



Bone fracture risk factors in prevalent hemodialysis patients

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Abstract

Bone fractures are an important cause of morbidity and mortality in hemodialysis (HD) patients. The aim of this study was to quantify the incidence of fractures in a cohort of prevalent HD patients and evaluate its relationship with possible risk factors. We performed a retrospective analysis of 341 patients, since they started HD (median of 51 months). Demographic, clinical, and biochemical parameters as well as vascular calcifications (VC) were evaluated. Fifty-seven episodes of fracture were identified with a median HD vintage of 47 months (incidence rate of 31 per 1000 person-years). Age ($p < 0.001$), female gender ($p < 0.001$), lower albumin ($p = 0.02$), and higher VC score ($p < 0.001$) were independently associated with increased risk of fracture, while active vitamin D therapy ($p = 0.03$) was associated with decreased risk. A significantly higher risk of incident fracture was also associated with higher values of bone-specific alkaline phosphatase (bALP) ($p = 0.01$) and intact parathyroid hormone (iPTH) levels either < 300 pg/mL ($p = 0.02$) or > 800 pg/mL ($p < 0.001$) compared with 300–800 pg/mL. In conclusion, bone fracture incidence in HD patients is high and its risk increases with age, female gender, lower serum albumin, and with the presence of more VC. Prevalent HD patients with low or high iPTH levels or increased bALP also had a higher fracture risk. Therapy with active vitamin D seems to have a protective role. Assessment of fracture risk and management in dialysis patients at greatest risk requires further study.

Keywords Bone fracture · Chronic kidney disease · CKD-MBD · Dialysis

Introduction

Bone fractures are an important cause of morbidity and mortality in hemodialysis (HD) patients [1]. Declining kidney function is associated with abnormalities of bone and mineral metabolism that predispose patients to an increased risk of fracture [2]. The mineral and bone abnormalities accompanying chronic kidney disease are collectively known as chronic kidney disease—mineral and bone disorder (CKD-MBD).

Features specific to CKD-MBD, such as hyperphosphatemia, diminished activation of vitamin D, secondary hyperparathyroidism, and elevated fibroblast growth factor-23, associated with exposure to medications altering bone metabolism in patients with CKD are likely to contribute to fracture risk [1]. However, the true fracture risk in dialysis patients and its relationship with surrogate markers of CKD are yet poorly defined.

In dialysis patients, the incidence of hip fracture has been reported to be 17.4-fold higher compared with the general population. It is noteworthy that in these patients, the mortality rate is 64% at 1 year, compared to a rate of 15–20% in the general population [3]. In addition, the fracture occurs at an earlier age than that of the general population, 16 and 13 years for men and women, respectively [4].

The link between fractures and vascular calcifications (VC), another major component of CKD-MBD, is also yet uncertain. In CKD and dialysis patients, VC has been shown to correlate with low trabecular bone volume and indices of low bone turnover [5, 6]. Adragão et al. described an

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association between low bone volume and coronary calcifications in patients who were in dialysis for more than 6 years [6]. Of note, VC has a strong correlation with low bone volume in CKD patients; however, little is known about inter-relationship between VC and fractures in dialysis patients.

The aim of this study was to quantify the incidence of bone fractures in a cohort of prevalent HD patients and evaluate its relationship with potential risk factors, such as inflammatory, mineral, and bone parameters as well as with the presence of VC.

Materials and methods

Study design

This was an observational, retrospective, single-center (two dialysis units sharing the same medical team) study of a cohort of prevalent HD patients.

Patients

All adult (> 18 years of age) prevalent (receiving dialysis > 90 days) HD patients were included in the study. An informed consent was obtained from all individual participants included. The study was approved by the Ethics Committee of NephroCare Portugal.

Three hundred and forty-one patients were evaluated retrospectively, since they started HD, with a median follow-up of 51 (4–378) months, 206 (60%) males and 135 (40%) females, with a mean age of 68.7 ± 13.6 years at the beginning of HD. All patients were submitted to post-dilution online hemodiafiltration with a dialysate magnesium (Mg) concentration of 0.5 mmol/L and dialysate calcium (Ca) concentration of 1.25 or 1.5 mmol/L. High flux membranes (helixone-Fresenius®, Bad Homburg, Germany) and ultrapure water (evaluated monthly by kinetic chromogenic test) were used.

One hundred and fifty-six (46%) patients had diabetes, and 116 (34%) had hypertension. Coronary artery disease was diagnosed in 109 (32%) patients, cerebrovascular disease in 85 (25%) and peripheral vascular disease in 89 (26%). Mean body mass index (BMI) at the start of HD was 27.1 ± 4.8 kg/m².

Regarding CKD-MBD treatment targets, patients were treated according to 2003K/DOQI clinical practice guidelines for bone metabolism and disease [7]. During the study, 99 (29%) patients were taking active forms of vitamin D: 44 (13%) patients under oral alfacalcidol, with a median dose of 2 (1–9) µg/week, and 55 (16%) under intravenous paricalcitol, with a median dose of 5 (2.5–15) µg/week. All patients were receiving ‘native’ vitamin D supplementation with cholecalciferol 3 times per week after HD. Forty-five (13%)

were under calcimimetic (oral cinacalcet) with a median dose of 30 (15–90) mg/day, and ten (3%) of the patients were submitted to parathyroidectomy. None of the patients was taking another anti-osteoporotic treatment.

A total of 314 (92%) patients were under epoetin beta therapy, with a mean dosage of 77 ± 19 IU/kg per week per g/dl. The target for ferritin was between 200 and 800 ng/mL for all patients, and if needed, only intravenous iron saccharate was used.

During the studied period, 116 (34%) patients were under therapy with phosphate binders: 69 (20%) patients were taking calcium acetate/magnesium carbonate with a median dose of 1675 (1340–6030) mg/day, 27 (8%) patients were under sevelamer with a median dose of 3200 (1600–4800) mg/day, and 20 (6%) were taking sucroferric oxyhydroxide with a median dose of 1000 (500–1500) mg/day. Two hundred and twenty-five (66%) patients did not take phosphate binders.

Fracture status

Fractures that occurred during the follow-up of the study were determined by patients interview and chart review and classified as fragility fractures if resulting from trauma equivalent to a fall from standing height, or less [8]. High trauma fractures and fractures of fingers, toes, face, and skull were excluded. All fractures were confirmed by radiographs or radiology reports.

Biochemical analysis

Serum Ca, serum phosphorus (P), total intact parathyroid hormone (iPTH), bone-specific alkaline phosphatase (bALP), hemoglobin, albumin, and C-reactive protein (CRP) were recorded quarterly during the study follow-up. Ca was corrected for hypoalbuminemia by the addition of 0.8 mg/dL to the Ca concentration for each 1 g/dL decrease in albumin concentration from 4.0 g/dL [9]. Total iPTH was evaluated by immunochemiluminescence using a second-generation assay (Immulite 2000, Siemens Medical Solutions Diagnostics, Los Angeles, CA) and normal range of values is 10–65 pg/mL. Albumin was measured using a colorimetric assay and CRP was evaluated by an immunoturbidimetric assay.

All blood samples were collected before dialysis in mid-week sessions.

Vascular calcification score

VC was evaluated in all patients at the beginning of HD. To assess VC, we used a simple vascular calcification score (SVCS) developed by Adragão et al. [10]. This SVCS is based on the analysis of plain radiographic films of pelvis

and hand. Pelvis films were divided into four sections by two imaginary lines: a horizontal line over the upper limit of both femoral heads and a median vertical line over the vertebral column. Hand films were divided for each hand by a horizontal line over the upper limit of the metacarpal bones. Pelvis films evaluated iliac and femoral arteries (ileo-femoral score) and hand films evaluated radial and digital arteries (hand score). Any VC lining the vessel walls either in an irregular pattern or in a linear pattern was considered. The presence of VC in each section was rated as 1 and its absence as 0. The final score was the sum of all sections and ranged from 0 to 8.

Adragão et al. [10] found that an SVCS ≥ 3 was associated with an increase in cardiovascular events and mortality.

Statistical analysis

Follow-up begins at the start of HD for each patient and continues until the date of last recorded serum laboratory results in November of 2017. The incidence of fracture was expressed as the total number of fractures per 1000-patient-years of follow-up.

For statistical analysis, the arithmetic means of the quarterly laboratory results obtained during the follow-up were used. Variables were expressed as frequencies for categorical variables, mean values with SD for normally distributed variables, and median (interquartile ranges) values for non-normally distributed variables. Differences in mean values between patients with and without fractures were evaluated using the unpaired Student's *t* test for parametric data and the Mann–Whitney *U* test for nonparametric data.

Kaplan–Meier survival analysis was used to calculate the hazard ratio (HR) for fractures associated with the three iPTH groups; log-rank tests were calculated and compared with the survival curves between the groups. Binary regression was used for multivariable analysis (95% CI). Variables entered in multivariable analysis were age, female gender, time on HD, diabetes, BMI, serum albumin, bALP, iPTH < 300 or > 800 pg/mL, therapy with active vitamin D and SVCS ≥ 3 . Statistical analysis was performed with SPSS system 23.0 (SPSS Inc., Chicago, IL, USA). A $p < 0.05$ was considered statistically significant.

Results

Incidence of fractures

There were 57 episodes of fragility fractures during the study follow-up (median of 51 months) which corresponds to an overall incidence rate of 31 per 1000 person-years. The sites of fracture were: forearm—23% ($n = 13$), leg—23% ($n = 13$), hip—17% ($n = 10$), arm—14% ($n = 8$), spine—13%

($n = 7$), and ribs—10% ($n = 6$). Three (5%) patients presented more than one episode of fracture and 7 (12%) patients who had a fracture during the study had already presented a fragility fracture prior to the beginning of HD. Prior kidney transplantation was not associated with more fractures. The median HD time to first fracture was 47 months.

Univariable analysis

Compared with patients without fractures, patients that presented episodes of fracture were more frequently female ($p < 0.001$), older ($p = 0.01$), diabetic ($p < 0.001$), with lower BMI ($p = 0.02$), longer HD vintage ($p < 0.001$), lower albumin levels ($p < 0.001$), and higher bALP values ($p = 0.01$). These patients were also under less active vitamin D therapy ($p = 0.002$) and presented a higher SVCS ($p < 0.001$) (Table 1). Therapy with phosphate binders or cinacalcet was not associated with fractures.

Since U-shaped curve association of fracture risk and iPTH level was observed in our population (Fig. 1), patients were stratified by different iPTH levels in three groups (iPTH < 300 , $300 < \text{iPTH} < 800$, iPTH > 800 pg/mL). There were 33 episodes of fracture in the group with iPTH < 300 pg/mL ($n = 172$)—fracture incidence rate of 39 per 1000 person-years. Only 9 episodes of fracture occurred in the group with iPTH between 300 and 800 pg/mL ($n = 136$)—fracture incidence rate of 17 per 1000 person-years. In the group with iPTH > 800 pg/mL ($n = 33$), there were 15 episodes of fracture—incidence rate of 78 per 1000 person-years.

Kaplan–Meier fracture-free survival analysis also demonstrated that patients with mean iPTH levels < 300 (HR: 2.88; $p = 0.01$) or > 800 pg/mL (HR: 3.48; $p < 0.001$) throughout the follow-up presented a significantly higher fracture risk compared to those with iPTH between 300 and 800 pg/mL (Fig. 2).

Multivariable analysis

In the multivariable analysis, age ($p < 0.001$), female gender ($p < 0.001$), time on HD ($p < 0.001$), lower levels of albumin ($p = 0.02$), higher values of bALP ($p = 0.01$), iPTH < 300 or > 800 pg/mL ($p = 0.006$), and the presence of a higher SVCS (≥ 3) ($p < 0.001$) were associated with the presence of fractures. On the contrary, active vitamin D therapy was associated with less fracture risk ($p = 0.03$) (Table 2).

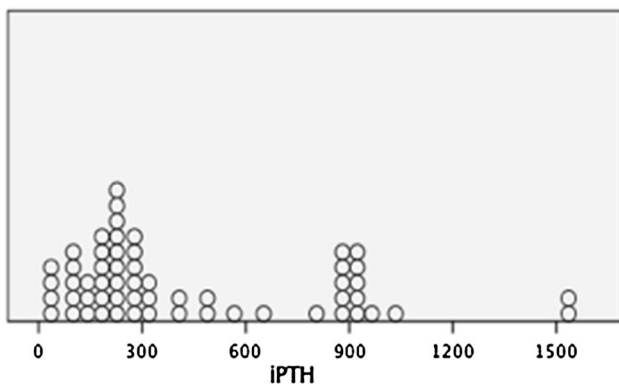
Discussion

Our study found an incidence of fragility fracture in prevalent HD patients of 31 per 1000 person-years, which is nearly three times greater than that reported for elderly

Table 1 Clinical, biochemical, and vascular calcification parameters in patients with and without fragility fractures (univariable analysis)

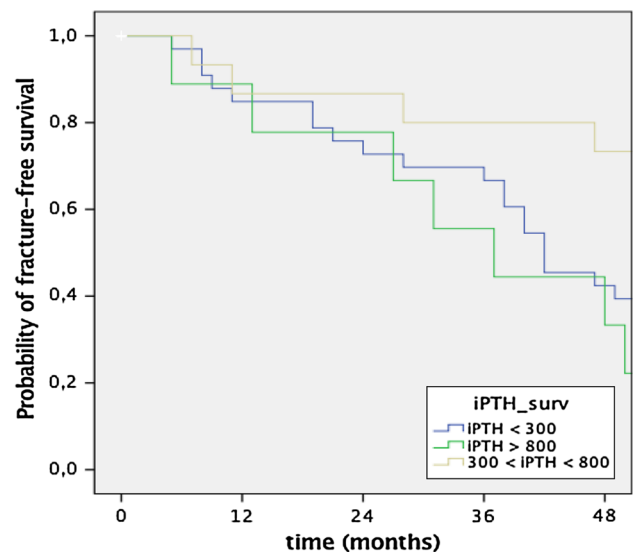
	Without fractures (n=287)	With fractures (n=54)	p
Age (years)	67.3 ± 13.6	71.2 ± 13.7	0.01
Female gender (%)	36.6	54.4	< 0.001
HD vintage (months)	44	93	< 0.001
Prior kidney transplantation (%)	9	10	NS
Diabetes mellitus (%)	40.4	52.6	< 0.001
Hypertension (%)	32.3	35.1	NS
Coronary disease (%)	31.3	34.1	NS
Peripheral vascular disease (%)	24.7	27.2	NS
Cerebrovascular disease (%)	22.8	26.6	NS
BMI (Kg/m ²)	27.7 ± 5.3	25.1 ± 3.7	0.02
Phosphate binders therapy (%)	36.6	33.2	NS
Active vitamin D therapy (%)	36.1	19.8	0.002
Calcimimetics therapy (%)	14.2	12.3	NS
Parathyroidectomy (%)	2.5	4.5	NS
Hemoglobin (g/dL)	11.4 ± 0.9	10.9 ± 0.8	NS
CRP (mg/dL)	0.8 ± 0.4	1.1 ± 0.5	NS
Albumin (g/dL)	4.0 ± 0.3	3.7 ± 0.4	< 0.001
Calcium (mg/dL)	9.0 ± 0.7	9.1 ± 0.6	NS
Phosphorus (mg/dL)	4.5 ± 1.3	4.3 ± 1.2	NS
bAP (ug/L)	24	33	NS
iPTH (pg/mL)	343	329	NS
Vascular calcification score (0–8)	4	6	< 0.001

BMI body mass index, *CRP* C-reactive protein, *bAP* bone alkaline phosphatase, *iPTH* intact parathyroid hormone

**Fig. 1** U-shaped distribution of the population regarding iPTH levels (each circle represents one patient)

patients without CKD [11]. This incidence rate is similar to that presented in the Dialysis Outcomes and Practice Patterns Study (DOPPS) [12] and the US Renal Data System [13]; however, in our study, we analyzed all radiologically proven fractures, whether hospitalized or not, which may have overestimated the incidence rate.

Incident vertebral fractures were identified in 13% of the patients of our HD cohort, compared with a prevalence

**Fig. 2** Patients fracture-free survival according to iPTH levels (Kaplan–Meier analysis)

of 55.3% in a study of 387 patients by Fusaro et al. [14]. The authors in that study determined the prevalence of historical vertebral fractures in HD patients, irrespective

Table 2 Independent predictors of fragility fractures (multivariable analysis)

Dependent variable	Independent variables	HR	95% CI	<i>p</i>	<i>R</i> ²
Fractures	Age	3.17	2.05–3.89	< 0.001	0.638
	Female gender	1.82	1.32–2.26	< 0.001	
	HD vintage	2.21	1.87–2.55	< 0.001	
	Diabetes mellitus	1.16	0.89–2.37	0.07	
	BMI	1.11	0.81–3.11	0.08	
	Serum albumin	0.87	0.77–0.91	0.02	
	bAP	1.21	1.16–1.33	0.01	
	iPTH < 300 or > 800 pg/mL	1.24	1.18–1.29	0.006	
	Active vitamin D therapy	0.89	0.86–0.95	0.03	
	Vascular calcification score ≥ 3	1.52	1.43–1.61	< 0.001	

BMI body mass index, *bAP* bone alkaline phosphatase, *iPTH* intact parathyroid hormone

of symptoms, identified radiologically using specialized, quantitative vertebral morphology software (MorphoX-Press), whereas we identified the incidence of new symptomatic fractures [14].

Like other studies, demographic risk factors, including female gender, older age, diabetes, low BMI, longer dialysis vintage, and a previous history of fracture, were also highly associated with an increased risk of fracture [15]. Our data are also consistent with the previous reports that have shown an association between risk of fractures in the HD population and lower serum albumin [16] and no significant fracture association with serum Ca and P [17].

Blayney et al. [18] reported that a higher serum total alkaline phosphatase (ALP) was associated with a higher incidence of hospitalization for fracture in the analysis of the DOPPS study. Coco et al. [3] analyzed 56 hip fracture patients on dialysis, and they found that age, albumin, PTH, and ALP were independent predictors. In addition, Kaji et al. [19] investigated 183 HD patients and found that serum ALP was significantly higher in HD patients with hip fracture than in those without hip fracture.

ALP is mainly a biochemical marker of bone turnover, and it is usually used to monitor metabolic bone disease, particularly the management of CKD-MBD. A higher ALP might be associated with fracture through high bone turnover [20]. Indeed, Park et al. [21] found that serum ALP was negatively associated with bone mineral density assessed by dual-energy X-ray absorptiometry in HD patients. However, ALP is primarily secreted by the liver and bone, and a small amount is also secreted by the intestine, kidneys, and leukocytes. Thus, monitoring of bALP is preferred in the assessment of bone mineral metabolism [22]. In a single-center cohort study, Iimori et al. [23] investigated 485 HD patients with a median follow-up time of 39.9 months, and they found that serum bALP was associated with any type of incident fracture. Our results also showed that higher values of serum bALP are a predictor of fragility fractures in prevalent HD patients.

Our study demonstrated, by Kaplan–Meier survival analysis, that fracture risk was U-shaped and associated with serum iPTH levels when patients were stratified by different iPTH levels in three groups (iPTH < 300, 300 < iPTH < 800, iPTH > 800 pg/mL). It is known that the level of PTH in CKD patients may suggest the histologic change associated with bone fracture. When serum PTH level is < 150 pg/mL, the fracture is most likely due to adynamic bone disease or osteomalacia. However, in patients with higher PTH (> 600 pg/mL), the main cause of fractures is most likely to be due to osteitis fibrosa, which is prone to developing fractures, despite frequently increased trabecular bone mass [24]. Although within the PTH range of 150–300 pg/mL, many patients may exhibit either one or the other forms of renal osteodystrophy [25]. Unfortunately, we lack evidence of an association between fracture incidence and the histologic type of bone disease. Despite definitive proof, low or high bone turnover favors fractures as both increase bone fragility. This might be explained in part by the absence of analysis of cortical bone, which is predominantly affected in CKD [26].

Both high and low circulating PTH levels can be associated with a high fracture rate and mortality risk [12, 16, 17]. Interestingly, serum PTH levels, just before the occurrence of a new fracture, are associated with the increased risk of fracture, in contrast to baseline or time-averaged serum PTH levels [23]. Long-term exposure to high PTH could induce a preferential loss of cortical bone, which could be even more pronounced in female than in male patients with CKD stage 5D [27].

Our study showed a possible protective role of active vitamin D in preventing fractures in HD patients. Active vitamin D administration is associated with increased bone strength in animal models [28] and a prospective, randomized, placebo-controlled, double-blind study showed improved bone mineral density (BMD) assessed by dual-energy X-ray absorptiometry (DEXA) with lowering of plasma PTH levels [29]. Poor performance on tests of neuromuscular

function also may identify those at higher risk of fracture in CKD. This is likely to reflect, in part, their higher risk of falls due to impaired muscle strength. The mechanism underlying this association is not clear, but a reduction in active vitamin D seems to be important [30, 31].

We believe that instead of restricting active vitamin D therapy to the control of secondary hyperparathyroidism, physiological doses of vitamin D receptor agonists should be given to all CKD patients, even those with normal or low PTH, to add to all vitamin D beneficial effects [32].

In addition, native vitamin D supplementation should be performed to all patients to assure 25-hydroxyvitamin D level above 30 ng/mL [32]. In non-CKD populations, pooled data from 11 double-blind, randomized, controlled trials of oral native vitamin D supplementation demonstrated an association, although not significant, of vitamin D (≥ 800 IU daily) and reduced hip fracture and any nonvertebral fracture in participants with 65 years of age or older [36]. Nevertheless, in CKD patients, we still have insufficient evidence correlating the correction of serum 25-hydroxyvitamin D level with reduced fracture risk [33, 34].

Even though the pathogenic factors linking VC and bone fragility are not clear, low bone volume, evaluated using bone biopsy, was found to be a significant risk factor for VC in HD patients [5, 6]. In addition, low bone volume has been recognized as an important risk factor for the occurrence of fractures in both the general population [35] and dialysis patients [36].

Schulz et al. [37] also demonstrated that patients with the highest degree of aortic calcification had the lowest bone density. In the same cohort followed for 2 years, bone loss was greater in patients with progressive VC [37]. In agreement with these results, another study has shown that after 4 years of follow-up, subjects with the most severe aortic calcification had not only a lower bone mass, but also a higher incidence of new osteoporotic fractures [38]. Therefore, it is reasonable to assume that dialysis patients with evident VC are more likely to experience a fracture. Our results showed that prevalent HD patients with a higher VC score presented an increased risk of fractures.

Older CKD patients are also prone to develop osteoporosis. The features of osteoporosis in CKD patients are low trabecular bone volume and disrupted micro-architecture, even without significant abnormalities in mineralization and bone turnover [39]. Bone loss is mostly from cortical bone in subjects with CKD-MBD, and their iPTH, bALP, Klotho, sclerostin, and fetuin A levels are pronouncedly altered [36]. Due to the high prevalence of osteoporosis and CKD-MBD in CKD subjects, both conditions are commonly existent simultaneously. However, in reality, the CKD-MBD is more complex than osteoporosis and CKD-MBD influences bone quality, contributes to high rates of

fracture, and, most importantly, may facilitate the appearance of VC in CKD patients. Although they both result in bone fragility, they do have different pathophysiology to destroy the bone. Osteoporosis is induced by excessive osteoclastic bone resorption, deficient osteoblastic activity, and bone formation in postmenopausal woman and subjects with aging process. However, CKD-MBD is related to altered mineral metabolism and the imbalance of pro- and anti-calcification factors which induced either high or low turnover bone disease in CKD patients [27].

There are some limitations to this study. First, the retrospective and observational nature of this study precludes the conclusions of a causal relationship. Second, we did not evaluate the BMD of the participants, although the ability of BMD, as measured by DEXA in dialysis patients to predict the risk of fractures, is still weak [27]. Third, this was a single-center study, so the results cannot be generalized. However, all of the participants were treated by the same physicians and underwent uniform laboratory measurements during the observation period, which guaranteed the accuracy of our results.

Conclusions

The incidence of bone fragility fractures in HD patients is high and its risk increases with age, female gender, low serum albumin and with the presence of more VC. Prevalent HD patients with low or high iPTH levels or increased bALP also had a higher fracture risk. Vitamin D therapy seems to have a protective role. Assessment of fracture risk and management in dialysis patients at the greatest risk requires further study.

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Author contributions PJM, IL, CG, and AF collaborated in study design. PJM, IL, and AR collected the data. PJM wrote the manuscript. IL, AA, AR, DN, CJ, IA, MM, CF, TA, CG, and AF participated in the final revision of the manuscript.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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