Abstract

Background: Bone disease is common in patients undergoing hemodialysis. It is the result of bone turnover abnormalities and the decrease of bone mineral density (BMD). We aimed to determine the usefulness of serum bone turnover markers and BMD measurement by dual-energy x-ray absorptiometry (DXA) in hemodialysis patients.

Methods: We conducted a cross-sectional study including 90 hemodialysis for more than 12 months. Bone mineral density was assessed by DXA. Peripheral blood samples were obtained from each patient before dialysis in a fasting state within a week of the DXA. Biochemical variables of calcium and phosphate were measured. One bone formation marker (bone-specific alkaline phosphatase (bAP), one bone resorption marker (carboxy-terminal telopeptides of type 1 collagen(CTX)) were measured. Total alkaline phosphatase (TAP), intact parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23) which is a bone-derived hormone were also measured.

Results: CTX values were 6.25 times higher than the normal limit of the assay. Bone alkaline phosphatase levels were less than 10 ng/mL in 28.8% of cases. 23% of patients have osteoporosis and 45% have osteopenia. Femoral BMD had negative correlations with age and PTH levels. FGF23 levels were significantly increased in patients with osteoporosis affecting the lumbar. The levels of bAP and CTX showed a positive correlation. Both circulating bAP and CTX levels showed also positive correlations with PTH levels. Fractures, observed in 12.2% of cases, were associated with low PTH values and the existence of osteoporosis.

Conclusions: Our study showed that osteoporosis and fracture are common in dialysis patients. The reduced BMD was associated with advanced age and elevated levels of PTH. Markers of bone turnover and FGF23 may play a role in the diagnosis of bone disease in hemodialysis patients. DXA measurement is necessary for the monitoring for bone loss.

Keywords: Osteoporosis, Hemodialysis, Fracture, Bone mineral density, Fibroblast growth factor 23, Bone specific alkaline phosphatase, Carboxy-terminal telopeptide of type 1 collagen

Background
Bone disease is highly prevalent in patients with chronic kidney disease on dialysis (CKD-5D) [1]. It can induce serious bone health problems, especially fragility fractures. Bone disease in patients with CKD-5D is the result of bone turnover abnormalities and the decrease of bone mineral density (BMD). Bone biopsy remains the gold standard for the diagnosis of bone turnover abnormalities. However, it is an invasive method and repetitive assessment of bone status cannot be possible. Measurements of serum bone turnover markers are not common practice in the management of CKD-5D patients [1]. Fibroblast growth factor-23 (FGF23) is a circulating factor produced by osteocytes. This hormone inhibits phosphate reabsorption and renal production of 1,25(OH) vitamin D. FGF23 regulates phosphate and vitamin D. This hormone plays an important role in bone metabolism of patients with chronic kidney disease [2]. Moreover, the assessment of bone mass in patients under dialysis is not yet codified. Both bone resorption and bone formation markers in patients with CKD-5D may be up- or down-regulated by systemic hormones such as parathormone. The measurement of BMD by dual-energy x-ray absorptiometry (DXA) is recommended only in patients with a history of
fractures. Multiple factors are associated with reduced 
BMD and may affect bone health [3].

This study aimed to determine the usefulness of serum 
bone turnover markers by measuring one bone forma-
tion marker (bone-specific alkaline phosphatase) and 
one bone resorption marker (carboxy-terminal telopep-
tides of type 1 collagen) and the usefulness of the BMD 
by DXA in patients with CKD-5D. We aimed also to as-
sum the frequency and risk factors of osteoporosis and 
osteoporotic fracture in hemodialysis patients.

Methods
Patients
We conducted a cross-sectional study including patients 
in maintenance hemodialysis three times weekly for 
more than 12 months.

Exclusion criteria included patients younger than 20 
years, premature menopause (occurring before the age of 
40), prolonged immobilization and patients receiving treat-
ments related to mineral metabolism (long-term steroids, 
hormone replacement therapy, and bisphosphonate). Pa-
tients with a history of gastrectomy, parathyroidectomy, 
neoplasia or hysterectomy were excluded from this study. 
Patients with disease that may affect bone such as chronic 
inflammatory bowel disease, cirrhosis, and endocrinopa-
thies except diabetes were also excluded.

Demographic and clinical data, including age, gender, 
anthropometric measurements, body mass index 
(weight/height²), comorbidities, menopausal status, eti-
ology of kidney disease, and duration of dialysis were 
collected. We inquired also about low trauma fractures 
since starting dialysis.

Measurements of biochemical variables
Peripheral blood samples were obtained from each 
patient before dialysis in a fasting state within a 
week of the DXA. Biochemical variables of calcium 
and phosphate were measured using an in vitro 
photometric assay for automated clinical chemistry 
analyzers.

Plasma intact PTH (PTH) levels were measured using 
chemiluminescent microparticle immunoassay. Normal 
values range from 15-65 pg/mL.

Serum concentrations of 25(OH) vitamin D (25(OH)D) 
were measured using chemiluminescent immunoassay.
Vitamin D deficiency was defined as 25(OH)D values 
lower than 10 ng/mL, vitamin D insufficiency was defined as 
25(OH)D values between 10 and 30 ng/mL [4]. 
Recommended rates of vitamin D ranged between 30 
and 70 ng/mL.

Bone alkaline phosphatase (bAP), a marker of osteo-
blastic activity, was measured using an immunosorben-
type 1 collagen (CTX), a 
marker of osteoclastic activity, was measured by chemi-
luminescent immunoassay.

Fibroblast growth factor 23 (FGF23) was measured 
with the ELISA technique. Normal values range from 30 
to 176 pg/mL.

Measurements of BMD
Dual-energy X-ray absorptiometry (DXA) was per-
formed to assess bone mineral density (BMD). Instrument 
quality control was performed regularly. Bone 
mass density, expressed in gm/cm², was measured at the 
lumbar spine, total hip, femoral neck, and total body.

In the lack of diagnostic criteria for defining osteopor-
osis in men and premenopausal women, we used WHO 
criteria as a cutoff point. Osteopenia correspond to T-
score more than −2.5 SD but less than −1 SD. Osteoporo-
sis was defined as T-score less than or equal to −2.5 SD 
in at least one of these sites: lumbar spine, femoral neck 
or total hip [5].

Fragility fractures
Fragility fractures were defined as fractures resulting 
from low-trauma (fall from standing-height or lower).

Lateral dorsal and lumbar spine X-rays were per-
formed to assess vertebral fracture.

Statistical analysis
Statistical Package for Social Sciences (SPSS) version 
19.0 was used to perform statistical analysis. Means and 
standard errors were calculated. Comparisons were per-
formed using Student’s t-test and analysis of variance (ANOVA) for normally distributed variables. The chi-
square test was used to analyze categorical data. The 
multiple linear regression was performed to identify pre-
dictors of low bone mass. The significance level was set 
at < 0.05. Correlations were reported as either the Pear-
son correlation coefficient.

Results
Patients’ characteristics
A total of 90 patients were included in the study. All of 
them were Caucasian. There were 58 men (64%) with a 
sex ratio of 1.8. The mean age was 53.01 years [20; 89]. 
Sixty-eight percent of patients were under the age of 50 
years. There were 8 post-menopausal women. The dur-
ation of hemodialysis was less than 5 years in 61% of pa-
tients whereas it was more than 10 years in only two 
cases. The calcium intake was noted in 97% of cases 
with a mean dose of 1.89 g daily [0.5; 3]. Only 30% of pa-
tients were orally supplemented with 0.5 microg of alfa-
calcidol daily.

Hyperphosphatemia was noted in 62.22% and hypocal-
cemia was found also in 62.22%. Fifty-six percent of
patients have PTH values between 2 and 9 times the upper normal limit of the assay. However, 19% of patients have PTH values less than 2 times the upper normal limit of the assay. Insufficiency and deficiency of vitamin D were found respectively in 41.11 and 44.44% of cases. CTX values were 6.25 times higher than the normal limit of the assay. Only 6 patients had CTX levels within the normal range. Bone alkaline phosphatase levels were less than 10 ng/mL in 26 cases and higher than 25 ng/mL in 31 cases. Table 1 summarized the clinical and biological characteristics of patients.

Prevalence of osteoporotic fracture
Osteoporotic fractures were noted in 12.22% of cases (n = 11) and had occurred after the age of 50 years in 9 cases. Vertebral fractures are the most common type of osteoporotic fractures, found in 6 patients, followed by hip fractures noted in 3 cases. For the other two cases, there were wrist fracture and tibial fracture.

Table 1 Clinical and biological characteristics of patients

| Characteristic                          | Mean ± SD                              |
|----------------------------------------|----------------------------------------|
| Age, mean ± SD years                   | 53.01 ± 14.66                          |
| Height, mean ± SD cm                   | 162.78 ± 9.77                          |
| Weight, mean ± SD Kg                   | 68.33 ± 13.48                          |
| Body mass index, mean ± SD kg/m²       | 25.79 ± 4.67                           |
| Smoking (n (%))                        | 50 (55.5)                              |
| Adequate exposure to sunlight (n (%))  | 55 (61)                                |
| Comorbidities                          |                                        |
| Diabetes (n (%))                       | 38 (42)                                |
| Hypertension (n (%))                   | 60 (66)                                |
| Dyslipidemia                           | 12 (13)                                |
| Duration of dialysis, mean ± SD years  | 3.94 ± 1.99                            |
| Causes of CKD                          |                                        |
| Diabetic nephropathy (n (%))           | 30 (33.3)                              |
| Vascular nephropathy (n (%))           | 6 (6.6)                                |
| Glomerulonephritis (n (%))             | 40 (44.5)                              |
| Amyloidosis (n (%))                    | 1 (1.2)                                |
| Polycystic kidney disease (n (%))      | 4 (4.4)                                |
| Tubulointerstitial nephropathy (n (%)) | 9 (10)                                 |
| Calcium (2–2.25 mmo/L)                 | 2.08 ± 0.32                            |
| Phosphate (2–2.25 mmo/L)               | 1.84 ± 0.57                            |
| Albumin (30-45 mmol/L)                 | 35.45 ± 5.64                           |
| Total alkaline phosphatase (60–220 U/L)| 88.35 ± 72.56                          |
| PTH (12-65 pgmL)                       | 425.7 ± 380.8                          |
| 25 OH-vitamin D (ng/L)                 | 15.76 ± 11.58                          |
| bAP (ng/mL)                            | 26.84 ± 26.99                          |
| CTX (ng/mL)                            | 2.49 ± 1.51                            |
| FGF 23 (pg/mL)                         | 221.87 ± 248.96                        |

Data are presented as mean ± standard deviation, CKD Chronic kidney disease, PTH Parathyroid hormone, bAP bone alkaline phosphatase, CTX C-terminal telopeptide of type I collagen, FGF 23 Fibroblast growth factor 23

Prevalence of osteoporosis
As shown in Table 2, osteoporosis was common among patients undergoing hemodialysis. 23% of patients have osteoporosis and 45% have osteopenia. Osteoporosis affected the hip more than the spine.

Correlation between biological parameters
There was a positive correlation between bAP and CTX. Moreover, both bone markers showed positive correlations with serum PTH levels. Table 3 demonstrated correlations between biological parameters.

Associated factors of BMD
As illustrated in Table 4, patients with osteoporosis were older than patients without osteoporosis. Men had higher DXA BMD than women at only the total body (1.160 ± 0.141 vs. 1.053 ± 0.105 g/cm², p < 10⁻³).

The mean BMD was significantly lower among patients with a history of diabetes at the total hip femoral (0.894 ± 0.162 in patients with diabetes vs. 0.894 ± 0.162 in patients without diabetes, p: 0.003). Diabetic nephropathy was the most common etiology associated with decreased BMD at the femoral site whereas patients with polycystic kidney disease tended to have higher BMD than the other patients (0.789 ± 0.118 g/cm² in patient with diabetic nephropathy vs. 0.980 ± 0.249 in patient with polycystic kidney disease, p: 0.031).

Parathyroid hormone levels were significantly increased in patients with osteoporosis affecting the total hip. Fibroblast growth factor 23 levels were significantly increased in patients with osteoporosis affecting the lumbar. However, vitamin D levels did not differ significantly between patients with and without osteoporosis.

The Pearson’s correlations between clinical, anthropometric, biological and BMD were presented in Table 5.

As shown in Table 6, age and PTH levels significantly predicted the total hip BMD.

Associated factors of fractures
As demonstrated in Table 7, PTH levels were significantly lower in patients with fractures. Besides, patients with osteoporosis had more osteoporotic fractures than patients without osteoporosis.

Discussion
Patients with chronic kidney disease on dialysis (CKD-5D) are at increased risk of osteoporosis and fractures than the general population [6]. In this bone DXA densitometry-based study, we detected that osteoporosis was common in dialysis patients, observed in 23% of cases. Indeed, literature data showed that the prevalence of osteoporosis varied from 4 to 47% at the lumbar spine and from 10 to 64% at the femoral site [7–15]. Moreover, Avramovski et al. [16] demonstrated that the
progression of bone mass loss was significantly greater in chronic hemodialysis patients than in general population patients. Using DXA assessment, Sit D et al. [13] showed that the lumbar spine was the region with the highest prevalence of osteoporosis. However, other studies are consistent with our study showing that osteoporosis affected the total hip (20%) more than the lumbar spine (9%). DXA technology can overestimate the BMD measured in the lumbar because of the existence of osteophytes and aortic calcification, frequently observed in hemodialysis patients [17].

Bone mass loss is considered as the consequence of several factors in hemodialysis patients. Several studies are consistent with our study showing that BMD decreased as age increased [14, 17, 18]. The effect of gender on bone mass in hemodialysis is controversial [19, 20]. We found that BMD was significantly lower in women at the total body. The impact of diabetes on BMD is not yet clear. According to the study of Elder et al., we found that BMD at total hip was lower among dialysis patients with diabetes [21].

Chronic kidney disease is associated with hyperphosphatemia and hypocalcemia, observed in 62.22% in our patients, and induce secondary hyperparathyroidism. Fifty-six percent of patients have PTH values between 2 and 9 times the upper normal limit of the assay as recommended by KDIGO [1]. Observational studies demonstrated that PTH values at the extremes (lower than 2 times and more than 9 times) are associated with an increased relative risk of death in dialysis patients.

### Table 2 Results of bone mass in hemodialysis patients

|                  | BMD (g/cm²) | T-score (SD) | Osteopenia | Osteoporosis |
|------------------|-------------|--------------|------------|--------------|
| Lumbar spine     | 1.156 ± 0.218 | –0.465 ± 1.748 | 30 33 | 8 9 |
| Total hip        | 0.854 ± 0.152 | –1.44 ± 1.14  | 40 44 | 18 20 |
| Femoral Neck     | 0.877 ± 0.150 | –1.3 ± 1.15   | 45 50 | 12 13.33 |
| Overall          | –           | –             | 42 45 | 18 23 |

*BMD Bone mineral density, SD Standard deviation, N Number, %: percentage*

### Table 3 Pearson’s correlation between biological parameters

|             | TAP          | Vitamin D   | PTH          | bAP        | CTX          |
|-------------|--------------|-------------|--------------|------------|--------------|
| TAP         | –            | −0.234**    | 0.430***     | 0.850***   | 0.558***     |
| Vitamin D   | −0.234**     | –           | −0.121       | −0.212     | −0.089       |
| PTH         | 0.430***     | −0.121      | –            | 0.559***   | 0.578***     |
| bAP         | 0.850***     | −0.212      | 0.559***     | –          | 0.701***     |
| CTX         | 0.558***     | −0.089      | 0.578***     | 0.701***   | –            |
| FGF 23      | 0.062        | 0.247*      | −0.169       | −0.642     | −0.058       |

*Date are presented as the r value in Pearson’s correlation test * p < 0.05, ** p < 0.01, *** p < 0.001. TAP Total alkaline phosphatase, PTH Parathyroid hormone, bAP bone alkaline phosphatase, CTX C-terminal telopeptide of type I collagen, FGF 23 Fibroblast growth factor 23*

### Table 4 Comparison of clinical and biological characteristics between patients with and without osteoporosis

|                  | Normal          | Osteopenia      | Osteoporosis   | p   |
|------------------|-----------------|-----------------|----------------|-----|
| Age (years)      |                 |                 |                |     |
| Lumbar           | 52.03 ± 14.18   | 52.55 ± 14.26   | 65.87 ± 10.07  | 0.034 |
| Total hip        | 49.58 ± 15.02   | 51.71 ± 12.86   | 63.94 ± 11.39  | 0.001 |
| All              | 50.06 ± 15.09   | 50.42 ± 13.50   | 63.94 ± 11.39  | 0.001 |
| Age of onset of HD (years) |            |                 |                |     |
| Lumbar           | 49.33 ± 14.42   | 49.03 ± 14.57   | 63.37 ± 10.02  | 0.031 |
| Total hip        | 50.06 ± 15.09   | 48.84 ± 13.58   | 60.5 ± 11.64   | 0.001 |
| All              | 46.87 ± 14.71   | 48.21 ± 14.16   | 63.85 ± 14.82  | < 10^3 |
| PTH (pg/mL)      |                 |                 |                |     |
| Lumbar           | 410.67 ± 402.97 | 496.15 ± 385.55 | 430.16 ± 383.98 | 0.425 |
| Total hip        | 265.87 ± 237.20 | 518.56 ± 420.46 | 512.46 ± 426.62 | 0.013 |
| All              | 249.01 ± 217.38 | 516.89 ± 414.78 | 512.46 ± 426.62 | 0.006 |
| Vitamin D (ng/mL)|                 |                 |                |     |
| Lumbar           | 14.29 ± 10.50   | 19.00 ± 13.44   | 15.76 ± 11.68  | 0.185 |
| Total hip        | 16.61 ± 10.71   | 16.28 ± 11.38   | 13.25 ± 14.03  | 0.59  |
| All              | 16.80 ± 10.74   | 16.11 ± 11.13   | 13.25 ± 14.03  | 0.576 |
| CTX (ng/mL)      |                 |                 |                |     |
| Lumbar           | 2.50 ± 1.58     | 2.60 ± 1.46     | 1.85 ± 1.06    | 0.45  |
| Total hip        | 2.41 ± 1.51     | 2.57 ± 1.55     | 2.38 ± 1.46    | 0.84  |
| All              | 2.25 ± 1.36     | 2.71 ± 1.64     | 2.38 ± 1.46    | 0.43  |
| bAP (ng/mL)      |                 |                 |                |     |
| Lumbar           | 25.23 ± 27.27   | 30.99 ± 30.22   | 20.77 ± 9.41   | 0.54  |
| Total hip        | 22.80 ± 25.93   | 29.18 ± 30.26   | 27.51 ± 22.18  | 0.67  |
| All              | 19.48 ± 19.73   | 31.33 ± 32.08   | 27.51 ± 22.18  | 0.21  |
| FGF 23 (pg/mL)   |                 |                 |                |     |
| Lumbar           | 192.90 ± 242.32 | 194.50 ± 229.21 | 428.13 ± 275.64 | 0.039 |
| Total hip        | 203.32 ± 203.32 | 278.28 ± 278.28 | 250.28 ± 250.28 | 0.731 |
| All              | 185.37 ± 203.32 | 229.46 ± 278.28 | 240.43 ± 250.28 | 0.731 |

*HD Hemodialysis, PTH Parathyroid hormone, bAP bone alkaline phosphatase, CTX C-terminal telopeptide of type I collagen, FGF 23 Fibroblast growth factor 23*

Significant at p < 0.05 set in boldface
Table 5 Pearson’s correlation between clinical, anthropometric, biological and BMD

|                           | BMD L | BMD TH | BMD FN | BMD FA | BMD TB |
|---------------------------|-------|--------|--------|--------|--------|
| Age                       | 0.134 | -0.289** | 0.212  | 0.290** | 0.190  |
| Duration of dialysis      | 0.072 | -0.021  | -0.060 | 0.016  | -0.121 |
| BMI                       | 0.073 | -0.082  | -0.020 | -0.095 | 0.014  |
| Albumin                   | 0.057 | -0.05   | 0.111  | -0.131 | -0.027 |
| TAP                       | -0.083| -0.144  | -0.109 | -0.294**| -0.277**|
| PTH                       | -0.140| -0.275**| -0.232*| -0.326**| -0.343***|
| Vitamin D                 | -0.004| 0.239*  | 0.216* | 0.142  | 0.091  |
| bAP                       | -0.122| -0.176  | 0.182  | -0.299**| -0.353***|
| CTX                       | 0.022 | -0.055  | -0.071 | -0.260*| -0.206  |
| FGF 23                    | -0.670| -0.149  | 0.780  | -0.054 | -0.08  |

Date are presented as the r value in Pearson’s correlation test * p < 0.05, ** p < 0.01, *** p < 0.001. BMD Body mass density, TH Total hip, FN Femoral Neck, FA Forearms, TB Total Body, PTH Parathyroid hormone, bAP bone alkaline phosphatase, CTX C-terminal telopeptide of type I collagen, FGF 23 Fibroblast growth factor 23

Nevertheless, until now, there is no reference range of PTH values corresponding with normal bone turnover [22]. As in our study, Taal et al. [7] showed that the total hip BMD had a negative correlation with PTH. Besides, TAP correlated negatively with BMD in the total body. We didn’t find an association between the serum albumin level and BMD. Even if Huang et al. [23] found a positive correlation between serum albumin levels and femoral neck BMD in dialysis patients. Lai et al. [24] showed that there was no relationship between these parameters.

Even if CTX is cleared by the kidney, our study showed that circulating bAP and CTX levels are correlated with serum PTH levels. Serum CTX levels have been found to predict bone loss in patients under dialysis [25, 26]. Several studies have also demonstrated that CTX concentrations are raised in patients with CKD-5D and correlate well with BMD measurements [27]. Moreover, Maeno et al. [26] reported that CTX levels significantly correlate with annual bone loss with sensitivity and specificity at respectively 41 and 83%.

Nevertheless, in another study, serum CTX levels were not different between patients with and without loss of BMD at the distal radius [28].

FGF23 plays an important role in regulating bone mineralization. In our study, FGF23 levels were significantly increased in patients with osteoporosis affecting the lumbar. High FGF23 levels were associated with reduced osteoid thickness in children undergoing dialysis [29]. However, in other studies, BMD was not correlated with serum FGF23 levels [30].

Insufficiency on vitamin D, observed in 41.11% in our study, is common among dialysis patients [31–35]. There has been much debate about the relationship between vitamin D and BMD. Several studies have demonstrated that low vitamin D level induced a decrease of cortical BMD in the presumed healthy adult [36]. Our study revealed a positive correlation between vitamin D levels and femoral BMD.

Fracture rates, observed in 12.1% in our study, are greatly increased in dialysis patients compared to the
general population [37]. From our study, it is evident that lower PTH value was associated with an increased risk of osteoporotic fracture. It has been demonstrated that both high and low PTH levels can be associated with a high fracture rate [38, 39].

Another finding of interest in our study is that osteoporotic fractures were associated with the existence of osteoporosis. In a meta-analysis, Jamal et al. suggested that BMD is lower in patients with stage 5 CKD who have fractures [40]. The relationship between BMD measured by DXA and fracture in dialysis patients remains unclear.

There are numerous limitations to our study. First, it is a cross-sectional study. Besides, some other factors which might be associated with osteoporosis such as dosage of heparin and hypogonadism were not studied.

**Conclusion**

Our study showed that osteoporosis and fracture are common in patients under dialysis. We highlighted that bone mass loss is the consequence of several factors including age, diabetes and elevated levels of PTH. Osteoporotic fracture risk was associated with the existence of osteoporosis suggesting that DXA measurement is mandatory for the monitoring of bone loss. Our study showed also that both circulating bAP and CTX levels correlated positively with PTH levels. We suggest that bone metabolic markers including BAP and CTX may accurately reflect bone turnover. FGF23 levels were significantly increased in patients with lumbar osteoporosis. Certainly, FGF23 plays a role in the pathogenesis of bone disease in patients with CKD-5D. Other larger longitudinal studies are necessary to codify the assessment of bone disease.

**Abbreviations**

25(OH)D: 25(OH) vitamin D; bAP: bone-specific alkaline phosphatase; BMD: Bone mineral density; CKD-5D: Chronic kidney disease on dialysis; CTX: Carboxy-terminal telopeptides of type 1 collagen; DXA: Dual-energy x-ray absorptiometry; FGF23: Fibroblast growth factor 23; PTH: Intact parathyroid hormone; TAP: Total alkaline phosphatase

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**Authors’ contributions**

MS has drafted the work. HS has substantively revised the work. AB has made substantial contributions to the analysis of data. LL, has made substantial contributions to the interpretation of data. WS, SR, IG and MS have made substantial contributions to the acquisition of data. FBM has made substantial contributions to the design of the work. ME has approved the submitted version. EC has made substantial contributions to the design of the work. ME has approved the final manuscript. HS has substantively revised the work. AB has made a critical contribution to the conception of the work. All authors read and approved the final manuscript.

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**Availability of data and materials**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Ethics approval and consent to participate**

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**Consent for publication**

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**Competing interests**

The authors declare that they have no competing interests.

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