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2025 Singapore consensus statements on the management of osteoporosis

Eighty new consensus statements integrate the latest clinical evidence with practical considerations for the management of osteoporosis in Singapore. (See full article, p. 252)

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Integrating inflammation and nutritional status: Monocyte-to-albumin ratio as a novel prognostic marker in nasopharyngeal cancer

Mark Kit Lim¹ MRCSEd, Tze Choong Charn² MMED (Otorhinolaryngology), Boon Huat Bay³ PhD

Nasopharyngeal cancer (NPC) is a prominent head and neck cancer, with a multifactorial aetiology that includes Epstein-Barr virus (EBV) infection, genetic susceptibility, and environmental exposures. Notably, the incidence of NPC is expected to show an approximately 35% increase in new cases (from 133,354 cases to 179,476 cases) and an approximately 42% increase in NPC-related deaths (from 80,008 deaths to 113,851 deaths) from 2020 to 2040.¹ NPC has a striking geographic predilection, with the highest number of NPC cases and deaths occurring in East Asia and Southeast Asia.¹ Interestingly, the American Association for Cancer Research has designated April as the Head and Neck Cancer Awareness Month, although NPC, which belongs to this group of cancers, is not as prevalent in the West. The high proportion of NPC cases presenting at a locally advanced stage, estimated at approximately 70%,² underscores the need to identify strategies that can enhance the therapeutic effectiveness of contemporary treatments, such as concurrent chemoradiotherapy (CCRT). For recurrent and metastatic diseases, the treatment modalities include induction chemotherapy with gemcitabine-cisplatin, and immunotherapy with immune-checkpoint inhibitors (specifically toripalimab and camrelizumab), with plasma EBV-DNA levels guiding the monitoring of treatment response and recurrence.³ One effective approach to risk stratification and treatment optimisation is the use of prognostic biomarkers.

The study by Ni et al.,⁴ which highlights the monocyte-to-albumin ratio (MAR) for prognostication in NPC patients, is thus timely. In this study, the authors reported that pretreatment MAR was an independent prognostic marker in NPC patients who had undergone CCRT. This retrospective cohort study included 860 eligible patients treated between 2010 and 2014, who met the inclusion criteria of having newly diagnosed non-metastatic NPC with no history of other cancers or inflammatory conditions. All patients received CCRT (comprising radical intensity-modulated radiation therapy and platinum-based chemotherapy either weekly or every 3 weeks), and

had pretreatment EBV-DNA assessment. The cohort was categorised into 2 groups, a high-MAR group and a low-MAR group, based on a maximum selection log-rank statistic-derived cut-off. NPC patients in the low-MAR group had a significantly higher overall survival rate than those in the high-MAR group. Additionally, multivariate analysis identified tumour stage, age, nodal stage, body mass index, and MAR as independent prognostic factors for overall survival in NPC patients. They subsequently developed a new nomogram-based prognostic model that incorporated MAR, along with the other identified independent prognostic variables, to predict overall survival in NPC patients. It is worth noting that the prognostic performance of MAR in immunotherapy-treated NPC remains unknown because the study predated the use of immunotherapy.

Considering that the study by Ni et al.⁴ evaluated the prognostic value of integrating inflammation and nutritional markers, what is the underlying rationale for these factors in influencing the outcomes of NPC patients following CCRT? Since Stephen Paget's seminal paper on the cooperation between tumour cells (which he called "seed") and the organ microenvironment (which he named "soil"),⁵ known as the "seed and soil" hypothesis, the tumour microenvironment (TME) has gained much attention for its role in tumour progression and metastasis.⁶ The TME in NPC is a dynamic and complex network of tumour-associated cells, including tumour-infiltrating immune cells, cancer-associated fibroblasts, and tumour endothelial cells, as well as non-cellular components such as the extracellular matrix, chemokines, cytokines, and metabolites, which interact closely to shape tumour development and progression.⁶ The immune landscape of NPC, which is generally closely associated with EBV infection, contains both anti-tumour immune cells (including cytotoxic T lymphocytes, natural killer cells, and M1-like macrophages) and immunosuppressive cells that facilitate tumourigenesis (including regulatory T lymphocytes, myeloid-derived suppressor cells, and M2-like macrophages).^{6,7} Tumour-associated

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macrophages (TAMs) are abundant in the TME, and undifferentiated M0 macrophages can differentiate into anti-tumour cytotoxic M1-like macrophages or immunosuppressive M2-like macrophages.^{6,7} As TAMs are recruited from circulating monocytes that infiltrate tumour tissue through chemotactic factors,⁷ peripheral blood monocytes may serve as an easily accessible surrogate marker for TAMs within the TME.

Apart from monocyte counts, the other variable in the MAR index is albumin, a functional protein synthesised by the liver, an organ that is essential to the systemic inflammatory response. Albumin is a marker of nutrition and is a negative acute-phase reactant that decreases in inflammation. In the context of systemic inflammation, hepatic synthesis of albumin is downregulated and catabolic loss is increased through capillary leak. Therefore, albumin levels may reflect both malnutrition and persistent systemic inflammation driven by active malignancy.⁸ A decline in albumin levels has also been shown in studies to confer a poorer survival prognosis in NPC patients,⁹ thus aligning with the findings of Ni et al.⁴ Furthermore, Fang et al.¹⁰ identified albumin, monocyte count, and the systemic immune-inflammation index (platelet $\times$ neutrophil / lymphocyte) as independent prognostic factors for overall survival in non-metastatic NPC, which, when combined into an Inflammation Nutrition Risk Score, had predictive value similar to that of established prognostic tools, including TNM staging and EBV-DNA levels.

Thus far, genetic mutations, including *TP53* mutations and microRNA expression levels, have been found to correlate with disease prognosis and progression in NPC patients.¹¹ However, to date, only the plasma EBV-DNA levels in NPC patients have been translated into clinical practice.^{12,13} As reported by Ni et al.,⁴ integrating inflammatory and nutritional indicators may have significant potential for predicting disease outcomes in NPC patients. Wider adoption of this composite index could lead to pretreatment optimisation of nutritional status to improve survival outcomes in NPC patients. It is also imperative that cross-laboratory and cross-population standardisation of MAR units and cut-offs, as is applicable to all other inflammation indices, be completed before clinical adoption.

Beyond NPC, the MAR, combined with neutrophil percentage-to-haemoglobin ratio and carcinoembryonic antigen, has also been reported to be effective in detecting non-small cell lung cancer (NSCLC).⁸ Hence, MAR has also been explored as a diagnostic discriminator in NSCLC, suggesting biological relevance beyond NPC. Thus, prognostic validation in other cancers remains limited. In the future, the prognos-

tic utility of MAR should be further investigated across other cancer types.

Ethics statement

Not applicable, as no study participants were recruited.

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.

Keywords: cancer, chemoradiotherapy, otorhinolaryngology, pathology, prognosis

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Prognostic value of the monocyte-to-albumin ratio in nasopharyngeal carcinoma: A retrospective cohort study

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ABSTRACT

Introduction: Although monocyte and albumin levels have been associated with survival in various malignant tumours, their specific prognostic significance in nasopharyngeal carcinoma (NPC) remains under-explored. This study seeks to examine the relationship between the monocyte-to-albumin ratio (MAR) and overall survival (OS) in NPC patients to create a precise prediction model.

Methods: The authors retrospectively analysed data from 860 NPC patients who underwent concurrent chemoradiotherapy. The optimal cut-off for MAR was determined using the maximum selection log-rank method. Univariate and multivariate Cox proportional hazards models were applied to identify factors significantly related to OS. A predictive nomogram was then developed and rigorously validated for its accuracy.

Results: The optimal MAR threshold was determined to be 11.63, effectively categorising the 860 NPC patients into 2 prognostic subgroups (hazard ratio 0.56; 95% confidence interval [CI] 0.41–0.77, $P < 0.001$). The predictive nomogram exhibited strong predictive capability for OS, factoring in T stage, N stage, MAR value, body mass index, and age over 45 years. The concordance index (C-index) of the traditional tumour–node–metastasis staging system was found to be 0.64 (95% CI 0.57–0.70), which was less than the C-index of the nomogram (0.68; 95% CI 0.64–0.72) for OS.

Conclusion: MAR was identified as an innovative and independent prognostic factor in NPC patients, presenting a potential biomarker for personalised treatment strategies.

Keywords: concurrent chemoradiotherapy, monocyte-to-albumin ratio, nasopharyngeal carcinoma, nomogram, prognosis

CLINICAL IMPACT

What is New

- The monocyte-to-albumin ratio (MAR) is identified as a novel, independent prognostic biomarker for nasopharyngeal carcinoma (NPC).
- MAR uniquely reflects the combined burden of tumour-promoting inflammation (e.g. tumour-associated macrophage infiltration) and systemic malnutrition.

Clinical Implications

- As a readily accessible and cost-effective blood-based index, MAR facilitates early and precise risk stratification in clinical practice.
- Integrating MAR into routine pretreatment assessments can help optimise therapeutic strategies and improve long-term surveillance for NPC patients.

INTRODUCTION

The incidence of nasopharyngeal carcinoma (NPC) is notably elevated in southern China, North Africa, and Southeast Asia (up to 35 cases per 100,000 inhabitants), revealing significant geographical disparities.¹ Approximately 70% of NPC patients are diagnosed with locally advanced disease, contributing to an estimated 80,000 deaths annually from this malignancy worldwide.² The tumour–node–metastasis (TNM) staging system is a cornerstone for forecasting

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prognosis and informing treatment approaches in NPC.¹ Concurrent chemoradiotherapy (CCRT) is recognised as the standard treatment for locally advanced NPC.^{1,3} Nonetheless, notable variability in prognosis exists among patients even when categorised under the same TNM staging and treatment modalities.^{4,5} This discrepancy underscores the limitations of the TNM system in capturing the biological diversity inherent in NPC.

Recent research emphasises the critical interplay between the tumour microenvironment (TME) and immune responses, alongside the influence of nutritional and metabolic conditions on tumour advancement and metastasis.⁶⁻⁸ Current investigations have indicated that indicators reflecting inflammation and nutritional status significantly affect the prognosis of various malignancies, including NPC. Specifically, systemic inflammatory responses can drive tumour metastasis by promoting angiogenesis and preventing cellular apoptosis. Furthermore, nutritional deficits that are often reflected by low haemoglobin levels can lead to tumour hypoxia, which further accelerates angiogenesis and worsens the patient's prognosis. Metrics such as the ratios of inflammatory markers (e.g. neutrophils, lymphocytes, platelets, and C-reactive protein) and nutritional status indicators (e.g. controlled nutritional status and prognostic nutritional index) have been investigated extensively.⁹⁻¹¹ Composite indicators that amalgamate these parameters have proven to be more effective in tumour diagnosis and prognosis than single indicators.¹² Consequently, researchers are increasingly focusing on composite biomarkers that fuse inflammation and nutritional aspects for improved risk stratification among NPC patients. The monocyte-to-albumin ratio (MAR) represents such a composite index, integrating inflammatory markers with nutritional parameters to provide insights into a patient's systemic inflammatory state and nutritional health.¹³ In many cancers, monocytes that infiltrate tumour tissues can differentiate into tumour-associated macrophages (TAMs), which constitute a crucial component of TME.¹⁴ These TAMs generally polarise into 2 distinct subtypes: M1-like and M2-like TAMs. Notably, the M2-like TAMs play a critical role in promoting malignant metastasis, invasion, and treatment resistance.¹⁵ Therefore, peripheral monocyte levels offer a practical reflection of the systemic TAM burden. By specifically utilising monocytes rather than overall leukocyte counts, MAR highlights the crucial intersection of TAM-driven tumour-promoting inflammation and cancer-related malnutrition. However, studies examining the significance of MAR in NPC are still limited.

This research aims to investigate the correlation between pre-treatment MAR levels and the prognosis of NPC patients receiving CCRT.

METHODS

Patients

This retrospective analysis included 860 patients with histologically confirmed NPC who received treatment at Sun Yat-sen University Cancer Center between January 2010 and December 2014. Inclusion criteria were as follows: (1) imaging and histological evaluations confirmed untreated, non-metastatic NPC; (2) no history of other tumours or inflammatory conditions; (3) treatment via radical intensity-modulated radiation therapy (IMRT); (4) platinum-based concurrent chemotherapy administered during IMRT, either weekly or every 3 weeks; (5) peripheral blood tests and Epstein-Barr virus (EBV) DNA assessments specific to NPC completed prior to treatment. All patients were staged according to the 8th American Joint Committee on Cancer TNM staging system. This study was approved by Sun Yat-sen University Cancer Center's Ethics Committee (SL-B2023-537-01), which waived the necessity for written informed consent. All procedures were conducted in compliance with the principles outlined in the 1964 Helsinki Declaration and its amendments. Medical histories, imaging data, and pathological reports were reviewed to extract data within 7 days following diagnosis. Treatment protocols and follow-up routines adhered to established guidelines. Patients were stratified into 3 body mass index (BMI) categories: <24, 24–27.9, ≥28 kg/m². MAR was defined as the ratio of monocyte counts (number/mm³) to albumin levels (g/L).^{16,17}

Statistical analysis method

Sample size calculation was not performed due to a lack of prior data to justify the establishment of prognostic models. Of the 860 enrolled participants, 174 events were documented during the follow-up, ensuring that in the multivariate model, a minimum of 10 events per variable was maintained for adequate evaluative capacity.¹⁸ MaxStat R package (by Torsten Hothorn) along with the Kaplan-Meier method was utilised to identify the optimal cut-off value and develop survival curves, followed by a log-rank test.¹⁹ The proportional hazards assumption was evaluated using Schoenfeld residual analysis. Only variables with a *P* value of <0.10 in the univariate analysis were included in the multivariate Cox model. A nomogram was subsequently constructed based on the findings from the multivariate analysis.

The efficacy of the nomogram was evaluated using calibration curves, the concordance index (C-index), and the area under the curve (AUC) through time-dependent receiver operating characteristic (ROC) analysis. Statistical significance was established

at a 2-sided $P < 0.10$. All statistical computations were performed using R software version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient characteristics

Table 1 outlines the baseline characteristics of the 860 NPC patients included in this study at Sun Yat-sen University Cancer Center. The median age of the participants was 45 years (range: 18–84 years), with 423 patients (49.2%) older than 45 years and 437 patients (50.8%) aged 45 years or younger. The majority were male (639 cases, 74.3%), while females constituted approximately one-quarter of those studied (221 cases, 25.7%). Most patients were diagnosed with World Health Organization type III carcinoma (98.5%). The EBV-DNA value was ≥ 4000 copies/mL in nearly one-third of the patients. Using the identified MAR cut-off value of 11.63 (Fig. S1), patients were classified into 2 groups: a high MAR group with scores greater than 11.63 ($n=232$) and a low MAR group with scores less than or equal to 11.63 ($n=628$).

Survival data and overall survival (OS) across different MAR groups

The median OS observed in the study population was 123.2 months (interquartile range: 87.8–136.1 months). A total of 174 events were recorded throughout the study duration. The OS rates at 1, 3, 5, and 10 years were recorded at 98.1%, 93.6%, 88.6%, and 80.3%, respectively. Analysis using the Kaplan-Meier method indicated that patients in the low MAR group had a significantly higher survival rate compared to those in the high MAR group (Fig. 1; hazard ratio 0.56; 95% confidence interval [CI] 0.41–0.77, $P < 0.001$).

Univariate and multivariate analyses

Univariate analyses revealed that T stage, N stage, EBV-DNA status, MAR value, BMI category, and age were statistically significant predictors of OS ($P < 0.10$). These variables were incorporated into the multivariate Cox model. The variance inflation factor was calculated for the selected variables, all of which were less than 10. A multicollinearity diagnostic confirmed that severe multicollinearity was absent. Fig. S2 illustrates the diagnostic diagram for assessing proportional hazards, indicating that the multivariate model adheres to the proportional hazards assumption. The multivariate analysis identified T stage, age, N stage, BMI category, and MAR value as independent prognostic factors for OS in NPC patients treated with CCRT (Table 2).

Establishing a new prognostic model grounded in MAR

Drawing from the 5 independent prognostic variables identified in the multivariate analysis, a new nomogram prognostic model was established to estimate patient survival probabilities (Fig. 2). For example, a 56-year-old patient classified as T2 N3 with a BMI of 25 and a MAR score exceeding 11.63 had a total score of 18.75 ($2.75 + 6 + 7.94 + 0 + 2.06$), with corresponding 1-, 3-, 5-, and 10-year OS rates of 96.86%, 88.32%, 79.20%, and 64.96%, respectively.

Assessment of the predictive performance of the new prognostic model

The C-index for OS determined for the nomogram was 0.68 (95% CI 0.64–0.72), outperforming the C-index of the traditional TNM staging system, which was 0.64 (95% CI 0.57–0.70), thereby demonstrating satisfactory discriminatory power. Calibration plots for OS (Fig. 3A) depicted the concordance between predicted and actual survival frequencies. Fig. 3B presents the time-dependent ROC curve, illustrating the prognostic accuracy of the newly formulated prediction model, which surpassed that of the conventional TNM staging system. Fig. 3C illustrates the decision curve analysis curves that compare the net advantages of the current prediction model against that of the traditional TNM staging approach. This nomogram evidenced superior predictive accuracy relative to the standard TNM staging system.

DISCUSSION

To the best of the authors' knowledge, this study is the first to examine MAR's predictive value for OS in NPC patients undergoing CCRT. The results indicate that patients with pre-treatment MAR levels below 11.63 enjoy significantly improved OS compared to those with levels at or above 11.63. Furthermore, multivariate analysis confirmed MAR as an independent prognostic indicator. The authors developed a user-friendly nomogram based on MAR for practical clinical application.

The conventional TNM staging system primarily categorises disease stages according to the anatomical extent of tumour invasion, directing further treatment strategies. However, this framework lacks sufficient predictive accuracy and personalisation for NPC patients receiving CCRT. This study successfully integrates the novel nutritional-inflammatory marker MAR into a prognostic framework, promoting individualised prognostic evaluations among diverse patient populations. This model provides clinicians with a timely and cost-efficient biomarker to support clinical decision-making.

Table 1. Baseline characteristics of the study participants.

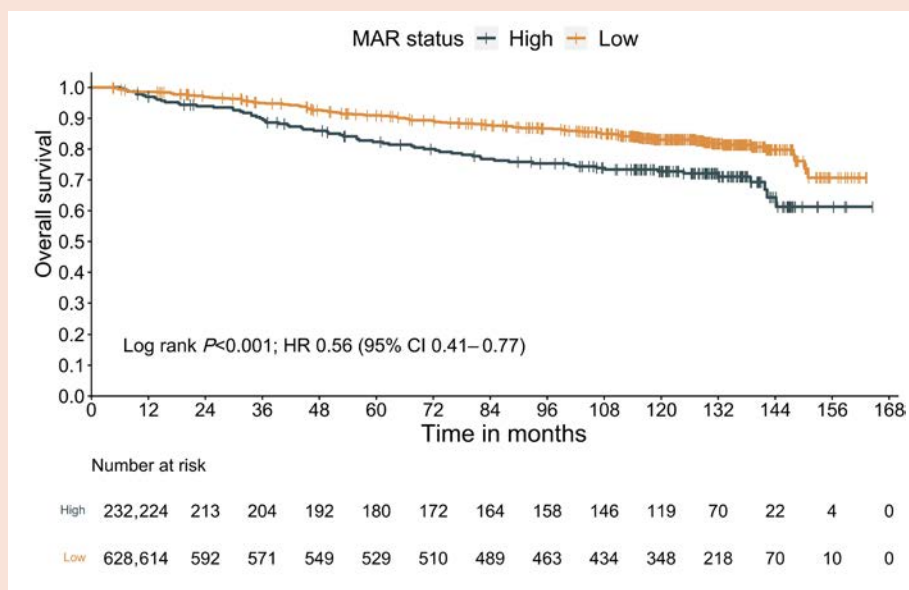
Characteristic	All (n=860)	%
Age		
>45 years	423	49.2
≤45 years	437	50.8
Sex		
Female	221	25.7
Male	639	74.3
Histological type		
WHO I/II	13	1.51
WHO III	847	98.5
HGB		
<113 g/L	27	3.14
113–151 g/L	547	63.6
≥151 g/L	286	33.3
LDH		
<245 U/L	50	5.81
≥245 U/L	810	94.2
T stage		
T1	42	4.88
T2	165	19.2
T3	523	60.8
T4	130	15.1

Table 1. Baseline characteristics of the study participants. (Cont'd)

Characteristic	All (n=860)	%
N stage		
N0	81	9.42
N1	464	54.0
N2	271	31.5
N3	44	5.12
BMI		
<24 kg/m ²	518	60.2
24–27.9 kg/m ²	294	34.2
≥28 kg/m ²	48	5.58
EBV-DNA		
<4000 copy/mL	580	67.4
≥4000 copy/mL	280	32.6
ALB		
≥40 g/L	788	91.6
<40 g/L	72	8.37
MAR		
>11.63	232	27.0
≤11.63	628	73.0

ALB: albumin; BMI: body mass index; EBV-DNA: Epstein-Barr virus DNA; HGB: haemoglobin; LDH: lactate dehydrogenase; MAR: monocyte-to-albumin ratio; WHO: World Health Organization

Fig. 1. Survival curves obtained with Kaplan-Meier analysis between different MAR groups (the hazard ratios reported were unadjusted).



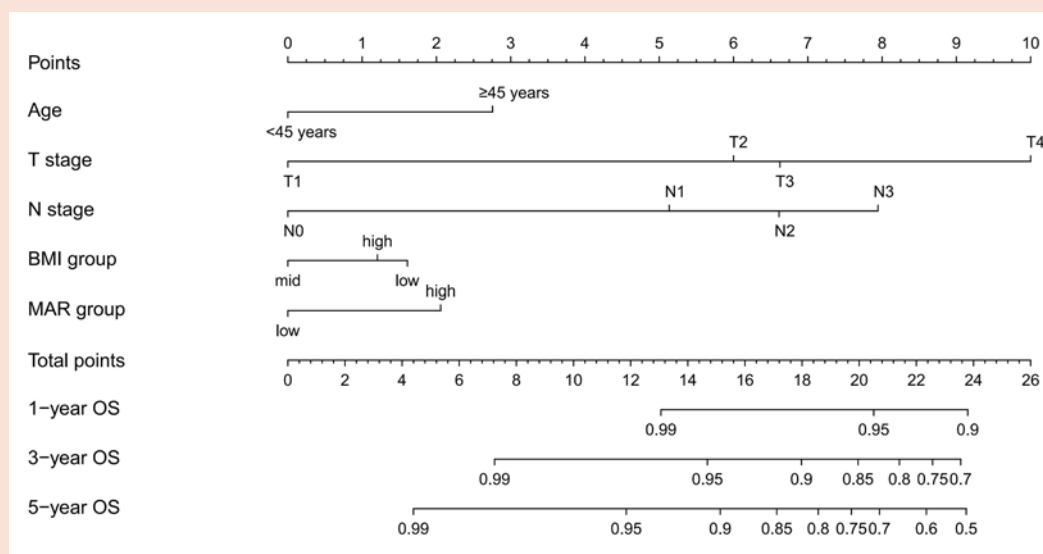
CI: confidence interval; HR: hazard ratio; MAR: monocyte-to-albumin ratio

Table 2. Univariate and multivariate Cox regression analyses of OS.

Characteristic	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age				
≥45 years	1		1	
<45 years	0.57 (0.42–0.77)	<0.001	0.54 (0.40–0.74)	<0.001
Sex				
Female	1			
Male	1.14 (0.81–1.62)	0.455		
Histological type				
WHO I/II	1			
WHO III	0.45 (0.18–1.09)	0.0778		
HGB				
<113 g/L	1			
113–151 g/L	1.43 (0.53–3.87)	0.485		
≥151 g/L	1.40 (0.51–3.86)	0.517		
LDH				
≥245 U/L	1			
<245 U/L	0.61 (0.35–1.05)	0.0758		
T stage				
T1	1		1	
T2	4.12 (0.98–17.26)	0.053	3.77 (0.90–15.83)	0.070
T3	4.50 (1.11–18.26)	0.035	4.22 (1.04–17.15)	0.044
T4	9.21 (2.23–37.99)	0.002	8.36 (2.02–34.66)	0.003
N stage				
N0	1		1	
N1	2.77 (1.21–6.33)	0.016	2.93 (1.28–6.73)	0.011
N2	3.60 (1.56–8.32)	0.003	3.90 (1.68–9.10)	0.002
N3	5.01 (1.90–13.20)	0.001	4.98 (1.86–13.34)	0.001
BMI				
<24 kg/m ²	1		1	
24–27.9 kg/m ²	0.71 (0.51–0.99)	0.046	0.93 (0.47–1.84)	0.826
≥28 kg/m ²	0.82 (0.41–1.61)	0.554	0.69 (0.49–0.97)	0.035
EBV-DNA				
<4000 copy/mL	1		1	
≥4000 copy/mL	1.62 (1.20–2.20)	0.002	1.34 (0.98–1.83)	0.071
MAR				
>11.63	1		1	
≤11.63	0.56 (0.41–0.77)	<0.001	0.64 (0.47–0.87)	0.004

ALB: albumin; BMI: body mass index; EBV-DNA: Epstein-Barr virus DNA; HGB: haemoglobin; HR: hazard ratio; LDH: lactate dehydrogenase; MAR: monocyte-to-albumin ratio; OS: overall survival; WHO: World Health Organization
HRs estimated by Cox proportional hazards regression. All statistical tests were 2-sided.

Fig. 2. Nomogram of the current prognostic model for individualised survival predictions.



BMI: body mass index; MAR: monocyte-to-albumin ratio; OS: overall survival

Variability in prognosis among patients with identical TNM stages further emphasises the need for biological insights that transcend anatomical descriptions. Prior research suggests that including nutritional and inflammatory indicators can enhance clinical prognosis precision. Elevated monocyte counts have been linked to substantial tumour burden, potentially leading to poorer outcomes in specific solid tumours.²⁰⁻²² Additionally, albumin levels represent malnutrition and inflammatory states, frequently correlating with adverse prognoses and increased mortality rates in cancer patients.^{23,24} The MAR index—a ratio of monocyte counts to albumin concentrations—effectively reflects systemic inflammation and nutritional status. This retrospective analysis illustrates a significant association between pre-treatment MAR scores and OS in 860 NPC patients receiving CCRT, with scores below 11.63 correlating with improved OS (HR 0.56, 95% CI 0.41–0.77, $P < 0.001$). This highlights MAR's potential as a biomarker for predicting both clinical prognosis and treatment outcomes in NPC patients. Furthermore, this predictive nomogram model that integrates MAR with TNM staging outperforms traditional models, enhancing prognosis prediction accuracy.

It is important to recognise that the systemic inflammatory response is critical in tumour development and the treatment process, serving as a determinant of survival rates across various cancer types.²⁵ Inflammatory cells engage with tumour cells to facilitate angiogenesis, remodel the extracellular matrix, and sustain an inflammatory microenvironment conducive to metastasis.²⁶ Monocytes are pivotal to innate immunity, migrating into tumour tissues

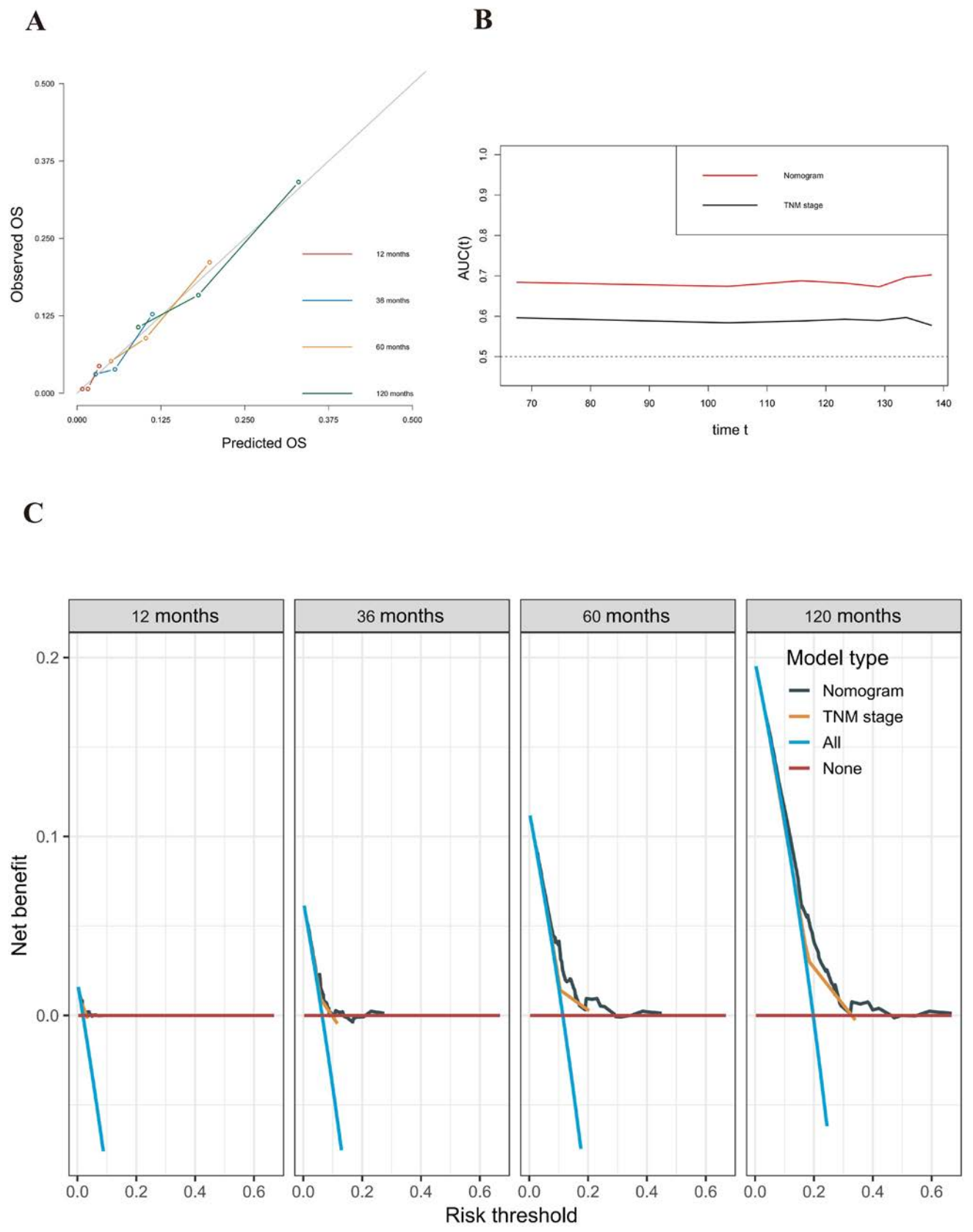
and differentiating into TAMs when influenced by inflammatory conditions, thus promoting tumour progression.⁸ This interaction illustrates the dual impact of both inflammation and nutritional status on tumour dynamics, as increased tumour load often results in hypoproteinaemia due to nutritional inadequacies amid heightened inflammatory responses.²⁷⁻³³ Therefore, recent studies also highlight that combining these inflammatory and nutritional markers can effectively predict patient survival in NPC.³⁴⁻³⁷

The findings corroborate previous studies that identified age, N stage, T stage, and BMI score as independent prognostic factors for OS in NPC patients undergoing CCRT.³⁸ The nomogram developed in this study acts as a roadmap for tailored treatment planning, allowing clinicians to intensify treatment interventions (e.g. neoadjuvant or adjuvant chemotherapy) for higher-scoring patients while simultaneously addressing their nutritional and inflammatory support needs.

Limitations

The MAR metric is dynamic, subject to fluctuations influenced by various factors, which can impact the stability of consequent analyses. Additionally, the predictive model was generated from data sourced from a single centre, necessitating validation through high-quality datasets from multiple institutions. Furthermore, retrospective study designs are often vulnerable to selection bias, which may influence the accuracy of the results. Moreover, since this study relied entirely on retrospective blood tests, there was a lack of corresponding tissue slides to visually

Fig. 3. Assessment of predictive performance of the prognostic model. (A) Calibration plot of the nomogram model at 1, 3, 5, and 10 years. (B) Time-dependent ROC curves compared the predictive accuracy of the current model and the traditional TNM stage. (C) DCA curves compared the net benefit rate of the current model and the traditional TNM stage.



AUC: area under the curve; DCA: decision curve analysis; OS: overall survival; ROC: receiver operating characteristic; TNM: tumour–node–metastasis

confirm monocyte infiltration. Future research will prioritise prospective multicentre studies incorporating pathological imaging to address these limitations and enhance the accuracy and overall applicability of the predictive model.

CONCLUSION

In conclusion, the findings highlight MAR as a novel nutritional-inflammatory biomarker that can serve as a significant predictor of survival rates in NPC patients undergoing CCRT. The prognostic capabilities of the MAR score nomogram exceed those of traditional staging methods, demonstrating its potential to refine prognostic tools. This newly developed predictive nomogram represents a reliable, efficient, straightforward, affordable, and non-invasive means for stratifying patients based on their responses to CCRT.

Supplementary materials

Fig. S1. Cut-off value of MAR.

Fig. S2. Proportional hazards diagnostic plot.

Declaration

The authors declare 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. There is no conflict of interest or funding to declare. The authors also confirm that no generative artificial intelligence (AI) or AI-assisted technologies were used in the preparation or writing of this manuscript.

Ethics statement

Approval was obtained from the Sun Yat-sen University Cancer Center's Ethics Committee (SL-B2023-537-01), which waived the requirement for written informed consent. All procedures were conducted in accordance with the principles of the 1964 Helsinki Declaration and its amendments.

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The effect of pulse steroid therapy on bone density and turnover: A systematic review and meta-analysis

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ABSTRACT

Introduction: Chronic exposure to glucocorticoids (GC) is a leading cause of secondary osteoporosis and fractures. While the skeletal effects of long-term oral GC are well-established, the bone effects of intermittent high-dose intravenous pulse methylprednisolone therapy remain less clearly defined. This study aimed to evaluate its impact on skeletal health in adults not receiving anti-osteoporosis treatment.

Methods: This meta-analysis was conducted according to PRISMA guidelines and prospectively registered. PubMed, Scopus, Embase, and Google Scholar were searched up to September 2025. Studies included longitudinal cohort and case-control studies with appropriate comparators and randomised controlled trials reporting pre- and post-intravenous methylprednisolone bone outcomes.

Results: Eight studies (n=192, 72% females) were included. Pulse intravenous methylprednisolone did not significantly reduce bone mineral density (BMD) at the lumbar spine (mean difference [MD] 0.01 g/cm²; 95% confidence interval [CI] -0.02 to 0.03), femoral neck (MD -0.01 g/cm²; 95% CI -0.03 to 0.01), or total hip (MD -0.03 g/cm²; 95% CI -0.06 to 0.01) over a mean follow-up period of 5.5 months. Trabecular bone score showed no significant pooled change (MD -0.01 g/cm²). In contrast, procollagen type-1 N-terminal propeptide (MD -36.95 ng/mL; 95% CI -56.86 to -17.03) and C-terminal telopeptide (MD -0.19 ng/dL; 95% CI -0.32 to -0.07) significantly decreased. Serum 25-hydroxyvitamin D increased modestly, while serum calcium and parathyroid hormone remained unchanged.

Conclusion: Pulse intravenous methylprednisolone does not cause short-term BMD loss, though it is associated with measurable suppression of bone turnover markers. Larger controlled studies with standardised sampling, peripheral site assessment, and fracture outcomes are needed to determine long-term skeletal risk from pulse regimens.

Keywords: endocrinology, neurology, osteoporosis, pulse methylprednisolone, rheumatology

CLINICAL IMPACT

What is New

- Pulse intravenous methylprednisolone was not associated with short-term loss of lumbar spine or hip bone mineral density (BMD).
- Bone turnover markers were suppressed, indicating early effects on bone remodelling that are not captured by BMD alone.
- Limited fracture reporting precludes firm conclusions regarding fracture risk.

Clinical Implications

- Stable short-term BMD should not be equated with skeletal safety during pulse intravenous methylprednisolone therapy.
- Patients at high fracture risk or receiving repeated/ high cumulative doses may still warrant careful skeletal risk assessment and preventive management.

INTRODUCTION

Glucocorticoids (GC) are potent anti-inflammatory agents used for the treatment of various acute autoimmune and inflammatory disorders. Current studies estimate that the prevalence of GC use among countries varies between 0.5 and 21%.¹⁻⁴ Although they are highly effective, GCs are known to have negative impacts on skeletal health, particularly when administered at high doses and/or for a prolonged period.⁵⁻⁷ Among individuals receiving long-term GC therapy, the estimated prevalence of osteoporosis or fractures is up to 50%, rendering GCs the most common form of secondary (iatrogenic) osteoporosis.^{8,9} Thus, it is recommended to carry out a fracture risk assessment at GC initiation and to start

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bone-protective strategies in patients at moderate to high risk of fracture, particularly for those receiving the equivalent of ≥ 2.5 to 5 mg prednisolone daily for ≥ 3 months.¹⁰

GC-induced skeletal harm is most pronounced in the trabecular-rich regions, such as the vertebrae and proximal femur.¹¹ GC therapy increases the risk of hip and vertebral fractures by at least two- and threefold, respectively, compared with individuals without GC exposure.¹¹ Bone loss occurs most rapidly after GC initiation, with the most rapid decline occurring within the first year of GC therapy at a bone loss rate of 6 to 12%. This later slows to a rate of approximately 3% per year subsequently.¹² Consistent with this early bone loss rate, fracture risk is highest within the first 3 to 6 months after GC initiation, reflecting early osteoclast activation, increased osteoblast apoptosis, and reduced osteoblast proliferation.¹³ In individuals initially commenced on GC, fracture incidence was 5.1% (95% confidence interval [CI] 2.8–8.2%) for vertebral fractures and 2.5% (95% CI 1.2–4.2%) for non-vertebral fractures. For chronic GC users (>6 months), the corresponding incidences were 3.2% (95% CI 1.8–5.0%) and 3.0% (95% CI 0.8–5.9%), respectively.¹⁴ More importantly, fracture risk is influenced by current GC dose and cumulative GC exposure.¹⁰ Even low doses of GC ≤ 2.5 mg per day have been associated with increased risk of vertebral fractures,⁹ and doses above the 2.5 mg per day threshold have been shown to increase the risk of spine and hip fractures.^{10,15} Cumulative GC exposure is similarly important: higher doses of GCs ≥ 30 mg per day increase the risk of fragility fractures, with peak fracture incidence at 12 months. Indeed, fracture rate rises with cumulative GC exposure from an average 4.6 per 1000 person-years (95% CI 3.8–5.4) at <0.675 g of cumulative GC to a nearly threefold rate of 13.4 per 1000 person-years (95% CI 10.7–16.7) at a cumulative GC dose of ≥ 5.4 g.¹⁶

Mechanistically, GCs increase skeletal fragility through direct and indirect pathways. GCs directly suppress bone formation by inhibiting osteoblast differentiation, promoting osteoclast apoptosis while reducing osteocyte viability, leading to deterioration of bone microarchitecture and overall quality, ultimately increasing bone fragility. GCs also influence bone remodelling indirectly through suppression of anabolic pathways, including the growth hormone axis, while promoting insulin resistance and muscle catabolism, further compounding skeletal fragility. While the association between chronic GC exposure and adverse skeletal outcomes (including bone loss and fragility fractures) is well established, the impact of intermittent high-dose intravenous pulse methylprednisolone therapy remains less clearly defined.^{10,17} To date, relatively few studies have directly

assessed bone outcomes associated with intermittent pulse methylprednisolone use, and no clear quantitative synthesis of these skeletal effects is available. The authors therefore conducted this systematic review and meta-analysis to clarify the current evidence base. The authors hypothesised that intermittent pulse intravenous methylprednisolone may exert adverse skeletal effects that are detectable in short-term bone turnover markers, even if changes in bone mineral density (BMD) are less readily apparent over short follow-up periods. Accordingly, the authors evaluated the effects of intermittent pulse intravenous methylprednisolone therapy on skeletal health by investigating changes in BMD, bone turnover markers, fracture rate, and bone biochemistry in adults who did not receive osteoporosis therapy.

METHODS

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹⁸ As only published data were used, Institutional Review Board approval was not required. The study protocol was prospectively registered in the International Database of Registered Systematic Reviews (<https://doi.org/10.17605/OSF.IO/VFMJR>).

Selection criteria

Eligible studies were identified through comprehensive searches of PubMed, Scopus, Embase, and Google Scholar, including all publications up to September 2025. Studies were included if they met the following criteria: (1) case-control study, cohort study, longitudinal study or randomised controlled trial; (2) reported at least 1 outcome of interest; (3) conducted in humans; (4) available in full text; and (5) English-language published studies. The authors excluded: (1) duplicate or overlapping cohorts; (2) case-control or cross-sectional studies without control groups; (3) case reports, case series, editorials, protocols, opinion pieces, commentaries, abstracts, and review articles; or (4) grey literature, including conference abstracts and unpublished reports (these sources lacked sufficient methodological detail and complete outcome data for reliable extraction and quality assessment).

Search strategy

The search strategy was developed using the Population, Intervention, Comparison, Outcome (also known as PICO) framework.¹⁹ The population group consisted of patients receiving pulse intravenous methylprednisolone, with or without maintenance GC therapy. The intervention was exposure to pulse intravenous methylprednisolone, and the comparator group was baseline (pre-exposure) measurements

obtained prior to treatment initiation. Outcomes of interest included BMD, bone turnover markers, fracture incidence, and use of osteoporosis treatment. The full search terms are provided in Supplementary Table S1.

Data extraction

Data extraction was performed independently by 4 investigators using a 3-stage process. In the first stage, titles and abstracts were screened, with full texts retrieved when necessary. In the second stage, full-text articles and their reference lists were reviewed for eligibility. In the third stage, study objectives, methods, and suitability for inclusion were critically appraised. Discrepancies were resolved by consensus, with adjudication by third and fourth reviewers. When essential data were unavailable, corresponding study authors were contacted for clarification or provision of unpublished data.

Extracted data included study characteristics and reported outcomes: patient age; underlying disease conditions resulting in GC therapy; pulse intravenous methylprednisolone regimens; radiological measures (BMD, trabecular bone score [TBS]); bone turnover markers, e.g. procollagen type 1 N-terminal propeptide (P1NP), C-terminal telopeptide (CTX), osteocalcin, hydroxyproline, bone-specific alkaline phosphatase (bsALP); bone biochemistry (serum calcium, 25-hydroxyvitamin D, intact parathyroid hormone; and urine calcium/creatinine ratio); and fracture rate. All included full-text articles were reviewed and approved by all authors prior to final data extraction.

Data synthesis and analysis

Meta-analysis was performed when at least 2 or more studies reported the same outcome in a numerical outcome (e.g. BMD, bone turnover markers, fracture rates). Small study effects and publication bias were assessed using funnel plots (log odds against inverse standard error).

Risk-of-bias assessment

Risk of Bias was evaluated using the Risk of Bias In Non-randomized Studies—of Exposures (ROBINS-E) tool (Supplementary Table S2).²⁰ ROBINS-E evaluates the quality of the study based on 7 domains, including exposure classification, deviations from intended exposures, missing data, outcome measurement, and selective reporting. Each domain was rated as low risk, some concerns, high risk, or very high risk of bias. Four reviewers independently performed assessments for risk of bias, with disagreements resolved through discussion.

Statistical analysis

All analyses were performed using RevMan version 5.3 (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen) using random-effects models. When standard deviations (SDs) were not reported, they were estimated from *P* values or imputed using pooled SDs from comparable studies: $\sqrt{(\sum(N \times SD^2) / \sum N)}$.

For continuous variables, mean difference (MD) was used given its clinical interpretability. Analyses were repeated using standardised mean difference to assess robustness across heterogeneous measurement approaches (e.g. different densitometry platforms and laboratory assays). Apart from statistical significance ($P < 0.05$), a 4% change in BMD was prespecified as the least significant change (LSC).^{21,22}

Statistical heterogeneity was assessed using the I^2 statistic, with $P < 0.10$ considered as statistically significant, and $I^2 \geq 50\%$ indicating substantial heterogeneity. Potential sources of heterogeneity were explored through sensitivity analyses after exclusion of outlier studies (defined a priori as those with opposing effect directions, disproportionately large effect sizes, or high risk of bias), followed by recalculation of pooled effect estimates.

Quality of evidence was assessed by the Grading of Recommendations, Assessment, Development, and Evaluations (also known as GRADE) approach.²³

RESULTS

The initial database search identified 4195 records. After removing 461 duplicates, 3734 articles were available for screening. Of these, 3655 articles were excluded based on the predefined eligibility criteria; 79 articles underwent full-text review, of which 69 were excluded, leaving 10 publications (8 studies) in the final review. The 8 included studies comprised 6 cohort studies, 1 retrospective study, and 1 randomised trial. Of the 8 studies, 4 studies recruited patients with Graves' disease, 2 studies included patients with multiple sclerosis, and 2 studies recruited individuals with mixed rheumatological conditions (Fig. 1). Table 1 summarises the study characteristics and sample sizes ranging from 10 to 45 participants, yielding a total sample of 192 patients (72% female). Means (SDs) of age and body mass index were 49.4 (18.13) years and 25.2 (8.56) kg/m², respectively.

Bone mineral density

Eight studies (10 publications)^{24–33} reported BMD outcomes before and after pulse methylprednisolone. One study³⁴ reported T-scores and Z-scores only, which could not be reliably converted to BMD values;

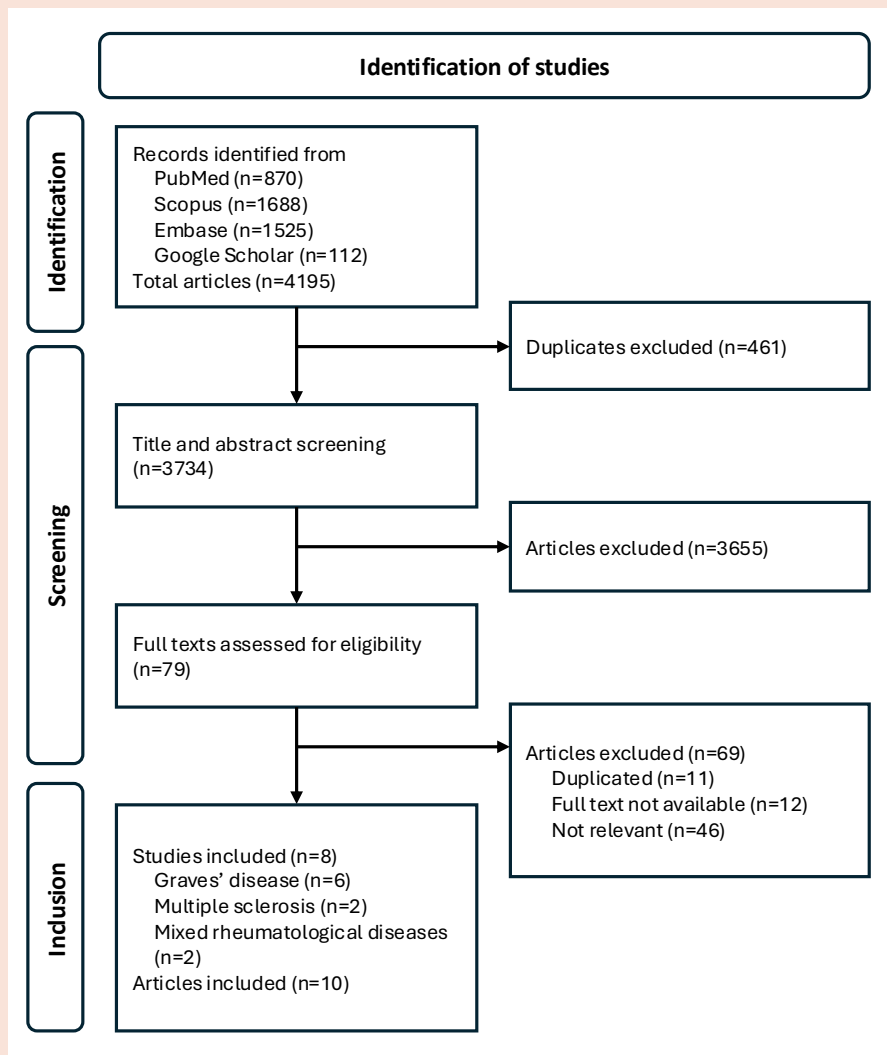
Table 1. Summary of included studies.

Reference	Study type	Population	Intervention	No.		Gender Male/ Female	Age Mean (SD)	BMI
				Intervention	Control			
Hu, 2020 ³²	Retrospective cohort	Moderate-to-severe active Graves' disease ophthalmopathy	Intravenous MP 0.5 g once per week x 6 weeks, then intravenous MP 0.25 g per week for 6 weeks	16 with 2 courses	-	19/26	42.5 (13.24)	-
				45 with 1 course	-			
Harsløf, 2023 ²⁵	Prospective cohort	Active Graves' disease orbitopathy with clinical activity score 3 or more		32	-	11/21	52.9 (10.2)	25.45
Rymuza, ^a 2022 ²⁷	Prospective cohort	Moderate-to-severe active Graves' disease orbitopathy, euthyroid		23	-	3/20	54 (12)	26.5
Censi, 2018 ²⁴	Prospective cohort	Active Graves' disease orbitopathy		11	-	1/10	56 (47–71)	24.5
Rymuza, ^a 2019 ²⁹	Prospective cohort	Moderate-to-severe active Graves' disease orbitopathy, euthyroid		35	-	6/29	47 (22–66)	27
Rymuza, ^a 2022 ²⁸	Prospective cohort	Moderate-to-severe active Graves' disease orbitopathy, euthyroid		15	-	2/13	53.6 (40–74)	28
Simeakis, 2023 ³⁰	Prospective cohort	Newly diagnosed multiple sclerosis	Intravenous MP 1g x 5 days followed by PO prednisolone tapering over 21 days	25	-	15/10	-	26.72
Zorzon, 2004 ³¹	Prospective randomised trial	Multiple sclerosis	Regular pulses of MP (1 g/day for 5 days, every 4 months for 3 years, then every 6 months for 2 years) + pulses of MP for relapses	25	61	7/18	-	-
			Pulses of MP for relapses only	18		7/11		
Frediani, 2004 ³³	Prospective randomised trial	Active rheumatoid arthritis	Intervention: intravenous MP 1 g for 3 alternate days, repeated monthly if disease still active Control: oral MP 16 mg/day for at least 1 month, tapered to minimum 4 mg/day	31	31	5/12	-	-
Haugeberg, 2004 ²⁶	Prospective cohort	Various rheumatic disorders requiring intravenous MP pulse treatment	Intravenous MP pulses (dose and schedule varied based on disease and patient's response), with or without concomitant oral prednisolone	38 including 14 without oral prednisolone	-	8/30	48.4 (16.3)	24.9

BMI: body mass index; MP: methylprednisolone; PO: per os/by mouth; SD: standard deviation

^a Recognised as the same study in 3 publications.

Fig. 1. PRISMA flow chart.



hence, it was excluded from the analysis. No significant changes were observed in BMD at femoral neck (MD -0.01 g/cm²; 95% CI -0.03 to 0.01; quality of evidence: low ⊕⊕○○), the lumbar spine (MD 0.01 g/cm²; 95% CI -0.02 to 0.03; quality of evidence: low ⊕⊕○○), or total hip (MD -0.03 g/cm²; 95% CI -0.06 to 0.01; quality of evidence: low ⊕⊕○○) following pulse methylprednisolone therapy (all I² = 0%; fixed-effect models applied) that was administered over a weighted mean of 5.5 months (range 3 to 12 months). The lower limit of 95% CI for the BMD changes at femoral neck and lumbar spine did not exceed the prespecified LSC. Of the 2 studies^{24,28} that reported TBS, no significant difference was detected (MD -0.02; 95% CI -0.10 to 0.07; I² = 0%; fixed-effect; quality of evidence: very low ⊕○○○) (Fig. 2).

Bone turnover markers

Five studies^{24,25,27,30,32} reported bone turnover markers. Both P1NP (MD -36.95 ng/mL; 95% CI -56.86 to -17.03;

quality of evidence: low ⊕⊕○○) and CTx (MD -0.19 ng/dL; 95% CI -0.32 to -0.07; quality of evidence: low ⊕⊕○○) showed significant reductions following pulse methylprednisolone treatment (I² ≥ 50%; random-effects models applied) (Fig. 3).

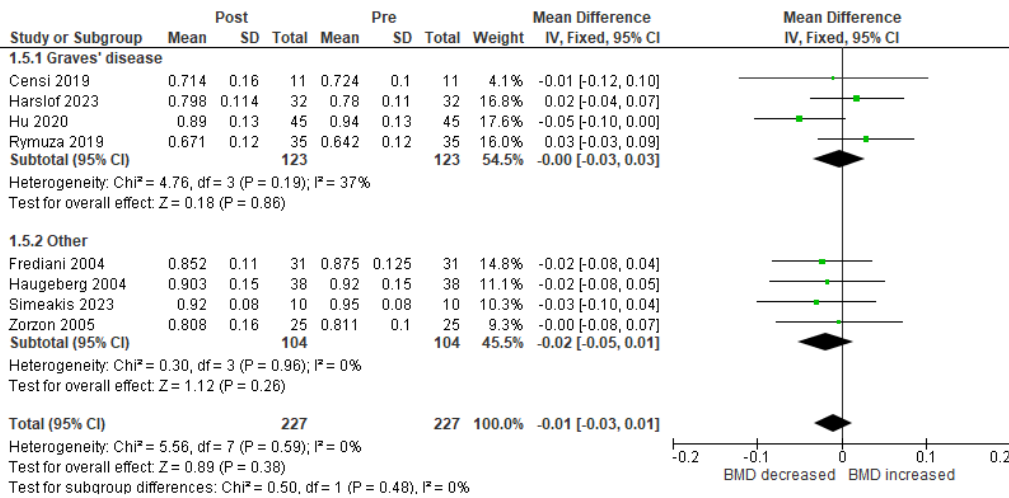
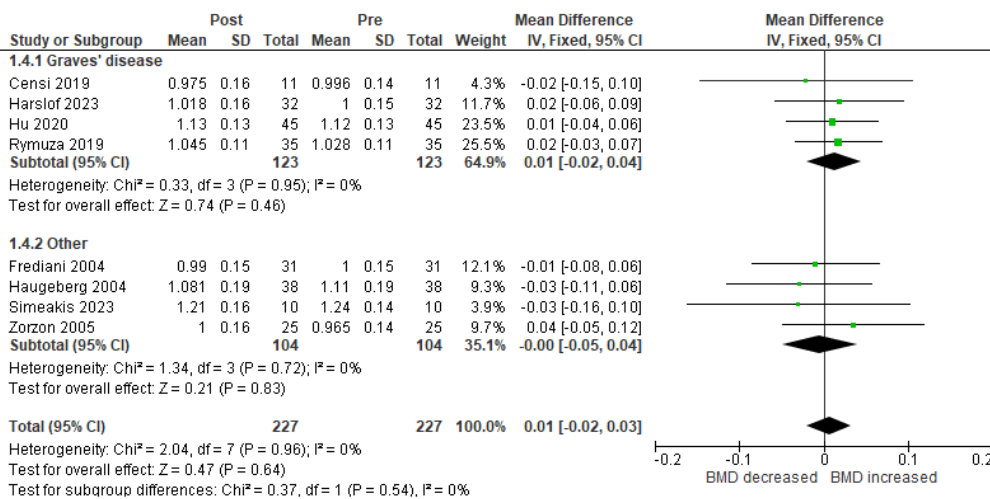
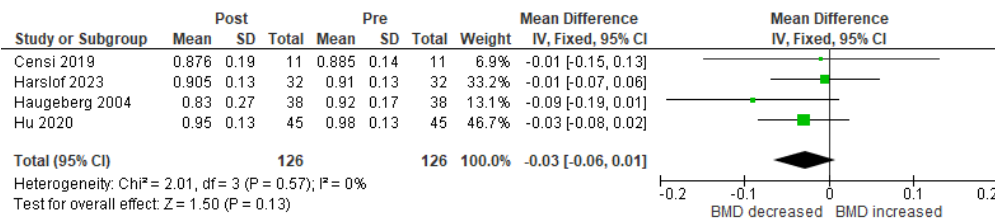
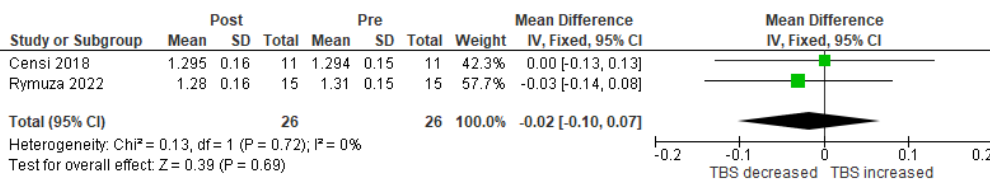
Biochemistry

Serum 25-hydroxyvitamin D levels significantly increased after treatment (MD 1.03 ng/mL; 95% CI 0.24 to 1.83; I² = 0%; fixed-effect; quality of evidence: low ⊕⊕○○).^{24,27,29,30,32} No significant changes were observed in serum calcium^{29,30,32} or intact parathyroid hormone^{24,27,29,30,32} concentrations (Fig. 4).

Subgroup analysis

A subgroup analysis comparing Graves' disease^{24,25,27-29,32} with other conditions (multiple sclerosis^{30,31} and rheumatological diseases) revealed no significant changes in BMD within either subgroup. Both P1NP and CTx significantly decreased in the Graves' disease

Fig. 2. Forest plots of bone mineral density and trabecular bone scores.

A: Bone mineral density of femoral neck**B: Bone mineral density of lumbar spine****C: Bone mineral density of total hip****D: Trabecular bone score**

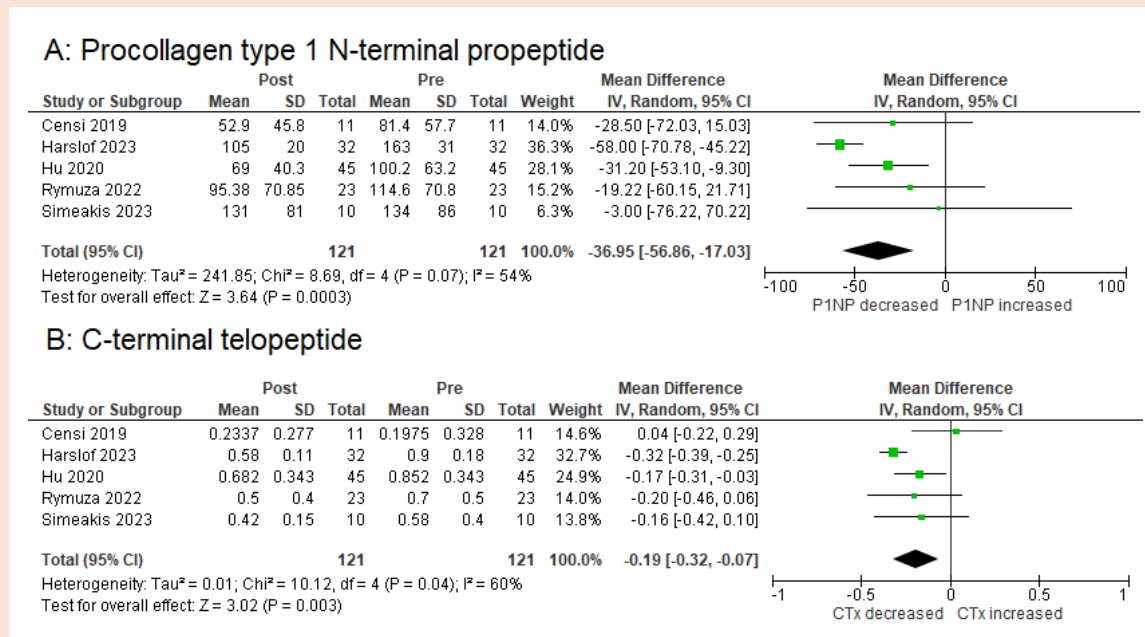
BMD: bone mineral density; CI: confidence interval; df: degrees of freedom; IV: inverse variance; SD: standard deviation; TBS: trabecular bone score

Table 2. Quality of evidence and sensitivity analysis.

Variables	No. of studies	Mean difference (confidence interval)	Quality of evidence	Reasons	Sensitivity analysis ^a Mean (confidence interval)
Bone mineral density of femoral neck	8	-0.01 (-0.03 to 0.01) g/cm ²	Low ⊕⊕○○	Observation studies	-0.01 (-0.03 to 0.02) g/cm ²
Bone mineral density of lumbar spine	8	0.01 (-0.02 to 0.03) g/cm ²	Low ⊕⊕○○	Observation studies	0.01 (-0.02 to 0.04) g/cm ²
Bone mineral density of total hip	4	-0.03 (-0.06 to 0.01) g/cm ²	Low ⊕⊕○○	Observation studies	-0.03 (-0.07 to 0.01) g/cm ²
Trabecular bone score	2	-0.02 (-0.10 to 0.07)	Very Low ⊕○○○	Observation studies (small number)	-0.03 (-0.14 to 0.08)
Procollagen type 1 N-terminal propeptide	5	-36.95 (-56.86 to -17.03) ng/mL	Low ⊕⊕○○	Observation studies	-37.47 (-60.55 to 14.38) ng/mL
C-terminal telopeptide	5	-0.19 (-0.32 to -0.07) ng/dL	Low ⊕⊕○○	Observation studies	-0.25 (-0.34 to -0.15) ng/dL
Serum 25-hydroxyvitamin D level	4	1.03 (0.24 to 1.83) ng/mL	Low ⊕⊕○○	Observation studies	1.11 (0.31 to 1.91) ng/mL
Serum calcium level	3	-0.00 (-0.04 to 0.03) mmol/L	Low ⊕⊕○○	Observation studies	-0.00 (-0.04 to 0.03) mmol/L
Intact parathyroid hormone level	4	3.29 (-1.40 to 7.97) pg/mL	Very Low ⊕○○○	Observation studies (inconsistent result)	1.66 (-4.81 to 8.13) pg/mL

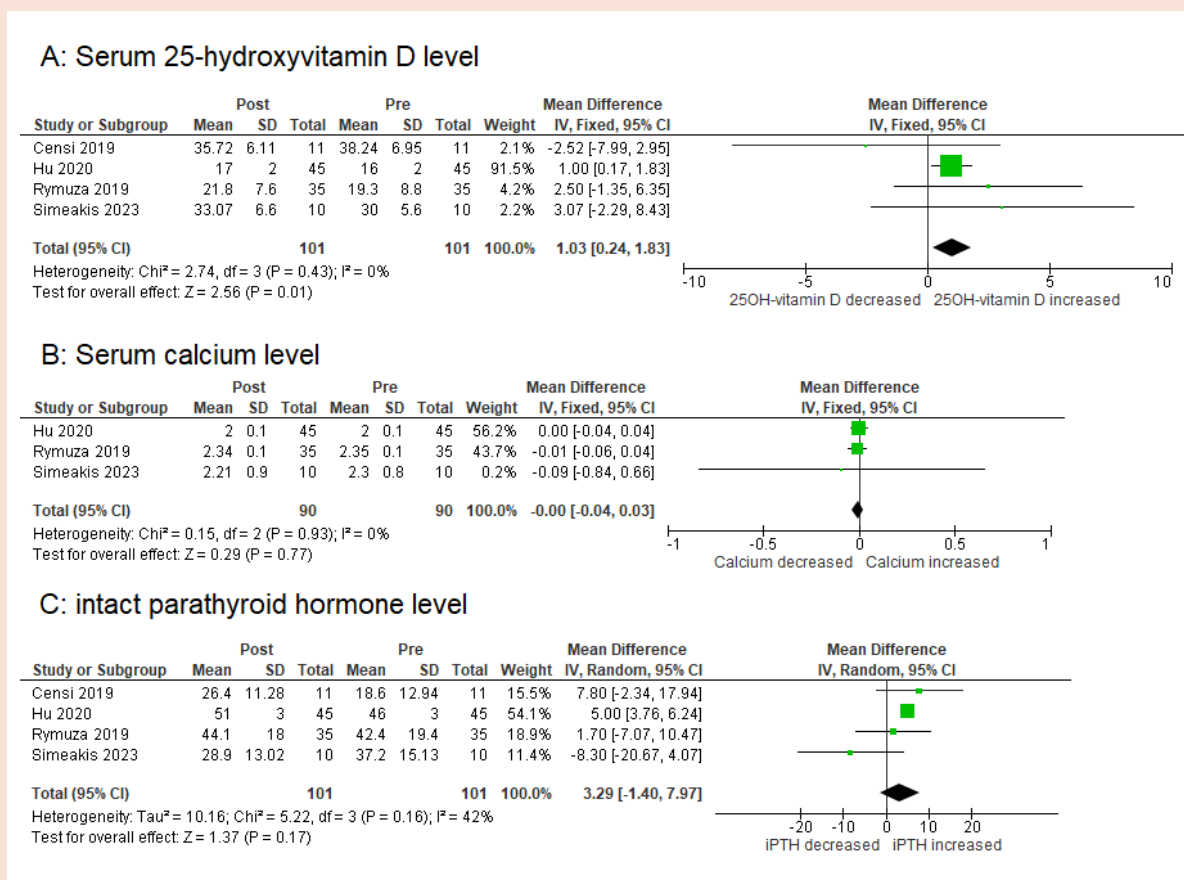
^a Mean difference of meta-analyses excluding Censi (2018),²⁴ Zorzon (2004),³¹ and Frediani (2004)³³ for their overall risk of bias: some concerns.

Fig. 3. Forest plots of bone turnover markers.



CI: confidence interval; CTx: C-terminal telopeptide; df: degrees of freedom; IV: inverse variance; P1NP: procollagen type 1 N-terminal propeptide; SD: standard deviation

Fig. 4. Forest plots of bone biochemistry.



CI: confidence interval; df: degrees of freedom; iPTH: intact parathyroid hormone; IV: inverse variance; SD: standard deviation

osteoblast differentiation and activity, in part through inhibition of the Wnt signalling pathway.^{36,37} GCs also increase the expression of Dickkopf-1 and sclerostin, reduce proliferation of osteoprogenitor cells, and promote differentiation of mesenchymal stem cells into adipocytes rather than osteoblasts.³⁶ These effects result in a sustained reduction in osteogenesis. The low P1NP levels observed in this study are consistent with this biology, and suggest that even intermittent high-dose methylprednisolone exposure may lead to prolonged suppression of osteoblast function lasting for months to years.^{35,38} The interpretation of reduced CTx is more complex. GCs have mixed and potentially biphasic effects on bone resorption. Initially, GC use has been associated with early bone resorption driven by increased osteoclast activity and attenuation of osteoblast-lineage suppression.³⁸ Over time, osteoclast activity declines due to reduced receptor activator of nuclear factor kappa-B ligand production from suppressed osteoblasts, leading to variable trajectories in resorption markers.³⁸ Apart from the effect of GCs on osteoclasts, GCs can induce osteocyte apoptosis, leading to variable levels of CTx at different time points.³⁹ In pulse methylprednisolone regimens, the timing of sampling is therefore particularly important: CTx measured during or soon after a pulse may be elevated whereas the CTx measured weeks later may be reduced.⁴⁰ Thus, the concurrent decreases in P1NP and CTx most likely reflect overall suppression of bone remodelling, with a more prominent and sustained inhibitory effect on bone formation. Clinically, this pattern is consistent with a low-turnover skeletal state and may explain the lack of significant BMD changes after a short course of intravenous pulse methylprednisolone therapy. Furthermore, the drug-free intervals in pulse methylprednisolone therapy may allow partial recovery of remodelling signals and normalisation of osteoclast activity.^{41,42} Nevertheless, persistent suppression of bone formation may still have implications for longer-term bone health.

TBS provides a surrogate index of trabecular bone architecture and predicts fracture risk independent of BMD.⁴³ In this analysis, no significant decline in TBS was observed after pulse intravenous methylprednisolone therapy. However, individual studies have reported divergent results. Rymuza et al.²⁸ reported a decline in TBS in individuals with mild to moderate Graves' disease orbitopathy treated with pulse intravenous methylprednisolone, whereas earlier studies by Censi et al.²⁴ observed no demonstrable effect of pulse intravenous methylprednisolone on TBS in individuals with Graves' orbitopathy. Clinically, this suggests that the effect of pulse intravenous methylprednisolone on TBS may be modest and context-specific, and that absence of decline in TBS

does not necessarily exclude deterioration in bone quality in susceptible subgroups.

The results are broadly consistent with comparative studies suggesting less BMD loss with pulse regimens compared with chronic daily GCs. Frediani et al.³³ conducted a randomised trial of 31 women with active rheumatoid arthritis who received either chronic oral methylprednisolone or intermittent methylprednisolone pulse therapy. After 12 months, chronic methylprednisolone therapy led to significant declines in BMD at the total hip, femur, and lumbar spine while no change in BMD was observed in the pulse methylprednisolone group.³³ Handa et al.³⁴ studied 49 patients with dermatological conditions treated with daily prednisolone or intravenous dexamethasone at 4-weekly intervals. The authors found that individuals receiving intermittent intravenous dexamethasone experienced less reduction in lumbar spine T-score than those treated with daily oral prednisolone, consistent with differential effects across trabecular-rich (spine) versus cortical-rich (radius) bone by GC regimen. Among the limited studies reporting fracture outcomes, Zonana-Nacach et al.⁴⁴ found in 539 patients with systemic lupus erythematosus that higher cumulative prednisone exposure was significantly associated with osteoporotic fractures, whereas each additional intravenous methylprednisolone pulse was associated with only a small, non-significant increase in fracture risk (relative risk 1.3, 95% CI 1.0–1.8; $P=0.07$). Similarly, in the retrospective 10-year study by Cheng et al.⁴⁵, no vertebral compression fractures were reported among 46 patients with active systemic sclerosis treated with pulse methylprednisolone therapy, although 21 patients had also received long-term low-dose oral glucocorticoids.

From a clinical standpoint, these findings suggest that short-term stability in BMD following pulse intravenous methylprednisolone should be interpreted cautiously. Baseline fracture risk assessment remains important, especially in patients with high underlying osteoporosis risk or recurrent pulse methylprednisolone exposure. While BMD is unchanged, changes in bone turnover markers are detectable and early fracture risk in GC exposure can be driven by markers not captured in bone imaging. Notably, the absence of a measurable short-term decline in BMD should not be equated with absence of fracture risk, as GC exposure may impair bone strength through mechanisms not fully captured by areal BMD alone.

Furthermore, early fracture risk associated with chronic oral GC therapy could only be partly explained by BMD loss, as excess GC also impairs bone mineralisation and microarchitecture, and could predispose to falls via muscle myopathy. Thus, clinicians should

avoid over-reliance on BMD alone and consider vertebral fracture assessment, prior fracture history, fall risk, or even consider using TBS where available.^{9,35} Most of the studies in this analysis have focused on assessment of bone density in lumbar spine and hip. Handa et al. reported that patients receiving intermittent intravenous dexamethasone had a significantly greater decline in radial head BMD compared with those on daily oral prednisolone, reinforcing the variable sensitivities of skeletal cells to GC regimens.³⁴ Distal radius BMD may be particularly relevant in younger individuals in predicting upper-limb fracture risk,⁴⁶ and may need to be considered in young individuals receiving intermittent pulse methylprednisolone therapy.^{47,48} Finally, current guidance and risk prediction tools have not addressed the implications of pulse intravenous methylprednisolone therapy. The Fracture Risk Assessment Tool, also known as FRAX (University of Sheffield, Sheffield, UK), treats GC exposure dichotomously with dose adjustments designed for daily regimens, making translation to intermittent high-dose pulses challenging. Until further evidence emerges, patients undergoing pulse intravenous methylprednisolone treatment with a high risk of fractures should be managed in the same way as those on long-term oral glucocorticoids. This includes providing calcium and vitamin D supplementation, along with standard lifestyle measures that align with the principles for preventing glucocorticoid-induced osteoporosis.

This analysis has several strengths, including a well-structured research question defined within a framework, and formal risk-of-bias assessment that improved methodological rigour and transparency. Nonetheless, several limitations should be acknowledged. Only 8 studies involving 192 participants were included, which restricts statistical power and limits robustness and generalisability of the pooled findings. Moreover, the mean follow-up of approximately 5.5 months may be insufficient to detect clinically meaningful changes in BMD and is inadequate for assessing fracture outcomes, which generally require longer observation periods. Additionally, there was substantial clinical heterogeneity across the included studies. The study populations varied widely, including individuals with Graves' disease,^{49,50} multiple sclerosis,^{51,52} and rheumatological or other inflammatory conditions,⁵³⁻⁵⁵ all of which may independently influence bone metabolism through differences in inflammatory burden,⁵⁶ mobility,^{57,58} endocrine status,⁵⁹ nutritional factors,⁶⁰ and concomitant therapies.⁶¹ In addition, pulse intravenous methylprednisolone regimens differed across studies in dose, cumulative exposure, frequency, and duration, which may differentially affect skeletal outcomes. This variability

reflects differences in the design and clinical context of the available primary studies and thus represents an inherent limitation of the current evidence base. Furthermore, inconsistent reporting of incident fractures, limited TBS data, and heterogeneity in bone turnover marker assays and sampling time points further constrained interpretation. Although within-person pre-/post-comparisons may reduce some confounding, the small number of studies precluded meaningful subgroup analyses. Accordingly, the findings should be interpreted cautiously, and larger longitudinal studies with longer follow-up are needed.

CONCLUSION

In conclusion, pulse intravenous methylprednisolone therapy does not significantly alter spine or hip BMD over the short-term, but it suppresses bone formation and resorption markers, indicating early effects on bone remodelling. Although pulse regimens may be less detrimental to BMD than chronic daily GC exposure, current evidence is insufficient to conclude that fracture risk is negligible, particularly among high-risk patients or those receiving repeated or high cumulative doses. From a clinical perspective, preservation of short-term BMD should not be equated with skeletal safety; baseline fracture risk assessment remains important, and clinicians should not rely on BMD alone when evaluating patients receiving pulse intravenous methylprednisolone. Future well-designed controlled studies should directly compare pulse and chronic regimens with standardised timing of turnover marker sampling, incorporate bone quality assessments such as TBS at peripheral skeletal sites such as the radius, and include fracture and fall outcomes.

Ethics statement

Not applicable, as no participants were recruited.

Declaration

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

Supplementary materials

Table S1. Search strategy.

Table S2. Risk of Bias (ROBINS-E).

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2025 Singapore consensus statements on the management of osteoporosis

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ABSTRACT

Introduction: Osteoporosis is a progressive disease characterised by changes in bone structure leading to fragility fractures. In Singapore, it is a significant health concern with a high prevalence, and is expected to increase as the population ages. These consensus statements aim to provide scientifically grounded recommendations for the management of osteoporosis, to standardise its management in Singapore and promote multidisciplinary collaboration.

Methods: An expert panel comprising 18 representatives from 10 Singapore medical bodies developed consensus statements based on current evidence and through multiple online meetings. Each panellist voted on each statement independently using a 3-point Likert scale (Agree, Neutral, Disagree). Consensus (total ratings of "Agree") was set a priori at $\geq 80\%$, with statements not reaching this threshold excluded for lacking consensus.

Results: The expert panel reached consensus on 80 consensus statements. These include 10 statements on screening, risk factors, and fracture risk assessment; 7 statements on initial bone mineral density testing; 5 on the indications for pharmacotherapy; 20 on osteoporosis pharmacotherapy; 24 on treatment targets, treatment monitoring, and follow-up bone mineral density testing; and 14 statements on the prevention and management of medication-related osteonecrosis of the jaw.

Conclusion: The consensus statements in this paper guide clinicians in using the latest evidence and expert opinion to inform appropriate diagnostic and therapeutic approaches for the management of osteoporosis. These statements are not intended to replace current guidelines, but rather to support clinical decision-making and help develop individualised, patient-centred management plans based on the patient's demographics, clinical characteristics, and preferences.

Keywords: bone mineral density, consensus, fractures, osteoporosis, pharmacotherapy

CLINICAL IMPACT

What is New

- These consensus statements integrate the latest clinical evidence with practical considerations in the management of osteoporosis in Singapore.
- The statements align with and complement the Agency for Care Effectiveness Clinical Guidance published on 15 August 2025 on thresholds, pharmacotherapy options, and referral triggers.

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Clinical Implications

- Clinicians should stratify patients by fracture risk and implement personalised, patient-centred treatment pathways that escalate rapidly for very high-risk individuals.
- Long-term management requires careful planning of transitions in pharmacotherapy, and appropriate specialist referral and multidisciplinary management as the patient's condition evolves during management.

INTRODUCTION

Osteoporosis is a progressive disease characterised by a decrease in bone mineral density (BMD) secondary to pathophysiological alterations in the bone microstructure that predispose patients to fragility fractures. It is a global health problem that has caused significant morbidity and mortality, leading to a lower quality of life and increasing healthcare costs.¹

In the Asia-Pacific region, a study involving 9 member countries of the Asian Federation of Osteoporosis Societies found that the number of hip fractures will increase from 1,124,060 in 2018 to 2,563,488 in 2050.² In Singapore, a systematic review reported a prevalence of 8.5% among all adult men, 6.8% among women aged 45–69 years, and 35.7%–59% among all adults aged 60 years and above.¹

While the incidence of femoral neck fractures among adults 45 years old and above was 611 per 100,000 person-years or lower, estimates among women 75 years old and older were much higher (up to 1369 per 100,000 person-years).¹

According to Singapore data, 36,082 first hip fractures were recorded in an 18-year study period in the new millennium—from 2000 to 2017—where the incidence of hip fracture admissions continued to rise from 1487 to 2729 fractures/year, in keeping with an ageing population.³ Singaporean women have twice the hip fracture rate of men, and risk factors are related to menopausal osteoporosis and low oestrogen levels and bioactivity.^{4–6} Osteoporosis in women is also more prominent among those with low body mass index (BMI), Chinese ethnicity, sleep apnoea, chronic joint pain, and weak muscle strength.^{7–10}

Despite the burden of osteoporosis, it remains under-treated in Singapore, and more than 54% of primary care physicians reported barriers to osteoporosis management, including low familiarity with patient follow-up (18%), pharmacological treatments (11%), and interpretation of BMD (9%).¹¹ To address some of these gaps, these consensus statements were developed to provide practical, context-specific recommendations to guide healthcare professionals

across specialties—including primary care physicians, specialists, and allied health providers—in clinical decision-making for the screening, diagnosis, and management of osteoporosis to improve patient outcomes and reduce the burden of osteoporotic fractures in Singapore.

While several international and Asia-Pacific consensus statements have been published on the management of osteoporosis, these recommendations are often developed in the context of heterogeneous healthcare systems and may not fully address practice realities in Singapore. This Singapore consensus was developed to complement existing regional guidance by providing context-specific recommendations that reflect epidemiology, healthcare infrastructure, access to diagnostics and therapies, and prevailing clinical practice patterns in Singapore, with an emphasis on practical implementation across multidisciplinary care settings.

Importantly, these consensus statements aim to supplement the Agency for Care Effectiveness (ACE) Clinical Guidance (“Osteoporosis: Diagnosis and Management”) published in 2025 by expanding the discussion on various topics, including screening, pharmacotherapy, treatment targets, treatment response, patient monitoring and follow-up, and medication-related osteonecrosis of the jaw (MRONJ).¹²

METHODS

An expert panel was formed to represent several medical specialties involved in the management of osteoporosis, including endocrinologists, rheumatologists, geriatricians, obstetricians and gynaecologists, orthopaedic surgeons, dentists and dental surgeons, and primary care physicians with an interest in osteoporosis. To achieve this, the following societies were invited to nominate 2 representatives each to the expert panel: the Osteoporosis Society (Singapore); the Singapore Dental Association; the Endocrine and Metabolic Society of Singapore; the Society for Geriatric Medicine Singapore; the Singapore Orthopaedic Association; the Obstetrical and Gynaecological Society of Singapore; the College of Dental Surgeons; the Singapore Society of Rheumatology; the Chapter of Endocrinology; and the College of Obstetricians and Gynaecologists. A total of 18 experts accepted the nominations from their respective societies.

A steering committee comprising 3 specialists (2 endocrinologists, 1 family physician) conducted a formal literature review using Medline/PubMed, Embase, the Cochrane Library, and Google Scholar. The retrieved literature was then assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.¹³ The level of evidence was graded as follows: (1) high (i.e.

high confidence that the true effect is similar to the estimated effect); (2) moderate (i.e. true effect is probably close to the estimated effect); (3) low (i.e. true effect might be markedly different from the estimated effect); and (4) very low (i.e. very low certainty of the true effect). The level of evidence was modified if variations in the estimated clinical effects—due to ethnicity, cultural context, healthcare infrastructure, access to resources, and prevailing clinical practice—were observed and differed from the published findings.

A modified Delphi process was used in the consensus process. This included structured, predefined items, qualitative as well as semi-structured or quantitative ratings, and 2 to 3 rounds of voting, unlike a traditional Delphi approach.¹⁴ Based on the findings of the literature review, a steering committee developed comprehensive consensus statements focusing on osteoporosis screening, risk factor assessments, diagnostics, therapeutic approach, monitoring, and follow-ups. The statements, together with the evidence, were reviewed by the entire expert panel over online meetings and email correspondence. The meetings were led by the steering committee and moderated by an independent methodologist. The consensus process required expert panels to indicate their agreement with the various statements by voting using a standardised voting sheet. Panel members independently rated their level of agreement with each draft statement on a 3-point Likert scale (Agree, Neutral, Disagree). Statements underwent 2 to 3 Delphi rounds and 3 rounds of voting. Statements that achieved at least 80% agreement at “Agree” were accepted as consensus recommendations. Statements that did not reach consensus despite multiple iterations (e.g. specific fracture risk thresholds for treatment initiation) were either excluded or presented with explicit acknowledgement of lack of consensus; in such cases, individualised clinical judgement was encouraged.

Statements that achieved consensus were classified as follows: “Strong” if the benefits of the intervention outweigh the undesirable effects and was chosen by most well-informed individuals, attaining high percentage of consensus agreement; “Weak” if there was uncertainty in the desirable and undesirable effects of the intervention due to low quality of evidence, or an alternative intervention was available; “good practice statement” (GPS) if the recommendation was based on clinical expert opinion.

RESULTS

The expert panel reached consensus on 80 statements. These include 10 statements on screening, risk factors, and fracture risk assessment; 7 statements on initial BMD testing; 5 statements on the indications for pharmacotherapy and 20 statements on the various pharmacological agents for osteoporosis; 24 statements on treatment targets, treatment monitoring, and follow-up BMD testing; and 14 statements on the prevention and management of MRONJ.

DISCUSSION

Screening, risk factors, and fracture risk assessment

Early identification of individuals at risk and the use of targeted screening strategies for osteoporosis and fragility fractures are fundamental to effective fracture prevention. The expert panel recommends that risk factors for fragility fractures be assessed in all postmenopausal women as well as men 60 years old and above. Well-recognised risk factors include a history of fragility fracture, family history of osteoporosis, being of Chinese ethnicity, a history of falls, a BMI of <20 kg/m², early menopause (≤45 years old), lifestyle factors such as smoking and alcohol consumption, poor dietary calcium intake, long-term use of medications that accelerate bone loss, and chronic conditions such as diabetes mellitus or inflammatory rheumatic diseases.¹²

Table 1. Statements 1–3.

Statement	Quality of evidence	Level of consensus (% agree)	Strength of recommendation
1. All postmenopausal women should be assessed for risk factors for fragility fractures.	Low	83	Strong
2. All men aged 60 and above should be assessed for risk factors for fragility fractures.	Low	86	Strong
3. OSTA can be used for osteoporosis risk assessment in postmenopausal Singaporean women of Asian ethnicity.	Moderate	86	Strong

OSTA: Osteoporosis Self-Assessment Tool for Asians

In Singapore, the Osteoporosis Self-Assessment Tool for Asians (OSTA) may be used for osteoporosis risk among postmenopausal Singaporean women of Asian ethnicity.¹⁵ OSTA stratifies risk using only 2 variables: age (years) and weight (kg). Patients are classified as high (score >20), moderate (score 0–20), or low risk (score <0) (Supplementary Fig. S1), providing a simple and practical guide in the primary care setting to identify those who should undergo BMD testing. The overall performance of OSTA is known to vary between populations, as demonstrated in various studies. Among postmenopausal women in Beijing, OSTA was shown to have a sensitivity of 69.6% and a specificity of 75.1%.¹⁶ For postmenopausal women in rural India, OSTA had a sensitivity of 88.5% and a

specificity of 41.7%.¹⁷ For Thailand, pooled estimates for sensitivity and specificity were 84% and 61%, respectively.¹⁸ In Hong Kong, a recent study found that in women under 65 years old, OSTA had a sensitivity of 67.8% and specificity of 63.4%; in older women, sensitivity was high at 97.3%, but specificity was low (18.1%).¹⁹ In contrast, a newly developed scale (Chinese Osteoporosis Screening Algorithm, or COSA) had improved sensitivity and specificity in the Singapore population in Hong Kong.¹⁹ Lastly, a Singapore study found that a modified cut-off point of -1.2 had a sensitivity of 76% and a specificity of 74%.²⁰ Future studies should be conducted to assess the specificity and sensitivity in Singapore among different ethnicities and age groups.

Table 2. Statements 4–10.

Statement	Quality of evidence	Level of consensus (% agree)	Strength of recommendation
4. Fragility fractures are fractures that result from mechanical forces that would not ordinarily result in fracture (i.e. low-level or low-energy trauma).	High	89	Strong
5. Risk factors for fragility fractures include previous fragility fracture; family history of osteoporosis or fragility fracture; BMI <20 kg/m ² ; early menopause (45 years old or younger); low calcium intake (<500 mg/day); alcohol intake >2 units/day; smoking; prolonged immobility; history of falls; medications that may increase bone loss (e.g. glucocorticoids use >3 months in the last year or prednisolone dose >5 mg daily, aromatase inhibitors, androgen deprivation therapy); and diseases that may increase risk of fractures (e.g. diabetes or inflammatory rheumatic disease).	Moderate	89	Strong
6. Clinicians should exercise clinical judgement in undertaking fracture risk assessment. Individualise fracture risk assessment according to patients' clinical risk factors and relevant medical history.	Low	100	GPS
7. Femoral neck BMD (g/cm ²) is recommended for use in the FRAX calculator.	High	100	Strong
8. The presence of lower scores in other BMD sites requires consideration of FRAX adjustments and clinical judgement to individualise fracture risk assessment.	Moderate	89	Strong
9. Individuals with type 2 DM should have 1 of the following adjustments considered in the calculation of their fracture risks: (1) substitute rheumatoid arthritis with type 2 DM in FRAX; or (2) reduce the T-score by 0.5 deviations; or (3) add 10 years to the age.	Moderate	89	Strong
10. Authors recommend defining a VHR category as follows: - Clinical: Presence of any of the following—recent fragility fracture in the last 1 year; history of multiple previous fragility fractures; more than 2 fragility fractures while on treatment; T-score ≤-3.0; high fall risk; or long-term use of bone-harming medications. - FRAX-based: MOFP or HFP that is ≥20% above the applicable intervention threshold, whether fixed, age-dependent, or plateau thresholds.	Low	89	Strong

BMD: bone mineral density; BMI: body mass index; DM: diabetes mellitus; FRAX: Fracture Risk Assessment Tool; GPS: good practice statement; HFP: hip fracture probability; MOFP: major osteoporotic fracture probability; RA: rheumatoid arthritis; T2DM: type 2 diabetes mellitus; VHR: very high risk of fracture

Fragility fractures (i.e. fractures caused by low-energy trauma, which is quantified as a force equal to or less than that of a fall from standing height) can occur in any bone in the body, but their most common locations are in the spine, hip, and wrist. In a 2016 Singapore retrospective observational study, a history of fragility fracture was reported in 7% of women aged 50 and above.²¹ Likewise, a 2019 Singapore population-based study highlighted the age-adjusted incidence of hip fractures in adults aged 50 and above: 253 and 125 per 100,000 in women and men, respectively.²²

The expert panel highlighted the importance of fracture risk stratification and individualised fracture risk assessment, including the use of validated tools such as the Fracture Risk Assessment Tool (FRAX). The FRAX tool estimates an individual's 10-year risk of hip or major osteoporotic fracture based on age, body mass index, and additional risk factors.²¹ A randomised controlled trial found that compared with usual care, community-based screening using FRAX and commencement of anti-osteoporosis treatment reduced the incidence of hip fractures in women aged 70–85 years.²³

The expert panel underscores that in addition to the parameters included in FRAX, the clinician should also consider other individual patient-related factors, such as mobility, comorbidities, medication use, and lifestyle factors. Type 2 diabetes (T2DM), in particular, affects FRAX calculations, which tend to underestimate fracture risk in T2D. Therefore, individuals with T2DM should have 1 of the following adjustments considered in the calculation of their fracture risks: (1) substitute rheumatoid arthritis with T2DM in FRAX; or (2) reduce the T-score by 0.5 deviations; or (3) add 10 years to the age.

The expert panel also emphasised that the BMD at the femoral neck is the value recommended for use in FRAX, as the FRAX model was developed and validated using femoral neck measurements. Hence, this value provides the most robust and least confounded predictor of hip fracture risk.

Patients with major osteoporotic fracture probability (MOFP) or hip fracture probability (HFP) $\geq 20\%$ above the applicable interventional threshold are considered at very high risk of fractures (VHR). The presence of a recent fragility fracture in the last 1 year, history of multiple fragility fractures, more than 2 fragility fractures while on treatment, T-scores of ≤ -3.0 , high fall risk, or chronic medication use that leads to rapid bone loss (such as aromatase inhibitors and high-dose glucocorticoids) are also hallmarks of VHR. Patients with VHR represent a subset that requires more aggressive therapy and follow-up.²⁴

It should be noted that the expert panel was unable to reach consensus on the specific FRAX threshold

to recommend in these consensus statements. While 72% agreed to adopt the thresholds recommended by the 2025 ACE Clinical Guidance,¹² 28% advocated for a hybrid FRAX-based intervention threshold (i.e. fixed thresholds [MOFP $\geq 14\%$, HFP $\geq 3.5\%$] from 50 to 65 years old; age-dependent thresholds from >65 to 74 years old; and plateau thresholds from ≥ 75 years old, using the 75-year-old values [23.9% MOFP, 9.45% HFP]).²⁵ The former had undergone an ACE cost-effectiveness analysis, and a unified recommendation on the intervention thresholds simplifies decision-making. However, a non-negligible minority raised concerns about the potential for overtreatment in the upper extreme of age. Given the lack of consensus, the expert panel suggests a holistic approach, with FRAX as one factor in the decision to treat.

Initial BMD testing

BMD testing by dual-energy x-ray absorptiometry (DXA) remains the gold standard for diagnosing osteoporosis and monitoring treatment.²⁶ A T-score of ≥ -1.0 indicates normal bone density. On the other hand, a T-score of < -1.0 to > -2.5 indicates osteopenia, and a T-score of ≤ -2.5 indicates osteoporosis.²⁶

The expert panel recommends initial BMD testing for all postmenopausal women aged ≥ 65 years and for those with fragility fractures. In addition, BMD testing may be suggested for postmenopausal women aged 65 years and below with 1 risk factor for fragility fractures; for men aged 70 years and above; and for men aged 50 to 69 years with 1 risk factor for fragility fractures.

Measuring BMD using DXA at the central skeletal sites (typically L1–L4 and hip femoral neck or total hip) is considered best practice for diagnosing osteoporosis and assessing fracture risk.²⁷ Central sites combine cortical and trabecular bone and correlate strongly with risk of major osteoporotic fractures, particularly hip fractures.

In some circumstances, however, measurements at the lumbar spine or hip may be unreliable or uninterpretable owing to age-related degenerative changes (osteophytes, vertebral compression, or scoliosis), hip prosthesis or other hardware, obesity beyond the limits of table positioning, or other artefacts that distort results. In such situations, the International Society of Clinical Densitometry allows use of the distal one-third radius (forearm) as an alternate site for diagnosis.²⁸

Pharmacotherapy

Pharmacological therapy is indicated in individuals with established osteoporosis or those at high risk of fracture. Hence, it is recommended in the following patients: (1) postmenopausal women and men ≥ 50

Table 3. Statements 11–17.

Statement	Quality of evidence	Level of consensus (% agree)	Strength of recommendation
11. BMD is recommended in all postmenopausal women >65 years old.	Low	94	Strong
12. BMD is suggested for postmenopausal women ≤65 years old with one risk factor for fragility fracture.	Low	89	GPS
13. BMD is suggested for men aged ≥70 years old.	Low	83	GPS
14. BMD is suggested for men 50–69 years old with 1 risk factor for fragility fractures.	Low	83	GPS
15. BMD is recommended for those with fragility fractures	Moderate	94	Strong
16. BMD should be measured by dual energy X-ray absorptiometry (DXA) scanning on at least two central skeletal sites, typically the lumbar spine (L1–L4) and the hip.	Moderate	94	Strong
17. If the standard skeletal sites are deemed unsuitable for DXA scanning, measurement of the distal 1/3 radius as an alternative site is recommended.	Low	83	Strong

BMD: bone mineral density; DXA: dual-energy X-ray absorptiometry; GPS: good practice statement

Table 4. Statements 18–22.

Statement	Quality of evidence	Level of consensus (% agree)	Strength of recommendation
Indications for pharmacotherapy			
18. Pharmacotherapy is recommended in postmenopausal females who have had any fragility fracture	High	89	Strong
19. Pharmacotherapy is recommended in males ≥50 years old who have had any fragility fracture	Moderate	89	Strong
20. Pharmacotherapy is recommended in postmenopausal females with T-score ≤-2.5	High	83	Strong
21. Pharmacotherapy is recommended in men with T-score ≤-2.5	Moderate	83	Strong
22. Individuals who obtained FRAX scores above the recommended threshold of treatment should consider the commencement of pharmacotherapy.	Low	83	Strong

FRAX: Fracture Risk Assessment Tool

years old who have had any fragility fracture; (2) postmenopausal females and men with T-scores of ≤-2.5; and (3) those who obtained a FRAX score above the recommended threshold of treatment.^{12,29,30} The goal of osteoporosis treatment is to reduce fracture risk by improving bone strength.

Menopausal hormonal therapy (MHT) should be considered for fracture risk reduction in appropriately selected postmenopausal women, particularly those within 10 years of their final menstrual period.^{31–33} In this time window, the balance of benefits and harms is most favourable for bone protection, provided contraindications are absent and class individual

cardiometabolic and breast cancer risks are assessed. Early menopause (ages 40–45) warrants particular attention. Continuation of MHT up to the average age of natural menopause mitigates skeletal sequelae of prolonged oestrogen deficiency.⁵ Tibolone may be considered for women ≤60 years old, recognising that use beyond this age is generally discouraged due to increased stroke risk.³⁴ These recommendations are concordant with contemporary regional guidance emphasising individualised risk–benefit appraisal.^{24,29,35}

A selective oestrogen receptor modulator (SERM) is an appropriate therapeutic alternative for postmenopausal women at risk of vertebral fractures who

Table 5. Statements 23–28.

Statement	Quality of evidence	Level of consensus (% agree)	Strength of recommendation
Menopausal hormone therapy			
23. Consider menopausal hormone therapy to reduce the risk of osteoporosis and/or fragility fractures in postmenopausal women within 10 years of menopause.	Moderate	83	Strong
24. The increased risk of adverse events associated with menopausal hormone therapy should be carefully weighed against its benefits.	Very low	94	GPS
25. SERMs should be considered as a treatment option for postmenopausal women with osteoporosis at risk of vertebral fractures who cannot tolerate other agents, if there are no problematic hot flashes.	Moderate	83	Strong
26. SERMs may be particularly useful in younger postmenopausal women at risk of vertebral fracture with a prior or family history of breast cancer.	Moderate	89	Strong
27. Menopausal hormone therapy should be considered in women with early menopause (40–45 years old) until at least the age of 50 years old.	Moderate	83	Strong
28. Tibolone may be considered in postmenopausal women ≤ 60 years old. However, its use in older women is not recommended due to an increased risk of stroke.	Moderate	100	Strong

GPS: good practice statement; SERM: selective oestrogen receptor modulator

cannot tolerate, or decline, other first-line agents and who do not experience problematic vasomotor symptoms.^{26,36} Their vertebral fracture efficacy and potential breast cancer risk-modifying profile support targeted use, most notably in younger postmenopausal women with a personal or family history of breast cancer and predominant spinal fragility risk.^{37,38} As SERMs have limited efficacy for hip and non-vertebral fractures, clinicians should assess their suitability based on the individual patient's fracture pattern and overall risk profile, consistent with an individualised approach to fracture reduction.³⁶

Oral bisphosphonates are recommended as first-line therapy for patients at high fracture risk owing to their robust antifracture efficacy, long-term safety data, accessibility, and cost-effectiveness.^{12,39} Therapy should be reassessed after 5 years for oral regimens and after 3 years for intravenous zoledronate to determine if the treatment target has been reached or whether continuation of treatment is indicated.⁴⁰ Furthermore, assessment of the risk and benefit of bisphosphonate treatment should be considered after 3 to 5 years of therapy in view of the higher risk of adverse effects such as atypical femoral fractures (AFF) in the Asian population.^{41–43} Patients who fail to achieve treatment targets (e.g. those with incident fractures on therapy, clinically significant BMD decline beyond the least significant change, or persistently

elevated bone turnover markers) should be transitioned to an alternative therapy, including a different class where adherence to oral bisphosphonate was high.⁴⁰

Parenteral antiresorptives (zoledronate, denosumab) are appropriate for those with poor oral tolerance, malabsorption, adherence barriers, or sub-optimal response, and are likewise indicated when rapid fracture risk mitigation is required.^{44–46} Additionally, denosumab is appropriate for patients who require pharmacotherapy but have contraindications to, or intolerance of, bisphosphonates, and may be considered in VHR states when anabolic therapy cannot be initiated.

All non-bisphosphonate therapy, and especially denosumab therapy, should not be interrupted without a transition plan to switch to an anti-resorptive, if necessary, before a final transition to bisphosphonate. Discontinuation of denosumab is associated with a rebound increase in bone turnover, rapid loss of accrued BMD, and, in some cases, multiple spontaneous vertebral fractures.^{47,48} Where cessation is necessary, timely antiresorptive coverage (preferably with an intravenous bisphosphonate if denosumab therapy has been ongoing for more than 2.5 years) is recommended to attenuate rebound effects. Specialist referral is advisable in the presence of significant BMD decline, incident vertebral fractures, or rising bone turnover markers around discontinuation.

Table 6. Statements 29–38.

Statement	Quality of evidence	Level of consensus (% agree)	Strength of recommendation
Antiresorptive therapy			
29. Oral bisphosphonate therapy is recommended as first-line treatment in patients at VHR.	High	100	Strong
30. In patients at VHR who are unable to be commenced on osteoanabolic treatment, IV zoledronate, or SC denosumab is recommended.	Moderate	94	Strong
31. Parenteral antiresorptive treatments such as zoledronate and denosumab are recommended for patients who do not respond adequately to oral bisphosphonate therapy.	Moderate	94	Strong
32. Oral bisphosphonate therapy should be reassessed after 5 years of therapy.	Low	89	Strong
33. Intravenous bisphosphonate therapy should be reassessed after 3 years of therapy.	Moderate	83	Strong
34. Individuals or patients who have not achieved their target of osteoporosis treatment after 3–5 years of BP use should consider changing to an alternative drug class	Moderate	89	Strong
35. Denosumab may be considered in patients with VHR.	Moderate	89	Strong
36. Denosumab is recommended in patients requiring pharmacotherapy but who have contraindications to or cannot tolerate bisphosphonate therapy.	Moderate	89	Strong
37. Denosumab therapy should not be interrupted in patients at VHR (no drug holiday).	Moderate	89	Strong
38. For patients experiencing a significant reduction in BMD, occurrence of vertebral fractures, or a rise in BTM ^a after discontinuing denosumab, referral to a specialist is recommended to advise on an alternative therapy.	Moderate	89	Strong

BMD: bone mineral density; BP: bisphosphonate; BTM: bone turnover marker; IV: intravenous; SC: subcutaneous; VHR: very high risk of fractures

^a If available in clinical practice.

Table 7. Statements 39–42.

Statement	Quality of evidence	Level of consensus (% agree)	Strength of recommendation
Anabolic agents			
39. Anabolic agents (teriparatide or romosozumab) should be considered as first-line therapy for patients with very high fracture risk.	Moderate	83	Strong
40. It is recommended that the 12-month course of romosozumab therapy should be followed by antiresorptive treatment (denosumab or bisphosphonate).	Moderate	89	Strong
41. Teriparatide may be continued for more than 2 years if clinically indicated.	Low	94	Weak
42. In patients who require discontinuation of teriparatide, switching to an antiresorptive agent is recommended.	Moderate	94	Strong

For VHR patients, such as those with recent vertebral fractures, multiple fragility fractures, very low T-scores, or other indicators of imminent risk, anabolic-first strategies (teriparatide or romosozumab) are recommended.^{44,49,50} Romosozumab is typically administered for 12 months and must be followed immediately by an antiresorptive agent to preserve gains.⁴⁰ Teriparatide may be extended beyond 24 months when clinically justified, with subsequent antiresorptive consolidation likewise imperative.⁵¹ Accumulating evidence indicates that anabolic-then-antiresorptive sequences yield larger BMD gains and greater fracture risk reduction—a finding now echoed in Asia-Pacific consensus and regional guidelines, with supportive real-world data emerging from East Asian cohorts.^{40,50}

Treatment targets and response, monitoring, and follow-up

The consensus statements on treatment targets, response assessment, and follow-up monitoring in osteoporosis provide a structured framework for optimising patient care. These recommendations emphasise the dual objectives of reducing fracture

risk and ensuring long-term treatment safety, while allowing for individualised strategies based on patient risk profiles and therapeutic responses.

In patients with osteoporosis defined by a T-score ≤ -2.5 , the primary treatment goal is to achieve a T-score above this high-risk threshold coupled with the absence of incident fragility fractures. This approach is consistent with both Asian and international guidelines that advocate for “treat-to-target” strategies in osteoporosis based on increasing evidence of fracture risk reduction with BMD improvement.^{51–53} A T-score of > -2.5 should be considered the minimal target; patients with other important risk factors might warrant higher T-score targets (for example, in individuals with a history of fracture, a higher T-score target of -2.0 might be appropriate).⁵¹ When patients demonstrate a sub-optimal response, manifested by new fragility fractures, clinically significant BMD decline beyond the least significant change (LSC), or persistently elevated bone turnover markers, systematic evaluation is required. This includes confirming treatment adherence, excluding secondary causes of osteoporosis, and, where appropriate, referral to a specialist.^{12,40}

Table 8. Statements 43–46.

Statement	Quality of evidence	Level of consensus (% agree)	Strength of recommendation
43. For patients with T-score ≤ -2.5 , the treatment target is a T-score of > -2.5 and no recent fractures.	Low	89	Strong
44. Osteoporosis therapy should be continued when treatment target has not been achieved.	Moderate	89	Strong
45. For patients initiated on treatment with a baseline T-score above -2.5 (i.e. in the osteopenic range), an adequate response to therapy may be defined as a stable BMD or an increase at the total hip or lumbar spine that exceeds the institution's least significant change value.	Moderate	94	Strong
46. In patients who do not respond well to pharmacotherapy, evaluate treatment adherence, screen for secondary causes of osteoporosis and consider referral to a specialist.	Low	89	Strong

BMD: bone mineral density

Table 9. Statements 47–51.

Statement	Quality of evidence	Level of consensus (% agree)	Strength of recommendation
47. Switching to an anabolic agent may be considered in patients who do not respond well to antiresorptive therapy.	Moderate	89	Strong
48. The addition of teriparatide may be considered in patients with inadequate response to denosumab.	Low	89	Weak
49. Osteoporosis therapy should be restarted if there is bone loss, especially at the hip.	Low	89	Strong
50. Osteoporosis therapy should be restarted if incident fragility fractures occur.	Moderate	94	Strong
51. Bisphosphonate therapy may be temporarily interrupted in patients who have achieved their osteoporosis treatment targets.	Low	94	Strong

The consensus further provides clear direction on therapeutic sequencing. For patients inadequately responding to oral bisphosphonates, parenteral antiresorptive agents such as zoledronate or denosumab are recommended. These agents offer greater potency, parenteral convenience, and superior adherence, particularly in patients with gastrointestinal intolerance or poor compliance with oral therapy.⁴⁰

Switching to an anabolic agent, such as teriparatide or romosozumab, may be considered in patients who continue to fracture or exhibit declining BMD despite potent antiresorptive therapy.^{40,54} Furthermore, in selected cases, adding teriparatide to denosumab may be considered, particularly when bone turnover suppression is inadequate. The DATA and DATA-Switch studies provide evidence for this combination and sequential strategy, underscoring the principle of personalised therapy pathways.⁵⁵ For patients who achieve treatment targets on bisphosphonates, temporary interruption (commonly termed a “drug holiday”) may be considered if they are no longer at high risk of fractures. This strategy aims to minimise rare, long-term adverse effects, such as AFF and MRONJ, while preserving antifracture benefit from bisphosphonate skeletal retention. However, ongoing monitoring is essential, as therapy should be promptly re-initiated in cases of BMD decline, especially at the hip, or following incident fragility fractures. Denosumab, in contrast, should not be interrupted without alternative antiresorptive coverage, given the well-established risk of rebound bone loss and multiple vertebral fractures on discontinuation.⁵⁶

Monitoring is a cornerstone of effective long-term osteoporosis management. The consensus recommends that patients undergo a clinical review within 3–6 months of treatment initiation, followed by reassessment every 6–12 months to evaluate treatment adherence, emerging adverse effects, and evolving fracture risk. BMD measurement remains central to monitoring. The expert panel emphasises individualising repeat DXA intervals based on age, baseline BMD, treatment type, and fracture risk. A 1–2 year interval is generally appropriate after initiating therapy, with shorter intervals warranted for those at high risk of rapid bone loss, such as patients receiving glucocorticoids or aromatase inhibitors. For untreated patients, testing frequency should reflect baseline fracture risk, with longer intervals in low-risk patients and closer monitoring in moderate-to-high-risk individuals if the results would alter clinical management. Importantly, follow-up BMD testing should only be performed when results are likely to influence patient decisions, to avoid unnecessary investigations.⁵⁷

The expert panel highlights technical limitations in comparing BMD across different DXA devices.

Quantitative comparisons or LSC calculations cannot be reliably made between machines unless cross-calibration has been performed.⁵⁷ Therefore, patients should ideally return to the same DXA device for follow-up measurements, provided that in vivo precision and LSC values are established and meet international standards. Even machines from the same manufacturer may differ in precision, reinforcing the importance of standardised monitoring protocols. However, if returning to the same BMD facility is not possible, the clinician may use their clinical judgement when reviewing the results. When long-term care is transferred to another facility or treating institution, BMD should be performed at the follow-up facility to maintain long-term continuity of care.

The expert panel suggests that the use of bone turnover markers (BTMs) should be confined to specialists familiar with their interpretation and clinical applicability. While BTMs can provide early signals of treatment response and adherence, their variability and lack of standardisation limit their routine clinical use.⁵⁸ Selective application in specialist centres allows integration with research-grade protocols and expert interpretation, minimising the risk of misclassification in general practice.

The expert panel emphasises counselling of patients regarding preventive measures and monitoring for rare adverse events, particularly AFF and MRONJ, in patients receiving long-term antiresorptive therapy.^{59,60} Patient education enhances vigilance for prodromal symptoms such as thigh pain in AFF or oral symptoms in MRONJ, enabling earlier intervention.

Fig. 1 shows a proposed management algorithm based on fracture risk, including pharmacotherapy and follow-up. The authors underscore that pharmacotherapy should be individualised according to the patient's specific fracture risk, patient preferences, comorbidities, and the safety profile of the various medications.

Medication-related osteonecrosis of the jaw (MRONJ)

MRONJ is an uncommon but clinically significant adverse event of antiresorptive therapy.⁶¹ The consensus statements on MRONJ balance the prevention of oral complications with uninterrupted fracture risk reduction, an approach consistent with Singapore and international guidance.^{12,60}

Before antiresorptives are initiated, patients should undergo a structured dental risk assessment by the primary physician, receive oral hygiene education on tooth brushing and flossing, and have active dental disease treated. Extractions of non-restorable teeth and prosthesis adjustment should be completed where feasible.⁶⁰ Importantly, treatment for those

Table 10. Statements 52–66.

Statement	Quality of evidence	Level of consensus (% agree)	Strength of recommendation
52. Regularly reassess fracture risk and the requirement for osteoporosis therapy in patients not receiving therapy, but who remain at increased fracture risk.	Low	94	Strong
53. It is recommended to clinically review patients after initiating pharmacological therapy, and individualise the follow-up plan according to patient's clinical risk and treatment.	Low	86	Strong
54. It is recommended that patients be reviewed 3–6 months after initiating pharmacological therapy for osteoporosis.	Low	83	Strong
55. It is recommended to follow up with patients every 6–12 months after initial clinical assessment, to assess for potential medication side effects and therapy adherence.	Low	89	Strong
56. Measurement of bone turnover markers should be confined to specialist practice.	Low	94	Strong
57. The use of FRAX is not recommended for monitoring response to pharmacotherapy.	Low	89	Strong
58. Counselling and monitoring for rare adverse effects such as AFF and ONJ is recommended for patients on antiresorptive therapy.	Moderate	89	Strong
59. Repeat BMD testing intervals must be individualised, considering a patient's age, baseline BMD, the type of pharmacological treatment, and the presence of clinical risk factors that are associated with bone loss.	Very low	94	Strong
60. Follow-up BMD is suggested at 1–2 years after initiating pharmacotherapy depending on individual risk factors and type of osteoporosis treatment.	Low	94	Strong
61. Shorter intervals between BMD testing may be indicated in the presence of factors associated with rapid change in BMD. ^a	Low	89	Strong
62. Follow-up BMD testing should be undertaken with clearly defined objectives and when the results are likely to influence patient management.	Low	94	Strong
63. In untreated patients, follow-up BMD testing should be performed according to their underlying fracture risk. Those at low risk may have repeat BMD testing at longer intervals while those at moderate-high risk may have a repeat BMD testing at closer intervals if this is undertaken with clear objectives and likely to change their clinical management.	Low	94	Strong
64. It is not possible to quantitatively compare BMD or to calculate a LSC between facilities without cross-calibration.	Moderate	89	Strong
65. Patients should ideally return to the same DXA device that was used to perform their most recent prior study, provided that the facility in vivo precision and LSC values are known and do not exceed established maximum values.	Moderate	89	Strong
66. BMDs done on DXA machines of different manufacturers should not be compared directly and even different models from the same manufacturer may have varying precision and accuracy. If different DXA devices of the same brand are used in follow-up testing, the in vivo precision and least-significant-change values should be known and should not exceed established maximum values.	Moderate	89	Strong

AFF: atypical femoral fracture; BMD: bone mineral density; DXA: dual-energy X-ray absorptiometry; FRAX: Fracture Risk Assessment Tool; LSC: least significant change; ONJ: osteonecrosis of the jaw

^a Shorter intervals between BMD testing may be indicated in the presence of factors associated with rapid change in BMD. Examples include the use of certain medications such as glucocorticoids, aromatase inhibitors, androgen deprivation therapy, and osteoanabolic therapies; medical disorders such as malabsorption and severe systemic inflammatory diseases; and other conditions such as prolonged immobilisation, bariatric surgery, and premature ovarian insufficiency ("premature menopause").

Fig. 1. Proposed management algorithm based on fracture risk, including pharmacotherapy and follow-up.

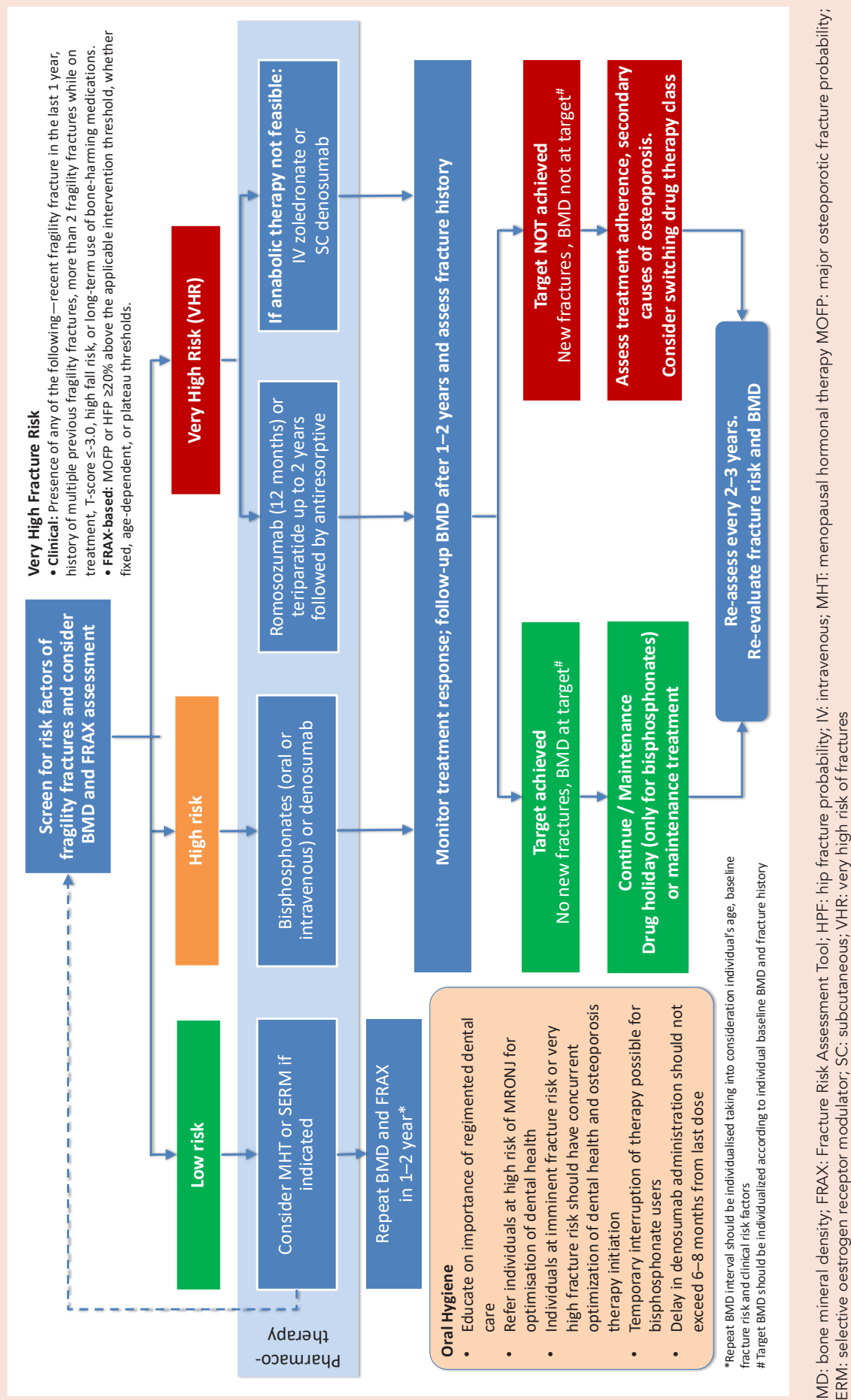


Table 11. Statements 67–73.

Statement	Quality of evidence	Level of consensus (% agree)	Strength of recommendation
67 MRONJ is a rare complication of osteoporosis therapy in patients without preexisting dental conditions/disease (endodontic lesions/periodontal lesions).	Low	89	Strong
Prior to osteoporosis therapy			
68. Patients should be educated on the importance of regimented dental care prior to commencement of osteoporosis therapy.	Low	94	Strong
69. Consider the patients' risk factors ^b for MRONJ prior to starting osteoporosis therapy.	Very low	89	GPS
70. In patients considered at high risk of MRONJ, consider referral for dental assessment for optimisation of dental health.	Low	94	Strong
71. Patients at imminent fracture risk or very high fracture risk should consider initiation of osteoporosis therapy with concurrent optimisation of dental health ^a to prevent further delay in fracture risk reduction.	Low	100	Strong
72. Discuss with each patient the risks and benefits of delaying initiation of anti-osteoporosis therapy while awaiting dental assessment.	Very low	94	GPS
73. For patients at high risk ^b of MRONJ, there should be consultation between the prescribing physician and the dentist regarding the plan of osteoporosis treatment.	Very low	89	GPS

GPS: good practice statement; MRONJ: medication-related osteonecrosis of the jaw

^a Extraction of teeth with poor prognosis, resolution of periodontal and endodontic lesions.

^b Systemic comorbidities that affect overall healing; active oral infections, such as but not limited to periodontal or endodontic disease; presence of poor-fitting dental prosthesis; smoking, use of glucocorticoid or chemotherapy, etc.

at very high fracture risk should not be unduly delayed. Dental optimisation in non-cancer patients can proceed in parallel to avoid harm from deferring pharmacotherapy, reflecting recommendations from the ACE Clinical Guidance (2025) and the 2022 American Association of Oral and Maxillofacial Surgeons' (AAOMS) Position Paper on MRONJ.^{12,60}

When invasive dental procedures are required during therapy, multidisciplinary planning is essential. For bisphosphonates, routine "drug holidays" are not supported by current evidence. A 2022 systematic review and meta-analysis and a 2025 update both found no significant reduction in MRONJ with temporary interruption versus continuation, supporting an individualised approach to drug holidays in individuals on bisphosphonates undergoing major dental procedures.^{62,63}

Denosumab warrants particular care because of the risk of rebound bone turnover and multiple vertebral fractures with delayed doses. Guidance recommends scheduling elective procedures 6–8 weeks before the next 6-monthly denosumab injection. Treatment should then be resumed once mucosal healing is established. Denosumab administration

should not be delayed beyond 6–8 months from the last dose.^{46,64}

If MRONJ occurs, management should be individualised and stage-based, and the choice of surgical and conservative management, as well as the risk-benefit of temporarily ceasing osteoporosis therapy, should be discussed with the patient after consulting with his/her primary physician. Early disease often responds to conservative care (analgesics, antimicrobial rinses, short courses of antibiotics), whereas advanced lesions may require surgical intervention. The AAOMS 2022 update and regional statements endorse this tiered approach, and emphasise that any suspension of antiresorptives must weigh the rare but serious risk of MRONJ against the substantially higher risk of osteoporotic fractures with treatment interruption.^{60,64}

Taken together, the consensus underscores integrated care, including proactive dental optimisation before or alongside osteoporosis treatment; careful peri-operative timing to avoid extended treatment gaps; and stage-appropriate management when lesions arise. This approach aligns practice in Singapore with current evidence while prioritising

Table 12. Statements 74–80.

Statement	Quality of evidence	Level of consensus (% agree)	Strength of recommendation
Patients undergoing osteoporosis therapy and require extensive/invasive dentoalveolar surgery			
74. For patients at high risk ^a of MRONJ on antiresorptive therapy, the primary physician should be consulted regarding the risk-benefit of temporary treatment interruption (drug holiday).	Low	89	Strong
75. Patients at high risk of MRONJ ^a should have appropriate dental peri-operative measures (such as optimising oral hygiene, use of antibiotics, post-op review at 2/4/8 weeks).	Low	89	Strong
76. In patients on bisphosphonates, a temporary interruption of therapy may be permitted if the prescribing physician determines the risk is low, to allow full mucosa/bony healing prior to resumption of the drug.	Low	100	Weak
77. Elective dental procedure should be performed 6–8 weeks before the next 6-monthly denosumab injection.	Very low	94	Strong
78. In patients on denosumab who are scheduled for invasive dental procedures, the delay in the next dose of denosumab should not exceed 6 to 8 months from the last dose.	High	86	Strong
79. Specialist advice is suggested for challenging cases of high-risk patients on denosumab treatment.	Very low	94	GPS
For patients who develop MRONJ while undergoing osteoporosis therapy			
80. The choice of surgical and conservative management (antimicrobials/analgesics) and the risk-benefit of temporary cessation of osteoporosis therapy should be discussed with the patient after consulting with his/her primary physician.	Very low	94	GPS

GPS: good practice statement; MRONJ: medication-related osteonecrosis of the jaw

^a Longer duration of antiresorptive therapy, bisphosphonates more than 5 years, or any duration of bisphosphonates with comorbidities that affect overall healing; previous history of MRONJ; mandible>maxilla.

fracture prevention, which carries a far greater burden than MRONJ in osteoporosis populations.

Limitations

While this 2025 expert consensus provides a comprehensive framework for managing osteoporosis in Singapore, it also has limitations. Due to the limited availability of clinical trials in Singapore regarding pharmacological approaches and fracture prevention related to osteoporosis, most consensus statements are based on current international evidence and studies conducted predominantly in white postmenopausal female populations. Likewise, the efficacy and safety of therapeutic interventions within the Singapore population may vary, despite strong international clinical evidence, due to variations in genetic profiles, diet, lifestyle patterns, and the presence and severity of comorbidities.

Moreover, not all statements have reached consensus, such as FRAX-based intervention thresholds; hence, recommendations are augmented by clinical expert opinion and judgment rather than unanimous consensus, emphasising the importance of further

validation studies within Singapore. These consensus statements were also developed with consideration of evidence-based best treatment practices globally; their implementation in the Singapore population may be limited by resource availability and healthcare reimbursement practices. Further studies and evidence are required to fully assess the cost-effectiveness of these recommended statements to ascertain their clinical application in the Singapore population. As evidence continues to evolve in the field of osteoporosis management, these statements will require updates in due time and may not always be applicable as new trials and evidence emerge.

CONCLUSION

The consensus statements presented in this paper aim to guide clinicians using the most up-to-date evidence and collective expert opinion and to assist Singapore clinicians in implementing best practices. This reflects a maturing landscape in osteoporosis care, moving from reactive fracture prevention toward proactive disease modification and long-term bone health preservation. Effective implementation requires not

just clinician awareness but also health system-level efforts, such as improving access to DXA scanning, embedding osteoporosis screening within primary care workflows, and integrating fracture services in hospitals, all of which are critical for translating consensus into practice. Cost-effectiveness, patient adherence, and equitable access across socioeconomic strata remain challenges that must be addressed in parallel. Public health messaging and patient education on bone health, nutrition, fall prevention, and medication safety will also be essential to ensure long-term impact. Further work is also needed to validate intervention thresholds and to clarify long-term sequencing of anabolic and antiresorptive agents. Finally, these recommended consensus statements do not intend to replace current guidelines, but rather to augment clinical decision-making and develop an individualised, patient-centred management approach according to the patient's demographics, clinical characteristics, and preferences.

Supplementary Fig. S1. OSTA for risk assessment in postmenopausal women.

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Ethics statement

This research did not involve the collection of patient data, human participants, or biological samples. All analyses were conducted on publicly available, published literature.

Declaration

The 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.

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Lessons from Discover-NOW programme: Transforming chronic kidney disease care in North West London

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ABSTRACT

Chronic kidney disease (CKD) is a rising global public health emergency. Singapore faces one of the world's highest CKD prevalence rates at 15.6%, projected to reach 25% by 2035. This is driven by an ageing population and increasing rates of diabetes, hypertension, and obesity. The UK faces similar pressures, with CKD affecting over 10% of its population and costing the National Health Service an estimated GBP7 billion annually.

To address this, the Discover-NOW programme in North West London developed a transformative project, bringing together partners across both primary and secondary care. This project aims to identify barriers that prevent optimal management for those at risk of or already living with CKD, and to co-develop solutions to overcome them.

Priorities identified were to improve the identification and screening of patients with CKD, support accurate coding and documentation of CKD in primary care, enhance patient understanding and self-management of kidney disease, and promote treatment optimisation of CKD patients within primary care. Key innovations included electronic searches to identify undiagnosed, uncoded, and unoptimised CKD; integration of automated diagnostic guidance into laboratory results; creation of educational materials; and embedding decision-support templates aligned with the latest evidence-based guidelines into electronic medical records.

This initiative provides transferable insights into how healthcare systems across the world can integrate early CKD detection, system-wide data integration, and population-level prevention strategies to strengthen the capacity of primary care in the management of early CKD, eventually shifting from a reactive dialysis-centric model towards proactive kidney preservation.

Keywords: CKD screening, early detection of CKD, family medicine, nephrology, optimisation of therapy in CKD

INTRODUCTION

Chronic kidney disease (CKD) is a global public health emergency, resulting in significant health and economic burden. In Singapore, the prevalence of CKD is 15.6%, above the global prevalence

of 9.1%, and is projected to rise to a staggering 25% by 2035.¹ This is driven by Singapore's ageing population and the high prevalence rate of risk factors, such as diabetes, obesity, and hypertension. As CKD progresses, patients will require kidney replacement therapy in the form of dialysis or kidney transplant. Based on data from the Singapore Renal Registry, 6 new patients are diagnosed with end-stage kidney disease (ESKD) daily.² This amounts to 2249 new dialysis patients per year, representing an increase in incidence of kidney failure of 56% between 2011 and 2021. This places tremendous pressure on healthcare resources, imposes greater demands for new dialysis centres, and impacts enormously on the quality of life of the affected individuals.

However, this epidemic is not a problem unique to Singapore. In the UK, there are approximately 7.2 million people living with CKD equivalent to more than 10% of the entire population. The total annual economic burden of kidney disease in the UK is GBP7 billion, half of which is contributed to by the cost of ESKD treatment alone. This figure also accounts for the additional GBP372 million in productivity loss for people living with ESKD and those who support them, in addition to GBP225 million in transport costs for patients receiving dialysis.³

Preserving, instead of replacing kidney function

Traditionally, both in Singapore and in the UK, the approach to CKD management has been secondary care-based, with interventions often only being implemented when significant damage has already occurred. This trend is also evident in many other long-term conditions where management is often reactive rather than proactive. Patients with kidney disease are often reviewed in secondary care when CKD is advanced, if CKD is rapidly progressing, and when immune-mediated glomerulonephritis or genetic cause of CKD is suspected.⁴ While such thresholds are intended to ensure efficient use of specialist resources, they may inadvertently shift the emphasis away from earlier identification and proactive risk stratification.⁵

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Consequently, individuals with early kidney disease, such as those with preserved estimated glomerular filtration rate (eGFR) but with persistent albuminuria, are frequently overlooked.⁵ This results in missed opportunities for early therapeutic intervention, including optimised blood pressure control, glycaemic management, renin-angiotensin-aldosterone system (RAAS) blockade, and use of sodium-glucose cotransporter-2 inhibitors (SGLT-2i), all of which have been shown to slow CKD progression. Albuminuria has long been recognised as an independent risk factor for cardiovascular disease (CVD) and all-cause mortality.⁶ Therefore, the prevailing secondary-care-centred model contributes not only to sub-optimal patient outcomes but also to increased healthcare costs associated with the management of CVD and ESKD. To change this trajectory, there is a pressing need to shift from replacing to preserving kidney function. Strengthening the capacity of primary care to identify and optimally manage CKD early is critical to slowing disease progression and improving population health outcomes.

The North West London Discover-NOW experience

North West London (NWL) has one of the highest incidence of ESKD in the UK.⁷ CKD poses significant challenges in NWL due to high levels of social deprivation, ethnically diverse populations, and variations in clinical practice. To address these challenges, this transformational project brought together partners across both primary and secondary care, working collectively to identify barriers that prevent optimal

management for those at risk of or already living with CKD, and to co-develop and test solutions. The project was funded by the National Health Service National Prioritisation Programme and ran between April 2021 and April 2023. This partnership also included people with lived experience of CKD and experts in patient and public involvement and engagement, and in health inequalities and public health from the NWL Applied Research Collaboration. The project management was supported by Imperial College Healthcare Partners (ICHP) and included support from AstraZeneca via their non-promotional partnership with ICHP.

The project had 4 phases: discovery, co-design, testing, and implementation, as shown in Table 1. The following section describes the identified solutions in more detail.

Patient identification

One of the issues highlighted was that primary care clinicians have difficulties identifying patients at risk or with CKD who have been missed and require review. Electronic automated searches were developed in EMIS and SystmOne, the 2 electronic primary care electronic medical record (EMR) systems utilised across NWL that identify patients who require review and categorised them into 4 cohorts: (1) patients with test results indicating CKD who might need further tests and/or coding; (2) patients who fall within NICE recommendations for CKD screening who have not been screened; (3) patients on the CKD register who have not been reviewed; and (4) those with coded CKD whose care has not been optimised. Primary

Table 1. Phases of the Discover-NOW project.

Phase	Description
Discovery	Semi-structured interviews were conducted with individuals at risk of developing chronic kidney disease (CKD), patients with CKD, general practitioners, nephrologists, pharmacists, and nurse to: - map the current CKD pathways - identify challenges preventing early-stage CKD management - prioritise which challenges to solve
Co-design	Workshops were held to co-create solutions with patients and clinicians to solve the prioritised challenges from the discovery phase. Four key ideas were identified for further development into solutions: - A CKD diagnosis pathway with an education programme for patients - Enhancing primary care test results with CKD clinical advice and management guidelines - A risk stratification search and contact process that enables primary care to identify high-risk CKD patients - An improved annual review pathway for type 2 diabetes and hypertension patients to encourage identification and management of CKD Subsequently, effective solutions were developed to: - Improve the identification and screening of patients with CKD - Support accurate coding and documentation of CKD in primary care - Enhance patient understanding and self-management of CKD - Promote optimisation of treatment of CKD patients within primary care settings
Testing	Four patient workshops and weekly developmental sessions were organised with the clinical group to test and iterate the solutions developed.
Implementation	Solutions were rolled out to primary care.

care clinicians can then use a visualisation dashboard to track their progress against targets and prioritise patients for intervention (Fig. 1).

Screening

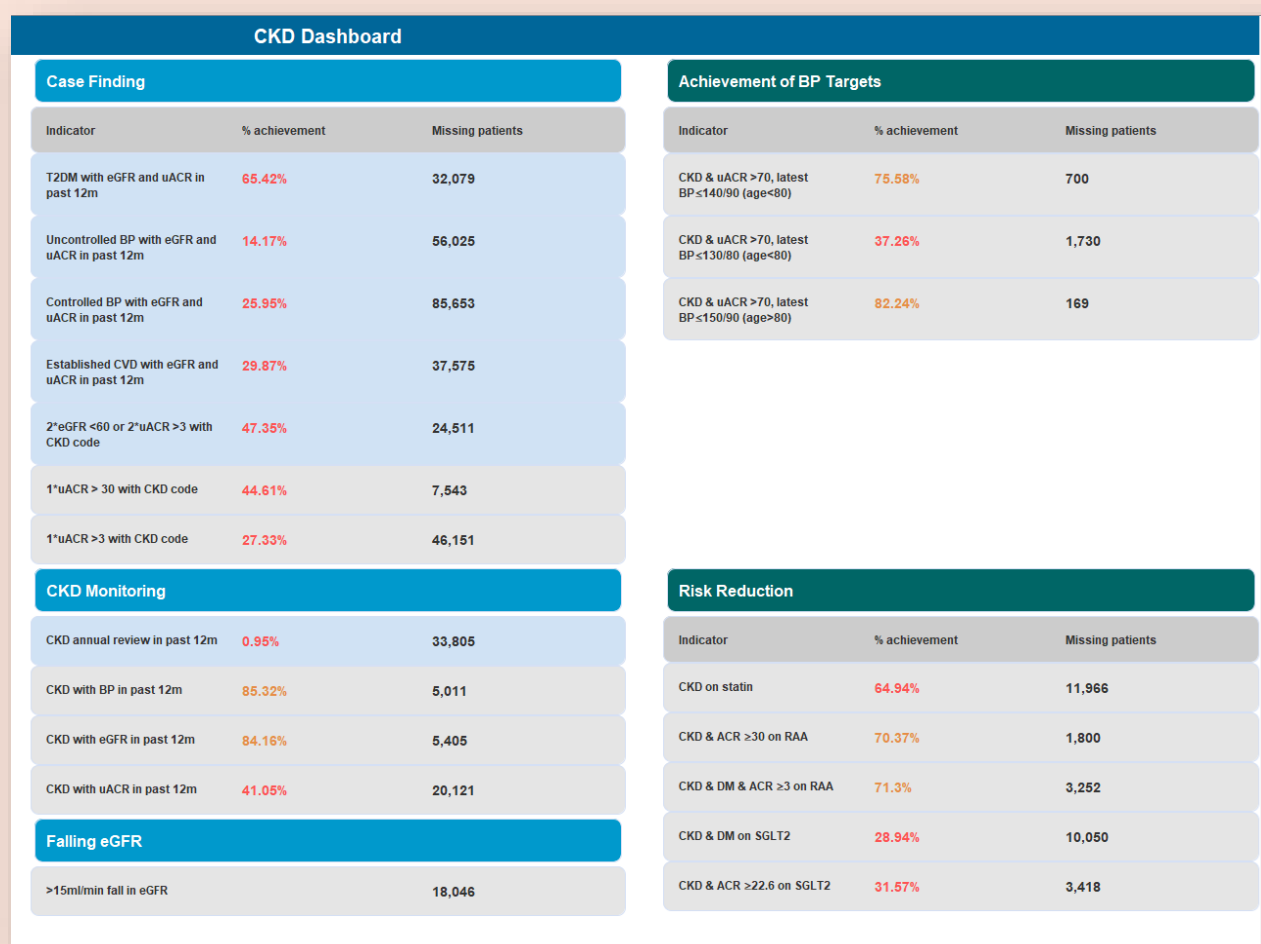
A significant challenge in the early detection of CKD is the silent nature, especially in its early stages. Although urine albumin-creatinine ratio (uACR) is a key indicator of early kidney damage, it is often not completed in practice, even when ordered, in contrast to serum creatinine. Insights from interviews revealed that patients were unaware of the links between diabetes, hypertension, and CKD; unclear about the purpose of uACR test; and their urine samples were not collected if they were not the first sample of the day. To address this, a leaflet explaining the purpose and importance of a uACR test in layman's terms was created. A video was made to support primary care practice staff to standardise the urine sample collection

process. The video emphasises a few points, namely, patients with hypertension require screening, not just those with diabetes; urine samples should be collected opportunistically from patients even if they are not first of the day; and how to select tests in EMR.

Coding and diagnosis

Many individuals at risk or with CKD are not identified, and their conditions are not consistently coded in primary care systems. Patients coded for CKD are associated with lower risk of acute kidney injury, unscheduled care, cardiovascular admissions, and death compared with those with uncoded CKD. These benefits stem from the downstream effects of clinical coding, such as automated prescribing alerts to avoid nephrotoxic medications, pharmacological recommendations according to albuminuria, monitoring frequency according to CKD stages, and vaccination reminders.⁸ Therefore, the team deve-

Fig. 1. CKD dashboard for primary care physicians to track their progress against targets and prioritise patients for intervention.



ACR: albumin-creatinine ratio; BP: blood pressure; CKD: chronic kidney disease; CVD: cardiovascular disease; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; RAA: renin-angiotensin-aldosterone inhibitor; SGLT: sodium-glucose cotransporter 2 inhibitor; T2DM: type 2 diabetes mellitus; uACR: urine albumin-creatinine ratio

loped automated coding guidance from pathology laboratories to be sent with eGFR and uACR results to primary care (Table 2). In addition, practices will see a status alert for patients who have had 2 eGFRs <60 ml/min/1.73 m² within 3 months and have not been coded for CKD or have an incorrect code.

Non-pharmacological treatment, including population health interventions and behaviour nudges to improve outcomes, remain a largely untapped opportunity in managing CKD. Patients who have been coded were signposted to different resources for

kidney education, namely, “Know Your Kidneys” virtual education session; YouTube videos on “Understanding CKD” in the commonest local languages such as English, Gujarati, and Polish; Kidney Care UK website; and access to peer support via National Kidney Federation helpline. These resources were available directly from the EMRs.

Optimisation

In the last decade, several new therapies have been added to the armamentarium to retard CKD

Table 2. Examples of automated coding guidance, provided alongside results.

Result	Comment
eGFR of 45–59 ml/min/1.73 m ²	If not acute kidney injury, consider coding for CKD stage G3a (requires 2 eGFRs taken 3 months apart and uACR). Consider appropriate CKD management, including RAASi, SGLT-2i, BP control, and review CVD risk factors.
uACR of 3–70 mg/mmol	If new, repeat morning sample uACR within 2 weeks. Consider coding for CKD and appropriate CKD management, including RAASi, SGLT-2i, BP control, and review CVD risk factors.

BP: blood pressure; CKD: chronic kidney disease; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; RAASi: renin-angiotensinogen-aldosterone system inhibitor; SGLT-2i: sodium-glucose cotransporter-2 inhibitor; uACR: urine albumin-creatinine ratio

Fig. 2. EMIS CKD review and management template.

ACEi: angiotensin-converting enzyme inhibitor; ACR: albumin-creatinine ratio; ARB: angiotensin II receptor blocker; BP: blood pressure; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; SGLT2i: sodium-glucose cotransporter-2 inhibitors; T2DM: type 2 diabetes mellitus; uACR: urine albumin-creatinine ratio

progression beyond RAAS inhibitors, including SGLT-2i and non-steroidal mineralocorticoid receptor antagonist finerenone. However, these evidenced-based therapies are not well integrated into care protocols or individual care plans, resulting in large gaps between guideline-recommended treatment and actual clinical practice. The Discover-NOW project developed integrated template proformas within the EMRs to support primary care clinicians to manage and optimise CKD patients according to the latest guidelines. Some features include coding table to confirm CKD staging and simplified optimisation guidelines to ensure patient has been recommended the latest therapy (Fig. 2). One of the optimisation guides was adopted from the London Kidney Network, an optimisation pathway for adults with CKD called “3 in 3”—3 key actions within 3 months to save lives.⁹ It provides guidance to initiate statin and RAAS blockade in the first month, SGLT-2i in the second month and thereafter initiate further BP lowering agents in the third month to achieve prespecified individualised BP targets.

Relevance to Singapore healthcare system

Internationally, there are other early CKD care models including Taiwan’s pay-for-performance programme, which incentivise longitudinal disease tracking, multi-disciplinary care, and patient education.¹⁰ North East London has pharmacists with specialist training support primary care pharmacists in medicine optimisation.¹¹ In Singapore, the HALT-CKD (Holistic Approach to Lowering and Tracking Chronic Kidney Disease) programme, which systematically recruits and tracks patients with risk factor control at the primary care level, is excellent as it focuses on registry-based monitoring once CKD has been identified.¹² However, to achieve a significant shift from treatment to prevention in Singapore, it is vital to focus attention upstream in the disease pathway and to utilise EMRs to identify undiagnosed, uncoded, and unoptimised CKD.

The Discover-Now initiative addresses this gap through system-level redesign, rather than isolated clinical interventions, to improve early identification and management of CKD at a population level. Primary and secondary care worked with input from those with lived experience, to consider what issues impede good practice in relation to CKD and how these impediments can be overcome. Integrating automated coding guidance into laboratory results and embedding decision-support templates aligned with latest evidence-based guidelines into EMRs help to reduce variation in practice and narrow the knowledge-implementation gap.

CONCLUSION

Discover-Now’s success was dependant on the systematic approach taken, strong primary-secondary care collaboration, sustained clinical engagement, and interoperable laboratory data. These factors may not be uniformly present across different healthcare systems. While the project demonstrated strong system-level engagement, translation into meaningful patient outcomes depends on sustained adherence and a high-quality therapeutic patient-clinician relationship. Nevertheless, this initiative provides transferable insights into how healthcare systems across the world can integrate early CKD detection, system-wide data integration, and population-level prevention strategies to shift from reactive dialysis-centric model towards proactive kidney preservation. In Singapore, leveraging the highly digitalised National Electronic Healthcare Records alongside the new Healthier SG CKD care protocol, which aims to shift the city-state away from hospital-centric care to a more population-centred preventive model, presents a timely and strategic opportunity to strengthen primary care’s role in mitigating the growing burden of kidney disease.¹³

Ethics statement

Not applicable, as no study participants were involved.

Declaration

The authors 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 Discover-NOW consortium secured GBP250,000 funding from the National Insights Prioritisation Programme to run a multidisciplinary project to understand the challenges in early CKD pathways, and co-design and test innovations that address these challenges to sustainably improve patient outcomes.

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Primary sinonasal DLBCL: High prevalence of MCD subtype and CNS risk

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Dear Editor,

Primary sinonasal diffuse large B-cell lymphoma (SN-DLBCL) is a rare extranodal (EN) lymphoma subtype. A nationwide retrospective cohort study from Denmark reported an incidence of 0.14 per 100,000 person-years, with 5-year overall survival (OS) and progression-free survival (PFS) rates of 56% and 50%, respectively.¹ However, robust nationwide, population-based incidence data for SN-DLBCL outside Denmark remain scarce. In Asian populations, sinonasal lymphomas are more commonly represented by extranodal natural killer/T-cell (EN NK/T-cell) lymphoma, and data specific to SN-DLBCL are limited.² Consequently, the clinical behaviour, molecular characteristics and risk of central nervous system (CNS) involvement in SN-DLBCL are not well-defined, particularly in Asian cohorts. This study reports a single-centre retrospective case series of SN-DLBCL in an Asian population.

In this retrospective study, 8 patients with primary SN-DLBCL were identified, all of whom were pathologically confirmed by biopsy. The baseline characteristics, treatment regimen and outcome of these patients are summarised in Table 1.

The median age at diagnosis was 61.5 years (range, 56–74), and 5 patients were male. The clinical presentation was characterised by a high prevalence of nasal obstruction (62.5%), periorbital swelling with pain (50%) and diplopia (50%), collectively highlighting the locally aggressive nature of SN-DLBCL. In this cohort of 8 patients, next-generation sequencing (NGS) was performed in 7 patients, except 1 patient pathologically diagnosed at an outside hospital before referral. Genetic analysis demonstrated that all 7 patients were classified as the *MYD88/CD79B*-mutated (MCD) (85.7%, 6/7)/MCD-like (14.3%, 1/7) subtype DLBCL. In this study, MCD referred to cases with co-occurring *MYD88* and *CD79B* mutations, whereas MCD-like referred to cases harboring *MYD88* mutation without *CD79B* mutation. The most common additional mutations were in *PIM1* (71.4%, 5/7) and *KMT2D* (42.9%, 3/7). Alterations in *KMT2C*, *EP300*,

NOTCH1 and *MPEG1* were each found in 28.6% of the cohort (2/7). This predominant molecular feature is consistent with previous studies³ and bears a strong resemblance to the profile of primary CNS DLBCL. CNS involvement is an uncommon complication, occurring in approximately 2–10% of patients with DLBCL, and carries a very poor prognosis.⁴ The CNS-International Prognostic Index (CNS-IPI) is the most commonly used tool for estimating risk of CNS recurrence, and CNS prophylaxis is recommended for high-risk patients.⁵ In the rituximab era, several additional high-risk features not captured by the CNS-IPI have been recognised, including dual expression of myelocytomatosis oncogene/B-cell lymphoma 2; the activated B-cell-like molecular subtype; certain EN sites involvement (testicular, uterine, breast); and intravascular large B-cell lymphoma.⁶ Furthermore, involvement of anatomical sites in the head and neck region (e.g. paranasal sinuses, hard palate) and areas close to the CNS (epidural space, dura, paravertebral region and orbit) has also been reported to confer an increased risk.⁷ A few studies have reported the association between SN-DLBCL and an increased risk of CNS involvement. Murawski et al.⁸ analysed 11 consecutive trials from the German High-Grade Non-Hodgkin Lymphoma Study Group. Ninety-three SN-DLBCL patients were identified out of 4155 patients (2.24%), and further analysis revealed that only paranasal sinus involvement was associated with a relative high risk of CNS relapse (2-year incidence 6.4%). Eriksen et al. analysed 116 SN-DLBCL patients registered in the Danish National Pathology Registry between 1980 and 2018. Among these patients, 30 of 116 (25.9%) developed recurrence and localised spread/progression, with 9 had CNS involvement.⁹ In this cohort, 2 of 8 patients (25%) presented with CNS involvement at diagnosis and 1 patient suffered from first CNS disease after complete remission (CR). At diagnosis, Cases 2 and 3 presented with CNS involvement, and successfully achieved CR induced by rituximab-cyclophosphamide, doxorubicin

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Table 1. Baseline characteristics, therapeutic regimen and outcome of primary SN-DLBCL patients.

No.	Sex	Age	IHC/FISH	NGS (tier I variants, genes)	Symptoms	Site of involvement at diagnosis	AA stage	Treatment regimen	Best response	CNS relapse	Status at last follow-up
1	M	74	Non-GCB	U/K	Nasal symptoms: nasal obstruction, rhinorrhoea Eye symptoms: periorbital swelling, periorbital pain, epiphora, diplopia Facial symptoms: facial swelling, facial pain	Nasal cavity, paranasal sinuses	IVA	R-CHOP R-HD-MTX	CR	Yes	PFS: 9.83 months OS: 17.00 months Outcome: died of CNS relapse
2	F	62	Non-GCB Triple expression EBER (-) No MYC rearrangements	MYD88 CD79B KMT2D B2M CREBBP TP53	Facial symptoms: facial swelling, facial pain	Paranasal sinuses, lymph node, CNS	IVA	R-MTX-CHOP	CR	Yes	PFS: 20.37 months OS: 20.37 months Outcome: died of CNS relapse
3	F	59	GCB Triple expression EBER (-) No MYC rearrangements	MYD88 CD79B PIM1 KMT2C BTG1 IRF8	Eye symptoms: diplopia, blurred vision, limited eye movement	Paranasal sinuses, lymph node, bone marrow, CNS	IVB	R-MTX-DA-EPOCH plus Orelabrutinib	CR	No	PFS: 25.80 months OS: 25.80 months Outcome: alive with CR
4	M	61	GCB EBER (-) No MYC rearrangements	MYD88 CD79B PIM1 KMT2D EP300 BTG2 DTX1	Nasal symptoms: nasal obstruction, rhinorrhoea, epistaxis	Nasal cavity, paranasal sinuses, bone marrow	IVB	Pola-R-CHP R-HD-MTX Auto-HSCT Orelabrutinib	CR	No	PFS: 19.07 months OS: 19.07 months Outcome: alive with CR
5	M	56	Non-GCB EBER (-) No MYC rearrangements	MYD88 CD79B PIM1 KMT2C MPEG1 NOTCH1 PRDM1	Eye symptoms: periorbital swelling, periorbital pain, limited eye movement	Paranasal sinuses	IA	R-DA-EPOCH R-HD-MTX Orelabrutinib	CR	No	PFS: 20.87 months OS: 20.87 months Outcome: alive with CR

Table 1. Baseline characteristics, therapeutic regimen and outcome of primary SN-DLBCL patients. (Cont'd)

No.	Sex	Age	IHC/FISH	NGS (tier I variants, genes)	Symptoms	Site of involvement at diagnosis	AA stage	Treatment regimen	Best Response	CNS relapse	Status at last follow-up
6	F	66	Non-GCB Double expression EBER (-) MYC-IGH rearrangements	MYD88 CD79B NOTCH1 CIITA	Nasal symptoms: nasal obstruction, hyposmia	Nasal cavity	IA	R-DA-EPOCH R-HD-MTX	CR	No	PFS: 10.37 months OS: 10.37 months Outcome: alive with CR
7	M	61	GCB Triple expression EBER (-) No MYC rearrangements	MYD88 PIM1 CCND3 SGK1	Nasal symptoms: nasal obstruction, rhinorrhoea, hyposmia Eye symptoms: periocular swelling, periocular pain	Nasal cavity, paranasal sinuses	IB	Pola-R-CHP R-HD-MTX	PR	No	PFS: 6.63 months OS: 6.63 months Outcome: alive with PR
8	M	66	GCB Triple expression EBER (-) No MYC rearrangements	MYD88 CD79B PIM1 KMT2D EP300 MPEG1 TRAF3	Nasal symptoms: nasal obstruction, epistaxis Eye symptoms: periocular pain, periocular swelling, diplopia	Nasal cavity, paranasal sinuses	IB	Pola-R-CHP	U/K	No	PFS: 4.33 months OS: 4.33 months Outcome: alive with disease

AA stage: Ann Arbor stage; auto-HSCT: autologous hematopoietic stem cell transplantation; CHOP: cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate and prednisone; CNS: central nervous system; CR: complete remission; EBER: Epstein-Barr virus-encoded ribonucleic acid; F: female; FISH: fluorescence in situ hybridisation; GCB: germinal centre B-cell; IGH: immunoglobulin; IHC: immunohistochemistry; LN: lymph node; M: male; MTX: methotrexate; MYC: myelocytomatosis oncogene; NGS: next-generation sequencing; OS: overall survival; PFS: progression-free survival; PR: partial remission; Pola-R-CHP: polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin and prednisone; R: rituximab; R-DA-EPOCH: dose-adjusted etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone and rituximab; R-HD-MTX: rituximab and high-dose methotrexate; U/K: unknown

hydrochloride, vincristine sulphate and prednisolone-like immunochemotherapy combined with high-dose methotrexate (HD-MTX). Case 2 declined subsequent consolidation therapy with autologous hematopoietic stem cell transplantation (auto-HSCT) and maintenance therapy with Bruton's tyrosine kinase (BTK) inhibitors, experienced isolated CNS relapse 6.4 months after completion of induction chemotherapy, and died 7 months after relapse. In contrast, Case 3 received BTK inhibitor therapy throughout the induction, consolidation and maintenance phases, which may have contributed to sustained remission and prolonged survival. Of the remaining 6 patients without CNS involvement at diagnosis, all have either completed or are currently scheduled to receive 2 cycles of HD-MTX as CNS prophylaxis. Long-term outcomes differed by treatment. Case 1 managed without auto-HSCT consolidation or BTK inhibitor maintenance, achieved initial CR but developed an isolated fatal CNS relapse 15.77 months after completion of induction chemotherapy. In contrast, Cases 4 and 5, who received auto-HSCT and/or BTK inhibitor therapy, have maintained sustained CR. With a median follow-up of 19.07 months (range, 4.33–25.80) for the entire cohort, the median CNS involvement-free survival was 20.37 months (95% confidence interval 0.00–49.75). Neither median PFS nor OS had been reached (Supplementary Fig. S1).

Findings show that SN-DLBCL patients predominantly exhibited an MCD/MCD-like molecular subtype and demonstrated a high frequency of CNS involvement. This propensity may be attributed to both the anatomical proximity of the sinonasal region to the CNS and the intrinsically aggressive molecular features. Therefore, the NGS testing appears essential for risk stratification. In resource-limited settings, a cost-effective alternative, such as digital polymerase chain reaction to detect key mutations (e.g. *MYD88* and *CD79B*), should be considered to identify patients with the MCD molecular profile. These clinical observations further suggest that a prophylactic strategy consisting only 2 cycles of HD-MTX may be insufficient for patients with the MCD/MCD-like subtype of SN-DLBCL. Therefore, the authors recommend that CNS prophylaxis with HD-MTX be combined with auto-HSCT consolidation and/or BTK inhibitors maintenance, which has shown promising CNS penetrance and efficacy in genetically MCD subtype. However, these observations are tempered by limitations, including the single-centre, retrospective design, small sample size, limited follow-up duration and variations in treatment regimens, which may affect statistical power, the assessment of long-term relapse risk, and the generalisability of the findings, under-

scoring the need for further studies to validate these results and develop evidence-based management strategies.

Supplementary material

Fig. S1. Kaplan–Meier curves of the 8 primary SN-DLBCL patients for CNS involvement-free survival, progression-free survival and overall survival.

Ethics statement

This study was approved by the Institutional Ethics Committee of Xuanwu Hospital, Capital Medical University, Beijing, China (2025-010-002).

Declaration

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Keywords: CNS prophylaxis, CNS risk, molecular feature, primary sinonasal diffuse large B-cell lymphoma, survival

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Prevalence of wrist injuries and return-to-work barriers among nurses and therapists in Singapore

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Dear Editor,

Musculoskeletal disorders, such as wrist injuries, represent a substantial occupational health concern for healthcare workers who perform patient handling tasks, as these activities often involve repetitive movements, awkward postures and heavy lifting that increase the risk of these conditions. Overseas studies showed that an estimated 55–91% of physical therapists experienced work-related musculoskeletal disorders during their careers, most often at lower back, neck, upper back and shoulders,¹ while an estimated 26% of nurses had upper extremity pain over a 12-month period.² In Singapore, musculoskeletal disorders represent the most reported occupational disease with healthcare as the second most affected industry,³ while a Singapore study found that hand injuries accounted for over one-third of workplace injury claims.⁴

Beyond physical discomfort, patients with wrist injuries faced various biopsychosocial challenges in their journey of returning to work.⁵ These challenges are especially relevant in healthcare in view of the high physical work demands, potential organisation barriers such as inadequate workplace accommodations and limitations in the use of wrist protective devices from infection control policies, and the inherent nature of nursing and therapy care where work modifications are difficult to implement.

To better understand the burden of wrist injuries among healthcare workers, the authors conducted a cross-sectional, anonymous, self-administered online survey in Woodlands Hospital, Singapore to assess prevalence and risk factors of wrist injuries among nurses and therapy staff, as well as associated concerns and barriers to return to work. Nurses, healthcare assistants, physiotherapists, occupational therapists, therapy assistants and speech therapists employed during the study period in July 2023 were included. The survey, administered over the FormSG platform, included detailed history of wrist injuries, individual and workplace risk factors of wrist injuries, and return-to-work concerns and barriers. To improve response rate,

various publicity channels were leveraged, including hospital email broadcast and department communication channels. Ethics clearance was granted by the National Healthcare Group Domain Specific Review Board (2023/00151).

A total of 386 healthcare workers participated, comprising 68 physiotherapists, occupational therapists and therapy assistants, and 317 nurses and healthcare assistants, with higher response rate among therapy staff (72%) than nursing staff (23%). Respondents were mostly below 40 years old (80%), females (80%), Singaporeans or permanent residents (69%), worked over 2 years in Woodlands Hospital (65%), worked in inpatient settings (54%) and performed direct patient care (98%).

The study found a significant prevalence of self-reported wrist injuries, with 107 respondents (28%) experiencing such injuries since entering the healthcare sector and 75 (19%) reporting injuries after starting work at Woodlands Hospital. Among the 107 respondents with prior wrist injuries, the majority (72 participants, 67%) agreed their wrist injuries were attributed to or exacerbated by work, yet only 6 (8%) of these respondents submitted internal injury incident reports. As under-reporting may hinder timely intervention and provision of necessary workplace support, there may be a need to review current mechanisms and workplace culture around injury reporting.⁶

While over 90% of the 107 respondents with wrist injuries have returned to full job duties, 37 respondents (35%) continued to experience symptoms that impeded their work. This is concerning, as persistent symptoms could compromise staff well-being and patient safety—a sentiment echoed by 51 respondents (48%) who believed their injuries could affect patient safety (Table 1). These findings are consistent with prior studies showing musculoskeletal injuries can have long-term functional impacts, increase risk of errors or reduce quality of care.⁷

The study also identified gaps in return-to-work support, with 66 respondents (62%) with wrist injuries

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Table 1. Perceptions of impact of wrist injury on return to work, among those with prior wrist injury after joining healthcare (n=107).

Perceptions	Rating, no. (%)				
	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
1. I believe my wrist injuries will affect patient safety.	5 (4.7)	17 (15.9)	34 (31.8)	33 (30.8)	18 (16.8)
2. I was given feedback that my wrist injuries would lead to patient safety issues.	20 (18.7)	25 (23.4)	54 (50.5)	5 (4.7)	3 (2.8)
3. My performance appraisal (e.g. total performance management) has been affected because of my wrist injury.	31 (29.0)	24 (22.4)	43 (40.2)	5 (4.7)	4 (3.7)
4. I feel that my job security is affected because of my wrist injury.	21 (19.6)	22 (20.6)	41 (38.3)	18 (16.8)	5 (4.7)
5. I believe my work could have been modified temporarily so that I could return to work earlier.	5 (4.7)	11 (10.3)	51 (47.7)	29 (27.1)	11 (10.3)
6. Having alternative job options in the workplace would be useful as I recover from my wrist injury.	1 (0.9)	4 (3.7)	37 (34.6)	42 (39.3)	23 (21.5)
7. The duration of medical leave issued by my doctors was adequate for my wrist injuries.	2 (1.9)	15 (14.0)	64 (59.8)	23 (21.5)	3 (2.8)
8. The duration of light duties issued by my doctors was adequate for my wrist injuries.	5 (4.7)	8 (7.5)	74 (69.2)	16 (15.0)	4 (3.7)
9. It is challenging to find available light duties within my normal job duties that I can do.	2 (1.9)	5 (4.7)	34 (31.8)	34 (31.8)	32 (29.9)
10. I received good support from my direct supervisor after my wrist injury.	4 (3.7)	12 (11.2)	63 (58.9)	19 (17.8)	9 (8.4)
11. I feel that my direct supervisor takes my injury seriously.	3 (2.8)	9 (8.4)	60 (56.1)	27 (25.2)	8 (7.5)
12. I feel that my colleagues take my injury seriously.	1 (0.9)	8 (7.5)	56 (52.3)	34 (32.0)	8 (7.5)
Among subgroup of respondents who used wrist supportive device (n=56)					
13. Due to infection control measures, I have experienced difficulties wearing a splint/brace while at work.	1 (1.8)	1 (1.8)	5 (8.9)	18 (32.1)	31 (55.4)
14. Wearing a splint/brace at work has affected how I perform my normal duties.	1 (1.8)	6 (10.7)	10 (17.9)	14 (25.0)	25 (44.6)
Among subgroup of respondents who had been given light duties (n=12)					
15. I had to perform work activities, which exceeded the light duty restrictions identified by my doctor.	1 (8.3)	0 (0.0)	3 (25.0)	5 (41.7)	3 (25.0)
16. The light duty restrictions identified by my doctors were helpful.	1 (8.3)	1 (8.3)	5 (41.7)	3 (25.0)	2 (16.7)

finding it challenging to find suitable light duties, 61 respondents (57%) being uncertain that they could suggest to their supervisor ways to modify their work to reduce discomfort, and only a small number (12 participants, 11%) received light duties. Out of the 12 respondents who were given light duties, 67% agreed that they performed work activities that exceeded the light duty restrictions given by their doctor. At the same time, utilisation of occupational medicine's return-to-work services remained low at 9% among the 107 respondents with wrist injuries, even though 52% were aware of these services. Greater access to and uptake of return-to-work programmes could better facilitate reintegration of injured staff,⁸ support sustained workforce participation and address patient safety concerns.

Among 56 injured respondents who were given wrist protective devices, a significant proportion (84%) admitted to non-compliance due to work-related factors, with many perceiving these devices hindered job performance (70%) and posed infection control challenges (88%). These barriers highlight the need for a more tailored approach to work accommodations to address practical challenges in the use of these devices. Collaboration between occupational medicine and infection control could be useful to identify feasible accommodations and promote adherence to protective measures without compromising job performance or infection control standards.⁹

The study identified higher injury prevalence among staff from intensive care units (12 out of 27 respondents, 44%) and emergency department (11 out of 41 respondents, 27%) even after stratifying by work duration. This association may be attributed to the physically demanding work nature in these settings, particularly frequent patient turning and handling, which has been shown to increase ergonomic risk.¹⁰ Targeted interventions, such as ergonomic training and equipment modification, may be useful in these departments.

While this study is limited by the low response rate and reliance of self-reported data, which raised the possibility of non-responder, recall and reporting biases, it is likely the first Singapore study to assess factors influencing return to work from wrist injuries, with actionable results that are applicable in Singapore hospitals. This letter raises awareness of work-related wrist musculoskeletal disorders and low utilisation of occupational health services, which could support healthcare professionals with these disorders. Addressing identified barriers and risk factors through organisational, ergonomic and cultural interventions

is essential to safeguard staff well-being and maintain patient safety.

Ethics statement

This study was approved by the National Healthcare Group Domain Specific Review Board (2023/00151).

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 study received funding from Woodlands Hospital, Singapore - FY23 Small PROjects Utilising Teams (SPROUTS) I Grant (SGD5000). This is an internal grant by Woodlands Hospital to support research within the institution. The funder has no role in the study design, data collection and analysis, data interpretation or writing of the manuscript.

Keywords: *health policy, healthcare workers, occupational medicine, return to work, wrist injuries*

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Clinical utility of frozen section for submandibular gland tumours in the era of Milan classification

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Dear Editor,

Salivary gland tumours are rare, with less than 10% occurring in the submandibular gland and most arising from the parotid gland.¹ Fine needle aspiration and cytology (FNAC) is commonly performed as part of initial workup for a submandibular gland mass. However, some patients will have indeterminate FNAC, i.e. non-diagnostic, atypia of unknown significance (AUS) and salivary gland neoplasm of uncertain malignant potential (SUMP) with a risk of malignancy (ROM) ranging from 15–35%, as per the Milan System for Reporting Salivary Gland Cytopathology (MSRSGC),² which has been validated for submandibular gland tumours in the authors' previous study.³ Intraoperative frozen section (FS) serves as a second opportunity to diagnose malignancy and to evaluate for nodal spread if suspicious lymph nodes are seen intraoperatively. As per the latest National Comprehensive Cancer Network (NCCN) guidelines for salivary gland cancers,⁴ elective neck dissection can be considered for high-grade and/or T3/T4 tumours, and therapeutic neck dissection is recommended for clinically node positive cases. Hence, FS can guide the surgeon in deciding whether to proceed with neck dissection during index operation.

However, FS has its limitations including freeze artifacts, time constraints, and lack of ancillary studies during intraoperative consultation for conclusive diagnosis.⁵ Submandibular gland tumours are also morphologically diverse, which can make histopathologic diagnosis challenging.⁶ Compared to parotid tumours, submandibular gland tumours are rarer, more often malignant, and have a different histological subtype distribution.¹ Most published studies have focused on parotid tumours, since it is the most common salivary gland tumour. Few studies have evaluated how FS of submandibular gland tumours impacts intraoperative management or its diagnostic accuracy.

We retrospectively reviewed the electronic medical records of 49 patients who underwent submandibular

gland excision with pre-operative FNAC and intraoperative FS from May 2008 to December 2023 in Tan Tock Seng Hospital, Singapore, with the aim of studying (1) the diagnostic accuracy of FS in detecting malignancy and (2) its impact on intraoperative decision making, i.e. whether to proceed with neck dissection. Among the 92 patients, 49 underwent submandibular gland excision with pre-operative FNAC had intraoperative FS. Decision for FS was made by the physician based on their clinical suspicion of malignancy, influenced by various factors including history, imaging findings and pre-operative FNAC. Among those who did not undergo FS (43/92), a large proportion (86.0%) had benign disease.

The authors found that FS performs well in detecting malignancy in submandibular gland tumours, with high sensitivity and specificity (Table 1), which is corroborated by other studies with similar findings.^{7,8} FS was also found to be particularly valuable in patients with indeterminate FNAC pre-operatively. Among the 32 patients with indeterminate results on FNAC, i.e. non-diagnostic, AUS, SUMP, FS was able to definitively rule out malignancy in 18 (56.3%) patients and diagnose malignancy in 4 (12.5%) patients. If the tumour is likely to be T3 and above based on pre-operative imaging, FS can help by confirming malignancy and enabling clinicians to proceed with neck dissection. In this study's cohort, in 1 malignant case (7.1%) with indeterminate FNAC, the confirmation of malignancy on FS, combined with pre-operative imaging that indicated that the tumour stage would be at least T3, supported immediate neck dissection and helped avoid revision surgery.

Lymph nodes were sent for FS in 8 patients, 5 benign and 3 malignant, when noted to be clinically suspicious. We found that by confirming absence of nodal disease, FS helped to avoid unnecessary therapeutic neck dissection in these malignant cases. Four out of 14 malignant tumours were lymphomas (28.6%), of which FS showed either lymphoid rich

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Table 1. Sensitivity and specificity of frozen section (FS) in detecting malignancy when indeterminate FS is excluded or included.

Excluding indeterminate FS					
FS	Histology		Sensitivity, %	Specificity, %	
	Benign	Malignant			
	Malignant	0 (FP)			5 (TP)
	Benign	30 (TN)			1 (FN)
Including indeterminate FS					
FS	Histology		Sensitivity, %	Specificity, %	
	Benign	Malignant			
	Malignant	5 (FP)			13 (TP)
	Benign	30 (TN)			1 (FN)

FP: false positive; FN: false negative; FS: frozen section; TP: true positive; TN: true negative

lesion or atypical lymphoid proliferation. While the diagnosis of lymphoma is difficult to make on FS as immunostaining is required and histopathology is considered the gold standard for diagnosis of lymph node pathologies,⁹ the identification of lymphoid cells on FS helped the surgeon to decide intraoperatively not to proceed with elective neck dissection as it is not indicated for either lymphoma or benign lymphoid changes.

In cases where FNAC was classified as MSRSGC category IVa, i.e. benign neoplasm, 12/13 (92.3%) were benign on FS, 1 (7.7%) was indeterminate, and all were benign on final histology. Based on the MSRSGC, the ROM for category IVa is <3%. Given the low ROM, the added value of FS in these patients is limited, since intraoperative FS is unlikely to change management.

Due to difficulties in determining grade of malignancy, FS may have limited utility in influencing a clinician's decision to proceed with neck dissection during index operation. In this study, FS was not able to diagnose the grade of malignancy in all cases. With 39 subtypes of salivary gland pathologies described in the fifth edition of the World Health Organization Classification, salivary gland tumours have a wide range of morphological features and can pose as a diagnostic challenge to the pathologist at FS.⁶ Furthermore, immunohistochemistry staining or diagnostic molecular pathology tests, such as next-generation sequencing, may be required in challenging cases with poorly differentiated histomorphology.¹⁰ Given the technical and time constraints of FS, it is often not possible to conclude the grade of malignancy, and clinicians may have to await final histology to determine if elective

neck dissection is necessary, particularly for tumours that are T1/T2.

This study has a few limitations, namely, small sample size and retrospective study design precluding the standardisation of clinical practice. A larger scale, prospective study will be useful in drawing more conclusive evidence regarding the utility of FS in submandibular gland lesions.

In conclusion, FS demonstrates high diagnostic performance for detecting malignancy in submandibular gland tumours, particularly in patients with indeterminate preoperative FNAC. However, in terms of influencing intraoperative decision making, the utility of FS in T1/T2 tumours is limited by its inability to reliably distinguish grade of malignancy intraoperatively, and decisions regarding neck dissection should therefore await final histopathology. The authors propose a targeted approach in which FS should be considered for cases with indeterminate preoperative FNAC and high clinical or radiological suspicion of advanced, i.e. T3/T4 or metastatic disease, where confirmation of malignancy on FS can facilitate decision for neck dissection during the index operation.

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Ethics statement

This was a retrospective review of medical records where no identifiable data was collected. The study was approved by National Healthcare Group Domain Specific Review Board, Singapore (2024-3222).

Declaration

No funding was received for this study. 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.

Keywords: fine needle and aspiration, frozen section, Milan classification, otorhinolaryngology, submandibular gland neoplasms, submandibular gland tumors

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Advanced care planning and influences of hepatocellular carcinoma for liver cirrhosis patients: An Asian perspective

Danelle Lai¹, Marianne Anastasia De Roza^{2,3} FRCP

Dear Editor,

Liver cirrhosis is a significant cause of morbidity and mortality in Singapore. Decompensated liver cirrhosis patients have a poor prognosis with a median survival of less than 2 years.¹ These patients often suffer from a high symptom burden with progressive deterioration compounded by acute and life-threatening decompensating events, which can be unpredictable.² It is thus important for physicians to incorporate advanced care planning (ACP) to align goals of cares as part of their management.

As there is very limited data on ACP specifically for liver cirrhosis patients in Singapore and Asia, the authors reviewed electronic ACP discussion records at their hospital, Sengkang General Hospital in Singapore, from January 2018 to December 2024, to investigate barriers to ACP, overall ACP outcomes, and the influence of hepatocellular carcinoma (HCC) diagnosis on ACP preferences for liver cirrhosis patients. ACP outcomes were tracked up till June 2025.

Only 72 (10.0% of cohort) liver cirrhosis patients were identified to have ACP discussion records, with mean age of 71.69 years, 51.39% of male sex, and 73.61% of Chinese ethnicity. Thirty-one patients had HCC (43.06%). Forty-one patients rejected or did not complete ACP (56.94%). For all patients who completed ACP (31/72), the median number of ACP counselling sessions was 1 and the median total time spent on discussion was 60.0 (interquartile range [IQR] 45.0–60.0) minutes. The median duration between ACP introduction and death was 54.0 (IQR 19.0–139.0) days. For preferred place of death, a majority of patients chose their own home (11/31, 35.5%), followed by no preference (10/31, 32.3%), and hospital (8/31, 25.8%). Differences between HCC and non-HCC patients for preferred place of death were not statistically significant ($P=0.946$). For preferred place of care, 80% (12/15) of HCC patients selected their own home or long-term care facilities over the hospital, compared

to 25% (4/16) of non-HCC patients ($P=0.0105$). Logistic regression analysis revealed that HCC patients were far more likely to select their own home or long-term care facilities over the hospital, compared to non-HCC patients (odds ratio [OR] 12.0, $P=0.004$, confidence interval [CI] 0.788–4.182). For preferred medical intervention, most patients (29/31, 93.5%) chose limited additional intervention, and all patients opted not to attempt cardiopulmonary resuscitation (Table 1).

Reasons for ACP rejection/non-completion were: death before completion (11/28, 39.3%), lack of readiness to discuss ACP (9/28, 32.1%), family-centredness (7/28, 25.0%), and patient condition hindering ACP discussion (1/28, 3.6%) such as encephalopathy. Reasons categorised under “lack of readiness” theme included: (1) patients that simply indicated unreadiness to discuss ACP (6/9, 66.7%); (2) patient preference to discuss ACP when situation arises (2/9, 22.2%); (3) patient perception that ACP is unnecessary (1/9, 11.1%). Reasons for “family-centredness” included: (1) patient preference to leave decision to family (2/7, 28.6%); (2) family excluding patient from decision-making (2/7, 28.6%); (3) family does not want patient to know their diagnosis (1/7, 14.3%); (4) family unready for ACP discussion (1/7, 14.3%); and (5) family does not want patient to think about end of life (1/7, 14.3%).

The findings show that incomplete ACPs in liver cirrhosis were due mostly to the lack of timely ACP initiation as patients died before ACP could be completed. This could be contributed by the unpredictable disease course of end-stage liver disease leading to prognostic uncertainty from physicians, especially if liver transplant is an option,³ and resulting in delays of ACP discussions.⁴ This is congruent with data from the West, whereby ACP discussions often commenced only when patients experienced severe deterioration and prognosis was poor.⁵ Second, patients’ lack of readiness to discuss ACP was likely

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Table 1. Baseline demographics and advanced care planning data.

Variables		Cohort (n=72)	HCC patients (n=31)	Non-HCC patients (n=41)	P value
Age, mean (SD)		71.69 (11.98)	69.55 (12.24)	73.32 (11.67)	0.188
Sex, no. (%)					0.144
Male		37 (51.39)	19 (61.29)	18 (43.90)	
Female		35 (48.61)	12 (38.71)	23 (56.10)	
Race, no. (%)					0.454
Chinese		53 (73.61)	24 (77.42)	29 (70.73)	
Malay		10 (13.89)	5 (16.13)	5 (12.20)	
Indian		7 (9.72)	1 (3.23)	6 (14.63)	
Others		2 (2.78)	1 (3.23)	1 (2.44)	
Religion, no. (%)					0.934
Christian		7 (9.72)	4 (12.90)	3 (7.32)	
Buddhist		4 (5.56)	2 (6.45)	2 (4.88)	
Taoist		7 (9.72)	2 (6.45)	5 (12.20)	
Muslim		9 (12.50)	5 (16.13)	4 (9.76)	
Hindu		3 (4.17)	1 (3.23)	2 (4.88)	
Catholic		4 (5.56)	2 (6.45)	2 (4.88)	
Free thinker		2 (2.78)	1 (3.23)	1 (2.44)	
Unspecified		36 (50.00)	14 (45.16)	22 (53.66)	
ACP outcomes, no. (%)					0.580
Completed		31 (43.06)	15 (48.39)	16 (39.02)	
Not completed/rejected		41 (56.94)	16 (51.61)	25 (60.98)	
ACP discussion process	No. of ACP counselling sessions, median (IQR)	1 (1–1)	1 (1–1)	1 (1–1)	0.366
	Total time spent on discussion (minutes), median (IQR)	60.0 (45.0–60.0)	45.0 (42.5–60.0)	60.0 (60.0–60.0)	0.072
	Duration between ACP introduction and death (days), median (IQR)	54.0 (19.0–139.0)	73.0 (17.0–135.0)	52.5 (21.0–147.8)	0.846
Preferred place of death (for completed ACP n=31)	Hospital	25.8% (8/31)	26.7% (4/15)	25.0% (4/16)	0.946
	Own home	35.5% (11/31)	40.0% (6/15)	31.3% (5/16)	
	Long-term care facilities (hospice, nursing home)	6.5% (2/31)	6.7% (1/15)	6.3% (1/16)	
	No preference	32.3% (10/31)	26.7% (4/15)	37.5% (6/16)	
Preferred place of care (for completed ACP n = 31)	Hospital	48.4% (15/31)	20.0% (3/15)	75.0% (12/16)	0.0105
	Own home	32.3% (10/31)	46.7% (7/15)	18.8% (3/16)	
	Long-term care facilities (hospice, nursing home)	19.4% (6/31)	33.3% (5/15)	6.3% (1/16)	
Care plans (for completed ACP n=31)	Limited additional intervention	93.5% (29/31)	86.7% (13/15)	100% (16/16)	0.226
	Do not resuscitate	100% (31/31)	100% (15/15)	100% (16/16)	

ACP: advanced care planning; IQR: interquartile range; SD: standard deviation

due to the distressing nature of ACP discussions. The idea of mortality underpins the discussion, and patients may not have come to terms with their prognosis. This is especially significant, where death is considered a taboo topic in Asian culture. Cirrhosis patients may also harbour excessively optimistic perceptions of their prognosis, which could influence them to pursue more aggressive interventions rather than palliative options.⁶ Lastly, family-centredness, which is the dominant role family members play in decision-making, was another prominent factor contributing to ACP non-completion/rejection. In Singapore's Asian cultural context, family-centred values and customs are deeply rooted into its social fabric. Collective input often takes precedence over individual autonomy and families play a central role in guiding healthcare choices. Asian family members are given substantial decision-making power in ACP discussions, particularly for elderly patients.⁷

The results also revealed a statistically significant association between HCC diagnosis and preferred place of care, with HCC patients preferring long-term care facilities or their own homes over the hospital (OR 12.0, $P=0.004$, [CI 0.788–4.182]). This could be attributed to the higher certainty of poor prognosis in HCC patients compared to non-HCC patients, which compels HCC patients to prioritise comfort. This is similar to a study on decompensated liver cirrhosis patients in the West, which showed that HCC liver cirrhosis patients had statistically significant higher odds of receiving hospice care compared to non-HCC liver cirrhosis patients.⁸

In conclusion, ACP completion rates for liver cirrhosis patients in Singapore are low, and important barriers identified were lack of timely initiation, lack of readiness, and family-centredness. Additionally, HCC diagnosis influences care plans, with HCC patients preferring to stay out of the hospital and non-HCC patients preferring hospitalisation. Knowledge of the barriers to ACP and the influence of HCC diagnosis may aid healthcare providers in guiding patients towards their most ideal ACP decisions that can satisfy their goals of care and wishes. ACP is an integral part of patient care in liver cirrhosis and should be encouraged earlier on in disease management.

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Ethics statement

This study was approved by SingHealth Centralised Institutional Review Board. Informed consent from patients was not required as authors used an existing dataset that was stripped of all identifying information (ECOS Ref: 2024-2251).

Declaration

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Keywords: end-of-life care, end-stage liver disease, goals of care, hepatic decompensation, palliative care

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How clinicians should prioritise the use of artificial intelligence in Singapore's healthcare system: Correspondence

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Dear Editor,

The readers writing this letter read with interest Hwang et al.'s article on augmented intelligence in healthcare,¹ and agree that it would be most responsible for artificial intelligence (AI) to enhance, rather than replace clinical judgment. The more urgent question for Singapore's clinicians today is therefore not whether to use AI, but where to prioritise its deployment for responsible, meaningful impact.

AI is already embedded in several parts of Singapore's healthcare system, including triaging, community screening, and operational management.²⁻⁵ As adoption grows, the challenge shifts from experimentation to disciplined scaling. Poorly chosen deployments risk inefficiency and erode trust, whereas well-targeted applications can improve clinical outcomes, reduce administrative load, and enhance system resilience.

Singapore's integrated public healthcare clusters, robust data infrastructure such as the National Electronic Health Record, and strong governmental support create favourable conditions for AI implementation.⁶ However, this also raises expectations for disciplined governance. Past data breaches and rapid digitisation have heightened public sensitivity to privacy and accountability, underscoring that technical feasibility alone cannot justify adoption.⁷

Population health needs further sharpen the focus. With an ageing population, rising chronic disease burden, and a national emphasis on preventive and community-based care under Healthier SG, AI that supports early detection, longitudinal risk management, and continuity of care offers the highest value.

To guide responsible adoption, the readers recommend that clinicians assess AI initiatives across 5 dimensions: (1) clinical value: demonstrable improvements in outcomes, safety, or clinician capacity; (2) workflow integration: minimal disruption and seamless

incorporation into existing routines; (3) data readiness: reliable, representative data suited to the intended task; (4) ethics and governance: clear accountability, transparency, and safeguards for patient trust; (5) scalability and sustainability: capacity for long-term support and system-wide implementation.²² Applications scoring strongly across these dimensions merit prioritisation; those driven mainly by novelty or vendor interest should be approached cautiously.

AI will increasingly influence healthcare delivery in Singapore. The key question is whether this evolution occurs reactively or under deliberate clinical leadership. Clinicians play a central role in identifying where AI truly adds value, where it distracts, and where it may inadvertently harm. By emphasising augmentation over automation, prevention over reaction, and integration over fragmentation, clinicians can ensure AI strengthens the core values of Singapore's healthcare system. The future of AI in healthcare should be defined not by technical capability, but by clinical relevance.

Declaration

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Ethics statement

Not applicable, as no human or animal participants were involved.

Keywords: AI adoption, augmented intelligence, clinical domains, healthcare transformation, operational domains

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Table 1. Clinical and operational domains where AI should be prioritised to further value-add to Singapore's healthcare system.

Clinical domains	
Diagnostics	AI's maturity is the strongest in pattern-recognition tasks such as radiology, ophthalmology, and pathology. Singapore already uses validated tools for chest radiography triage and diabetic retinopathy screening. ^{3-5,8-9} The most appropriate use cases are those that triage or augment clinical review rather than make autonomous decisions. Clinicians should prioritise diagnostic AI where disease burden is high, early detection improves outcomes, workload is variable, and outputs are explainable. In contrast, areas with limited data, subjective labels, or unclear downstream pathways should be deprioritised.
Decision support	Chronic disease management is well suited for AI-enabled risk stratification and treatment optimisation due to its structured data and stable guidelines. ⁹⁻¹¹ Assistive, not prescriptive tools that surface options or flag deviations support clinical judgment while improving consistency. Prioritisation should focus on domains with well-defined pathways, high variability driven by workload constraints, and transparent, contestable recommendations.
Longitudinal monitoring and preventive care	As care shifts upstream, predictive models that identify patients at risk of deterioration or poor adherence align directly with national preventive care priorities. ¹²⁻¹⁴ AI is most valuable when paired with primary care ownership, digital engagement tools, and clear escalation pathways. Priority should be given to systems enabling anticipatory action rather than retrospective insight.
Operational domains	
Clinical documentation and administrative work	Among all applications, AI-assisted documentation offers the most immediate, broad-based benefits. It directly reduces administrative burden, a major contributor to clinician burnout, without altering clinical decisions. ¹⁵⁻¹⁶ Singapore's strong interest in generative AI for documentation reflects its potential to transfer time and attention to patient care. ^{3,17}
Resource allocation and capacity management	AI that improves bed assignment, operating theatre scheduling, and patient flow addresses bottlenecks that contribute to crowding and delays. ^{2-3,18} Such systems are particularly beneficial where demand is predictable, decisions are time-sensitive, and coordination is complex.
Patient engagement and access	Chatbots, appointment optimisation tools, and digital triage platforms can improve access and promote appropriate self-care. ^{2-4,9,19-21} Clinicians should prioritise solutions integrated with trusted national platforms and aligned with established guidelines, while ensuring they complement but not replace human interaction.
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Authors' reply

Dear Editor,

The authors thank the readers for their thoughtful response to the article on augmented intelligence in healthcare.¹ The authors agree that the key question is not whether to use artificial intelligence (AI), but how to prioritise its deployment responsibly within the health system. Their proposed domains and evaluation criteria are well aligned with the current evidence that AI performs best in structured, high-volume tasks such as imaging triage, chronic disease risk stratification, and documentation. These support our 3-fold considerations for augmented intelligence in healthcare.² First, AI in healthcare requires humans (including the AI company or hospital management) to take final responsibility. Second, engagement and involvement are required in AI implementation. Third, the future is not about whether AI is used but why AI is not being used.

In reply to the readers responding to the paper, the authors offer 3 additional considerations. First, technical validation must be coupled with implementation science. Prospective accuracy does not guarantee clinical impact. Real-world studies show that effectiveness depends on workflow integration, clinician behaviour, and continuous monitoring for performance decay or dataset shift.³⁻⁵ Post-deployment audit and recalibration should therefore be mandatory components of scaling.

Second, augmentation requires safeguards against automation bias. Human-AI interaction research demonstrates that clinicians may over-rely on algorithmic outputs, particularly under time pressure.^{6,7} Systems should incorporate calibrated uncertainty, transparent outputs proportional to clinical risk, and clear override mechanisms to preserve clinical judgment and patient safety.

Third, prioritisation must explicitly address equity and longitudinal value. Algorithmic bias and differential performance across demographic groups are well-documented.^{8,9} In a multi-ethnic population, validation across strata and fairness audits are essential. Beyond efficiency, AI should be evaluated for measurable impact on preventive care, continuity, and patient-centred outcomes.

Singapore's integrated clusters and national data infrastructure position it well for disciplined scaling. The appropriate paradigm remains augmentation: AI should extend human capacity while preserving accountability, equity, and professional judgment.

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