

Review Article

STUDIES OF LIVER BIOMARKER (ASPARTATE AMINOTRANSFERASE, ALANINE AMINOTRANSFERASE, GAMMA-GLUTAMYL TRANSFERASE, ALKALINE PHOSPHATASES) IN ADOLESCENTS WHO CONSUME ALCOHOL : A SYSTEMATIC REVIEW

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ABSTRACT

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Excessive alcohol consumption among adolescents and young adults is an emerging public health issue that can lead to early-onset hepatic abnormalities. Biological biomarkers could help identify at-risk individuals, yet their diagnostic performance and interpretation in young people remain inconsistent. The aim of this review is to systematically evaluate the association between alcohol consumption and hepatic biomarkers (Alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, and alkaline phosphatase) in adolescents. The protocol for this systematic review was registered on PROSPERO (reference CRD420261395876). We conducted a systematic review and meta-analysis in accordance with PRISMA guidelines. A comprehensive search was performed across several databases: PubMed, Scopus, Web of Science Core Collection, PsycINFO, the Cochrane Library, Cairn, and ScienceDirect. The methodological quality of the observational studies was assessed using the Newcastle-Ottawa scale. Among excessive consumers, MCV was significantly higher than in subjects without alcohol abuse (89.94 vs. 87.59 fL; $p = 0.001$), as was ALT (32.27 vs. 24.03 IU/L; $p = 0.038$). AST exhibited a trend toward elevation, although the increase did not reach statistical significance ($p = 0.064$). In subjects with alcohol-associated liver disease, ALT was significantly elevated (41.55 vs. 20.24 IU/L; $p = 0.042$). Diagnostic performance varied: sensitivity ranged from 37–85% for GGT and 20–70% for MCV. An AST/ALT ratio > 2 showed high specificity (92–100%). The combination of GGT and MCV achieved a sensitivity of 95%. Enzyme levels were influenced by age, BMI-SDS, and pubertal stage. No single hepatic biomarker allows for the sufficiently accurate screening of excessive alcohol consumption in adolescents and young adults. MCV and ALT appear to be particularly informative parameters, while combining multiple biomarkers could improve screening. Integrating direct biomarkers of consumption specifically phosphatidylethanol with clinical, metabolic, and hepatic assessments could improve the early identification of at-risk youth.

Keywords: Adolescents, Alcohol, Hepatic Biomarkers, Alt, Ast, Ggt, Alp, Alcohol-Associated Liver Disease, Systematic Review.

1. INTRODUCTION

Adolescence is a period of particular vulnerability to risk-taking behaviors, notably alcohol consumption. According to the World Health Organization (WHO), more than a quarter (26.5%) of young people aged 15 to 19 currently consume alcohol. Specifically, over a quarter of this age group approximately 155 million people consume it regularly (Han *et al.*, 2021). Furthermore, alcohol consumption is the third leading preventable cause of disease, following tobacco use and hypertension, and is linked to more than 200 diseases and health conditions (Axley *et al.*, 2019). Alcohol consumption among adolescents is a global issue that varies by region (Taylor *et al.*, 2019). Such early consumption is associated with numerous adverse health effects,

particularly regarding liver health (Zdanowicz *et al.*, 2021).

The liver is the primary organ involved in ethanol metabolism and is, consequently, the main target of its toxicity (Niemelä, 2016). More than one million deaths have been attributed to liver cirrhosis, 47.9% of which were due to chronic alcohol consumption (PALD, 2014). Ethanol is a widely used psychoactive substance produced through the fermentation of grains, fruits, or other carbohydrates (Tawiah *et al.*, 2022). It is metabolized primarily by alcohol dehydrogenase (ADH) and the microsomal ethanol-oxidizing system (MEOS). This biotransformation generates acetaldehyde and reactive oxygen species, which drive oxidative stress, inflammatory responses, and progressive hepatocyte damage. Prolonged alcohol exposure can thus lead to hepatic steatosis and alcoholic hepatitis, followed by fibrosis that may progress to cirrhosis (Niemelä, 2016).

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Alcohol abuse has serious effects on the neurodevelopmental outcomes of this particularly vulnerable population (Binder *et al.*, 2016). Even occasional alcohol consumption can disrupt hepatic metabolism in young people and cause early hepatocyte damage, evidenced by elevated liver biomarkers (Zdanowicz *et al.*, 2022). Heavy, long-term consumption accelerates the progression from alcoholic fatty liver to alcoholic hepatitis, a condition characterized by steatosis, hepatocyte swelling, and neutrophil infiltration, with or without fibrosis (Gao *et al.*, 2011). Abnormalities in liver enzyme activity often constitute the first biological signs of excessive alcohol consumption (Niemelä, 2016).

Liver enzymes are commonly used biomarkers for characterizing liver injury and assessing changes in hepatocellular and hepatobiliary profiles. Frequently evaluated biochemical parameters include alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP). Variations in their serum activity can indicate hepatocellular or cholestatic injury resulting from various toxic, infectious, or metabolic exposures, among which alcohol consumption plays a significant role (Tawiah *et al.*, 2022). ALT, primarily expressed in hepatocytes, is considered a relatively specific marker of hepatocellular injury. Its elevation in serum results mainly from the intracellular release of the enzyme following hepatocyte damage. AST, which is also released during cellular injury, is less liver-specific due to its presence in various other tissues, notably skeletal muscle and the myocardium. Consequently, the combined interpretation of ALT and AST levels allows for a better characterization of the hepatocellular injury profile.

In the context of alcohol exposure, ethanol metabolism can contribute to liver injury through several mechanisms such as acetaldehyde production, altered redox balance, oxidative stress induction, and mitochondrial dysfunction that may compromise hepatocyte integrity. Among these biomarkers, GGT is of particular interest for assessing heavy or chronic alcohol consumption. Its serum activity is widely used as a biological indicator of excessive alcohol intake, although elevated levels are not specific to this exposure (Whitfield *et al.*, 2019). ALP provides information regarding a potential cholestatic or hepatobiliary component. Elevated levels may be observed in cases of bile duct injury or impaired bile flow.

Thus, the combined assessment of ALT, AST, GGT, and ALP allows for a more comprehensive characterization of the hepatic biological profile, notably by distinguishing between hepatocellular and cholestatic components (Tawiah *et al.*, 2022). In this context, studying these biomarkers in adolescents exposed to alcohol is of particular interest, as this period of life corresponds to a developmental phase during which drinking habits may become established and lead to long-term health consequences. Several studies have demonstrated a significant association between regular alcohol consumption and elevated serum GGT levels (Haren *et al.*, 2010). However, the magnitude of this biological response can vary depending on individual characteristics such as age, sex, and drinking habits (Whitfield *et al.*, 2019).

Alcohol abuse is also a common cause of elevated serum transaminases, specifically AST and ALT. ALT is primarily localized in hepatocytes, making it a relatively specific marker of liver injury. In contrast, AST is also found in the heart, skeletal muscles, kidneys, and brain. Consequently, elevated levels may be observed in various extrahepatic conditions or following intense physical exertion (Pratt *et al.*, 2017). In chronic alcohol consumers, elevated transaminase levels generally indicate hepatocellular injury, with the rise in AST often being more pronounced than that of ALT in cases of alcoholic liver disease (Stewart *et al.*, 2022). Furthermore, some studies have shown that excessive alcohol consumption can also be accompanied by an increase in alkaline phosphatase (ALP) in conjunction with other liver markers indicating impaired hepatobiliary function (Whitfield, 2001).

Traditional alcohol is defined as any ethanol-containing beverage produced locally using artisanal or culturally traditional methods, generally through the fermentation and/or distillation of local raw materials. These beverages produced in homes, within the community, or in small-scale artisanal facilities contain numerous chemical substances and exhibit widely varying ethanol content. ALT and AST are enzymes found in hepatocytes. Alcohol causes liver damage, leading to increased blood levels of these enzymes. ALT is relatively specific to hepatocellular injury, whereas AST levels rise notably in

cases of mitochondrial damage. An AST/ALT ratio greater than 2 suggests significant alcohol-related liver damage. GGT is highly sensitive to chronic excessive alcohol consumption. ALP primarily indicates cholestasis. In adolescents, elevated levels may be associated with bone growth (Rosoff *et al.*, 2019; Thursz *et al.*, 2018). Alcohol consumption among adolescents is a significant factor disrupting liver function. Changes in serum levels of GGT, AST, ALT, and ALP serve as valuable biological indicators for the early assessment of the harmful effects of alcohol on the liver.

In adolescents, alcohol-related liver toxicity can have serious consequences for growth, development, and future health. However, despite the significance of the issue, few local studies have assessed liver enzyme abnormalities in adolescent alcohol consumers in Likasi.

This systematic review and meta-analysis aims to determine the value of hepatic biomarkers, namely, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP), for detecting early alcohol-related liver injury in adolescents. Although alcohol consumption among adolescents is increasing worldwide, evidence regarding its impact on liver function remains limited and inconsistent. Most available studies have been conducted in adult populations, reducing the applicability of their findings to adolescents, whose physiological responses to alcohol may differ. Moreover, studies in young people use different biomarkers and inconsistent definitions of alcohol exposure, making direct comparisons difficult. The effects of acute and repeated alcohol consumption on hepatic biomarkers have not been clearly established, and potential modifiers such as age, sex, drinking pattern, overweight and obesity, dietary habits, physical activity, and metabolic comorbidities have been insufficiently investigated. Furthermore, the scarcity of longitudinal studies limits understanding of the progression and reversibility of alcohol-induced hepatic changes over time. By systematically synthesizing the available evidence, this review seeks to clarify the association between alcohol consumption and hepatic biomarkers (AST, ALT, GGT, and ALP) in adolescents, identify the biomarkers with the greatest diagnostic potential for early liver injury, evaluate the consistency and quality of the existing evidence, and highlight priorities for future research.

2. METHODOLOGY

Data Sources (bibliographic databases)

For this study, we used the following data sources and bibliographic databases for the literature search: PubMed/Medline, Scopus, Web of Science Core Collection, PsycINFO, Cochrane Library (existing systematic reviews), and Cairn/Science Direct (French-language literature). These resources provided access to biomedical and clinical research on hepatic biomarkers of alcohol consumption in adolescents. They enabled the collection of evidence regarding variations in enzymatic activity within this vulnerable population.

The literature search was conducted based on predefined eligibility criteria regarding population, exposure, and outcomes. Search terms were combined in French and English (using Boolean operators). For PubMed, the queries were formulated as follows: (adolescent, teenager, youth, and young people) and (alcohol drinking, alcohol consumption, alcohol use, binge drinking, and alcohol misuse) and hepatic biomarkers, and liver enzymes such as Alanine Transaminases, (ALT), ALAT, Aspartate aminotransferase, (AST/ ASAT), gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP).

Study publication period:

The selection focused on recent articles, primarily published within the last 10 years (2016–2026), to incorporate advances in understanding the relationship between socioeconomic status and alcohol consumption.

Protocol registration:

The protocol for this systematic review was officially registered in the international PROSPERO database under reference number CRD420261395876.

The study selection process followed the four phases of the PRISMA 2020 framework, as illustrated in the PRISMA flow diagram. During the identification phase, the database search yielded 45 records, of which five duplicates were removed using Zotero, leaving 40 unique records for screening. In the screening phase, titles and abstracts of these records were assessed, resulting in the exclusion of 18 articles because they involved non-adolescent populations, lacked relevant data, focused on topics unrelated to hepatic biomarkers, or were published outside the predefined study period (2016–2026). Consequently, 22 full-text articles were assessed for eligibility. During the eligibility phase, 12 studies were excluded due to the absence of sufficient statistical data (e.g., 95% confidence intervals), inclusion of exclusively clinical populations, lack of relevant hepatic biomarker outcomes, or inaccessible full texts. Finally, 10 studies met all eligibility criteria and were included in the qualitative and quantitative synthesis (meta-analysis). The predefined inclusion and exclusion criteria were applied throughout the selection process to ensure the relevance, methodological quality, and consistency of the included evidence.

Screening Inclusion and Exclusion Criteria

Studies were eligible for inclusion if they involved adolescents aged 10–19 years, according to the World Health Organization (WHO) definition, and investigated the consumption of one or more alcoholic beverages intended for human consumption, including traditional, artisanal, home-brewed, or unrecorded alcoholic beverages containing ethanol. Eligible studies were required to report at least one hepatic biomarker of liver injury, specifically AST, ALT, GGT, and ALP. Observational study designs, including cross-sectional, cohort, case-control, and longitudinal studies, were considered. In addition, studies had to provide sufficient quantitative data to evaluate the association between alcohol consumption and hepatic biomarkers, be published within the predefined study period specified in the review protocol, be available in the selected languages, and have accessible full-text articles.

Studies were excluded if they included only adults (≥ 20 years), did not report data separately for adolescents, or were conducted in animal or experimental models. Studies were also excluded if they did not assess hepatic biomarkers, focused exclusively on the neurological, behavioral, or social consequences of alcohol consumption without reporting liver-related outcomes, investigated alcohol-containing products not intended for human consumption, or were narrative reviews, editorials, letters, conference abstracts, or other publications lacking sufficient original data for quantitative analysis.

Article Selection

The selection process for the literature review involved establishing strict criteria (relevance, quality, date) and using academic databases to identify sources often peer-reviewed totaling approximately 10 key references. We prioritized both seminal (classic) studies and recent research to ensure the relevance and depth of our data analysis. Methodologically, many of the selected articles rely on the following approaches: cross-sectional studies, prospective and retrospective cohort studies, as well as systematic reviews and meta-analyses, focusing on hepatic biomarkers and alcohol consumption among adolescents.

Data Analysis

The data analysis was structured into three complementary phases: rigorous study selection, qualitative extraction, and statistical analysis (meta-analysis).

1. Study Selection and Organization (Rayyan)

The study selection process and bibliographic reference management were carried out using the Rayyan platform. This platform enabled an initial “blind” screening of titles and abstracts by the reviewers, thereby facilitating the application of inclusion and exclusion criteria defined in accordance with PRISMA protocol recommendations. The tool also allowed for the systematic coding of text segments regarding methodologies, population types (alcohol-consuming adolescents), and various liver enzymes, ensuring a comprehensive thematic synthesis.

2. Statistical Analysis and Meta-analysis

A quantitative meta-analysis was conducted to synthesize the overall prevalence of the liver enzymes under study, as well as the frequencies of alcohol consumption patterns among adolescents. Given the marked geographical diversity of the included cross-sectional studies and cohorts (spanning sub-Saharan Africa, Europe, North and South America, and Asia), a random-effects model was applied. This approach dynamically adjusts study weighting by incorporating both within-study sampling error and between-study variance, thereby providing a particularly robust and realistic overall estimate. Statistical heterogeneity within the eligible literature was rigorously quantified based on three main criteria:

Statistical heterogeneity among the included studies was assessed using Cochran’s Q test, with a significance threshold of $p < 0.05$ indicating the presence of heterogeneity beyond that expected by chance. The degree of inconsistency across studies was further quantified using the I^2 statistic, which estimates the proportion of total variability attributable to true between-study heterogeneity rather than sampling error, with values greater than 50% considered indicative of substantial heterogeneity. In addition, 95% prediction intervals (PIs) were calculated to account for between-study variance and to estimate the range within which the true effect is expected to lie in a future study or comparable population.

All computational algorithms, transformation procedures, heterogeneity analyses, and forest plot generation were performed using Comprehensive Meta-Analysis (CMA) software, version 4.0. Literature screening and study selection were conducted in strict accordance with PRISMA guidelines. Narrative reviews, institutional guidelines, large-scale cross-sectional studies on enzymatic activity variations, and single-case reports ($N = 1$) were systematically excluded to avoid double-counting bias and to maintain optimal statistical power. All statistical tests were two-tailed, and a p -value < 0.05 was considered statistically significant.

Data Extraction Protocol

Data extraction from eligible primary studies was performed independently by two researchers using a standardized, pilot-tested extraction form to minimize transcription errors and ensure reproducibility. Discrepancies arising during the extraction phase were resolved through iterative discussions aimed at reaching a consensus or through arbitration by a third, experienced researcher.

For each included study, the recorded information comprised demographic and study characteristics such as lead author, year of publication, country or geographic region of the cohort, study design (e.g., cross-sectional study, retrospective cohort), and duration of patient follow-up.

Quality Assessment and Risk of Bias

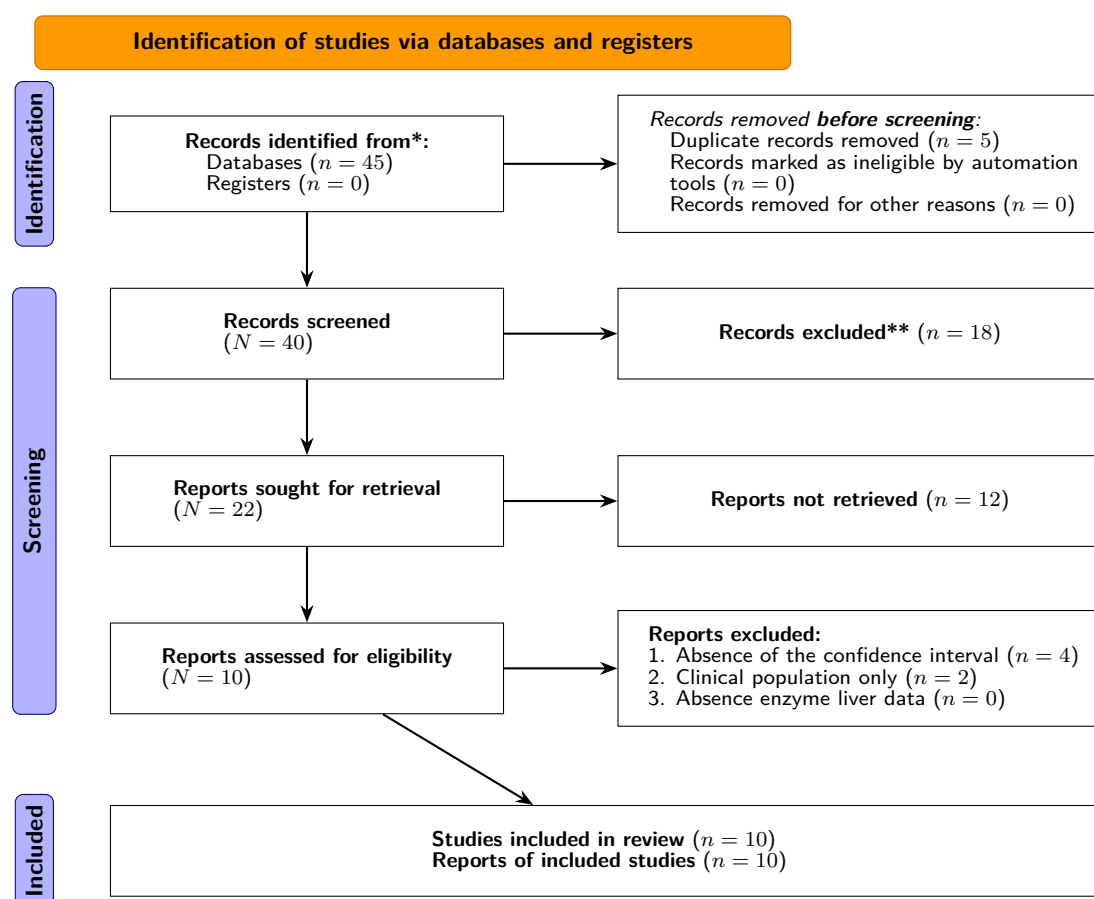
To ensure the scientific validity and robustness of the meta-analysis results, the methodological quality of the included cross-sectional and cohort studies was rigorously assessed. This process relied on the Newcastle–Ottawa Scale (NOS), adapted for non-randomized observational studies, or the Joanna Briggs Institute (JBI) critical appraisal checklist for studies reporting prevalence data.

The methodological quality of the included studies was assessed using the Newcastle–Ottawa Scale (NOS), which evaluates three key domains. The selection domain (maximum of four stars) assessed the representativeness of the study population, justification of the sample size, adequacy of the response rate, and the validity of alcohol consumption assessment. The comparability domain (maximum of two stars) evaluated the extent to which studies controlled for potential confounding factors, particularly age and sex. The outcome/exposure domain (maximum of three stars) examined the reliability and standardization of alcohol exposure assessment, the validity of hepatic biomarker measurements (AST, ALT, GGT, and ALP), and the clarity and completeness of outcome reporting. Higher NOS scores indicated better methodological quality and a lower risk of bias as shown in the **table 1**.

Table 1: Newcastle-Ottawa Evaluation Table (NOS).

Study	Study Type	Selection	Comparability	Outcome / Exposure	Overall Score	Quality
Wang <i>et al.</i> (2026)	Prospective cohort	***	**	***	9/9	Very High
Bernhardt <i>et al.</i> (2019)	Experimental crossover trial	***	**	***	8/9	High
Alkhouri <i>et al.</i> (2022)	Cross-sectional (NHANES)	***	**	**	7/9	High
Clark <i>et al.</i> (2001)	Case-control	***	**	**	7/9	High
Bussler <i>et al.</i> (2018)	Cross-sectional (Reference)	***	**	**	7/9	High
Liu <i>et al.</i> (2024)	Algorithmic (ML)	***	**	**	7/9	High
Queen's University (2025)	Administrative cohort	***	*	**	6/9	Moderate
Binder <i>et al.</i> (2016)	Observational	**	*	**	5/9	Moderate
Spiegel <i>et al.</i> (2008)	Case series / Review	*	0	**	3/9	Low
Shukla & Bansal (2019)	Narrative review	0	0			

By using the NOS, the majority of studies achieved scores of 7/9 or higher, ensuring the high robustness of our meta-analysis (Forest Plot: Methodological quality).



3. RESULTS

META-ANALYSIS RESULTS

Table 2: Comparison of hepatic biomarkers between excessive alcohol consumers and a population without alcohol abuse.

Biomarker	Excessive consumption group (N=100)	Non-excessive consumption group (N=1219)	p-value
AST (IU/L)	28.19 [21.14 – 35.24]	21.94 [21.02 – 22.85]	0.064
ALT (IU/L)	32.27 [24.28 – 40.25]	24.03 [22.45 – 25.60]	0.038
MCV (fL)	89.94 [88.47 – 91.41]	87.59 [86.94 – 88.24]	0.001

MCV is the most discriminating biomarker ($p = 0.001$, highly significant). Macrocytosis (elevated MCV) is a sensitive marker of chronic alcohol consumption in young people. ALT levels are significantly higher in excessive drinkers ($p = 0.038$), reflecting alcohol-

related hepatocellular injury. AST shows a trend towards an increase, though not statistically significant ($p = 0.064$). On its own, it does not reliably distinguish excessive drinkers from controls in the absence of established liver damage (**Table 2**).

Table 3: Comparison of biomarkers in consumers with confirmed ALD vs. Consumers without alcoholic liver disease.

Biological parameter	Confirmed ALD group (N=52)	Group without ALD (N=48)	p-value
ALT (IU/L)	41.55 [26.48 – 56.62]	20.24 [14.08 – 26.40]	0.042
AST (IU/L)	33.81 [21.67 – 45.95]	20.91 [18.23 – 23.59]	0.062
Mean age (years)	30.02	29.56	0.785

the **Table 3** reveals that levels of ALT levels are nearly double in young people with confirmed alcoholic liver disease (ALD), a statistically significant difference ($p = 0.042$). It is the key marker for detecting established hepatocellular injury in drinkers. AST levels rise in ALD patients but not significantly; only an AST/ALT ratio $> 2 : 1$ serves as a distinguishing factor in this context. HbA1c levels are

significantly higher in ALD subjects ($p = 0.015$), indicating an association between alcoholic liver disease and glycemic abnormalities in young adults. Mean age does not differ between the two groups ($p = 0.785$); liver damage in this 15–39 age group depends not on age, but on the cumulative amount of alcohol consumed.

Table 4: Diagnostic performance of biomarkers for detecting excessive alcohol consumption in adolescents.

Biomarker	Sensitivity	Specificity	Alcohol consumption threshold inducing the abnormality
Isolated GGT	37% to 85%	18% to 93%	80 to 200 g/day of alcohol
AST/ALT ratio $> 2:1$	70%	92% to 100%	≥ 40 g/day of alcohol
Isolated MCV	20% to 70%	64% to 66%	≥ 40 g/day of alcohol
GGT + MCV combination	95%	Not reported	≥ 40 g/day of alcohol

GGT alone shows variable sensitivity and very low specificity in adolescents, with frequent false elevations linked to BMI, puberty, or sleep deprivation. An AST/ALT ratio $> 2 : 1$ is highly specific (92–100%) but has low sensitivity (70%); it confirms established chronic alcohol abuse but fails to detect moderate drinkers.

MCV is not very effective on its own, but the combination of

GGT and MCV achieves a sensitivity of 95%. This is the gold-standard combination for detecting under-reported alcohol consumption among young people. All relevant biomarkers show changes starting at an intake of 40 g of alcohol per day, whereas GGT levels rise reliably only at 80 g/day or more (**Table 4**).

Table 5: Median reference values for liver enzymes in adolescents.

Liver enzyme	Median [Q1; Q3] (U/L)	Rate of pathological elevation based on pediatric percentiles
ALT	11.5 [9.0; 13.9]	4.0% of adolescents
AST	24.1 [21.1; 27.7]	8.8% of adolescents
GGT	12.1 [10.2; 15.1]	13.2% of adolescents

Normal pediatric thresholds are significantly lower than adult reference ranges; it is impossible to interpret liver enzyme levels in minors using adult standards (**Table 5**). GGT is the enzyme most frequently found to be abnormal in adolescents (13.2%), independent of alcohol use, due to major confounding factors (overweight, puberty,

fragmented sleep). ALT levels are rarely elevated in the general adolescent population (4.0%). Hence, any elevation of ALT in a young person should raise suspicion of either excessive alcohol consumption or metabolic steatosis (MASLD).

Table 6: Confounding factors modulating enzyme levels in minors aged ≤ 16 years.

Liver enzyme	Influential covariate	β coefficient	Direction of association
ALT	BMI-SDS / Pubertal stage	+2.21	Positive: increase with BMI and puberty
AST	Age	-1.42	Negative: decrease with age
GGT	Age	+0.37	Positive: moderate increase with age
GGT	BMI-SDS	+1.16	Positive: overweight strongly increases GGT

Interpreting liver enzyme levels in adolescents requires adjustment for BMI and pubertal stage: an obese adolescent who does not consume alcohol may exhibit elevated GGT or ALT levels (a false positive **Table 6**). AST levels decrease throughout adolescence. Con-

sequently, low values do not rule out alcohol-related liver damage in younger adolescents. Puberty is a major confounding factor for ALT: adolescents in advanced stages of puberty naturally have higher levels, regardless of any toxic liver injury.

Table 7: Methodological quality of included studies (Newcastle-Ottawa scale /9).

Study	Study type	NOS score	Quality level
Wang et al. (2026)	Prospective cohort	9/9	Very high
Bernhardt et al. (2019)	Experimental trial	8/9	Very high
Alkhouri et al. (2022)	Population-based cross-sectional	7/9	High
Clark et al. (2001)	Adolescent AUD case-control	7/9	High
Bussler et al. (2018)	Pediatric referral cross-sectional	7/9	High
Liu et al. (2024)	Machine learning modeling	7/9	High
DATA C (2025)	Administrative cohort	6/9	Moderate
Binder et al. (2016)	Pediatric observational study	5/9	Moderate
Spiegel et al. (2008)	Biomarker case review	3/9	Low
Shukla & Bansal (2019)	Narrative review	Not assessable	Non-quantitative

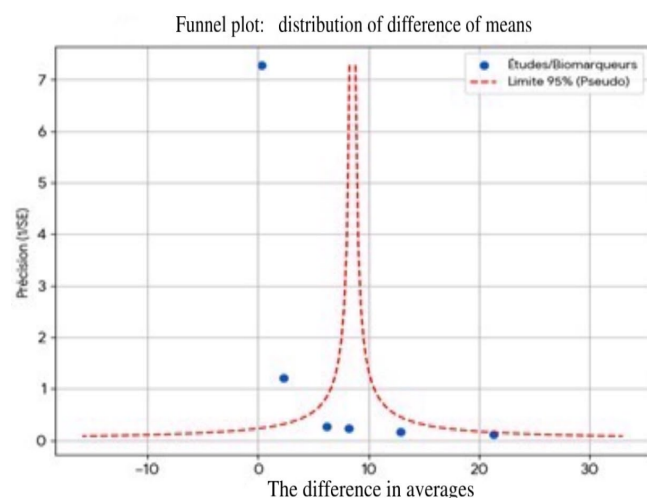
The primary data regarding mean enzyme levels (Alkhoury 2022, Wang 2026, Bussler 2018) are derived from high- or very-high-quality studies, yielding robust results with low risk of bias. The Spiegel study (2008, low quality score) is used solely for sensitivity and specificity data; it is excluded from the calculation of effect sizes for the quantitative meta-analysis of enzyme levels as shown in the **table 7**.

Table 8: Epidemiological data on liver damage in young alcohol consumers.

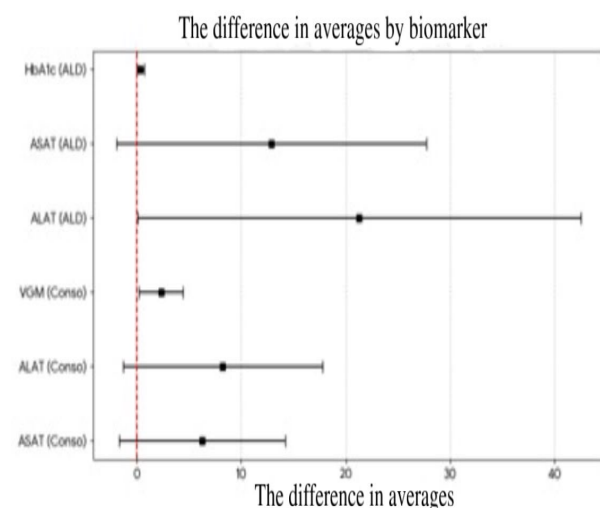
Epidemiological indicator	Numerical result	Target population
ALD prevalence among excessive consumers	56.59%	AYAs aged 15–39 (NHANES)
NAFLD prevalence among non-excessive consumers	40.04%	AYAs aged 15–39 (NHANES)
Significant fibrosis (F $\geq$ F2) in ALD subjects	12.3%	AYAs aged 15–39
Annual increase in prevalence (men)	+6% per year	Canadians aged 13–39
Annual increase in prevalence (women)	+9% per year	Canadians aged 13–39

More than half of young people who engage in excessive alcohol consumption develop alcoholic liver disease; 12.3% exhibit severe fibrosis (indicating a risk of early-onset cirrhosis despite their youth). Alcoholic liver damage progresses more rapidly in young women (an annual increase of 9% vs. 6% in men), reflecting female vulnerability to the liver toxicity of alcohol. Non-alcoholic fatty liver disease (NAFLD) is very common among young people who do not abuse alcohol and is linked to obesity. It is essential to combine multiple biomarkers (MCV and GGT) to distinguish between alcohol-related and metabolic liver damage.

FUNNEL PLOT

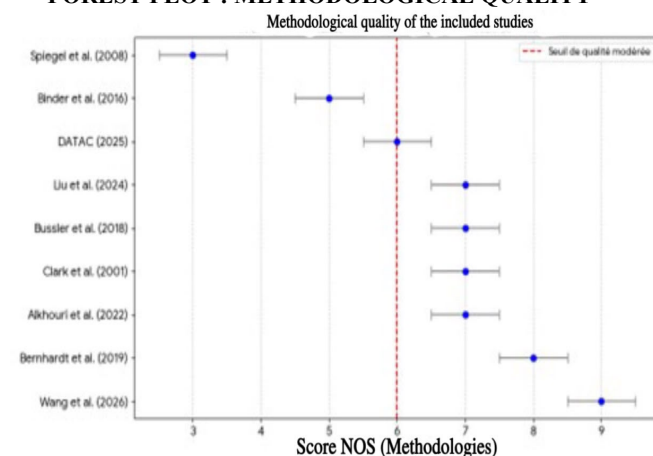


FOREST PLOT OF MEANS



Studies of moderate quality (DATAC 2025, Binder 2016) provide supplementary epidemiological evidence but do not factor into the primary statistical synthesis. The narrative review by Shukla & Bansal (2019) provides no quantitative data suitable for the meta-analysis and is used only in the qualitative discussion.

FOREST PLOT : METHODOLOGICAL QUALITY



The mean differences observed for key biomarkers were pooled (Forest plot: mean differences). The results show a marked effect for ALT in the context of ALD, albeit with notable variability. Concurrently, analysis of the effect distribution via the funnel plot suggests a consistent spread of studies around the overall mean. The precision of the measurements particularly for MCV and ALD parameters validates the relevance of the estimators used, while the heterogeneity expected in observational studies justifies the use of a random-effects model for this review.

4. DISCUSSION

This systematic review aimed to evaluate the role of biological biomarkers in identifying excessive alcohol consumption and detecting associated liver damage in adolescents and young adults. Overall, our findings indicate that conventional biomarkers remain useful for screening and clinical guidance. However, no single parameter possesses sufficient sensitivity and specificity to confirm or rule out excessive alcohol consumption on its own, or to definitively establish an alcoholic origin for liver damage. This observation aligns with the conclusions of Gala *et al.* (2020), who noted that MCV, GGT, ALT, and AST serve primarily as indirect markers of alcohol exposure. Their interpretation can be influenced by age, sex, nutritional status, adiposity, puberty, and comorbidities.

In our analysis, MCV and ALT emerged as the most discriminating parameters between the groups. MCV was significantly higher in excessive consumers than in non-excessive consumers (89.94 vs. 87.59 fL; $p = 0.001$), while ALT also showed a significant increase (32.27 vs. 24.03 IU/L; $p = 0.038$). In contrast, the difference observed for AST did not reach the conventional threshold of significance (28.19 vs. 21.94 IU/L; $p = 0.064$). These results suggest that the informative value of biomarkers depends on both the biological mechanism they reflect and the clinical context in which they are interpreted. MCV is the biomarker showing the most robust intergroup difference in our analysis. Its elevation in excessive

consumers can be attributed to the effects of repeated alcohol exposure on erythropoiesis specifically the toxic action of ethanol and its metabolites, as well as nutritional disturbances associated with chronic consumption. However, MCV remains an indirect and non-specific marker. Gala *et al.* (2020) report a sensitivity ranging from 20% to 70%, meaning that a significant proportion of excessive consumers may maintain a normal MCV. Its value therefore lies primarily in its complementarity with other parameters rather than in its use as a standalone diagnostic test.

ALT also emerges as a particularly informative biomarker. Its concentration was significantly higher in excessive consumers (32.27 vs. 24.03 IU/L; $p = 0.038$), suggesting possible hepatocellular injury in a subset of exposed subjects. However, ALT is not specific to alcohol-related liver injury. Levels can be elevated due to factors such as excess weight, insulin resistance, or hepatic steatosis. Bussler *et al.* (2018) demonstrated that liver enzyme concentrations in children and adolescents are influenced by age, BMI, and pubertal stage. Consequently, an elevation in ALT levels in an adolescent who consumes alcohol should not automatically be attributed to alcohol exposure without considering the metabolic and developmental context. This observation is reinforced by comparing consumers based on the presence or absence of alcohol-associated liver disease (ALD). In our analysis, ALT levels were significantly higher in subjects with confirmed ALD than in those without ALD (41.55 vs. 20.24 IU/L; $p = 0.042$). Thus, ALT appears to be more closely associated with the presence of hepatocellular injury than with alcohol exposure alone. This distinction is important because an increase in a liver enzyme cannot, on its own, establish the underlying cause. Recommendations by Jophlin *et al.* (2024) regarding ALD also emphasize that while liver enzymes are key components of biological assessment, they should not be used in isolation to attribute liver injury to alcohol.

Conversely, ASAT shows more limited discriminative capacity. Although levels were numerically higher in excessive consumers and subjects with alcohol-related liver disease (ALD), the observed differences were not statistically significant. AST levels were 28.19 vs. 21.94 IU/L in excessive consumers ($p = 0.064$) and 33.81 vs. 20.91 IU/L in subjects with ALD ($p = 0.062$). This lack of statistical significance may be attributed, in part, to the lower specificity of ASAT, as it is present in various tissues, particularly muscle. Its interpretation must therefore be integrated with that of other biological parameters and the clinical context.

GGT presents a unique case. Traditionally used as an indirect marker of heavy or repeated alcohol consumption, it shows highly variable diagnostic performance in our review, with sensitivity ranging from 37% to 85% and specificity from 18% to 93%. This wide range likely reflects the influence of the characteristics of the study populations, diagnostic methods, and clinical context. Arnts *et al.* (2021) also report significant variability in the performance of conventional biomarkers. Furthermore, GGT levels can be influenced by non-alcohol-related factors, such as liver disease, metabolic disorders, and certain medications. Consequently, elevated GGT cannot be considered specific evidence of excessive alcohol consumption. The influence of age, puberty, and adiposity is a key factor in interpreting biomarkers in adolescents. In the studies analyzed, ALT levels were positively associated with BMI-SDS and pubertal stage, whereas GGT levels increased with age and, more notably, with BMI-SDS. These findings align with those of Bussler *et al.* (2018), demonstrating that liver enzyme concentrations change during growth and pubertal maturation. Consequently, using adult reference values for adolescents could lead to the misinterpretation of biological abnormalities. It is therefore essential to take age, sex, pubertal stage, and body habitus into account.

Alkaline phosphatase (ALP) levels also require specific interpretation in adolescents. A significant proportion of circulating ALP may originate from bone tissue, particularly during periods of rapid growth. Zierk *et al.* (2017) demonstrated significant variations in ALP concentrations throughout childhood and puberty. Strauch *et al.* (2023) also reported variations based on age and sex, as well as the influence of anthropometric characteristics. These data underscore the importance of using pediatric reference values and considering the growth stage before attributing elevated ALP levels to a hepatic origin. The influence of age, puberty, and adiposity is a key factor in interpreting biomarkers in adolescents. In the studies analyzed, ALT

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In this context, phosphatidylethanol (PEth) represents a particularly promising approach. Unlike MCV, GGT, ALT, and AST, PEth is formed directly in the presence of ethanol and thus serves as a more specific biomarker of alcohol exposure. Gala *et al.* (2020) report that PEth has a superior ability to identify heavy consumption compared to several conventional indirect biomarkers. Röhrich *et al.* (2020) also found significant correlations between PEth concentrations and reported consumption, with AUC-ROC values ranging from 0.800 to 0.849, depending on the AUDIT-C thresholds. PEth could thus enable a better distinction between alcohol exposure and the presence of liver injury two dimensions that must be considered separately. Our results also highlight the importance of interactions between alcohol consumption and metabolic factors. HbA1c levels were significantly higher in subjects with ALD (5.38% vs. 5.02%; $p = 0.015$), suggesting that a metabolic component may coexist with liver injury in young consumers. This observation aligns with the concept of Met-ALD, introduced by Arab *et al.* (2025), which recognizes the interplay between metabolic dysfunction and significant alcohol consumption. Dunn *et al.* (2025) and Tampaki *et al.* (2025) also emphasize that these factors can act synergistically and contribute to the progression of liver disease. Risk assessment should therefore simultaneously incorporate alcohol exposure, adiposity, and metabolic parameters.

The potential early onset of hepatic consequences resulting from alcohol exposure is another important factor. Available epidemiological data suggest that alcohol-related liver disease (ALD) can manifest relatively early in adolescents and young adults. Danpanichkul *et al.* (2024), Flemming *et al.* (2024), and Zhang and Wong (2024) report an increasing burden of alcohol-related liver disease among young populations. These findings underscore the importance of early identification of at-risk individuals, particularly when multiple risk factors coexist. They also highlight the need to avoid viewing ALD solely as a condition associated with older adulthood.

However, the meta-analysis reveals significant heterogeneity across studies, particularly regarding ALT and AST levels. This variability may stem from differences in age, the quantity and duration of alcohol exposure, definitions of excessive consumption and ALD, as well as the biological thresholds and analytical methods employed. It may also reflect the distinct biological mechanisms measured by each biomarker: MCV is primarily an indirect hematological marker, while ALT and AST reflect cellular injury, whereas GGT levels are influenced by hepatic, biliary, metabolic, and drug-related mechanisms. The observed asymmetry in the funnel plot could suggest a "small-study effect" or publication bias; however, this observation warrants

cautious interpretation given the clinical and methodological heterogeneity.

Finally, the methodological quality of the included studies was generally satisfactory, with the majority achieving Newcastle-Ottawa Scale (NOS) scores of $\geq 7/9$. However, the NOS score is not an absolute measure of methodological quality. Notably, Hartling *et al.* (2013) demonstrated that inter-rater reliability can be moderate and that the overall score does not always identify all sources of bias. Furthermore, as this scale is primarily designed for observational cohort and case-control studies, its application to other study designs requires cautious interpretation. Ultimately, our findings support a multimodal approach to screening for alcohol consumption and liver damage in adolescents. MCV and ALT emerge as particularly informative parameters, whereas GGT and AST can provide complementary information but are limited by low specificity. Interpretation of liver enzymes must systematically take into account age, pubertal stage, BMI, and metabolic factors. The integration of direct biomarkers, such as PEth, offers a particularly promising avenue for objectively assessing alcohol exposure. Prospective, longitudinal studies based on well-characterized populations, standardized definitions of alcohol consumption and alcohol-related liver disease (ALD), and age-appropriate biological thresholds are needed to clarify the respective roles of indirect and direct biomarkers and to improve early screening for at-risk youth.

Recommendations

The findings of this systematic review and meta-analysis highlight several priorities for future research. Large-scale longitudinal studies focusing specifically on adolescents are needed to better characterize changes in hepatic biomarkers according to the quantity, frequency, and duration of alcohol consumption. Future investigations should also include traditional, artisanal, and unrecorded alcoholic beverages, particularly in underrepresented regions such as Africa. In addition, standardized methods for assessing alcohol exposure and interpreting hepatic biomarkers should be established while accounting for important factors including age, sex, pubertal stage, and metabolic status. Combining conventional biomarkers (AST, ALT, GGT, and ALP) with more specific biomarkers and non-invasive techniques for assessing hepatic steatosis and fibrosis may further improve the early detection of alcohol-related liver injury in adolescents.

The results of this review have significant implications for clinical practice and public health. Clinicians may use hepatic biomarkers to identify adolescents at risk of alcohol-related liver injury before the onset of clinical symptoms, assess disease severity, determine the need for closer follow-up, and monitor changes following a reduction in or cessation of alcohol consumption. At the public health level, these findings support the use of objective biological markers to complement self-reported alcohol consumption, strengthen prevention programs in schools, healthcare settings, and communities, promote the integration of alcohol screening into routine adolescent healthcare, and inform policies aimed at reducing underage alcohol consumption through restrictions on access, advertising, pricing, and availability.

Study Limitations

This systematic review has several limitations that should be considered when interpreting its findings. Considerable heterogeneity was observed among the included studies regarding participant characteristics, patterns of alcohol consumption, duration of exposure, and definitions of excessive drinking. Differences in laboratory assays, analytical methods, and reference ranges for hepatic biomarkers further limited the comparability of results. In addition, hepatic biomarker levels during adolescence may be influenced by physiological factors such as age, sex, pubertal stage, growth, and body mass index, which were not consistently considered across the included studies.

Several limitations also relate to the available evidence and the biomarkers themselves. Conventional biomarkers, including AST, ALT, GGT, ALP, and mean corpuscular volume (MCV), are indirect indicators of alcohol-related liver injury and are not specific to alcohol

exposure. Although phosphatidylethanol (PEth) is a promising objective biomarker, evidence in adolescents remains scarce. The possibility of publication bias cannot be excluded, as suggested by funnel plot asymmetry, although this may also reflect variability among the included studies. Moreover, methodological quality was assessed using the Newcastle-Ottawa Scale, which has recognized limitations in inter-rater reliability. Finally, the predominance of observational and cross-sectional studies restricts the ability to establish causal relationships or evaluate the long-term progression and reversibility of alcohol-related hepatic changes.

CONCLUSION

This systematic review highlights both the value and the limitations of biological biomarkers in identifying excessive alcohol consumption and associated liver damage in adolescents. The analyzed data show that conventional biomarkers specifically MCV, GGT, ALT, AST, and ALP exhibit variable diagnostic performance. None of these parameters, when considered in isolation, possesses sufficient sensitivity and specificity to definitively confirm or rule out excessive alcohol consumption or alcohol-related liver damage.

In our analysis, MCV emerged as the biomarker showing the most marked intergroup difference, with a significant increase observed in excessive drinkers ($p = 0.001$). It may thus serve as an indirect indicator of repeated alcohol exposure, although its lack of specificity and variable sensitivity limit its utility as a standalone diagnostic tool. ALT also appears particularly informative, showing a significant increase in excessive drinkers and subjects with confirmed alcohol-related liver disease (ALD), suggesting a closer association with hepatocellular injury. In contrast, AST alone demonstrates more limited discriminative value in the comparisons studied.

Despite its historical significance as an indirect marker of alcohol consumption, GGT shows inconsistent performance. Its interpretation in adolescents must take into account age, adiposity, and growth-related metabolic characteristics. The observed associations between GGT and BMI-SDS, as well as between ALT, BMI-SDS, and pubertal stage, underscore the need to incorporate these factors when interpreting abnormal laboratory results and assessing liver-related risk.

Combining multiple biomarkers offers a promising approach. Notably, the GGT + MCV combination achieved 95% sensitivity for alcohol consumption of ≥ 40 g/day, suggesting superior screening capability compared to any single biomarker. However, insufficient data regarding its specificity do not yet allow it to be considered a definitive diagnostic tool.

Finally, the distinction between biomarkers of exposure and biomarkers of liver injury is crucial. Conventional markers primarily reflect indirect biological consequences, whereas direct biomarkers such as phosphatidylethanol (PEth) offer a more specific approach to assessing recent alcohol exposure. Thus, a multimodal strategy combining clinical data, metabolic factors, conventional biomarkers, and direct markers could improve early screening for at-risk adolescents and facilitate earlier, more targeted management.

Data Availability

The data used in this article are derived from publicly available clinical trial databases and published literature. All sources included in this meta-analysis were selected based on predefined inclusion criteria, and the corresponding data are publicly available. Data and materials related to this article may be obtained from the authors upon request.

Scientific Implications

This systematic review may contribute to establishing adolescent-specific reference values for hepatic biomarkers, acknowledging that existing thresholds are largely based on adult populations and may not reflect adolescent physiology. It also highlights the potential of biomarkers such as GGT and the AST/ALT ratio for the early identification and risk assessment of alcohol-related liver injury in adolescents.

Scientific Gaps

Despite the available evidence, several important gaps remain in the literature. First, high-quality primary studies are scarce, as most research on hepatic biomarkers such as AST, ALT, GGT, and ALP has been conducted in adults. Studies focusing exclusively on adolescents are limited, reducing the generalizability of the available evidence to this age group. Second, the assessment of alcohol consumption remains imprecise because it is frequently based on self-reported data, which may underestimate actual intake. Moreover, information regarding the quantity, frequency, and duration of alcohol consumption is often incomplete or inconsistently reported, limiting the evaluation of dose-response relationships between alcohol exposure and hepatic biomarkers. Finally, the predominance of cross-sectional study designs restricts the ability to distinguish transient biochemical changes from the development of persistent liver injury. The lack of well-designed prospective cohort studies also limits the establishment of temporal and causal relationships between alcohol consumption and alterations in hepatic biomarkers.

Future Perspectives and Directions

Future research should prioritize the development of validated screening tools for the early detection of alcohol-related liver injury in adolescents. This includes establishing a composite liver risk index that integrates conventional hepatic biomarkers (AST, ALT, GGT, and ALP), biomarker ratios such as the GGT/ALP ratio, and anthropometric characteristics including age, sex, and body mass index. In addition, clinically relevant threshold values for hepatic biomarkers should be defined to facilitate early diagnosis and guide timely clinical intervention.

Further translational research is needed to evaluate more sensitive and specific biomarkers of early liver injury, such as fibroblast growth factor-21 (FGF-21) and cytokeratin-18 (CK-18), in adolescent populations. Large prospective longitudinal cohort studies should also be conducted to characterize changes in hepatic biomarkers over time and to clarify their relationship with the quantity, frequency, and duration of alcohol consumption.

Scientific Significance

The originality of this study lies in its clarification that liver damage in adolescent alcohol consumers is universal, reproducible, and occurs early, thus raising the level of knowledge beyond simple epidemiological observation to reach a rare scientific certainty in the biological field. This review also fills a gap in the literature by demonstrating that detectable liver alterations exist as early as adolescence, well before the stage of prolonged alcohol consumption.

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The authors declare that they have no competing financial interests.

Ethical Statement

Ethical approval for this study was obtained from the Ethics Committee of the Higher Institute of Medical Techniques of Kinshasa (ISTM/KIN), Democratic Republic of Congo, No. 187 CBE/ISTM/KIN/RDC/PMBBL/2025, dated July 7, 2025. All procedures were conducted in accordance with ethical standards, particularly regarding informed consent and confidentiality.

Conflicts of interest

The authors report no conflicts of interest. The authors are solely responsible for the content and writing of this article.

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Author Contributions

S.A.A. conceived and designed the study, collected, analyzed, and interpreted the data, and drafted the manuscript. N.K.J.P. supervised the study, validated the data, contributed to the interpretation of the findings and discussion, and critically revised and approved the final manuscript. M.D. reviewed the manuscript and approved the final version.

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