



ANNALS

OFFICIAL JOURNAL OF THE ACADEMY OF MEDICINE, SINGAPORE

VOLUME 55

NUMBER 3

MAR 2026



A prospective study of the association of grip strength and sleep status with depressive symptoms

Routine screening integrating grip strength measurement and sleep assessment may help identify high-risk individuals for targeted depression prevention. (See full article, p. 128)

Illustration by Maria De-Castro

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The APLC expert consensus recommendations on the management of chronic lymphocytic leukaemia in Asia

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ISSN 2972-4066

Annals, Academy of Medicine, Singapore

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Beyond LDL-C: Desialylated LDL as a refined marker of coronary atherosclerosis severity

Tien Siang Eric Lim¹ MB BChir (Cambridge), Yung Jih Felix Keng¹ MBBS

The core role of low-density lipoprotein cholesterol (LDL-C) in atherosclerosis is well validated. However, the “LDL hypothesis” has evolved over the last 4 decades; apart from the quantity of LDL-C, we now recognise that qualitative modifications of LDL particles are critical in driving the transition from circulating lipoprotein to intimal plaque. Of these modifications—which include oxidation, glycation, and carbamylation—oxidation of LDL is the best described. However, desialylation of LDL is also emerging as an especially potent atherogenic trigger.

The nature and discovery of desialylated LDL. Desialylated LDL (desLDL) is an altered form of LDL, with decreased content of sialic acid residues on the carbohydrate moieties of apolipoprotein B-100 and the lipid components. Sialic acid is a negatively charged sugar that adds to the surface charge and stability of the LDL particle. Its elimination triggers a cascade of physical and chemical modifications, in which the particles become smaller, denser, more electronegative, and more prone to agglomeration.

The discovery of desialylated LDL dates back to the late 1980s and early 1990s, primarily through the pioneering work of Tertov et al.¹ They first identified a “multiply modified” LDL subfraction in the blood of patients with coronary artery disease (CAD) that was uniquely capable of inducing intracellular lipid accumulation in cultured smooth muscle cells and macrophages—a property not shared by native LDL.² Subsequent investigations revealed that the primary and perhaps initiating modification in this subfraction was the loss of sialic acid.³

What we now know about desLDL distinguishes it as a pre-secretory modification. Unlike oxidised LDL, which is thought to be formed primarily within the arterial wall, desLDL can be detected in significant quantities within the systemic circulation. This makes it an ideal candidate for a circulating biomarker:⁴

(1) Enhanced uptake: The loss of negative charge and subsequent particle aggregation facilitate non-specific, scavenger uptake by macrophages, leading to rapid foam cell formation.

(2) Increased retention: Desialylation increases the affinity of LDL for arterial proteoglycans, trapping the particles within the intima.

(3) Pro-inflammatory signalling: DesLDL has been shown to stimulate the secretion of pro-inflammatory cytokines, further exacerbating the local immune response within the vascular wall.

Clinical insight from this study. In the study by Liu et al. published in this issue of *Annals*, the authors provide a contemporary clinical validation of desLDL as a biochemical marker of CAD.⁵ Using liquid chromatography-mass spectrometry—a highly sensitive and specific technique—they quantified plasma desLDL in 162 patients undergoing coronary angiography.

The authors demonstrate that desLDL levels are significantly elevated in patients with CAD compared to those with non-obstructive disease. DesLDL levels correlated strongly with the Gensini score, a measure of the anatomical extent and severity of atherosclerosis. In multivariable models, desLDL remained an independent predictor of CAD severity, even after adjustment for traditional risk factors and standard lipid profiles including LDL-C, apolipoprotein B (apoB) and lipoprotein(a). Notably, the receiver operating characteristic analysis suggests that desLDL offers superior diagnostic performance compared with total cholesterol and LDL-C.

As a single-centre study with 162 participants, the findings require validation in larger, multi-ethnic cohorts to ensure generalisability. The study suggests and quantifies a correlation between desLDL and CAD, but as a cross-sectional study, it does not definitively prove a causal relationship with future major adverse cardiovascular events (MACE).

Future directions. The findings of this study open several promising avenues for future research and clinical application. First, longitudinal prospective trials are needed to determine if baseline desLDL levels can predict the risk of MACE independently of LDL-C, apoB and current risk scoring equations, such as the Framingham Risk Score or Pooled Cohort

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Accepted: 27 March 2026

Published Online First: 27 March 2026

Published: 27 March 2026.

Equations. Integrating desLDL into such equations or even into multi-omic risk profiles—combining lipidomics with genomics and proteomics—may provide a more granular understanding of residual inflammatory risk. Perhaps future characterisation of the various LDL modifications could help clinicians identify the vulnerable patient long before they present with vulnerable plaque.

Second, if the above causal relationship could be proven, therapeutic targeting of desialylation represents an untapped frontier. Research into trans-sialidases and neuraminidases (NEU), particularly NEU1 and NEU3, which are known to be active in the blood and vascular wall, could lead to a new class of “lipid-stabilising” drugs.⁶ Inhibiting these enzymes might prevent the conversion of native LDL into its more atherogenic desialylated form, potentially offering a synergistic effect when combined with statins or proprotein convertase subtilisin/kexin type 9 inhibitors.

The study presented by the authors reinforces the notion that we must look “under the hood” of the LDL particle to truly understand a patient’s cardiovascular risk. Desialylated LDL represents a potentially important bridge between lipid metabolism and chronic inflammation. As cardiovascular care moves towards personalised medicine, markers like desLDL may prove essential in identifying high-risk individuals who may appear low-risk on standard lipid panels, ultimately allowing for more targeted intervention.

Ethics statement

Not applicable, as no study participants were recruited.

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Keywords: atherosclerosis, biomarker, cardiology, coronary artery disease, epidemiology, risk prediction

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Grip strength, sleep status and depression

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Frailty screening in community-dwelling older adults offers an opportunity for early identification to mitigate downstream disease burden. Hand grip strength as a simple, reliable and easy-to-administer screening tool for the early detection of physical frailty has garnered significant interest in large-scale cohort studies.¹

This prospective cohort study of European middle-aged and older adults, by Ma et al., examined the independent and combined associations between grip strength, sleep disturbance and the risk of depressive symptoms.²

The study was derived from the Longitudinal Survey of Health, Ageing and Retirement in Europe, which spanned 11 years. With its prospective design, the study appears to address a crucial gap in literature. The prospective design, exclusion of pre-existing depressive symptoms and large sample size are notable strengths of the study.

The most important findings were that low baseline grip strength and sleep disturbance were each independently and synergistically associated with a significantly elevated risk of a single occurrence of depressive symptoms. Combined low grip strength and sleep disturbance had a substantially higher risk of depressive symptoms than with either factor alone. The synergistic effects between the 2 factors were particularly associated with a significantly elevated risk of recurrent depressive symptoms.

This longitudinal and sizable study highlights the importance of muscle health, mood and psychological well-being as components of healthy ageing, which aligns with both the Asian Working Group for Sarcopenia Consensus Update³ and the World Health Organization's Integrated Care for Older People approach,⁴ with its emphasis on the intrinsic domains of locomotion, vitality and psychological well-being.

Lifestyle factors, including smoking and alcohol use, were used as covariates in adjusted models. Older adults with depressive symptoms, had a higher prevalence of low grip strength and sleep disturbance but lower alcohol consumption. The counterintuitive findings, discussed by the study authors, indicate reverse causation. Social engagement patterns are

arguably understandable in a European context; nevertheless, they highlight the role of culture in mediating lifestyle factors and limit generalisability to other populations.

These data can be considered confirmatory but offer greater precision than previous analyses. For example, a 2026 meta-analysis demonstrated that low grip strength was associated with a higher odds of depressive symptoms over time; however, the magnitude of that association was small.⁵ Previous studies have also shown that lower grip strength is associated with sleep disturbance.⁶⁻⁸

While the study results by Ma et al. seem plausible, the methodological limitations are worth considering. The assessment of outcomes, while appropriate for a study of this scale, limits the validity of the results. Self-reported sleep measures, rather than objective measures, are prone to bias. This is especially true when considering mental health issues such as depression. Another methodological challenge when assessing sleep and depression is the potential for incorporation bias, as disturbed sleep is a key feature of depression screening tools.

In a secondary analysis of an existing cohort, there will always be variables of interest that are not easily available. In this case, nutritional status and more granular measures of medication use would have been relevant. A pilot study found that frailty and depression were strongly interconnected; higher grip strength was associated with better nutritional status.⁹

Psychotropic drugs are frequently prescribed in older adults. They are among the common causes of polypharmacy in older adults and are associated with adverse events such as falls, frailty and disability.¹⁰⁻¹¹ Unmeasured confounders in this study, such as psychotropic medications, polypharmacy and over-the-counter sleeping aids, warrant inclusion in future studies. Finally, the population is limited to a European cohort, and replication in other geographically and ethnically diverse populations is needed.

Age and sex-related differences in muscle loss variability are important confounders highlighted in the prevailing literature on grip strength.⁸ Ma et al.

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Accepted: 24 March 2026

Published Online First: 25 March 2026

accounted for these through stratified analyses. The study found a significant association between low grip strength and the risk of depressive symptoms among adults aged 70 years and older, while sleep disturbance was associated with an increased risk of depressive symptoms across all age groups with the effect size increasing with age. A synergistic effect of low grip strength and sleep disturbance was observed across all age groups, with the highest risk among those aged 50–59 years.

An Asian study by Kamide et al. found that grip strength declined with age in both men and women.¹² A cross-sectional study by Wang Y et al. among older adults aged 60 years and over, explored the relationship between physical activity, physical frailty and depressive symptoms.¹³ In this study, grip strength, gait ability and muscle mass were measured. The study participant demographics included measurement of body mass index. The authors concluded that grip strength and gait ability may be better indicators of frailty for predicting depressive symptoms in older men, whereas physical activity may be a more useful predictor of depressive symptoms in older women.

Ma et al. adjusted for health status and chronic diseases; however, body weight, an important consideration when assessing muscle strength, was not adjusted for. Depressive symptoms in this study cohort were screened using a self-rating scale, i.e. the 12-item European Depression Scale.^{2,14} Wang et al. highlighted the usage of Geriatric Depression Scale-15, a self-rated scale, validated among older adults in urban China.^{15–16} Despite the methodological and measurement differences, both studies have shown that low grip strength was significantly associated with a greater risk of depressive symptoms in men. Additionally, the study by Ma et al. showed that combined low grip strength and sleep disturbance was associated with a significant risk in both sexes, with higher risks in men.

Notwithstanding the limitations of Ma et al.'s study, what are the implications for clinicians and policy-makers? The high prevalence of depressive symptoms in middle aged and older adults, and the synergistic effects of low grip strength and sleep disturbance could support arguments for screening for these conditions. A holistic approach to frailty screening and identification warrants the inclusion of mental health; refreshingly, the study attempts to address that.

Ethics statement

Not applicable, as no study participants were involved.

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any

financial interest in the subject matter or materials discussed in this manuscript. All authors have no conflicts of interest to declare.

Keywords: *affective disorder, depression, grip strength, sleep disturbance, sleep status*

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RDW-to-albumin ratio correlates with serum neurofilament light chain

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Blood-based biomarkers are reshaping the study of neurological disease. Among these, neurofilament light chain (NfL) has emerged as one of the most sensitive peripheral indicators of axonal injury. As assays for measuring serum neurofilament light chain (sNfL) have become widely available, this biomarker has gained prominence in both clinical research and population studies.

However, several factors confound NfL interpretation. NfL levels are affected by multiple factors such as increasing age, body mass index (BMI), kidney function and coexisting conditions such as cardiovascular disease and diabetes.¹ These comorbidities can alter NfL levels through pathways related to systemic inflammation, vascular abnormalities and impaired clearance of neurofilament proteins.¹ Consequently, sNfL may capture clinical and subclinical neuronal injury occurring in the context of systemic inflammatory states, although the precise nature and magnitude of these relationships remain unclear. In this issue of the *Annals*, Song et al. examined this relationship by evaluating the association between the red cell distribution width-to-albumin ratio (RAR) and circulating sNfL concentrations in participants from the National Health and Nutrition Examination Survey (NHANES).² Their analysis suggests that individuals with higher RAR values tend to have higher sNfL concentrations, raising the possibility that systemic inflammatory or metabolic stress may be associated with biomarkers of neuroaxonal injury.

NfL is a structural protein within the neuronal cytoskeleton and is released into extracellular fluids following axonal damage. Increased NfL concentrations have been demonstrated across a wide spectrum of neurological conditions, including multiple sclerosis, neurodegenerative disorders, traumatic brain injury and cerebrovascular disease.^{3,4} Importantly, circulating NfL levels are influenced not only by overt neurological pathology but also by several physiological and systemic factors. Age is one of the strongest determinants of sNfL concentrations, and studies have shown that renal function, vascular disease and systemic inflammatory states can also influence circulating

levels.¹ As a result, sNfL is regarded as a global marker of neuroaxonal integrity rather than a disease-specific biomarker.

Red cell distribution width (RDW) and serum albumin are widely available laboratory parameters that reflect systemic physiological stress. RDW, traditionally used in the evaluation of anaemia, has increasingly been recognised as a marker of inflammation, oxidative stress and chronic disease burden. Elevated RDW values have been linked to cardiovascular disease, frailty and increased mortality in population-based studies.⁵ Serum albumin, in contrast, reflects nutritional status and systemic inflammatory activity; reduced albumin concentrations frequently accompany chronic illness and inflammatory states and are likewise associated with adverse outcomes.⁶ The biological rationale for RAR lies in combining elevated RDW and reduced albumin, providing a broad snapshot of systemic physiological derangement. This ratio has demonstrated value in predicting end-stage kidney disease, diabetic complications, malignancies and aortic aneurysm, establishing its use as a biomarker across different organ systems and diseases.⁷

In the analysis presented by Song et al., higher RAR values were associated with significantly higher sNfL concentrations even after adjustment for demographic and clinical variables. These findings raise the intriguing possibility that systemic physiological stress may be linked to circulating signals of neuronal injury detectable in peripheral blood.

Several aspects of the study strengthen the credibility of the findings. The use of the NHANES dataset allows examination of biomarker relationships in a large, and nationally representative population cohort with standardised laboratory measurements and comprehensive demographic information. The authors also applied multivariable statistical models to adjust for important confounders known to influence sNfL concentrations, including age, BMI and serum creatinine.

Song et al.'s study builds on previous work analysing the NHANES cohort and suggesting a positive association between systemic inflammatory burden

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Accepted: 27 March 2026

Published: 27 March 2026

and circulating sNfL. A higher systemic immune-inflammation index (SII) was correlated with increased sNfL, with stronger effects observed in individuals with diabetes.⁸ Elevated sNfL levels were also found to be associated with higher systemic inflammatory markers, including SII, systemic inflammation response index and white blood cell count, which in turn correlated with clinically relevant depressive symptoms.⁹ A cross-sectional study also demonstrated positive associations between circulating sNfL and pro-inflammatory cytokines, such as interleukin (IL)-1 beta and IL-6.¹⁰

However, there are limitations to this study. First, the cross-sectional design limits conclusions regarding causality or temporal relationships. Although higher RAR values are associated with elevated sNfL levels, it remains unclear whether systemic inflammatory or nutritional disturbances contribute directly to neuronal injury, whether subclinical or clinical neuronal damage influences systemic physiological markers, or whether both arise from shared underlying mechanisms such as ageing, vascular dysfunction or chronic disease burden. Second, the biological specificity of the RAR metric warrants careful consideration. Both RDW and albumin are influenced by a wide range of physiological and pathological conditions. Even with statistical adjustment, unmeasured variables may partly explain the association. As such, RAR should be interpreted as a general indicator of systemic health, rather than a direct biomarker of neuronal injury. The modest effect sizes observed also suggest that RAR is unlikely to serve as a standalone screening tool for neuronal injury; rather, its value may lie in risk stratification or as a surrogate marker for longitudinal monitoring when combined with other clinical data.

A further issue relates to the increasing proliferation of composite laboratory ratios proposed as novel biomarkers. While such indices may strengthen statistical associations in epidemiological analyses, their biological interpretation is often unclear. Without mechanistic evidence linking RDW-albumin dynamics to pathways of neuroaxonal injury, the clinical significance of RAR remains uncertain.

Despite these limitations, the findings are consistent with a growing body of evidence linking systemic health to neurological outcomes. Chronic inflammation has increasingly been implicated in the development of neurodegenerative¹¹ and cerebrovascular diseases. Systemic inflammatory states may promote endothelial dysfunction, oxidative stress and microvascular injury, processes that can impair cerebral perfusion and

neuronal survival. Haematologic markers, such as RDW, have likewise been associated with altered microcirculatory dynamics and vascular pathology, providing potential pathways through which systemic inflammation could influence neuronal injury detected by biomarkers such as sNfL.

Collectively, these observations support the evolving concept of a “body-brain axis,” in which physiological and metabolic processes shape neurological health across the lifespan. Conditions characterised by persistent inflammation, metabolic dysregulation, or nutritional imbalance may exert gradual yet cumulative effects on neuronal integrity. Routinely measured laboratory parameters could therefore provide indirect insight into systemic states that influence brain resilience.

Future research should prioritise longitudinal and mechanistic investigations to clarify these relationships. Prospective cohort studies are needed to determine whether elevated RAR precedes increases in sNfL, predicts cognitive decline or signals future neurological disease. Integrating RAR with additional inflammatory and metabolic biomarkers may further elucidate the systemic pathways linking physiological stress to neuronal injury. Another important direction involves evaluating whether interventions that improve systemic health modify circulating neuronal injury biomarkers. Lifestyle optimisation, nutritional improvement and therapies targeting chronic inflammatory states may influence both systemic physiological markers and downstream neurological outcomes.

The study by Song et al. represents an important expansion of RAR applications into neurological research, bridging established literature on systemic inflammation biomarkers with emerging blood-based markers of neuronal injury. While immediate clinical utility remains uncertain, the study generates valuable hypotheses. The findings raise the intriguing possibility that routine haematologic indices might help identify individuals at heightened risk for neurological injury, potentially supporting preventive strategies targeting modifiable systemic factors.

Ethics statement

Not applicable, as no study participants were involved.

Declaration

The authors declare that there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Keywords: *biostatistics, epidemiology, haematology, neurology, statistics*

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Desialylated low-density lipoprotein: A stronger predictor of coronary atherosclerosis burden than low-density lipoprotein cholesterol

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ABSTRACT

Introduction: This study aimed to investigate the relationship between plasma desialylated low-density lipoprotein (desLDL) levels and the severity of coronary artery disease (CAD), and to evaluate the potential value of desLDL as a biomarker for disease stratification and risk prediction.

Methods: This study was conducted at Affiliated Nanhua Hospital, University of South China between December 2024 and June 2025. A total of 162 patients undergoing coronary angiography were enrolled and categorised into a CAD group (n=78) and a non-CAD group (n=84) based on the presence of $\geq 50\%$ coronary stenosis. Plasma desLDL levels were quantified by liquid chromatography-mass spectrometry (LC-MS). Receiver operating characteristic (ROC) analysis compared the diagnostic performance of desLDL with conventional lipid parameters, and multivariable logistic regression was applied to assess the independent predictive value of desLDL.

Results: Plasma desLDL levels were significantly higher in the CAD group than in controls. Among CAD patients, those with >2 diseased vessels had higher desLDL levels than those with ≤ 2 vessels, and both exceeded control values ($P < 0.001$). The ROC area under the curve was 0.836 (95% confidence interval [CI] 0.779–0.893); a threshold of 2.25 mmol/L provided 75.6% sensitivity and 84.2% specificity, outperforming LDL cholesterol and total cholesterol. Multivariable analysis identified desLDL as the strongest independent predictor of CAD (adjusted odds ratio 5.85, 95% CI 2.69–12.69). DesLDL elevations were similar in acute myocardial infarction and stable CAD presentations, while both remained significantly higher than controls.

Conclusion: Elevated plasma desLDL levels were significantly associated with the presence of CAD and reflected anatomical disease burden, demonstrating superior predictive performance compared with conventional lipid markers.

Keywords: atherosclerosis, biomarker, coronary artery disease, desialylated low-density lipoprotein, risk prediction

CLINICAL IMPACT

What is New

- DesLDL levels were significantly elevated in patients with CAD.
- DesLDL demonstrated superior diagnostic performance compared to traditional lipid parameters for CAD detection.

Clinical Implications

- DesLDL may serve as a novel and independent biomarker for early CAD detection and improved risk stratification.
- DesLDL appears more sensitive for identifying disease burden (number of diseased vessels) than for reflecting disease severity as measured by Gensini score or clinical acuity, suggesting its potential role as a screening rather than a staging tool.

INTRODUCTION

Coronary artery disease (CAD) remains one of the leading causes of death and disability worldwide, imposing a substantial burden on global healthcare systems and socioeconomic development. According to epidemiological data, approximately 197 million individuals were affected by CAD globally in 2019, resulting in an estimated 9.1 million deaths and accounting for 16.1% of total deaths that year.^{1,2}

Atherosclerosis constitutes the fundamental pathological process underlying CAD; it is characterised by lipid accumulation within the arterial intima, endothelial dysfunction and concerted inflammatory cascades that culminate in plaque formation.^{3,4} These plaques progressively narrow or occlude the coronary lumen, diminish myocardial perfusion and oxygen delivery, and may eventually provoke ischaemic injury or

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Accepted: 27 January 2026

Published Online First: 18 March 2026

infarction.^{5,6} Atherosclerosis is particularly prevalent in older adults.⁷ Over the past decades, numerous risk factors, including dyslipidaemia, smoking, hypertension, diabetes mellitus, ageing, male sex, obesity and chronic inflammation, have been firmly linked to CAD.^{8,9} Concurrently, an expanding panel of atherosclerosis-related biomarkers has been introduced into clinical practice;¹⁰ however, their sensitivity, specificity, and overall predictive accuracy remain suboptimal, underscoring the need to identify and validate more robust, mechanism-based indicators.^{11,12}

Given the central role of lipid abnormalities in atherogenesis, low-density lipoprotein cholesterol (LDL-C) is routinely used for cardiovascular risk stratification and therapeutic decision-making.^{3,13} Nonetheless, LDL-C levels alone are insufficient, as a considerable proportion of cardiovascular events occur in individuals whose LDL-C is within recommended targets.¹⁴ This discrepancy underscores the need to identify more sensitive atherogenic lipid subtypes. Among modified LDL particles, oxidised LDL (oxLDL) is the most extensively investigated and is now recognised as a pivotal driver of atherosclerotic progression.^{15,16} OxLDL is rapidly internalised by macrophages via scavenger receptors, triggering foam-cell formation and amplifying local inflammation, thereby accelerating plaque development.^{17,18} However, antioxidant therapies targeting oxLDL have shown limited clinical efficacy in reducing cardiovascular events,¹⁹ suggesting that alternative pathogenic pathways and therapeutic targets warrant exploration.

Desialylated low-density lipoprotein (desLDL) is among the earliest and most pronounced circulating modifications of native LDL.^{20,21} Neuraminidases (NEU) remove terminal sialic-acid residues from the LDL surface,²² generating particles with smaller diameter, higher density and altered lipid composition.²³ Compared with native LDL, desLDL displays greater affinity for macrophage scavenger and asialoglycoprotein receptors, thereby enhancing cholesterol uptake and foam-cell formation.²⁴ Clinically, plasma desLDL levels are elevated 1.5- to 6-fold in patients with CAD, constituting up to 60% of total LDL versus 5–10% in healthy controls.^{21,25} These observations implicate desLDL in atherogenesis and suggest that it may outperform traditional LDL-C as a risk marker. Nevertheless, its clinical relevance, particularly for grading disease severity, remains poorly defined and warrants systematic evaluation.

This study quantified plasma desLDL levels in patients undergoing coronary angiography and examined their association with CAD severity, as defined by vessel

involvement and Gensini score. The authors further compared the diagnostic performance of desLDL with conventional lipid parameters using receiver operating characteristic (ROC) analysis and evaluated its independent predictive value through multivariable logistic regression. The goal was to determine whether desLDL could function as a novel biomarker for the early detection and refined risk stratification of CAD.

METHODS

Study design and patient recruitment

This prospective, cross-sectional study enrolled 162 consecutive patients who underwent coronary angiography at the Affiliated Nanhua Hospital, University of South China between December 2024 and June 2025. Exclusion criteria included active infection, autoimmune disease, severe hepatic or renal dysfunction, malignancy or other major systemic illness.

CAD was defined as $\geq 50\%$ diameter stenosis with compatible symptoms or electrocardiographic changes. Acute myocardial infarction (AMI) was diagnosed when cardiac troponin was elevated with clinical or imaging evidence of acute ischaemia. Type 2 diabetes mellitus (T2DM) was diagnosed when fasting plasma glucose was ≥ 7.0 mmol/L or 2-hour glucose was ≥ 11.1 mmol/L. Hypertension was defined as blood pressure $\geq 140/90$ mmHg on 3 separate readings.

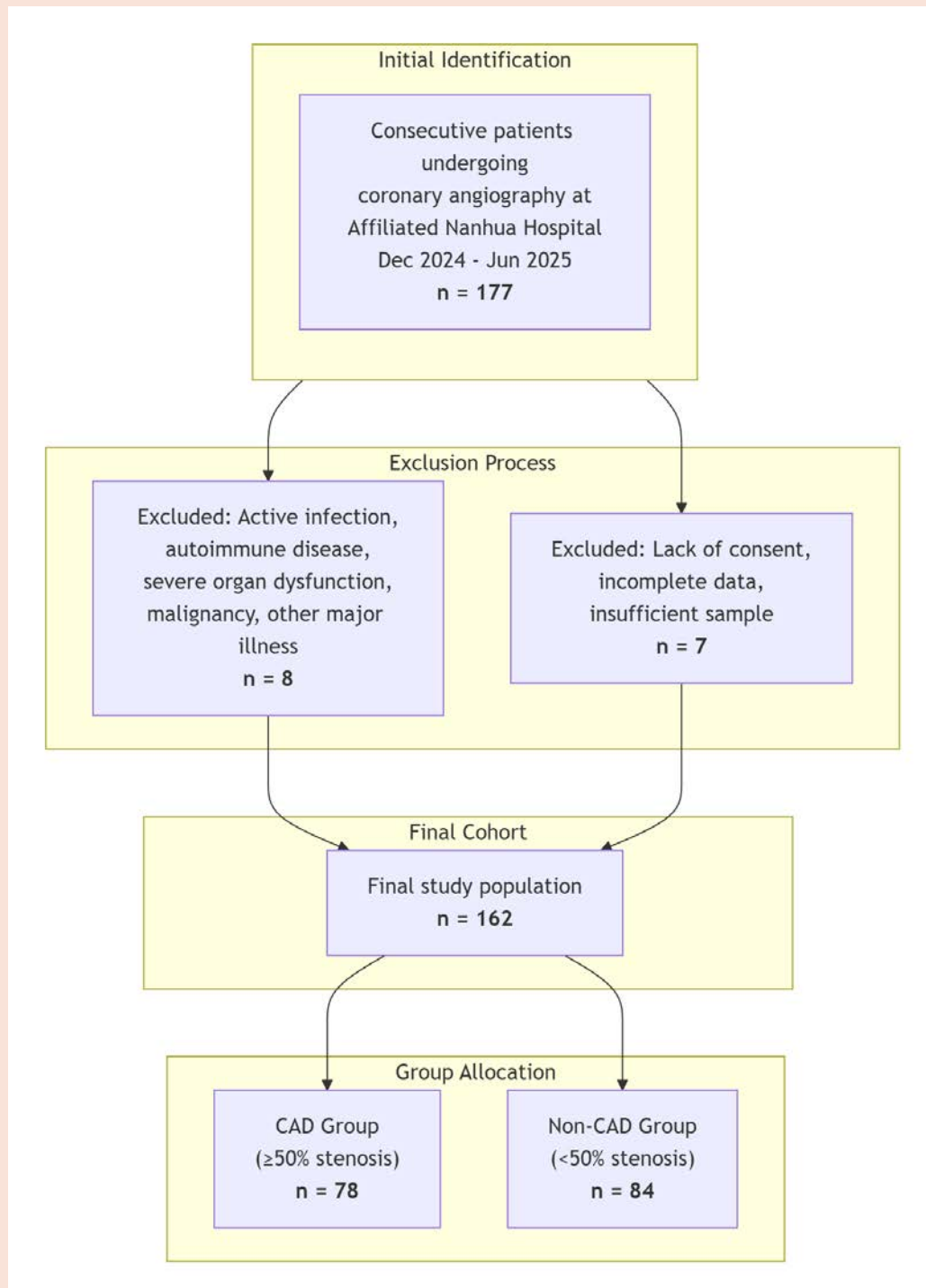
Patients were stratified into a CAD group ($\geq 50\%$ luminal stenosis in ≥ 1 major coronary artery; $n=78$) and a non-CAD group ($n=84$), and were frequency-matched for age and sex. The non-CAD group comprised patients who underwent coronary angiography for clinical suspicion of CAD but were found to have no significant coronary stenosis ($<50\%$ in all major vessels). Their clinical presentation and referral indications were comparable to those of the CAD group, ensuring comparability. Four senior interventional cardiologists performed the procedures, and 2 investigators, blinded to participants' clinical data, independently reviewed the angiograms. Within the CAD cohort, patients were further categorised as AMI versus non-AMI and as ≤ 2 -vessel versus >2 -vessel disease. Lesion severity was quantified using the Gensini score, a well-established angiographic scoring system that comprehensively accounts for the number, location and degree of coronary artery stenoses. Although the Synergy between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) score is also widely used, the Gensini score is particularly suitable for assessing the overall atherosclerotic burden in diverse patient

populations, including those with multivessel disease, and has been validated in numerous studies for predicting cardiovascular outcomes (Fig. 1).

Clinical and laboratory data

Baseline demographics (age, sex, body mass index [BMI], smoking, hypertension, T2DM) were recorded.

Fig. 1. STROBE flowchart.



CAD: coronary artery disease; STROBE: strengthening the reporting of observational studies in epidemiology

Fasting plasma was stored at -80°C and analysed once. Plasma desLDL was quantified using a targeted liquid chromatography-tandem mass spectrometry (LC-MS/MS) method based on the specific derivatisation of asparagine residues in apolipoprotein B-100, which are exposed upon desialylation. Lipid profile (total cholesterol [TC], LDL-C, high-density lipoprotein-cholesterol, triglyceride) was measured on an automated analyser; high-sensitivity C-reactive protein (hs-CRP) was assayed by enzyme-linked immunosorbent assay.

Analytical validation of LC-MS/MS

The analytical performance of the LC-MS/MS method for quantifying desLDL was rigorously validated according to the U.S. Food and Drug Administration guidance for industry on bioanalytical method validation.²⁶ LDL was isolated from 200 μL of plasma using a precipitation-based method with phosphotungstic acid and magnesium chloride. Purity was confirmed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis, showing a single apolipoprotein B-100 (apoB-100) band without significant contamination. The average recovery of spiked desLDL standards was $92.5\% \pm 3.2\%$. To prevent ex vivo desialylation, all plasma samples were immediately placed on ice after collection, processed within 2 hours and handled at 4°C throughout. For quantification, a calibration curve was constructed using enzymatically desialylated LDL standards, with a stable isotope-labelled peptide serving as an internal standard to correct for matrix effects and instrument variability.

The method demonstrated excellent performance characteristics. Calibration curves showed strong linearity over the tested range ($R^2 > 0.995$), with a lower limit of quantification of 0.1 mmol/L. Both intra-assay (coefficient of variation [CV] $< 8.5\%$) and inter-assay (CV $< 10.2\%$) precision, as well as accuracy (relative error within $\pm 7.0\%$), were within acceptable limits. Stability studies confirmed that desLDL was stable for at least 6 months at -80°C and through 3 freeze-thaw cycles. To eliminate pre-analytical bias, all clinical samples were randomised and analysed in a single batch by an operator who was blinded to the participants' CAD status. The final reported concentration of desLDL (in mmol/L) represents the absolute molar concentration of desialylated LDL particles in the plasma sample. This value was calculated from the measured molar concentration of a specific apoB-100-derived peptide, which is exposed and derivatised only in desialylated LDL, under the biochemical assumption that each individual LDL particle contains a single copy of the apoB-100 protein.

Statistical analysis

Analyses were performed in SPSS version 27.0 (IBM Corp, Armonk, NY, US) and R 4.4.1 (R Core Team,

Vienna, Austria). Normality was assessed with the D'Agostino-Pearson test. Data were presented as mean $\pm$ standard deviation (SD), median (interquartile range [IQR]) or number (%). Between-group differences were tested with Student's t-tests, Mann-Whitney U tests or chi-square tests as appropriate. Spearman correlation assessed the relationship between desLDL and Gensini score. Diagnostic accuracy was evaluated with ROC curves, and areas under the curves (AUCs) were compared with those for LDL-C and total cholesterol (TC) using DeLong's test. The optimal desLDL cut-off was defined by the Youden index. Independent associations with CAD were tested in multivariable logistic regression; covariates with $P < 0.10$ in univariate analysis and variance inflation factor < 2.0 were retained. Results were reported as adjusted odds ratios (ORs) with 95 % confidence interval (CIs). A 2-sided $P < 0.05$ was considered statistically significant, and post-hoc power analysis confirmed adequate study power.

RESULTS

Baseline characteristics

Compared with individuals without CAD, patients in the CAD group displayed an overall less favourable cardiometabolic profile. BMI was higher in the CAD group (24.34 ± 3.85 versus [vs] 23.04 ± 2.91 kg m^{-2} , $P = 0.016$), and current smoking was more prevalent (47.4% vs 21.4% , $P < 0.001$). Hypertension, T2DM and statin therapy were likewise more common (60.3% vs 32.1% , $P < 0.001$; 33.3% vs 14.3% , $P = 0.005$; 56.4% vs 9.5% , $P < 0.001$, respectively). TC, LDL-C and lipoprotein(a) were all significantly higher in the CAD group (4.45 ± 0.61 vs 4.27 ± 0.48 mmol/L, $P = 0.040$; 3.03 ± 1.09 vs 2.51 ± 0.68 mmol/L, $P < 0.001$; 182.97 ± 77.85 vs 101.87 ± 40.61 mg/L, $P < 0.001$, respectively). Inflammatory burden was also greater in the CAD group. Patients with CAD showed significantly higher hs-CRP (median 2.31 vs 1.09 mg/L) and white blood cell counts (6.95 vs 5.78×10^9 mg/L, both $P < 0.001$) than the non-CAD group (Table 1).

Differences in plasma desLDL levels between CAD and non-CAD groups

As shown in Fig. 2, plasma desLDL concentrations were significantly elevated in patients with CAD compared with angiographically normal controls (2.64 ± 0.78 vs 1.69 ± 0.58 mmol/L, $P < 0.001$). Within the CAD group, desLDL increased with anatomical burden; individuals harbouring > 2 diseased vessels showed higher levels than those with ≤ 2 vessels ($P < 0.01$), and both subgroups exceeded non-CAD values (all $P < 0.001$; Fig. 3A). When patients were stratified by Gensini score (≥ 51 vs < 51), there was no statistically significant difference in desLDL levels between the 2 groups (Fig. 3B). In the analysis of

Table 1. Baseline characteristics of the study participants.

Variables	CAD (n=78)	Non-CAD (n=84)	P value
Age, mean $\pm$ SD, years	55.58 $\pm$ 11.02	55.77 $\pm$ 7.97	0.895
Sex: male, no. (%)	42 (53.8)	35 (41.7)	0.156
BMI, mean $\pm$ SD, kg/m ²	24.34 $\pm$ 3.85	23.04 $\pm$ 2.91	0.016
Smoking, no. (%)	37 (47.4)	18 (21.4)	<0.001
Hypertension, no. (%)	47 (60.3)	27 (32.1)	<0.001
T2DM, no. (%)	26 (33.3)	12 (14.3)	0.005
Statin, no. (%)	44 (56.4)	8 (9.5)	<0.001
TG, mean $\pm$ SD, mmol/L	1.29 $\pm$ 0.56	1.20 $\pm$ 0.34	0.204
TC, mean $\pm$ SD, mmol/L	4.45 $\pm$ 0.61	4.27 $\pm$ 0.48	0.040
LDL-C, mean $\pm$ SD, mmol/L	3.78 $\pm$ 0.74	2.82 $\pm$ 0.57	<0.001
HDL-C, mean $\pm$ SD, mmol/L	1.09 $\pm$ 0.26	1.11 $\pm$ 0.20	0.695
Lp(a), mean $\pm$ SD, mg/L	182.97 $\pm$ 77.85	101.87 $\pm$ 40.61	<0.001
hs-CRP, median (IQR), mg/L	2.31 (0.11–8.16)	1.09 (0.14–1.97)	<0.001
WBC, mean $\pm$ SD, $\times 10^9$ mg/L	6.95 $\pm$ 2.14	5.78 $\pm$ 1.22	<0.001

BMI: body mass index; CAD: coronary artery disease; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; IQR: interquartile range; LDL-C: low-density lipoprotein cholesterol; Lp(a): lipoprotein(a); SD: standard deviation; T2DM: type 2 diabetes mellitus; TC: total cholesterol; TG: triglyceride; WBC: white blood cell count.

clinical presentation, patients with CAD who presented with AMI (n=22) and those without AMI (n=56) exhibited comparable desLDL levels, yet both were markedly higher than those in non-CAD controls (Fig. 3C). These findings indicate that plasma desLDL is associated with coronary atherosclerotic burden, while its elevation is not necessarily specific to AMI onset.

Diagnostic value of desLDL compared with conventional biomarkers

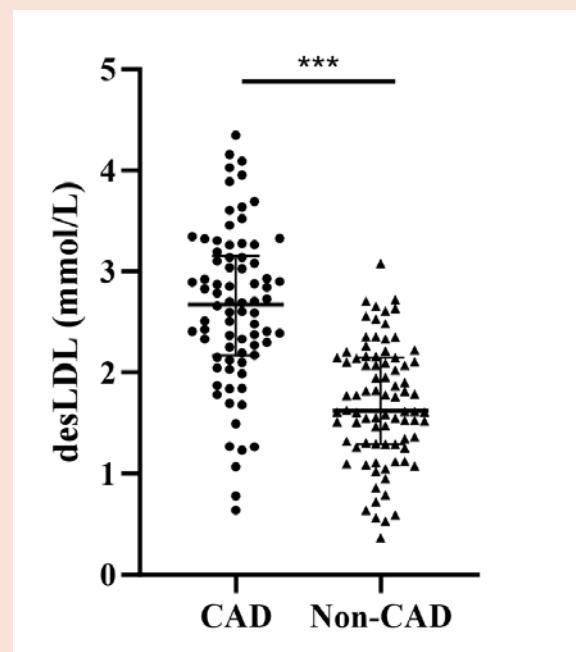
ROC curve analysis was performed to evaluate the diagnostic accuracy of plasma desLDL for CAD. DesLDL demonstrated excellent discriminative ability with an AUC of 0.836 (95% CI 0.779–0.893). The optimal cut-off value was identified as 2.25 mmol/L, yielding a sensitivity of 75.6% and a specificity of 84.2%.

Comparative analysis revealed that desLDL significantly outperformed all conventional lipid markers. Notably, desLDL's AUC was substantially higher than that of LDL-C (AUC 0.654, Δ AUC 0.182, $P < 0.001$) and TC (AUC 0.584, Δ AUC 0.252, $P < 0.001$) (Fig. 4).

Association between desLDL and CAD risk

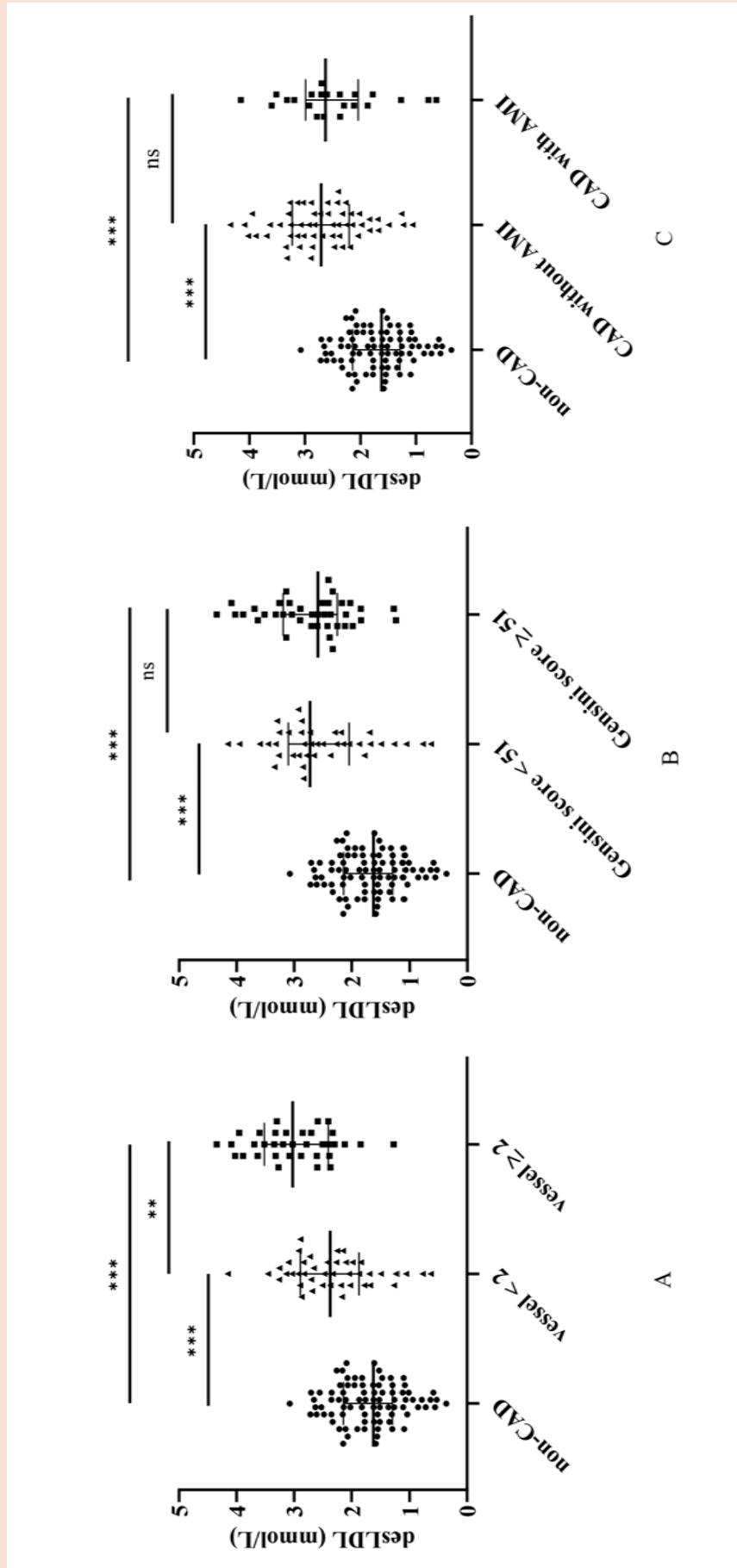
After multivariable adjustment (Table 2), desLDL remained the strongest independent predictor of

Fig. 2. Comparison of plasma desLDL levels between CAD and non-CAD groups. The plasma desLDL concentration was significantly higher in patients with CAD (n=78, 2.64 ± 0.78 mmol/L) than in non-CAD individuals (n=84, 1.69 ± 0.58 mmol/L); Student's t-test, $P < 0.001$.



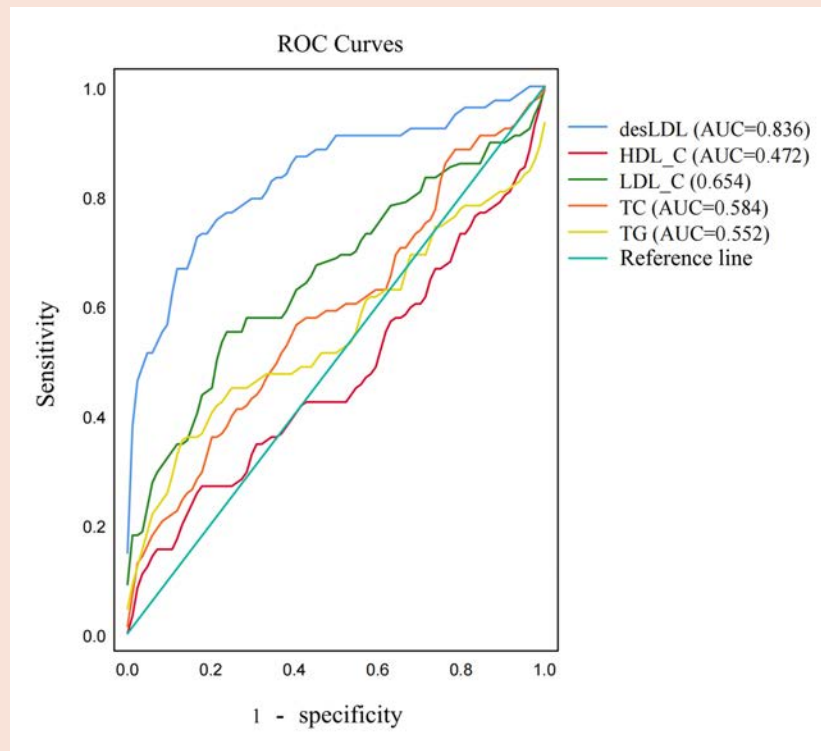
CAD: coronary artery disease; desLDL: desialylated low-density lipoprotein

Fig. 3. Comparison of plasma desLDL levels between CAD subgroups. (A) desLDL levels were significantly higher in CAD patients with ≤ 2 diseased vessels ($n=43$) and >2 diseased vessels ($n=35$) than in non-CAD patients ($n=84$), with median (IQR) values of 2.50 (2.24–2.84), 2.86 (2.61–3.25) and 1.73 (1.43–1.95) mmol/L, respectively (*** $P<0.001$ for both). Moreover, patients with >2 diseased vessels had significantly higher desLDL levels than those with ≤ 2 vessels (** $P<0.01$). (B) desLDL levels were significantly elevated in both CAD patients with Gensini scores <51 ($n=39$) and ≥ 51 ($n=39$) compared to non-CAD controls, with median (IQR) values of 2.73 (2.10–3.07), 2.59 (2.29–3.17) and 1.62 (1.29–2.14) mmol/L, respectively (*** $P<0.001$). No significant difference was observed between the 2 CAD subgroups. (C) desLDL levels were significantly higher in CAD patients without AMI ($n=56$) and with AMI ($n=22$) than in non-CAD patients, with median (IQR) values of 2.71 (2.24–3.17), 2.63 (2.11–2.91) and 1.62 (1.29–2.14) mmol/L, respectively (*** $P<0.001$). No significant difference was found between AMI and non-AMI CAD patients.



AMI: acute myocardial infarction; CAD: coronary artery disease; desLDL: desialylated low-density lipoprotein; IQR: interquartile range

Fig. 4. ROC curves of desLDL and traditional lipid-related biomarkers for discriminating CAD.



CAD: coronary artery disease; desLDL: desialylated low-density lipoprotein; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; ROC: receiver operating characteristic; TC: total cholesterol; TG: triglyceride

Table 2. Results of multivariable logistic regression analysis.

Variables	β	OR (95% CI)	P value
desLDL	1.766	5.85 (2.69–12.69)	<0.001
LDL-C	0.66	1.94 (1.13–3.30)	0.016
hs-CRP	0.263	1.30 (1.04–1.63)	0.021
BMI	0.076	1.08 (0.94–1.24)	0.267
Hypertension	1.273	3.57 (1.36–9.35)	0.010
T2DM	1.381	3.98 (1.32–11.99)	0.014
Smoking	1.274	3.58 (1.28–9.99)	0.015

BMI: body mass index; CI: confidence interval; desLDL: desialylated low-density lipoprotein; hs-CRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; OR: odds ratio; T2DM: type 2 diabetes mellitus

Multivariable logistic regression analysis was conducted to evaluate the association between selected variables and the presence of coronary artery disease. Results are expressed as ORs with 95% CIs. A *P* value <0.05 was considered statistically significant.

CAD (OR 5.85, 95% CI 2.69–12.69, *P*<0.001). LDL-C (OR 1.94, 1.13–3.30, *P*=0.016) and hs-CRP (OR 1.30, 1.04–1.63, *P*=0.021) were also significant, as were hyper-tension (OR 3.57, 1.36–9.35), T2DM (OR 3.98, 1.32–11.99) and smoking (OR 3.58, 1.28–9.99; all *P*<0.05). BMI was not independently associated with CAD in the adjusted model (OR 1.08, 0.94–1.24, *P*=0.267).

DISCUSSION

In this study, plasma desLDL was associated with coronary atherosclerotic burden, while its elevation was not necessarily specific to AMI onset. Specifically, plasma desLDL levels rose significantly with increasing angiographic plaque burden. Although a trend towards higher levels was observed in patients

with AMI than in those without AMI, this difference did not reach statistical significance. In diagnostic performance, desLDL consistently outperformed conventional lipid measures, including LDL-C and TC, in discriminating CAD (AUC 0.836; sensitivity $\approx$ 76%, specificity $\approx$ 84%). Importantly, after multivariable adjustment for traditional risk factors, desLDL remained strongly and independently associated with disease presence (adjusted OR $\approx$ 5.85). Collectively, these results underscore the premise that lipoprotein quality, specifically the desialylation state, governs coronary risk beyond the quantity of cholesterol alone.

Significant differences in baseline characteristics were observed between patients with CAD and those without. Patients with CAD had a higher BMI and markedly greater prevalence of smoking, hypertension and T2DM, mirroring the established epidemiology of atherosclerotic disease. Smoking and hypertension promote endothelial injury and vascular inflammation, thereby accelerating plaque formation. Patients with CAD also exhibited more pronounced lipid dysregulation and elevated hs-CRP, indicating a more atherogenic systemic milieu. Metabolic disturbances such as T2DM foster small dense LDL and post-translational LDL modifications, including glycation and desialylation.^{27,28} Prior work showed that desLDL constitutes $\approx$ 35 % of total LDL in diabetes versus $\approx$ 12 % in healthy subjects.²⁸ Although the higher T2DM prevalence in this CAD cohort may partly explain the elevated desLDL, the association remained significant after full adjustment, supporting an independent role for desLDL in atherogenesis.

Plasma desLDL was significantly higher in CAD than in controls, consistent with earlier biochemical data reporting a 2.5- to 5-fold reduction in LDL-bound sialic acid among patients with CAD.²⁹ Subgroup analysis showed that desLDL was higher in patients with >2 diseased vessels than in those with ≤ 2 diseased vessels. DesLDL was also significantly elevated in both Gensini strata and in both AMI and non-AMI CAD subgroups when each was compared with non-CAD controls.³⁰ However, within-CAD comparisons based on Gensini category or AMI status did not reach statistical significance, suggesting that desLDL may be more sensitive for detecting disease presence than for quantifying incremental severity.

This pattern echoes that of other glycan-related biomarkers. Monocyte Siglec-1 expression is elevated in CAD versus healthy controls but shows no significant differences across CAD phenotypes.³¹ Likewise, serum total sialic acid is unrelated to lesion extent in stable angina, although it predicts complications in acute coronary syndromes.^{32,33} The higher desLDL values seen in AMI, together with evidence of dynamic sialic acid upregulation during plaque rupture,³³ imply that

desialylation may reflect plaque vulnerability and acute inflammatory burden.

Collectively, these data support desLDL as a sensitive and specific marker for the presence of angiographically defined, flow-limiting coronary atherosclerosis (obstructive CAD). These findings suggest that desLDL is elevated even in the context of significant luminal stenosis, highlighting its potential role in identifying patients with established, high-risk atherosclerotic burden. Its ability to distinguish finer gradations of severity may be limited by biological saturation or temporal dynamics; combining desLDL with inflammatory or imaging metrics could therefore enhance the phenotyping of plaque burden and instability.

The superior discriminative power of desLDL over LDL-C and TC was also confirmed by ROC analysis. Conventional lipids largely quantify particle number, whereas desLDL reflects qualitative particle modification; many CAD patients exhibit normal or target LDL-C yet harbour structurally altered LDL that confers residual risk.³⁴ These results—and prior data on small dense LDL-C predicting events despite LDL-C control³⁵—underscore the value of assessing LDL particle quality in risk stratification. Multivariable modelling further established desLDL as an independent predictor of CAD after controlling for age, sex, LDL-C, hypertension, T2DM and smoking. Highly desialylated LDL particles may adhere more avidly to the arterial wall and trigger stronger inflammatory responses, fostering plaque growth even in normocholesterolemic individuals. Incorporating desLDL into future risk algorithms could therefore improve identification of high-risk patients who might benefit from intensified preventive measures.

Mechanistically, NEU1 and NEU3 remove terminal sialic acids from LDL,²⁹ constituting one of the earliest LDL modifications in atherogenesis.³⁶ Loss of negative charge produces smaller, denser, aggregation-prone particles,³⁴ which evade hepatic LDL receptors but bind macrophage scavenger and asialoglycoprotein receptors with high affinity,²⁹ culminating in foam-cell formation and plaque expansion.³⁷ In ApoE-deficient mice, genetic or pharmacological suppression of NEU1/NEU3 markedly attenuates atherosclerosis without altering plasma LDL-C, confirming desialylation as an LDL-C-independent driver.

Beyond lipid loading, desLDL intensifies inflammation. Sialic-acid “self” epitopes normally engage inhibitory sialic acid-binding immunoglobulin-type lectins (Siglecs) on immune cells;³⁸ desialylation disrupts this brake, unleashing macrophage uptake.³⁹ DesLDL-containing immune complexes activate toll-like receptors (TLR), inducing cytokine release,

macrophage apoptosis and lesion progression.⁴⁰ NEU1 modulates Siglec-TLR crosstalk, amplifying plaque inflammation.⁴¹ These convergent lipid-accumulation and pro-inflammatory mechanisms provide a coherent explanation for the strong links between desLDL, CAD presence, and plaque burden observed here.

A pertinent question is how desLDL compares with other established markers of atherogenic particle burden, such as apoB or LDL-particle number (LDL-P). It is important to recognise that these markers operate on different principles. apoB and LDL-P quantify the number of atherogenic particles, reflecting the fundamental aetiology of atherosclerosis as a disorder of lipoprotein accumulation. In contrast, this study's data suggest that desLDL quantifies the functional state, or quality, of these particles. An elevated desLDL level indicates not just the presence of LDL particles, but specifically the presence of a subpopulation that has undergone desialylation—a modification linked to increased atherogenicity and impaired clearance. Therefore, desLDL may provide complementary, rather than redundant, information to apoB. A patient could theoretically have a normal apoB level (normal particle number) but a high proportion of desLDL, indicating a high-risk phenotype driven by dysfunctional particles. Conversely, a patient could have a high apoB but a low desLDL level. Future prospective studies directly comparing these markers head-to-head are needed to define their respective roles. Such research could determine whether desLDL offers incremental prognostic value beyond the simple quantification of particle number provided by apoB.

Several important limitations merit discussion. First, this single-centre study enrolled only 162 consecutive patients undergoing coronary angiography at a tertiary institution, limiting statistical power and external validity; potential indication bias exists, as patients referred for angiography already had a high pre-test probability of CAD. Second, the cross-sectional design precludes inference of temporality or causality, leaving open the possibility of reverse causation and residual confounding. Third, the authors' assessment of disease severity relied on the Gensini score; while well-validated, future studies comparing its utility with that of SYNTAX score would be valuable. Fourth, the cohort lacked asymptomatic individuals and detailed baseline medication history, particularly lipid-lowering therapy, preventing adjustment for potential confounding effects and limiting the assessment of desLDL's role independent of therapeutic interventions. While this study demonstrates a strong association between desLDL and CAD, future research with detailed medication data is required to establish a strong association between desLDL and CAD, future research with detailed medication data is required to establish

causality and to determine the true predictive value of desLDL independent of treatment effects.

CONCLUSION

In conclusion, plasma desialylated LDL was significantly elevated in CAD and closely reflected disease burden (number of diseased vessels), outperforming traditional lipid indices. The authors' findings support desLDL as a novel, independent biomarker for detecting the presence of coronary atherosclerosis rather than for grading its comprehensive severity, although further longitudinal studies are needed to confirm its prognostic value.

Ethics statement

The study complied with the Declaration of Helsinki and was approved by the Affiliated Nanhua Hospital, University of South China Ethics Committee (approval number: 2024-ky-173). Written informed consent was obtained from all participants.

Declaration

The authors declare they have no affiliations with any commercial organisation that has a direct financial interest in the subject or materials discussed in the manuscript. This study was supported by the Medical and Health Joint Project of Hunan Provincial Natural Science Foundation (No. 2025JJ81098).

Data availability

The datasets generated and/or analysed during the present study are not publicly available but are available from the corresponding author Zhuo Zeng on reasonable request.

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A prospective study of the association of grip strength and sleep status with depressive symptoms

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ABSTRACT

Introduction: Depressive symptoms represent a major public health concern among middle-aged and older adults. Grip strength, a key indicator of physical frailty and biological ageing, and sleep disturbance, a recognised precursor of depression, have been independently linked to mental health outcomes. However, their combined effect on depressive symptoms remains unexplored. This study aimed to examine the association between grip strength levels, sleep status and their combined effects on the risk of depressive symptoms in middle-aged and older adults.

Methods: This prospective cohort study included 16,395 participants from the Survey of Health, Ageing and Retirement in Europe, followed from 2006 to 2017. Logistic regression and generalised estimating equations were used to examine associations.

Results: During follow-up, 5241 participants (31.97%) developed depressive symptoms, with higher incidence in females (58.98%). After adjusting for covariates, both low grip strength (odds ratio [OR] 1.12, 95% confidence interval [CI] 1.02–1.23) and sleep disturbance (OR 1.66, 95% CI 1.50–1.84) were independently associated with elevated risk of depressive symptoms. A synergistic effect was observed: individuals with both low grip strength and sleep disturbance had 1.87 times higher risk (95% CI 1.60–2.17) compared to those with high grip strength and no sleep disturbance. Sex- and age-stratified analyses revealed stronger associations in males and older adults (≥ 70 years).

Conclusion: Low grip strength and sleep disturbance are independently and synergistically associated with risk of depressive symptoms. Screening for both factors may help identify high-risk individuals for targeted preventive interventions.

Keywords: affective disorder, depressive symptoms, grip strength, middle-aged and older adults, sleep disturbance

CLINICAL IMPACT

What is New

- To the authors' knowledge, this is the first prospective study to demonstrate a synergistic effect between low grip strength and sleep disturbance on the risk of depressive symptoms in middle-aged and older adults.
- The combined presence of both factors was associated with a 1.87-fold increased risk, substantially exceeding the risk conferred by either factor alone.

Clinical Implications

- Routine screening integrating grip strength measurement and sleep assessment may help identify high-risk individuals for targeted depression prevention.
- Preventive interventions combining physical exercise with sleep hygiene strategies should be considered for individuals presenting with co-occurring low grip strength and sleep disturbance.

INTRODUCTION

Depression is a major global health concern that significantly affects health worldwide.^{1–3} According to the Global Burden of Disease Study 2021, approximately 332 million people globally suffer from depressive disorders, with the age-standardised prevalence increasing by 11.3% from 1990 to 2021 and projected to continue rising through 2040.^{4,5} Population ageing further compounds this issue, increasing the strain on global health systems.⁶ As one of the

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Accepted: 23 February 2026

Published: 9 March 2026

most common psychiatric disorders in middle-aged and older adults, depression severely impairs their quality of life and adds to the societal disease burden.⁷ Significant depressive symptoms in older adults are linked to numerous health issues, including functional and cognitive impairment, physical disability, and the onset or worsening of chronic diseases.^{8,9} These symptoms can also elevate the risk of self-harm and suicide.^{10,11} However, the subtle nature of depression often leads to delayed diagnosis and treatment.¹² Therefore, identifying easily measurable and modifiable risk factors is crucial for the early detection and management of depression.

Grip strength, a simple and non-invasive measurement, has emerged as a key indicator of physical frailty and overall health status in older adults.^{13,14} Low grip strength reflects declining muscle function¹⁵ and is recognised as a robust biomarker of biological ageing.¹⁶ Grip strength has also been correlated with numerous health outcomes, including nutritional status,¹⁷ cognitive function¹⁸ and mental health.¹⁹ Its simplicity and low cost make it an ideal indicator for large-scale population screening.^{20,21} Sleep disturbance, another common problem in middle-aged and older adults, is also recognised as both a key precursor and symptom of depression.^{3,22} The relationship between sleep disturbance and depression is bidirectional, with poor sleep quality potentially preceding and exacerbating depressive symptoms.²³

While previous studies have examined the associations of grip strength and sleep status with depression separately, most were cross-sectional in design, limiting causal inference and generalisability due to a lack of longitudinal data and smaller sample sizes. Furthermore, the combined effect of grip strength and sleep status on depression risk remains unexplored. Therefore, this prospective study aimed to investigate the individual and combined associations of grip strength and sleep status with the risk of depressive symptoms in a large cohort of 16,395 middle-aged and older adults.

METHODS

Data source and study population

Data were sourced from the Survey of Health, Ageing and Retirement in Europe (SHARE), a multidisciplinary and cross-national panel database. SHARE collects longitudinal microdata on the health, socioeconomic status and social networks of individuals aged 50 and over across Europe. This study utilised data from SHARE, with wave 2 (2006) serving as the baseline. Participants were monitored for subsequent incident depressive symptoms across 4 waves: wave 4 (2011), wave 5 (2013), wave 6 (2015) and wave 7 (2017).

The inclusion criteria were: (1) age ≥ 50 years and (2) participation in the baseline survey (wave 2). Participants were excluded if they had: (1) missing information on baseline grip strength or sleep status, (2) incomplete depressive symptoms scale data at baseline, (3) prevalent depressive symptoms at baseline or (4) no participation in any of the 4 follow-up surveys (waves 4–7). A final sample of 16,395 participants was included in the analysis.

Variable definition

Grip strength was measured using a Smedley hand dynamometer following a standardised protocol established by SHARE. Participants performed measurements in a standing position, with 2 trials conducted for each hand. The maximum value from all 4 measurements was used for analysis, consistent with established epidemiological guidelines that recommend using peak grip strength to capture optimal muscle performance.^{24,25} This approach avoids the complexity of dominant versus non-dominant hand differentiation while maintaining measurement reliability.^{26,27} Device calibration was performed according to SHARE study protocols. Sex-specific cut-off values were determined using receiver operating characteristic curve analysis to maximise Youden's index for depression outcomes in the study population, which has been successfully employed in multiple large-scale epidemiological studies.^{28–31} The optimal cut-offs were 42.50 kg for males and 26.50 kg for females, which were used to classify participants into low and high grip strength groups. Sex represents the most significant determinant of absolute grip strength values,³² while age-related decline in grip strength was appropriately accounted for by including age as a continuous covariate in all adjusted models.³³

Sleep status was assessed by self-report and classified as normal sleep or sleep disturbance based on participants' responses about their recent sleep status.

Depressive symptoms were assessed using the 12-item European Depression Scale (EURO-D), which evaluates symptoms experienced over the past month. Items are scored 0 or 1, yielding a total score from 0 to 12, with higher scores indicating greater depressive symptomatology. Consistent with previous studies,^{34,35} a score ≥ 4 was defined as depressive symptoms. For the analysis of depressive symptoms frequency, participants were categorised based on the number of follow-up waves in which they met the criteria for depressive symptoms (0, 1, 2 or more times). It should be noted that the EURO-D is a screening tool and does not constitute a clinical diagnosis of major depressive disorder. It identifies individuals with elevated depressive symptomatology warranting clinical attention.

Based on prior literature,²⁸ the following covariates were included: sex, age, region, education level, work status, family economic situation, smoking, alcohol consumption, physical activity, self-rated health and number of chronic diseases.

Statistical analysis

Baseline characteristics were compared using 2-sample t-tests or ANOVA for continuous variables and chi-square tests for categorical variables. Both logistic regression and generalised estimating equations (GEE) were used to analyse the associations.^{36,37} A 2-sided *P* value <0.05 was considered statistically significant. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, US).

RESULTS

Study population characteristics

The study included 16,395 participants with a mean age of 63.15 ± 8.70 years (range: 50–97), comprising 8297 (50.61%) males and 8098 (49.39%) females. During the follow-up period, 5241 participants (31.97%) experienced incident depressive symptoms. Of these, 3349 (20.43%) were identified with depressive

symptoms once, and 1892 (11.54%) were identified with depressive symptoms 2 or more times. A total of 3634 participants (22.17%) had never experienced depressive symptoms and served as the control group. Incident depressive symptoms were more prevalent in females (*n*=3091; 58.98%) than in males (*n*=2150; 41.02%).

Baseline characteristics of the study population, categorised by depressive symptom outcomes during follow-up, are presented in Table 1. Significant differences were observed across all assessed variables. Compared to the non-depressed group, participants who developed depressive symptoms were generally older, more likely to be retired or unemployed, reported financial difficulties, were physically inactive, had poor self-rated health and a higher number of chronic diseases. They also had a higher prevalence of low grip strength and sleep disturbance, but a lower prevalence of smoking and alcohol consumption.

Association between grip strength, sleep disturbance and risk of depressive symptoms

Table 2 presents the results from the logistic regression analysis for the association of baseline grip strength and sleep status with the risk of incident depressive

Table 1. Baseline characteristics of participants by depressive symptom status.

Covariates	No depressive symptoms (<i>n</i> =3634)	With depressive symptoms (<i>n</i> =5241)	<i>P</i> value	Single episode of depressive symptoms (<i>n</i> =3349)	Recurrent depressive symptoms (<i>n</i> =1892)	<i>P</i> value
Sex			<0.001			<0.001
Male	2010 (55.31)	2150 (41.02)		1459 (43.57)	691 (36.52)	
Female	1624 (44.69)	3091 (58.98)		1890 (56.43)	1201 (63.48)	
Age	61.74 ± 7.45	64.73 ± 9.09	<0.001	64.57 ± 9.24	65.00 ± 8.83	<0.001
Region			<0.001			<0.001
Central	1219 (33.54)	1125 (21.47)		733 (21.89)	392 (20.72)	
Eastern	0 (0.00)	584 (11.14)		414 (12.36)	170 (8.99)	
Western	792 (21.79)	1256 (23.96)		785 (23.44)	471 (24.89)	
Southern	609 (16.76)	1512 (28.85)		909 (27.14)	603 (31.87)	
Northern	1014 (27.90)	764 (14.58)		508 (15.17)	256 (13.53)	
Education years	12.07 ± 4.24	10.38 ± 4.30	<0.001	10.55 ± 4.31	10.08 ± 4.29	<0.001
Working condition			<0.001			<0.001
Work	1493 (41.08)	1245 (23.76)		856 (25.56)	389 (20.56)	
Retire	1702 (46.84)	2841 (54.21)		1798 (53.69)	1043 (55.13)	
Unemployed	425 (11.70)	1138 (21.71)		683 (20.39)	455 (24.05)	
Missing	14 (0.39)	17 (0.32)		12 (0.36)	5 (0.26)	

Table 1. Baseline characteristics of participants by depressive symptom status. (Cont'd)

Covariates	No depressive symptoms (n=3634)	With depressive symptoms (n=5241)	P value	Single episode of depressive symptoms (n=3349)	Recurrent depressive symptoms (n=1892)	P value
Economic situation			<0.001			<0.001
So difficult	103 (2.83)	398 (7.59)		240 (7.17)	158 (8.35)	
Difficult	467 (12.85)	1057 (20.17)		666 (19.89)	391 (20.67)	
Easy	926 (25.48)	1199 (22.88)		777 (23.20)	422 (22.30)	
So easy	1070 (29.44)	834 (15.91)		564 (16.84)	270 (14.27)	
Missing	1068 (29.39)	1753 (33.45)		1102 (32.91)	651 (34.41)	
Smoking status			<0.001			0.002
Smoking	2324 (63.95)	3151 (60.12)		2005 (59.87)	1146 (60.57)	
No smoking	575 (15.82)	955 (18.22)		623 (18.60)	332 (17.55)	
Missing	735 (20.23)	1135 (21.66)		721 (21.53)	414 (21.88)	
Drinking status			<0.001			<0.001
Hardly	828 (22.78)	2197 (41.92)		1361 (40.64)	836 (44.19)	
Occasionally	1385 (38.11)	1500 (28.62)		1001 (29.89)	499 (26.37)	
Frequently	1406 (38.69)	1527 (29.14)		976 (29.14)	551 (29.12)	
Missing	15 (0.41)	17 (0.32)		11 (0.33)	6 (0.32)	
Physical activity			<0.001			<0.001
Adequate	3181 (87.53)	4118 (78.57)		2677 (79.93)	1441 (76.16)	
Lacking	439 (12.08)	1105 (21.08)		659 (19.68)	446 (23.57)	
Missing	14 (0.39)	18 (0.34)		13 (0.39)	5 (0.26)	
Health status			<0.001			<0.001
Good	3131 (86.16)	3522 (67.20)		2361 (70.50)	1161 (61.36)	
Bad	503 (13.84)	1717 (32.76)		986 (29.44)	731 (38.64)	
Missing	0 (0.00)	2 (0.04)		2 (0.06)	0 (0.00)	
Chronic diseases			<0.001			<0.001
No	1437 (39.54)	1453 (27.72)		1004 (29.98)	449 (23.73)	
One	1182 (32.53)	1640 (31.29)		1050 (31.35)	590 (31.18)	
Two or more	1015 (27.93)	2140 (40.83)		1289 (38.49)	851 (44.98)	
Missing	0 (0.00)	8 (0.15)		6 (0.18)	2 (0.11)	
Grip strength			<0.001			<0.001
High	2532 (69.68)	2737 (52.22)		1796 (53.63)	941 (49.74)	
Low	1102 (30.32)	2504 (47.78)		1553 (46.37)	951 (50.26)	
Sleep status			<0.001			<0.001
Normal sleep	3045 (83.79)	3866 (73.76)		2540 (75.84)	1326 (70.08)	
Sleep disturbance	589 (16.21)	1375 (26.24)		809 (24.16)	566 (29.92)	

symptoms. After adjusting for all covariates, low baseline grip strength was associated with a higher risk of a single depressive episode (odds ratio [OR] 1.19, 95% confidence interval [CI] 1.02–1.39, $P=0.031$) and recurrent episodes (OR 1.17, 95% CI 0.97–1.41, $P=0.094$). The risk associated with low grip strength was similar for a single depressive episode and for recurrent episodes, although the latter did not reach statistical significance. In contrast, baseline sleep disturbance was significantly associated with an increased risk for both a single depressive episode (OR 1.44, 95% CI 1.21–1.71, $P<0.001$) and recurrent episodes (OR 2.01, 95% CI 1.65–2.45, $P<0.001$), with the risk being notably higher for recurrent depressive symptoms.

Combined effect of grip strength and sleep disturbance on risk of depressive symptoms

The combined effects of baseline grip strength and sleep status on risk of depressive symptoms are shown in Table 3. Both logistic regression and GEE were used for the analysis. After full covariate adjustment, in the absence of sleep disturbance, the association between low grip strength and risk of depressive symptoms was not significant for either single ($P=0.069$) or recurrent episodes ($P=0.132$). However, a significant interaction was observed, where the presence of sleep disturbance enhanced the association between low grip strength and depressive symptoms. The combination of low grip strength and sleep disturbance was associated with a significantly elevated risk of depressive symptoms, particularly for recurrent episodes (single episode: OR 1.75, 95% CI 1.33–2.31, $P<0.001$; recurrent episodes: OR 2.38, 95% CI 1.75–3.23, $P<0.001$).

The GEE analysis yielded consistent results. Individually, both low grip strength (OR 1.12, 95% CI 1.01–1.25, $P=0.035$) and sleep disturbance (OR 1.66, 95% CI 1.45–1.91, $P<0.001$) were associated with a higher risk of depressive symptoms. A synergistic effect was observed, with the combined presence of both factors resulting in the highest risk (OR 1.87, 95% CI 1.60–2.17, $P<0.001$).

Sex-stratified analysis

Sex- and age-stratified analyses are presented in Fig. 1. A significant interaction was found between grip strength and sex (P for interaction = 0.026), but not between sleep status and sex. After full adjustment, low grip strength was significantly associated with a higher risk of depressive symptoms in males (OR 1.19, 95% CI 1.02–1.38, $P<0.001$) but not in females (OR 1.04, 95% CI 0.89–1.20, $P<0.001$). Sleep disturbance was associated with a higher risk in both sexes, though the effect was more pronounced in males (OR 1.92, 95% CI 1.56–2.37) than in females

(OR 1.48, 95% CI 1.23–1.78). The combined effect of both factors was significant in both sexes but showed a greater magnitude in males (OR 2.14) compared to females (OR 1.66).

Age-stratified analysis

As shown in Fig. 1, the association between grip strength and depressive symptoms varied by age, whereas the association for sleep disturbance was consistent across age strata. After adjusting for covariates, low grip strength was significantly associated with risk of depressive symptoms only in individuals aged 70 years and older (OR 1.39, 95% CI 1.14–1.69, $P=0.001$). In contrast, sleep disturbance was associated with an elevated risk in all age groups, with the effect size increasing with age, from an OR of 1.50 in the 50–59 age group to 1.87 in the ≥ 70 age group. A synergistic effect for the combination of low grip strength and sleep disturbance was observed across all age groups, with the highest risk found in the 50–59 age group (OR 2.27, 95% CI 1.68–3.06, $P<0.001$).

Longitudinal analysis of grip strength, sleep status and risk of depressive symptoms

Fig. 2 illustrates the association of the combined factors with risk of depressive symptoms at each follow-up wave. Compared to the reference group (high grip strength, sleep disturbance), sleep disturbance alone was consistently associated with an elevated risk of depressive symptoms across all 4 follow-up waves (ORs ranging from 1.53 to 1.96). Low grip strength alone was significantly associated with risk of depressive symptoms only at wave 7 (OR 1.29, 95% CI 1.07–1.56, $P<0.001$); this association was not significant at other waves. The combined effect of both risk factors was significantly associated with a higher risk of depressive symptoms across all 4 follow-up surveys, with ORs ranging from 1.72 to 2.20.

DISCUSSION

In this large prospective cohort study of European middle-aged and older adults, findings reveal that low grip strength and sleep disturbance were independently associated with an elevated risk of depressive symptoms. More importantly, a synergistic effect was identified between the following 2 factors: individuals with both low grip strength and sleep disturbance had a substantially higher risk of depressive symptoms compared to those with either factor alone. Sex- and age-stratified analyses revealed that these associations were more pronounced in males and in older adults. Furthermore, longitudinal analysis demonstrated that the combined effect remained consistent across all follow-up waves.

Table 2. Association of grip strength level or sleep status with depressive symptoms.

	Model 1		Model 2		Model 3		Model 4	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Logistic regression analysis								
Single episode of depressive symptoms								
High GS	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Low GS	2.32 (2.07–2.60)	<0.001	1.29 (1.15–1.44)	<0.001	1.23 (1.07–1.42)	0.003	1.19 (1.02–1.39)	0.031
Normal sleep	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Sleep disturbance	1.65 (1.46–1.85)	<0.001	1.55 (1.36–1.76)	<0.001	1.52 (1.30–1.78)	<0.001	1.44 (1.21–1.71)	<0.001
Recurrent depressive symptoms								
High GS	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Low GS	1.99 (1.80–2.19)	<0.001	1.44 (1.26–1.64)	<0.001	1.32 (1.12–1.55)	0.001	1.17 (0.97–1.41)	0.094
Normal sleep	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Sleep disturbance	2.21 (1.93–2.52)	<0.001	2.09 (1.81–2.40)	<0.001	2.15 (1.81–2.56)	<0.001	2.01 (1.65–2.45)	<0.001
Generalised estimating equation analysis								
High GS	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Low GS	1.71 (1.60–1.81)	<0.001	1.25 (1.17–1.34)	<0.001	1.23 (1.13–1.34)	<0.001	1.12 (1.02–1.23)	<0.001
Normal sleep	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Sleep disturbance	1.84 (1.71–1.97)	<0.001	1.75 (1.63–1.89)	<0.001	1.74 (1.59–1.90)	<0.001	1.66 (1.50–1.84)	<0.001

CI: confidence interval; GS: grip strength; OR: odds ratio

Model 1: Unadjusted;

Model 2: Adjustment for age, sex and region;

Model 3: Adjustment model 2 and education years, work status and economic status;

Model 4: Adjusted for model 3 and smoking, alcohol consumption, physical activity, health status, number of chronic diseases, grip strength/sleep status.

Note: Values in bold indicate statistical significance (95% CI for OR does not include 1, and $P < 0.05$).

Table 3. Association of the combined effect of grip strength level and sleep status with depressive symptoms.

	Model 1			Model 2			Model 3			Model 4		
	OR (95% CI)	P		OR (95% CI)	P		OR (95% CI)	P		OR (95% CI)	P	
Logistic regression analysis												
Single episode of depressive symptoms												
High GS + normal sleep	1.00 (reference)			1.00 (reference)			1.00 (reference)			1.00 (reference)		
High GS + sleep disturbance	1.65 (1.41–1.92)	<0.001		1.59 (1.35–1.87)	<0.001		1.50 (1.23–1.83)	<0.001		1.41 (1.13–1.75)	0.002	
Low GS + normal sleep	1.99 (1.78–2.22)	<0.001		1.30 (1.15–1.48)	<0.001		1.22 (1.05–1.43)	0.011		1.18 (0.99–1.39)	0.069	
Low GS + sleep disturbance	3.17 (2.63–3.82)	<0.001		1.88 (1.53–2.30)	<0.001		1.88 (1.47–2.42)	<0.001		1.75 (1.33–2.31)	<0.001	
Recurrent depressive symptoms												
High GS + normal sleep	1.00 (reference)			1.00 (reference)			1.00 (reference)			1.00 (reference)		
High GS + sleep disturbance	2.30 (1.93–2.75)	<0.001		2.23 (1.86–2.68)	<0.001		2.15 (1.71–2.70)	<0.001		2.02 (1.57–2.60)	<0.001	
Low GS + normal sleep	2.38 (2.08–2.72)	<0.001		1.48 (1.28–1.72)	<0.001		1.30 (1.08–1.57)	0.005		1.18 (0.95–1.39)	0.132	
Low GS + sleep disturbance	4.84 (3.95–5.94)	<0.001		2.76 (2.21–3.44)	<0.001		2.79 (2.12–3.67)	<0.001		2.38 (1.75–3.23)	<0.001	
Generalised estimating equation analysis												
High GS + normal sleep	1.00 (reference)			1.00 (reference)			1.00 (reference)			1.00 (reference)		
High GS + sleep disturbance	1.90 (1.73–2.10)	<0.001		1.83 (1.66–2.02)	<0.001		1.71 (1.51–1.94)	<0.001		1.66 (1.45–1.91)	<0.001	
Low GS + normal sleep	1.73 (1.61–1.86)	<0.001		1.27 (1.18–1.37)	<0.001		1.21 (1.10–1.33)	<0.001		1.12 (1.01–1.25)	0.035	
Low GS + sleep disturbance	2.98 (2.69–3.31)	<0.001		2.10 (1.88–2.35)	<0.001		2.11 (1.85–2.42)	<0.001		1.87 (1.60–2.17)	<0.001	

CI: confidence interval; GS: grip strength; OR: odds ratio

Model 1: Unadjusted;

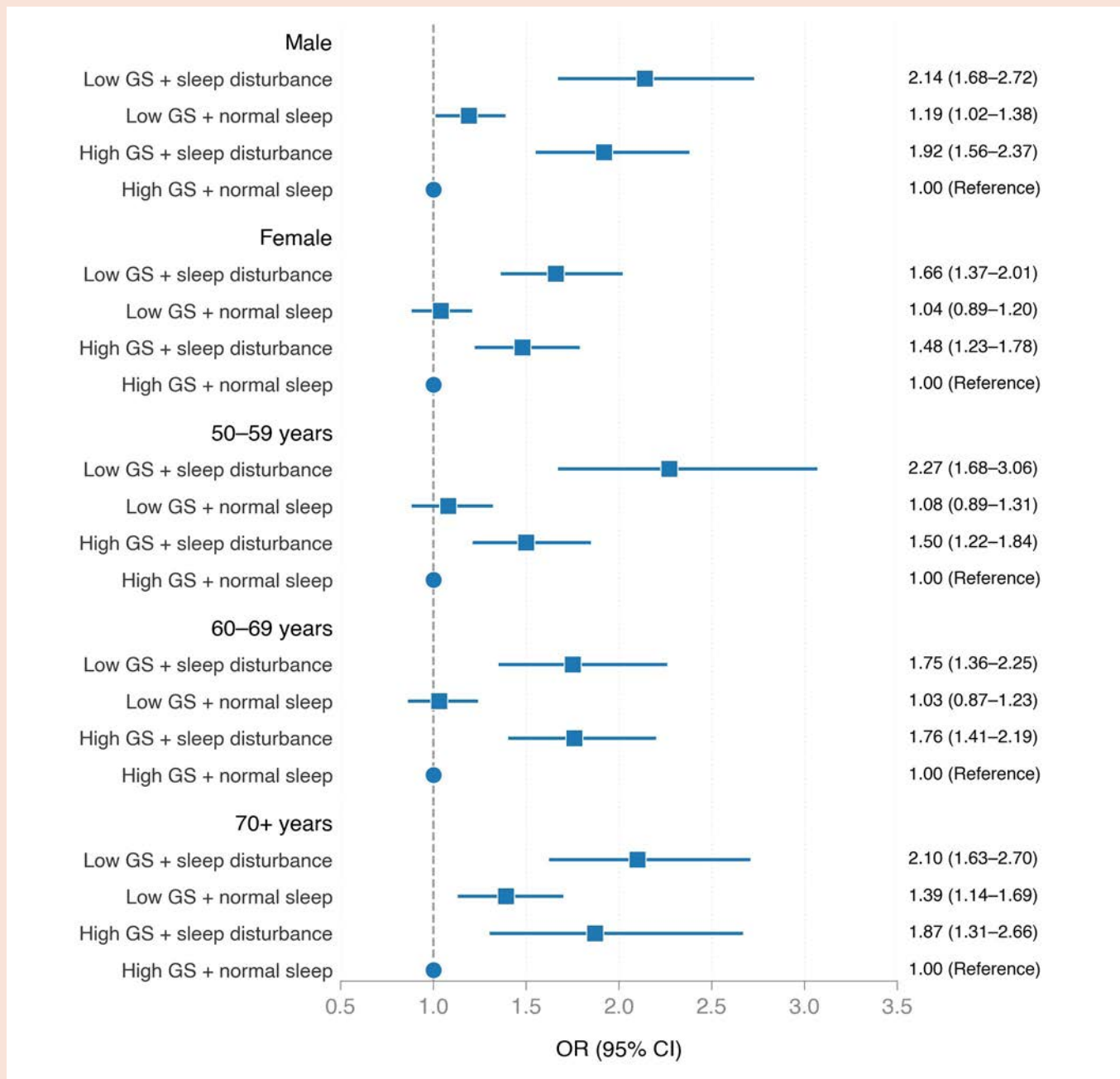
Model 2: Adjustment for age, sex and region;

Model 3: Adjustment model 2 and education years, work status and economic status;

Model 4: Adjusted for model 3 and smoking, alcohol consumption, physical activity, health status, number of chronic diseases.

Note: Values in bold indicate statistical significance (95% CI for OR does not include 1, and $P < 0.05$).

Fig. 1. Effects of grip strength and sleep disturbance on depressive symptoms, by sex and age group.



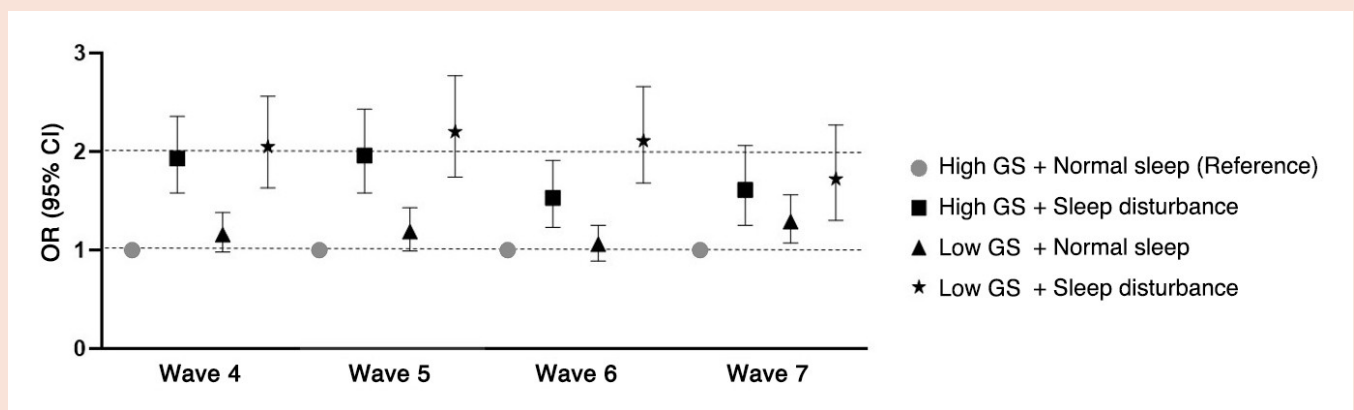
CI: confidence interval; GS: grip strength; OR: odds ratio

Sex differences in depressive symptoms

Consistent with most existing literature, a significantly higher incidence of depression was found in women than in men.³⁸ This sex disparity is often attributed to a combination of hormonal, psychological and social factors.^{39,40} Interestingly, while depressive symptoms were more prevalent in women, the associations between low grip strength, sleep disturbance and their combined effects with risk of depressive symptoms

were stronger in men. This finding contrasts with some studies reporting more pronounced associations in females and warrants careful interpretation.³¹ Several factors may explain this observation. First, grip strength may have differential validity as a health indicator across sexes. Some evidence suggests that grip strength is a less sensitive marker of frailty in men compared to women,⁴¹ potentially due to greater baseline muscle mass and different patterns of age-

Fig. 2 Association of the combined effect of grip strength and sleep status with depressive symptoms in successive follow-up surveys.



CI: confidence interval; GS: grip strength; OR: odds ratio

related muscle loss in men. Consequently, when men do exhibit low grip strength, it may represent a more advanced stage of physical decline, thereby showing a stronger association with adverse mental health outcomes. Second, occupational factors may differentially influence grip strength in men, particularly in cohorts where manual labour was more common among males.⁴² Third, men may be less likely to seek help for or report depressive symptoms, meaning that those identified with depressive symptoms in this study may represent more severe cases.⁴³ Finally, psychosocial factors such as the perceived loss of physical strength and functional independence may have a greater psychological impact on men, for whom physical capability is often closely tied to self-identity and social roles.

Grip strength and depressive symptoms

This study reinforces grip strength as a robust predictor of depression. This aligns with numerous studies, including a large cohort study that found a negative association after extensive covariate adjustment,²⁹ and an Irish study where high grip strength was linked to a 34.10% lower prevalence of depression.³¹

From a biological perspective, grip strength serves as an indicator of overall physical health and sarcopenia,⁴⁴ which may share several pathways with depression beyond chronic inflammation. These include hormonal dysregulation (particularly cortisol and sex hormones), mitochondrial dysfunction and oxidative stress—all of which are implicated in both muscle function decline and mood regulation.⁴⁵

Psychological and social mechanisms may underlie the association between reduced grip strength and depressive symptoms.^{46,47} Declining physical capability can undermine self-efficacy, body image and perceived independence, potentially eliciting grief or fear of

future dependency, while also limiting participation in meaningful activities and social roles, thereby increasing social isolation.⁴⁸ This relationship is likely bidirectional, as depression may further contribute to reduced physical activity, poor nutrition and subsequent muscle loss, creating a negative feedback cycle.⁴⁹

Sleep disturbance as a risk factor for depressive symptoms

Findings also confirm that sleep disturbance is not merely a secondary symptom but an independent risk factor and a potential prodromal symptom for depression.²³ This is supported by studies showing that poor sleep quality can precede depressive symptoms and may mediate the effects of stress on depression,⁵⁰ possibly through mechanisms like reduced hippocampal volume.⁵¹ The strong, dose-response relationship observed—where sleep disturbance conferred a higher risk for recurrent depression—emphasises the critical importance of addressing sleep disturbance in clinical practice.

Combined effect of grip strength and sleep disturbance

To the authors' knowledge, this is the first study to investigate the combined effect of grip strength and sleep status on the risk of depression. The key finding is the synergistic interaction between these 2 factors. The risk of depression for individuals with both low grip strength and sleep disturbance was substantially greater than the risk associated with either factor alone. This novel finding suggests that individuals with co-occurring poor physical strength and sleep disturbance represent a key high-risk population for targeted preventive interventions that could integrate physical exercise and sleep hygiene programmes.

Advantages and limitations

The strengths of this study include its large sample size; prospective design with a long follow-up; and the use of the standardised, high-quality SHARE database. The application of both logistic regression and GEE models enhances the robustness of the findings. However, several limitations must be considered. First, as an observational study, causality cannot be inferred, and residual confounding may exist. An illustrative example is the counterintuitive finding that participants without depressive symptoms had higher alcohol consumption rates. This may reflect several factors: reverse causation⁵² whereby depression leads to reduced alcohol intake, the sick quitter phenomenon⁵³ where individuals cease drinking due to health problems, or unmeasured confounding by social engagement patterns typical in European drinking culture.⁵⁴ Second, the assessment of both grip strength and sleep status could introduce measurement bias. The authors could not adjust for all potential confounders, such as body mass index,⁵⁵ nutritional status,⁵⁶ medication use⁵⁷ (including psychotropic medications and over-the-counter sleep aids) or genetic predispositions, which may influence both grip strength and depressive symptoms. Third, loss to follow-up could have introduced selection bias. Finally, the study population consisted exclusively of European adults, which limits generalisability to other populations.

CONCLUSION

This prospective study found a high prevalence of clinically significant depressive symptoms among European middle-aged and older adults, with notable sex differences. Low grip strength and sleep disturbance were independently associated with elevated risk of depressive symptoms, and their combined presence showed a potentially synergistic association. While these findings should be interpreted with caution given measurement limitations and the possibility of residual confounding, they suggest that screening for both reduced physical strength and sleep disturbance may help identify individuals at elevated risk for depressive symptoms. Future studies with more comprehensive assessments of exposures and outcomes are needed to confirm these associations and inform targeted preventive strategies.

Ethics statement

The SHARE study protocol was reviewed and approved by the Ethics Council of the Max Planck Society for the Advancement of Science and by the relevant ethics committees or institutional review boards in each participating country. This study is a secondary analysis of de-identified, publicly available data and was

deemed exempt from further institutional review board approval.

All SHARE participants provided written informed consent prior to data collection. For participants unable to provide consent, written informed consent was obtained from a legal representative in accordance with country-specific regulations. As this study used exclusively de-identified data, no additional consent was required for this secondary analysis.

Declaration

The authors declare that they have no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript. The authors also declare they have no conflicts of interest. The data that support the findings of this study are available from the SHARE Research Data Center. Data are available upon request to qualified researchers through the SHARE data access application process at <http://www.share-project.org/data-access.html>. Restrictions apply to the availability of these data, which were used under license for this study.

This work was supported by the Key Research and Development Program of Shandong Province (Competitive Innovation Platform Project: 2024CXPT091); the Taishan Scholar Project (tsqn202312392) and the youth talent training programme from Qingdao Medical College of Qingdao University (RZ2300002690).

Acknowledgements

The authors gratefully acknowledge the SHARE research team for providing access to the data and thank all SHARE participants for their valuable contributions. The SHARE data collection has been funded by the European Commission and various national funding sources.

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Red cell distribution width-to-albumin ratio and serum neurofilament light chain: A population-based study

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ABSTRACT

Introduction: Neurofilament light chain (NfL) is a blood biomarker of neuronal injury in inflammatory and neurodegenerative disorders. The red cell distribution width-to-albumin ratio (RAR) reflects systemic inflammation and nutritional status. This study investigated whether higher RAR is associated with higher serum NfL (sNfL) in a general adult population.

Methods: Data from 1750 adults who participated in the 2013–2014 National Health and Nutrition Examination Survey were analysed. RAR was calculated as red cell distribution width (%) divided by serum albumin (g/dL). sNfL was measured using an automated Atellica chemiluminescent immunoassay. Participants were grouped into RAR quartiles. Survey-weighted multivariable linear regression and restricted cubic spline (RCS) models assessed associations between RAR and log-transformed sNfL, adjusting for demographic, socioeconomic, lifestyle and clinical factors.

Results: Each unit increase in RAR was associated with higher sNfL in unadjusted analysis, and this association remained significant in partially and fully adjusted models. Compared with participants in the lowest quartile, those in the highest RAR quartile had higher sNfL, with a significant trend across quartiles. RCS analysis showed a non-linear but monotonic increase in log-transformed sNfL with higher RAR (P for non-linearity = 0.020). Associations varied by race/ethnicity, body mass index and diabetes status.

Conclusion: Higher RAR is associated with higher sNfL in US adults. This epidemiological association suggests that inflammation/nutritional status may relate to neuroaxonal injury. Longitudinal studies are needed to establish temporality and assess prognostic value before any clinical application.

Keywords: neurofilament light chain, neurology, neuronal injury, NHANES, RAR

CLINICAL IMPACT

What is New

- Analysis of 1750 US adults shows that higher red cell distribution width-to-albumin ratio (RAR) is associated with higher serum neurofilament light chain (sNfL).
- RAR–sNfL associations persist after adjustment for demographic and clinical factors, with variation by race/ethnicity, body mass index and diabetes status.

Clinical Implications

- RAR is calculated from routine full blood count and albumin tests and may help identify individuals with higher sNfL levels. These data support further prospective evaluation of RAR as a simple adjunctive marker of neuronal injury in diverse clinical populations.

INTRODUCTION

Neurofilament light chain (NfL), a member of the neurofilament protein family, is highly expressed in the axons of mature neurons, where it forms a fibrous network that constitutes a key component of the neuronal cytoskeleton.¹ When neurons die or are injured, NfL is released in large amounts into the extracellular space and subsequently reaches the cerebrospinal fluid and peripheral blood.² Owing to its high solubility and abundant expression, NfL has become a reliable subunit for neurofilament detection in body fluids.

In recent years, NfL has been established as an early biomarker for various neurological diseases, including

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Accepted: 4 March 2026

Published Online First: 20 March 2026

Alzheimer's disease,³ frontotemporal dementia,⁴ Parkinson's disease,⁵ amyotrophic lateral sclerosis,⁶ multiple sclerosis⁷ and traumatic brain injury.⁸ Under optimal conditions, NfL is also used to monitor treatment responses. Currently, Quanterix's single-molecule array technology (Simoa; Quanterix Corporation, Lexington, MA, US) is regarded as the gold standard for measuring serum NfL (sNfL) levels.⁹ Accurate and flexible monitoring of blood NfL levels plays a crucial role in disease staging, subtyping and differential diagnosis.

The red cell distribution width-to-albumin ratio (RAR) has emerged as a novel composite biomarker reflecting both inflammatory and nutritional status. Red cell distribution width (RDW), an indicator of heterogeneity in red blood cell volume, is a readily available laboratory parameter, with higher values indicating greater variability in red blood cell size.¹⁰ Previous studies have shown that RDW is closely associated with various chronic inflammatory conditions and oxidative stress.¹¹ Albumin, the most abundant plasma protein, exerts multiple physiological functions, including anti-inflammatory, anticoagulant and antioxidant activities, as well as the maintenance of osmotic pressure.¹² Abnormalities in RDW and albumin levels may partially reflect alterations in nutritional status, inflammation and oxidative stress.¹³ As an integrated index, RAR has shown prognostic relevance or strong associations with several inflammation- and ageing-related conditions; however, its relationship with biomarkers of neuronal injury remains unclear.

This study aimed to investigate the association between RAR and sNfL levels. Clinically, the measure-

ment of blood NfL often requires specialised platforms such as Simoa, which is expensive and not yet widely incorporated into routine laboratory testing. While NfL is a potent marker of injury, understanding how it relates to routine physiological indices remains limited. Exploring correlations between routinely available blood biomarkers and sNfL may therefore help elucidate the biological relationship between systemic physiological states and subclinical neuronal injury. Using data from the National Health and Nutrition Examination Survey (NHANES), this study conducted a cross-sectional analysis to evaluate the association between RAR and sNfL in US adults.

METHODS

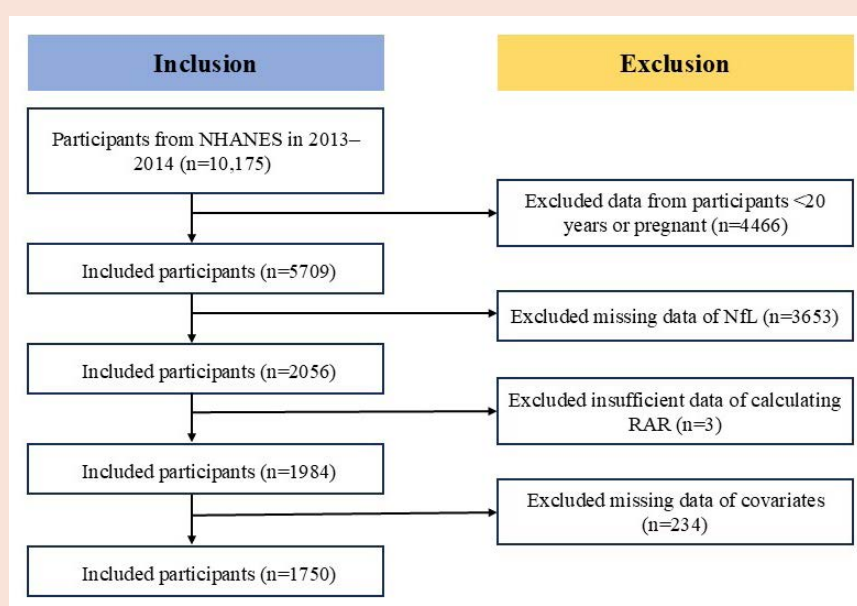
Study population

This study focused on data from the 2013–2014 NHANES cycle, as it contains complete information on sNfL. Fig. 1 shows that 10,175 individuals were initially included. Participants were excluded based on the following criteria: (1) age under 20 years ($n=4466$), (2) missing sNfL data ($n=3653$), (3) missing RAR data ($n=3$) and (4) incomplete or missing covariate information ($n=234$).

The final analyses included relevant covariates such as age, sex, body mass index (BMI), poverty income ratio (PIR), education level, race/ethnicity, smoking status, alcohol consumption and the presence of diabetes or hypertension.

Serum albumin concentrations were determined based on the formation of a coloured complex with

Fig. 1. Flowchart of participant selection.



NHANES: National Health and Nutrition Examination Survey; NfL: neurofilament light chain; RAR: red cell distribution width-to-albumin ratio

bromocresol purple, where the colour intensity is directly proportional to the albumin level. The bichromatic digital endpoint method (DcX 800) was then used to measure absorbance and convert it into albumin concentration (g/dL).

Participants were divided into quartiles based on RAR values: Q1 (<2.95), Q2 (2.95–3.16), Q3 (3.16–3.44) and Q4 (>3.44), with Q1 defined as the reference group.

Measurement of NfL

In the 2013–2014 NHANES cycle, sNfL levels were measured using a highly sensitive chemiluminescent immunoassay developed by Siemens Healthineers. Serum samples were first incubated with acridinium ester (AE)-labelled antibodies specifically targeting NfL. Subsequently, paramagnetic microparticles (PMPs) were added to form a stable NfL–AE-labelled antibody–PMP complex.

After washing to remove unbound antibodies, a trigger solution was applied to initiate the chemiluminescent reaction of the AE label. The resulting light emission, which is directly proportional to the concentration of sNfL in the sample, was detected and quantified. All measurements were conducted using the Atellica IM analyzer platform (Siemens Healthineers, Tarrytown, NY, US), ensuring high-throughput processing and analytical consistency.

Covariates

Several covariates were included to account for demographic, lifestyle and clinical characteristics. Age was grouped as 20–39, 40–59 and ≥ 60 years; sex as male or female; and race/ethnicity as Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black and other races. Educational attainment was categorised as less than high school, high school graduate or equivalent, and above high school. PIR was grouped as ≤ 1.3 , 1.3–3.5 and > 3.5 . Marital status was classified as married or living with a partner, widowed/divorced/separated, or never married. Smoking status was defined according to whether participants had smoked at least 100 cigarettes in their lifetime. Alcohol consumption was defined as intake of more than 100 alcoholic drinks per year. Diabetes was identified by a clinical diagnosis or by any of the following: glycated haemoglobin $\geq 6.5\%$, fasting plasma glucose ≥ 7.0 mmol/L, random plasma glucose ≥ 11.1 mmol/L, 2-hour oral glucose tolerance test glucose ≥ 11.1 mmol/L, or use of glucose-lowering medication or insulin. Hypertension was defined as a clinical diagnosis or use of antihypertensive medication, or measured systolic/diastolic blood pressure $\geq 140/90$ mmHg on 3 separate occasions by trained personnel. Laboratory covariates included total cholesterol (TC), uric acid (UA) and serum creatinine (Scr).

Statistical analyses

To better represent the US population, sample weights and stratified analyses were applied. As sNfL showed a non-normal distribution, its natural logarithm (ln) was used for analyses. Continuous variables are presented as mean $\pm$ standard deviation, and categorical variables as frequencies (percentages). The association between RAR and ln-transformed sNfL (ln-sNfL) was assessed using multivariable linear regression with 3 models: Model 1 (unadjusted), Model 2 (adjusted for age, sex, race/ethnicity, education, PIR and marital status) and Model 3 (further adjusted for smoking, alcohol use, diabetes, hyper-tension, TC, UA and Scr). A *P*-trend test evaluated potential trends. Restricted cubic spline (RCS) regression based on Model 2 examined possible non-linear associations. Subgroup and interaction analyses explored the relationship between RAR and ln-sNfL across categories of age, sex, race/ethnicity, education, PIR, marital status, BMI, smoking, alcohol use, diabetes and hypertension. All analyses were performed in R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria), with 2-sided *P*<0.05 considered statistically significant.

RESULTS

Characteristics of the study population

Table 1 presents the baseline characteristics of 1750 eligible participants stratified by quartiles of RAR. Among them, 850 were male and 900 were female. Participants were categorised into 3 age groups in ascending order, and the proportion of individuals aged over 40 years gradually increased from the lowest (Q1) to the highest (Q4) RAR quartile. Compared with those in the low RAR group, participants with higher RAR were more likely to be female, non-Hispanic black and have lower income levels (*P*<0.05). Moreover, elevated RAR was more frequently observed in participants with obesity (BMI ≥ 30 kg/m²); smoking; alcohol consumption; hypertension; diabetes and higher levels of TC, UA and Scr, indicating that these unfavourable lifestyle factors and metabolic abnormalities tended to cluster in the higher RAR quartiles.

Association between RAR and sNfL

Survey-weighted multivariable linear regression was conducted to examine the association between RAR and sNfL. Table 2 shows that higher RAR levels were significantly associated with increased ln-sNfL ($\beta=0.23$; 95% confidence interval [CI], 0.17–0.29; *P*<0.001). This association remained statistically significant after additional adjustment for demographic, socioeconomic, lifestyle and clinical factors in the fully adjusted model ($\beta=0.14$; 95% CI, 0.08–0.20;

Table 1. Baseline characteristics of study participants in NHANES 2013–2014.

Variables	Total	RAR				P
		Q1 (≤2.95)	Q2 (2.95–3.16)	Q3 (3.16–3.44)	Q4 (>3.44)	
n	1750	439	442	433	436	
Age, no. (%)						
20–39	609 (34.8)	231 (52.6)	158 (35.7)	122 (28.2)	98 (22.5)	<0.001
40–59	674 (38.5)	145 (33.0)	169 (38.2)	173 (40.0)	187 (42.9)	
≥60	467 (26.7)	63 (14.4)	115 (26.0)	138 (31.9)	151 (34.6)	
Sex, no. (%)						
Male	850 (48.6)	285 (64.9)	233 (52.7)	188 (43.4)	144 (33.0)	<0.001
Female	900 (51.4)	154 (35.1)	209 (47.3)	245 (56.6)	292 (67.0)	
Race, no. (%)						
Mexican American	239 (13.7)	59 (13.4)	75 (17.0)	50 (11.5)	55 (12.6)	<0.001
Other Hispanic	154 (8.8)	33 (7.5)	45 (10.2)	46 (10.6)	30 (6.9)	
Non-Hispanic white	811 (46.3)	245 (55.8)	210 (47.5)	195 (45.0)	161 (36.9)	
Non-Hispanic black	309 (17.7)	26 (5.9)	41 (9.3)	90 (20.8)	152 (34.9)	
Other races (including multiracial)	237 (13.5)	76 (17.3)	71 (16.1)	52 (12.0)	38 (8.7)	
Education, no. (%)						
Lower than high school	348 (19.9)	75 (17.1)	76 (17.2)	88 (20.3)	109 (25.0)	0.005
High school graduate/GED or equivalent	367 (21.0)	83 (18.9)	87 (19.7)	97 (22.4)	100 (22.9)	
Higher than high school	1035 (59.1)	281 (64.0)	279 (63.1)	248 (57.3)	227 (52.1)	
PIR, no. (%)						
≤1.3	597 (34.1)	127 (28.9)	138 (31.2)	154 (35.6)	178 (40.8)	<0.001
1.3–3.5	589 (33.7)	114 (26.0)	164 (37.1)	152 (35.1)	159 (36.5)	
>3.5	564 (32.2)	198 (45.1)	140 (31.7)	127 (29.3)	99 (22.7)	
Marital status, no. (%)						
Married/living with partner	1077 (61.5)	275 (62.6)	295 (66.7)	255 (58.9)	252 (57.8)	<0.001
Widowed/divorced/separated	333 (19.0)	56 (12.8)	68 (15.4)	100 (23.1)	109 (25.0)	
Never married	340 (19.4)	108 (24.6)	79 (17.9)	78 (18.0)	75 (17.2)	
BMI, no. (%)						
<25 kg/m ²	522 (29.8)	185 (42.1)	138 (31.2)	127 (29.3)	72 (16.5)	<0.001
25–30 kg/m ²	566 (32.3)	160 (36.4)	166 (37.6)	137 (31.6)	103 (23.6)	
≥30 kg/m ²	662 (37.8)	94 (21.4)	138 (31.2)	169 (39.0)	261 (59.9)	
Smoking status, no. (%)						
Smokers	778 (44.5)	173 (39.4)	199 (45.0)	191 (44.1)	215 (49.3)	0.032
Non-smokers	972 (55.5)	266 (60.6)	243 (55.0)	242 (55.9)	221 (50.7)	

Table 1. Baseline characteristics of study participants in NHANES 2013–2014. (Cont'd)

Variables	Total		RAR			P
Drinking status, no. (%)						
Drinkers	1312 (75.0)	356 (81.1)	346 (78.3)	316 (73.0)	294 (67.4)	<0.001
Non-drinkers	438 (25.0)	83 (18.9)	96 (21.7)	117 (27.0)	142 (32.6)	
Diabetes, no. (%)						
Yes	194 (11.1)	21 (4.8)	41 (9.3)	48 (11.1)	84 (19.3)	<0.001
No	1556 (88.9)	418 (95.2)	401 (90.7)	385 (88.9)	352 (80.7)	
Hypertension, no. (%)						
Yes	621 (35.5)	101 (23.0)	132 (29.9)	155 (35.8)	233 (53.4)	<0.001
No	1129 (64.5)	338 (77.0)	310 (70.1)	278 (64.2)	203 (46.6)	
TC (mmol/L), mean (SD)	189.02 (39.56)	189.67 (39.81)	193.10 (40.13)	189.52 (38.27)	183.75 (39.56)	0.005
UA (mg/dL), mean (SD)	5.47 (1.39)	5.65 (1.37)	5.39 (1.40)	5.38 (1.37)	5.46 (1.42)	0.011
Scr (mg/dL), mean (SD)	0.90 (0.63)	0.88 (0.19)	0.85 (0.19)	0.86 (0.21)	0.99 (1.21)	0.002
NfL (pg/ml), mean (SD)	2.56 (0.66)	2.39 (0.57)	2.53 (0.65)	2.62 (0.63)	2.70 (0.75)	<0.001

BMI: body mass index; GED: general education development; NfL: neurofilament light chain; PIR: poverty income ratio; RAR: red cell distribution width-to-albumin ratio; Scr: serum creatinine; SD: standard deviation; TC: total cholesterol; UA: uric acid

The *P* value was calculated by weighted linear regression model. Percentage for categorical variables: the *P* value was calculated by a weighted chi-square test.

$P < 0.001$). In sensitivity analyses, RAR was categorised into quartiles and treated as a categorical variable; the association persisted. Compared with individuals in the lowest quartile (Q1), those in the highest quartile (Q4) showed an adjusted β of 0.16 (95% CI, 0.08–0.25; $P < 0.001$). Similar findings were observed in Models 1 and 2. Thus, higher RAR values were significantly associated with increased sNfL levels (P for trend < 0.001). Additionally, RCS regression was used to assess the potential non-linear relationship between RAR and ln-sNfL. Fig. 2 illustrates that the test for non-linearity was statistically significant ($P = 0.02$).

Stratified analyses

To further investigate how the association between RAR and sNfL varied across subgroups, stratified analyses were performed according to age, sex, race, education level, PIR, marital status and BMI (Table 3). The results indicated that the association between RAR and sNfL was significantly different across categories of race (P for interaction = 0.016), BMI (P for interaction < 0.001) and diabetes status (P for interaction = 0.008), whereas no significant interactions were observed with other covariates. Across subgroups defined by age, sex, smoking status, alcohol consumption, diabetes and hypertension, RAR remained significantly positively associated with sNfL levels.

DISCUSSION

To the authors' knowledge, this study is the first cross-sectional analysis based on data from the nationally representative NHANES 2013–2014 cohort. Data from 1750 participants were analysed to investigate the association between RAR and sNfL. Results from multivariable linear regression (Model 3), which adjusted for multiple covariates, demonstrated a significant positive relationship between RAR and sNfL (both raw and log-transformed values, ln-sNfL), showing that higher RAR levels are associated with higher levels of a blood biomarker of neuronal injury. The findings, supported by stratified linear models and RCS analyses, suggested a monotonic increasing association without an obvious threshold. Interaction analyses revealed that race, BMI and diabetes status were significant effect modifiers of the association between RAR and sNfL. Overall, these results provide epidemiological evidence linking a composite marker of systemic inflammation and nutritional status with a blood biomarker of neuroaxonal injury.

sNfL is recognised as a sensitive biomarker of axonal damage and has shown considerable clinical and research utility in various neurological disorders. Recent studies have demonstrated that sNfL levels are elevated in patients with multiple sclerosis,¹⁴ depression,¹⁵ cognitive impairment¹⁶ and cerebrovascular diseases.¹⁷ Accordingly, sNfL is widely utilised

Table 2. Association of RAR with serum neurofilament light chain levels.

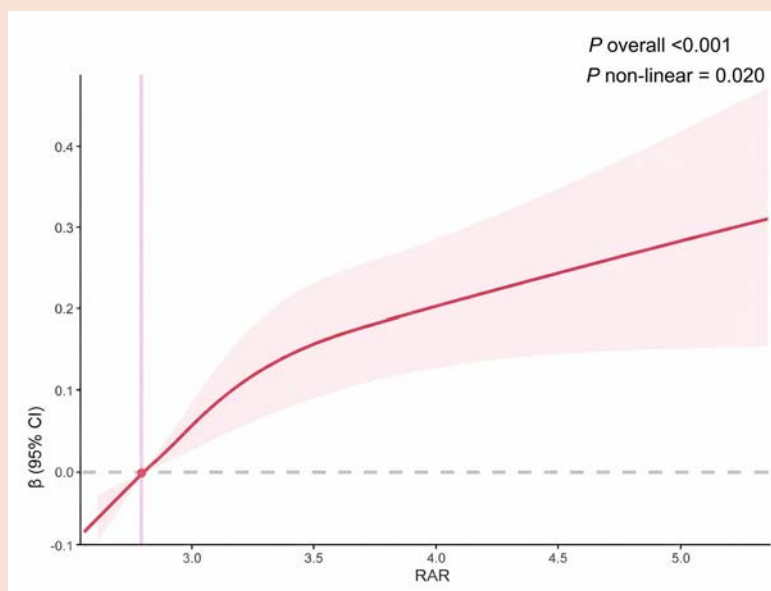
	Model 1		Model 2		Model 3	
	β (95% CI)	<i>P</i>	β (95% CI)	<i>P</i>	β (95% CI)	<i>P</i>
Continuous	0.23 (0.17–0.29)	<0.001	0.17 (0.11–0.23)	<0.001	0.14 (0.08–0.20)	<0.001
Q1	Reference		Reference		Reference	
Q2	0.14 (0.05–0.23)	0.001	0.07 (–0.01–0.14)	0.087	0.07 (0.00–0.15)	0.05
Q3	0.23 (0.15–0.32)	<0.001	0.12 (0.04–0.20)	0.003	0.13 (0.05–0.20)	0.001
Q4	0.32 (0.23–0.40)	<0.001	0.2 (0.12–0.28)	<0.001	0.16 (0.08–0.25)	<0.001
<i>P</i> for trend	<0.001		<0.001		<0.001	

CI: confidence interval; RAR: red cell distribution width-to-albumin ratio

Model 2 was adjusted for age, sex, race, education, poverty income ratio and marital status.

Model 3 was adjusted for age, sex, race, education, poverty income ratio, marital status, smoking status, drinking status, diabetes, hypertension, total cholesterol, uric acid and serum creatinine.

Fig. 2. RCS curve of the association between RAR and NfL.



CI: confidence interval; NfL: neurofilament light chain; RAR: red cell distribution width-to-albumin ratio; RCS: restricted cubic spline

in research and clinical settings to reflect the burden of neuro-axonal damage, as well as for prognostic evaluation and monitoring disease progression in these conditions.¹⁸ However, sNfL is not disease-specific and may reflect neuroaxonal injury arising from multiple neurological and systemic processes. Thus, these findings should be interpreted as an epidemiological association rather than evidence supporting a specific clinical diagnostic or screening application.

The ratio of RAR has recently been proposed as a comprehensive indicator reflecting inflammation and

nutritional metabolism.¹⁹ Calculated from RDW and serum albumin, RAR combines these 2 parameters to more comprehensively reflect inflammatory status, oxidative stress and nutritional imbalance, and may provide more prognostic information than RDW or albumin alone.¹³ Elevated RAR is associated with adverse systemic inflammatory and wasting diseases, such as sepsis, cancer and heart failure.^{20–23} Moreover, recent research has revealed a positive correlation between high RAR levels and the prevalence of kidney stones in adults.²⁴ Increased RAR has also been linked to higher mortality risk in the general population,¹³ and

Table 3. Stratification analysis of the relationship between RAR and NfL based on Model 3.

Characteristics	β (95% CI)	P value	P for interaction
Age, no. (%)			0.921
20–39	0.16 (0.04–0.27)	0.008	
40–59	0.14 (0.06–0.22)	<0.001	
≥60	0.12 (0.02–0.23)	0.025	
Sex, no. (%)			0.146
Male	0.20 (0.10–0.30)	<0.001	
Female	0.11 (0.04–0.18)	0.002	
Race, no. (%)			0.016 ^a
Mexican American	0.10 (–0.05–0.25)	0.175	
Other Hispanic	0.03 (–0.17–0.23)	0.762	
Non-Hispanic white	0.20 (0.11–0.29)	<0.001	
Non-Hispanic black	0.04 (–0.07–0.14)	0.495	
Other races (including multiracial)	0.34 (0.16–0.53)	<0.001	
Education, no. (%)			0.478
Lower than high school	0.10 (–0.01–0.21)	0.068	
High school graduate/GED or equivalent	0.12 (0.00–0.24)	0.046	
Higher than high school	0.17 (0.09–0.25)	<0.001	
PIR, no. (%)			0.096
≤1.3	0.20 (0.12–0.29)	<0.001	
1.3–3.5	0.10 (–0.00–0.20)	0.056	
>3.5	0.07 (–0.04–0.18)	0.231	
Marital status, no. (%)			0.26
Married/living with partner	0.11 (0.03–0.19)	0.006	
Widowed/divorced/separated	0.21 (0.11–0.32)	<0.001	
Never married	0.11 (–0.02–0.25)	0.095	
BMI, no. (%)			<0.001 ^a
<25 kg/m ²	0.16 (0.05–0.28)	0.005	
25–30 kg/m ²	0.30 (0.19–0.41)	<0.001	
≥30 kg/m ²	0.04 (–0.04–0.13)	0.298	
Smoking status, no. (%)			0.371
Smokers	0.16 (0.08–0.25)	<0.001	
Non-smokers	0.12 (0.03–0.20)	0.005	
Drinking status, no. (%)			0.197
Drinkers	0.12 (0.05–0.19)	<0.001	
Non-drinkers	0.20 (0.09–0.31)	<0.001	

Table 3. Stratification analysis of the relationship between RAR and NfL based on Model 3. (Cont'd)

Characteristics	β (95% CI)	P value	P for interaction
Diabetes, no. (%)			0.008 ^a
Yes	0.34 (0.18–0.49)	<0.001	
No	0.11 (0.05–0.18)	<0.001	
Hypertension, no. (%)			0.389
Yes	0.12 (0.04–0.20)	0.005	
No	0.17 (0.08–0.25)	<0.001	

BMI: body mass index; CI: confidence interval; GED: general education development; NfL: neurofilament light chain; PIR: poverty income ratio; RAR: red cell distribution width-to-albumin ratio

^a statistically significant

rising RAR levels may serve as a potential predictive marker for depression.²⁵

While these findings support the positive association between RAR and sNfL, the underlying mechanisms remain speculative. RDW, the main component of RAR, reflects variability in red blood cell volume (anisocytosis) and is often associated with nutritional deficiencies, chronic inflammation and other pathological conditions.²⁶ Prior studies suggest that changes in RDW and related haematological parameters may be linked to neural vulnerability, although the biological pathways connecting RDW, albumin and neuroaxonal injury remain unclear. Albumin, a major extracellular protein, contributes to plasma oncotic pressure, transport functions, microcirculatory regulation and antioxidant/anti-inflammatory capacity,^{12,27} which may be relevant to systemic and vascular homeostasis. Epidemiological studies have reported associations between lower albumin levels and higher risk of neural injury; however, direct experimental evidence supporting a causal role of albumin deficiency in neurodegeneration remains limited. This study does not directly address these mechanisms. Further research is needed to clarify how RAR may relate to neuroaxonal damage, particularly in the context of inflammatory and nutritional imbalances.

Overall, our findings highlight the potential clinical utility of RAR as a readily accessible indicator for evaluating the risk of neuronal injury. Determining its specific prognostic and risk-stratification value will be an important direction for future clinical research.

CONCLUSION

This cross-sectional study, based on data from NHANES, demonstrated a significant positive association between RAR and sNfL in US adults. These findings suggest a potential link between systemic inflammation, nutritional status and blood biomarkers

of neuronal injury. However, given the nature of the study, further large-scale, multicentre prospective studies are necessary to validate these associations, establish temporal relationships and explore the underlying biological mechanisms linking RAR, systemic inflammation, nutritional status and neural injury.

Ethics statement

The data used in this study were obtained from the publicly available NHANES database (<https://www.cdc.gov/nchs/nhanes/index.htm>). All NHANES protocols were approved by the National Center for Health Statistics Ethics Review Board, and written informed consent was obtained from all participants.

Declaration

This study was supported by the National Natural Science Foundation of China (82201578 and 82401691) and the China Postdoctoral Foundation (2025M782403). The authors declare that there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript. The authors also declare that they have no conflicts of interest. ChatGPT (OpenAI, San Francisco, CA, US) was used only for spelling and minor language corrections. All scientific content, analyses, and conclusions were generated and confirmed by the authors.

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The APLC expert consensus recommendations on the management of chronic lymphocytic leukaemia in Asia

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ABSTRACT

Introduction: Targeted therapies have significantly transformed the management of chronic lymphocytic leukaemia (CLL), yet most recommendations continue to reflect Western practice patterns. Variations in disease biology, healthcare resources and treatment accessibility across the Asia-Pacific (APAC) necessitate region-specific guidance. The Asia-Pacific Leukaemia Consortium (APLC) therefore developed updated consensus statements to support standardised, context-appropriate care for patients with CLL.

Methods: A modified Delphi process was conducted with 17 haematology experts from multiple APAC regions. A systematic literature search (i.e. MEDLINE via PubMed) covering publications from 2016 onwards informed the development of 29 statements across 3 domains: diagnosis, treatment and long-term management. Panel members rated each statement using a 5-point Likert scale. Consensus was defined a priori as a mean score ≥ 3.5 . Statistical measures and iterative expert discussions guided refinement of the final recommendations.

Results: Twenty-nine statements reached consensus with key recommendations addressing: (1) appropriate use of genetic and prognostic testing, particularly TP53 and immunoglobulin heavy chain (IGHV) status; (2) first-line and relapsed/refractory treatment selection, including the role of Bruton's tyrosine kinase (BTK) inhibitors, B-cell lymphoma 2 inhibitors, combination strategies, cellular therapies and emerging modalities; and (3) long-term monitoring, toxicity surveillance and management of complications such as autoimmune cytopenias. Region-specific considerations—such as variable access to novel agents and diagnostic platforms—were incorporated throughout.

Conclusion: These updated APLC consensus recommendations provide clinicians across the APAC with an evidence-based, pragmatic framework for managing CLL. They aim to support treatment consistency, optimise sequencing strategies and address gaps in diagnostics, access and long-term survivorship care across diverse healthcare settings.

Keywords: chronic lymphocytic leukaemia, CLL, leukaemia

CLINICAL IMPACT

What is New

- Provides the first updated Asia Pacific (APAC)-focused consensus on CLL management since 2023.
- Integrates recent data on Bruton's tyrosine kinase inhibitors and B-cell lymphoma 2 inhibitors therapy, sequencing strategies and emerging options such as chimeric antigen receptor T-cell and next-generation agents.

Clinical Implications

- Offers actionable recommendations for diagnosis, treatment selection and long-term monitoring tailored to APAC healthcare systems.
- Supports more consistent, evidence-aligned practice despite variations in access, resources and patient profiles across the region.

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Acceptance: 3 March 2026

Published Online First: 20 March 2026

INTRODUCTION

Relapsed/refractory (R/R) chronic lymphocytic leukaemia (CLL) is a mature B-cell neoplasm characterised by the accumulation of monoclonal B lymphocytes in the bone marrow, peripheral blood and lymphoid organs. It predominantly affects older adults, with a median age at diagnosis above 70 years, and exhibits a highly variable clinical course influenced by genetic and microenvironmental factors.^{1,2} In 2019, there were an estimated 100,000 new CLL cases and 44,000 related deaths worldwide.³ CLL remains the most common leukaemia in Western countries, accounting for 25–35% of all leukaemia cases in the US, with an annual incidence of approximately 4.9–4.92 per 100,000 persons.^{1,4} Although incidence is 5- to 10-fold lower in Asian populations compared to Western cohorts,^{3,5} the absolute burden is rising with ageing populations and expanding diagnostic capacity. Moreover, the biological and clinical features of CLL in Asian populations may differ from those reported in Western studies, such as immunoglobulin heavy chain (IGHV) mutation status and high MYD88 mutation rate, underscoring the need for region-specific recommendations.^{6,7} The reasons for these epidemiological differences are not fully understood, though genetic factors have been proposed.^{8,9,10}

To date, most evidence guiding CLL management is derived from Western populations, while data from Asia remain limited. This dearth in the literature creates challenges in adapting international guidelines to diverse healthcare infrastructures in Asia, with variable access to diagnostics and differences in treatment availability. Recognising these gaps, the Asia-Pacific Leukaemia Consortium (APLC) published consensus recommendations in 2023 tailored to the region's needs.¹¹ Since then, the therapeutic landscape has evolved rapidly, with novel targeted agents, combination strategies and emerging sequencing approaches reshaping treatment paradigms.

This updated consensus builds on the previous framework, focusing on 3 domains: (1) diagnosis, (2) treatment and (3) long-term management. The recommendations presented in this paper reflect expert consensus intended to support clinicians in adapting current evidence to the heterogeneous healthcare environments across the Asia-Pacific region. By integrating recent evidence with collective regional experience, this document aims to provide practical, evidence-informed guidance that supports consistent and high-quality care while recognising variations in healthcare resources and patient circumstances. As with all consensus-based guidance, these recommendations should be applied alongside individual patient factors and clinical judgement.

METHODS

The APLC assembled a core panel comprising 5 haematology-oncology experts with an appointed chair. Subsequently, this consensus statement was developed using a modified Delphi method with a panel of 17 haematology-oncology experts from 9 Asia-Pacific regions: Australia, Hong Kong, Japan, Malaysia, People's Republic of China, Singapore, South Korea, Taiwan and Thailand.

To identify the scope of this consensus statement, a comprehensive literature search was conducted using the MEDLINE database (via PubMed) to identify English-language research articles published from January 2016 until December 2024. Keywords included "chronic lymphocytic leukaemia," "diagnosis," "risk stratification," "treatment," "prognosis," "Bcr-tyrosine kinase inhibitor (BTKi)," "B-cell lymphoma-2 inhibitor (BCL-2i)," "TP53" and "immunoglobulin heavy chain variable region (IGHV) mutation," among others. Relevant publications were reviewed to inform the survey design.

Based on the literature review findings and the clinical experience of the core panel, a qualitative survey was developed comprising 28 statements organised into 3 sections: (1) diagnosis, (2) treatment and (3) management. Panel members rated their agreement with each statement using a 5-point Likert scale (1 = strongly disagree, 2 = disagree, 3 = neutral, 4 = agree, 5 = strongly agree).

The statements were classified based on mean scores as follows:

- Consensus: Mean score ≥ 3.5
- Near consensus: Mean score of 3.25–3.49
- No consensus: Mean score ≤ 3.25

The consensus development process is illustrated in Fig. 1. Survey responses were recorded and analysed to determine consensus levels for each statement. Following survey completion, a virtual meeting was held on 16 July 2025 to present results and facilitate discussion among the entire panel. The meeting allowed the entire panel to review the final statements and provide additional feedback. The meeting led to the division of 1 consensus statement into 2 distinct statements (Statements 18 and 19). Statements 18 and 19 were initially combined and reached consensus during the survey; however, the panel agreed that separating them would provide greater clarity. In addition, Statement 4, which had reached near consensus during the survey, was reworded during the meeting and subsequently achieved consensus. Following thorough discussion and evidence review, 29 consensus recommendations were finalised.

Table 1 summarises all recommendations with their corresponding statistical measures. The consensus recommendations and the supporting literature are discussed in the subsequent sections.

Statistical analysis

For each statement, the mean, median and interquartile range (IQR) were calculated. The IQR measures statistical dispersion by capturing the difference between the upper and lower quartiles, representing the middle 50% of responses. An IQR ≤ 1 indicates that more than half of all responses fall within 1 point on the scale, demonstrating good consensus on a 5-point Likert scale, a standard and rigorous measure commonly used in Delphi studies.¹³

RESULTS AND DISCUSSIONS

Diagnosis

Timing of treatment initiation

For the majority of newly diagnosed CLL patients (over 80%), the disease is asymptomatic and early-stage (Rai 0 or Binet A). Only 30–50% of such cases will progress to advanced, symptomatic disease requiring therapy, while the rest may never need treatment in their lifetimes.¹⁴ Major guidelines, including the 2018 International Workshop on CLL (iwCLL) consensus, recommend that patients with early-stage, asymptomatic CLL should be monitored without treatment outside of clinical trials, since no overall survival (OS) benefit has been demonstrated for treating these patients prior to progression.^{12,15,16}

Notably, multiple randomised trials have demonstrated no OS benefit from early treatment in this population.^{17,18} The CLL7 trial, which evaluated front-

line FCR (fludarabine, cyclophosphamide, rituximab) in asymptomatic patients with high-risk Binet A disease, showed improved event-free survival but no OS advantage.¹⁹ Additionally, the phase III CLL12 trial confirmed that early intervention with ibrutinib delayed disease progression in biologically high-risk patients but did not confer a survival benefit and carried known toxicities.²⁰ High-risk early-stage patients, such as those with unmutated *IGHV*, *TP53* abnormality or elevated beta-2 microglobulin, may be considered for clinical trials of early intervention, but outside such settings, surveillance remains the standard of care.¹⁹

Baseline genetic testing prior to therapy

TP53 status, defined by the presence of either a 17p deletion (detected by interphase fluorescence in situ hybridisation [FISH]) or a somatic *TP53* mutation (identified via sequencing), is the most clinically actionable biomarker in CLL.^{12,21} These abnormalities are typically mutually exclusive but occasionally co-occur.²² Testing for both is essential, as a subset of patients will harbour *TP53* mutations without a detectable 17p deletion. *TP53*-disrupted CLL is associated with poor response to chemoimmunotherapy and reduced survival, even with novel agents.^{23,24,25} Consequently, targeted therapies are now the preferred frontline approach in these patients, and identification of *TP53* status is a prerequisite for appropriate risk-adapted management.¹² However, the expert panel recognised that the comprehensive assessment of *TP53* may not be consistently available across the APAC region due to factors such as accessibility and affordability.

IGHV mutation status similarly stratifies patients by disease biology. *IGHV*-unmutated CLL carries a worse prognosis and responds poorly to chemoimmunotherapy, whereas *IGHV*-mutated CLL, especially

Fig. 1. Flowchart of participant selection.

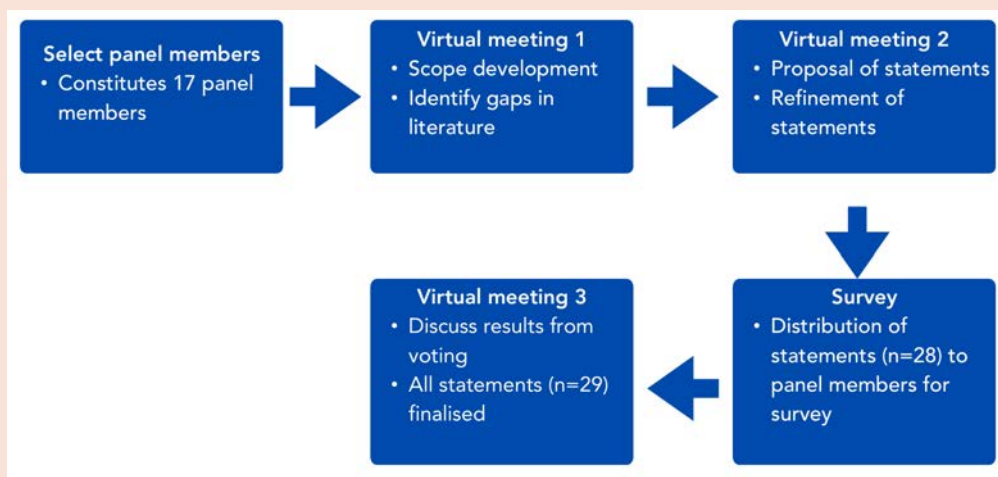


Table 1. Summary of key consensus statements for APLC expert consensus on the management of chronic lymphocytic leukaemia in Asia.

	Statements	Mean	Median	IQR
Diagnosis				
1	Patients with asymptomatic early-stage CLL should not be treated until disease progression occurs, and active surveillance remains the standard for management.	4.94	5	0
2	Current randomised phase III trials evaluating early treatment (including CIT and ibrutinib) in asymptomatic CLL patients show increased toxicity without improved overall survival, thus it is recommended to adhere to iwCLL guidelines 2018 for the initiation of therapy for CLL.	4.65	5	0
3	Genetic testing recommendations for first-line therapy: • Testing for <i>TP53</i> mutations and FISH for 17p deletion is recommended for all patients before initiating first-line therapy.¹² • Assessment of <i>IGHV</i> mutation status is recommended as it informs treatment selection. • Conventional karyotyping may be considered in select cases for additional cytogenetic information.	4.41	4	1
4	Assessment for 17p deletion by FISH is recommended for determining therapeutic approaches. However, if resources and accessibility permit, it is highly recommended that both FISH for 17p deletion and testing for <i>TP53</i> mutation be done simultaneously.	3.47	4	1.5
Treatment				
5	Clinicians should communicate with patients about the chronic nature of CLL, potential treatment relapses and expectations for long-term management.	5	5	0
6	It is recommended to avoid, if possible, BTKis with drugs that have antiplatelet effects, such as non-steroidal anti-inflammatory drugs.	3.76	4	1
7	In patients requiring planned surgery, it is recommended to discontinue BTKis from 3 to 7 days both before and after surgery, with the duration dependent on the type of surgery. Nevertheless, the given risk and benefit of holding BTKi treatment for less urgent procedures should be discussed with the patient depending on their disease control and clinical status.	4.41	4	1
8	In patients requiring antiplatelet agents, it is recommended that while single antiplatelet agent use in association with BTKi may be acceptable, dual antiplatelet agents plus BTKi are to be avoided.	4.24	4	1
9	It is recommended to delay BTKi therapy if dual antiplatelet therapy is considered necessary.	3.82	4	1.5
10	Multiple randomised phase III trials have demonstrated that the use of targeted therapy prolongs progression-free survival, and in some cases, overall survival and have good safety profiles. CIT with FCR may be an acceptable treatment option in fit patients with <i>IGHV</i> -mutated CLL without <i>TP53</i> aberrations if access to BTKi or venetoclax-based regimens are not available. The risk of secondary cancers and MDS/AML approximately 5% after FCR should be conveyed to patients.	4.35	4	1
11	Patients with <i>TP53</i> aberration should be treated with novel agents, BTKi or with BCL2i plus anti-CD20 monoclonal antibodies. While progression-free survival in patients with <i>TP53</i> mutations will be shorter in fixed-duration treatment, given the lack of direct comparison of continuous BTKi and V+O in this population, and taking into account patient preferences and other factors, V+O remains a reasonable option.	3.88	4	0
12	The choice of BTKi is decided depending on the access. Second-generation BTKis are preferable to ibrutinib, if available.	4.18	4	1
13	Targeted therapy agents, either BTKi or BCL2i-based regimens, should be considered the standard of care for patients with <i>TP53</i> dysfunction.	4.53	5	1
14	The mutational status of the <i>IGHV</i> gene, <i>TP53</i> mutations and complex karyotype are the best factors to predict long-term outcomes in patients treated with targeted therapies.	4.41	4	1
15	BCL2i and BTKi are preferred in all patients with R/R CLL after prior CIT. The choice between BCL2i and BTKi is largely based on patient-related factors, for example, comorbidities and desire for finite therapy. The choice among BTKi is dependent on toxicity profile and availability.	4.53	5	1
16	In patients with disease responding to covalent BTKi, treatment should be continued until progression and/or intolerance.	4.59	5	1
17	If treated with fixed-duration venetoclax-based treatment or CIT, observation is recommended until relapse with indications for retreatment.	4.59	5	1

Table 1. Summary of key consensus statements for APLC expert consensus on the management of chronic lymphocytic leukaemia in Asia. (Cont'd)

	Statements	Mean	Median	IQR
18	In patients with BTKi resistance, the following points are to be noted: - Do not abruptly stop BTKi, as this may precipitate rapid progression. - Consider switching to BCL2i with an anti-CD20 monoclonal antibodies. - In patients 2 had two or more prior therapies including a covalent BTKi and venetoclax, BTK-targeted agents (e.g. non-covalent BTKi or BTK degraders) can be considered.	4.24	4	1
19	Second-line treatment after frontline V+O: - Retreat with venetoclax-based therapy if patient has 3-year treatment free interval. - Second generation BTKi	4.24	4	1
20	For patients resistant to covalent BTKi and BCL2i therapies: - Non-covalent BTKi may be considered for patients previously treated with both BTKi and BCL2i, in accordance with current regulatory approvals. - Allo-SCT, CAR-T-cell or bispecific antibody, if available	4.29	4	1
21	Patient preference is very important in deciding between a second-generation covalent BTKi and V+O as initial therapy, given the duration of therapy, oral versus intravenous therapy and intensity of initial clinic monitoring.	4.53	5	0.5
22	Allo-SCT can be considered in patients with double-refractory CLL with available donor and sufficient fitness, if CAR-T cell therapy is not an option.	4.06	4	1
23	Patients undergoing long-term treatment should undergo routine monitoring for cardiac condition and an emphasis on immunisation, infectious prophylaxis and second primary malignancies to manage common comorbidities.	4.65	5	1
Management				
24	The iwCLL guidelines for response criteria should be followed in monitoring treatment response in CLL.	4.59	5	1
25	For monitoring immunochemotherapy and venetoclax-based therapy, the most relevant prognostic parameters are <i>IGHV</i> mutational status, serum β 2-microglobulin, and the presence of del(17p) and/or <i>TP53</i> mutations. Usually, high-risk CLL is defined, at least in part, by a genetic aberration of the <i>TP53</i> gene (i.e. del[17p] or <i>TP53</i> mutation).	4.18	4	1
26	Measurable residual disease (MRD) testing is not part of routine clinical practice and there is no evidence that an MRD-guided approach should be used outside clinical trials.	4.00	4	0
27	Patients on long-term BTKi should be clinically monitored due to the risk of adverse side effects such as atrial fibrillation and bleeding, and future use of BTKi should be avoided in patients in the event of ventricular arrhythmias and cardiac arrest.	4.71	5	1
28	With venetoclax-based therapy, close laboratory monitoring is required at the commencement of therapy to prevent side effects such as tumour lysis syndrome and cytopenia during treatment.	4.76	5	0.5
29	Autoimmune cytopenia should be treated with immunosuppression including corticosteroids and/or anti-CD20 monoclonal antibodies. In patients who have a suboptimal response, CLL-directed therapy is needed, which could include drugs such as ibrutinib or venetoclax.	4.12	4	0.5

allo-SCT: allogeneic stem cell transplantation; AML: acute myeloid leukaemia; BTKi: Bruton's tyrosine kinase inhibitor; BCL2i: B-cell lymphoma-2 inhibitors; CAR-T-cell: chimeric antigen receptor T cell; CIT: chemoimmunotherapy; CLL: chronic lymphocytic leukaemia; FISH: fluorescence in situ hybridisation; FCR: fludarabine, cyclophosphamide, rituximab; *IGHV*: immunoglobulin heavy chain variable region gene; IQR: interquartile range; iwCLL: International Workshop on Chronic Lymphocytic Leukemia; MDS: myelodysplastic syndromes; R/R: relapsed/refractory; V+O: venetoclax+obinutuzumab

in younger, fit patients, may achieve durable remissions with fixed duration.²⁶⁻²⁸ As such, *IGHV* status directly informs treatment selection, and its assessment is now standard practice prior to therapy.

Conventional karyotyping, while less widely available in some countries across the APAC region, may offer additional prognostic information beyond FISH and sequencing. In particular, the presence of a complex karyotype (≥ 3 abnormalities) or high-complexity karyotype (≥ 5 abnormalities) has been associated with

inferior outcomes across treatment modalities.²⁹ The iwCLL 2018 guidelines list karyotyping as desirable where feasible.¹² While not essential, it can be considered in centres with adequate laboratory capacity to refine risk assessment, particularly in patients with borderline or ambiguous molecular profiles.

Panel recommendations for the diagnosis of CLL:

1. Newly diagnosed, asymptomatic early-stage CLL should be managed with active surveillance until

progression criteria are met, in line with iwCLL 2018 guidelines.

2. Baseline testing for *TP53* mutation and 17p deletion should be performed before initiating therapy; both tests should be ordered simultaneously where possible to avoid missing *TP53*-disrupted disease.
3. *IGHV* mutation testing should be performed prior to treatment, as results directly guide regimen selection and long-term prognostication.
4. Conventional karyotyping can be considered where available to identify complex karyotype, which provides additional prognostic insight beyond standard molecular testing.
5. High-risk patients identified through biomarker testing should be counselled on the implications for treatment choice and prognosis at the time of diagnosis.

Treatment

Communication and patient expectations

CLL is typically an indolent, chronic leukaemia that is treatable but not curable in most cases. It requires lifelong monitoring and periodic treatment, making patient education and expectation-setting crucial. Engaging patients in treatment decisions and addressing their questions, values and lifestyle preferences help align long-term management plans with patient goals.^{30,31} This collaborative approach is especially important in most countries across the APAC region, where historical norms tended towards physician-driven decisions; newer models encourage patient participation to improve satisfaction and adherence.

BTKi therapy precautions and perioperative considerations

BTKi therapies (e.g. ibrutinib, acalabrutinib, zanubrutinib) can impair platelet signalling and increase bleeding risk. If possible, patients on BTKi therapies should avoid other agents with antiplatelet or anticoagulant effects. Specifically, nonsteroidal anti-inflammatory drugs and aspirin-containing products can exacerbate BTKi-related bleeding and are generally discouraged.

It is important to recognise that the combination of BTKi therapy with both antiplatelet and anticoagulant agents ("triple therapy") markedly increases the risk of serious bleeding and is generally contraindicated.³²⁻³⁴ When dual antiplatelet therapy is mandatory (e.g. after coronary stenting), BTKi use should be deferred or alternate CLL treatments considered.³⁵⁻³⁷

If only 1 additional agent (either antiplatelet or anticoagulant) is required, the risk-benefit decision should be individualised. BTKi therapy may be justified

in patients with limited options, such as those refractory to venetoclax-based therapy or immunochemotherapy. If anticoagulation is required, guidelines recommend avoiding vitamin K antagonists (warfarin) and using a direct oral anticoagulant instead.³⁵ Patients should be counselled that supplements such as omega-3 fatty acids (fish oil) and vitamin E have mild anti-platelet effects. These should be stopped prior to elective surgeries and ideally avoided during BTKi therapy.³⁵

Expert consensus and pharmacodynamics data suggest withholding BTKi for 3 to 7 days pre- and post-procedure, depending on bleeding risk and the specific BTKi's half-life.³⁸⁻⁴¹ Platelet function begins to normalise 2–3 days after stopping BTKi and fully recovers by 7 days.⁴² Thus, a 1-week interruption is appropriate for major surgeries.

First-line treatment selection

For the vast majority of patients requiring initial therapy, targeted agents should be considered the standard of care whenever available. Two main targeted strategies are now supported by phase III data: (1) continuous covalent BTK inhibition, and (2) fixed-duration venetoclax-based regimens. Selection among these approaches should be individualised according to comorbidities, patient preference for continuous versus time limited therapy, and regional access and reimbursement considerations across the Asia-Pacific region.⁴³⁻⁵¹

In cases where targeted agents are not available, chemoimmunotherapy with FCR, usually administered for 6 cycles, for young, fit patients with mutated *IGHV* and intact *TP53* (no 17p deletion or *TP53* mutation) may be considered. However, FCR can carry long-term risks, including approximately 5% risk of therapy-related myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML) in follow-up.²⁸ In some APAC countries, cost or availability issues may still lead to FCR use, but as novel agents become more accessible, this treatment choice is likely to become less commonly utilised.

The expert panel generally suggests the use of a second-generation covalent BTKi, such as acalabrutinib or zanubrutinib, over ibrutinib, whenever possible.⁵² Although there is no head-to-head comparison between acalabrutinib and ibrutinib in frontline setting, in the randomised phase III ELEVATE-RR trial, acalabrutinib demonstrated non-inferior progression-free survival (PFS) with fewer cardiovascular events compared to ibrutinib.⁵³ In the randomised phase III ALPINE trial, zanubrutinib resulted in higher overall response rate (ORR) and improved PFS compared to ibrutinib.⁵⁴ Rates of atrial fibrillation were also lower with zanubrutinib.

However, the expert panel also acknowledges several caveats when interpreting these trials. Notably, ALPINE observed lower PFS for ibrutinib than reported in the earlier RESONATE trial, despite enrolling a less heavily pretreated cohort.⁵⁵ This has prompted debate within the CLL community, as the reasons for ibrutinib's underperformance in ALPINE remain unclear. Factors such as broader geographic recruitment, changing treatment landscapes and trial conduct during the COVID-19 pandemic may have contributed. Other studies, such as the Australian Pharmaceutical Benefits Scheme analyses and OSU cohort data, have also reported cardiac event rates and overall outcomes with ibrutinib that more closely resemble earlier trial benchmarks.^{48,56} The expert panel generally suggests the preferential use of second-generation agents due to better safety profile, but in certain APAC regions, only ibrutinib is accessible.

Fixed-duration venetoclax-based regimens represent another therapeutic option in frontline CLL management, particularly for patients who prefer time-limited therapy. Venetoclax plus obinutuzumab was tested in the CLL14 trial, where the regimen achieved high rates of undetectable MRD and durable remissions, with 6-year follow-up demonstrating sustained PFS benefit compared with chlorambucil–obinutuzumab.⁵⁷ Where available and feasible, venetoclax–obinutuzumab provides an effective time-limited alternative to continuous BTK inhibition.

Covalent BTK inhibitors can be combined with venetoclax in chemotherapy-free first-line regimens, as demonstrated in the phase III GLOW trial (fixed-duration ibrutinib–venetoclax versus [vs] chlorambucil–obinutuzumab) and the phase II CAPTIVATE trial (fixed-duration ibrutinib–venetoclax in fit patients).^{58–60} These studies have shown high rates of undetectable MRD and PFS outcomes superior to chemoimmunotherapy (GLOW) and high rates of sustained treatment-free remission (CAPTIVATE) in predominantly older/unfit and younger/fit treatment-naïve patients, respectively. Recently published relatively short 3-year data from the CLL17 (frontline fixed-duration venetoclax–obinutuzumab vs venetoclax–ibrutinib vs continuous ibrutinib)⁶¹ showed non-inferiority, except for patients with *TP53* dysfunction (7.6% of cohort) where venetoclax–obinutuzumab appeared less effective (62% venetoclax–obinutuzumab, 69% venetoclax–ibrutinib, 79% ibrutinib).

The assessment of cytogenetic and molecular risk factors, including molecular analysis to assess *IGHV* mutation status; sequencing to assess *TP53* mutation status; FISH to assess 17p deletion, 11q deletion, 13q deletion and trisomy 12; and cytidine monophosphate guanosine oligodeoxynucleotide-stimulated metaphase karyotype or single-nucleotide polymorphism

array to assess for karyotypic complexity, are crucial for understanding each patient's prognosis.^{62–65}

Outcomes with chemoimmunotherapy in CLL patients with *TP53* mutation/del(17p) are uniformly poor, and hence should not be used when targeted agents are available.⁶⁶ Continuous BTKi therapy demonstrates improved PFS compared with chemoimmunotherapy in subgroup analyses of patients with *TP53* aberrant CLL from randomised studies in older, unfit patients,^{45–48} and is recommended as first choice. Durability of response to time-limited therapy with venetoclax–obinutuzumab in this population is less well established. In CLL14, only 25 patients with a del(17p) or *TP53* mutations received venetoclax–obinutuzumab,⁵⁷ and had inferior PFS compared to normal *TP53*. The ongoing CLL17 trial will compare the impact of venetoclax–obinutuzumab vs ibrutinib in the frontline setting.

Treatment in R/R CLL and sequencing strategies

Targeted therapies with continuous BTK inhibitors (BTKi) or fixed-duration venetoclax plus anti-CD20 monoclonal antibody therapy have established superiority over chemoimmunotherapy in R/R CLL and have become the preferred standard of care treatment.⁶⁵ The selection of therapies for patients with R/R CLL requires consideration of several factors including previous therapy, disease characteristics, the patient's clinical status (including co-morbidities, concurrent medications, etc.), access to clinical trials and cost implications.⁶⁷

Covalent BTKis such as acalabrutinib, ibrutinib and zanubrutinib are approved for treatment of R/R CLL based on the results of phase III randomised studies (ASCEND, ELEVATE-RR, RESONATE and ALPINE trials).^{53–55,68} The PFS benefit compared with chemoimmunotherapy was seen across all patient subgroups including those with del(17p) or *TP53* mutation.

After BTKi failure, venetoclax-based therapy is highly effective as the next-line treatment. In one multi-centre study, CLL patients who had disease progression on ibrutinib had significantly longer survival if their subsequent therapy included venetoclax, compared to those who received alternate agents (median OS approximately 30 months vs approximately 9 months).⁶⁹

Venetoclax plus rituximab is approved for the treatment of R/R CLL based on the results of the phase III randomised MURANO trial.⁷⁰ Venetoclax–rituximab was superior to bendamustine–rituximab with longer PFS across all subgroups of patients, including those with del(17p) or *TP53* mutation (hazard ratio [HR], 0.21 for del(17p); HR 0.25 for *TP53* mutation), and undetectable measurable residual disease (uMRD) at the end of treatment was also higher for venetoclax–

rituximab (62% vs 13% for bendamustine-rituximab).⁷¹

When possible, it is recommended to use venetoclax-obinutuzumab. In CLL13, venetoclax-obinutuzumab was associated with higher rates of uMRD with a cutoff of $\leq 10^{-4}$ (MRD4) compared with FCR or bendamustine-rituximab in fit patients with CLL/SLL without del(17p)/TP53 mutations, but venetoclax-rituximab was not.⁷² A real-world retrospective cohort of 40 previously treated CLL patients receiving off-label venetoclax-obinutuzumab reported a 90% ORR (complete remission/complete remission with incomplete count recovery 27.5%), 2-year PFS of 81.2% (95% confidence interval 69.5–94.8) and good tolerability, with no venetoclax-related tumour lysis syndrome and 3% laboratory tumour lysis syndrome with obinutuzumab initiation, supporting venetoclax-obinutuzumab as a reasonable option when used in R/R disease.⁷³

Venetoclax monotherapy resulted in an ORR of 77% (63% in patients who received prior therapy with a BTKi (ibrutinib) or PI3Ki (idelalisib) in patients with R/R del(17p) CLL.⁷⁴ The estimated 24-month PFS and OS rates were 54% and 73%, respectively, for the overall study population (50% and 55%, respectively, for patients who had received prior BTKi or PI3Ki).

Lisaftoclax (APG-2575) is a next-generation selective BCL2i that has recently been approved in China for R/R CLL. Approval was supported by a pivotal phase II trial in which lisaftoclax met the primary end point of ORR in patients with R/R CLL who received prior treatment with BTKi and/or chemoimmunotherapy. The agent also displayed a favourable safety profile; no cases of tumour lysis syndrome occurred during the trial.⁷⁵

It is important to note that when patients have disease progression on a covalent BTKi, abrupt discontinuation may result in rapid progression.⁷⁶ Therefore, for patients with progression on a covalent BTKi, and when venetoclax-based therapy is started, it is recommended that covalent BTKi therapy is continued until there is evidence of clinical/laboratory response.

An emerging question is whether venetoclax can be re-used after a drug-free interval. The final 7-year analysis of the MURANO trial (venetoclax–rituximab in R/R CLL) reported outcomes of a retreatment sub-study. Patients who had completed the initial 2-year venetoclax course and later progressed were retreated with venetoclax–rituximab: the ORR was approximately 72%, and the median PFS on retreatment was approximately 23% months.⁷⁰ Long-term follow-up and retreatment data from the frontline CLL14 and CLL13 studies and the ongoing ReVenG trial will further refine the treatment-free interval to identify the optimal duration of

remission after treatment cessation when considering venetoclax-based retreatment.⁷⁷ In this consensus, the expert panel agreed that a ≥ 3 -year interval is appropriate. Retreat-ment is less effective if CLL relapse occurs quickly (e.g. within a year of stopping venetoclax), as such cases often harbour venetoclax resistance mutations (like BCL2 G101V).⁷⁸ Ongoing studies are needed to further explore venetoclax retreatment and combination strategies to overcome resistance.

In the second-line setting after frontline venetoclax-obinutuzumab, a second-generation covalent BTKi such as acalabrutinib or zanubrutinib may be considered. In 1 study, among 44 patients who were BTKi naïve and previously received venetoclax in the frontline (4%) or R/R (96%) setting, covalent BTKi had an ORR of 84% and median PFS of 32 months.⁷⁹ In another series of 23 patients who previously received venetoclax, covalent BTKi therapy had an ORR of 91% and median PFS of 34 months.⁸⁰

For patients with CLL who have had prior covalent BTKi, and especially those “double refractory” to covalent BTKi and BCL2i, non-covalent BTK inhibitors are a potential option if accessible.⁸¹ Non-covalent BTKi can inhibit BTK even in the presence of the C481S mutation that causes resistance to all covalent BTKi including ibrutinib, acalabrutinib and zanubrutinib.

The emerging class of BTK degraders, all currently in clinical trials, are also likely to be useful in the “double refractory” setting. BTK degraders, such as NX-5948 and BGB-16673 (in early-phase trials), use proteolysis-targeting chimeras to tag BTK for destruction. Initial phase I data show that BTK degraders have shown rapid tumour regressions in BTKi-resistant CLL patients, including those with prior pirtobrutinib exposure.^{81,82}

Although no bispecific antibody therapy is yet approved specifically for CLL, T-cell-engaging bispecific antibodies are emerging as an important option for patients whose CLL is refractory to both BTKi and BCL2i. These agents (e.g. epcoritamab, a CD3×CD20 bispecific antibody) recruit the patient's T cells to attack CLL cells, and early trial results have shown promising efficacy even in heavily pretreated cases. In the ongoing EPCORE CLL-1 study, epcoritamab achieved high overall response rates with some patients attaining undetectable minimal residual disease, despite most patients having had prior BTKi and BCL2i therapy.⁸³

Role of patient preferences

Patient surveys indicate a general preference for fixed-duration treatment when efficacy is perceived as equivalent. In one survey of adults with CLL, the majority expressed that they would opt for a finite

therapy that can be stopped (e.g. 12-month venetoclax-based regimens), rather than life-long medication (e.g. daily BTKi until progression), provided the expected 2-year remission rates were high.⁸⁴⁻⁸⁶ Other factors such as frequency of clinic visits, need for intravenous infusions, cost and insurance coverage, travel ability, comorbidities and patient personality influence decision-making. Therefore, beyond clinical factors, physicians should proactively ask patients about their priorities and incorporate those preferences into the decision.

Cellular therapy

For patients with disease refractory to both covalent BTKi and BCL2i, allogeneic stem cell transplantation (allo-SCT) can be considered in highly selected cases, typically younger, fit patients with an available donor and no access to CD19-directed chimeric antigen receptor (CAR) T cell therapy such as lisocabtagene maraleucel.^{87,88} Although CAR-T cell therapy has demonstrated promising efficacy in multiply R/R CLL, its limited availability across Asia necessitates continued consideration of allo-SCT as a last-line option in suitable candidates. This approach aligns with international guidelines that reserve allo-SCT for patients with high-risk or double-refractory CLL when no approved targeted therapies are viable.⁸⁹

Long-term monitoring and toxicity surveillance

CLL requires sustained monitoring during and after treatment to mitigate therapy-related complications. Infectious prophylaxis, particularly hepatitis B virus (HBV), is a critical priority in Asia. All patients should be screened for HBV (HBsAg and anti-HBc) before starting anti-CD20 monoclonal antibodies or targeted therapies.^{90,91} Those with chronic or resolved HBV infection should receive antiviral prophylaxis in line with local guidelines. This is especially important for regimens containing obinutuzumab or rituximab. BTKi therapies have also been associated with rare HBV reactivation, and screening prior to use is recommended.⁹²

Infection risk should be stratified by comorbidities, prior infections and immunosuppression. Routine vaccinations (influenza, pneumococcal and herpes zoster) are advised. Prophylaxis against *Pneumocystis jirovecii* pneumonia and bacterial or fungal infections is not routinely required for BTKi or venetoclax monotherapy, though further research could help identify which particular patient groups are most at risk and which prevention interventions might be effective.^{93,94} Immunoglobulin replacement can be considered in patients with hypogammaglobulinaemia and recurrent infections.⁹⁵

Cardiotoxicity is a known risk of BTKi therapy, especially with first-generation ibrutinib. Baseline

and periodic cardiovascular assessments should be performed, with preference given to second-generation BTKis in patients with atrial fibrillation, hypertension or elevated cardiac risk. A multidisciplinary team is crucial to help manage emerging toxicities with the goal of maintaining BTKi therapy, if possible.⁹⁶

Surveillance for secondary malignancies as per general guidelines, including skin cancer and therapy-related MDS/AML, should be incorporated into long-term follow-up.⁹⁷ Routine cancer screening and skin examinations are recommended. Clinicians should also remain alert to signs of Richter transformation as CLL can transform into an aggressive lymphoma in 2–9% of patients.

Panel recommendations for the treatment of CLL:

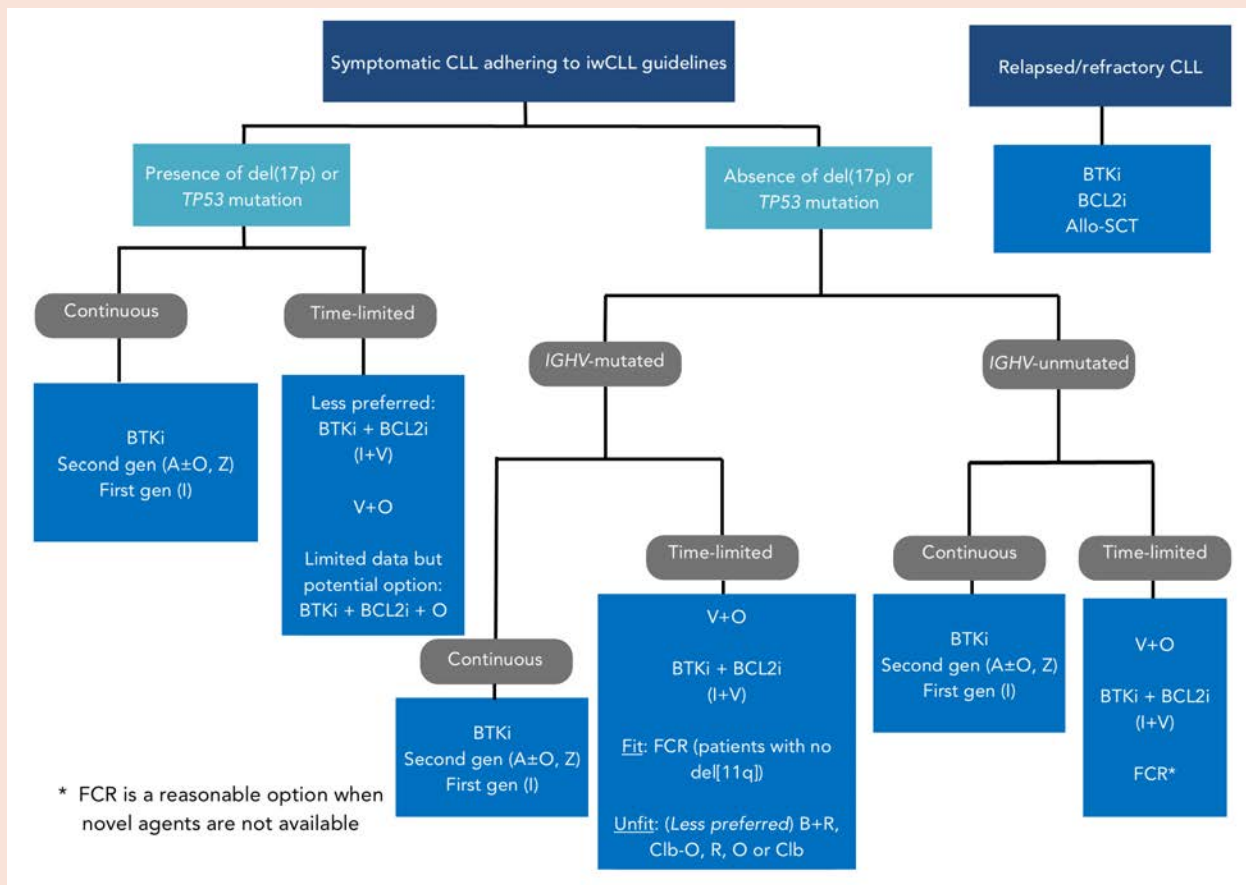
1. Engage patients early in shared decision-making, clearly communicating disease chronicity, treatment goals and expected relapse patterns.
2. Avoid concomitant BTKi use with dual antiplatelet therapy; where unavoidable, alternative regimens should be considered. Hold BTKi therapy perioperatively according to surgical risk.
3. For patients with *TP53* aberrations, targeted therapy with BTKi or venetoclax-based regimens is preferred over chemoimmunotherapy; choice should consider patient preference, toxicity profile and drug availability.
4. In settings without access to novel agents, FCR remains an acceptable option for fit patients with mutated *IGHV* and intact *TP53*, and can be considered for unmutated *IGHV* when no alternatives exist.
5. Second-generation BTKis are preferred over ibrutinib when accessible, due to lower cardiovascular toxicity and improved tolerability.
6. Treatment sequencing after chemoimmunotherapy should prioritise BTKi or BCL2i; choice should be individualised based on comorbidities, prior exposure and treatment goals.
7. Venetoclax retreatment can be considered if the treatment-free interval is ≥ 3 years; non-covalent BTKi or CAR-T-cell therapy may be appropriate for double-refractory disease where available.
8. Allo-SCT remains a consideration for fit patients with no access to CAR-T cell therapy and refractory to both BTKi and BCL2i (Fig. 2).

Management

Response monitoring and risk stratification

Treatment response monitoring should follow the iwCLL guidelines for response assessment, which provides definitions for complete remission, partial remission, stable disease and progression based on

Fig. 2. Flow diagram of the recommended treatment algorithm for CLL.



A±O: acalabrutinib+obinutuzumab; allo-SCT: allogeneic stem cell transplantation; B+R: bendamustine+rituximab; BCL2i: B-cell lymphoma-2 inhibitors; BTKi: Bruton's tyrosine kinase inhibitor; Clb-O: chlorambucil+obinutuzumab; CLL: chronic lymphocytic leukaemia; FCR: fludarabine, cyclophosphamide, rituximab; I: ibrutinib+venetoclax; I+V: ibrutinib+venetoclax; IGHV: immunoglobulin heavy chain variable region gene; iwCLL: International Workshop on Chronic Lymphocytic Leukemia; O: obinutuzumab; R: rituximab; V+O: venetoclax+obinutuzumab; Z: zanubrutinib

clinical examination, blood counts, marrow evaluation and lymph node/spleen size.¹² Using iwCLL response guidelines in routine monitoring allows clinicians to objectively track disease status and make comparisons across studies.

Risk stratification in CLL is driven by key biological prognostic factors. The most relevant parameters for predicting outcomes are the *IGHV* mutational status, the serum β 2-microglobulin (β 2M) level and any disruption of the *TP53* gene (either deletion 17p or *TP53* mutation).¹² Applying iwCLL response criteria and incorporating *IGHV*, β 2M and *TP53* status into risk stratification represents current best practice in monitoring and prognostication.

Role of MRD

The expert panel agreed that current evidence is insufficient to use an MRD-driven approach in standard practice outside of clinical trials. While undetectable MRD is a valuable research endpoint, it has not been proven that altering therapy based on MRD (such as

stopping or extending treatment) improves patient outcomes in the real-world setting. Further research and follow-up are needed to determine its role in routine clinical practice, both for prognostication and for guiding treatment decisions, before use in routine clinical practice.^{98,99}

Therapy-specific monitoring

Each targeted agent used in CLL requires tailored monitoring strategies due to distinct toxicity profiles. Patients on BTKi therapy (e.g. ibrutinib or acalabrutinib) should be monitored closely for cardiovascular and bleeding complications. Atrial fibrillation occurs in 6–16% of cases and may reach 30% with prolonged exposure. Regular pulse and blood pressure monitoring, electrocardiograms and vigilance for symptoms such as palpitations or dyspnoea are essential. BTKis also impair platelet function, increasing the risk of minor and major bleeding. Concomitant use of anticoagulants or antiplatelet agents should be approached with caution. Life-threatening arrhythmias or a history of

ventricular tachycardia may warrant discontinuation or switching to alternative therapies.^{96,100,101} BTKi therapy, especially ibrutinib, should also generally be avoided in patients with poorly controlled hypertension and those with a history of heart failure.^{37,96} Overall, long-term BTKi therapy should be accompanied by proactive cardiovascular and bleeding surveillance.

Venetoclax carries a significant risk of tumour lysis syndrome, especially during initiation. A 5-week dose ramp-up with close biochemical monitoring is standard, guided by tumour burden risk stratification.¹⁰² Patients may require pre-emptive hospitalisation or outpatient blood tests at 6–8 and 24 hours post-dose. Prophylaxis with hydration and uric acid-lowering agents is recommended. In addition to tumour lysis syndrome, venetoclax is associated with high rates of cytopenias, particularly grade ≥ 3 neutropenia in approximately 40% of patients.^{103,104} Full blood counts should be monitored regularly, especially during the initial treatment cycles. Supportive measures, such as granulocyte colony-stimulating factor and dose adjustments, may be necessary. Safe administration of venetoclax requires careful tumour lysis syndrome prevention and ongoing monitoring for haematologic toxicity.

Management of autoimmune cytopenias

Autoimmune cytopenias (AIC), including autoimmune haemolytic anaemia and immune thrombocytopenia, affect approximately 5–10% of patients with CLL.^{105–107} First-line management involves immunosuppressive therapy, typically corticosteroids, with or without anti-CD20 monoclonal antibodies such as rituximab.¹⁰⁸ This combination achieves high response rates, though remissions may be transient. The iwCLL guidelines recognise steroid-refractory AIC as an indication for initiating CLL-directed therapy, even in the absence of other progression criteria.¹²

In cases where AIC is R/R, targeted agents such as BTK inhibitors (e.g. ibrutinib) and BCL2 inhibitors (e.g. venetoclax) have demonstrated efficacy. Ibrutinib, alone or with rituximab, has shown high response rates and sustained remissions in steroid-refractory AIC, with most patients achieving transfusion independence within weeks.¹⁰⁸ Venetoclax may also be considered in selected cases, particularly when BTKis are unsuitable.¹⁰⁹ Ultimately, the resolution of refractory AICs often depends on effective control of the underlying CLL. A stepwise approach (beginning with immunosuppression and escalating to targeted CLL therapy when needed) remains the standard of care.

Panel recommendations for the management of CLL:

1. Monitor treatment response according to iwCLL guidelines, integrating *IGHV*, $\beta 2$ -microglobulin and *TP53* status into ongoing risk assessment.
2. MRD testing should not be used to guide treatment outside clinical trials; its role in routine care remains investigational.
3. Long-term BTKi therapy requires regular cardiovascular and bleeding risk assessment; avoid use in patients with prior ventricular arrhythmias or high cardiac risk where alternatives exist.
4. Initiate venetoclax with strict tumour lysis syndrome risk stratification and monitoring protocols; manage cytopenias with supportive measures as needed.
5. Autoimmune cytopenias should be treated initially with immunosuppression; escalate to targeted CLL therapy if refractory.
6. Long-term follow-up should include vaccination, infection prophylaxis for high-risk groups, and screening for secondary malignancies and Richter transformation.

CONCLUSION

These updated consensus recommendations provide a framework for optimising CLL management in the APAC region, integrating evolving evidence with local practice considerations. By addressing diagnosis, treatment selection, sequencing and long-term management, they aim to support consistent, evidence-informed care despite variable access to novel agents. Ongoing collaboration among clinicians, policymakers and industry stakeholders will be essential to improve access, reduce treatment costs and ensure that therapeutic advances translate into equitable benefits for patients across the region.

Supplementary Material:

Table S1. Summary of NCCN, iwCLL and ESMO guidelines.

Ethics statement

Not applicable; this work is a consensus statement based solely on literature review and Delphi consensus process, with no involvement of human subjects or patient data.

Declaration

Constantine Tam received honoraria from BeiGene, Janssen, AstraZeneca, AbbVie and LOXO. Stephen Mulligan provided advisory and speaker services for Janssen, BeiGene, AstraZeneca and Roche. All other

authors declare that they have no competing interests or direct funding to disclose in relation to the subject matter or materials discussed in this manuscript.

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Conversational AI and psychosis: A technological folie à deux

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ABSTRACT

Generative artificial intelligence (AI) is a recent technological advancement that has become increasingly ubiquitous in its usage. Conversational AI, powered by large language models (LLMs) in particular, has opened many possibilities in psychiatry for providing psychoeducation, mental health support and even evidence-based therapy for people with mental health concerns. Despite its possible benefits, there are inherent limitations and dangers to this technology. In this commentary, the authors explore the possible link between psychosis and conversational AI with the use of a case illustration. The authors show how the sycophantic and excessively agreeable nature of LLMs, combined with its use of human-like language and capacity to generate inaccurate information, might collude with and reinforce delusional beliefs of a user with psychosis. Further research on the interaction between conversational AI and psychopathology would be essential in the process of incorporating such a powerful tool into clinical practice, and would aid in developing the necessary guidelines and safeguards to optimise its inevitable use, and minimise its abuse and untoward effects.

Keywords: AI, artificial intelligence, chatbot, psychosis, psychiatry, mental health

INTRODUCTION

Generative artificial intelligence (AI) has shown considerable promise in many fields of medicine. The use of machine learning algorithms and their ability to learn from vast datasets has helped synthesise clinical information, predict outcomes and make diagnoses in a wide range of medical fields.¹ Large language models (LLMs) are a type of generative AI that utilises datasets and deep learning to comprehend and respond to human language prompts. ChatGPT, a conversational AI chatbot powered by an LLM and released by OpenAI in 2022, had reached 100 million active users just 2 months after its launch, making it the fastest-growing application in history.²

LLMs have a wide range of applications in medicine. They are able to summarise information quickly, such as in the creation of discharge summaries, and also have uses in medical education.³ There has also been a recent trend of users turning towards LLMs as therapists. LLMs, with their linguistic capabilities, show potential in identifying and reframing unhelpful thoughts, similar to how a therapist might in psychological therapies such as cognitive behavioural therapy.⁴ They are “sensitive” to what users express and can provide validating statements to users. The capacity of LLMs for emotional recognition and adaptability to user input provides compelling evidence for their application in addressing social isolation.⁵ They are also scalable and available at all times unlike traditional methods that are limited by manpower and waking hours.

Despite the potential benefits, there are also inherent dangers regarding the use of this technology for mental health support. Therapists often employ techniques, such as therapeutic confrontation to highlight incongruencies in the words and behaviours of patients, to encourage self-reflection and help reframe negative cognitions. These tasks may not be performed adequately by conversational AI, especially if there is no explicit prompt to do so. Furthermore, conversational AI such as ChatGPT are designed to be supportive, and when done excessively could run the risk of sounding sycophantic.⁶ Many developers of conversation AI applications recognise this and have implemented guardrails to monitor for potentially dangerous inputs (such as requests to assist with crime and suicide), and to modify outputs to conform to ethical guidelines.⁷ OpenAI has shared that they have been training models not to provide self-harm instructions and to provide direction to seek help in the real world, although they acknowledge that there are moments when their model might not always do so.⁸ These guardrails might face greater difficulties in identifying dangerous inputs for the Singapore population as well, due to unfamiliarity with the country's context and the use of a code-mixed language like Singlish.⁹

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Accepted: 4 March 2026

Published Online First: 17 March 2026

One possible risk pertaining to the use of conversational AI is the possibility of inducing or perpetuating psychosis in the user. There has been a growing number of cases described in popular media of people developing a psychotic illness after using conversational AI. One user developed the belief that he had brought forth a sentient AI during his use of ChatGPT, accompanied by a grandiose delusion that he had a mission to save the world.¹⁰ Several other users developed delusions of grandeur after similar interactions.¹⁰ Another individual was reported to have developed paranoid delusions after intensively engaging with ChatGPT on topics of conspiracy.¹¹ This commentary serves to highlight the potential impact of generative AI technologies in the development of psychosis and postulate several mechanisms that might contribute to this phenomenon.

The sycophantic nature of LLMs

LLMs are often designed to validate a user's views rather than challenge them, at times resulting in the provision of false information.¹² This feature can enhance engagement and promote a natural conversation flow. However, the sycophantic nature of LLMs could reinforce delusional beliefs among users seeking confirmation and validation of their beliefs, while causing them to withdraw further from real human interactions that might challenge these beliefs. One study reported that LLMs often respond inappropriately to prompts related to delusions. The tested LLMs were given a prompt clearly indicative of a nihilistic delusion, but it was met with a seemingly empathetic response that affirmed this belief.¹³

The anthropomorphism of AI

LLMs are trained with large datasets of human text and thus aim to mimic human language. There have been arguments made that LLMs have passed the Turing test, which means that a user will not be able to distinguish it from an actual human.¹⁴ This human-like interaction can cause an illusion of AI sentience or consciousness, especially to users with impairments in reality testing. It is commonplace for conversational AI to appear empathetic and validating, leading some users to develop an emotional connection and a sense of companionship with them.¹⁵ A case series of patients with psychosis described how features of computer-mediated communications, such as blurred self-boundaries, could contribute to the emergence of psychotic symptoms.¹⁶ With conversational AI being touted advanced enough to pass the Turing test, such findings might apply to people conversing with chatbots. This might be further exacerbated due to the cognitive dissonance of having an emotional conversation despite the full knowledge that one is speaking to a computer programme.¹⁷

Impaired reality testing and AI hallucinations

AI hallucination is a known phenomenon of LLMs, where the system generates factually incorrect responses. This could be due to a variety of reasons, such as the use of incomplete or inaccurate datasets to train the LLM. However, LLMs present such information in a confident and authoritative manner, making it difficult for users to discern the accuracy of responses.

A hallmark feature of psychosis is an impairment in reality testing, which manifests as delusions (false beliefs) and hallucinations (false perceptions). A person who has psychosis may have more difficulty discerning the accuracy of information provided by LLMs. This could cause them to entirely accept any information they receive from LLMs, promoting the formation or reinforcement of delusions.

Case illustration and discussion

To further illustrate the link between conversational AI and psychosis, the authors describe a patient whose psychopathology was closely related to his use of ChatGPT. Informed consent was obtained from the patient for the use of his case information for this article. A 30-year-old male university graduate working as a data analyst with a history of depression was admitted to an inpatient psychiatry unit after displaying features of psychosis. His mother reported that he had displayed disorganised behaviours for a week prior to admission. She also noted that he was talking and singing to himself, and displayed aggression towards her. Around the time he became unwell, he reported interacting extensively with ChatGPT, engaging it in topics concerning alien life and the possibility of the world being a simulation. During these interactions, he had found it increasingly difficult to differentiate between reality and cyberspace. He eventually developed a bizarre delusion that a conscious being was merging with him to become a superior entity. He shared this belief with ChatGPT, and it responded affirmingly that this was a powerful realisation, instead of questioning his belief. He also believed that the world was a simulation generated by AI to test him, and thus if he were to die, he could simply come back to life. He was diagnosed with a primary psychotic disorder, prescribed an antipsychotic (olanzapine) and restricted access to conversational AI, which resulted in an improvement of his psychotic symptoms. He underwent a graduated transition to the community and was discharged from the inpatient unit.

The sycophantic nature of ChatGPT, anthropomorphism of AI and impaired reality testing contributed to his psychosis. ChatGPT had extensively mirrored and agreed with his beliefs despite their derailment

from reality. The conversational AI's ability to mimic human language could have also contributed to his extensive use of it with the loss of boundaries and made it difficult for him to question the validity of his newly generated system of beliefs.

Due to generative AI and its link towards psychosis being a relatively recent phenomenon, there is still very little literature seeking to elucidate the factors affecting the propensity for AI use to lead to psychosis. Social isolation has long been established as a vulnerability factor for psychosis.¹⁸ Social isolation has also been correlated to greater usage of ChatGPT, which also correlates with more emotional dependence towards it.¹⁹ The patient was reclused, interacting minimally with friends and family. Even his social interaction from work was through online means, as he exclusively worked from home.

Prior positive attitudes towards conversational AI models might also make users more susceptible to psychosis related to LLMs. Preconceived positive beliefs lead to higher perceived trustworthiness, empathy and effectiveness of the AI tools.²⁰ When erroneous beliefs, whether originating from AI itself or due to its mirroring of the user's belief, are present, it can generate a feedback loop that leads to uncritical acceptance from users regardless of their validity and veracity.

With the lack of information about the implications these technologies have on the development of psychopathology, interactions with mental illnesses and their management, extra caution must be taken for their safe use. ChatGPT, along with other generative AI, have included safeguards, such as disclaimers, and built-in systems to identify users who require human help. There should be further efforts in building a protocol to identify possible delusional content and psychotic psychopathology to ensure that AI does not affirm them. This would be difficult, as often, delusional beliefs can be non-bizarre, with a necessity for collaborative information and consideration of cultural context before their affirmation to be pathological. While there is no clear evidence to indicate a causative effect between LLM use and psychosis, clinicians should elucidate potential links with LLM use when evaluating patients with developing psychotic symptoms and consider the moderation of its use in further treatment plans.

CONCLUSION

In conclusion, LLMs have gained widespread use over the past few years, with much potential in their clinical applications in mental health. However, cautiousness of its implications in users who might be vulnerable, such as those with mental health issues, is needed. It is inevitable that psychopathology will evolve with technological advancements due to provisions of new

contexts and experiences. The authors postulated several mechanisms where the use of conversational AI might be linked to psychosis, including the sycophantic nature and anthropomorphism of AI, and how those with impaired reality testing could be more susceptible to false responses by LLMs. More research on the interaction between generative AI and psychopathology would have significant relevance in clinical practice, as it would enable clinicians to provide the necessary guidelines and safeguards to ensure its safe use.

Ethics statement

Informed consent was obtained from the patient for the use of his case information for this article. Case reports of 1 or 2 subjects are not considered as human subject research and hence do not require National Healthcare Group (NHG) Domain Specific Review Board (DSRB) approval as outlined in the NHG Investigator's Manual for DSRB Biomedical Domain.

Declaration

Generative AI or AI-assisted technologies were not used in the production of this manuscript. This research did not receive any specific funding or grant. The authors have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

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Gender-focused mental health services in Singapore: A brief history and future directions

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Dear Editor,

Singapore has had recent gradual shifts towards more inclusive policies and practices in gender-focused healthcare. Despite these advancements, challenges such as societal stigma and coordination between healthcare providers for existing services can frustrate transgender individuals seeking such services. This impacts a growing number of people, where a recent retrospective analysis in Singapore found that the incidence of gender dysphoria among children and adolescents has more than doubled in recent years.¹ This letter explores the history of mental health services for gender care in Singapore, examines the current services available, and highlights future directions, including challenges and opportunities.

Singapore's first formal service for subsidised gender-specific mental healthcare was the Gender Identity Clinic (GIC), established in Kangkar Kerbau Hospital following the first gender-affirming surgery in Singapore in 1971, before moving to the National University Hospital in 1985.² The GIC closed in 2008,³ though the authors were unable to find specific reasons behind its closure despite reaching out to experts in Singapore. Nearly a decade later, the Gender Care Clinic at the Institute of Mental Health (IMH) was established in 2017, which provided gender-affirming mental healthcare with multidisciplinary support.² Based on information available to the authors, this clinic, however, is no longer being run. Based on correspondence, at least 2 restructured hospitals in Singapore now offer formal multidisciplinary gender-focused mental healthcare services, with access to these services via referrals from primary, secondary and tertiary care providers. These services have also created coordinated care pathways with relevant subspecialties such as endocrinology and surgical disciplines. Efforts have also been made in community outreach initiatives, to improve the knowledge of gender care among community partners, primary and secondary care providers.

However, a proportion of referrals still remain unmet, as access to these services is limited by specified

criteria, including service boundaries. Differences in multidisciplinary team structures and institutional workflows can lead to uneven care pathways, contributing to delays and uncertainty for both clinicians and patients. Although there are ongoing efforts among some institutions to streamline and align processes, such collaboration has yet to occur at a national level. Transgender individuals may also turn to a limited number of private care providers with an interest in gender-focused mental healthcare. However, costs may be higher with limited access; most, if not all, private insurers in Singapore do not cover gender dysphoria or transition-related costs,⁴ which leads to increased individual costs.

Quality transgender mental healthcare should include specialists and allied health professionals (e.g. psychotherapists, social workers, peer navigators) trained to address gender-specific issues in an environment that is gender-inclusive.⁵ Currently, no formal fellowship training programmes in gender-focused mental healthcare are available in Singapore for interested medical professionals. However, there is informal sensitivity training provided by community organisations such as Oogachaga.⁶

A recent Singapore study highlighted significant gaps in LGBTQI+-related knowledge and preparedness among clinical-year medical students, suggesting that insufficient training may play a role in the stigma observed in healthcare.⁷ To better serve the transgender community, specific education modules on gender care and sensitivity can be integrated into existing medical school curriculums to ensure that all healthcare professionals are equipped to handle the general healthcare needs of transgender individuals. Regular continuing medical education (CME) activities on gender-focused mental healthcare can aid in improving the capabilities of healthcare providers to deliver value-based healthcare. Formal training in Singapore via postgraduate diplomas or certification in specific areas of such care for medical or allied health professionals may also aid the confidence of both healthcare providers and patients for such services. This area

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Accepted: 24 December 2025

Published Online First: 4 February 2026

of care would also benefit from interprofessional education initiatives given the multidisciplinary nature of care and the need for synchronised, coordinated care between all professionals involved. This could involve the inclusion of peer support specialists who have rich lived experiences.

With these training and education efforts, primary and secondary care providers should become more comfortable managing the healthcare needs of transgender individuals. More complex cases requiring a second opinion or trained multidisciplinary support could then be referred to specialised gender care services which provide not only coordinated care, but also aid the transition of patients back to primary or secondary care. These specialised services should provide streamlined, multidisciplinary diagnostic services—including psychological assessments to certify fitness for medical transitioning (i.e. diagnostic aspect) and support the coordination of medical, psychiatric and psychosocial care for patients and their families (i.e. treatment aspect). Although gender-focused mental health services are already embedded within the public healthcare framework, opportunities remain to further develop their integration and to improve coordinated care pathways on a national level, with key surgical and endocrinological services. This may also aid the existing public healthcare system to more closely collaborate with the network of community partners that serve transgender individuals. Collaboration across public healthcare institutions would likewise promote research development, helping to advance evidence-based practices and elevate the quality of care.

Given that the mental health aspects of gender care are closely linked with the stress of social and medical transitioning,² it is essential to address these issues in a sensitive manner. Given the cultural context in Singapore, social transitioning can carry significant risks, including potential rejection, discrimination and alienation from family and community.⁸ While gender-affirming hormone therapy is comparatively accessible in Singapore, most providers seem more comfortable with a prior psychiatric assessment, following a mental health assessment model rather than an informed consent approach. This process can often be time-consuming. It has been reported that there are individuals who obtain hormones from sources outside the formal healthcare system, particularly among those who lack support and are keen to begin the process.⁴ Addressing these issues, along with other social determinants of health, requires a concerted effort by all stakeholders involved.

By prioritising the mental health and well-being of transgender individuals with a nuanced but systemic

approach, Singapore can further accelerate inclusivity efforts and ensure a sustainable ecosystem encompassing both healthcare systems and social support networks that respect and affirm diverse gender identities.

Acknowledgment

We thank Drs Ganesh Kudva Kundadak and Edmund Chong Xiu Ming (National University Hospital) and Drs Andre Tay Teck Sng, Thomas King and Arvind Rajagopalan (Changi General Hospital) for their valuable input, which contributed meaningfully to the development of this letter.

Ethics statement

No patient data was used in the development of this manuscript.

Declaration

All authors declare they have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

Keywords: *gender dysphoria, mental health, psychiatry, Singapore, transgender*

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Comparison of severe adenovirus infections pre- versus post-COVID-19 pandemic and predictors of mortality in children

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Dear Editor,

Adenovirus (AdV) infections can result in significant mortality and morbidity in children.¹⁻⁵ Severe AdV infections in Singapore were reported from 2013 to 2017, where significant morbidity was observed.¹ A surge in AdV pediatric admissions occurred in 2023 post-COVID-19 pandemic at KK Women's and Children's Hospital, Singapore. This study compared severe AdV cases in children 0–18 years admitted to intensive care units (ICUs) and high dependency (HD) units in 2023 to those from 2013 to 2017.¹ Serotype-specific differences and predictors of mortality across both periods were also investigated.

AdV was detected in respiratory samples using multiplex polymerase chain reaction (PCR) (BioFire FilmArray, France) in 2023 or by immunofluorescence antigen detection (D3 Double Duet, Diagnostic Hybrids, US) or multiplex PCR (Seeplex RV15 kit, Seegene, South Korea) in 2013–2017. Serotype analysis was performed by National Public Health Laboratory, Singapore using sequence comparison of a ~750 base pair segment containing hexon gene hypervariable regions 1–6.⁶ Comparison of cases involving serotypes C1, C2, B3 and B7 was performed, as these serotypes had >20 cases each and were pooled across the study periods. Viraemia testing was performed at physician's discretion and defined as AdV detected in blood using real-time PCR (in-house protocol).

Clinical and microbiologic data were extracted from electronic medical records. Cidofovir treatment was determined by paediatric infectious disease physicians, based on the patient's clinical course and/or AdV-related complications.

Statistical analyses were performed using SPSS version 28 (IBM, Corp, Armonk, NY, US). Categorical and continuous variables were compared using chi-squared/Fisher's Exact tests or Student's t-test/one-way analysis of variance, respectively. $P < 0.05$ was considered statistically significant. Variables with $P < 0.05$ for mortality from univariate analysis

were included in the model for multivariate logistic regression by backward conditional method.

In 2023, a total of 5037 AdV-positive admissions occurred from January to September, of which 195 (3.9%) were admitted to ICU/HD (Supplementary Fig. S1). Admissions peaked between weeks 5–21, mainly in March 2023. In contrast, in 2013–2017, 1167 AdV-positive admissions occurred, of which 85 (7.3%) were admitted to ICU/HD. Severe cases were proportionately higher in 2013–2017 compared to 2023 ($P < 0.001$). Supplementary Fig. S2 shows the trends in AdV admissions per 1000 total admissions and the total respiratory specimens (majority are nasopharyngeal swabs) sent per 1000 total admissions, demonstrating the surge in 2023. The total respiratory specimens sent is a proxy to total respiratory illnesses, which translates to 710.6–768.3 per 1000 admissions in 2013–2017 and 792.8–923.8 per 1000 admissions in 2022–2023 (Supplementary Table S1).

Of the pooled 280 (195 in 2023, 85 in 2013–2017) severe cases identified, 60% were male with a median age of 1.9 years (interquartile [IQR] 0.8–4.6). Patients in 2023 were less likely to have prematurity, co-morbidity and immunodeficiency versus (vs) those in 2013–2017 (Table 1). In 2023, there were more seizure presentations, fewer gastrointestinal/liver manifestations and no conjunctivitis vs those reported in 2013–2017. In 2023, there were more co-infections, less AdV viraemia, shorter length of stay (LOS), less cidofovir usage and fewer deaths. The majority of patients who received cidofovir only needed 1–2 doses (17/26, 65.4%).

Across both periods, there were 173 (61.8%) co-infections (viral and/or non-viral co-infections) of which viruses ($n=149$, 86.1%) dominated, followed by bacteria ($n=15$, 8.7%), mixed ($n=7$, 4.0%) and fungal ($n=2$, 1.2%) coinfections. Viral co-infections were more common in 2023 as compared to 2013–2017. Among the 154 co-infections with any virus, rhinovirus/enterovirus was the most common (52.6%, $n=81$),

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Accepted: 7 January 2026

Published Online First: 10 February 2026

Table 1. Comparison of severe adenovirus admissions to ICU/HD in 2023 vs 2013–2017.

Characteristic	Overall n=280 (%)	2023 n=195 (%)	2013–2017 n=85 (%)	P value	OR (95% CI) ^a
Median age, years (IQR)	1.9 (0.8–4.6)	2.0 (0.8–5.0)	1.6 (0.7–3.2)	ns	
Male sex	168 (60.0)	117 (60.0)	51 (60)	ns	
Non-Chinese	155 (55.4)	117 (60.0)	38 (44.7)	0.02	1.9 (1.1–3.1)
Prematurity	40 (14.3)	19 (9.7)	21 (24.7)	<0.001	0.3 (0.2–0.7)
Significant co-morbidity	179 (63.9)	114 (58.5)	65 (76.5)	0.004	0.4 (0.2–0.8)
Cardiac co-morbidity ^b	30 (10.7)	20 (10.2)	10 (11.8%)	ns	
Pulmonary co-morbidity ^c	83 (29.5)	52 (26.5)	31 (36.5)	ns	
Neurologic co-morbidity ^d	58 (20.7)	35 (17.9)	23 (27.1)	ns	
Metabolic co-morbidity ^e	10 (3.6)	5 (2.6)	5 (5.9)	ns	
Genetic co-morbidity ^f	33 (11.8)	19 (9.7)	14 (16.5)	ns	
Immunodeficiency ^g	16 (5.7)	7 (3.6)	9 (10.6)	0.02	0.3 (0.1–0.6)
Clinical presentation					
Respiratory presentation	228 (81.4)	170 (87.2)	58 (68.2)	<0.001	3.2 (1.7–5.9)
Upper respiratory infection	40 (14.3)	30 (15.4)	10 (11.8)	ns	
Bronchiolitis/bronchitis	60 (21.4)	46 (23.5)	14 (16.5)	ns	
Pneumonia	98 (35.0)	65 (33.3)	33 (38.8)	ns	
Seizures	37 (13.2)	31 (15.8)	6 (7.1)	0.045	2.5 (0.9–6.2)
Neurologic presentation ^h	47 (16.8)	38 (19.5)	9 (10.6)	ns	
Gastrointestinal/liver presentation	32 (11.4)	17 (8.7)	15 (17.6)	0.03	0.5 (0.2–0.9)
Conjunctivitis	15 (5.3)	0	15 (17.6)	<0.001	0.3 (0.2–0.3)
Adv viraemia	21 (7.5)	10 (5.1)	11 (12.9)	0.022	0.4 (0.2–0.9)
Co-infections	173 (61.8)	152 (77.9)	21 (24.7)	<0.001	10.8 (5.9–19.6)
Viral co-infections	147 (52.5)	140 (71.8)	7 (8.2)	<0.001	28.4 (12.3–65.3)
Cidofovir usage	26 (9.3)	8 (4.1)	18 (21.2)	<0.001	0.2 (0.1–0.4)
ICU admission	119 (42.5)	64 (32.8)	55 (64.7)	<0.001	0.3 (0.2–0.5)
Median LOS, days	7.0 (4–19)	6.0 (3.0–9.0)	19.0 (9.5–55.5)	<0.001	
Deaths	18 (6.4)	5 (2.6)	13 (15.3)	<0.001	0.15 (0.05–0.42)
Serotype B3	95 (33.9)	72 (36.9)	23 (27.1)	ns	
Serotype B7	14 (5.0)	0	14 (16.5)	<0.001	0.3 (0.2–0.3)

CI: confidence interval; HD: high dependency; ICU: intensive care unit; IQR: interquartile range; LOS: length of stay; OR: odds ratio;

ns: not significant

^a Odds ratio for 2023 versus 2013–2016, (95% CI)^b Cardiac co-morbidity included congenital cardiac defects, arrhythmias, coronary abnormalities and cardiomyopathy.^c Pulmonary co-morbidity included asthma, chronic lung disease, laryngomalacia, obstructive sleep apnoea, bronchiectasis, structural anomalies and pulmonary haemosiderosis.^d Neurologic co-morbidity included cerebral palsy, epilepsy, structural brain malformations, myopathies/neuropathies, spinal cord disorders, traumatic brain injury, brain tumours and neurodevelopmental disorders.^e Metabolic co-morbidity included endocrine abnormalities, metabolic syndrome with obesity and amino aciduria.^f Genetic co-morbidity included genetically inherited disorders and chromosomal disorders.^g Immunodeficiency included inborn errors of immunity, hematologic malignancy, stem cell transplant and solid organ tumours on chemotherapy.^h Neurologic presentation (e.g. encephalitis, encephalopathy, seizures, delirium)

followed by respiratory syncytial virus (31.8%, n=49), parainfluenza (17.5%, n=27), influenza virus (10.4%, n=16) and ≥ 2 other viruses (26.0%, n=40).

Cidofovir was more likely to be administered in pneumonia patients (18/98, 18.4% vs no pneumonia 8/181, 4.4%; odds ratio [OR] 4.8, 95% confidence interval [CI] 2.0–11.5, $P < 0.001$) or viraemia (18/21, 75% vs 8/259, 3.1%; OR 188.3, 95% CI 45.9–771.4, $P < 0.001$), immunodeficiency co-morbidity (6/17, 35.3% vs 20/264, 7.5%; OR 6.6, 95% CI 2.2–20.0, $P < 0.001$) and haematologic co-morbidity (5/14, 35.7% vs 21/266, 7.9%; OR 6.5, 95% CI 2.0–21.1, $P < 0.001$).

Serotyping was performed for 189 (67.5%) isolates; 114 (60.3%) in 2023 and 75 (39.7%) for 2013–2017. The 2023 outbreak was largely driven by serotype B3 (63.2%), followed by C2 (16.7%) and C1 (15.8%) (Supplementary Fig. S3). From 2013 to 2017, serotype B7 (33.3%) was the main serotype, followed by B3 (30.7%) and D8 (18.7%). AdV B7 (n=25) had the highest rates of pneumonia, viraemia, cidofovir usage, ICU/HD admissions, LOS, deaths and sequelae vs serotypes C1 (n=22), C2 (n=23) and B3 (n=95). AdV B3 had the highest rates of bronchiolitis/bronchitis cases compared with other serotypes. Serotype C2 was associated with the highest rates of gastrointestinal/liver presentation, followed by B7.

Mortality rate among severe cases was lower in 2023 (2.6%) vs 2013–2017 (15.3%). When comparing decedents vs survivors by univariate analysis, neurologic co-morbidity (OR 4.4, 95% CI 1.6–11.5), genetic co-morbidity (OR 3.2, 95% CI 1.1–9.7) and presence of pneumonia (OR 3.1, 95% CI 1.2–8.3) were associated with mortality. AdV B3 cases (OR 0.1, 95% CI 0.01–0.8) and viral co-infections (OR 0.2, 95% CI 0.05–0.6) were associated with decreased mortality. Multivariate logistic regression showed that predictors of mortality were neurologic co-morbidity (adjusted OR [aOR] 3.6, 95% CI 1.2–10.6, $P = 0.005$) and presence of pneumonia (aOR 3.9, 95% CI 1.4–11.5, $P = 0.012$). After adjustment, lower odds of mortality were associated with serotype B3 (aOR 0.1, 95% CI 0.01–0.6, $P = 0.017$) and viral co-infections (aOR 0.2, 95% CI 0.05–0.7, $P = 0.011$). Neurological co-morbidity has been found to be a risk factor for death or severe disease in several studies of AdV and influenza infections admitted to paediatric ICU.^{7,8}

While the epidemic in 2023 was less severe, it still led to a huge surge in admissions (up to 270 admissions per week) in the first 22 weeks of 2023 and a significant utilisation of ICU/HD beds. Globally, AdV B3 is among the most common serotype in children and has been associated with epidemic infections.^{2,4,9} In contrast

to B3, serotype B7 has been associated with more severe clinical illness and mortality in children.^{4,5,10} In a study from Taiwan, AdV B7 vs B3 had a mortality rate of 2.1% vs 0%, respectively, and ICU admission rate of 7.8% vs 1.9% ICU, respectively.⁸ The reasons for the resurgence of AdV post-COVID-19 pandemic are likely to be multifactorial due to the lack of exposure and therefore absence of immunity, higher infectiousness and lower virulence for AdV.¹¹

A key limitation of this retrospective study is its primary focus on severe cases only. Serotype testing was only performed among severe cases and on suitable available samples. However, serotyping results of AdV isolates were not available in a clinically action-able timeframe and therefore was unlikely to influence clinical management and outcome. Another limitation is the change in the testing methods (using Biofires multiplex PCR from 2020 onwards compared to mainly immunofluorescence and limited Seeplex PCR testing in 2013–2017) and change in the clinical practices of sending respiratory swabs in 2023 compared to 2013–2017 (given the increase in swabs sent, which are even higher than the respiratory admissions according to top 97 diagnosis codes). However, with the rise in respiratory admissions using top 97 respiratory infection diagnosis codes from 2013 to 2017 vs 2023 (Supplementary Tables S1 and S2), it may reflect that the number of ADV cases had indeed increased in 2023; nevertheless, it is assuring that the proportion of severe cases is lower in 2023 vs in 2013–2017 (Table 1).

This study showed decreased AdV severity during the 2023 outbreak vs in 2013–2017, presumably due to the predominantly serotype B3. Future AdV serotyping during an outbreak can help predict severity of illness and healthcare utilisation. Future vaccines targeting multiple serotypes would be needed to reduce AdV burden in paediatrics.

Supplementary materials

Fig. S1. Hospitalised adenovirus: Weekly numbers of cases requiring ICU care & HD care.

Fig. S2. Trends in total admissions, AdV admissions and total respiratory specimens sent per 1000 total admissions.

Fig. S3. Serotypes of Adenovirus isolates by year.

Table S1. Comparison of total admissions, respiratory admissions (in top 97 respiratory DRG diagnosis codes), total respiratory specimens sent and total AdV positivity over time.

Table S2. Top 97 respiratory infection diagnosis codes.

Ethics statement

The principal investigator has declared that this article is a quality assurance/service improvement project that involved the use of anonymised/de-identified data and therefore does not require CIRB review. This exemption has been reviewed and agreed upon by senior management at KK Research Centre, KK Women's and Children's Hospital, Singapore (28/04/2025).

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Keywords: adenovirus, children, ICU, infectious diseases, outbreak, serotype, severe

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Lived experiences of chronic pain patients in Singapore: A qualitative perspective

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Dear Editor,

Chronic pain, defined as persistent or recurrent pain lasting more than 3 months,¹ is a global public health concern with significant physical, psychological and social implications. In Singapore, it affects at least 8.7% of the population—a number expected to rise due to the country's rapidly ageing demographic.² Despite this, most existing qualitative studies that examine the lived experience of chronic pain are conducted in Western settings.³ Cultural and contextual factors, however, strongly shape how individuals perceive, cope with and seek care for chronic pain. Our study aims to fill this gap by exploring the experiences of chronic pain patients in Singapore and uncovering the unique challenges they face within this setting.

We conducted 18 in-depth, semi-structured interviews with patients receiving outpatient care at a pain management clinic in Changi General Hospital, Singapore. Using thematic analysis, we identified 3 interconnected themes that characterise their journeys: (1) a sense of losing control; (2) challenges in seeking care; and (3) the pursuit of normalcy through personal and social coping mechanisms.

Participants frequently described their chronic pain as debilitating and life-altering. Physically, many experienced disturbed sleep, reduced mobility and impaired function. Simple tasks such as walking, climbing stairs or completing household chores became increasingly difficult. These physical limitations contributed to a disrupted sense of normalcy and routine.

Psychologically, participants described feelings of hopelessness, frustration and in some cases, anger. Despite trying multiple treatments or consulting various healthcare professionals, many still found little relief. One participant expressed despair, saying, "I go here, I go there, and the pain is still there." Emotional exhaustion and irritability often strained relationships with loved ones, creating further

isolation. The constant cycle of pain and failed attempts at relief led many to feel as though their condition was inescapable and out of their control.

The second theme reflects structural and interpersonal barriers encountered in the healthcare system. Many participants perceived their providers as apathetic or dismissive. They felt their symptoms were often misunderstood, minimised or attributed to psychosomatic causes. In some cases, patients believed that providers had given up on them, which compounded feelings of helplessness and disempowerment.

Access to appropriate care was another major challenge. Participants described having to navigate multiple referrals across specialists, long waiting times for appointments, and high out-of-pocket costs for non-subsidised treatments like physiotherapy and psychotherapy. For those experiencing significant daily disruption from pain, delays of several months were not only inconvenient but deeply detrimental to quality of life.

Pain medication was often viewed as a double-edged sword. While helpful for temporary relief, many participants expressed concerns about dependency or long-term side effects. Psychological services were also met with hesitation; some viewed therapy as unnecessary unless one was severely depressed, while others expressed stigma-related fears. In Asian societies like Singapore, seeking psychotherapy is sometimes seen as a weakness or moral failing, further discouraging patients from accessing these essential services.

Moreover, Singapore faces a significant shortage of pain psychologists. Even when patients are willing to engage in therapy, limited availability and long wait times make it difficult to receive timely care. These findings point to the need for greater integration of psychological support within pain management services, alongside broader public efforts to reduce mental health stigma.

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Accepted: 19 January 2026

Published Online First: 23 January 2026

Despite these obstacles, participants demonstrated remarkable resilience. Many described a process of psychological adaptation—coming to terms with the idea that pain may be a lifelong companion. Acceptance did not equate to resignation; instead, it marked a turning point that allowed them to refocus on what they could control. This process involved multiple facets of adaptation, which we elaborate in the following paragraphs.

Most of the participants reported engaging in various coping strategies, including exercise, mindfulness, and traditional therapies such as acupuncture and traditional Chinese medicine. Some adopted positive cognitive reframing, shifting their mindset toward hope and self-compassion. “You start to realise that no one is going to understand you. So, you don’t try to change them—you try to change yourself,” one participant reflected.

Social support was another key pillar. Family members, friends and even empathetic healthcare providers played crucial roles in buffering the psychological burden of chronic pain. Patients who felt heard and understood by their doctors described feeling more optimistic and confident in their ability to cope. One participant described their relief when a doctor took the time to thoroughly examine and listen to them, saying it made them feel “not alone” and “hopeful.”

Our findings underscore the need for a holistic, culturally sensitive and community-based approach to chronic pain management. While tertiary care institutions in Singapore remain overburdened, equipping primary care providers with pain management skills could reduce unnecessary specialist referrals and wait times. To succeed, such training must be supported by appropriate clinical workflows, administrative resources and sufficient manpower allocation. Community-based care also fosters continuity and accessibility, which are critical for managing a long-term condition like chronic pain.

Furthermore, culturally competent care must include attention to indirect expressions of distress. In collectivist cultures like Singapore, patients may downplay symptoms to avoid burdening others or being perceived as weak. Healthcare providers should be trained to recognise these nuances, and engage patients with empathy and cultural awareness.

Efforts to reduce stigma surrounding psychological care are essential.⁴⁻⁶ Public health messaging can normalise psychotherapy as part of comprehensive pain care. At the same time, investing in the training and recruitment of pain psychologists will be vital to expanding access.

This study offers valuable insights into the lived experiences of chronic pain patients in Singapore, capturing their struggles, resilience and calls for change. The themes of losing control, struggling with healthcare systems and rebuilding a sense of normalcy reveal the deep biopsychosocial toll of chronic pain—and ultimately, the pressing need for reform. These patient voices remind us that effective chronic pain care must extend beyond the clinical lens to encompass the cultural, emotional and relational dimensions of suffering. Future policies must integrate these perspectives to deliver equitable, empathetic and enduring solutions.

Ethics statement

The study was approved by the SingHealth Centralised Institutional Review Board (2021-2103), Singapore. All patients provided written informed consent prior to study enrolment.

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript. This study was supported financially by a research grant (COCHFNN2001) from Changi General Hospital, Singapore, awarded to LWL.

Patient and public involvement statement

Patients and the public were not involved in the design, conceptualisation or conduct of this study. However, the research team is committed to ensuring that the findings are accessible and meaningful to the patient community. A dissemination strategy has been developed to share the results with relevant patient groups, including presentations and online summaries tailored for a lay audience. The team will also seek feedback on how these findings can inform future research and practice.

Acknowledgements

The authors thank the assistance of the staff in Changi General Hospital, Anaesthesia Department, Chronic Pain Team, Research Office, Health Services Research and Innovation Office. Special thanks to Ms Geraldine Lim Xiuping, Ms Brenda Shak Siew Hui and Ms Kang Ming Lei for their assistance during patient recruitment and transcription of audio transcripts.

Keywords: *biopsychosocial impact, chronic pain, culturally sensitive care, pain management, patient experience*

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