
Measurement	Self-report + PEth/EtG; standardized blood collection timing; record abstinence days	Inaccurate measurement Complex confounding	Essential
Stratification	Simple ALD/MetALD/MASLD; binge/spread-out; early/advanced; sex	Complex confounding	Essential
Validation	Multicenter prospective cohort; longitudinal repetition; external validation; prespecified sample size for low-dose stratum; interdisciplinary team	Lack of direct comparison Ethics and cost	Optional

Note: This table is a proposed framework by the authors based on literature [52–58] and the analysis in this article, not a direct data source; PEth, phosphatidylethanol; EtG, urinary ethyl glucuronide; PLT, platelet count. (ALD, alcohol-related liver disease; MetALD, metabolic dysfunction and alcohol-related liver disease; MASLD, metabolic dysfunction-associated steatotic liver

disease; PEth, phosphatidylethanol; EtG, urinary ethyl glucuronide; GGT, gamma-glutamyl transferase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PLT, platelet count; APRI, AST-to-platelet ratio index; FIB-4, fibrosis-4 index)

8 Conclusions and Limitations

Existing ALD dose-response studies show clear divergence in the selection of liver function indicators, which makes conclusions difficult to compare across studies. Different indicators differ markedly in sensitivity to alcohol exposure: GGT and the AST/ALT ratio are more sensitive than ALT alone. Using ALT as the sole indicator tends to underestimate alcoholic liver injury, flattening the dose-response curve and thus overestimating the low-risk drinking threshold. However, the AST/ALT ratio may fall in advanced cirrhosis because both AST and ALT decrease, so it is more suitable for excluding advanced fibrosis. Clinical judgment should combine platelet count, FIB-4, and other measures. The controversy over the protective effect of moderate drinking also needs to be re-examined. It may arise from abstainer bias, healthy drinker bias, socioeconomic confounding, and uncalibrated alcohol exposure.

In clinical practice, assessment of ALD patients should avoid relying solely on ALT. GGT, the AST/ALT ratio, and liver synthetic function indicators should be combined for comprehensive judgment. For primary healthcare institutions, GGT and the AST/ALT ratio are routine liver function test items, require no additional equipment, and are highly practical. For qualified institutions, objective alcohol markers such as PEth can be introduced to calibrate dose assessment, and non-invasive scores such as APRI and FIB-4 can be used to assist fibrosis assessment.

From the perspective of evidence-based medicine, the core conclusion of this article, that different effect indicators lead to differences in slopes and thresholds, should be defined as “low to moderate quality”. We used a narrative GRADE-like assessment framework. As described in Section 4, the evidence comes mainly from indirect comparisons across studies and is at risk of ecological fallacy and measurement heterogeneity bias. Therefore, the current conclusions based on indirect comparisons should be assigned an evidence level of “low to moderate” and urgently require confirmation by prospective same-cohort multi-indicator fitting studies. Future studies need to unify criteria for selecting effect indicators, control relevant confounding factors, and introduce objective

alcohol markers to calibrate dose data in order to build more accurate and comparable dose-response models. Only when both the dose side and the effect side are precise can the dose-response relationship be reliable and provide a solid evidence base for early identification, risk stratification, and public health policy making for ALD.

Author contributions

Jingyi Li: Writing-review & editing, Writing-original draft, Visualization, Investigation. Lin Xu: Writing-review & editing, Writing-original draft, Visualization, Investigation, Funding acquisition. Runmin Li: Writing-review & editing, Investigation, Funding acquisition. Yuanke Chen: Writing-review & editing, Investigation. Guihong Zheng: Writing-review & editing, Supervision, Project administration, Funding acquisition. Huansong Li: Writing-review & editing, Supervision, Conceptualization, Funding acquisition, Project administration.

Acknowledgements

This work was supported by the College Students' Innovation and Entrepreneurship Training Program (S202510320016, 202410320034Z), the Graduate Research and Innovation Practice Program Project (2025XKT0964, 2024XKT1533, 2024XKT1576), the Open Fund of Anhui Engineering Laboratory for Conservation and Sustainable Utilization of Traditional Chinese Medicine Resources (TCMRPSU-2022-11), the Xuzhou City Clinical Medical Expert Team Introduction Project (2018TD005), the National Natural Science Foundation of China (81703523), the Funded by Basic Research Program of Jiangsu (BK20170244), and the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD).

Conflict of interest

The authors declare that they have no conflict of interest.

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