Attributes of Pathological Fractures in a Nigerian myeloma cohort

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Abstract

Multiple Myeloma (MM) is a plasma cell tumor usually characterized by lytic bone lesions. Pathological Fracture (PF) is a debilitating condition that usually affects a patient's psychomotor functions, treatment modality, morbidity, and outcome. We evaluated the associations, characteristics, and impact of PF on survival in a group of Nigerian myeloma cohort. A 10-year (2011-2021) retrospective review of MM data from Nigerian tertiary hospital haemato-oncology unit to evaluate attributes of PFs in myeloma cohort. Sixty-six patients had MM of which 23 had PF while forty-three had no fractures. Of the number with PF, 18 had lytic bone lesions, while 20 had bone pains. Monoclonal Immunoglobulin G was predominant followed by Immunoglobulin A. Significant correlations existed between hemoglobin level (r=0.446, p=0.002); platelet count (r=-0.347, p=0.041), serum calcium (r=0.471, p=0.006) and bone pains; as well as between urea level (r=-0.787, p=001), creatinine level (r=-0.853, p=0.001) and renal impairment respectively. PFs are associated with diabetes, peptic ulcer disease, hypertension, nephropathy, and arthritis. Bortezomib-based regimen was the choice treatment. Overall survival was 16 (69.6%) with 7 (30.4%) mortality. PF is common amongst the myeloma cohort with the spine being the most common site. It is associated with significant comorbidities like hypertension, diabetes, peptic ulcer disease, and paraplegia and is characterized by severe debilitating bone pains, anemia, hypercalcemia, raised plasma monoclonal immunoglobulin, renal impairment, loss of man-hour at work, and psychosocial imbalance. The impact of the fracture has increased morbidity and mortality and has reduced the median survival duration to as low as 4 years.

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Introduction

Multiple Myeloma (MM) is a malignancy of clonal plasma cells and these plasma cells originate from post-germinal center B-lymphoid cells.[1] MM is a disease that affects the older age group and it is noted to be the second most common hematological malignancy after lymphomas.[2,3]

Myeloma bone disease frequently occurs in MM patients and it is noted to be present in about 66% of the patient at presentation while virtually all the patient has it during the course of the disease.[4] Pathological Fracture (PF) is one of the several forms of presentation of myeloma bone disease.[5] Other forms of presentation include bone pains, spinal cord compression, and hypercalcemia.[6]

Bone remodeling is a dynamic process in adults needed to keep the bone healthy and to have the ability to sustain mechanical load. Under physiologic conditions, this process is achieved by a delicate balance between bone resorption mediated by osteoclasts and bone formation mediated by osteoblasts.[7] This process is uncoupled in myeloma bone disease following the binding of the malignant plasma cells to the bone marrow matrix with resultant increased osteoclastic activity and reduced or absent osteoblastic activity.[8] Upon binding of the malignant plasma cells to the bone marrow stromal cell, there is a release of osteoclast activation factors like interleukin-6, interleukin 1β, tumor necrosis factor-α, and macrophage inhibitory factor 1-α.[9] These osteoclast activating fac-

tors work through the Receptor Activator of Nuclear Kappa β (RANK), Receptor Activator of Nuclear Kappa β Ligand (RANKL) and Osteoprotegerin (OPG) pathway.[9] Osteoclasts express RANK which needs to be bound unto by RANKL expressed on bone marrow stromal cells to effect osteoclast activation.[10] On the flip side, OPG produced by bone marrow stromal cells also binds to RANK and inhibits osteoclast activation as such limiting osteoclastogenesis.[10] In MM, the ratio of RANKL to OPG is skewed in favor of RANKL, and the more the skewing towards RANKL, the more the prognosis is impacted negatively.[11,12] The essence of this work therefore is to assess the overall impact of PF in MM patients in our center.

This imbalance explained above in association with treatment-related factors like the use of steroids is responsible for the PF seen in MM.[13] PF in MM as well as in other malignant conditions have been shown to negatively affect outcome.[14] Specifically for MM, PF significantly increases the risk of mortality.[15]

The Durie-Salmon Staging System[16] is used to calculate the stage of myeloma by measuring parameters like hemoglobin concentration, serum calcium level, and the presence of bone lesions on imaging studies to determine the extent of the myeloma. Also calculated is the amount of the M protein in the blood and urine as well as the status of kidney function.

Materials and Methods

This was a 10-year retrospective review of MM data from the Nigerian tertiary hospital, the University of Nigeria Teaching Hospital (UNTH) Ituku-Ozalla Enugu haemato-oncology unit. The data was collected over a period of 10 years, between July 2011 and July 2021 from case notes of patients diagnosed with MM.

Ethical approval was obtained from the University of Nigeria Teaching Hospital (UNTH) Health Research Ethical Committee with reference number NHREC/05/01/2008B-FWA00002458-1RB00002323.

The data collected was analyzed using Statistical Package for Social Sciences (SPSS) software version 25.0 (SPSS Inc., Chicago, IL, USA) and expressed in tables and figures. Descriptive statistics was used to compute proportions and percentages, and to summarize categorical and continuous variables. Pearson correlation analysis and Mann-Whitney test were used to test for the relationship between variables and significance was set at $p<0.05$.

Results

Of the 66 patients (37 males & 29 females), 23 (34.8%) had PF out of which 12 (52.2%) were males (M) and 11 (47.8%) females (F), with M:F of 1.1:1 while 43(65.2%) had no fractures, as shown in Tables 1, 2 and 3. Their age ranged from 35 to 89 with a mean of 58.7±8.2 years. Out of the 23 with PF, 18(78.3%) had lytic bone lesions while 20 (95.2%) had bone pains.

Of the 23 PF observed in this study, 20 were located in the axial skeleton while 3 involved other skeletal sites as shown in Table 4. None of the cohort developed fractures after diagnosis and during treatment.

Erythrocyte Sedimentation Rate (ESR) was >150mm/1st hr in 11(47.8%) patients. Nineteen (82.6%) had Bence Jones proteinuria. Twenty-one (91.3%) had monoclonal protein. Immunoglobulin G 12(52.2%) was predominant followed by Immunoglobulin A 5(21.7%). The Durie-Salmon Staging System[16] was used as shown in Table 5. Of the 66 patients, 50 (76%) were in stage III while 16 (24%) were either in stage I or II. Among those that had PF, there were significant correlations between hemoglobin level (r=0.446, p=0.002); platelet count (r=-0.347, p=0.041), serum calcium (r=0.471, p=0.006), and bone pains. Significant correlations were also observed between urea level (r=-0.787, p=001), creatinine level (r=-0.853, p=0.001), and renal impairment respectively.

Of the 66 cohort, 51 (77.3%) were alive while 15 (22.7%) died in the course of treatment and the parameters recorded in them were the last measurement made before their demise. A test of significance difference in the chosen parameters among the cohort showed that there was a significant difference in serum levels of protein in g/L (U=135.0, p=0.0002) and albumin in g/L (U=239.0, p=0.0280), whereas there was no significant difference in age in years (U=297.5, p=0.1956), sex, Hb in g/dL (U=300.5, p=0.2117), ESR in mm/1st hr (U=295.5, p=0.1333), leucocyte count in 10^9/L (U=374.5, p=0.9086) and calcium in mg/dL (U=323.0, p=0.3641) respectively, as shown in Figures 1-6.

Myeloma PF is associated with diabetes (75%), peptic ulcer disease (75%), hypertension (85%), nephropathy (65%), and arthritis (55%) as observed in 23 (100%) patients that had PF in the cohort.

Bisphosphonate-like zoledronic acid was administered to all the 66 (100%) myeloma patients studied, while 22 (96%) of those that had PF had significant improvement in their bone health fol-

Table 1. Sex distribution of the myeloma cohort.

Gender	Frequency	Percentage (%)
Male	37	56.1
Female	29	43.9
Tota	66	100

Table 2. Age distribution of the myeloma cohort.

Age range (years)	Frequency	Percentage (%)
35-45	7	10.6
46-56	14	21.2
57-67	33	50.0
68-78	9	13.6
79-89	3	4.6
Total	66	100

Table 3. Age distribution of the myeloma cohort.

Pathologic fracture	Frequency	Percentage (%)
Yes	23	34.8
No	43	65.2
Total	66	100

Table 4. Distribution of pathological fractures based on skeletal site.

Skeletal site	Frequency	Percentage (%)
Axial skeleton Skull vertebrae (2) Thoracic vertebrae (10) Lumbar vertebrae (8)	20	87.0
Femoral & trochanter	3	13.0
Total	23	100

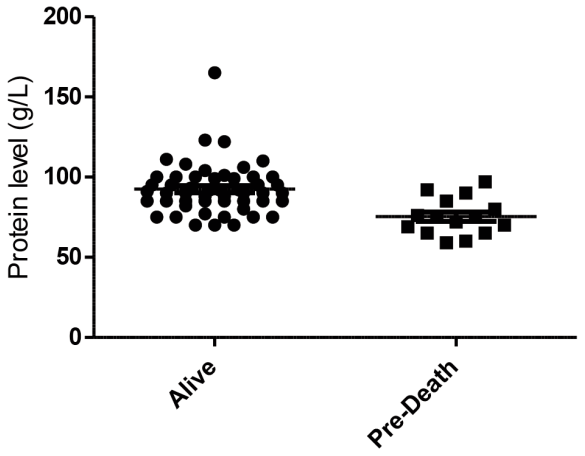

Figure 1. Scatter plot showing the distribution of last measured serum protein in the 15 patients before death (median protein =75, Interquartile Range, IQR: 65-85) and 51 (median protein =90, IQR: 85-100) alive myeloma cohort.

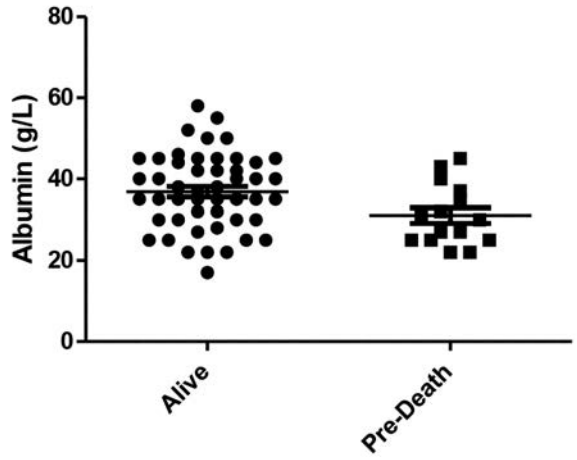

Figure 2. Scatter plot showing the distribution of last measured serum albumin in the 15 pre-death state (median albumin =30, Interquartile Range, IQR: 25-37) and 51 alive (median albumin =35, IQR: 30-44) myeloma cohort.

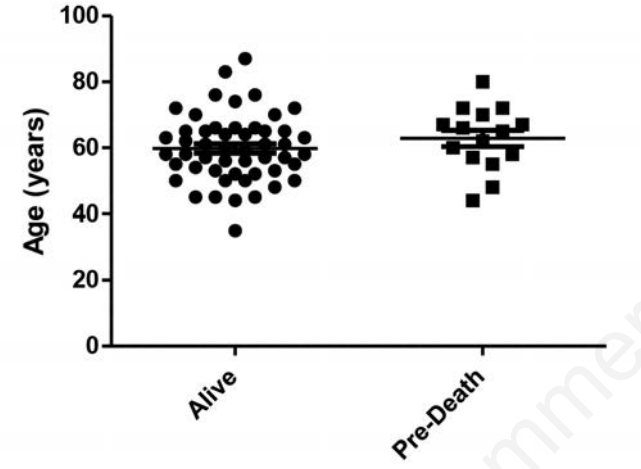

Figure 3. Scatter plot showing the last age distribution in years recorded in the 15 patients before death (median age =65, Interquartile Range, IQR: 57-70) and 51 alive (median age =59, IQR:53-65) myeloma cohort.

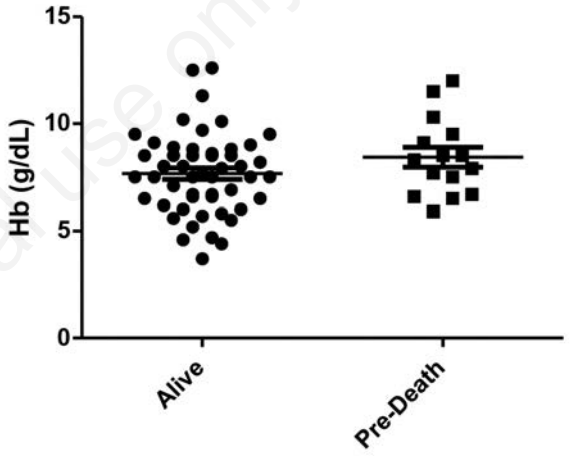

Figure 4. Scatter plot showing the last measured Hemoglobin (Hb) (g/dL) recorded in the 15 patients before death (median Hb =8.3, Interquartile Range, IQR: 6.7-9.5) and 51 alive (median Hb =7.5, IQR: 6.5-8.8) myeloma cohort.

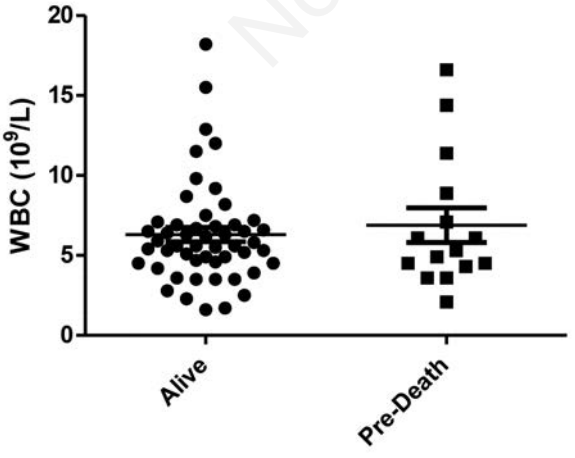

Figure 5. Scatter plot showing the last measured White Blood Cells (WBC) (109/L) recorded in the 15 patients before death (median WBC =5.3, Interquartile Range, IQR: 4.3-8.9) and 51 alive (median WBC =5.6, IQR: 4.5-6.9) myeloma cohort.

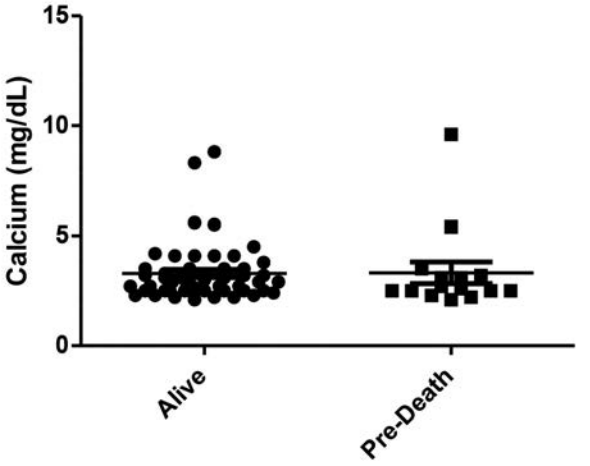

Figure 6. Scatter plot showing the last measured Hemoglobin (Hb) (g/dL) recorded in the 15 patients before death (median Hb =8.3, Interquartile Range, IQR: 6.7-9.5) and 51 alive (median Hb =7.5, IQR: 6.5-8.8) myeloma cohort.

lowing such treatment (r=205, p=0.0001). Bortezomib-based regimen was the choice treatment and 55 (83.3%) patients were treated with it while 11 (16.7%) were placed on other regimens like Cyclophosphamide, Vincristine, Cytosine Arabinoside, and Prednisolone (CVAP); lenalidomide and dexamethasone.

The values of the last total serum protein measured in the 66 cohort before death (15) and in those that were alive (51) showed a significant difference (U=135.0, p=0.0002).

The values of last serum albumin in the 66 cohort before death (15) and in those that were alive (51) showed a significant difference (U=239.0, p=0.0280).

The age distribution of the 66 cohort before death (15) and in those that were alive (51) showed no significant difference (U=297.5, p=0.1956).

The Hemoglobin (Hb) distribution of the 66 cohort, before death (15) and in those that were alive (51) showed no significant difference (U=300.5, p=0.2117).

The total WBC distribution of the 66 cohort, before death (15) and in those that were alive (51) showed no significant difference (U=374.5, p=0.9086).

The serum calcium distribution of the 66 cohort, before death (15) and in those that were alive (51) showed no significant difference (U=323.0, p=0.3641).

The overall survival amongst the myeloma cohort was 51 (77%) with 15 (23%) being mortality. Among the 23 patients that had PF in the cohort, 16 (69.6%) survived while 7 (30.4%) died in the course of treatment.

The median survival duration amongst the dead patients was 4 years depending on the stage of the disease at which the diagnosis was made.

Discussion

PF is a key clinical presentation in MM as it determines survival and adversely impacts the course of the disease. Our work showed that at the time of diagnosis, a smaller number of patients with MM had developed PF. This is in keeping with a work nationwide study done in Sweden though the percentage of patients with PF was slightly less than our own finding.[17] However, a multi-center study done in Nigeria still showed a smaller number of MM patients with PF at the point of diagnosis but this figure is way higher than what we discovered in our own center-based study.[18] Compared to the Western world, the reason why we may have a greater number of PF at the point of diagnosis may be explained from the standpoint of poor human and material resources which would ultimately delay the chances of picking the disease at a fairly early stage.[19] As such, a diagnosis of MM is delayed since patients are moved around several health facilities because of the other presenting features like renal impairment, and bone pains.[19]

Concerning bone pain, it was found to be the major clinical feature amongst MM patients that had PF. Bone pain has been reported by many studies as a common clinical feature amongst MM patients[18,20] so it is not surprising that virtually all MM patients with PF in this study presented with bone pains. Various mechanisms like skeletal damage, neuropathy, intraosseous pressure, and acidity of marrow have been put forward as the pathologic basis for bone pain seen in myeloma.[21] Based on the aforementioned, it is not surprising that bone pain is a very common presentation in our study as we found a large proportion of the study group had lytic lesions at the point of presentation to our facility.

The axial skeleton appears to be the most common site of PF in this study showing the spine as the most common and then with involvement of the pelvis and the ribs. This pattern is in keeping with other works that looked at sites of PF which puts the spine, especially the lower thoracic and lumber vertebrae as the commonest site for PF.[22,23] PF in MM has a predilection for the axial skeleton especially the spine because the axial skeleton is the site to which is still involved in active hemopoiesis. Vertebral fracture remarkably increases mortality, especially in older MM patients. This increased mortality may be affected by several situations like loss of mobility with functional dependence, increased risk of venous thromboembolism, and high chances of surgical intervention with attendant risks.[15,23,24]

A very interesting finding from this work is the fact that the development of PF is associated with comorbidities like diabetes, hypertension, peptic ulcer disease, and arthritis.[25] This is due to the frequent use of high-dose steroids (up to 40 mg per day) in our myeloma cohort. Steroid forms the basis of most lymphoid malignancy treatments, especially with their attendant lympholytic properties.[26,27] Apart from hypertension and diabetes, other comorbidities reported to be associated with PF in MM include osteoporosis, and chronic obstructive airway disease.[22,23] Diabetes and chronic obstructive airway disease have been noted to reduce trabecular bone density in females as a result of decreased collagen cross-linking.[23,27] However, caution needs to be exercised with this kind of finding as it may be a chance finding since no concrete physiologic relationship can establish a link between PF in MM and such comorbidities. Limitations of this study include the low sample size which will not permit a concrete generalizability of findings, and financial constraints which have limited the number of investigations and molecular studies that could have been done to strongly support the findings observed in this study.

We recommend further studies on PF in MM patients that will be more robust, sufficiently powered, and using a large sample size such that a number of unanswered questions that will influence health policy will be addressed.

Conclusions

PF is very common amongst the myeloma cohort with the spine being the commonest site as shown in this study. It is associated with significant comorbidities like hypertension, diabetes, peptic ulcer disease, and paraplegia. It is characterized by severe debilitating bone pains, anemia, hypercalcemia, raised plasma monoclonal immunoglobulin, renal impairment, loss of man-hours at work, and psychosocial imbalance. The impact of the fracture has increased the morbidity and mortality of the affected patients and has reduced the median survival duration to as low as 4 years.

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