Bone 200 (2025) 117578

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Full Length Article

The number of vertebral fractures in indolent systemic mastocytosis is influenced by presence of the KIT-mutation

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ARTICLE INFO

Keywords:
Osteoporosis
Tryptase
Mast cells
Bone mineral density (BMD)
Pain
Smoking

ABSTRACT

Systemic mastocytosis (SM) is a rare disease characterized by aggregation of mast cells in the skin or extracutaneous organs. Disease subtypes range from cutaneous to systemic mastocytosis with highly malignant forms, indolent systemic mastocytosis (ISM) being the most frequent subtype. In ISM, mast cells infiltrate bone marrow, with some patients developing osteoporosis and fractures. However, fractures do not occur in all ISM patients.

In this retrospective one-center study, we analyzed data from patients evaluated for osteoporosis diagnosed with ISM according to WHO criteria between 2006 and 2019. ISM patients (n = 42) comprised 76.2 % women (n = 32), had a mean age of 52.2 ± 12 years, and presented with skin lesions in 80.5 % (n = 33). Osteoporosis was diagnosed in 42 % (n = 15) according to the WHO definition (T-score ≤ −2.5). Fractures were either peripheral in 19 % (n = 8), or to the spine in 43 % (n = 18); both fracture types presented in 14 % (n = 6). All fracture types correlated to femoral BMD T-scores. The presence of the somatic gain-of-function mutation in the KIT receptor tyrosine kinase (KIT-mutation) in bone biopsy was associated with a significantly greater number of fractures ($p = 0.024$) and correlated to the number of vertebral fractures in individual patients ($p = 0.03$). Neither tryptase levels, postmenopausal status, nor bone turnover markers were indicators of an increase in vertebral or peripheral fractures in ISM patients. Smoking was associated with more fractures, however the effect disappeared dependent on KIT-mutation. Those with skin lesions had better femoral BMD T-scores (right femur: −1.05 ± 0.99 vs −2.26 ± 0.59, $p = 0.008$; right femoral neck: −1.21 ± 0.99 vs −2.22 ± 0.55, $p = 0.0023$).

In conclusion, we demonstrate the influence of the KIT-mutation on the severity of fractures in osteoporosis patients with the final diagnosis of ISM. Our results suggest that, in the presence of the KIT-mutation in ISM patients without skin lesions, the timely onset of anti-osteoporotic treatment might be of value.

1. Introduction

Mastocytosis is defined as an infiltration of clonal mast cells either in the skin (cutaneous mastocytosis; CM) or at least one extracutaneous organ (systemic mastocytosis; SM). Although this hematologic disease is rare and affects only 1 in 10,000 humans [1], it plays a role in the differential diagnosis of osteoporosis. In a patient cohort suffering from osteoporosis, 0.5 % were found to have indolent systemic mastocytosis [2]. Studies on bone biopsies revealed an incidence of 1.25 %; in patients younger than 45 years of age as high as 2.25 % [3]. Besides bone loss, patients may present a huge number of symptoms including pruritus, urticaria, flushing, angioedema, anaphylaxis, as well as gastrointestinal symptoms [4]. The systemic form is categorized into the subtypes indolent systemic mastocytosis (ISM), bone marrow mastocytosis (BMM), smoldering mastocytosis (SSM), systemic mastocytosis with associated myeloid neoplasm (SM-ANM), aggressive systemic mastocytosis (ASM), mast cell leukemia (MCL), and mast cell sarcoma [5]. ISM is the most frequent form [6]. >90 % of patients with mastocytosis possess

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https://doi.org/10.1016/j.bone.2025.117578
Received 19 February 2025; Received in revised form 2 July 2025; Accepted 4 July 2025
Available online 6 July 2025

somatic gain-of-function mutations in the KIT receptor tyrosine kinase, primarily an aspartic acid to valine substitution (D816V) in the second catalytic domain, which results in enhanced survival and cell autonomous growth of neoplastic mast cells (MC) [7].

One extracutaneous organ often affected by ISM is bone. Consequently, 20 to 37 % of ISM patients have osteoporosis associated with a high number of vertebral fractures [8,9]. Male gender, high levels of bone resorption (serum type I collagen C-telopeptide), low hip bone mineral density, absence of maculopapular cutaneous mastocytosis, and alcohol intake at the time of ISM diagnosis were independent predictors of future fractures [10]. As cause of osteoporosis, the local infiltration of mast cells into the bone marrow as well as the release of mast-cell mediators has been hypothesized [11,12]. However, not all patients with mast cell infiltration have fractures.

In the differential diagnosis of secondary forms of osteoporosis in our center, the measurement of tryptase levels has increased the diagnosis of mastocytosis. However, mastocytosis is still not included as a risk factor of developing fractures in the S3 German Osteoporosis Guidelines. Furthermore, in those without fractures, the best point in time to start treatment to prevent fractures remains unclear. The aim of this study was therefore to identify possible causes of fractures in patients with the final diagnosis of ISM undergoing evaluation for osteoporosis in our bone clinic.

2. Methods

2.1. Patients

Patients with confirmed mastocytosis diagnosed either by or referred to our clinic between 2006 and 2019 were analyzed retrospectively (N = 104). Patients were either diagnosed with ISM and referred by the Department of Dermatology, Venereology and Allergology for evaluation of bone involvement, or were referred to us because of reduced bone mineral density and/or pathological fractures for unknown reasons. ISM was diagnosed through a differential diagnosis process including bone biopsy and referred for the final diagnosis of ISM to the Department of Dermatology, Venereology and Allergology. Other forms of secondary osteoporosis according to the 33 risk factors as suggested by the S3 German Osteoporosis Guidelines [13] (such as family history, menopausal status, tobacco use, alcohol consumption, hyperthyroidism, hyperparathyroidism, hypercortisolism, past or current use of steroids, different medication) were carefully assessed. Other possible causes of osteoporosis were excluded with the aid of a panel of biochemical tests, including urinary and serum calcium (corrected for albumin concentrations), serum phosphate, creatinine, 25-hydroxy-vitamin D (25OHD), parathyroid hormone (PTH), thyrotropin, luteinizing hormone (LH), and testosterone. Postmenopausal status was determined by measuring LH, follicular stimulation hormone (FSH), and estrogen. All the analyses were completed at the central laboratory of amedes Medical Services (amedes Medizinische Dienstleistungen) in Göttingen.

All data were available in the form of electronic medical records (Medistar) and included information on patient history, clinical and laboratory parameters, as well as DXA measurements and fractures. The following items were documented: patient age, body mass index (BMI), non-traumatic spine and peripheral fractures, osteoporosis risk factors, back pain using the visual analogue scale (VAS), dual energy x-ray absorptiometry measurements (DXA), osteoporosis-specific medication and specific information regarding mastocytosis (allergies, skin lesions, performed biopsies, and information on KIT-mutations). Eleven patients were treated with osteoporosis-specific medication (bisphosphonate n = 10; denosumab n = 1) before initial presentation to our clinic and to an extent before the diagnosis of ISM. All patients with osteoporosis and fractures were offered a bone biopsy for differential diagnosis or to determine the presence of mast cells in bone. Patients from the Department of Dermatology, Venereology and Allergology, Göttingen, already presented with biopsy results.

2.2. Fracture analysis

Patient history relating to spinal fractures was either controlled through lateral vertebral fracture assessment (VFA from DXA) or radiography, either from existing material or from x-rays initiated on presentation. In case of suspected new fractures, diagnosis was confirmed through magnetic resonance imaging (MRI). Osteoporotic fractures were corrected for non-osteoporotic forms and analyzed quantitatively following an algorithm modified after Genant [14]. Aspects of spine deformity were graded according to the difference between the anterior to the medium or posterior height of the individual vertebra, or the posterior height of directly adjacent upper or lower vertebrae. A vertebral fracture was defined with one of these indices as being <0.8, meaning a >20 % reduction in height. History of peripheral fractures relied on hospital discharge information.

2.3. Dual energy x-ray absorptiometry

DXA procedures were performed predominantly at the MVZ Endokrinologikum Göttingen with a GE Lunar Prodigy device manufactured by GE Healthcare. A minimum of two vertebrae had to be included for analysis while excluding fractured vertebrae. For patients measured externally with other DXA devices, only T-score and Z-score values were used for analysis. Thus, all the statistical analyses of BMD measurements took place with T-score and Z-score values only.

2.4. Laboratory parameters

A number of laboratory values were analyzed to evaluate for secondary osteoporosis, including mast-cell-specific tryptase and markers of bone formation (bone alkaline phosphatase (BAP), osteocalcin (OC)) and bone resorption (urinary deoxypyridinoline/creatinine (DPD)). Analyses were performed by Endokrinologikum Laboratories Hamburg and amedes Medical Services (amedes Medizinische Dienstleistungen) in Göttingen. In order to analyze urinary measurements, 24-hour collections of urine were used over two days; deoxypyridinoline/creatinine (DPD) and calcium were thus analyzed in two samples. The values presented are the means of the two 24-hour collections. Immunoassays used for analysis are listed in the supplements.

2.5. Bone biopsies

Bone biopsies were either already initiated by the Department of Dermatology, Venereology and Allergology, Göttingen and performed by the Department of Hematology and Medical Oncology. Biopsies initiated by us were performed by M. Metz of the Center for Hematology and Oncology in Göttingen. Bone specimens were transported to a specialized bone pathology center (M. Werner, Pathology, Vivantes Clinical Center Friedrichshain, Berlin, Germany). The bone specimens were divided into two parts. One part was sent to the Reference Center for Mastocytosis, Ludwig-Maximilian-University, Institute of Pathology (H.P. Horny). KIT-mutation status was evaluated according to the method used at the time of analysis, either by clamping PCR or Sanger Sequencing [15,16]. The other part was further processed for undecalcified histology as previously described [17]. Biopsies were analyzed macroscopically and microscopically [3].

2.6. Ethical considerations

The study was approved by the institutional review board of University Medical Center Göttingen (UMG) (5/4/20). All patients provided written informed consent to the clinical research in pseudonymized form.

2.7. Statistics

Data were analyzed using SPSS Version 28 or GraphPad 9. Data are presented as mean ± standard deviation (SD) in tables, or standard error of the mean (SEM) in figures. Figures were prepared using GraphPad 9. Non-parametric or parametric group calculations were two-tailed (Mann-Whitney-U or Kruskal-Wallis, unpaired Student's *t*-test, or one-way-ANOVA). Categorical parameters were analyzed using chi-square or Fisher's exact test as indicated in the tables and figures. The correlations were performed using a non-parametric, two-tailed Spearman's Rho test.

3. Results

ISM patients (n = 42) comprised 76.2 % women (n = 32), had a mean age of 52.2 ± 12 years of age, with 80.5 % (n = 33) presenting with skin lesions. Osteoporosis was diagnosed in 42 % (n = 15) according to the WHO definition (T-score ≤ −2.5). Fractures were described as peripheral in 19 % (n = 8) and spinal in 43 % (n = 18); both fracture types occurred in 14 % (n = 6). Baseline patient characteristics and statistics comparing ISM patients with fractures or without fractures are presented in Table 1. The patient groups were similar with respect to BMI. ISM patients with fractures were five years older, however the difference was not significant statistically. Patients were either diagnosed in the Department of Dermatology, Venereology and Allergology (n = 22; 52 %) or during differential diagnosis of osteoporosis or fractures (n = 20; 48 %). Skin lesions were present in 80 % of ISM patients (n = 33). The most notable outcome of Table 1 was the tendency towards a higher incidence of back pain reported in ISM patients with fractures.

Nearly all ISM patients were diagnosed through bone biopsy (95 %), whereas two were biopsied in the gastrointestinal tract (5 %). An analysis of the KIT-mutation was performed in 81 % of the ISM patients.

Table 1
ISM patient characteristics.

	With fractures[#] (n = 20)	Without fractures (n = 22)	p-Value[a,b]
Age (years): mean ± SD (range)	55.4 ± 13.6 (26; 84)	50.1 ± 10.1 (34; 67)	0.153[a]
Gender: n (%)	f: 15 (75); m: 5 (25)	f: 17 (77); m: 5 (23)	0.863[b]
Postmenopausal status: n (%*)	11 (55)	10 (46)	0.720[b]
BMI (kg/m^2): mean ± SD (range)	28.2 ± 5.1 (18.7; 39.1)	26.3 ± 4.4 (18.9; 34.7)	0.217[a]
Reason for first presentation: mastocytosis n (%)/osteoporosis n (%)	5 (25)/15 (75)	17 (77)/5 (23)	**<0.001**[b]
Osteoporosis risk factors with fx n (%)	20 (100)	13 (59)	**0.0015**[b]
Osteoporosis risk factors w/o fx n (%)	14 (70)	13 (59)	0.531[b]
Back pain (0–10): mean ± SD (range)	4.9 ± 1.9 (2; 8)	3.4 ± 2.5 (0; 7)	0.051
Skin lesions: n (%)	15 (75)	18 (82)	0.817
Biopsy: n (%)	Bone: 18 (90) Gastrointestinal: 2 (10)	Bone: 22 (100)	
Analysis of KIT-mutation: n (%)	17 (85)	17 (77)	
Basic osteoporosis medication: n (%)			
Vitamin D medication	16 (80)	10 (46)	**0.021**[b]
Calcium supplements	11 (55)	7 (32)	0.129[b]
Osteoporosis-specific medication: n (%)	9 (45)	2 (9)	**0.014**[b]

f: female; m: male; N: number of patients; SD: standard deviation; BMI: body mass index; [a]Student's *t*-test; [b]Fisher's Exact or Chi Square; $p < 0.05$; [#]vertebral and/or peripheral fractures; *percent patients, not percent women; Chi square incl. men; w/o fx: osteoporosis risk factors excluding fractures; with fx: risk factors including fractures. Significant p-values are marked in bold.

The patients referred by the Department of Dermatology, Venereology and Allergology, Göttingen, due to the diagnosis of mastocytosis and with the indication for bone biopsy presented with fewer fractures compared to patients diagnosed primarily for unclear osteoporosis with the final diagnosis of mastocytosis following bone biopsy. Osteoporosis-specific medication (bisphosphonates n = 10; denosumab n = 1) and vitamin D were prescribed in patients with fractures more frequently.

We further investigated parameters possibly influencing fracture occurrence in mastocytosis in our patients with and without fractures.

KIT-mutations in bone biopsies were detected in 71 % (n = 24) and were absent in the remaining 29 % patients (n = 10) (Fig. 1a; p = 0.024). Patients with a KIT-mutation presented a significantly greater number of fractures. The number of vertebral fractures per patient was also significantly higher in patients with KIT-mutation (Fig. 1b; p = 0.023). The number of peripheral fractures in patients with KIT-mutation was numerically higher compared to patients without KIT-mutation, albeit statistically insignificantly so (Fig. 1c; p = 0.57). Accordingly, patients with KIT wild type may have a better prognosis concerning the risk of fracture. There were no differences in BMD T-score between those with or without KIT-mutation (Fig. 1d).

Furthermore, we analyzed the effect of skin lesions, which occurred in approximately 80 % of our ISM patients. ISM patients with skin lesions presented fewer fractures per patient than ISM patients without skin lesions. The differences were neither significant for vertebral (p = 0.09) nor for peripheral fractures (p = 0.13) (Fig. 1e–g).

However, ISM patients without skin lesions (n = 5) had significantly lower BMD T-scores measured at the right femur and femoral neck than ISM patients with skin lesions (n = 18) (Fig. 1h and Table 2). No correlation to spine BMD could be detected.

To test for the influence of mast cell activity, we determined whether the number of fractures correlated to serum tryptase levels. Hence, we divided the mast-cell-specific parameter in quartiles and tested for differences concerning the average number of vertebral and peripheral fractures per patient (Fig. 1i–k). The number of fractures was identical in all four quartiles and did not increase with elevating tryptase levels. The high number of peripheral fractures in quartile two results from one patient alone, who suffered seven peripheral fractures.

In conclusion, neither tryptase levels nor the presence of skin lesions were indicators of an increase of vertebral or peripheral fractures in ISM patients. Skin lesions, however, seem to correlate with severity as determined by femoral, however not spinal BMD. In contrast, the severity of osteoporosis reflected by fractures and the number of vertebral fractures in the individual patient was reflected by the presence of the KIT-mutation.

We extended the analysis to include other risk factures. There was no difference in risk factors with respect to postmenopausal status in women, use of glucocorticoids, thyroid medication, proton pump inhibitors, or family history in relation to fracture risk. Other risk factors were mentioned by only one patient and analysis was not possible (weight loss, reduced menstrual cycles in women, traumatic peripheral fractures, hypogonadism). However, among ISM patients with fractures were significantly more smokers (n = 12 (60 %) versus n = 5 (23 %), respectively, $p < 0.05$). When smokers and non-smokers with and without KIT-mutation were compared, there was no difference in relation to fractures in smokers. In KIT-negative ISM patients the n = 2 smokers suffered from fractures whereas the n = 8 non-smokers were fracture-free (Fig. 2).

3.1. Fractures

Fractures occurring in ISM patients were mainly located at the spine (91 %), while nearly three in ten patients (28 %) suffered from both peripheral and vertebral fractures (Fig. 3a). Only 1 % (n = 2) of patients reported atypical peripheral fractures, sited at a finger or the tibia. All peripheral fractures were caused by at least minor trauma. Fractures to the spine were either single (n = 6; 30 %) or multiple (n = 12; 70 %). In

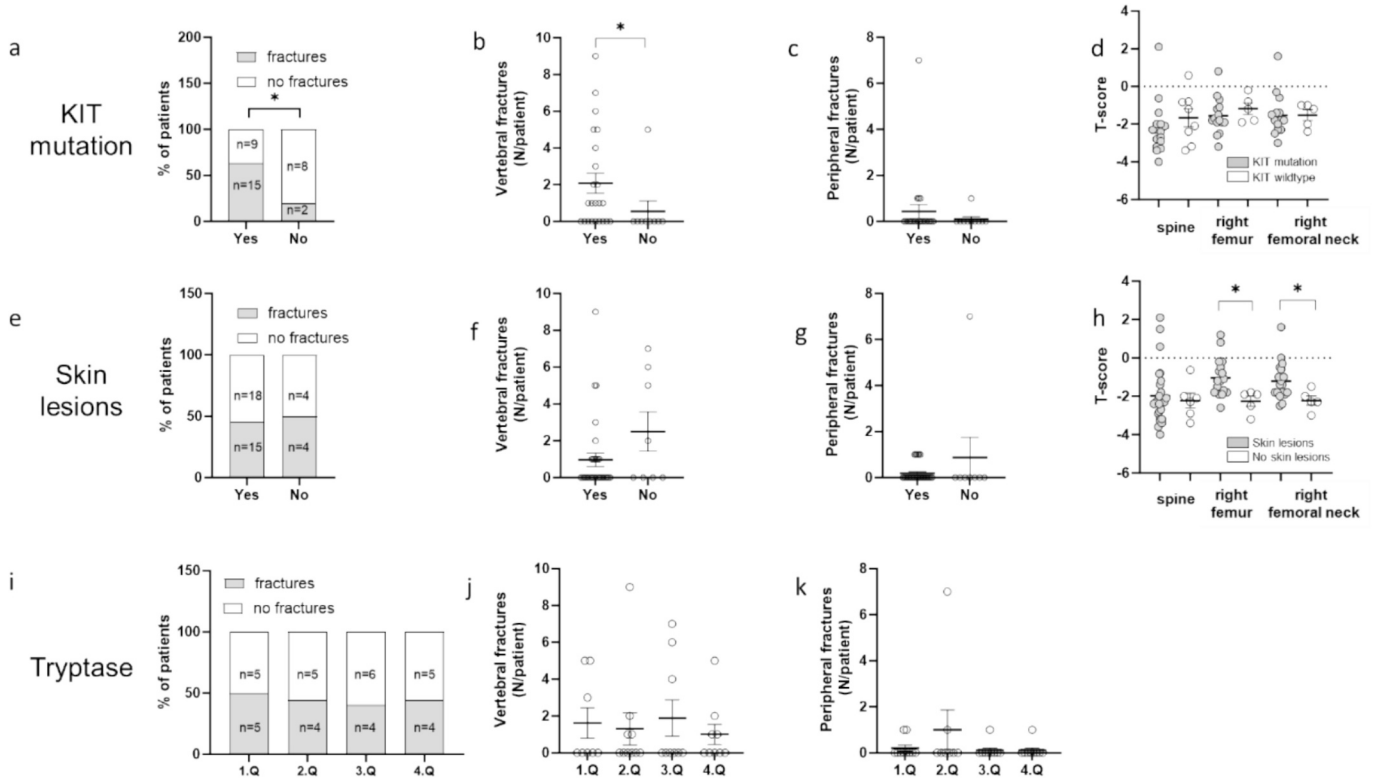


Fig. 1. Breaks down the number of patients and the presence of fractures or not for patients presenting the sign KIT-mutation (a–c), skin lesions (e–g), or tryptase (i–k), detailing the number of fractures according to type per patient for each presented sign. Bone mineral density (BMD) is depicted as T-score with or without the signs KIT-mutation (d) or skin lesions (h). Tryptase quartiles (i–k): 1. quartile: 3.6–21.4 ng/ml; 2. quartile: 21.4–34.4 ng/ml; 3. quartile: 34.4–81.5 ng/ml; 4. quartile: 81.5–173 ng/ml; N: number of fractures/patient; n = number of patients; error bar: SEM; *chi square (a, e, i) or Mann-Whitney (1b–d, f–h), Kruskal-Wallis (1i–k).

Table 2
T-scores in ISM patients with or without skin lesions.

	Skin lesion	No skin lesion	p-Value*
Spine T-score	n = 26	n = 5	
	−1.98 ± 1.49	−2.22 ± 0.94	0.91
Femur T-score	n = 18	n = 5	
Right total femur	−1.05 ± 0.99	−2.26 ± 0.59	**0.008**
Right femoral neck	−1.21 ± 0.99	−2.22 ± 0.55	**0.023**

* Mann-Whitney-U, significant p-values are marked in bold.

those ISM patients with multiple spinal fractures, five also suffered from peripheral fractures (Fig. 3b, c). The number of fractures varied from a single fracture to nine fractures per patient, whereas no fracture occurred at all in 22 ISM patients. One patient reported seven peripheral fractures caused by an accident. Furthermore, traumatic fractures are regarded as risk factors for osteoporosis [18]. Nevertheless, the differentiation of what defines a minor trauma is difficult for patient and physician. We therefore document and analyze all reported peripheral fractures.

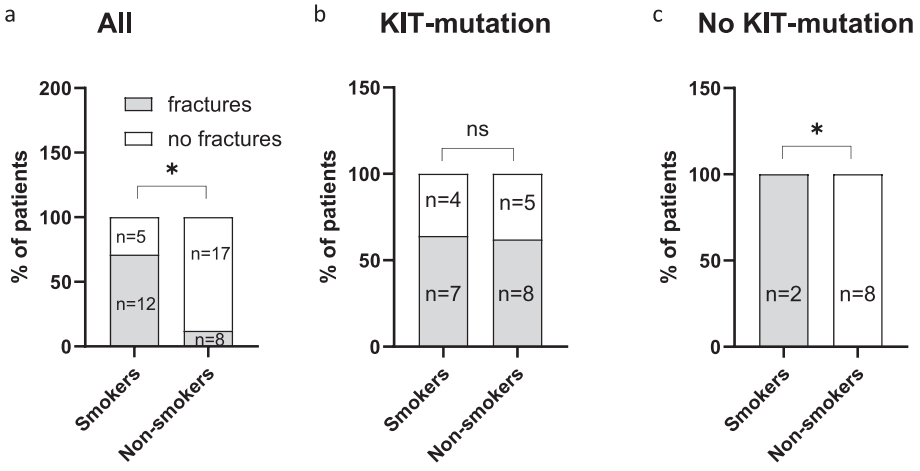
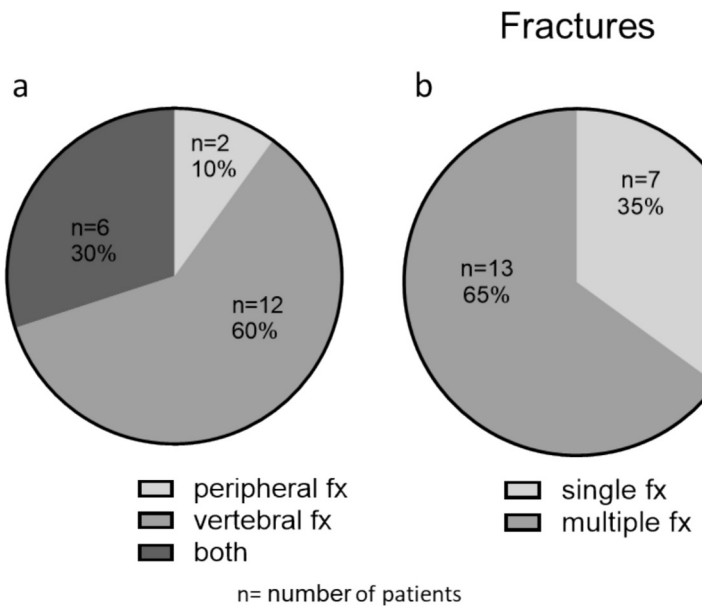


Fig. 2. Represents the number of patients with or without fractures representing the osteoporotic risk factor smoking (a) all patients (n = 42; KIT mutation was not analyzed in eight patients), (b) in patients positively tested for KIT mutation, (c) in patients without KIT-mutation; *Fisher's exact; n = number of patients.



c

Number of fx (N)	Spine n	Periphery n
0	24	34
1	6	6
2	2	
3	1	
4	2	
5	3	
6	1	
7	1	1*
9	1	
>1	1	1

Fig. 3. Fractures: percentage and number of (a) vertebral, peripheral fractures (fx), or both; (b) multiple and single fractures (fx) in ISM patients and (c) number of patients with fractures; all peripheral fractures were caused by some form of trauma (femoral neck (n = 2), rib (n = 2), arm/finger (n = 5) or leg (n = 2) *one patient reported seven peripheral fractures caused by trauma).

3.2. BMD values

Measurements of BMD T-scores and Z-scores are presented in Fig. 4 and Table S1. In addition, values were classified as normal (T-score ≥ −1), osteopenic (T-score < −1 and >−2.5) or osteoporotic BMD (T-score ≤ −2.5) (Fig. 4).

DXA values were consistently lower in the ISM group with fractures, with a significant difference in scores for the left femoral neck and

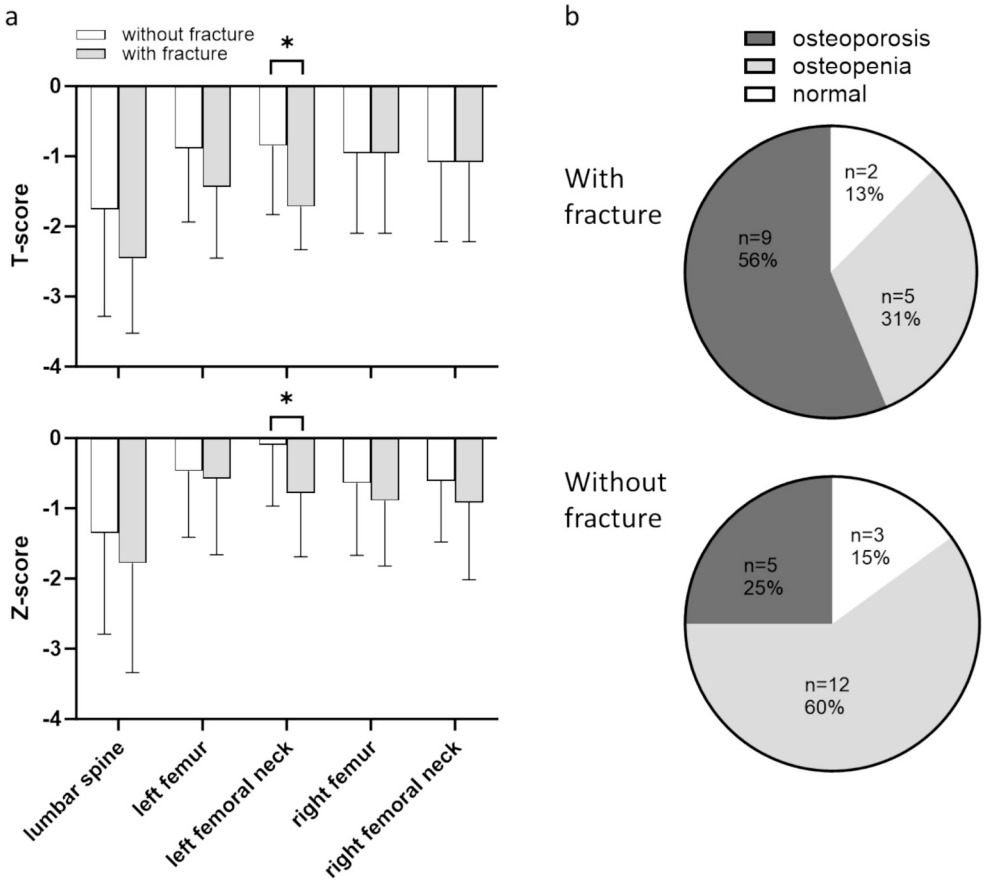


Fig. 4. T-scores and Z-scores in ISM patients: (a) DXA values at five locations in patients with or without fracture; (b) Percentage and number of ISM patients categorized as normal (T-score ≥ −1), osteopenic (T-score < −1 to >−2.5) or osteoporotic (T-score ≤ −2.5) BMD; n: number of patients.

tendencies were found for right femur and the right femoral neck (Table S1). Although most fractures were detected at the spine, BMD values at the spine were not significantly different between patients with or without fractures.

The classification of ISM patients with or without fractures into normal (T-score ≥ -1), osteopenic (T-score < -1 to > -2.5), or osteoporotic (T-score ≤ -2.5) bone resulted in a high proportion of patients in the ISM group with fractures presenting a T-score ≤ -2.5 (88 %). In contrast, only 25 % of patients in the group without fractures were classified with a T-score below −2.5 (Fig. 4). However, ISM patients with normal (n = 2) or osteopenic (n = 5) T-scores also suffered fractures.

Subsequently, we determined whether the number of vertebral or peripheral fractures correlate to BMD values within the ISM group with fractures when T-scores were available. The number of vertebral fractures was found to correlate significantly negatively with BMD at the left femoral neck: (T-score: $r_s = -0.613$; n = 12; p-value: 0.034).

When analyzing the two groups of ISM patients together (those with and without fractures), the correlation of fracture frequency to BMD at the left femoral neck was calculated as $r_s = -0.481$; n = 28; p = 0.01 for the T-score, and $r_s = -0.412$; n = 26; p = 0.037 for the Z-score. In addition, a significant negative correlation was found for the T-score at the spine (r_s: −0.403; n = 31; p = 0.025), meaning that lower T-scores resulted in a higher number of individual vertebral fractures in our study population.

Our results demonstrate an even better correlation of vertebral fracture frequency with T-scores at the femoral neck than with T-scores at the spine.

Taken together, a large proportion of patients with low T-scores was identified in both groups. We found the highest percentage of a T-score below −2.5 in the ISM group with fractures. Furthermore, DXA values were consistently lower in the ISM group with fractures. However, fractures did also occur in patients with normal bone mineral density or osteopenia.

3.3. Laboratory parameters

Laboratory parameters were analyzed for differential diagnosis and to identify differences especially in bone resorption and bone formation, and the mastocytosis-specific parameter tryptase. The results are depicted in Table 3.

The serum tryptase level was not significantly higher in ISM patients with fractures (Table 3) indicating no direct influence of mast cell activity as measured by tryptase levels on fractures. Moreover, no correlation for tryptase to the number of fractures in the total group of patients could be demonstrated. However, we did detect a positive correlation of tryptase to BMD at the femoral neck (T-score r_s 0.612, p = 0.009, n = 17, and Z-score r_s 0.52, p = 0.039, n = 16). No significant correlations were detected for bone turnover parameters or fractures when analyzed in those patients without specific osteoporosis treatment. However, there were positive correlations for BAP and T-score at the spine (r_s 0.518, p = 0.028, n = 18), as well as osteocalcin and Z-score at the femoral neck (r_s 0.68, p = 0.044, n = 9) reflecting higher BMD values with higher bone turnover. Glomerular filtration rate (GFR) levels were lower in those patients with fractures who were also 5 years older, although the differences in age were not significant.

4. Discussion

This study analyzed patients with indolent systemic mastocytosis (ISM) with and without vertebral or peripheral fractures to identify a possible prognostic marker for the prediction of osteoporosis leading to fractures. Patients were either referred by the Department of Dermatology, Venereology and Allergology, Göttingen for bone evaluation on the grounds of mastocytosis or presented themselves directly in the MVZ Endokrinologikum because of fractures and/or suspected osteoporosis.

Table 3
Laboratory parameters in patients with and without fractures.

Parameter (Normative values)	With fractures (n = 20) (Mean ± SD; range)	Without fractures (n = 22) (Mean ± SD; range)	p-Value*
Osteocalcin (µg/l): 4.0–12.0**	13.28 ± 4.16; (6.30–21.10) n = 10	16.77 ± 6.01; (8.4–26.80) n = 14	0.129
BAP (U/l):** Premenopausal: 11.6–29.6 Postmenopausal: 14.2–42.7	17.25 ± 0.50; (16.9–17.6) n = 2	20.21 ± 7.02; (11.4–29.9) n = 7	0.587
BAP (µg/l):** Premenopausal: <14.3 Postmenopausal: <22.4	26.98 ± 7.42; (16.2–38.6) n = 9	32.79 ± 12.0; (16.4–55.8) n = 12	0.217
25-OH-Vitamin D (nmol/l): Target value prevention >75 Deficiency: <50 Hypervitaminosis: >240	74.76 ± 40.54; (18.9–178.0) n = 19	59.16 ± 31.65; (22.60–174) n = 21	0.181
PTH (pmol/l): 1.70–6.89	4.34 ± 2.01; (0.90–9.86) n = 19	4.84 ± 2.39; (2.00–11.30) n = 22	0.491
Phosphate (mmol/l): 0.8–1.6	1.15 ± 0.19; (0.90–1.60) n = 19	1.16 ± 0.15; (0.87–1.44) n = 21	0.893
DPD (µg/g): 8.4–19.7**	19.90 ± 4.47; (12.40–26.27) n = 11	22.76 ± 8.29; (10.55–43.29) n = 20	0.678
Ca/24 h (mmol/d): 2.5–7.5	4.86 ± 3.61; (0.85–15.30) n = 18	5.52 ± 2.96; (0.50–12.15) n = 22	0.529
Tryptase (µg/l): <11.4	58.13 ± 51.54; (8.5–173.00) n = 16	54.96 ± 43.77; (3.60–165.0) n = 21	0.841
GFR (CKD-EPI) (ml/min/1,73qm): >60	90.36 ± 20.98; (67.0–139.0) n = 14	104.06 ± 15.87; (75.0–127) n = 18	**0.044**

SD: standard deviation; n: number of patients; BAP: bone alkaline phosphatase; Ca/24 h: calcium in 24 h-urine; PTH: parathyroid hormone; DPD = deoxypyridinoline crosslink; GFR: glomerular filtration rate. Bold: significant p-value.
* Student's *t*-test.
** Bone turnover markers in patients without specific anti-osteoporotic treatment (n = 31).

In those with bone biopsy, presence of the KIT-mutation was also analyzed. We demonstrate that the presence of KIT-mutation correlated to the occurrence of vertebral and numerically more peripheral fractures in our ISM patient cohort. We also analyzed the data for other osteoporosis risk factors in our patients and found no difference in postmenopausal status in women. We identified more smokers in the group with fractures; however, when patients with KIT-mutation were compared, there was no difference in fractures between smokers or non-smokers. We had only 10 ISM patients negative for KIT-mutation and the two smokers had fractures in contrast to the eight fracture free non-smokers. However, numbers are very small in these subgroups. Smoking may increase fracture risk by a factor of 1.5 above >10 cigarettes per day in osteoporosis patients [19], however we did not document the number of cigarettes per day. The effect of smoking could also be different in patients with mastocytosis and have more or less impact than in patients with other forms of osteoporosis. Nevertheless, our results do suggest that smoking increases fracture risk also in mastocytosis patients.

The question is now, how the KIT-mutation relates to fracture risk in ISM patients. The gain-of-function somatic mutations in the KIT tyrosine kinase domain, particularly the D816V mutation, are present in most patients with SM and constitutively activate KIT kinase activity [7,20]. However, it is unclear if the mutated KIT leads to the different clinical outcomes in mastocytosis patients. The interaction between KIT and its ligand, stem cell factor (SCF), plays a key role in regulating mast cell proliferation, maturation, adhesion, chemotaxis, and survival [21]. The

D816V mutation in KIT leads to constitutive activity of mast cells without the need for SCF. The thus continuously secreted cell mediators, e.g. histamine, TNF-α, IL-6, IL-11, and IFN-γ, are known to induce the synthesis of the receptor activator of the NFκb ligand (RANKL), a potent osteoclast-stimulating factor inducing an increase in bone resorption and thereby causing increased bone turnover with loss of bone, osteoporosis, and fractures. Therefore, the increased mast cell activity caused by D816V mutation in KIT could well be one causal factor for increased bone resorption in these patients. Conversely, data on the influence on bone formation are in part contradictory [22,23].

However, data on KIT and the severity of osteoporosis are contradictory. When analyzing patients with systemic mastocytosis defined by KIT mutation in bone biopsy, only 20 to 37 % of ISM patients have osteoporosis associated with a high number of vertebral fractures [8,9]. KIT is expressed in a number of cell types and dependent on the maturity of the cell [24]. Mice experiments with transgenic human KITD816V demonstrate only limited disease in 30 % of mice at old age when expressed in mature mast cells [25]. In contrast, conditional expression including hematopoietic precursors caused severe mastocytosis in 100 % already in young mice [26]. Also, data in human samples demonstrated KITD816V monocytes and mast cells as a proof for multilineage involvement KITD816V [27]. KIT mutation analyzed in bone marrow aspirates could therefore reflect expression in mast cells but also in other cell types.

From our results, KIT analysis does have a prognostic value in assessing the risk of fracture. To our knowledge, there are no other studies in which fractures depending on KIT-mutation status in bone biopsy specimen in ISM have been analyzed. Broesby-Olsen et al. did not detect any influence of the number of KIT D816V-positive cells in peripheral blood or in bone marrow on BMD in ISM patients, but they did not analyze fractures [28]. The method also differed; they analyzed the number of positive cells in bone marrow aspirates and peripheral blood, whereas we investigated bone biopsies, which in our study resulted in a positive or negative result, but no quantification. Barete et al. analyzed KIT D816V in skin or bone marrow aspirates in patients with bone involvement, osteoporosis, and osteosclerosis, and detected the mutation in 85 to 90 % of patients [29]. The study included more severe forms of mastocytosis beside ISM, possibly explaining the high KIT-mutation detection rate. In addition, osteoporosis was classified according to BMD and not to fracture [29]. It is worth noting here that BMD did not correlate to KIT-mutation in our patients. Another study also investigated KIT D816V in skin or bone marrow aspirates in patients with different severity forms of SM [30]. The use of bone marrow aspirates again differs from our procedure with a regular bone biopsy performed for histomorphometrical analysis of bone turnover in patients with osteoporosis of unclear origin and the analysis in those biopsies demonstrating an increase in mast cells. Certainly, also in these unfixed biopsies other bone marrow cells are still present. In addition, osteoclasts develop from monocytes also expressing KIT D816V [27]. The correlation of tryptase measured in bone marrow aspirates to fragility fractures in contrast to the missing correlation of KIT D816V to fragility fractures in the same study [30] would suggest that in bone marrow aspirates also multilineage cells express KIT, but the production of tryptase represents the mast cell burden in bone marrow. Analysis of KIT mutation in bone biopsy in our study was only performed in osteoporosis patients with increased mast cell number in bone biopsy, possibly explaining differences in results compared to other studies. Again, it has to be pointed out, that also the patient selection of young patients with osteoporotic fractures of unclear origin with increased tryptase levels were selected for bone biopsy representing a different study population compared to the analysis of patients with different forms of systemic mastocytosis.

Interestingly and not contradictory to our results, KIT-mutation in the skin demonstrated a tendency but failed to reach significance in the univariate and multivariate regression analysis for factors associated with fragility fractures [30].

Our study included only non-cutaneous KIT-mutation analysis and a different patient population, in half of the cases presenting for the differential diagnosis of fractures. Perhaps the detection of KIT-mutation represents a risk factor for these osteoporosis patients, whereas SM patients have a higher fracture risk in general.

BMD was significantly lower at the femur in patients without skin lesions. Even if the figures were not significant, the number of fractures per patient were higher in those without skin lesions. Our data are supported by other studies demonstrating that ISM patients without skin lesions had a significantly greater number of osteoporotic fractures [9,11]. However, others did not detect any differences concerning fractures [31]. From biopsy studies, the authors assumed that the bone loss is rather caused by the mast cell burden than the skin involvement [11]. Taken together, our data may be viewed as a hint that skin lesions in ISM patients may be a prognostic factor of the bone being affected less. Further studies have to clarify whether skin lesions do actually qualify as a prognostic factor for fractures.

Degboé et al. detected vertebral fractures in 23 % and peripheral fractures in 8 % of their ISM patients [8]. In our study, nearly half of the ISM group at MVZ Endokrinologikum presented vertebral fractures (43 %), mostly multiple vertebral fractures (67 %). Moreover, 75 % of the ISM patients suffering from vertebral fractures had multiple fractures. No further significant differences were found with respect to clinical parameters between those with and without fractures. Numerically, patients with fractures were five years older and had a significantly reduced kidney function, however eGFR still in the normal range. Patients with fractures were evidently treated with vitamin D and specific anti-osteoporotic medication more often. These results may be taken as a hint that older age is a possible risk factor as already suggested by others [30].

Consequently, our results confirm that multiple vertebral fractures are characteristic of ISM. This may be caused by the fact that trabecular bone is more compromised than cortical bone in ISM [11].

The number of ISM patients suffering from vertebral fractures was higher in our group compared to other studies [8,10]. One of the main reasons is patient selection. Patients come to the bone clinic because of suspected or confirmed osteoporosis. Hence, we diagnose more patients with osteoporosis and fractures, in contrast to the dermatology or hematology clinics analyzing all their patients with ISM. Another reason may lie in the fact that we documented all fractures and not only the non-traumatic fractures. However, this is justified by the finding that osteoporosis also affects high-traumatic fractures [18,32].

BMD values at the spine and femur were numerically lower in our patient group with fractures, and significant only for values at the femur reflecting cortical bone. In addition, spinal fractures correlated significantly negatively to femoral BMD.

In two other studies, fragility fractures were associated with hip BMD T-score [10,30]. Moreover, in patients with postmenopausal osteoporosis or osteoporosis of old age, femoral BMD correlates better to fracture risk than spinal BMD [33,34]. This is probable owing to increases in degenerative changes of the spine with age; calcification of the aorta also influences spinal BMD values. In addition, sclerotic lesions in the spine are described in ISM patients which would increase BMD of the spine [35].

Rossini et al. and van der Veer et al. did not detect any differences in BMD values between those with and without fractures in their patients [9,31]. In our study, some patients suffered fractures with normal BMD values. In addition, Degboé et al. reported that around 48 % of SM patients who suffered from fractures did not have osteoporotic BMD values [8]. We also know from postmenopausal osteoporosis that most spinal fractures occur in patients with osteopenia [36]. We know from patients with Type 2 Diabetes mellitus that fractures occur with normal BMD, however bone structure and bone quality are impaired [37]. As a consequence, low BMD does not seem to be any prerequisite for osteoporotic fractures in ISM patients. In the future, analysis with methods for bone structure and bone quality analysis like peripheral HRpQCT [38],

finite elemente analysis, trabecular bone score or the 3D-shaper technology [39] might help to clarify possible changes in bone quality leading to fracture.

We also investigated bone formation and resorption markers indicating bone turnover. In addition, patients treated with anti-osteoporotic medication with bisphosphonates, teriparatide or denosumab were excluded from the analysis owing to the influence of treatment on bone turnover.

Guillaume et al. detected a significant correlation between BAP, DPD, and serum tryptase level, when different subtypes including AdvSM were analyzed within the patient group [40]. Rossini et al. reported increased, decreased, and normal bone marker levels of BAP in ISM [31]. However, patients suffering from osteosclerosis have increased bone turnover markers, as demonstrated by several authors [31,35]. We also found a positive correlation between bone turnover markers and BMD scores. As a result, it may be hypothesized that the significant correlation in the study of Guillaume et al. was caused by the inclusion of patients with other subtypes or patients with osteosclerotic bone [40].

Interestingly, tryptase levels also correlated positively with some BMD scores. We did not correct tryptase serum levels for hereditary alpha-tryptasemia (HαT) which might have given different results [41,42]. Data using bone marrow tryptase demonstrated a correlation to fragility fractures principally proving the importance of mast cell burden for the bone [30].

The ISM group with fractures had a tendency to present significantly more back pain. We supposed that this is caused most likely by the high proportion of multiple, vertebral fractures in this group. Remarkably however, also patients without vertebral fractures reported a high back pain burden and there was no correlation of the pain score to the number of individual fractures. In addition, joint, bone, and muscle pain comprise part of the list of symptoms reported for patients with ISM [43], hinting to the possibility that the pain in our patients with mastocytosis could exist independently of fractures.

Our study is limited by the retrospective design. It was not possible to compare clinical parameters to a control group representing the normal population. Half of our patients are young patients with fractures referred to our center for unexplained osteoporosis. Therefore, our data cannot be directly compared to study populations with different severity forms of systemic mastocytosis. In a number patients we ruled out any other factors responsible for fractures including a genetic analysis for early osteoporosis. However, we cannot exclude other parameter of ISM not investigated by us also contributing to the bone phenotype in these patients. The analysis of KIT-mutation in bone was evaluated according to the method used at the time of analysis, either by clamping PCR or Sanger Sequencing, and not quantitatively, as is currently the case since recently. In addition, some patients were treated with specific anti-osteoporotic medication, which clearly influences results on BMD and bone turnover. The number of untreated patients with bone formation and resorption markers was therefore small. Strengths of our study include its well-defined sample of ISM patients with affected bone and fractures in a very rare disease.

In summary, in the analysis for the pathogenesis of fractures in osteoporosis patients with ISM, the presence of the KIT-mutations in bone biopsies were of major importance. Patients with the KIT-mutation had a significantly greater number of fractures reflecting the severity with which the bone is affected. Fractures correlated with femoral bone BMD values and also occurred with normal or osteopenic BMD levels. The number of smokers were higher in ISM patients with fractures, suggesting an additional effect of smoking on fracture risk in ISM. However, no difference was seen in those with KIT-mutation, indicating a much stronger effect of KIT compared to smoking.

Neither serum tryptase levels nor the presence of skin lesions were indicators for vertebral or peripheral fractures in ISM patients. Skin lesions, however, seem to correlate with severity as determined by femoral, however not spine BMD. Our results broaden the risk factors for fractures in ISM by adding the factor of KIT-mutation in bone biopsies.

In conclusion, we identified the KIT-mutation in bone biopsies as relevant to the severity of osteoporosis on analysis of the osteoporosis patient subgroup with proven ISM with and without fractures. Our data are in contrast to other data in bone marrow aspirates of mastocytosis patients with different systemic forms reflecting the complex expression and regulation of KIT depending on cell maturation and cell lineage in bone. Our results suggest that MC patients without skin lesions, low BMD at the femur or spine, smoking and KIT-mutation in bone should be carefully controlled and treated for osteoporosis in a timely fashion.

Further studies will have to investigate whether the results in osteoporosis patients can be reproduced through the quantitative assessment of KIT D816V allele burden in bone and/or in peripheral blood and whether tryptase levels corrected for the presence of HαT better reflect the disease burden than the normal serum tryptase levels measured in this study.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2025.117578.

CRediT authorship contribution statement

Christof Wilke: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Martina Blaschke:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Annette Lamersdorf:** Data curation. **Christina Heppner:** Data curation. **Michael Metz:** Writing – review & editing, Data curation. **Hans-Peter Horny:** Writing – review & editing, Formal analysis. **Mathias Werner:** Writing – review & editing, Methodology, Data curation. **Undine Lippert:** Writing – review & editing, Supervision, Investigation, Conceptualization. **Heide Siggelkow:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare no conflicts of interest.

Acknowledgement

We thank A. Entwistle for his assistance with the English of this manuscript. This study was supported by Elsbeth-Bonhoff Foundation. We acknowledge support by the Open access publication funds of the Göttingen University.

Data availability

Data will be made available on request.

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