Duration, dose, and responsiveness to erythropoiesis-stimulating agents and risk of osteoporotic fracture among patients with chronic kidney disease in Hong Kong: a nested case–control study

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Summary

Background Anaemia is a common complication of chronic kidney disease (CKD), often treated with erythropoiesis-stimulating agents (ESAs). The association between erythropoietin use and osteoporotic fractures in humans is yet to be fully elucidated. It is also unclear whether responsiveness to ESA treatment independently contributes to fracture risk. We aimed to evaluate the risk of osteoporotic fractures associated with ESA use in patients with chronic kidney disease (CKD).

Methods In this nested case–control study, we identified 19,720 patients newly diagnosed with CKD between 2005 and 2017 who received ESA treatment before Dec 31, 2022 from the Clinical Data Analysis and Reporting System, the territory-wide electronic health record database in Hong Kong. Patients were included irrespective of dialysis status (peritoneal dialysis, haemodialysis, and non-dialysis). Fracture cases were matched with up to 10 fracture-free controls, according to age, sex, and year of fracture, to investigate associations with ESA use. Fracture cases were defined as major osteoporotic fractures, including overall fractures and specific types (spine, humerus, wrist, and hip fractures), identified using ICD-9-CM codes. Main exposures of interest were duration of ESA treatment before fracture (index date), cumulative defined daily dose of ESA before index date, and ESA responsiveness. Responsiveness was defined as haemoglobin increase ≥1 g/dL within 2 months of ESA initiation. Conditional logistic regression was used to estimate odds ratios (ORs) adjusted for time since CKD diagnosis, comorbidities, fracture-related medications, frailty, CKD-related procedures, and laboratory values.

Findings In total, 959 osteoporotic fracture cases were matched with 9262 controls. Among the fracture types, the majority of cases were hip fractures (n = 622), followed by wrist (n = 164), humerus (n = 154), and spine fractures (n = 80). Fracture patients had a longer ESA treatment duration (mean 2.1 years [SD 2.1] vs. 1.4 years [SD 1.7]) and received a higher cumulative defined daily dose (mean 14,559.8 [SD 21,270.1] vs. 9610.3 [SD 15,702.0]) than their matched controls. Longer ESA treatment duration, but not cumulative dose, was independently associated with increased risks of overall fracture (OR per additional year 1.31; 95% CI 1.23–1.39) and hip fracture (1.28; 1.18–1.39). Results remained largely consistent after adjusting for anaemia severity, excluding patients with hyperparathyroidism, and in subgroup analyses. Additionally, ESA responders had a significantly higher fracture risk compared to non-responders (OR 1.36; 95% CI 1.14–1.63).

Interpretation Our findings suggest that prolonged ESA use and ESA responsiveness are associated with increased osteoporotic fracture risk in patients with CKD, highlighting the need for optimisation of treatment regimens for anaemia in patients with CKD to balance treatment benefits against fracture risk. Further research is warranted to better understand this association.

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Research in context

Evidence before this study

Although preclinical studies have suggested that exogenous erythropoietin may promote bone loss, whether erythropoiesis-stimulating agent (ESA) use is associated with fracture risks in humans is less clear. We searched PubMed for articles published before July 1, 2025, without language restrictions, using the terms ("erythropoiesis-stimulating agents" OR "erythropoietin") AND "fracture". Only two studies examined the relationship between ESA use and fracture risk in patients with chronic kidney disease (CKD). These studies found that higher doses of ESA were associated with an increased risk of fractures, particularly hip fractures, in haemodialysis patients. However, they did not account for the duration of ESA use and were limited to patients undergoing haemodialysis. Additionally, it remains unclear whether responsiveness to ESA treatment independently contributes to fracture risk. We aimed to address these knowledge gaps.

Added value of this study

This nested case–control study used the territory-wide electronic health record database in Hong Kong to investigate associations in ESA treatment (duration, dosage, responsiveness) and osteoporotic fractures in patients newly diagnosed with CKD (2005–2017, ESA treatment before Dec 31, 2022). Patients were included irrespective of dialysis status. In this cohort, the findings showed that a prolonged duration of ESA treatment, but not cumulative dose, was independently associated with an increased risk of osteoporotic fractures. The findings were consistent across analyses adjusted for anaemia severity and excluded patients with hyperparathyroidism. Additionally, ESA responders, defined by a significant increase in haemoglobin levels within 2 months of treatment initiation, had a higher fracture risk compared to non-responders. Subgroup analyses stratified by dialysis status showed significant associations between ESA duration and risk of overall and hip fracture for non-dialysis and peritoneal dialysis patients; estimates were non-significant for haemodialysis patients.

Implications of all the available evidence

Our results suggest an association between the duration and responsiveness of ESA use and an increased fracture risk. Given that ESA treatment is often administered over extended periods, there is a need for future research to focus on optimising anaemia management in patients with CKD.

Introduction

Anaemia is a common complication of chronic kidney disease (CKD) and is associated with an increased risk of adverse renal and cardiovascular events, hospitalisations, and mortality.[1] Erythropoietin, a hormone secreted by the kidney, plays a crucial role in regulating erythropoiesis. Preclinical studies suggest that erythropoietin influences bone metabolism[2] and facilitates bone healing.[3,4] Osteoblast-specific deletion of the erythropoietin receptor also led to defective bone formation and reduced trabecular bone mass with age.[5] On the other hand, exogenous erythropoietin has been found to enhance osteoclastogenesis[6] and the bone resorption process.[6,7]

Erythropoiesis-stimulating agent (ESA) are synthetic analogues of erythropoietin that increases erythropoiesis and hence haemoglobin levels in humans; anaemia in CKD is often treated with ESA therapy.[8–10] Osteoporosis is a bone disorder characterised by decreased bone mineral density (BMD) and altered bone microarchitecture that predisposes to an increased risk of fracture; in patients with CKD, CKD-associated osteoporosis further encompasses abnormalities in bone turnover, mineralisation, and volume within the spectrum of CKD-mineral and bone disorder (CKD-MBD).[11] ESA use has been linked to adverse clinical outcomes, including major adverse cardiac events and osteoporotic fractures.[12–15]

Osteoporotic fractures are a major clinical concern due to their significant contribution to morbidity and mortality.[16] A recent cohort study showed a dose-dependent association between ESA use and an increased 1-year risk of hip fractures in haemodialysis patients.[14] Nonetheless, the pharmacological effects of ESA on bone metabolism are expected to develop gradually,[17] and it remains unclear whether this association could be mediated by an increased propensity for falls. Also, potential confounding by indication may exist, as higher ESA dosages are often prescribed for patients with more severe anaemia, which itself is a known risk factor for fractures.[18] Moreover, the previous study used a data-driven (backward selection) approach to select covariates in the model which may miss out some other potential confounders.[14] Finally, prior studies have not accounted for the duration of ESA use, and the analyses were limited to patients

undergoing haemodialysis.[14,15] Thus, the relationship between ESA use and fracture risk remained far from clear. We aimed to address this knowledge gap.

Using a large dataset derived from electronic health records (EHRs), we conducted a territory-wide nested case–control study to investigate the association between ESA use and the risk of osteoporotic fractures, considering the duration and dosage of ESA treatment, as well as ESA responsiveness.

Methods

Study design and data sources

This population-based study used data from the Clinical Data Analysis and Reporting System (CDARS), a territory-wide EHR database managed by the Hong Kong Hospital Authority (HA). The HA provides public healthcare services through 43 public hospitals and 122 outpatient clinics, managing over 80% of all hospitalisations in Hong Kong.[19] The CDARS has an ethnically homogeneous population of ~92% Han Chinese.[20] Approximately 98% of hip fracture cases in Hong Kong are admitted to public hospitals managed by the HA.[21] The diagnostic codes for osteoporotic fractures in the EHRs have previously been validated, with a positive predictive value (PPV) of 96.8%.[22] Specifically, the PPV was 100% for humerus, wrist, and hip fractures, and 86% for spine fractures,[22] suggesting that the fracture data obtained from the EHRs was reliable.

Ethics

This study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB, reference number: UW 23–203). As all clinical data were based on anonymised EHRs, the need for informed consent was waived in accordance with relevant regulations in Hong Kong.

Study cohort

From the EHR database, we identified all patients who had an incident diagnosis of CKD between 2005 and 2017 and subsequently received ESAs before Dec 31, 2022 (end of study period). CKD was defined as at least two consecutive records of an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2, recorded at least 90 days apart. eGFR was calculated from serum creatinine using the Asian modified CKD-EPI equation.[23] Incident CKD was defined by the first sustained eGFR <60 mL/min/1.73 m^2, with a 1-year lookback since the year 2004 to ascertain incident status. Exclusion criteria included those who had missing information on date of birth or sex, aged below 50 years as of the index date, had a history of cancer or rare bone diseases (including osteogenesis imperfecta and Paget's disease of bone), or had received an ESA prescription prior to their CKD diagnosis. A flowchart of the patient selection is provided in Fig. 1.

Definition of cases and controls

We conducted a nested case–control study to examine the relationship between the duration and cumulative dose of ESA treatment with fracture risk over a long observational period. Cases were defined as major osteoporotic fractures, including overall fractures and specific types (spine, humerus, wrist, and hip fractures), identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes (Supplementary Table S1).[24] The date of fracture was assigned as the index date. For patients with multiple fractures, the earliest occurrence of any osteoporotic fracture was used as the index date for the analysis of overall fractures. For analyses of specific fracture types, the index date corresponded to the first occurrence of the respective fracture type. Controls were defined as patients without any osteoporotic or non-osteoporotic fractures (i.e., traumatic fractures; Supplementary Table S1) at index date.[25] For each case, we assigned the index date to the eligible controls and matched up to 10 controls per case without replacement, using exact matching on sex and age at the index year. Controls were ESA-eligible and at risk of fracture on their assigned index date.

Exposure variables

The approved ESAs for the treatment of renal anaemia in Hong Kong included epoetin alfa, epoetin beta, darbepoetin alfa, and methoxy polyethylene glycol-epoetin beta. Prescription doses of ESAs were standardised into defined daily dose (DDD) units in accordance with the World Health Organization's definitions.[26] The main exposures of interest were: (i) duration of ESA treatment, defined as the total time (in years) of ESA treatment before the index date, and (ii) cumulative dose, defined as the total cumulative DDD of ESA prescribed before the index date. Additionally, we considered ESA responsiveness as an exposure variable. ESA responders were defined as patients who achieved an increase in haemoglobin concentration of $\geq$1 g/dL within 2 months of initiating ESA treatment.[27]

Statistical analysis

Multivariable conditional logistic regression, stratified by matched pairs, was used to examine the association between ESA use and the risk of overall osteoporotic fracture, as well as specific fracture types. ESA use was assessed in terms of treatment duration (per year increase) and cumulative DDD (per 10,000-unit increase) in the main analysis. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were reported. ESA treatment duration and cumulative dose were initially modelled separately in two regression models and

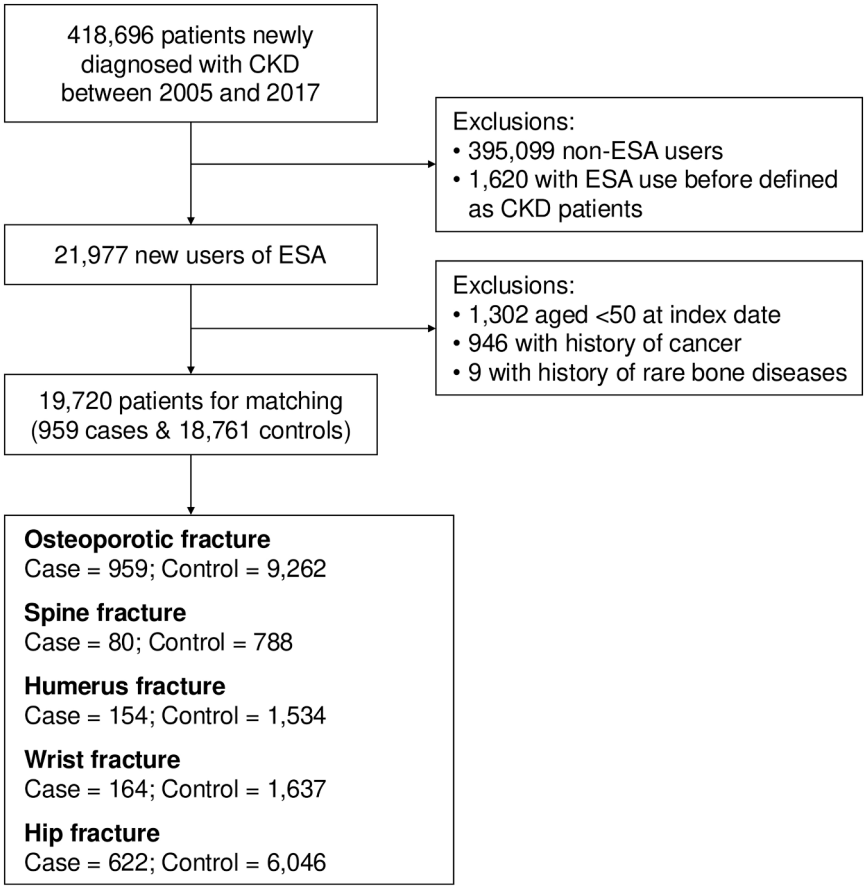

Fig. 1: Flowchart of patient selection.

subsequently included together in a single model to assess their independent associations with fracture risk, adjusting for each other. We considered a list of potential covariates based on the literature and data availability,[28,29] including time since CKD diagnosis (i.e., time since first qualifying eGFR <60 mL/min/1.73 m^2), hospital clusters, comorbidities within five years before the index date, frailty (defined using the Hospital Frailty Risk Score),[30] medications prescribed within 180 days before the index date, laboratory tests and dialysis records within 365 days before the index date, and history of kidney transplant. Comorbidities, dialysis records, and transplant history were identified using ICD-9-CM codes (Supplementary Table S2). Three incremental models were used. Model 1 (unadjusted model) was a conditional logistic regression model accounting only for the matching variables (age, sex, index year). Model 2 (minimally adjusted model) were further adjusted for the imbalanced covariates between osteoporotic fracture cases and controls that had a standardised mean difference (SMD) > 0.1,[31] including hypertensive diseases, pneumonia history, fall history, frailty, use of non-steroidal anti-inflammatory drugs, use of proton pump inhibitors, use of opioid analgesics, dialysis, blood haemoglobin levels, and serum calcium levels (Table 1). Model 3 (fully adjusted model) included all the potential covariates as listed in Table 1. There were no missing data for the covariates.

To address the potential correlation between duration and cumulative dose, we (i) conducted collinearity diagnostics using Pearson's correlation and variance inflation factor (VIF), (ii) fitted restricted cubic splines for duration and cumulative dose to allow flexible functional forms, and (iii) re-parameterised exposure variables as duration plus average daily dose instead of cumulative dose.

To assess potential interaction by age and sex, we added multiplicative interaction terms to the regression models and performed subgroup analyses when significant interaction effects with treatment duration or cumulative dose were observed. Moreover, as the pathophysiology between dialysis and non-dialysis patients with CKD may differ, we stratified the analysis by dialysis status (peritoneal dialysis, haemodialysis, and

non-dialysis) and additionally included dialysis vintage as a covariate in these models.

Several sensitivity analyses were performed to examine the robustness of our findings. First, to evaluate whether the relationship between ESA use and fracture risk was independent of anaemia severity, the models were further adjusted for the average haemoglobin concentration during the period from ESA initiation to the index date. Second, as secondary hyperparathyroidism (SHPT) could be a major factor associated with fracture risk in patients with CKD,[32–34] we conducted a sensitivity analysis excluding individuals with potential SHPT defined by any of: (i) history of parathyroidectomy (ICD-9 procedure code 06.8), (ii) a diagnosis of hyperparathyroidism within 5 years before index date (ICD-9252.0), or (iii) any elevated parathyroid hormone (PTH) record (>7.0 pmol/L) within 5 years before index date. Third, since adjusting for a single value of the latest laboratory may not adequately capture the chronic status, we additionally adjusted for the average value and the within-person variability (standard deviation [SD]) of haemoglobin, calcium, phosphate from ESA initiation to index date in the models. Fourth, ESA treatment duration was categorised into five groups (<1 year, 1 to <2 years, 2 to <3 years, 3 to <5 years, ≥5 years) to test for potential dose–response relationship. Fifth, as the PPV for spine fracture is lower (86%) than the other fracture types and may lead to potential misclassification,[22] we repeated the main analysis by excluding spine fracture from the osteoporotic fracture definition. Finally, to assess the impact of matching variables, we additionally included CKD status (stratified into CKD stage 3, CKD stage 4, CKD stage 5, peritoneal dialysis, haemodialysis, and transplant history) as a matching variable on top of age and sex.

Furthermore, as we observed a significant association of ESA treatment duration, but not dosage, with the risk of fracture, we performed an exploratory analysis to evaluate if ESA responsiveness was associated with an increased risk of fracture after adjusting for treatment duration, cumulative DDD, and the other covariates. Given that ESA responsiveness could also be a post-exposure mediator (Supplementary Figure S1), we additionally performed a post-hoc mediation analysis to estimate the direct effect (association between ESA duration and fracture risk independent of responsiveness), indirect effect (association due to responsiveness), total effect (direct + indirect effects), as well as the proportion mediated by responsiveness, under the strong assumption that there is no unmeasured confounding.[35]

All the analyses were performed using R (version 4.1.3). The R packages "Matching" (version 4.10.15) was used for the matching process; "survival" (version 3.8.3) was used for conditional logistic regression modelling; and "CMAverse" (0.1.0) was

Characteristic	Fracture cases	Matched controls	SMD
No. of patients	959	9262	–
Male, n (%)	443 (46.2)	4298 (46.4)	0.004
Age at index date, mean (SD)	74.78 (10.73)	74.44 (10.64)	0.032
Year of index date, n (%)			0.076
2006	3 (0.3)	13 (0.1)	
2007	3 (0.3)	10 (0.1)	
2008	5 (0.5)	34 (0.4)	
2009	13 (1.4)	105 (1.1)	
2010	17 (1.8)	129 (1.4)	
2011	26 (2.7)	238 (2.6)	
2012	30 (3.1)	298 (3.2)	
2013	49 (5.1)	482 (5.2)	
2014	64 (6.7)	611 (6.6)	
2015	67 (7.0)	629 (6.8)	
2016	75 (7.8)	734 (7.9)	
2017	81 (8.4)	778 (8.4)	
2018	98 (10.2)	942 (10.2)	
2019	97 (10.1)	954 (10.3)	
2020	95 (9.9)	950 (10.3)	
2021	106 (11.1)	1055 (11.4)	
2022	130 (13.6)	1300 (14.0)	
ESA duration (years), mean (SD)	2.12 (2.09)	1.39 (1.66)	0.387
Cumulative defined daily dose, mean (SD)	14,559.80 (21,270.14)	9610.26 (15702.01)	0.265
Responsiveness to treatment, n (%)	713 (74.3)	5983 (64.6)	0.213
eGFR within 365 days before index date, mean (SD)	9.22 (11.65)	9.36 (11.24)	0.013
Status of patients with CKD[b], n (%)			
CKD Stage 3	16 (1.7)	184 (2.0)	0.024
CKD Stage 4	44 (4.6)	596 (6.4)	0.081
CKD Stage 5	436 (45.5)	4641 (50.1)	0.093
Haemodialysis	136 (14.2)	1091 (11.8)	0.072
Peritoneal dialysis	298 (31.1)	2525 (27.3)	0.084
Transplant	29 (3.0)	220 (2.4)	0.04
Covariates	**Fracture cases**	**Matched controls**	**SMD**
Time since CKD diagnosis (years), mean (SD)	8.25 (3.73)	7.98 (3.76)	0.071
Hospital cluster, n (%)			0.070
Hong Kong East cluster	125 (13.0)	1327 (14.3)	
Hong Kong West cluster	119 (12.4)	1042 (11.3)	
Kowloon Central cluster	142 (14.8)	1328 (14.3)	
Kowloon East cluster	135 (14.1)	1237 (13.4)	
Kowloon West cluster	158 (16.5)	1687 (18.2)	
New Territories East cluster	151 (15.7)	1402 (15.1)	
New Territories West cluster	129 (13.5)	1239 (13.4)	
Comorbidities within five years before index date, n (%)			
Coronary heart diseases	280 (29.2)	2347 (25.3)	0.087
Congestive heart failure	224 (23.4)	2241 (24.2)	0.020
Cerebrovascular diseases	96 (10.0)	828 (8.9)	0.037
Hypertensive diseases	731 (76.2)	6631 (71.6)	0.106[a]
Arrhythmia and conductive disorders	147 (15.3)	1460 (15.8)	0.012
Chronic obstructive pulmonary diseases	57 (5.9)	590 (6.4)	0.018
Pneumonia history	295 (30.8)	2421 (26.1)	0.103[a]
Dementia	31 (3.2)	197 (2.1)	0.068
Hemiplegia/Paraplegia	7 (0.7)	125 (1.3)	0.061
Depression	36 (3.8)	242 (2.6)	0.065
Obesity	29 (3.0)	288 (3.1)	0.005

(Table 1 continues on next page)

Characteristic	Fracture cases	Matched controls	SMD
(Continued from previous page)			
Hyperlipidaemia	234 (24.4)	2117 (22.9)	0.036
Diabetes Mellitus	560 (58.4)	5284 (57.1)	0.027
Thyroid diseases	33 (3.4)	269 (2.9)	0.031
Connective tissue diseases	13 (1.4)	97 (1.0)	0.028
Chronic liver diseases	19 (2.0)	81 (0.9)	0.093
Fall history	237 (24.7)	1439 (15.5)	0.230[a]
Osteoporosis	9 (0.9)	83 (0.9)	0.004
Iron deficiency anaemia	72 (7.5)	728 (7.9)	0.013
Hospital Frailty Risk Score, mean (SD)	14.07 (7.31)	10.18 (6.96)	0.546[a]
Medication prescribed within 180 days before index date, n (%)			
Non-steroid anti-inflammatory drugs	46 (4.8)	177 (1.9)	0.161[a]
Proton pump inhibitors	598 (62.4)	4926 (53.2)	0.186[a]
Cardiac glycosides	9 (0.9)	122 (1.3)	0.036
Lipid regulating drugs	564 (58.8)	5866 (63.3)	0.093
Diuretics	679 (70.8)	6848 (73.9)	0.070
Anti-arrhythmic drugs	27 (2.8)	248 (2.7)	0.008
Beta-blockers	552 (57.6)	4984 (53.8)	0.076
Angiotensin-converting enzyme inhibitors	233 (24.3)	2203 (23.8)	0.012
Angiotensin II receptor blockers	233 (24.3)	2163 (23.4)	0.022
Nitrates	297 (31.0)	2597 (28.0)	0.064
Calcium channel blockers	783 (81.6)	7449 (80.4)	0.031
Peripheral vasodilators	6 (0.6)	97 (1.0)	0.046
Anticoagulants	277 (28.9)	2318 (25.0)	0.087
Anti-platelet drugs	488 (50.9)	4546 (49.1)	0.036
Antipsychotic drugs	120 (12.5)	1043 (11.3)	0.039
Antidepressants	91 (9.5)	767 (8.3)	0.042
Insulin	399 (41.6)	3498 (37.8)	0.079
Anti-diabetic drugs	262 (27.3)	2662 (28.7)	0.032
Corticosteroids	165 (17.2)	1588 (17.1)	0.002
Sex hormones	9 (0.9)	127 (1.4)	0.041
Anti-osteoporosis medication	16 (1.7)	91 (1.0)	0.060
Calcium supplementation	597 (62.3)	5594 (60.4)	0.038
Cinacalcet	38 (4.0)	234 (2.5)	0.081
Anti-gout medications	282 (29.4)	2901 (31.3)	0.042
Phosphate binders	63 (6.6)	450 (4.9)	0.074
Vitamin D supplementation	457 (47.7)	4010 (43.3)	0.088
Iron supplementation	524 (54.6)	4919 (53.1)	0.031
Oral	487 (50.8)	4580 (49.4)	0.027
Injection	68 (7.1)	574 (6.2)	0.036
Opioid analgesics	668 (69.7)	1765 (19.1)	0.183[a]
Antiepileptic drugs	70 (7.3)	505 (5.5)	0.076
Benzodiazepines	20 (2.1)	112 (1.2)	0.069
CKD related procedures/surgery, n (%)			
Dialysis within 365 days before index date	436 (45.5)	3631 (39.2)	0.127[a]
Kidney transplant history	39 (4.1)	293 (3.2)	0.048
Laboratory test within 365 days before index date, mean (SD)			
Serum creatinine (μmol/L)	663.83 (302.18)	659.42 (315.09)	0.014
Blood haemoglobin (g/dL)	9.32 (1.73)	9.62 (1.73)	0.172[a]
Serum phosphate (mmol/L)	1.58 (0.55)	1.58 (0.51)	0.002
Serum calcium (mmol/L)	2.17 (0.22)	2.20 (0.21)	0.134[a]
Serum urea (mmol/L)	24.33 (11.33)	24.65 (10.88)	0.029

Abbreviations: CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; SD, standard deviation; SMD, standardised mean difference. [a]Covariates with standardised mean difference (SMD) > 0.1 were included in the minimally adjusted models (model 2), and all the listed covariates were included in the fully adjusted models (model 3). [b]Status of CKD patients before index date; patients indicated as CKD stage 3–5 were those not on dialysis.

Table 1: **Characteristics of osteoporotic fracture cases and their matched controls.**

used for the mediation analysis.[35] To account for multiple comparisons (overall fracture and four fracture subtypes) and to mitigate type I error, we applied the Bonferroni adjustment and considered $p < 0.01$ (0.05/5) as statistically significant.

Role of the funding source

The study was not funded nor did it receive any support in the form of gifts, equipment, or drugs.

Results

Study cohort

After screening for inclusion and exclusion criteria, a total of 959 fracture cases and 18,761 controls were identified as eligible for matching in the nested case–control study (Fig. 1). For the matched cohort, 959 osteoporotic fracture cases were matched with 9262 controls. Among the fracture types, the majority of cases were hip fractures (n = 622), followed by wrist (n = 164), humerus (n = 154), and spine fractures (n = 80).

Fracture patients had a longer ESA treatment duration (mean 2.1 years [SD 2.1] vs. 1.4 years [SD 1.7]) and received a higher cumulative DDD (mean 14,559.8 [SD 21,270.1] vs. 9610.3 [SD 15,702.0]) compared to their matched controls (Table 1). Regarding baseline characteristics, fracture patients had a higher prevalence of hypertensive diseases, pneumonia, fall history, and had a higher mean frailty score; a higher proportion were on dialysis and used non-steroidal anti-inflammatory drugs, proton pump inhibitors, and opioid analgesics; and they also had lower blood haemoglobin and serum calcium levels, with SMD >0.1 for these covariates (Table 1). Similar patterns were observed across the osteoporotic fracture types and their matched controls (Supplementary Tables S3–S6). Trends in ESA type and fracture incidence are summarised in Supplementary Table S7.

Association of ESA use and fracture risk

Fig. 2 illustrates the association between ESA use and fracture risk. When analysed separately, longer ESA duration (aOR per year 1.28, 95% CI 1.22–1.34) and higher cumulative dose (aOR per 10,000 DDD 1.14, 95% CI 1.09–1.20) were associated with significantly higher odds of overall osteoporotic fracture in the fully adjusted models (Fig. 2A). Likewise, both longer duration (aOR 1.30, 95% CI 1.22–1.39) and higher cumulative dose (aOR 1.20, 95% CI 1.13–1.28) were associated with increased odds of hip fracture. However, when duration and cumulative dose were included in the same regression model, only duration remained significant for overall fracture (aOR per year 1.31, 95% CI 1.23–1.39) whereas cumulative dose was not significant (aOR per 10,000 DDD 0.97, 95% CI 0.91–1.03) (Fig. 2B). Similar pattern was

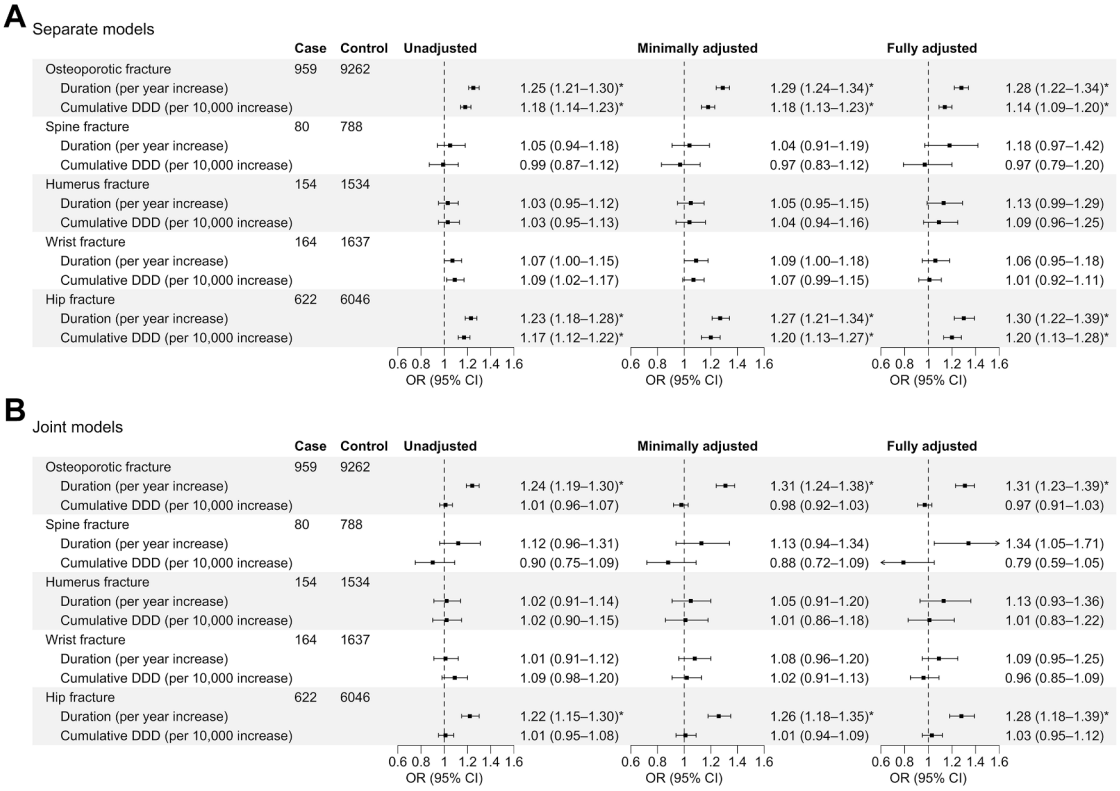

Fig. 2: Association of duration and cumulative defined daily dose (DDD) of ESA use with risk of osteoporotic fractures. **(A)** Duration and cumulative dose were modelled in separate models. **(B)** Duration and cumulative dose were modelled jointly in the same models. Odds ratios (OR) were obtained from conditional logistic regression models. The unadjusted models were only accounted for the matching factors (age, sex, calendar year). The minimally adjusted models included covariates with a standardised mean difference (SMD) > 0.1 between osteoporotic fracture cases and their matched controls, including hypertensive diseases, pneumonia history, fall history, frailty, use of non-steroid anti-inflammatory drugs, use of proton pump inhibitors, dialysis, blood haemoglobin, and serum calcium. The fully adjusted models included all the covariates listed in Table 1 including time since CKD diagnosis, hospital clusters, comorbidities, frailty, mediations, CKD related procedures or surgery, and laboratory test results. Asterisks (*) represent statistically significant associations after Bonferroni correction ($p < 0.05/5 = 0.01$, considering 5 outcomes). The error bars indicate 95% CI. Abbreviations: CI, confidence interval; DDD, defined daily dose; OR, odds ratio.

observed for spine fracture (duration aOR 1.34, 95% CI 1.05–1.71) and hip fracture (duration aOR 1.28, 95% CI 1.18–1.39), although the result for spine fracture was not statistically significant after correction for multiple testing.

Despite the moderate correlation between ESA treatment duration and cumulative dose (Pearson $r = 0.70$), all variables in the joint model had low VIF values (<5), indicating limited multicollinearity (Supplementary Table S8). Restricted cubic spline analyses showed a largely monotonic increase in fracture odds with longer duration but no significant association for cumulative dose (Supplementary Figure S2). Including average daily dose as exposure variable instead of cumulative dose yielded similar findings, where duration, but not average daily dose, was associated with higher fracture risk (Supplementary Figure S3).

Subgroup and sensitivity analysis

A significant interaction was observed between age and ESA treatment duration ($P_{interaction} = 0.001$), but not between age and cumulative dose ($P_{interaction} = 0.844$). Subgroup analysis stratified by the mean age (75 years) demonstrated a stronger association between ESA treatment duration and fracture risk in older patients aged ≥75 years compared to those aged <75 years (Supplementary Figure S4). No significant interaction was found between sex and ESA treatment duration or dose (data not shown). On the other hand, subgroup analyses stratified by dialysis status showed significant associations between ESA duration and risk of overall and hip fracture for non-dialysis and peritoneal dialysis patients, but the estimates were non-significant for haemodialysis patients (Supplementary Figure S5).

Multiple sensitivity analyses supported the robustness of these results. When further adjusted for the average haemoglobin level (as a proxy of anaemia severity), the association between treatment duration and fracture risk remained essentially unchanged, and mean haemoglobin itself was not associated with fracture (Fig. 3). Excluding patients with hyperparathyroidism (n = 3654) yielded similar estimates (fully adjusted aOR for duration 1.38, 95% CI 1.15–1.65) (Supplementary Figure S6). Results were also largely consistent after additionally modelling average values and within-person variability of haemoglobin, phosphate, and calcium (Supplementary Figure S7). When treatment duration was categorised, a dose–response relationship was observed with increasing ORs for longer treatment durations, indicating a higher fracture risk with prolonged ESA use (Supplementary Figure S8). Moreover, findings were unchanged when vertebral fractures were excluded from the overall fracture outcome definition (Supplementary Figure S9), and when CKD status was added to the matching process on top of age and sex (Supplementary Figure S10).

Association of ESA responsiveness with osteoporotic fractures

To explore whether ESA responsiveness explained the observed association between ESA duration and fracture risk, we analysed fracture risk among ESA responders vs. non-responders. ESA responders had a significantly higher odds of overall fracture (aOR 1.36, 95% CI 1.41–1.63) and hip fracture (aOR 1.40, 95% CI 1.11–1.75) compared to non-responders. Notably, the association between ESA treatment duration and fracture risk remained statistically significant in this model, indicating that duration-related risk is not fully explained by responsiveness (Fig. 4). As ESA responsiveness may lie on the causal pathway or act as a collider (Supplementary Figure S1), we additionally performed a post-hoc mediation analysis and found little evidence of mediation by responsiveness (proportion mediated −1.8%, 95% CI −4.6% to 1.2%; Supplementary Table S9).

Discussion

In this territory-wide nested case–control study, we found that a longer ESA treatment duration was consistently and independently associated with an increased risk of overall osteoporotic fracture and hip fracture among patients with CKD, whereas cumulative dose or average daily dose was not independently associated with fracture risk after accounting for duration. These findings were robust across various sensitivity and subgroup analyses. Furthermore, we showed that responsiveness to ESA was also associated with a higher fracture risk independent of treatment duration.

Our findings contrast with a previous US cohort study of haemodialysis patients, which reported that the dose of erythropoietin was associated with an increased 1-year fracture risk.[14] In our study, ESA treatment duration, rather than dose, was associated with fracture risk. Several factors may explain this discrepancy. First, the study populations were different, i.e., patients with CKD in our study (non-dialysis and dialysis) vs. haemodialysis patients in the previous study, who may receive different doses and have different disease profiles. The pathophysiology of dialysis and non-dialysis patients could also be different. Dialysis patients may have an increased risk of cardiovascular events due to electrolyte fluctuations[36] and an increased infection risk due to frequent hospital visits,[37] which may influence bone health.[38] Second, the prior study did not account for the potential confounding effect of a higher propensity for falls in patients with severe anaemia. This is

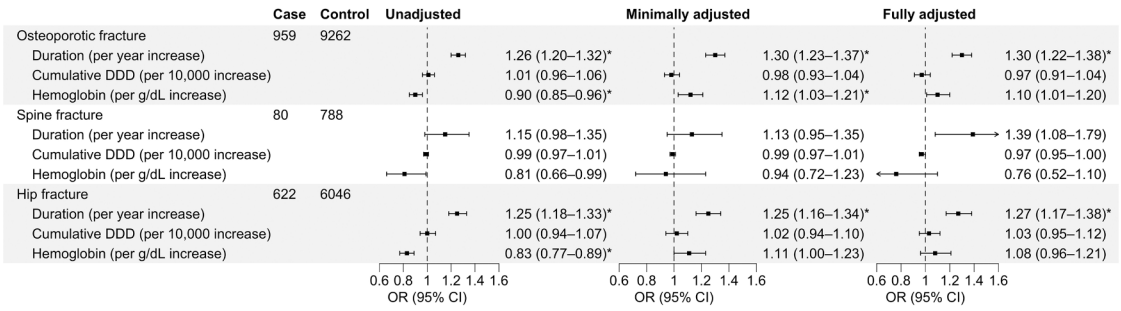

Fig. 3: Sensitivity analysis adjusted for average haemoglobin concentration (in g/dL) since initiating ESA. Odds ratios (OR) were obtained from conditional logistic regression models. The unadjusted models were only accounted for the matching factors (age, sex, calendar year). The minimally adjusted models included covariates with a standardised mean difference (SMD) > 0.1 between osteoporotic fracture cases and their matched controls, including hypertensive diseases, pneumonia history, fall history, frailty, use of non-steroid anti-inflammatory drugs, use of proton pump inhibitors, dialysis, blood haemoglobin, and serum calcium. The fully adjusted models included all the covariates listed in Table 1 including time since CKD diagnosis, hospital clusters, comorbidities, frailty, mediations, CKD related procedures or surgery, and laboratory test results. Asterisks (*) represent statistically significant associations after Bonferroni correction ($p < 0.05/5 = 0.01$, considering 5 outcomes). The error bars indicate 95% CI. Abbreviations: CI, confidence interval; DDD, defined daily dose; OR, odds ratio.

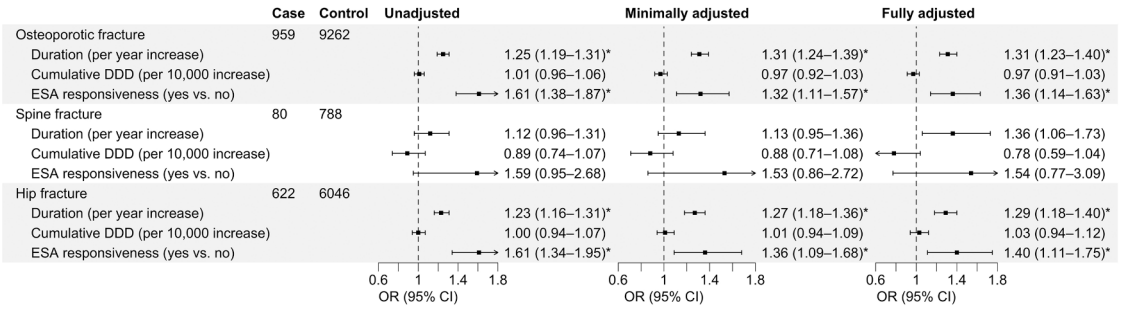

Fig. 4: Association of ESA responsiveness with risk of osteoporotic fractures. Odds ratios (OR) were obtained from conditional logistic regression models. The unadjusted models were only accounted for the matching factors (age, sex, calendar year). The minimally adjusted models included covariates with a standardised mean difference (SMD) > 0.1 between osteoporotic fracture cases and their matched controls, including hypertensive diseases, pneumonia history, fall history, frailty, use of non-steroid anti-inflammatory drugs, use of proton pump inhibitors, dialysis, blood haemoglobin, and serum calcium. The fully adjusted models included all the covariates listed in Table 1 including time since CKD diagnosis, hospital clusters, comorbidities, frailty, mediations, CKD related procedures or surgery, and laboratory test results. Asterisks (*) represent statistically significant associations after Bonferroni correction ($p < 0.05/5 = 0.01$, considering 5 outcomes). The error bars indicate 95% CI. Abbreviations: CI, confidence interval; DDD, defined daily dose; OR, odds ratio.

particularly relevant given the stronger association observed for hip fractures,[14] which are often linked to falls. In the current study, we have adjusted for the duration of ESA use, fall history, and haemoglobin levels in our analysis, which likely provides a more accurate assessment of the association between ESA use and fracture risk. Third, we included both duration and cumulative dose in the same model, while the previous study considered only erythropoietin dose.[14] In our joint models, the coefficient of duration has a conditional interpretation and represents the effect of extending treatment time given a fixed cumulative dose, whereas the coefficient of cumulative dose represents adding more dose at a fixed duration. Re-parameterising to duration and average daily dose yielded the same conclusion, where a "prolonged use of ESA" appeared to be more related to fracture risk than a "higher intensity at a fixed duration". Biologically, this pattern is consistent with cumulative exposure to erythropoietin receptor signalling over time, rather than short-term dose peaks, as a driver of the effects on bone metabolism. Notably, in our haemodialysis subgroup, point estimates were not statistically significant, which may be due to the smaller sample size or competing risks; thus, null findings in haemodialysis should be interpreted cautiously rather than as evidence of no effect.

The relationship between ESA use and bone metabolism is complex. Reduced haemoglobin levels have been associated with increased fracture risk,[39] and our previous Mendelian randomisation study also suggested a genetic causal relationship between higher haemoglobin levels and improved bone mineral density (BMD).[40] On the other hand, preclinical studies suggested that exogenous erythropoietin promotes bone loss, potentially through erythropoietin receptors on bone cells. For example, erythropoietin has been shown to increase osteoclast differentiation and bone resorption,[6,7] while knockdown of B cell-specific erythropoietin receptors in mice was associated with increased bone mass.[6] These findings suggest opposing effects of ESA on bone metabolism: a BMD-increasing effect via haemoglobin elevation and a deteriorating effect on overall bone health through erythropoietin receptor-mediated mechanisms. The net effect of ESA on fracture risk, as shown in our study, appears to favour bone loss. Also, previous studies reported no significant association between endogenous erythropoietin and fracture risk in patients with CKD,[41] although the dose of erythropoietin treatment is supraphysiological. Thus, these observations cannot be compared directly. Nevertheless, our hypothesis was indeed further supported by the analysis of ESA responsiveness.

In the ESA responsiveness analysis, we observed that ESA responders, but not non-responders, were significantly associated with an increased risk of fractures. Such observation may seem counter-intuitive as previous studies have shown that ESA non-responders are typically older,[42] have lower BMI,[42] iron deficiency,[43] increased inflammation,[43] poor nutritional status,[43] and increased risk of mortality.[44] All these factors are known to be risk factors of fracture; therefore, one would expect ESA non-responders to show increased susceptibility to fracture. However, we observed that ESA responders had a significantly higher fracture risk than non-responders, which provides evidence that the observed association is likely explained by the biological action of ESA. Notably, this observation is in line with animal studies showing that erythropoietin signalling enhances red blood cell production at the expense of BMD,[5,6,45] as high-dose exogenous not only increases red blood cell production but also promotes osteoclastogenesis[6] while inhibiting osteogenesis

at the same time.[46] However, we also acknowledge that conditioning on responsiveness, a post-exposure variable, can introduce mediation or collider bias. Accordingly, we (i) compared models with and without adjustment for responsiveness and found the duration-fracture association was essentially unchanged; and (ii) conducted a mediation analysis, which did not indicate that early haemoglobin rise mediated the duration-fracture relationship. These results reduce concern about major bias from conditioning on responsiveness, but these analyses are exploratory and warrant confirmation in future studies using designs less susceptible to time-varying confounding and collider structures.

Our results suggested that the risk of fracture increased per year of ESA treatment, highlighting the importance of optimising anaemia management in patients with CKD. ESAs are usually administered for a prolonged period of time and hence, clinicians should carefully weigh its benefits against potential risks, including fractures. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines strongly advocate iron therapy as the first-line treatment for CKD-related anaemia,[27] and recent updates further emphasise its pivotal role.[47] Our study provides additional support for these recommendations. Hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF–PHI), which stabilise HIF and enhance endogenous erythropoietin production in a titratable manner and are also included in KDIGO guidelines, offers a promising new alternative for treating renal anaemia.[48] Large multi-centre clinical trials have demonstrated its comparable efficacy in raising haemoglobin levels as ESAs in both dialysis-dependent and non-dialysis dependent patients with CKD.[49–52] However, the relationship of HIF–PHI use with fracture remains unstudied. Future trials and real-world studies are required to confirm whether the short-term high-dose regime or HIF–PHI use is optimal in treating renal anaemia without significant adverse effects on bone health.

This study has several strengths. First, it is the first real-world investigation to report the association between the duration and responsiveness of ESA use and fracture risk. Second, we have accounted for important confounders in our analysis, including haemoglobin levels and fall history. Third, this study leveraged high-quality data, for instance, we defined CKD using two measurements of eGFR and the fracture codes have previously been validated. Fourth, the nested case–control design minimised bias from changes in treatment patterns, as ESA prescriptions are often adjusted based on haemoglobin response and overall health status. Fifth, the large sample size (n > 10,000 patients) has provided us with sufficient statistical power. Lastly, our study had a long follow-up period for capturing fracture events, which is often costly and time-consuming in a clinical trial setting.

We also acknowledge several limitations. First, as an observational, nested case–control study, causality cannot be inferred. Second, instead of the 4-week period recommended by KDIGO guidelines,[27] we defined ESA responsiveness by haemoglobin increments within 2 months of treatment initiation,[53] reflecting real-world Hong Kong HA practice in which monthly haemoglobin testing is not consistently obtained, particularly in non-dialysis patients with CKD whose follow up visit is usually longer than 1 month. However, comparing with the standard guideline in defining ESA responsiveness, some non-responders defined using the 4-week criteria could be misclassified as responders using our 2-month criteria, although such misclassification would likely bias the association toward null, instead of the association that is observed in our analysis (i.e., association with an increased risk of fracture). Thus, we consider such bias would lead to under-estimation, instead of over-estimation, of the association. Third, despite extensive adjustment for comorbidities, medications, frailty, time since CKD diagnosis, dialysis vintage, and laboratory measures, unmeasured and residual confounding (e.g., related to bone-specific alkaline phosphatase, PTH, 25-hydroxyvitamin D, and serum albumin levels) cannot be ruled out. In particular, bone-specific alkaline phosphatase and PTH had high proportions of missingness (since they were not routinely measured) and were thus not included in our main models. However, sensitivity analyses excluding patients with evidence of hyperparathyroidism (defined by ICD-9 codes and elevated PTH levels) yielded consistent findings. Fourth, body weight or body mass index, a significant factor in determining the dose of ESA treatment, was not included in the analysis as it was not available from the EHRs. Future studies are needed to explore the association between the ESA dose per body weight and bone metabolism. Fifth, site-specific fracture results should be interpreted with caution due to potential under-reporting and misclassification of some fracture types such as spine fracture,[22] although results in the sensitivity analysis excluding spine fracture from the overall fracture definition were essentially unchanged. Since the biological effects of ESA on bone remodelling are unlikely to be site-dependent, the stronger association observed for hip compared to vertebral fractures may reflect the lower prevalence of vertebral fractures among patients with CKD, rather than true heterogeneity by skeletal site.[54] Sixth, although we summarised longitudinal laboratory trajectories and variability, time-varying confounding is still possible. Finally, our cohort comprises predominantly Chinese adults, which may limit generalisability to other ethnic groups. Moreover, in Hong Kong, ESAs are usually initiated for CKD-related anaemia not responsive to iron therapy, and the majority of ESA use in our study was in non-dialysis patients. This

could differ from other settings and replication in diverse populations is warranted.

In conclusion, longer ESA treatment duration and ESA responsiveness were independently associated with an increased risk of osteoporotic fractures in patients with CKD, regardless of treatment dose. Further studies are required to optimise the treatment regimen of anaemia in patients with CKD that can minimise fracture risk.

Contributors

SCH, FWTC and CLC designed the study. SCH, CWS and CLC contributed to data acquisition. SCH conducted statistical analysis. SCH and JKLM drafted the manuscript. FWTC, CWS, DYHY, ACFS, KCBT, GHYL and CLC critically revised the manuscript for methodological and intellectual content. SCH, JKLM and CLC accessed and verified the underlying data. All authors read and approved the final manuscript.

Data sharing statement

This study was conducted based on the EHR database managed by the Hong Kong Hospital Authority. The data contains confidential information and cannot be shared with the public due to third-party use restrictions. However, local academic institutions, government departments, or non-governmental organisations can apply for the access to data through the data sharing portal (https://www3.ha.org.hk/data/Provision).

Editor note

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Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103619.

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