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Review

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Dual etiology *vs.* MetALD: how MAFLD and MASLD address liver diseases coexistence

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Abstract

Fatty liver disease associated with metabolic dysfunction has emerged as a significant global health challenge. This condition often coexists with other liver diseases, such as alcohol-related liver disease and viral hepatitis, complicating both diagnosis and management. To address the limitations of the non-alcoholic fatty liver disease (NAFLD) classification, two alternative frameworks have been proposed: metabolic dysfunction-associated fatty liver disease (MAFLD) in 2020 and metabolic dysfunction-associated steatotic liver disease (MASLD) in 2023. A key difference between these definitions is how they consider fatty liver disease in relation to the coexistence of other liver conditions. MAFLD adopts a dual etiology concept, creating a unified classification system that aligns with contemporary clinical and epidemiological needs. In contrast, MASLD introduces a new term, MetALD (metabolic and alcohol-related/associated liver disease), to describe patients who have both metabolic

dysfunction and excessive alcohol intake. This review critically examines the clinical, research, and epidemiological implications of the differing approaches of MAFLD and MASLD, offering insights into their potential to enhance the understanding and management of multi-etiology liver diseases.

Keywords: MAFLD, NAFLD, MASLD, dual etiology, MetALD

INTRODUCTION

Fatty liver disease due to metabolic dysfunction poses a significant global health issue, primarily driven by rising rates of metabolic disorders, obesity, diabetes, and lifestyle-related factors. A recent meta-analysis indicates that approximately 38% of the global population are affected by this condition, highlighting its health, economic, and societal burden[1,2]. Beyond liver disease, dysfunction-associated fatty liver disease (MAFLD) is strongly associated with multiple extrahepatic conditions, including CVD, CKD, type 2 diabetes (T2D), and extrahepatic cancers[3].

With the increasing prevalence of fatty liver due to metabolic dysfunction, many patients also present with coexisting liver conditions, such as alcohol-related liver disease (ALD) or viral hepatitis. These overlapping conditions complicate both diagnosis and management, emphasizing the urgent need for more inclusive and clinically relevant classification systems of liver diseases[4].

For decades, the terms non-alcoholic fatty liver disease (NAFLD) and its corresponding diagnostic criteria - defined by the exclusion of significant alcohol consumption and other identifiable causes of hepatic steatosis - have shaped the understanding of the disease[5]. While the concept of NAFLD was groundbreaking when introduced, it has faced growing criticism for inadequately reflecting the multifaceted nature of fatty liver disease and the complex interplay of contributing factors, including both metabolic and alcohol-related elements[6-8]. Furthermore, its reliance on the vague term "non-alcoholic" has sparked controversy. This exclusion-based definition creates a misleading dichotomy between metabolic and other contributors to liver disease, especially concerning alcohol, thus limiting its clinical applicability[9].

To address these limitations, MAFLD was introduced in 2020 as a paradigm shift, emphasizing the positive inclusion of metabolic dysfunction as a core diagnostic criterion[10-13]. The MAFLD framework has been widely endorsed for its diagnostic clarity and clinical relevance, particularly in its ability to encompass overlapping etiologies and provide a more holistic understanding of disease progression[14-17]. Subsequently, in 2023, another term was introduced: metabolic dysfunction-associated steatotic liver disease (MASLD)[18]. While MASLD shares many diagnostic criteria with MAFLD, it also demonstrates notable differences in its conceptual framework and diagnostic approach, especially in how each definition addresses metabolic liver disease coexisting with other liver conditions[18].

To address cases of overlap, MAFLD introduced the dual etiology framework, which allows for the diagnosis of MAFLD to coexist with other liver diseases, such as ALD or viral hepatitis[9,12,19]. Conversely, MASLD proposes a separate term, metabolic-alcoholic liver disease (MetALD), to specifically identify cases where significant alcohol consumption (defined as 140 to 350 g/wk for females and 210 to 420 g/wk for males) and metabolic dysfunction overlap[18,20]. These differing approaches raise important questions about the optimal approach to dealing with patients with overlapping etiologies. Figure 1 illustrates this overlap and highlights the classification differences between MAFLD and MASLD.

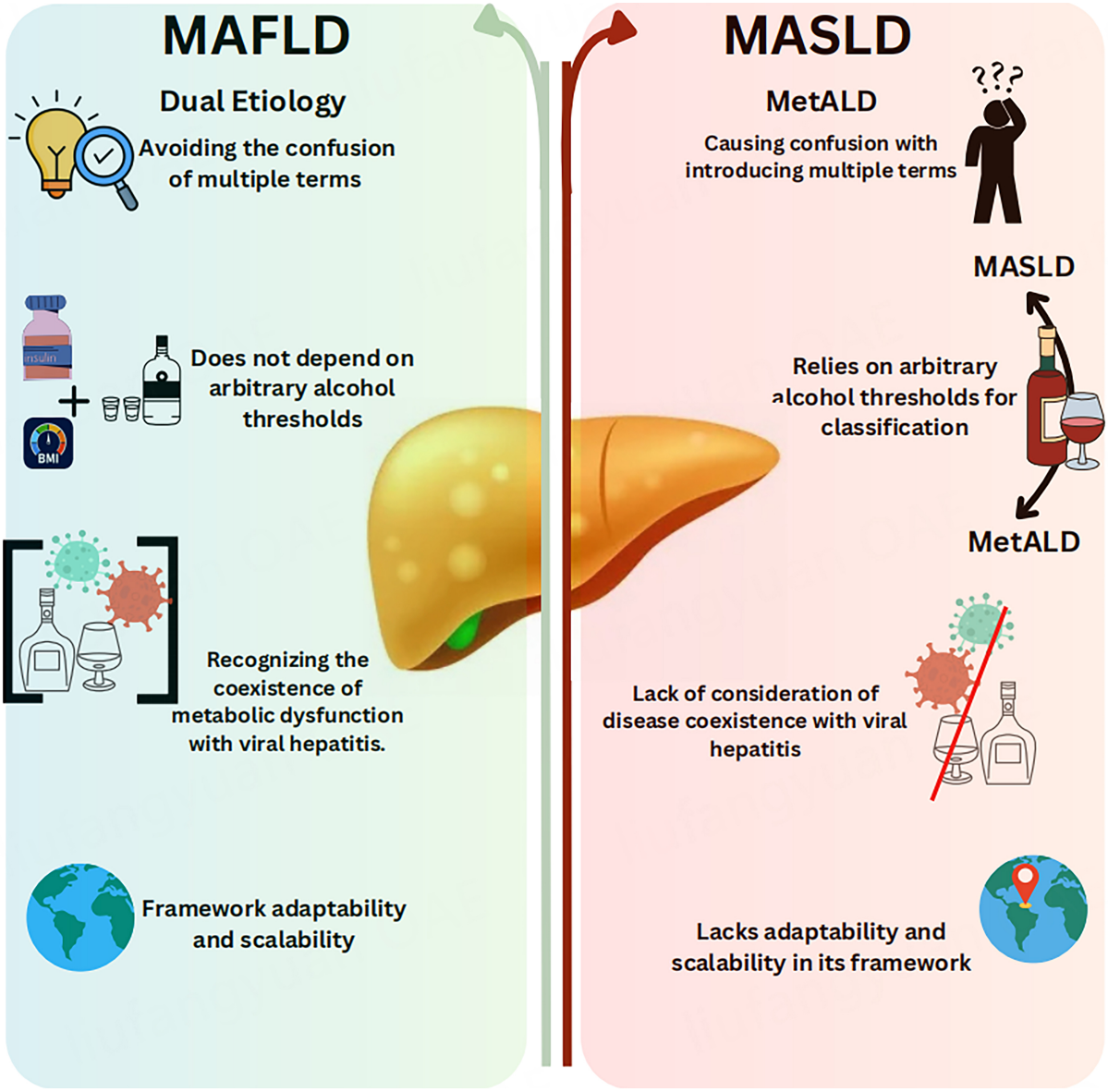

Figure 1. Comparison of the MAFLD and MASLD frameworks in addressing the coexistence of metabolic liver disease with other liver diseases. This figure highlights the distinct approaches and features of each framework. The figure was created using Canva software. MAFLD: Metabolic dysfunction-associated fatty liver disease; MASLD: metabolic dysfunction-associated steatotic liver disease; MetALD: metabolic-alcoholic liver disease.

This review explores how the two definitions - MAFLD and MASLD - address the coexistence of MAFLD with other liver conditions, including ALD and viral hepatitis. By highlighting the burden and prevalence of these overlaps, we aim to examine their strengths and challenges in accurately reflecting the complexity of fatty liver disease and advancing clinically relevant consensus. Our literature selection approach includes the primary databases used (PubMed, EMBASE) and keywords employed (MAFLD, MASLD, MetALD, dual etiology).

COEXISTENCE OF METABOLIC DYSFUNCTION-ASSOCIATED LIVER DISEASE WITH OTHER LIVER DISEASE ETIOLOGIES: GROWING BURDEN

The coexistence of MAFLD with other liver conditions, such as ALD and viral hepatitis, represents a significant and complex clinical challenge[21,22].

For instance, in the Asia-Pacific regions where chronic hepatitis B infection (CHB) is endemic, studies show a 32.8% prevalence of hepatic steatosis in CHB patients[23]. It has also been shown that in CHB patients undergoing antiviral therapy, persistent steatosis is associated with reduced fibrosis regression[24]. This overlap is not merely incidental; metabolic dysfunction amplifies liver disease progression, with patients exhibiting three or more metabolic risk factors facing a 2.32-fold higher risk of hepatocellular carcinoma (HCC) and a 2.72-fold increased risk of liver-related mortality[25]. Additionally, the coexistence of MAFLD and CHB has been linked to a doubling of chronic kidney disease (CKD) risk, highlighting its systemic impact beyond just accelerating liver disease progression[26].

In the case of chronic hepatitis C (CHC), hepatic steatosis is observed in 30%-45% of patients[27,28] and up to 50%-70% based on histology[29,30], with the prevalence of MAFLD in CHC patients ranging from 9%-38%[31]. CHC and MAFLD share common pathogenic mechanisms, including insulin resistance (IR), oxidative stress, and mitochondrial dysfunction, all of which exacerbate liver fibrosis and increase the risk of HCC[31-33]. Moreover, HCV-related steatosis is linked to hepatitis C-associated dysmetabolic syndrome (HCADS), which involves metabolic abnormalities such as hyperuricemia and arterial hypertension[34].

Studies have shown that the presence of MAFLD negatively impacts the progression and outcomes of CHC. Metabolic factors such as IR, obesity, and dyslipidemia, particularly in the context of HCV genotype 3, amplify the risk of fibrosis and HCC development, especially in patients with concomitant T2DM[35,36]. While earlier studies indicated that MAFLD reduced the efficacy of interferon-based antiviral therapies, the advent of direct-acting antivirals (DAAs) has resolved this issue, with MAFLD showing no detrimental effect on treatment success[37]. However, the persistent metabolic derangements associated with MAFLD, such as steatosis and dyslipidemia, remain significant contributors to long-term cardiovascular and liver-related complications in CHC patients[38].

Beyond viral etiologies, the coexistence of MAFLD and ALD is increasingly recognized, reflecting the global prevalence of metabolic dysfunction and widespread alcohol consumption, with 283 million individuals having alcohol use disorder[39]. Studies indicate that 39% of non-viral advanced liver disease cases involve both metabolic risk factors and moderate alcohol intake (10 to 20 g/day for women, 10 to 30 g/day for men)[40]. While modest alcohol consumption (< 30 g/day for males, < 20 g/day for females) was historically considered safe, recent evidence shows that even low amounts of alcohol can exacerbate fibrosis progression in MAFLD[41]. The interaction between ALD and MAFLD accelerates liver damage through shared mechanisms, including lipotoxicity, inflammation, and gut microbiome dysregulation, with genetic variants like *PNPLA3* further contributing to disease progression[21,42]. Additionally, alcohol consumption can dissociate IR from certain cardiometabolic risk factors, complicating patient classification[43].

In summary, the coexistence of metabolic dysfunction-associated liver disease with other liver conditions is a significant and frequently encountered issue. This overlapping occurrence substantially escalates the overall burden of liver-related and systemic complications and necessitates a comprehensive approach to management.

ADDRESSING THE COEXISTENCE OF LIVER DISEASES: MAFLD *VS.* MASLD FRAMEWORKS

Two definitions for liver disease due to metabolic dysfunction are currently utilized, namely MAFLD and MASLD. One of the fundamental differences between the two approaches is how they address the coexistence of liver diseases when metabolic dysfunction-associated liver disease coexists with another liver condition.

The MASLD framework introduces a distinct term called MetALD to address this issue. In this model, cases in which metabolic dysfunction and significant alcohol consumption occur simultaneously at one time point in the patient's course are classified as MetALD. In contrast, the MAFLD framework espoused the concept of dual etiology encompassing the coexistence of MAFLD with any other liver disease, including, but not limited to, alcohol consumption. This approach refrains from complicating the classification with the introduction of new terms. To better understand the implications of these differing approaches, the next section will provide a focused comparison based on key aspects such as clinical applicability, global suitability, research implications, and scalability.

FRAMEWORK ADAPTABILITY AND SCALABILITY

The frameworks for MAFLD and MASLD would have different implications for classification and adaptability.

MASLD, by introducing MetALD, describes cases involving alcohol consumption above specified thresholds with metabolic dysfunction. This differentiation emphasizes the role of alcohol but applies this logic selectively, overlooking other common liver diseases, such as viral hepatitis[44]. Following this logic of introducing various terms, should we also consider the role of viruses and develop new terms such as "MetHBVLD" (Metabolic dysfunction-related and Hepatitis B-Related Liver Disease) or "MetHCVLD" (Metabolic dysfunction-related and Hepatitis C-Related Liver Disease)? Furthermore, how should we manage patients who qualify for MetALD while also being positive for hepatitis viruses? The precedent for creating additional categories risks an overcomplication of classification systems, which could ultimately undermine their scalability and utility in clinical and research contexts.

In contrast, MAFLD integrates dual etiology within a unified framework, accommodating the coexistence of metabolic dysfunction alongside contributors like alcohol or viral hepatitis without creating separate terminology. This inclusive approach prevents fragmentation and ensures consistency in diagnosis and management across various clinical situations[14]. By treating overlapping contributors as coexisting factors within a single framework, MAFLD supports broader applicability and aligns with the evolving understanding of liver disease. Its cohesive structure avoids the complexity introduced by MASLD's segmentation, facilitating scalability and adaptability for both global clinical practice and research initiatives[45].

BEYOND THRESHOLDS: ADDRESSING ALCOHOL AND METABOLIC SYNERGY IN LIVER DISEASE

MASLD definition employs predefined alcohol thresholds to differentiate alcohol-driven liver disease, categorizing cases with significant alcohol consumption into separate MetALD classifications. While this approach aims to delineate alcohol's role as a primary contributor, it has substantial limitations.

Relying on arbitrary thresholds risks underdiagnosing or misclassifying cases where alcohol consumption falls below the specified limits but still exacerbates metabolic dysfunction. Emerging evidence suggests that even low or moderate alcohol intake can amplify IR, promote lipotoxicity, and accelerate liver damage, underscoring the shortcomings of arbitrary threshold-dependent classifications[46]. Moreover, such premature criteria fail to account for the complex interplay between alcohol and metabolic dysfunction, diminishing the diagnostic precision required to address dual etiology effectively.

Additionally, the MetALD framework overlooks the growing evidence that implicates alcohol produced by the gut microbiome as a contributor to liver injury. Endogenous ethanol production, driven by alcohol-producing gut bacteria such as Klebsiella pneumoniae, can mirror the effects of external alcohol consumption, leading to steatohepatitis and fibrosis[47].

Furthermore, relying on self-reported alcohol intake as the main measure for classifying MetALD presents additional challenges. Self-reports are frequently unreliable due to recall bias, cultural stigma, or intentional underreporting, particularly in regions where alcohol use is socially or culturally sensitive[47,48]. This introduces a potential for diagnostic inaccuracies, leading to misclassification of cases or failure to capture those in which alcohol intake exacerbates metabolic dysfunction[48].

Another critical challenge lies in the variability of alcohol consumption over time. Lifestyle changes, reductions in alcohol use following medical intervention, or intermittent binge drinking complicate the identification of MetALD. However, this aspect is completely ignored in the MetALD criteria, which focus solely on self-reported alcohol consumption. This oversight reflects a significant gap in MASLD's ability to consider alternative contributors to alcohol-related liver injury, further questioning its relevance in complex clinical scenarios.

In contrast, the MAFLD definition provides a more comprehensive framework by integrating alcohol as one of several potential co-contributors to liver disease without imposing rigid thresholds. This inclusive approach captures the entire spectrum of dual etiology, encompassing both exogenous and endogenous alcohol contributors, as well as cases with variable or moderate alcohol intake. The boundaries between MAFLD and ALD are the same as between MAFLD and any other liver disease. Thus, the MAFLD definition ensures diagnostic accuracy across diverse populations and clinical contexts, supporting a nuanced understanding of disease progression. Furthermore, its unified structure facilitates coordinated management strategies, aligning with the multifactorial nature of liver disease and ensuring relevance across global settings.

REGIONAL AND GLOBAL TRENDS IN LIVER DISEASE CO-OCCURRENCE

Globally, the coexistence of metabolic dysfunction with other liver diseases reflects distinct region-specific epidemiological patterns. In the Asia-Pacific region, the high prevalence of HBV infection significantly overlaps with metabolic dysfunction, particularly in countries such as China and South Korea, resulting in complex cases of metabolic-associated steatosis and viral liver disease[49-52]. In North America and Europe, metabolic dysfunction often coexists with HCV infection, particularly in populations with high rates of obesity and diabetes, such as individuals undergoing antiviral therapy for chronic HCV infection[53]. In Africa, metabolic dysfunction frequently intersects with HBV and liver diseases driven by infectious or toxic causes, including aflatoxin exposure[54], while MAFLD-HIV coexistence is also a growing concern due to HIV-associated metabolic dysfunction, inflammation, and ART-induced dyslipidemia[55]. Meanwhile, in Latin America, the high prevalence of obesity and diabetes contributes to the coexistence of metabolic-associated liver disease and ALD, closely mirroring the dual etiology concept[56].

MAFLD's flexibility allows it to address regional variations in liver disease co-occurrence without introducing additional terminologies[38], all within the same diagnostic framework. This adaptability ensures global applicability and relevance. In contrast, MASLD's selective use of MetALD focuses primarily on alcohol-related overlaps, potentially limiting its utility in regions where other contributors, such as viral hepatitis, are dominant.

From a therapeutic perspective, coexisting conditions necessitate integrated treatment strategies[57]. For instance, addressing IR or hyperlipidemia in a patient with viral hepatitis or ALD can subsequently improve disease outcomes, whereas failure to identify and manage underlying metabolic dysfunction may compromise the success of targeted therapies[58]. These patterns of coexistence, however, are not uniform worldwide; they are shaped by regional differences in disease prevalence, risk factors, and cultural influences, which further underscore the importance of adaptable frameworks in addressing global variations in liver disease.

THERE IS NO PRECEDENT FOR DUAL TERMINOLOGY IN OTHER DISEASES

Typically, in medical fields, coexisting conditions are managed collaboratively without the need for new terminologies[59]. For example, diabetes, dyslipidemia, and hypertension are managed as metabolic comorbidities without introducing additional terms to describe their overlap. Similarly, the coexistence of two autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus, does not require a distinct term. MAFLD follows this precedent by integrating dual etiology into a unified framework, ensuring seamless care coordination.

The introduction of MetALD, as proposed by MASLD, deviates from this established practice. Fragmenting liver disease terminology could complicate clinical workflows and create ambiguity in care coordination. Evidence from multidisciplinary models suggests that unified approaches lead to better patient outcomes, emphasizing the practicality of MAFLD's model over the segmented structure of MASLD[57].

CLINICAL AND RESEARCH IMPLICATIONS

MAFLD simplifies clinical management by addressing dual etiologies under a single framework, enabling integrated care for patients with metabolic dysfunction coexisting with alcohol or viral hepatitis. This unified approach supports interdisciplinary collaboration and ensures comprehensive treatment strategies tailored to the multifactorial nature of liver disease[60].

The transition to MAFLD has significant implications for the international classification of diseases (ICD) coding system, used globally to standardize disease classification in healthcare. A global survey revealed that 77.1% of experts advocate updating ICD-11 to include MAFLD, reflecting a consensus toward its adoption[61]. This update would improve diagnostic precision and ensure accurate epidemiological tracking by encompassing a broader spectrum of patients, particularly those with overlapping conditions. Under the current MASLD framework, patients with metabolic dysfunction and coexisting ALD labeled by a new term as "MetALD" may be excluded from proper classification, leading to underrepresentation in public health databases.

From an epidemiological perspective, adopting MAFLD allows for more accurate estimates of disease burden and better resource allocation, particularly among countries with limited resources that also bear the highest burden of the disease. This is a vital point, given the high prevalence of the disease and the fact that only a small proportion of patients concur with the serious consequences of it. In this regard, multiple studies demonstrated that MAFLD criteria effectively identify individuals with high-risk metabolic profiles

and an increased risk of disease progression compared to MASLD criteria[62]. This consistent identification over time facilitates early intervention and management, potentially improving patient outcomes.

CONCLUSION

The coexistence of fatty liver disease due to metabolic dysfunction with other liver diseases is both common and significant. This combination significantly increases the burden of both liver-specific and systemic complications, leading to worse outcomes such as advanced fibrosis, cirrhosis, HCC, CKD, and cardiovascular disorders. The synergistic effects of metabolic and non-metabolic factors highlight the complex interplay that drives disease progression, creating substantial challenges for accurate diagnosis and effective management[63].

The evolution of fatty liver disease terminology reflects the field's ongoing efforts to better capture the multifactorial and complex nature of this condition. Transitioning from the exclusionary framework of NAFLD to the inclusive, pathophysiology-driven approaches of MAFLD and MASLD represents significant progress.

Among the proposed definitions, MAFLD stands out as the most comprehensive and clinically relevant. By prioritizing metabolic dysfunction as the central criterion and accommodating multiple etiologies, MAFLD addresses the inherent limitations of exclusion-based definitions[64]. It recognizes the dynamic interplay between metabolic, alcohol-related, and other contributors to liver disease, providing a practical and inclusive approach that aligns with real-world clinical and research settings. Growing evidence suggests that MAFLD is superior in identifying both liver-related and extrahepatic outcomes of the disease[65-71] as well as in categorizing homogeneous groups of patients[71,72]. Furthermore, its adaptability to diverse populations and healthcare systems reinforces its utility as the preferred framework[73].

However, the ongoing debates surrounding these terminologies underscore the need for a unified framework that effectively incorporates overlapping etiologies, enhances diagnostic clarity, and ultimately improves patient outcomes. Establishing a unified definition is crucial for advancing the field. A standardized terminology would not only enhance diagnostic precision but also standardize research methodologies, enabling consistent data comparisons and facilitating the development of targeted therapeutic strategies[74].

DECLARATIONS

Authors' contributions

Conceptualization, investigation, writing - original draft, visualization, review and editing: Zerehpooshnesfchi S
Writing - review and editing: Lonardo A, Fan JG, Elwakil R, Tanwandee T, Altarrah MY, Örmeci N
Conceptualization, supervision, writing - original draft, writing - review and editing: Eslam M

Availability of data and materials

Not applicable.

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Conflicts of interest

Lonardo A is Editor-in-Chief of the journal *Metabolism and Target Organ Damage* and the Guest Editor of the Special Issue *The Evolving Nomenclature of the Metabolic Fatty Liver Syndromes: NAFLD/NASH and MAFLD/MASLD*; Eslam M is an Editorial Board member of the journal. They were not involved in any steps of editorial processing, notably including reviewer selection, manuscript handling, and decision making. The other authors declared that there are no conflicts of interest.

Ethical Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

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