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HIV and multiple myeloma: do patients present at a younger age? A perspective from a South African orthopaedic oncology unit

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Abstract

Background

Multiple myeloma (MM) is the third most common haematological malignancy and the most common malignancy affecting the skeletal systems of the elderly. Skeletal-related events (SREs) such as hypercalcaemia, bone pain, spinal cord compression, and pathological fracture are common sequelae of multiple myeloma bone disease (MMBD) and are the reasons patients might consult an orthopaedic surgeon. It has been established that infection with the human immunodeficiency virus (HIV) increases one's risk of developing haematological malignancies. However, there is scant literature on how HIV infection affects MMBD, particularly from a South African perspective. We hypothesised that MMBD presents at a younger age and with more advanced disease in HIV-positive individuals.

Methods

A retrospective single-centre descriptive study was undertaken of patients with newly diagnosed MM presenting with SREs to an orthopaedic oncology unit between 1 January 2016 and 31 December 2020. Patient demographic data (e.g., age, race and sex), biochemical and histopathological results, and whole-body X-rays (WBXR) were collected for each participant.

Results

Twenty-seven patients were included. The median age at presentation was 56 years (interquartile range [IQR]: 49–47). Regarding HIV infection, 19% (n = 5) were HIV-positive, 45% (n = 12) were HIV-negative, and 37% (n = 10) had an unknown status due to absent screening. The age at presentation in HIV-positive patients was 44 years (IQR: 41–51); in HIV-negative patients, it was 58 years (IQR: 48–66). The difference in age at presentation between HIV-positive and HIV-negative patients was statistically significant, with a Kruskal-Wallis p-value of 0.041. Among HIV-positive patients, 60% (n = 3) presented with International Staging System (ISS) stage III disease, while 50% (n = 10) of HIV-negative patients presented with ISS stage II disease, with the Fisher's exact p-value = 0.836 indicating an insignificant difference. The presenting complaint was mainly a pathological fracture in 67% (n = 20), predominantly affecting the femur in 50% (n = 10).

Conclusion

The majority of MM patients present to the orthopaedic surgeon with pathological fractures and commonly have more advanced disease. In our setting, when treating a young HIV-infected individual with a pathological fracture, one should always consider MM as a likely diagnosis.

Level of evidence: 4

Keywords: multiple myeloma, myeloma bone disease, skeletal-related events, HIV, pathological fracture

Introduction

Multiple myeloma (MM) is a disorder of plasma cells, ranking as the third most common haematological malignancy and the most prevalent malignancy affecting the elderly.[1,2] MM arises from the neoplastic transformation of plasma cells or their precursors, leading to the production of light- and heavy-chain immunoglobulins, along with resulting end-organ damage, hypercalcaemia, renal dysfunction, anaemia, and bone pain (collectively referred to as CRAB). The outcomes lead to significant patient morbidity and a reduction in overall survival.[3]

Multiple myeloma bone disease (MMBD) is characterised by osteolytic bone lesions predominantly in the cancellous bone of the vertebral bodies, ribs, and the metaphysis of long bones. Osteolytic bone destruction occurs due to the accumulation of myeloma cells in the bone marrow microenvironment, which is responsible for MM's symptoms and systemic effects.[1-4] Myeloma cells disrupt the homeostasis of bone metabolism, leading to increased bone resorption by overactive osteoclasts, and reduced bone formation due to suppressed or inactive osteoblasts.[3,5] Of the patients with MMBD, approximately 50% will experience skeletal-related events (SREs), such as hypercalcemia, spinal cord compression, bone pain that necessitates radiation therapy or surgical intervention, and pathologic fractures.[3,4,6,7] Among individuals diagnosed with MM, approximately 20% experience pathological fractures, with 40% encountering such fractures within the initial year of diagnosis, and 60% experiencing them over their lifetime.[3] There is a 20–40% increase in mortality rate in MM patients who sustain a pathological fracture when compared to those without a pathological fracture.[3,4,6,8,9]

Risk factors for developing MM have been reported to include advanced age, male sex, and African descent.[1-4,9,10] According to the Statistics South Africa (StatsSA) Census 2022, 81% of the South African population in 2022 was of black African descent.[11] The demographics of MM have rarely been examined in sub-Saharan Africa, with findings from a South African study involving 146 MM patients showing a mean age of presentation of 58 years.[12] These findings were consistent with another continental finding in an Egyptian population, which had a mean age of presentation for MM of 58.5 years.[13] A noteworthy finding in the local-based study was a lower mean age of presentation (51 years) among human immunodeficiency virus (HIV)-positive patients, and a consistently higher incidence of MM in people of African descent.[12] According to the World Health Organization (WHO), 66% of the global population diagnosed with HIV or acquired immunodeficiency syndrome (AIDS) lives in Africa, with 30% of them residing in South Africa.[14,15] A meta-analysis on the incidence of cancer in immunocompromised patients, including those with HIV, demonstrated an increased prevalence of malignancy in these individuals. However, the pathophysiological mechanism is poorly understood.[16] This is consistent with the finding that immunodeficiency caused by HIV infection increases one's risk of developing a malignancy, including MM.[16-20]

Plasma cell dyscrasias encompass a spectrum of conditions, ranging from an asymptomatic premalignant increase in plasma cells known as monoclonal gammopathy of undetermined significance (MGUS), progressing to smouldering multiple myeloma (SMM), and culminating in malignant forms such as MM and plasma cell leukaemia.[2,3] The International Myeloma Working Group (IMWG) guidelines are used to diagnose and stage these conditions. They also offer treatment recommendations.[21,22] There is limited research on the epidemiology of MM and the impact of co-infection with HIV in the local population, particularly from an orthopaedic oncological perspective.

Methods

We conducted a retrospective single-centre descriptive study of patients with newly diagnosed multiple myeloma (NDMM) who presented with SREs to an orthopaedic oncology unit between 1 January 2016 and 31 December 2020. The study aimed to identify the clinicopathological and radiological characteristics of patients with NDMM. Furthermore, the study aimed to 1) determine the demographics of patients presenting with MM, 2) identify the clinical and laboratory characteristics of patients presenting with MM, 3) outline the radiological presentation of MM, and 4) describe any differences in the presentation of MM between HIV-negative and HIV-positive patients. Our study hypothesised that MMBD presents at a younger age and with more advanced disease in HIV-positive patients.

Of the 39 patients who presented with NDMM during the study period, 31% (n = 12) were excluded due to incomplete data, and 69% (n = 27) had sufficient medical records and were included in the study analysis. Patient demographic data (e.g., age, race and sex), biochemical and histopathological results, and whole-body X-rays (WBXR) were collected for each case. The principal investigator entered all data into a Microsoft Excel spreadsheet.

Inclusion criteria were all individuals aged 18 years and above who received a new diagnosis of MM; and patients newly diagnosed with MM confirmed and presenting with an SRE to the Orthopaedic Tumour and Sepsis Unit. Criteria resulting in exclusion were those individuals diagnosed with MGUS and SMM; those with solitary plasmacytoma; and anyone with inadequate medical records.

Data analysis

The data was transferred to Stata version 17 for interpretation. To establish the demographics of patients presenting with MMBD, continuous data, age and normality were evaluated using the Shapiro-Wilk test and histogram plots. Since the data was not normally distributed, the median, interquartile range (IQR), was used. Categorical variables were summarised using frequencies and percentages. A pie chart was used to give a pictorial view of sex distribution. Frequencies and percentages were used to establish the presenting features of the individuals presenting with MMBD, and the results were presented in a table. Frequencies and percentages were used to establish the radiological presentation of MMBD, and the results were reported using pie/bar charts and tables. Frequencies and percentages were used to describe the differences in the International Staging System (ISS) stage and age by HIV infection. The Fisher's exact test was conducted to establish the significance between HIV infection and the ISS stage. In contrast, the Kruskal-Wallis test was used to compare the median age differences by ISS stage. Significance was set at 5%.

Results

One hundred per cent (n = 27) of the cohort were Africans. The median age was 56 years (IQR: 49–67). The age distribution is depicted in *Figure 1*. The age range spanned from 23 to 77 years. Sixty-seven per cent (n = 18) of the cohort were female, and 33% (n = 9) were male. The female-to-male ratio was 2:1. *Figure 2* illustrates the sex distribution of the patients. *Table I* outlines the clinical characteristics of the patients at presentation. Most patients, 74% (n = 20), presented with a pathological fracture, while 26% (n = 7) had an impending fracture at presentation. The ISS stage at presentation was as follows: 44% (n = 12) had

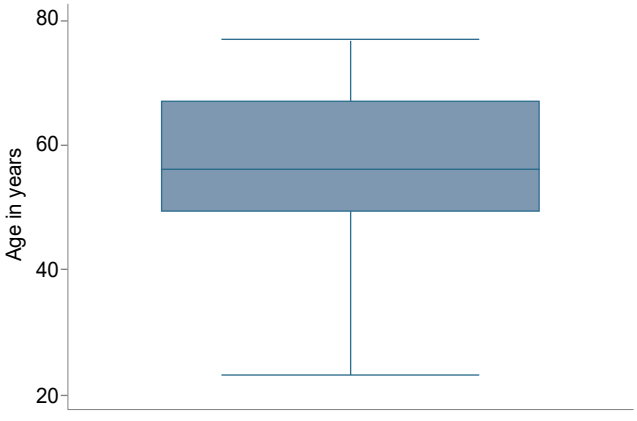


Figure 1. Age distribution

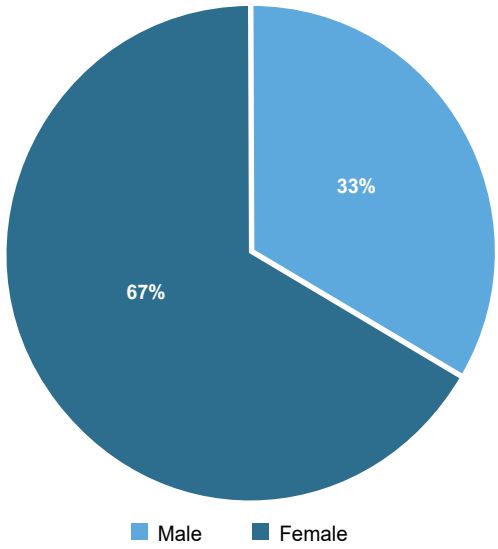


Figure 2. Sex distribution

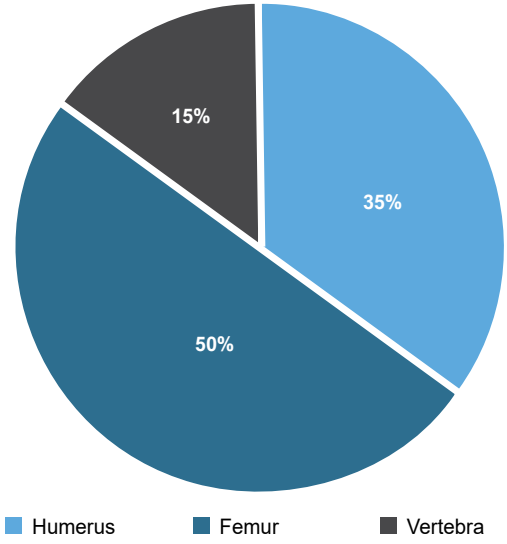


Figure 3. Pathological fracture site

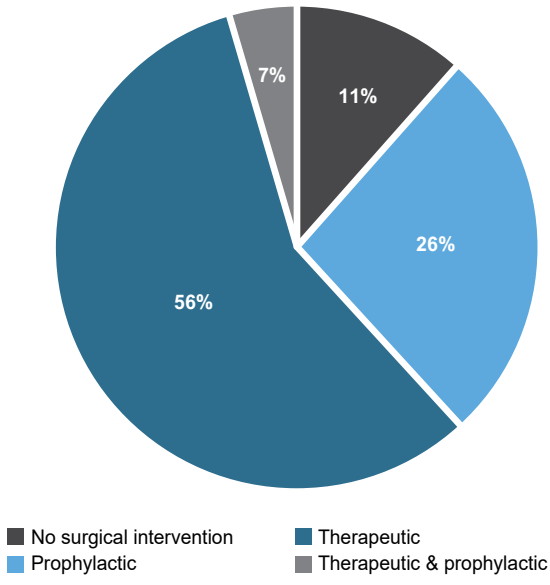


Figure 4. Indication for surgery

stage III disease, 41% (n = 11) had stage II disease, and 15% (n = 4) had stage I disease. The ISS stages of MM are as follows: ISS stage I (serum -2 microglobulin level 3.5 mg/L and serum albumin level 3.5 g/dL), ISS stage II (NOT ISS I or III) and ISS stage III (serum -2 microglobulin 5.5 mg/L).

Figure 3 illustrates the distribution of fracture sites among patients with pathological fractures. Fifty per cent (n = 10) had a femur fracture, 35% (n = 7) had a humerus fracture, and 15% (n = 3) had a spinal vertebra fracture. *Table II* displays the fracture side, and the anatomical bone segment categorised by the fracture site. Sixty per cent (n = 6) of the pathological femur fractures were right-sided, and 40% (n = 4) were left-sided. Furthermore, 40% (n = 4) of the pathological femur fractures were diaphyseal, while 30% (n = 3) were located at the neck of the femur, and another 30% (n = 3) were peritrochanteric. Regarding humerus fractures, 57% (n = 4) occurred on the right side, 29% (n = 2) on the left side, and 14% (n = 1) represented cases with bilateral fractures. Seventy-one per cent (n = 5) of the humeral fractures were diaphyseal, while 29% (n = 2) were situated at the proximal end of the humerus. Of the patients with vertebral body fractures, 100% (n = 3) were in the thoracic spine.

Figure 4 illustrates the indications for surgical treatment in patients diagnosed with MMBD. Fifty-six per cent (n = 15) underwent therapeutic surgical treatment, 26% (n = 7) received prophylactic surgical treatment, and 7% (n = 2) obtained both prophylactic and therapeutic treatments. These patients presented with a

Table I: Clinical features at presentation

Variable	Frequency	Percentage (%)
Pathological fracture		
No	7	26
Yes	20	74
ISS stage		
I	4	15
II	11	41
III	12	44

ISS: International Staging System

Table II: Pathological fracture side and bone segment

Variable	Femur n = 10 (%)	Humerus n = 7 (%)	Vertebra n = 3 (%)
Side			
Left	4	2	0
Right	6	4	0
Bilateral	0	1	0
Spine	0	0	3
Segment			
Diaphyseal	4	5	0
Neck of femur	3	0	0
Peritrochanteric	3	0	0
Proximal	0	2	0
Thoracic	0	0	3

Table III: Association between HIV status and ISS stage

HIV status	ISS stage			Total
	I	II	III	
Negative	2	6	4	12
Positive	1	1	3	5
Unknown	1	4	5	10
Total	4	11	12	27

HIV: human immunodeficiency virus; ISS: International Staging System

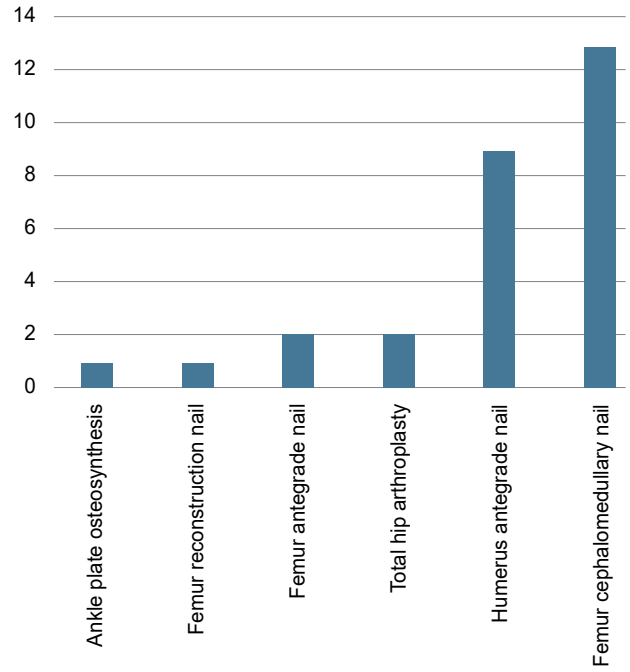


Figure 5. Surgical procedures performed

pathological fracture and an impending fracture of another bone. Eleven per cent (n = 3) did not have any surgical intervention. Of the 24 patients who underwent surgery, 28 surgical procedures were conducted. *Figure 5* illustrates the surgical procedures performed on the 28 extremities. Forty-six per cent (n = 13) received a femoral cephalomedullary nail, 32% (n = 9) received an antegrade humeral intramedullary nail, 7% (n = 2) received an antegrade femoral nail, 7% (n = 2) underwent primary total hip arthroplasty, 4% (n = 1) received a femoral reconstruction nail, and 4% (n = 1) received an ankle plate osteosynthesis.

Figure 6 illustrates the HIV status of the patients. Nineteen per cent (n = 5) were HIV-positive, while 44% (n = 12) were HIV-negative. The HIV status remained unknown for 37% (n = 10) of the patients as screening was not conducted. *Table III* outlines the relationship between the ISS stage and HIV status. Most HIV-positive individuals were found to have ISS stage III disease, while the majority of HIV-negative individuals presented with ISS stage II disease. However, there was no significant association between the ISS stage and HIV infection, as indicated by Fisher's exact p-value of 0.836. *Table IV* illustrates the difference in age at presentation based on HIV status. The HIV-infected patients had a median age of 44 years (IQR: 41–51), making them the youngest group. In contrast, the HIV-uninfected patients had a median age of 58 years (IQR: 48–66), indicating they were older on average. A significant age discrepancy existed between the groups, with a Kruskal-Wallis p-value of 0.041.

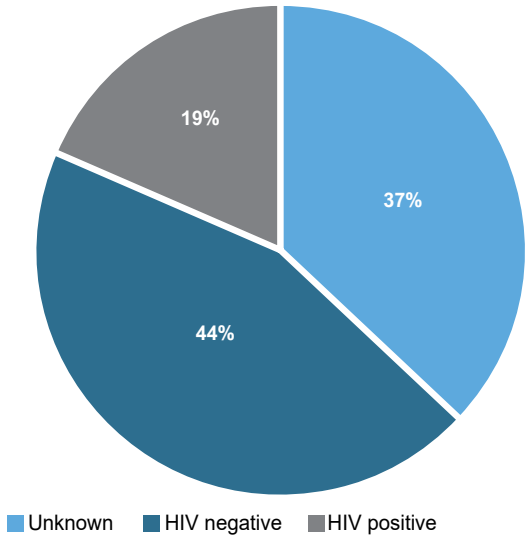


Figure 6. HIV status

Table IV: Age differences between patients by HIV status

HIV status	Mean	SD	Median	p25	p75
Negative	56	13.91	57.5	48	66
Positive	44	13.74	44	41	51
Unknown	63	9.06	61	56	70
Total	56	13.61	56	49	67

p: percentile

Discussion

Of the 27 patients who presented with MMBD, 19% (n = 5) were HIV-infected, compared to 44% (n = 12) who were HIV non-infected (*Figure 6*). When comparing these groups, variation was observed in the severity of disease at presentation. Sixty per cent of the HIV-infected population presented with ISS stage III disease. In comparison, half (50%) of the HIV non-infected population presented with less severe disease – ISS stage II (*Table III*). This was not a statistically significant difference in our study, and further investigation is needed to determine whether the HIV-infected population presents with more advanced disease.

However, a statistically significant finding between the two groups was age at presentation, with the HIV-infected population presenting at a younger age, namely 44 years (IQR: 41–51), compared to their non-infected counterparts who presented at 58 years (IQR: 48–66) (*Table IV*). Kimani et al. support the finding of a lower median age of MM presentation in HIV-positive populations.[17] The median age at presentation was 56 years (IQR: 49–67) (*Figure 1*). This aligns with the continental findings of de Groot et al. and El Husseiny et al., which indicate a mean age of 58 years.[12,13] The HIV-positive population not only has a higher incidence of haematological malignancies, including MM, but also a lower mean age of presentation.[16-18,20]

All the patients analysed were Africans, which underrepresents the other racial groups present in South Africa. According to the Statistics South Africa 2022 census, the composition of the unrepresented racial groups is Coloured (8%), White (7%), Indian/Asian (3%), and Other (0.4%).[11] Potential contributing factors to this finding include the high exclusion rate of eligible patients, at 31%, and the racialised nature of poverty and unemployment levels in South Africa, which results in a disproportionately higher number of Africans seeking healthcare in the public health sector services.[23] This may also reflect the demographics of the drainage areas served by the treating service. However, this aligns with the established risk factor of African descent for the development of MM.[1-3,24,25]

An unexpected demographic finding was a 2:1 female-to-male ratio (*Figure 2*), which is contrary to the reported risk factor, male sex, for the development of MM.[26] Possible explanations for finding more females than males presenting with SREs include that females have a lower peak bone mass than males, sex differences in bone mineral density (BMD) in older populations, and women having a lower BMD than their age-matched male counterparts. Moreover, postmenopausal women experience a faster decline in bone integrity than men of a similar age, whose rate of decline is slower.[27-29] This suggests that, in our study, the median female is

Table V: Mirels scoring system[37]

Variable	Score		
	1	2	3
Site	Upper limb	Lower limb	Pertrochanter
Pain	Mild	Moderate	Functional
Lesion	Blastic	Mixed	Lytic
Size	< 1/3	1/3–2/3	> 2/3

likely to have inferior bone quality when myeloma bone disease begins, relative to the median male. This may explain why women made up the majority of patients who experienced SREs. An alternative explanation for this variation could be the lack of cancer awareness among South African men and the difference in health-seeking behaviour among black men and women.[30-32]

SREs, complications arising from MM, and bone metastases from solid tumours, result in diminished quality of life, increased pain, and reduced overall survival.[33] They also place a significant economic strain on the public purse due to the rise in annual inpatient admissions, emergency visits, doctor consultations, laboratory services, and outpatient services. As a result, patients with SREs face considerably higher overall medical costs than those without.[34]

The first clinical staging system for MM was introduced by Durie and Salmon in 1975. This system consists of three stages: accurately determining myeloma tumour burden, and predicting treatment response and prognosis. Their staging system included the biochemical and radiological findings most significantly correlated with myeloma cell mass. This included serum haemoglobin, creatinine and calcium levels, serum and urine monoclonal immunoglobulins (M-component), and the extent of bone lesions.[35] Recently, the IMWG updated the ISS to the Revised International Staging System (R-ISS) for MM prognostication, appropriate for patients newly diagnosed with MM. It incorporates chromosomal abnormalities (CA) determined through interphase fluorescent in situ hybridisation and serum lactate dehydrogenase (LDH) levels alongside the original elements of the ISS staging system, which comprises serum beta-2-microglobulin and albumin levels.[21] However, CA was not routinely tested at our centre during the study period; therefore, the original ISS was used to stage the NDMM patients. As shown in *Table I*, most patients, 44% (n = 12) who presented with SREs had ISS stage III disease, 41% (n = 11) had stage II disease, and 15% (n = 4) had stage I disease. Our cohort exhibited more advanced disease than the 370 NDMM patients studied by Kanellias et al.[9]

Figure 1 outlines the SREs responsible for hospital admissions. Pathological and impending fractures accounted for 74% (n = 20) and 26% (n = 7) of admissions, respectively. *Figure 3* depicts the patients who experienced a pathological fracture (n = 20): 50% (n = 10) had femoral fractures, 35% (n = 7) had humeral fractures, and 15% (n = 3) had spinal fractures.

In the study by Kanellias et al., pathological fractures were mainly of the spine and ribs.[9] Surgery was performed on 88% (n = 24) of the patients, and a total of n = 28 extremities. *Figure 4* illustrates the indications for the surgical procedures performed, where 56% (n = 15) were therapeutic, 26% (n = 7) were prophylactic, and 7% (n = 2) had both prophylactic and therapeutic surgeries conducted. The decision to undertake prophylactic surgical intervention for impending pathological fractures is challenging but crucial, as a pathological fracture is a poor predictor of survival outcomes.[4,22] However, no consensus exists on the best criteria for diagnosing impending fractures.[36] Prophylactic surgery is less technically demanding and assists in maintaining the patient's functionality status. Our clinical unit employs Mirels' scoring system (*Table V*) to identify which patients need prophylactic surgery. However, we acknowledge the limitations of Mirels' scoring system, including its subjectivity, the lack of consideration for the underlying tumour type, and the fact that it exhibits fair-to-moderate interobserver variability yet demonstrates better intra-observer consistency.[37,38]

Of those who presented with fractures, the distribution of the fractures by anatomical bone segment (*Table II*) was as follows: of the n = 10 femur fractures, 40% (n = 4) were diaphyseal, 30% (n = 3) were of the neck of the femur, and 30% (n = 3) were in the peritrochanteric region. Of the n = 7 humerus fractures, 71% (n = 5) were diaphyseal, while 29% (n = 2) were of the proximal humerus. All (n = 3) vertebral fractures involved the thoracic spine. The higher incidence of pathological fractures in the extremities than in the axial skeleton is likely due to selection bias. Patients with spinal pathology are typically managed by either the orthopaedic spine unit or the neurosurgery division. The 11% (n = 3) of patients who presented with spine fractures and did not undergo surgery with the Tumour and Sepsis Unit were ultimately referred to the Orthopaedic Spine Unit for further management.

Figure 5 illustrates the surgical procedures performed. Forty-six per cent (n = 13) of the pathological femur fractures were treated with a femoral cephalomedullary nail, 7% (n = 2) with an antegrade femur nail, 7% (n = 2) with primary total hip arthroplasty and 4% (n = 1) with a femur reconstruction nail. All (n = 7) of the humerus fractures were addressed with an antegrade humeral nail. The single patient who presented with an ankle fracture, a rarity in MM, was treated with a plate osteosynthesis.[39]

Conclusion

MMBD is the most common malignant bone neoplasm affecting the elderly population, leading to considerable morbidity and putting significant pressure on healthcare resources. Most MM patients visit the orthopaedic surgeon with pathological fractures, making screening for impending fractures essential. Patients presenting with SREs often have more advanced ISS-stage disease and a worse prognosis. Further research is needed to understand the real impact of HIV on MM, especially considering the small sample size (n = 27) and the significant percentage of patients with an unknown HIV status (37%) in our study.

Finally, in our context, when treating a young HIV-infected patient who presents with a pathological fracture, one must always consider MM as a probable diagnosis.

Ethics statement

The authors declare that this submission is in accordance with the principles laid down by the Responsible Research Publication Position Statements as developed at the 2nd World Conference on Research Integrity in Singapore, 2010.
Before initiating the study, ethical clearance was obtained from the Human Research Ethics Committee (Medical) at the University of the Witwatersrand, under reference number M181184. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed written consent was not obtained from all patients for being included in this retrospective study.

Declaration

The authors declare authorship of this article and that they have followed sound scientific research practice. This research is original and does not transgress plagiarism policies.

Author contributions

OP: study conceptualisation, data capture, data analysis, manuscript preparation, revision and approval of final manuscript
TVN: manuscript revision and approval of final manuscript
PMK: study conceptualisation, manuscript revision and approval of final manuscript
ZL: study conceptualisation and approval of final manuscript

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