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Comparison of different intervention thresholds for the treatment of glucocorticoid-induced osteoporosis: a cross-sectional study

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Abstract

Background Glucocorticoid-induced osteoporosis (GIO) is the most common drug-induced osteoporosis. Early detection and treatment may decrease the fragility fractures. Several GIO guidelines exist, although they vary in recommended intervention thresholds for initiating pharmacologic treatment. This study aimed to evaluate the performance of intervention thresholds in treating GIO under various guidelines.

Methods Rheumatic disease patients receiving ≥ 2.5 mg/day prednisolone or equivalent for longer than 3 months between January 2013 and 2023 were retrospectively reviewed. Patients who were previously treated with anti-osteoporotic medications or had other secondary causes of osteoporosis were excluded. Bone mineral density (BMD) and Thailand-specific FRAX with glucocorticoid adjustment (GC-FRAX) were recorded. The performances of different intervention thresholds from six GIO guidelines (ACR 2022, Belgian 2022, TOPF 2021, Korean 2018, Malaysian 2015, and Japanese 2023) were examined against the incidence of actual fragility fractures.

Results This study included 226 rheumatic patients, with a mean (SD) age of 62.9 (10.1) years. Most of the patients were female (88.9%). The average (SD) daily dose, cumulative dose, and duration of glucocorticoid use were 4.6 (10.6) mg/day, 9,223.4 (9,223.4) mg, and 58.3 (55.8) months, respectively. Diagnoses included rheumatoid arthritis (59.8%), systemic lupus erythematosus (22%), inflammatory myositis (4.7%), systemic sclerosis (4.7%), and others. The prevalence of major osteoporotic fractures and hip fractures was 14.2% and 0.9%, respectively. The ten-year probabilities of major osteoporotic and hip fractures (FRAX) with and without BMD were 12.6 ± 9.1, 5.4 ± 6, 10.7 ± 7.2, and 4.6 ± 4.8, respectively. The mean (SD) ten-year FRAX probabilities of major osteoporotic and hip fractures were 12.6% (9.1) and 5.4% (6) with the inclusion of BMD result, and 10.7% (7.2) and 4.6% (4.8) without the inclusion of the BMD result. The sensitivity, specificity and accuracy of the ACR 2022, Belgian 2022, TOPF 2021, Korean 2018, Malaysian 2015, and Japanese 2023 guidelines were 100%/ 3.1%/ 16.8%, 93.8%/ 14.4%/ 25.7%, 93.8%/ 43.8%/ 50.9%, 100%/ 17.5%/ 29.2%, 78.1%/ 62.9%/ 65% and 100%/ 24.2%/ 35%, respectively.

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Conclusions Among evaluated guidelines, ACR 2022, Korean 2018, and Japan 2023 had the highest sensitivity for GIO treatment, while Malaysian 2015 showed the highest specificity and accuracy. These findings can improve clinical decision-making in GIO management for rheumatic disease patients.

Keywords Glucocorticoid-induced osteoporosis, Osteoporosis, Rheumatic disease, Systemic autoimmune disease, FRAX score, Glucocorticoid, Fragility fracture

Introduction

Glucocorticoid-induced osteoporosis (GIO) is one of the most common causes of secondary osteoporosis [1]. Glucocorticoids are anti-inflammatory and immunosuppressive drugs used in rheumatic diseases such as rheumatoid arthritis, systemic lupus erythematosus, primary Sjogren syndrome, and inflammatory myopathy. Glucocorticoids affect bone cells, including osteoblasts, osteocytes, and osteoclasts, through signaling pathways such as Wnt/sclerostin and RANKL/osteoprotegerin, affecting bone formation and resorption [2]. Glucocorticoids reduce osteoclast apoptosis while promoting osteoblast and osteocyte apoptosis, which impairs bone healing and increases fracture risk [3]. In addition, they induce secondary hyperparathyroidism by decreasing calcium absorption in the intestinal tract and the reabsorption of calcium in the renal tubules [4, 5]. Additionally, glucocorticoids inhibit the secretion of gonadotropin and growth hormone [6]. Furthermore, sarcopenia may result from prolonged and excessive exposure to glucocorticoids, which increases the risk of fractures and falls [7].

Currently, numerous guidelines for treating GIO have been developed by various countries or organizations. These guidelines include the American College of Rheumatology Guideline for the Prevention and Treatment of GIO 2022 (ACR 2022) [8], the Guidelines on the Management and Treatment for GIO of the Japanese Society for Bone and Mineral Research 2023 (Japan 2023) [9], the Update of the Malaysian clinical guideline on the Management of GIO 2015 (Malaysian 2015) [10], the Korean Guideline for the Prevention and Treatment of GIO 2018 (Korean 2018) [11], and the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis in Adult: Consensus Recommendations from the Belgian Bone Club 2022 (Belgian 2022) [12]. The Thai Osteoporosis Foundation Clinical Practice Guideline 2021 (TOPF 2021) [13] is the only official osteoporosis guideline in Thailand, although it does not include specific recommendations for GIO. Nonetheless, it accounts for glucocorticoid use by incorporating dose adjustments into the FRAX calculation. FRAX, the Fracture Risk Assessment Tool developed by the World Health Organization, estimates the 10-year probability of major osteoporotic fractures (MOF) (hip, spine, forearm, or shoulder) and hip fractures in individuals based on clinical risk factors, with or without bone mineral density (BMD) measurements [14].

The assessment and treatment thresholds of GIO differ between these recommendations. The Belgian 2022 [12], TOPF 2021 [13], and Malaysian 2015 [10] all included patients at higher doses of glucocorticoids (≥ 5.0-7.5 mg/day of prednisolone equivalent), while the ACR 2022 [8] and the Korean 2018 [11] included patients at the lowest dose of glucocorticoids (≥ 2.5 mg/day of prednisolone equivalent). Additionally, the ACR 2022 [8] had the highest pharmacologic intervention threshold based on the T-score (T-score ≤ -1.0), followed by the Belgian 2022 [12] (T-score ≤ -1.5), and the TOPF2021 [13] and the Korean 2018 [11](T-score ≤ -2.5). Moreover, the ACR 2022 [8], the Belgian 2022 [12], and the Korean 2018 [11] had the lowest pharmacologic intervention threshold based on the FRAX calculation (FRAX-hip ≥ 1% and FRAX-MOF ≥ 10%). On the contrary, the TOPF2021 [13] utilized the FRAX cutoff primarily at the hip site, at a value of ≥ 3%. Table 1 summarizes the pharmacologic intervention thresholds among the guidelines.

Given the differences among these recommendations, the objective of this study was to evaluate the performance of intervention thresholds for the treatment of GIO from different guidelines compared to the actual incidence of fragility fractures in rheumatic disease patients in real-world practice.

Materials and methods

A retrospective, cross-sectional, single-center study was conducted at the Rheumatic Unit, Department of Medicine, Phramongkutklao Hospital, between January 2013 and January 2023. Data was retrieved using the ICD-10 codes. The inclusion criteria were patients aged 18 years or older, diagnosed with rheumatic diseases including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), primary Sjogren's syndrome (pSS), systemic sclerosis (SSc), vasculitis, autoinflammatory diseases, and inflammatory myopathies (IIMs), and received a prednisolone equivalent dose of 2.5 mg/day or more for three or more months. Patients were excluded if they had previously received anti-osteoporotic drugs or had other secondary causes of osteoporosis, including type 1 diabetes mellitus, untreated hyperthyroidism, cirrhosis, malnutrition, osteogenesis imperfecta, hypogonadism, chronic kidney disease, or premature menopause (before age 45). Additionally, patients taking medications associated with osteoporosis, such as aromatase inhibitors or

Table 1 Similarities and differences in diagnosis, assessment, and pharmacologic intervention thresholds among glucocorticoid-induced osteoporosis recommendations and guidelines

	ACR 2022 [8]	Korean 2018 [11]	Belgian 2022 [12]	TOPF 2021 [13]	Malaysian 2015 [10]	Japan 2023 [28]
Dose definition of GIO (prednisolone equivalence)	≥ 2.5 mg/day	≥ 2.5 mg/day	≥ 5 mg/day	≥ 5 mg/day	≥ 7.5 mg/day (5 mg/day if FRAX > 20%)	Any
Pharmacologic intervention thresholds in patients aged ≥ 40–50 years if any of the following criteria are met						
T-score	< -1.0	≤ -2.5	≤ -1.5	≤ -2.5	NA	(Lumbar BMD) (%YAM)
FRAX	Hip > 1% MOF > 10%			Hip ≥ 3%	MOF > 10%	NA
Fracture	Osteoporotic fracture				NA	Osteoporotic fracture
Dose GC for start treatment	30 mg/day Cumulative dose > 5 gm/year		≥ 7.5 mg/day	x	≥ 7.5 mg/day	Any
Pharmacologic intervention thresholds in patients aged < 40–50 years if any of the following criteria are met.						
Z-score	Prednisolone > 7.5 mg/day Z-score < -3 Rapid bone loss ≥ 10% at Hip/spine			NA	NA	(Lumbar BMD) (%YAM)
Fracture	Osteoporotic fracture					
Dose GC for start treatment	30 mg/day Cumulative dose > 5 gm/year			NA	NA	any

BMD, Bone mineral density; GC, Glucocorticoids; GIO, Glucocorticoid-induced osteoporosis; NA, Not applicable

ACR 2022, the American College of Rheumatology Guideline for the Prevention and Treatment of GIO 2022; Korea 2018, Korean Guideline for the Prevention and Treatment of GIO 2018; Malaysia 2015, Update of the Malaysian clinical guideline on the management of GIO 2015; Belgian 2022, Prevention and Treatment of Glucocorticoid-Induced Osteoporosis in Adult: Consensus Recommendations from the Belgian Bone Club 2022; TOPF2021, Summary of the Thai Osteoporosis Foundation Clinical Practice Guideline on the diagnosis and management of osteoporosis 2021; Japan 2023, Guidelines on the management and treatment for GIO of the Japanese Society for Bone and Mineral Research 2023

GnRH agonists, or those without available BMD results were excluded.

Demographic data, the presence of comorbidities, glucocorticoid use (current dose, average dose, and cumulative dose), smoking, alcohol use, history of fragility fracture, and family history of hip fracture were collected. Glucocorticoid adjustment (GC-FRAX) was applied to calculate the FRAX scores for the probability of hip fracture and major osteoporotic fractures (MOF) in each patient, both with and without bone mineral density (BMD), utilizing a Thai reference (https://www.shefeld.ac.uk/FRAX/tool.aspx?country=9). For patients receiving low doses of glucocorticoids (< 2.5 mg of prednisolone daily or equivalent), the calculated probabilities for MOF decreased by 20%, and for hip fractures, by 35%. Conversely, for patients receiving high doses (> 7.5 mg of prednisolone daily or equivalent), there was an increase in estimated probabilities of 15% for MOF and 20% for hip fractures. For example, a patient on 10 mg of prednisolone per day with a standard FRAX score of 10% would have a GC-FRAX adjusted probability of 11.5% for MOF and 12.0% for hip fracture [15].

All patients underwent bone mineral density (BMD) measurement at the hip and lumbar spine and vertebral fracture assessment (VFA) using the GE-Lunar iDPX densitometer (GE Healthcare, Madison, WI, USA) after treatment with glucocorticoid for at least 3 months. Fragility fractures were retrieved from medical records, including morphometric (using Genant's classification) [16], clinical vertebral fracture, hip, and major osteoporotic fractures (i.e., proximal humerus and femur, wrist).

The study was conducted in accordance with the Helsinki Declaration and was approved by the Institutional Board Review of the Royal Thai Army Medical Department under approval number IRBRTA 0571/2566.

Statistical analysis

All statistical analyses were performed using the IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp. Released 2010. Data were presented as mean and standard deviation (SD), median, number (%), incidence, and interquartile range (IQR) for baseline characteristics. An independent *t*-test or Mann-Whitney U test and Chi-square test or Fisher's exact test were used to compare variables between patients with and without fragility fractures as appropriate. The performances of the intervention thresholds for initiating pharmacologic treatment of GIO from each guideline, including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and the area under the receiver operating characteristic curve (AUC), were examined against the incidence of actual fragility

fractures. P-values < 0.05 were considered statistically significant.

Results

A total of 2,099 patients with rheumatic diseases who received prednisolone at a dose ≥ 2.5 mg per day (or equivalent dose) for three or more months and underwent BMD measurements were included in the study. Of these, 1,873 patients were excluded because they were either previously treated with anti-osteoporotic medications or had other causes of secondary osteoporosis prior to BMD measurement.

Demographic and clinical characteristics

The study included 226 patients with rheumatic disease, with a mean ± SD age of 62.9 ± 10.1 years and an 88.9% female gender predominance. The flowchart for this investigation is presented in Fig. 1. The average (mean ± SD) of the daily dose, cumulative dose, and duration of glucocorticoids were 4.6 ± 10.6 mg/day, 9,223.4 ± 9,223.4 mg, and 58.3 ± 55.8 months, respectively (Table 2). The diagnoses included RA (59.8%), SLE (22%), inflammatory myositis (4.7%), systemic sclerosis (4.7%), and others.

Fracture risk assessment

Major osteoporotic fractures were observed in 32 patients (14.2%), including vertebral fractures in 29 patients (12.8%), distal radius fractures in 2 patients (0.9%), proximal humerus fracture in 1 patient (0.5%), and hip fractures in 2 patients (0.9%). Five patients experienced more than one type of fracture. The T-scores at the femoral neck, total hip, and L1-L4 were − 1.63 ± 1.21, -1.38 ± 1.02, and − 1.92 ± 0.93, respectively. The ten-year probability of major osteoporotic and hip fractures (GC-FRAX) was 12.6 ± 9.1, 5.4 ± 6, 10.7 ± 7.2, and 4.6 ± 4.8, respectively, with and without BMD (Table 2).

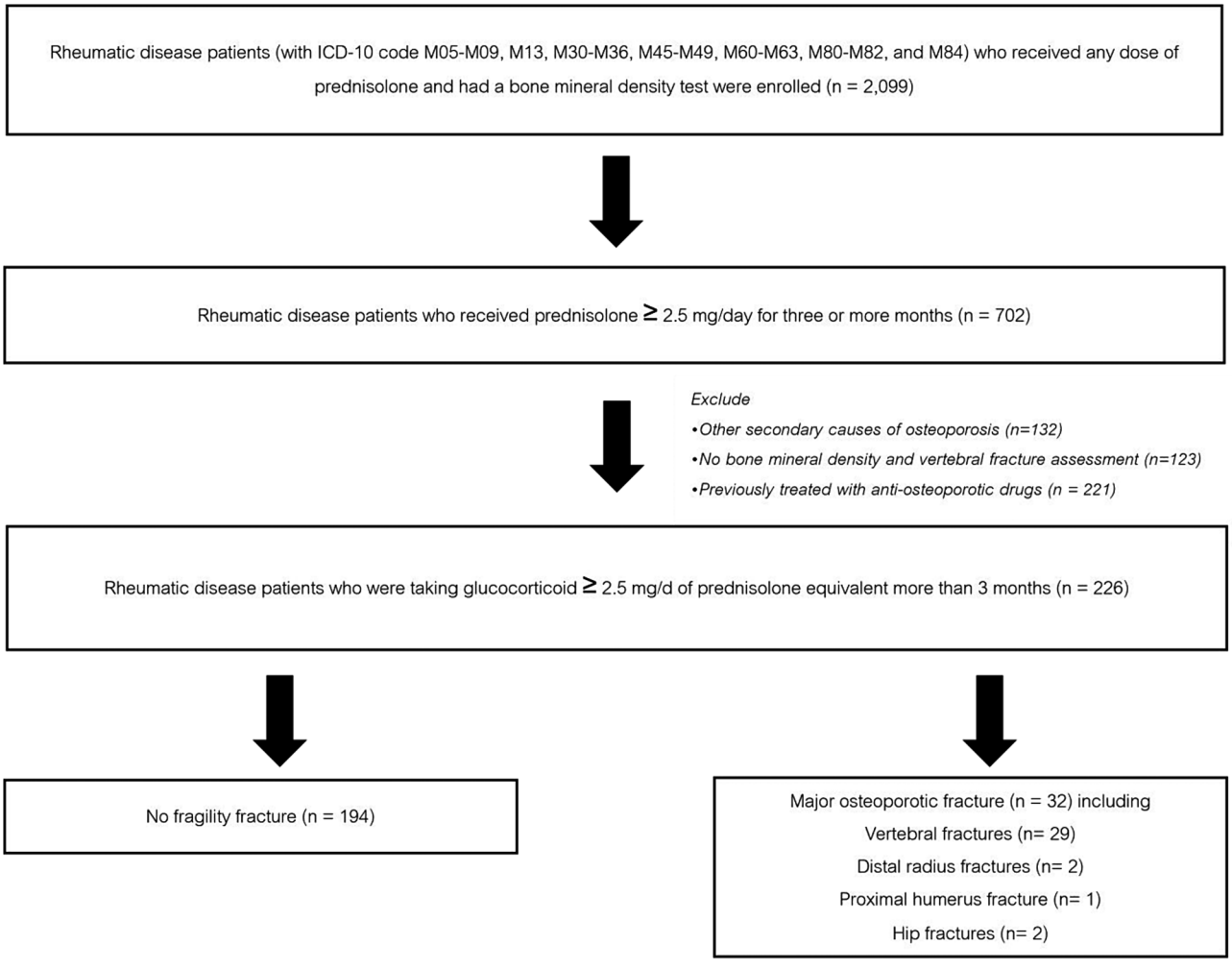

Fig. 1 Flowchart of the study

Table 2 Baseline characteristics of study patients

Patients' characteristics (*n* = 226)	Results
Demographics	
- Age, years (Mean ± SD)	62.9 ± 10.1
- Female, n (%)	201 (88.9)
- Menopause, n (%)	177 (78.3)
- Body mass index, kg/m^2 (Mean ± SD)	23.6 ± 4.2
Rheumatic diseases	
- Rheumatoid arthritis, n (%)	152 (59.8) *
- Systemic lupus erythematosus, n (%)	56 (22) *
- Inflammatory myopathies, n (%)	12 (4.7) *
- Systemic sclerosis, n (%)	12 (4.7) *
- Vasculitis, n (%)	10 (3.9) *
- Primary Sjogren's syndrome, n (%)	9 (3.5) *
- Autoinflammatory disease, n (%)	3 (1.2)
Glucocorticoid use (prednisolone dose equivalent)	
- Daily dose, mg/day (median, IQR)	2.5 (1.1, 5.0)
- Duration, month (median, IQR)	37.0 (16.8–83.3)
- Cumulative dose, mg (median, IQR)	5,999.2 (2,585.1–12,344.2)
Bone characteristics	
Fractures	
- Major osteoporotic fractures, n (%)	32 (14.2)
- Vertebral fractures, n (%)	29 (12.8)
- Distal radius fractures, n (%)	2 (0.9)
- Proximal humerus fracture, n (%)	1 (0.5)
- Hip fractures, n (%)	2 (0.9)
T-score	
- Lumbar	-1.63 ± 1.21
- Hip	-1.38 ± 1.02
- Femoral neck	-1.92 ± 0.93
Osteoporosis, defined as T-score ≤ -2.5 (n, %)	
- Lumbar	60 (26.5%)
- Total hip	34 (15.0%)
- Femoral neck	65 (28.8%)
GC-FRAX (n = 223), mean ± SD	
- FRAX MOF, with BMD (%)	12.61 ± 9.10
- FRAX Hip, with BMD (%)	5.40 ± 6.0
- FRAX MOF, without BMD (%)	10.65 ± 7.15
- FRAX Hip, without BMD (%)	4.57 ± 4.77

* Overlapping diseases (*n* = 24); some patients had clinical manifestations suggestive of multiple rheumatic diseases. SD: Standard deviation. IQR: Interquartile range. GC-FRAX: Glucocorticoid adjusted FRAX. MOF: Major osteoporotic fracture. BMD: Bone mineral density

Characteristics of glucocorticoid-induced osteoporosis patients with and without major osteoporotic and hip fractures

Table 3 shows that GIO patients with MOF demonstrated significantly lower T-scores and higher GC-FRAX than GIO patients without MOF when comparing T-score and GC-FRAX in rheumatic patients with and without major osteoporotic fracture. Although only two hip patients had hip fractures, the femoral neck and total BMD T-scores were significantly lower in patients with hip fractures than in those without. Additionally, the GC-FRAX-MOF

Table 3 Characteristics of glucocorticoid-induced osteoporosis patients with/without major osteoporotic and hip fractures

Variables	Major osteoporotic fracture (MOF)				Hip fracture (HF)			
	With fracture (*n* = 32)	Without fracture (*n* = 191)	Mean difference (95%CI)	*p*-value	With fracture (*n* = 2)	Without fracture (*n* = 221)	Mean difference (95%CI)	*p*-value
T-score at L1-4	-2.1 ± 1.44	-1.55 ± 1.16	-0.55 (-1.01, -0.09)	0.019	-2.9 ± 0.85	-1.62 ± 1.21	-1.28 (-2.97, 0.41)	0.137
T-score at total hip	-2.12 ± 1.13	-1.27 ± 0.95	-0.85 (-1.22, -0.48)	< 0.001	-4.35 ± 1.06	-1.36 ± 0.98	-2.99 (-4.37, -1.62)	< 0.001
T-score at FN	-2.63 ± 0.94	-1.81 ± 0.88	-0.82 (-1.16, -0.48)	< 0.001	-3.6 ± 1.41	-1.91 ± 0.92	-1.69 (-2.98, -0.41)	0.01
GC-FRAX with BMD, MOF (%)	25.17 ± 11.57	10.53 ± 6.68	14.64 (10.37, 18.91)	< 0.001	34.4 ± 26.02	12.41 ± 8.73	21.99 (-21.82, 25.48)	0.443
GC-FRAX with BMD, Hip (%)	12.43 ± 8.71	4.24 ± 4.49	8.19 (4.99, 11.39)	< 0.001	24.28 ± 21.74	5.23 ± 5.56	19.05 (-17.83, 21.39)	0.432
GC-FRAX without BMD, MOF (%)	20.61 ± 7.49	9.01 ± 5.61	11.6 (9.38, 13.82)	< 0.001	17.9 ± 7.21	10.59 ± 7.14	7.31 (-2.68, 17.3)	0.151
GC-FRAX without BMD, Hip (%)	10.07 ± 6.25	3.66 ± 3.79	6.41 (4.1, 8.72)	< 0.001	12.04 ± 9.85	4.5 ± 4.69	7.53 (0.92, 14.15)	0.026

CI: Confidence interval. GC-FRAX: Glucocorticoid-adjusted FRAX. MOF: Major osteoporotic fracture. BMD: Bone mineral density

Table 4 The performance of intervention thresholds for treating glucocorticoid-induced osteoporosis based on different guidelines against actual fragility fractures. Result reported in number (95% confidence interval)

Guidelines	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
ACR 2022	100 (89.1–100)	3.1 (1.14–6.61)	14.6 (10.2–19.9)	100 (54.1–100)	16.8* (12.2–22.3)	0.590 (0.494–0.685)
Korean 2018	100 (89.1–100)	17.5 (12.5–23.6)	16.7 (11.7–22.7)	100 (89.7–100)	29.2* (23.4–35.6)	0.587 (0.491–0.683)
Malaysia 2015	78.1 (60–90.7)	62.9 (55.7–69.7)	25.8 (17.4–35.7)	94.6 (89.1–97.8)	65 (58.4–71.2)	0.719 (0.627–0.810)
Belgian 2022	93.8 (79.2–99.2)	14.4 (9.8–20.2)	15.3 (10.6–21.1)	93.3 (77.9–99.2)	25.7* (20.1–31.9)	0.558 (0.457–0.559)
TOPF2021	93.8 (79.2–99.2)	43.8 (36.7–51.1)	21.6 (15.1–29.4)	97.7 (91.9–99.7)	50.9 (44.2–57.6)	0.704 (0.625–0.784)
Japan 2023	100 (89.1–100)	24.2 (18.4–30.9)	17.9 (12.6–24.3)	100 (92.5–100)	35* (28.8–41.6)	0.621 (0.530–0.711)

PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under the curve. CI: Confidence interval *Significant difference from Malaysian 2015 ($p < 0.05$)

ACR2022, the American College of Rheumatology Guideline for the Prevention and Treatment of GIO 2022; Korea2018, Korean Guideline for the Prevention and Treatment of GIO 2018; Malaysia2015, Update of the Malaysian clinical guideline on the management of GIO 2015; Belgian2022, Prevention and Treatment of Glucocorticoid-Induced Osteoporosis in Adult: Consensus Recommendations from the Belgian Bone Club 2022; TOPF2021, Summary of the Thai Osteoporosis Foundation Clinical Practice Guideline on the diagnosis and management of osteoporosis 2021; Japan2023, Guidelines on the management and treatment for GIO of the Japanese Society for Bone and Mineral Research 2023

without BMD was significantly higher in GIO patients with hip fractures.

The performance of intervention thresholds for treating GIO from different guidelines against the incidence of actual fragility fractures

The ACR 2022, Korean 2018, and Japan 2023 guidelines demonstrated an optimal sensitivity of 100% in this study. Similarly, the Thai 2021 and Belgian 2022 guidelines demonstrated high sensitivities of 93.8%, while the Malaysian 2015 guideline had a sensitivity of 78.1%. Nevertheless, the specificity indicated divergent tendencies. The Malaysian 2015 guideline showed the highest specificity of 62.9%, indicating that it helped reduce unnecessary pharmacologic interventions. This was followed by the Thai 2021 (43.8%), Japanese 2023 (24.2%), Korean 2018 (17.5%), Belgian 2022 (14.4%), and ACR 2022 (3.1%) guidelines, respectively. This study found that the Malaysian 2015 was the most accurate guideline regarding overall diagnostic accuracy, including sensitivity and specificity, at 65%. The accuracies of the Japanese 2023 (35%), Korean 2018 (29.2%), Belgian 2022 (25.7%), and ACR 2022 (16.8%) recommendations were lower than the Thai 2021 guideline, which had an accuracy of 50.9% (Table 4).

Discussion

Long-term glucocorticoid treatment is an essential component in the treatment of several medical diseases. In this study, the majority of rheumatic disease patients were elderly postmenopausal women (78.3%), with RA (59.8%), which was similar to other real-world GIO studies in Taiwan by Chen JF et al., [17] and Lai EL et al., [18], followed by SLE (22%), whereas the GIO study by Mok CC et al., [19] enrolled only SLE patients. The mean daily dose in this study was relatively low (4.6 mg/day), although it was consistent with previous studies with mainly RA patients [17, 18], which appeared to be lower than the study with SLE patients [19]. The cumulative prednisolone dose in the current study was higher than in others [17–19].

Despite the relatively low dose of glucocorticoids used in this study, adverse effects on bone mineral density were observed, particularly in RA patients with moderate to severe disease activity. Several studies have shown that RA itself is an independent risk factor for osteoporosis and fractures, even in the absence of glucocorticoid use [20, 21]. Chronic systemic inflammation, disease activity, functional impairment, and RA-related factors such as cytokine-driven bone resorption contribute to increased bone loss and fracture risk [22]. Although most GIO guidelines, including those evaluated in this study [8–13], use glucocorticoid dose, BMD, previous fracture, and FRAX as primary determinants for treatment initiation, they do not explicitly account for the additional fracture risk associated with RA. Notably, the FRAX tool includes RA as a risk factor, but does not account for serologies, disease activity and severity, deformities, or cumulative inflammatory burden [14]. Given that nearly 60% of this study population had RA, this study's findings and others have suggested that the intervention thresholds for GIO may need adjustment for RA patients according to disease status and treatment given. Furthermore, it is still controversial that the current treatment threshold for RA patients is appropriate [23–26]. Future research should explore RA-specific risk stratification to optimize treatment thresholds in this population.

This study found a lower rate of significant osteoporotic and hip fractures among rheumatic disease patients than previously reported, higher than in other studies [17–19]. The discrepancy could be explained by methodological differences as previous studies were higher than in others [17–19]. This study recorded fractures cross-sectionally, whereas other previous studies captured fractures cumulatively over time [17–19]. Furthermore, the study by Lai et al. included patients who had previously received osteoporotic treatment [18], indicating a fracture-prone

population, which was most likely related to their greater fracture incidence.

Among the guidelines evaluated, the ACR 2022 [8], Korean 2018 [11], and Japanese 2023 [9] had the highest sensitivity for GIO treatment, at 100%. This was likely due to GIO's low dose definition, higher BMD T-scores, and lower FRAX thresholds. In practice, these strategies facilitate early detection and treatment, ensuring that GIO patients at risk of fracture receive pharmacological therapies. However, this approach may result in the inefficient allocation of medical resources to individuals who do not require them, which is particularly relevant in low- and middle-income countries like Thailand. Furthermore, it might unnecessarily expose those who are at low risk to the long-term adverse effects of anti-osteoporotic drugs, such as osteonecrosis of the jaw and atypical femoral fractures. Meanwhile, the Malaysian 2015 demonstrated the highest specificity (62.9%) and accuracy (65%) due to the highest dose definition of GIO, followed by the TOPF 2021 [13], which has a more stringent threshold for pharmacologic interventions.

The ACR 2022 [8] and the International Osteoporosis Foundation and European Calcified Tissue Society (IOF-ECTS) GIO guidelines [27] were recently validated in a cohort of GIO patients from a single center in Taiwan which found accuracies of 28.3% and 51.8%, and AUCs with a 95% CI of 0.52 (0.44–0.61) and 0.608 (0.525–0.692), respectively [17]. Compared to other guidelines in this study and the Taiwanese study [17], the ACR 2022 appears to have the lowest accuracy. Nonetheless, the ACR 2022 was more accurate in the Taiwanese study (28.3%) than in this study (16.8%). The differences could be explained by the extended time over which fracture data was collected, which resulted in a higher fracture prevalence, enhancing the specificity of the ACR 2022. Furthermore, patients in the Taiwanese cohort were predominantly older and had RA. A study reported a higher fracture risk based on the FRAX score in RA patients compared to those with SLE [18]. These findings have shown that the more sensitive GIO guideline may be acceptable for individuals at higher risk of fracture, such as elderly RA patients using chronic glucocorticoids. In contrast, more specific and accurate GIO guidelines may be appropriate for patients with a lower risk of fractures and countries with limited resources.

The present study must be interpreted within its strengths and weaknesses. This is the first study to examine the performance of several recommendations' intervention thresholds for treating GIO that are available worldwide. BMD and VFAs were performed on all of the patients in this study. This study included a large sample size, which should be adequate for assessing osteoporotic risk in rheumatic disease patients. However, this study was retrospective, focusing exclusively on patients with rheumatic diseases who received BMD measurements. The study population was predominantly comprised of postmenopausal women, and their self-reported answers on the FRAX questionnaires may have been affected by recall bias, which could have influenced the results. Some guidelines, including the ACR 2022 and the Korean 2018 guidelines, have recommended a Z-score less than − 3.0 and rapid bone loss greater than or equal to 10% at the hip or spine as the indication to start pharmacologic treatment, although the data on the follow-up BMD was lacking in this study. Nonetheless, most patients were in menopausal status or older than 50, so the effect was trivial. Furthermore, the small number of hip fractures was insufficient to comprehensively analyze the GC-FRAX and T-score cut-offs related to hip fractures in GIO.

This study highlights the limitations of current risk prediction models and intervention thresholds based on FRAX and BMD, which may not fully capture the complexity of risk in diverse patient populations. Therefore, this underscores the need for tailored approaches that consider the unique characteristics of rheumatic disease patients by integrating patient-specific factors such as disease activity and cumulative glucocorticoid dose into fracture risk assessments. Future studies are warranted to close the knowledge gap in GIO treatment, particularly by improving fracture risk prediction by including disease-specific and patient-specific factors such as disease activity, cumulative glucocorticoid dose, and trabecular bone score. Additionally, validations of FRAX and BMD intervention thresholds in prospective, longitudinal, real-world cohorts, examining whether these thresholds remain consistent across diverse diseases and ethnicities, and cost-effectiveness studies are also needed.

In conclusion, this study provides valuable insights into the characteristics and challenges of managing GIO patients with rheumatic diseases. The prevalence of major osteoporotic and hip fractures in rheumatic disease patients with GIO was 14.2% and 0.9%, respectively. Our findings demonstrated differences in the sensitivity, specificity, and accuracy of several GIO treatment guidelines. Notably, the ACR 2022, Korean 2018, and Japanese 2023 guidelines had the best sensitivity, indicating their potential effectiveness in identifying at-risk individuals who could benefit from treatment. In contrast, the Malaysian 2015 and TOPF 2021 guidelines had the best specificity and accuracy, implying that they could better prevent overtreatment. In clinical practice, healthcare practitioners should consider disease-specific risks, overall fragility fracture risk profiles, and healthcare resources when selecting GIO recommendations, focusing on balancing sensitivity and specificity to provide the most effective and efficient care for GIO patients. Future research is needed to enhance the precision of fracture

risk assessment, optimize treatment strategies, and refine guideline recommendations for GIO.

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Author contributions
K.P. and S.C. conceptualized the study, developed the methodology, and wrote the original draft. K.P. was responsible for data acquisition and curation. K.P., S.C., and C.P. interpreted data. S.C. supervised the project. K.P., S.C., C.P., P.N., T.A., P.N., and R.P. reviewed and edited the final draft. All authors have approved the submitted version and agreed to be accountable for the author's own contributions.

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Data availability
Data are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Helsinki Declaration and was approved by the Institutional Board Review of the Royal Thai Army Medical Department under approval number IRBRTA 0571/2566. The consent to participate was waived since this was a retrospective study.

Consent for publication
Not applicable.

Generative AI and AI-assisted technologies in the writing process
Nothing to disclose.

Competing interests
The authors declare no competing interests.

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