CLINICO-PATHOLOGICAL PROFILE AND TREATMENT OF MULTIPLE MYELOMA AT KENYATTA NATIONAL HOSPITAL

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DECLARATION

This research proposal is my own original work and has not been presented for a degree at any other University.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ASCT	Autologous stem cell transplantation
BMA	Bone Marrow Aspirate
CA	Chromosomal abnormality
CD	Cluster of differentiation
CDKN2A	Cyclin-dependent kinase 2 inhibitor A
CDKN2C	Cyclin-dependent kinase 2 inhibitor C
DKK-1	Dickhof 1
DNA	Deoxyribonucleic acid
FDG-PET	Fluorodeoxyglucose-positron emission tomography
FGFR3	Fibroblast growth factor receptor 3
FISH	Fluorescence in situ hybridization
HDAC	Histone deacetylase
IARC	International Agency for Research on Cancer
ICD	International statistical classification of diseases
iFISH	Interphase fluorescent in situ hybridization
Ig	Immunoglobulin
IL-6	Interleukin-6
IMIDs	Immunomodulatory imide drugs
IMWG	International Myeloma Working Group
ISS	International staging system
KNH	Kenyatta National Hospital
LDH	Lactate dehydrogenase
LMIC	Low and middle income countries
MDE	Myeloma defining event
MDRD	Modification of diet in renal disease
MGUS	Monoclonal gammopathy of uncertain significance
MM	Multiple Myeloma
MMSET	Multiple Myeloma set domain

MP	Melphalan and prednisone
M-protein	Monoclonal protein
MPT	Melphalan, prednisone and thalidomide
MRI	Magnetic resonance imaging
NF-κB	Nuclear factor κB
NHIF	National Hospital Insurance Fund
NSAIDS	Non-steroidal anti-inflammatory drugs
PI	Proteasome Inhibitors
POEMS	Polyneuropathy, endocrinopathy, monoclonal plasma cells disease and skin changes
TP53	Tumour protein p53
UoN	University of Nairobi
VEGF	Vascular endothelial growth factor
WHO	World Health Organisation

ABSTRACT

Background

Multiple Myeloma (MM) is a chronic B-cell malignancy that involves proliferation of neoplastic clonal plasma cell in the bone marrow with circulating monoclonal immunoglobulins or constituent chains in serum and urine. It is a rare cancer with a lifetime risk of 0.76% and an age-adjusted incidence rate of 2.5-7.2 per 100,000 in high-income countries. There is a paucity of local data on the morbidity of MM.

Study Objective

To describe the pathological and clinical features, including myeloma defining events, and treatment of MM patients seen at KNH between 2014 and 2018.

Methods

This was a single centre descriptive retrospective study conducted at the medical records department at KNH. The study population included patients with a documented diagnosis of MM managed as an outpatient or inpatient between 1st January 2014 and 31st December 2018. Demographic data, pathology reports, laboratory results and clinical findings were transcribed and uploaded to a database.

Data Analysis

Analysis was done using Stata 16® software. Exploratory data analysis was done to identify missing values, check the skewness and normality of the data and to check significant associations. A multivariable cox regression model was used to test the association between presence of anaemia, renal dysfunction and hypercalcemia, and risk of mortality.

Results

A total of 207 patient files were included in the study. The median age at presentation was 60 years with a slight male preponderance. Bone pain was the predominant complaint in 59% (139/207) of patients, with 17% of patients with paraparesis or paraplegia at presentation. For patients who underwent imaging, osteolytic bone lesions were identified in 90.6% (126/139). Anaemia was present in 71% (147/207) patients, hypercalcemia in 55.4% and renal dysfunction in 38.2%. There were 27 different treatment regimens prescribed, most commonly the older-generation IMID, thalidomide and dexamethasone in 24.5% (45/184), with only 11 patients (6%) on bortezomib-based triplet therapy.

Conclusion

MM in KNH is a disease of the middle aged, affecting men and women almost equally and presenting mainly with bone pains and anaemia. Though there seems to be a general improvement in diagnosis and care, access to less toxic novel agents for treatment is still wanting.

CHAPTER 1: INTRODUCTION

Multiple Myeloma (MM) is a chronic B-cell malignancy that involves proliferation of neoplastic clonal plasma cell in the bone marrow with subsequent overproduction of monoclonal immunoglobulins or its constituent polypeptide chains (paraproteins) in serum and urine. According to the World Health Organization (WHO), MM is recognized as a disease distinct from other plasma cell disorders such as monoclonal gammopathy of uncertain significance (MGUS), solitary plasmacytoma of bone, systemic light-chain amyloidosis and POEMS (polyneuropathy, endocrinopathy, monoclonal plasma cells disease and skin changes) syndrome[1]. MM derives its distinctness from other plasma cell disorders by the manifestation of clinical symptoms caused by the pathophysiological effects of the circulating abnormal paraproteins, which lead to characteristic end-organ damage including renal dysfunction, anaemia, extensive skeletal lytic lesions and hypercalcemia.

The clinical consequences of circulating paraproteins resulting from MM are commonly referred to as Myeloma Defining Events (MDEs). One or more organs can be affected at a time and result in significant morbidity and mortality. Identifying indolent clinical manifestations of MM guides clinicians to have a heightened index suspicion to screen for MM when presented with a patient with unexplained clinical symptoms. Knudsen *et al* found that in Sweden, a raised serum calcium level was seen in 45% of MM patients in their population, while Othieno-Abinya *et al* found hypercalcemia in only 19% of MM patients in Kenya[2,3]. This may suggest that a normal serum calcium level in our population should not reduce the suspicion of MM in a patient. Similarly, anaemia appears to be more common in western populations, 72% in a US study[4], as compared to the results of Kenyan studies[2,5]. However, the cut-offs used in these studies varied which may impact how we interpret these differences, for example, varying from haemoglobin of less than 8.5 to less than 12g/dl in defining anaemia across different studies[2,4–7]. In 2014, the International Myeloma Working Group (IMWG), set cut-offs for the measurements of pathological features and laboratory measurements of clinical end-organ damage in MM which will ensure standard data on the status of multiple myeloma globally[8]. Severe end-organ damage also affects the treatment options available to the patient and may require use of adjunct supportive therapy that should be considered and anticipated in facilities, such as KNH, which provide care for MM patients.

Prior to the development of the alkylating agents, e.g. melphalan, in 1960 for management of MM, the average survival was less than a year[9]. With the advent of therapies such as autologous stem-cell transplantation (ASCT) in the 1980s, there was an associated increase in MM survival in developed countries. Advances in new therapies with proteasome inhibitors e.g. bortezomib, immunomodulators e.g. thalidomide, lenalidomide as well as combination therapy (using triplets-drugs from three different

classes) have led to even longer survival in high-income countries, with the United States reporting a 5-year survival rate of 50.7%[10], compared to 7.6% in Nigeria[11]. In 2004, Othieno-Abinya *et al*, found that majority of MM patients at KNH were on melphalan-based therapy, with no patients on new agents. Addition of a new agent, such as bortezomib, doubles the partial response rate and increases the complete response rate to therapy by more than seven-fold[12]. Through funding by the National Hospital Insurance Fund, three of the new drugs, namely bortezomib, thalidomide and lenalidomide are now available at KNH and in local private hospital pharmacies[13].

With the advent of updated diagnostic pathological and clinical criteria of MM internationally in 2014, there is a paucity of current data on the status of multiple myeloma in Kenya that is in line with the updated parameters as directed by the International Myeloma Working Group. The availability and improved accessibility of new treatments agents to patients at public facilities and whether they have been adopted by clinicians in their care of MM has also not been documented.

CHAPTER 2: LITERATURE REVIEW

2.1 EPIDEMIOLOGY

MM is a rare cancer, with a lifetime risk of 0.76%[10] and an age-adjusted incidence rate of 2.5-7.2 per 100,000 in Western Countries[14]. Globally, cases of MM have increased by 126% from 1990 to 2016, with older age contributing to more than half of the rise in cases[15]. The reported incidence rate is low in sub Saharan Africa but is on the rise following improved diagnostic capabilities and increased life expectancy[15]. There is no prevalence data available for Multiple Myeloma in Kenya in the Kenya cancer registry[16] or other East African registries[17]. In the West, it is considered a disease of the elderly, affecting those in their 7th-8th decades, with African American/blacks being two-three times more likely to be affected[18]. However, in Kenya, one previous study put the median age of presentation at 59 years of age[5], while another describes a majority of cases as occurring in the 6th-7th decade with a male : female ratio of 1.37:1[2].

The survival of MM patients can range from 6 months to over 10 years, with a median of 6 years[19], depending on stage of the disease at diagnosis and prognostic factors[20]. Despite improvements in treatment, MM is still characterized by frequent relapses and death due to disease progression, with MM accounting for approximately 19% of cancer mortality in the United States[21]. The mortality rate in Europe stands at 13 and 20 per 100 000 in males and females, respectively. Life expectancy of MM in Western countries has improved from < 1 year in the 1960s[22] to 5 to 7 years in patients receiving high dose chemotherapy with ASCT and 3 to 4 years in chemotherapy alone [23]. Locally, the follow-up duration and survival have been described as short[2] .

2.2 PATHOLOGY

Myeloma arises from an asymptomatic premalignant proliferation of monoclonal plasma cells that are derived from post–germinal-centre B cells. Multistep genetic and microenvironmental changes lead to the transformation of these cells into a malignant neoplasm. Abnormal genes in tumour plasma cells play a significant role in the pathogenesis of myeloma. MM is classified into subgroups based on the resultant gene profiles. Over 40% of MM have trisomies in neoplastic plasma cells (trisomic MM), while the greater majority involve translocations at chromosome 14 (q32.33) affecting immunoglobulin heavy chain production (IgH translocated MM)[27,28].

Myeloma is thought to evolve most commonly from a monoclonal gammopathy of undetermined clinical significance (MGUS) that progresses to smouldering myeloma and, finally, to symptomatic myeloma. Patients with MGUS develop MM at a rate of 1% per year[24]. Recent studies indicate that the diagnosis of symptomatic multiple myeloma is typically preceded by monoclonal gammopathy by two or more years[25].

MGUS is a premalignant plasma disorder present in more than 3% of the general population above 50 years of age[26]. It is characterised by benign overproduction of monoclonal "M" protein. It has distinct clinical types based on the protein produced, namely, non-IgM (IgG or IgA), IgM and IgD. While MGUS and MM share early chromosomal abnormalities, trisomies and immunoglobulin translocations, there are certain cytogenetic abnormalities involving MYC (8q 24), MAFB (20q12), and IRF4 (6p25) genes that occur commonly in MM but are quite rare in MGUS. Progression from MGUS to MM follows a "second hit" insult to a plasma cell clone through additional genetic abnormalities or change in the bone marrow microenvironment which lead to overproduction of stimulatory cytokines, activation of anti-apoptotic mechanisms and deregulation of the normal cell cycle ultimately leading to an altered bone microenvironment and increased angiogenesis.

2.3 CLINICAL PRESENTATION

Patients with early (smouldering) disease are generally asymptomatic at presentation while those with active disease may present with clinical features in keeping with myeloma related end-organ damage. Clinical symptoms result from the pathophysiological activity of myeloma cells and secreted immunoglobulins on bone marrow haematopoiesis, kidney function and bone lysis.

2.3.1 Osteolytic Bone Lesions and Hypercalcemia

In studies at both public and private hospitals in Kenya, bone pain was the most common initial complaint on presentation[2,5]. The adhesion of myeloma cells to extracellular matrix proteins e.g., collagen, fibronectin, laminin and vitronectin triggers the up-regulation of cell-cycle regulatory proteins and anti-apoptotic proteins. Within bone, subsequent increase in osteoclasts activity and suppression of osteoblasts via the DKK-1 (dickhof-1) pathway leads to formation of lytic bone lesions and subsequent symptomatic bone pain that is worse on movement[28]. Osteolytic lesions are seen on imaging in as many as 76% of patients in one study by Kiraka *et al*[5]. Bone lysis increases mobilisation of calcium from bone leading to hypercalcemia. Clinical complications include pathological fractures that require orthopaedic intervention and symptomatic hypercalcemia that may require medical treatment with bisphosphonates.

2.3.2 Anaemia

In 2003, Kyle *et al* found that 72% of MM patients managed at the Mayo Clinic, USA presented with anaemia[4]. In Kenya, up to half of the patients presented with anaemia[2] [Table 1]. Anaemia is thought to arise from increased infiltration of bone marrow by myeloma cells due to loss of apoptosis in clonal cells, as well as overexpression of Bcl2, death associated protein kinase and osteoprotegerin. Accumulation of myeloma cells compromises the function of the bone marrow, including erythropoiesis, leading to normocytic normochromic anaemia[28]. Other mechanisms by which anaemia develops include those postulated by Konig *et* al, who described a decrease in responsiveness of the pro-erythroblasts to erythropoietin and an increase in production of hepcidin, due to the state of chronic inflammation, leading to impaired iron utilization and worsening anaemia[29]. Anaemia leads to poor quality of life, increased cardiovascular morbidity and mortality in patients with MM, particularly if prompt transfusions of blood or blood products are not available[30,31].

2.3.3 Renal Dysfunction

In a 2009 multi-centre review of MM patients, Kleber *et al* found up to 25-50% of MM patients with mild renal disease (estimated glomerular filtration rate <60ml/min)[32], consistent with many western studies that found secondary renal dysfunction occurred in 20-40% of MM patients[3,28]. In local studies, the prevalence of renal dysfunction has been higher at 40 to 52%[2,5] [Table 1]. The IMWG recognises elevated serum creatinine of >177ummol/L as the cut-off for renal dysfunction in MM[8].

Excess production of immunoglobulins and/or their heavy chains (A, D, G, E, M) and light chains (kappa or lambda) by myeloma cells, and their subsequent secretion through renal filtration leads to kidney injury via tubulointerstitial lesions such as cast nephropathies[33]. In a 2003 review of MM patients at the Mayo clinic, Ma *et al* describe an adult acquired Fanconi-like syndrome secondary to functional impairment at the proximal tubule caused by serum free light chains[34]. Presence of free light chains may also lead to more kidney injury than intact immunoglobulin, with kidney failure noted to occur in 70% of patients who secrete more than 10 grams of light chains a day[3]. Other pathophysiological mechanisms of kidney injury in MM include hypercalcemia, volume depletion, uric acid nephropathy and use of nephrotoxic medications such as NSAIDS[33].

2.3.4 Infections

In a Swedish population-based study of 9253 MM patients, Blimark *et al* (2004) found that MM patients had a 7-fold increased risk of developing an infection compared to the general population with infections being the cause of death in 22% of MM patients in the first year of follow-up[35]. Recurrent infections may occur but generally improve once the patient is on definitive treatment[4,5]. Pneumonia from bacteria such as *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Klebsiella pneumoniae* and pyelonephritis from *Escherichia coli* and other gram-negative organisms occur most commonly[36].

2.4 SUMMARY OF PREVIOUS CLINICAL STUDIES ON MM

Due to the rarity of the disease, most local studies done on MM worldwide are retrospective and hospital based. This requires relying on the patients presenting at the hospital so as to be captured. In developed countries with good healthcare systems and active health-seeking behavior, there are several ongoing multiple myeloma registries that capture in hospital and population-based databases that enable them to monitor and study trends in myeloma morbidity, treatment and mortality.

Knudsen *et al* (1994) were able to draw from the regional medical database to identify cases of MM in the population and access their medical records from their national medical database[3]. Kyle *et al* (2003) was based at a large cancer treatment and referral centre in the United States of America, and were therefore to obtain a sample of 1027 patients from their hospital [4]. In sub Saharan Africa, there has been one prospective study looking at MM patients presenting at a tertiary hospital in South Africa over a period of five years. It was done as part of a PhD thesis and was able to glean more information on outcome of patients. However, the numbers were still small, with a sample population of 170 patients[6].

Mukiibi and Kyobe (1988) and Othieno-Abinya *et al* (2004) retrospectively studied medical records at KNH in different time periods describing the prevalence of anaemia, hypercalcemia and renal dysfunction in MM. In comparison, the latter study found significantly less anaemia, 81% compared to 50%, and less uremia and hypercalcemia in their study population than the former. They proposed that this could be from a trend in earlier presentation of patients in later years or reflective of their larger sample size, 173 patients compared to 73 patients.

Kiraka *et al* (2014) retrospectively looked at medical records for 74 patients at Aga Khan University Hospital, a private tertiary hospital in Nairobi[5]. They found more significant bone disease, renal dysfunction and hypercalcemia than the KNH-based studies. Renal dysfunction was found in 52% of patients at AKUH and 39% at KNH[2,5]. However, these studies used different clinical parameters to assess renal dysfunction, with Kiraka *et al* using serum creatinine and Othieno-Abinya *et al* looking at the serum urea. This may contribute to the perceived increase in cases of renal dysfunction among MM patients.

Table 1: Clinical and Pathological Profile of Multiple Myeloma Patients in Different Geographical Regions

Study	**Study setting**	**Methodology**	**Diagnostic pathological features**	**Bone pain as presenting complaint**	**Anaemia - Haemoglobin (Hb)**	**Renal dysfunction**	**Hypercalcemia S-Ca (serum calcium in millimole/litre)**
Mukiibi and Kyobe (1988) n=75	Kenyatta National Hospital	Retrospective study of medical records at the hospital (1980-1987)	-	Bone pain 66.7% Osteolytic lesions on skeletal survey 80%	Anaemia 81.3%	Uremia 54.7% Elevated serum creatinine 34.7%	Hypercalcemia 29.3%
Knudsen *et al*[3] (1994) n= 1353	Demographic study – Nordic Countries (1984-1986, 1990-1992)	Retrospective study of case records of patients reported to the Nordic Myeloma Working Group	-	-	-	49% [Creatinine >110 micromole/l]	45% [S-Ca >2.6mmol/l]
Patel M[6] (1999) n=170	Black patients at Christ Hani Hospital, South Africa	Prospective cohort study undertaken as part of PhD thesis in MM (1992-1997)	-	94%	81.1% [Hb <12g/dl]	17.2% [Creatinine >180 micromole/l]	38.5% [S-Ca >3mmol/l]
Kyle *et al*[4] (2003) n=1027	Mayo Clinic – USA	Retrospective review of records at the hospital (1985 – 1998)	-	58%	72% [Hb g/dl] • ≤8 - 7% • 8.1-10.0 –	48% [Creatinine >110 micromole/l]	28% [S-Ca >2.57 mmol/l]

					28% • 10.1-12 – 37%		
Othieno-Abinya *et al*[2] (2005) n= 173	Kenyatta National Hospital – Kenya	Retrospective study of medical records at the hospital (1994-2004)	BM plasmacytosis (74/173) • <10% in 8% • >30% in 71.6% Urine Bence-Jones 32.7% (52/174) Serum paraproteins 75% (56/173)	27.4%	50% [n=92] [Hb g/dl] • <8.5 – 34.8% • 8.5-9.9-15.2%	39.7% [n= 58] [Blood Urea Nitrogen >10.7mmol/l]	19.1% [n=42] [S-Ca >2.64mmol/l]
Kiraka *et al*[5] (2014) n=74	Aga Khan University Hospital – Kenya	Retrospective study of medical records at the hospital (1999-2011)	Monoclonal band on SPEP 76%	76%	47% [Hb <10g/dl]	52% [Creatinine >110 micromole/l]	34% [S-Ca >2.6mmol/l]
Nnonyelum *et al*[7] (2015) n=135	Eight tertiary Hospitals – Nigeria	Retrospective study of case notes from 8 tertiary hospitals in Nigeria (2005 to 2014)		74%	77% [Hb median 8.3g/dL, mean value of 8.4 ± 2.1g/dL]	35.9% [nephropathy]	S-Ca median of 2.7 mmol/l, mean 5 ±5.5 mmol/l

2.5 DIAGNOSTICS AND STAGING OF MULTIPLE MYELOMA

Multiple myeloma is currently diagnosed by the presence of ≥10% plasma cells (CD138 positive on immunohistochemistry) in bone marrow or tissue histology of an extramedullary plasmacytoma, and any one of the myeloma defining event such as evidence of end organ damage or presence of biomarkers of malignancy[8]. Previously, MM was diagnosed based on the presence of end-organ damage of hypercalcemia, renal failure, anaemia and bone lesions. However, with the advent of newer more effective treatments, the International Myeloma Working Group (IMWG) updated the diagnosis of MM to incorporate biomarkers for earlier detection of disease and initiation of treatment prior to onset of end organ damage[27] [See Appendix 2].

MM can be defined as either smouldering (asymptomatic) or active (symptomatic). Smouldering MM is where the M-protein in serum IgG is ≥3 g/dL, Immunoglobulin A >1 g/dL or Bence-Jones protein >1 g/24h and/or the bone marrow clonal plasma cells of ≥10% with absence of myeloma defining events or amyloidosis[8]. High risk smouldering MM patients may have treatment initiated while low risk patients may be subject to watchful waiting[37]. A high index of suspicion and accessible laboratory tests are required to diagnose high risk smouldering MM for timely treatment, particularly with newer less toxic agents.

Myeloma defining events (MDE), are defined as serum calcium >2.75mmol/L, renal dysfunction based on a serum creatinine of >177 μmol/L, haemoglobin of >20g/l (2g/dl) below the lower limit of normal or one or more osteolytic bone lesions on imaging. Biomarkers of malignancy as defined by the IMWG have been shown to lead to progression in 90% in 12-24 months[8,27], which justifies instituting prompt therapy in the absence of end organ damage [Appendix 2]. The following investigations can be used in the diagnosis of MM depending on local availability[38]:

- Bone marrow aspiration and/or trephine biopsy
- Serum and urine electrophoresis for monoclonal ‘M’ protein
- Serum free light chain assay
- Serum or urine immune-fixation (to determine the subtype of the ‘M’ protein)
- Serum β_2-microglobulin, albumin, serum immunoglobulins, and lactate dehydrogenase (LDH) measurement
- Standard metaphase cytogenetics and fluorescence in-situ hybridization (FiSH) on blood and tissue samples
- Skeletal survey by conventional radiography
- Whole body magnetic resonance imaging (MRI) or low-dose whole-body CT for better detection of bone and extramedullary disease

Of the investigations required to diagnose MM as per the 2014 IMWG criteria [Appendix 2], bone marrow aspirate and cytology or tissue histology is a major requirement. In a previous study done at KNH in 2004, only 72 of 173 patients treated for MM had bone marrow cytology reports as part of their diagnosis while only 56 patients had serum paraproteins measured[2]. With the advent of increased resources and new diagnostic guidelines, it would be beneficial to determine the uptake of these tests in the diagnosis of MM locally.

Staging and Prognosis

The International Staging System (ISS) uses serum β_2-microglobulin and albumin levels to determine the stage of disease[20]. Detection of β_2-microglobulin in serum is widely used in developed countries in diagnosis and staging of MM and is now available in Kenya. Aside from diagnostic testing, chromosomal abnormalities found on bone marrow aspirate samples may be used in classifying risk of disease to guide the plan of management. Generally, any chromosomal abnormality procures a poorer diagnosis than a normal karyotype, more specifically, t(4,14), deletion 17p13 and abnormalities of chromosome 1[28]. However, locally cytogenetic tests and FISH tests are only done in a handful of private laboratories and at a prohibitively high cost. High risk disease is characterised by chromosomal abnormalities such as hypodiploidy, t(4,14), d(17p13) and increased levels of serum β_2-microglobulin (ISS Stage 3) and elevated lactate dehydrogenase. Standard risk is characterized by chromosomal hyperploidy or t(11,14) and normal serum β_2-microglobulin and normal lactate dehydrogenase levels corresponding to ISS Stage 1[28].

Using the ISS, the overall survival for stage one patients was 62 months and 44 and 29 months for those in stage II and III respectively in Western countries[20]. Using a proposed revised ISS (R- ISS) from the United States, that is yet to be fully adopted, overall survival, where over 95% of patients received new MM treatments, stood at 87 months for stage II and 43 months for stage III and as yet undetermined for stage I[39] . There is currently no local data on staging of MM using the ISS staging and prognosis.

Table 2: Staging of Multiple Myeloma

Stage	**International Staging System**[40]		**Revised ISS**[39]
I	Serum β_2-microglobulin level <3.5mg/L	Serum albumin level ≥ 3.5g/dl	**Also:** CA by iFISH Standard risk - No high-risk CA LDH Serum LDH < the upper limit of normal
II	Not stage I or III		
III	Serum β_2-microglobulin level ≥ 5.5mg/L		**Also:** High risk - Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16) Serum LDH > the upper limit of normal
CA- Chromosomal abnormality, iFISH - interphase fluorescent in situ hybridization, LDH – Lactate Dehydrogenase			

2.6 TREATMENT

The gold standard for MM treatment is induction therapy followed by autologous stem cell transplant (ASCT) for eligible patients. ASCT prolongs progression-free survival and overall survival among patients and is recommended in patients under the age of 65 years with no substantial cardiac, lung, renal or hepatic dysfunction[41]. Eligible patients are started on 3 to 4 cycles of induction therapy then followed by stem cell harvest. The current recommendation is for early transplant as opposed to delayed transplant. ASCT may be given several times in the course of the disease. In younger patients with coexisting medical conditions or those above 75 years of age, less intensive approaches that limit toxic effects are considered[28]. ASCT with maintenance therapy had much higher 4 year overall survival rate, 81% compared to 65%, and progression-free survival rate, 43 months compared to 22 months, than patients

receiving chemotherapy alone with melphalan, prednisone and lenalidomide[41]. However, ASCT is currently not available in sub Saharan Africa with the exception of South Africa[15].

The only cure for MM is allogeneic stem cell transplant. However, allogeneic transplant is associated with high incidences of treatment related mortality and graft versus host disease[42]. A recent systematic review and meta-analysis found a lack of consistent survival benefit of allogeneic transplant in MM patients in standard risk patients as compared to ASCT due to high incidences of treatment related mortality at 44%[43]. However, allogeneic stem cell transplant was suggested for high cytogenetic risk patients with poor prognosis as the risk of disease progression is higher than that of adverse effects of the transplant.

Chemotherapy is given for MM for induction, treatment and as maintenance. There are various classes of agents used in MM.

1. Alkylating agents e.g. melphalan, cyclophosphamide
2. Immunomodulatory Imide Drugs (IMIDS) e.g. thalidomide, lenalidomide, pomalidomide
3. Proteasome Inhibitors (PI) e.g. bortezomib, carfilzomib, ixazomib
   Bortezomib, the first-in-class PI, has demonstrated striking clinical efficacy in MM. Proteasome inhibition stimulates multiple apoptotic pathways that are suppressed in MM. Ixazomib is an oral proteasome inhibitor.
4. Novel alkylators e.g. bendamustine
   Bendamustine acts by combining an alkylator structure with a purine analog ring. It is approved in Europe for use in combination with prednisone in MM patients ineligible for autologous stem cell transplantation and cannot receive PIs or thalidomide due to pre-existing neuropathy[44].
5. Monoclonal Antibodies
   An anti CD38 monoclonal antibody, daratumumab, has also been introduced in treatment of Multiple Myeloma[45]. Elotuzimab is a monoclonal antibody against SLAMF7, a signalling lymphocytic activation molecule.
6. Histone deacetylase (HDAC) inhibitors e.g. panobinostat, vorinostat
   This class of drugs was recently approved for treatment of relapsed MM[46]. They act by inhibition of histone deactetylator enzymes involved in the deacetylation of histone and non-histone cellular proteins. The HDAC inhibitors are thought to make MM cells more sensitive to death receptor-mediated apoptosis and also inhibit IL-6. This allows the drug to overcome cell-adhesion-mediated drug resistance within the bone marrow microenvironment[47].

Treatment Guidelines for Multiple Myeloma

There exist several combinations of drugs used in MM with varying degrees of clinical response[27,36,41,45,48]. The United States National Comprehensive Cancer Network guidelines recommend triplet therapy with a combination of bortezomib, lenalidomide and dexamethasone, or bortezomib, cyclophosphamide and dexamethasone as the standard of care for newly diagnosed MM patients who are transplant eligible. For those who are not transplant eligible, one can additionally use lenalidomide and low dose dexamethasone[49]. The European Society for Medical Oncology also recommends use of triplet therapy as well for those less than 65 years and physically fit or less than 70 years and in good medical condition; high dose therapy with bortezomib and dexamethasone combined with either thalidomide or cyclophosphamide can be given prior to ASCT. Bortezomib, melphalan and prednisone or lenalidomide with low dose dexamethasone is recommended for elderly patients or non-transplant eligible patients[50].

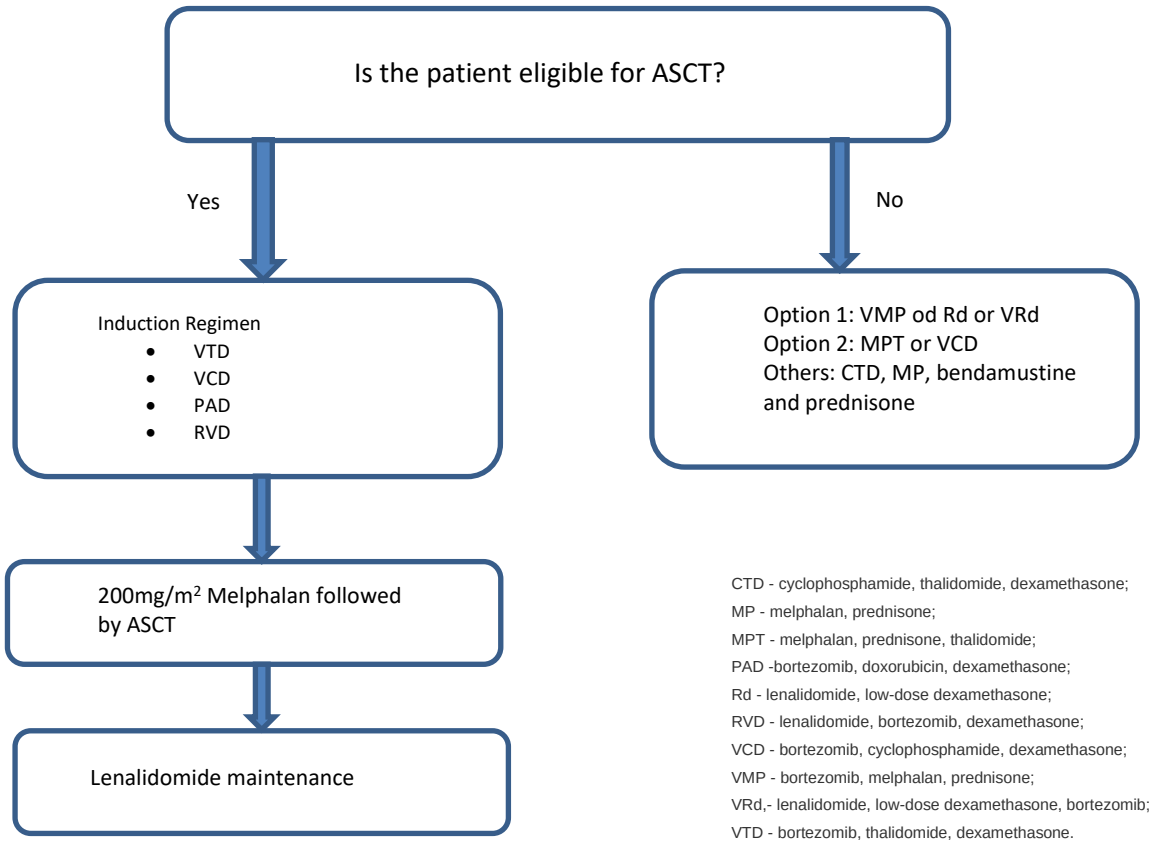

Figure 1: Algorithm for Treatment of Multiple Myeloma (Adopted from ESMO Clinical Practice Guidelines 2017[50])

However, such standard of care treatments of MM are expensive and many times unavailable in low and middle income countries (LMIC)[15]. Asian countries have developed a resource-stratified standard of care for MM based on availability and affordability of novel drugs in their setting[51]. Dexamethasone remains a cornerstone of therapy, with a combination of at least one novel drug, thalidomide or bortezomib (dual-therapy). Bortezomib is recommended for those with renal failure or increased risk of thrombosis. In the complete absence of novel drugs, they recommend dexamethasone combined with cyclophosphamide or

vincristine and liposomal doxorubicin[51].

In Kenya, as at 2004, Othieno-Abinya *et al*, found that the standard treatment of MM at KNH was melphalan-prednisone[2], which is similar to that of other African countries[5,26]. Introduction of a novel agent, such as an IMID or PI, has been associated with better outcomes with one study reporting that bortezomib added to the standard melphalan and prednisone treatment had a higher partial response rate 71% compared to 35% and complete response rate 30% compared to 4%[12]. This means that addition of just one of the newer agents in the treatment of multiple myeloma doubles the partial response rate and improves complete response to therapy by more than seven-fold. In line with the large body of evidence, the 2019 Kenya national cancer treatment protocols recommend bortezomib-based regimens as first-line treatment for both transplant-eligible and non-transplant eligible patients[52].

In 2016, the government has through NHIF committed itself to covering the care of cancer patients including procurement of newer agents and facilitating access to transplant therapy abroad[13]. Previously unavailable drugs such as bortezomib and lenalidomide have become available in Kenya. Where resources allow, patients have been managed on thalidomide or lenalidomide and bortezomib but there is no data on adoption and use of these agents at KNH since their introduction.

2.6.2 Supportive Treatment

MM patients present with complications from the disease itself and occasionally from chemotherapeutic agents which necessitate adjunct modalities of treatment adding to the economic cost of the disease. Symptomatic vertebral compression fractures and long bone fractures may require surgical orthopaedic intervention. As per accepted clinical practice, pain that is refractory to medical and surgical interventions, impending pathological fractures as well as spinal cord compression are indications for low dose radiation therapy (10-30 Gy)[53].

Apart from the action of bisphosphonates in inhibition of recruitment, maturation and activity of osteoclasts, Gordon *et al* (2002) described possible anti-myeloma activity by pamidronate and zoledronic acid[54]. Patients with bone lesions and adequate renal function can be safely started on intravenous bisphosphonates and on occasion, even for those without bone lesions on conventional imaging[53]. Hypercalcemia can be managed using bisphosphonates e.g. zoledronic acid and adequate hydration.

Persistent anaemia from the disease itself as well as following chemotherapy may require erythropoietic agents or/and blood transfusions. Recombinant erythropoietin can be used in patients with anaemia in MM with no other apparent cause. A double-blind clinical trial by Dammacco *et al*, showed that erythropoietin decreased the need for transfusion in MM patients by 19% (28% vs. 47%, $p=0.017$), increasing mean haemoglobin by 1.8g/dl compared to placebo ($p < 0.001$)[55].

Vaccinations and prophylaxis medications against pneumocystis jirovecii, herpes viruses and fungal infections are recommended for patients on high dose steroids and more so against herpes zoster in patients receiving bortezomib. For those IMIDS, concurrent thrombo-prophylaxis is recommended.

Supportive measures such as adequate hydration, avoidance of nephrotoxic agents and monitoring while on bisphosphonates help reduce worsening of renal function[53]. However, overt renal failure may occur requiring renal replacement therapy or renal transplant.

The disease burden of MM involves recognising the effect of the prevalence of complications of MM and the expected cost of the supportive management they require on the existing health system[56].

CHAPTER 3: JUSTIFICATION

Previous local studies describing the salient patient characteristics had reported variations in the affected demographic and disease system affected in Multiple Myeloma patients among the Kenyan population and those in other parts of Africa and Western countries. This study looked at a much broader population as compared to previous studies and provided much needed data on the pathological and clinical multiple myeloma disease locally. It was an update of a study done in KNH in 2004, done prior to availability of several diagnostic and treatment modalities that are in current use at KNH. The study also documented aspects of treatment such as use of previously unavailable novel treatments and utilisation of adjunct supportive therapies in the care of MM patients.

CHAPTER 4: RESEARCH QUESTION AND OBJECTIVES

4.1 Research Question

What is the clinical and pathological profile, prevalence of myeloma defining events and treatment of Multiple Myeloma at the Kenyatta National Hospital?

4.2 Broad Objective

To describe the pathological and clinical features, including myeloma defining events, and treatment of Multiple Myeloma patients seen at KNH between January 2014 and December 2018

Primary Objectives

1. To document the clinical and pathological profile of Multiple Myeloma patients at KNH
2. To describe the prevalence and burden of specific myeloma defining events (MDE) in Multiple Myeloma patients treated at KNH
3. To describe the treatment modalities of Multiple Myeloma patients at KNH

CHAPTER 5: METHODOLOGY

5.1 Study Site

This study was conducted at the records departments at KNH, the largest referral hospital in Kenya with established outpatient oncology clinic, radiotherapy department and oncology wards managing the bulk of cancer patients in Kenya. The computerised filing system was based on the ICD-10 classification and allows for retrieval of all file numbers corresponding to the ICD-10 C-90 diagnosis for MM.

5.2 Study Design

This was a single centre descriptive retrospective study.

5.3 Study Population

The study population included patients classified under ICD-10 diagnosis C-90 (Multiple Myeloma) managed at KNH hospital as an outpatient or in-patient between 1st January 2014 and 31st December 2018.

Case Definition

A case was defined as a file of a patient presenting at KNH between 1st January 2014 and 31st December 2018, with a diagnosis of multiple myeloma confirmed by at least one or more of the following diagnostic reports;

Bone marrow aspirate cytology report

Tissue histology report

Serum protein electrophoresis report

5.4 Eligibility Criteria

The study included all medical records/files for patients above 13 years with a documented diagnosis of multiple myeloma meeting the study's case definition, presenting at KNH between 1st January 2014 and 31st December 2018. Files with missing data on the diagnostic tests e.g. bone marrow report, serum electrophoresis or tissue histology showing plasma cells were excluded.

5.5 Sampling Procedure

The case records were examined at the point of diagnosis for data on the study variables. The sample size was approximated from an estimated population of 384 patients classified as having a diagnosis of MM at KNH, therefore the sample size calculation for finite populations (less than 10000) was used.

$$n' = \frac{NZ^2P(1-P)}{d^2(N-1)+Z^2P(1-P)}$$

Where

n' = sample size with correction for finite population

N = 384 which is the approximate number of available files

Z= confidence interval of 95% =1.96

P = estimated average prevalence of myeloma defining events – 27.4%. A previous study done at KNH by Othieno-Abinya *et al* found that the various clinical features of MM had prevalence ranging from 19.1 (hypercalcemia), 27.4% for bone pain, 39.5% for renal dysfunction and 50% for anaemia, 27.4% was used for the sample size calculation[2] (see Table 1).

d = margin of error of 5%

The sample size was calculated as 169 files to estimate prevalence of myeloma defining events in MM patients at KNH to a precision of 5%.

5.6 Research Tools

The primary study data was sourced from patient's medical records in the file and in the case of missing data, efforts were made to trace the reports at the respective KNH/UoN laboratories. Numbered sequential data extraction forms [see Appendix 1] were used to record all the variables required for each file onto a mobile phone or tablet that was connected to a database for data storage and subsequently use in analysis.

5.7 Data Collection and Extraction

This was a retrospective study conducted at two sites: the KNH records department and the CTC records department. A list of all files under ICD classification of C-90, which covers the diagnoses of multiple myeloma and other plasma cell disorders, from the period January 2014 to December 2018 from the main registry basis was obtained and file numbers given to KNH medical records officers to retrieve the files. The principal investigator counter-checked retrieved files against the master list to confirm the file number and checked each retrieved file for eligibility and case definition for MM as defined in the study protocol before extraction of the data from the files by the principal investigator or either of the two trained research assistants. The Cancer Treatment Centre (CTC) kept separate records for patients undergoing radiotherapy at KNH for various cancers including MM and a similar approach was undertaken. Variables of interest were recorded into a hardcopy and online data extraction form [see Appendix 1] and uploaded onto the Microsoft Excel database.

5.8 Study Variables

5.8.1 Primary presenting complaint

This was recorded as the presenting complaint of the patient on first presentation.

5.8.2 Pathological Profile of the patient

This was recorded from the case records and related to the 2014 IMWG diagnostic criteria (Appendix 2). The percentage of plasma cells found on bone marrow cytology and any biopsy report confirming plasma cells in bony or extra-medullary tissue was recorded. In patients with a measurement of circulating monoclonal protein on a serum protein electrophoresis profile, the spike of monoclonal protein bands, $\alpha 1$, $\alpha 2$, $\beta 1$, $\beta 2$ or γ, in grams per decilitre (g/dl) was recorded.

The presence of any of the following variables were recorded as part of the clinical and pathological profile of the patient.

a. Anaemia: defined as haemoglobin of <10g/dl
b. Renal dysfunction: defined as a serum creatinine of >177 μmol/L
c. Hypercalcemia: defined as serum calcium >2.75mmol/L
d. One or more osteolytic bone lesions on imaging on radiography, CT scan or MRI

Where available, the following biomarkers were recorded;

- Bone marrow cytology plasma cells ≥60%
- Involved/uninvolved serum free light chain ratio ≥100
- Abnormal MRI with more than one focal lesion with each lesion >5 mm

5.8.3 Staging

This was recorded as the initial serum β_2-microglobulin level in g/dl taken during management of the patient and used together with the serum albumin level in staging of the patient using the International Staging Score (ISS) for MM [Table 2].

5.8.4 Spectrum and Severity of Myeloma Defining Events

For laboratory tests on organ function, results of the initial test at presentation or at diagnosis were recorded. Only laboratory tests done within a month of diagnosis were included. Tests done more than thirty days from date of diagnosis were considered as missing and not recorded. This was then grouped according to the myeloma defining event and further classified based on severity.

5.8.4.1 Anaemia

The cut-off for anaemia in LMIC, including Kenya, as per the WHO anaemia diagnosis criteria is 12 g/dl[57]. As per the IMWG diagnostic criteria, anaemia in this study was broadly defined as haemoglobin of less than 10g/dl, which is determined as 2 g/dl (20g/l) lower than the lower limit in the normal population, and further defined by severity as follows:

- Mild 10 g/dl
- Moderate 7-9.9 g/dl
- Severe <7g/dl

5.8.4.2 Renal dysfunction

Renal dysfunction was recorded by serum creatinine levels of more than 177ummol/l at the time of diagnosis. This was in line with the 2014 diagnostic criteria by the International Myeloma Working Group.

5.8.4.3 Hypercalcemia

Hypercalcemia was defined as presence of an elevated serum calcium level of >2.75mmol/L. The corrected calcium level was calculated based on the patient's serum albumin level in g/dl and recorded.

5.8.4.4 Bone Disease

This was defined as history or presentation with a pathological fracture or osteolytic lesions based on imaging studies as reported in the file.

5.8.5 Definitive and Supportive Treatment

Treatment plans from the clinician notes and filed ward treatment sheets were used to record the drug and supportive therapies prescribed to the patient.

5.8.5.1 Definitive treatment

This was defined as the initial treatment regimen that the patient was put on after diagnosis. The treatment was recorded as the agents prescribed as per the physician notes or recorded on the patient's treatment chart.

5.8.5.2 Exposure to immunomodulatory and proteasome inhibitors over the course of the disease

This was defined as use of any of the agents listed below at any point over the course of therapy of the patient.

- Immunomodulatory Imide Drugs (IMID) i.e. Thalidomide, Lenalidomide, Pomalidomide
- Proteasome Inhibitor (PI) i.e. Bortezomib, ixazomib, carfilzomib

5.8.5.3 Supportive treatment prescribed over the course of the disease

- Bisphosphonates – prescription for any bisphosphonate given to the patient on file
- Transfusion of blood or blood products – prescription for whole blood transfusion or transfusion of any blood product on file
- Human recombinant erythropoietin prescription
- Renal replacement therapy – prescription for initiation of haemodialysis or peritoneal dialysis
- Radiotherapy – prescription for radiotherapy on file
- Surgery – any interventional surgery planned for MM-related symptomatology

5.9 Data Analysis

The data was exported to Microsoft Excel package and subsequently exported into a study STATA® file. Exploratory data analysis was done to identify missing values, check the skewness and normality of the data and to check significant associations.

Categorical variables e.g. sex, stage of disease, exposure to novel agent during treatment, presence of supportive treatment modality, were reported as frequencies with percentages. Continuous data variables e.g. age were be expressed as means and standard deviations if normally distributed or median and interquartile range if skewed The pathological profile was described according to the number of patients with bone marrow findings consistent with MM, those diagnosed via tissue histology, serum protein electrophoresis or presence of osteolytic bone lesions on imaging. The mean value of the percentage of plasma cell in bone marrow profile and the frequency and percentages of serum monoclonal protein spikes on SPEP were reported. The frequency of each myeloma defining event was reported and further classified by severity.

A multivariable cox regression model was used to test the association between presence of anaemia, renal dysfunction and hypercalcemia as independent variables, and time to outcome (death). Censoring was done at date of last known follow-up for those in whom mortality was not witnessed. In building the model, stepwise backward and forward elimination at the 10% level of significance was used to select variables to be retained in the final model. The final model was fitted to determine the significant

variables associated with mortality and reported as hazard rates. Significance set at the 5% level of significance for a two-sided test. After model fitting, a test of the proportional hazards assumption was performed and revealed no evidence of violation of this assumption.

For files that had been excluded due to missing diagnostic data despite a clinician documented diagnosis of MM, other investigational data was collected and analysed for meaningful differences with the included files using Pearson Chi-square tests.

5.10 Quality Assurance Methods

The principal investigator was responsible for verification of the completeness of each form online prior to submission into the database for quality assurance. By use of an online form software, certain pre-set parameters restricted the entry of multiple, inadequate or unsuitable values for each variable. Each form was then checked for completion prior to upload onto the database. For laboratory values, the records used were those done by KNH at presentation or earliest opportunity within a month of the diagnosis. Pathological reports from samples done at KNH and processed at KNH-approved outside laboratories were recorded.

5.11 Ethical Considerations

Ethical approval was obtained from the Ethics Committee at the KNH and permission sought from KNH administration prior to collection of data. Absolute confidentiality was observed. The principal investigator kept all the data collection tools including the tablets and computer used to analyse the data under lock and key. The patients were anonymized using unique numbers to ensure confidentiality.

CHAPTER 6: RESULTS

6.1 Study Population

A total of 384 file numbers were retrieved from the registries under the ICD classification of C-90 for multiple myeloma and other plasma cell disorders of which 58 were duplicates (same patient with receiving a different file number for radiotherapy clinic) leaving a total of 326 files. There were 41 files missing from the registries.

There were 52 files with other diagnoses that had been misclassified as C-90, while four were excluded because the diagnosis was a solitary plasmacytoma [Appendix 3]. Twenty-two files that had a clinician documented diagnosis of MM but no supporting diagnostic reports e.g. bone marrow aspirate report, SPEP or tissue histology were also excluded as they did not meet the case definition. However, as per the study protocol, available relevant investigational data was collected from these files (18 /22) and analysed for differences with the included files. There were no statistically significant differences between the two groups [Appendix 4]. In total, 207 files that met the case definition of MM were retrieved and included in the final analysis [Figure 2].

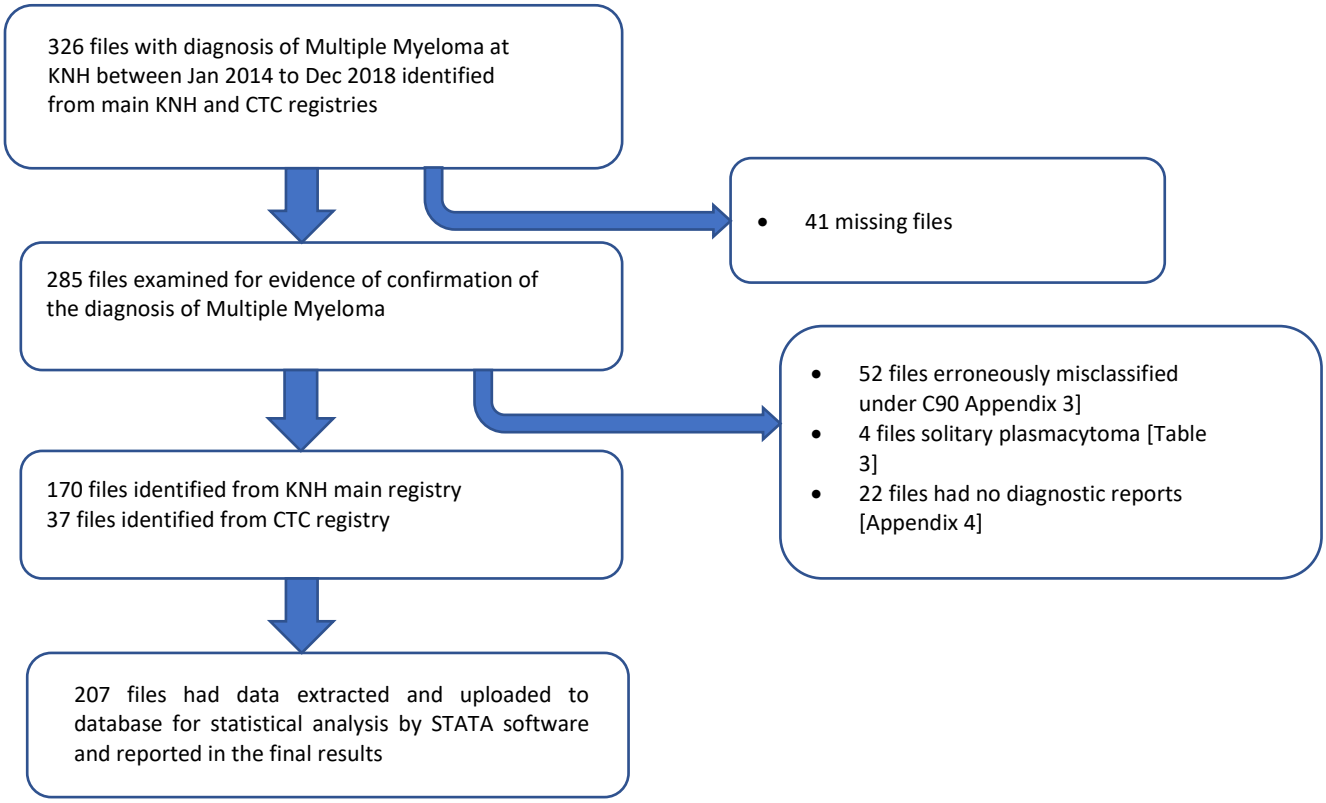

Figure 2: Flowchart of Study Recruitment

6.2 Patient Characteristics

The mean age of the patients was 58.5 years (SD 11.8) while the median age was 60 years (inter quartile range (IQR: 50 – 66) with 59% of the patients aged between 51 and 70 years, and only 6.5% under 40 years of age [Figure 3].

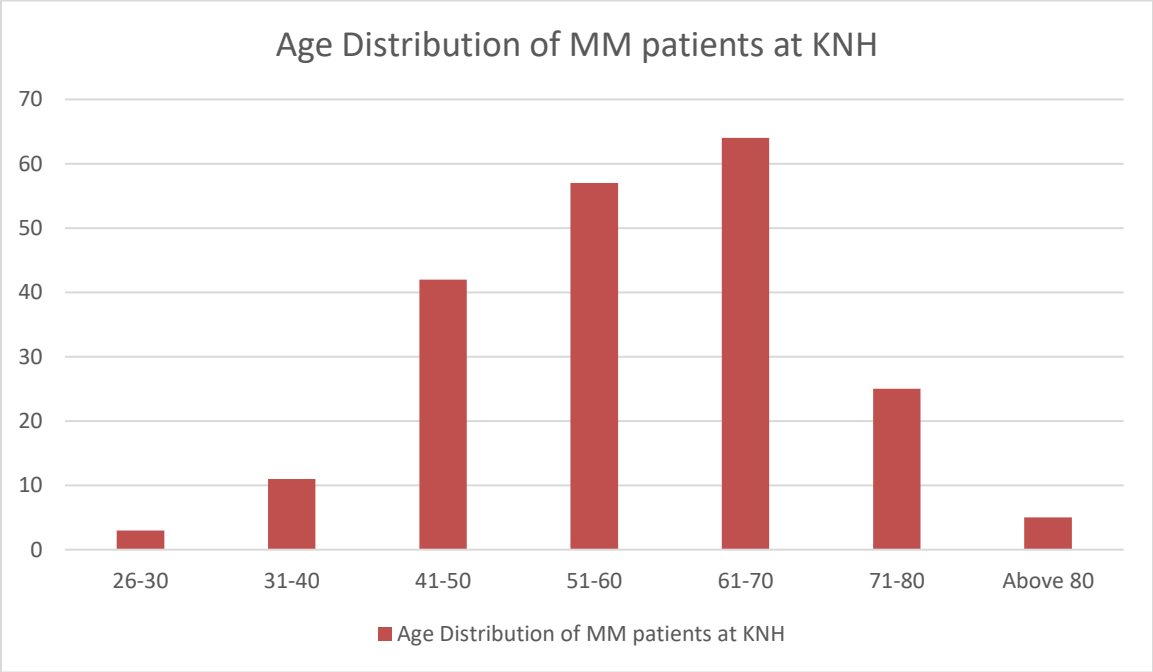

Figure 3: Age Distribution of Multiple Myeloma Patients at KNH

Males were 113 (54.6%) and females were 94 (45.4%). There were slight male preponderance, with a male: female ratio of 1.2:1. Twenty-five percent of the patients were from Kiambu and Muranga counties, with the rest coming from Nairobi and other counties in close geographical proximity to Nairobi.

Table 3: Baseline Characteristics of Patients with Multiple Myeloma at KNH

Patient Characteristics	Frequency	%
Total	**N=207**	
Age Mean	58.5 years	(SD 11.8)
Age Median	60 years	(IQR 50 -66)
Age categories (years)		
26-30	3	1.4
31-40	11	5.3
41-50	42	20.3
51-60	57	27.5
61-70	64	30.9
71-80	25	12.1
> 80	5	2.4
Gender		
Male	113	54.6
Female	94	45.4
County of residence		
Kiambu	33	15.9
Muranga	23	11.1
Nairobi	14	6.8
Nyeri	14	6.8
Machakos	14	6.8
Kisii	11	5.3
Makueni	11	5.3
Nyandarua	10	4.8
Meru	10	4.8
Others	67	32.4
Employment status	**[n=121]**	
Unskilled employment	63	52.1
Skilled employment	36	29.8
Retired	15	12.4
Unemployed	7	5.8

6.3 Clinical Presentation of Multiple Myeloma Patients at KNH

6.3.1: Presenting Complaints

Bone pain was the most common presenting complaint, seen in 135 out of 207 patients (59%) at their initial presentation. Isolated lower back pain, without any other major complaint, was present in 76 (33%) patients while lower back pain with paralysis and paresthesia of the lower limbs were recorded in 40 (17%) patients. Non-specified chest pain and other bone pain was the primary complaint in 26 (11%) patients. Pathological fractures were the primary complaint in 17 (7.4%) patients at diagnosis. Only 19 (8%) patients presented with symptoms suggestive of anaemia at diagnosis while 5 (2%) had bleeding tendencies and 7 (3%) came in with overt fluid overload [Figure 4].

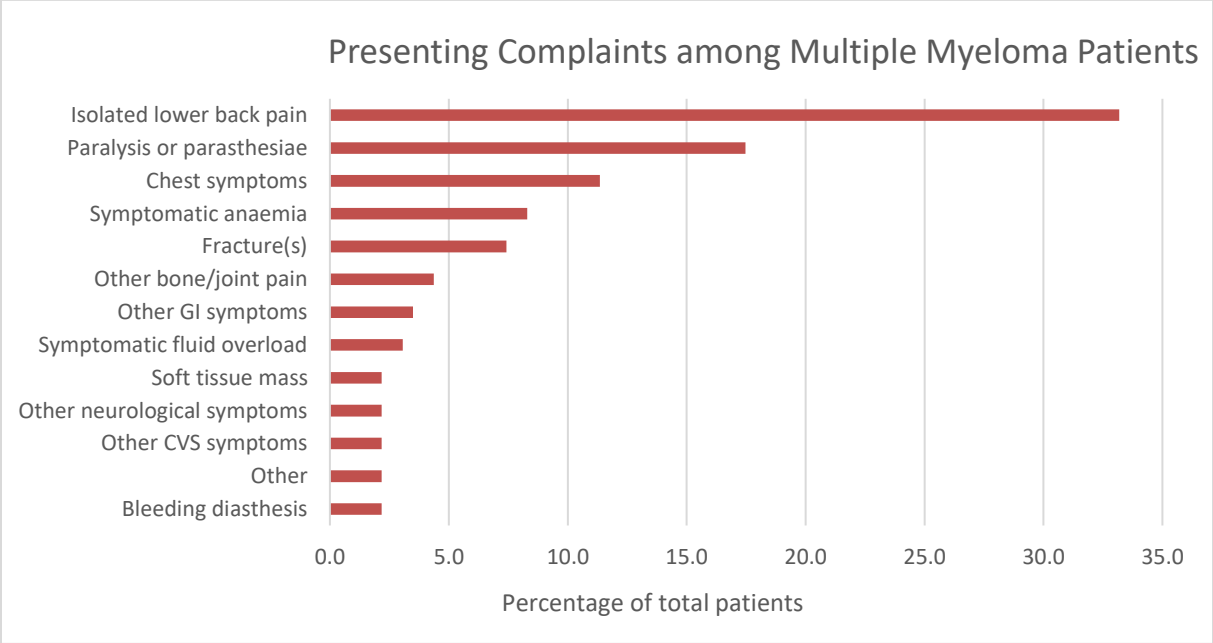

Figure 4: Frequency of Presenting Complaints among MM patients

6.3.2 Lifestyle Factors and Pre-Existing Conditions among MM Patients seen at KNH

Information on cigarette smoking and alcohol use was documented in 126 out of the 207 patient files (60.9%) but was not documented in 81 patients (39.1%) [Figure 5].

From those with smoking and alcohol data recorded, 89 out of 126 patients (70.6%) neither smoked nor took alcohol, 16 (12.7%) patients smoked and took alcohol, 11 (8.7%) only took alcohol and 10 (4.7%) smoked but did not take alcohol.

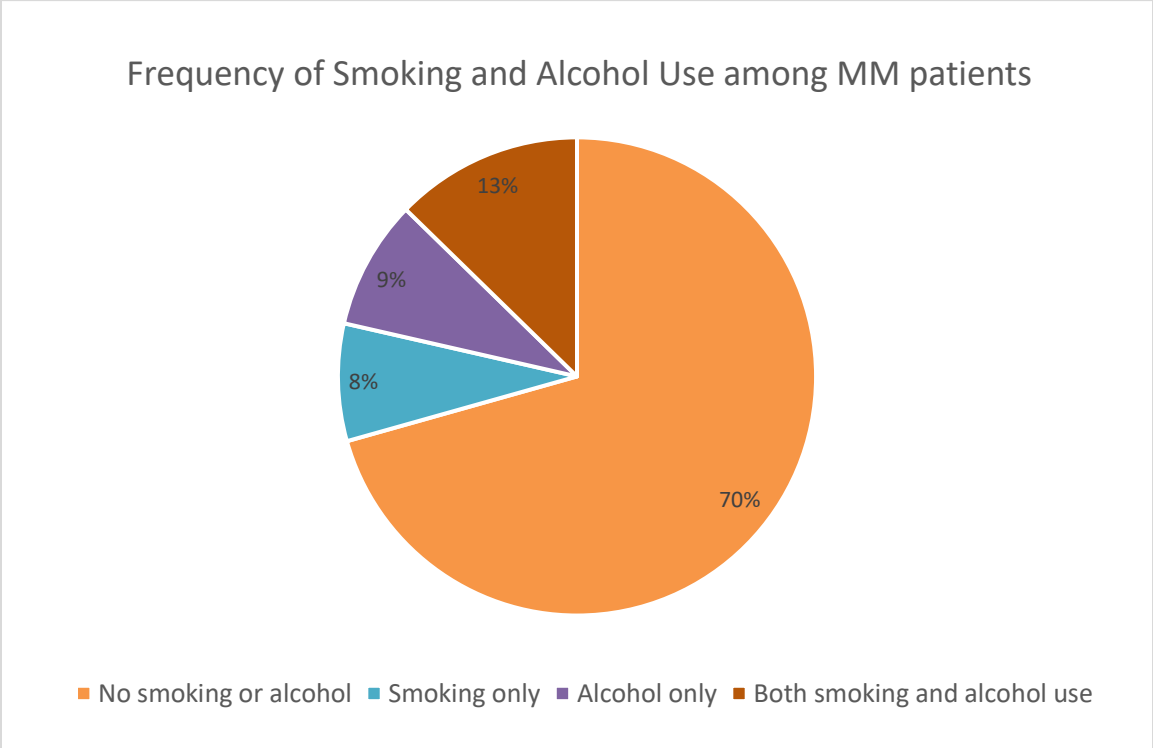

Figure 5: Smoking and Alcohol Use among Multiple Myeloma Patients

Information on pre-existing co-morbidities was recorded in 67 files (32.3%) out of 207 patients diagnosed with multiple myeloma at KNH [Figure 6]. This information was not documented for 140 patients (67.6%). The most common co-morbidity was hypertension in 40 of the 67 patients (59.7%), including those who had both hypertension and diabetes mellitus.

Of 104 patients who had had a HIV test done, only three (2.9%) were found to be HIV positive.

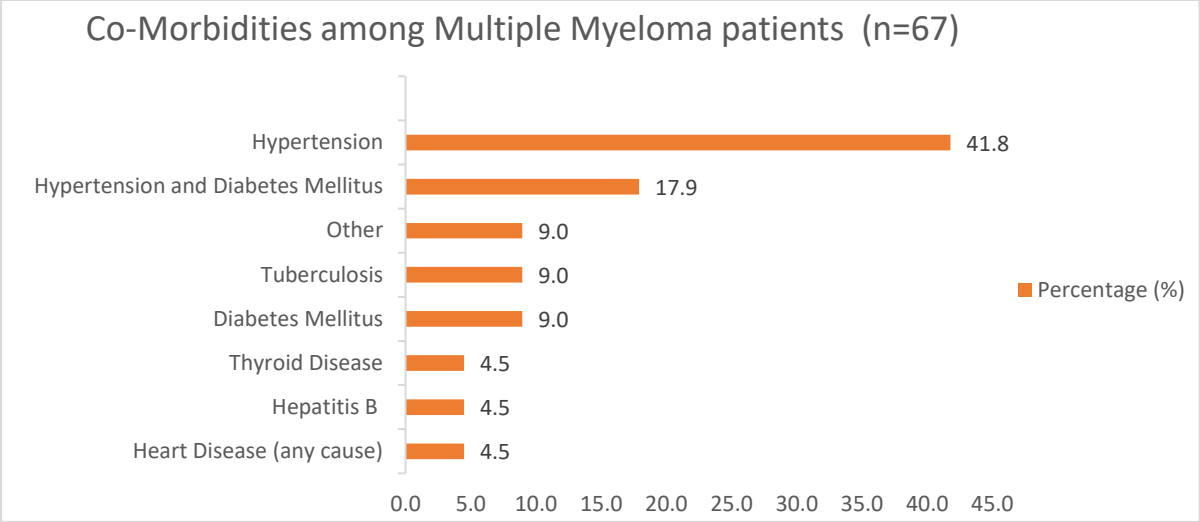

Figure 6: Co-morbidities among Multiple Myeloma Patients at KNH

6.3.3 Diagnosis and Staging of Multiple Myeloma at KNH

One-hundred and forty patients had a bone marrow aspirate cytology done as part of their diagnosis. Of these, 116 of them (82%), had more than 10% plasmacytosis of the bone marrow. High plasma cell infiltration of the bone marrow, described as more than 60% plasmacytosis, was found in 43 (30.7%) patients at diagnosis. The mean percentage plasmacytosis in the bone marrow was 43% plasma cells (SD: 28%).

Twenty-six (12.6%) of patients had a tissue biopsy done that were positive for presence of plasma cells.

A serum protein electrophoresis was done to diagnose MM in 139 (67.1%) patients [Figure 7]. M-protein was detected in 114 (82%) of the 139 tests done. The mean M-protein component at diagnosis was 35.52 g/l (SD 30.6g/l) with a median of 33.8g/l (IQR 5 -53g/l). 41 patients (19.8%) had a SPEP report but no BMA cytology or biopsy-proven plasmacytoma.

Other auxiliary diagnostic tests included urine test for Bence-Jones protein done in fifty-eight patients (25.3%) of which, 42 (73%) were positive and serum free light chain testing done in 16 (7.7%) patients. Ten patients (62.5%) had predominantly free kappa light chains and six (37.5%) had predominantly free lambda light chains.

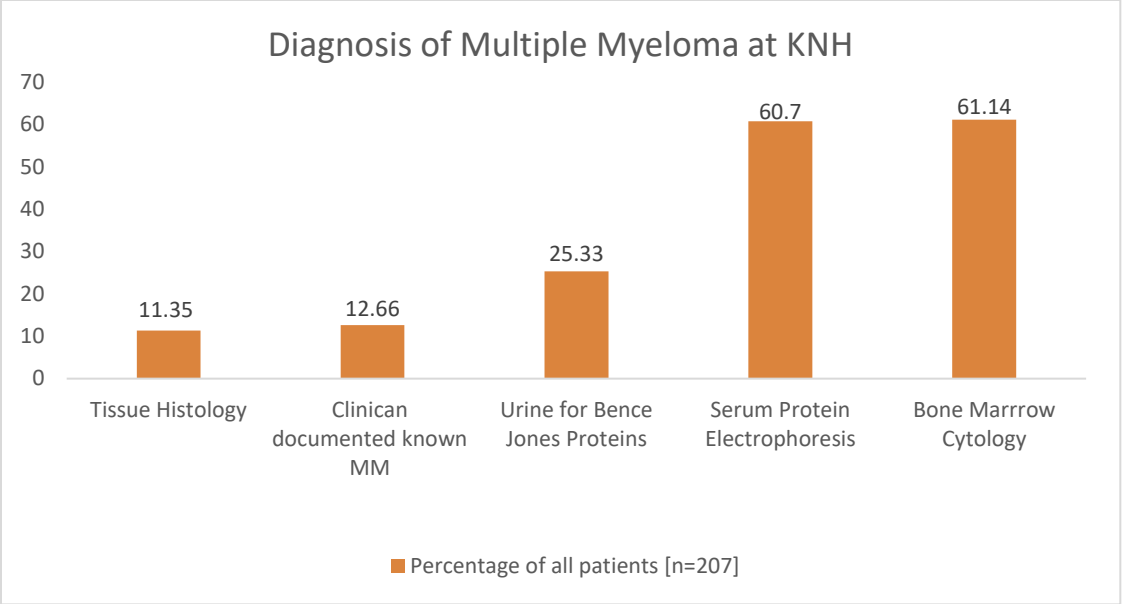

Figure 7: Diagnostic tests for Multiple Myeloma at KNH

Serum beta-2 microglobulin was tested in 21 (9%) of patients. All tests were done by external laboratories outside of KNH. Using the International Staging Score (ISS) [Table 2] for MM, 3 (14.3%) patients had stage 1 disease, 5 (23.8%) had stage 2, and 11 (52.4%) had stage 3 disease.

6.4 Myeloma Defining Events

All 207 patients included in the study had valid haemoglobin and serum creatinine levels on file that were used to determine the presence of MDEs. There were no missing reports. Serum calcium levels were available for 178 patients (86%), with no tests requested for 29 patients (14%). Imaging for skeletal osteolytic lesions was done in 139 patients (67.2%), with no imaging requested for in 68 patients (32.8%).

Anaemia, defined as haemoglobin less than 10g/dl, was present in 147 (71%) patients at diagnosis. Of the 147 patients that had anaemia, 88 (59.9%) had a moderate anaemia, defined as a haemoglobin level of between 7 and 9 g/dl. Renal dysfunction, defined by the IMWG as serum creatinine >177umol/l, was found in 79 (38.2%) patients at diagnosis. Hypercalcemia was present in 127 (55.4%) of patients at diagnosis (n=178).

Evidence of osteolytic bone lesions and/or compression fractures were seen in 126 patients (90.6%) out of 137 patients that had documented imaging. Magnetic Resonance Imaging (MRI) was the most common modality, done in 69 (50.4%) patients, 39 (28.5%) had a Computer Tomography (CT scan) and 29 (21.1%) had conventional x-ray radiography done.

Table 4: Prevalence of Myeloma Defining Events among Multiple Myeloma Patients at KNH

Myeloma Defining Events	Frequency	%
Anaemia	**[N=207]**	
No anaemia (Hb>10g/dl)	60	29.0
Mild (Hb 10g/dl)	5	2.4
Moderate (Hb 7-9.9 g/dl)	88	42.5
Severe (Hb<7 g/dl))	54	26.1
Renal function (Creatinine levels >177 umol/l)	**[N=207]**	
Renal dysfunction	79	38.2
Calcium levels (calcium level>2.75) [n=178]		
Hypercalcemia	127	55.5
Osteolytic bone lesions on imaging	**[n=137]**	
One or more >5mm osteolytic bone lesions	126	91.9%

6.5 Treatment

Treatment was prescribed in 184 out of 207 patients (88.9%). In 23 patients (11.1%), the treatment prescribed was not on file; some patients died before treatment was prescribed, some discharged before treatment was initiated, while some were referred to KNH for radiotherapy only and their chemotherapy was not documented.

There were 27 different combination treatment regimens for MM used at KNH within the study period [Table 6]. Forty-five of the 184 patients (24.5%) were initiated on combination therapy with thalidomide and dexamethasone, 40 (21.7%) patients were put on melphalan, prednisone and thalidomide and 36 (19.6%) were on melphalan and prednisone. Twenty-seven patients (13%) required a change to second-line therapy over the course of their treatment.

Table 5: Regimens used in Treatment of Multiple Myeloma at KNH

Treatment Regimen Prescribed	Frequency	%
Thalidomide+Dexamethasone	45	24.5
Melphalan+Prednisone+Thalidomide	40	21.7
Melphalan+Prednisone	36	19.6
Cyclophosphomide+Thalidomide+Dexamethasone	9	4.9
Bortezomib+Thalidomide+Dexamethasone	6	3.3
Bortezomib+Lenalidomide+Dexamethasone	6	3.3
Thalidomide+Prednisone	5	2.7
Melphalan +Prednisone+Cyclophosphamide	5	2.7
Prednisolone only	5	2.7
Cyclophosphomide+Dexamethasone	4	2.1
Melphalan+Thalidomide	3	1.6
Melphalan+Thalidomide+Dexamethasone	2	1.1
Lenalidomide only	2	1.1
Dexamethasone only	2	1.1
Cyclophosphomide+Prednisone	2	1.1
Lenalidomide+Dexamethasone	2	1.1
Bortezomib+Dexamethasone	2	1.1
Melphalan+Lenalidomide+Dexamethasone	1	0.5
Melphalan+Lenalidomide	1	0.5
Cyclophosphomide+Melphalan+Prednisone+Thalidomide	1	0.5
Thalidomide Only	1	0.5
Cyclophosphomide+Doxorubicin+Vincristine	1	0.5
Bortezomib+Pomalidomide+Dexamethasone	1	0.5
Thalidomide+Cyclophosphomide	1	0.5
Cyclophosphomide+Prednisone+Vincristine	1	0.5
Total	**184**	**100**

Table 6: Triplet Therapy Combinations used in First-Line Multiple Myeloma Treatment at KNH

	Frequency (N=184)	%
Triplet Therapy	**72**	**39.1%**
Melphalan-based	**49**	**26.6%**
Melphalan+Prednisone+Thalidomide	40	
Melphalan+Prednisone+Cyclophosphamide	5	
Melphalan+Thalidomide+Dexamethasone	2	
Melphalan+Lenalidomide+Dexamethasone	2	
Cyclophosphamide-based	**12**	**6.5%**
Cyclophosphamide+Thalidomide+Dexamethasone	9	
Cyclophosphomide+Doxorubicin+Vincristine	1	
Cyclophosphomide+Vincristine+Prednisone	1	
Cyclophosphomide+Doxorubicin+Vincristine	1	
Bortezomib-based	**11**	**6%**
Bortezomib+Thalidomide+Dexamethasone	6	
Bortezomib+Lenalidomide+Dexamethasone	4	
Bortezomib+Pomalidomide+Dexamethasone	1	

6.5.1 Exposure to IMIDs and Proteosome Inhibitors

IMIDs and proteasome inhibitors were prescribed in 80% of patients (148 out of 184) over the course of their treatment, as part of either first-line or second-line therapy. Among IMIDs, thalidomide was the most commonly prescribed drug in this group, prescribed to 110 patients of all patients with the less toxic novel IMID, lenalidomide prescribed in only 15. Among proteasome inhibitors, bortezomib was prescribed in a total of 22 patients as part of dual or triplet, first-line or second-line regimens [Figure 9].

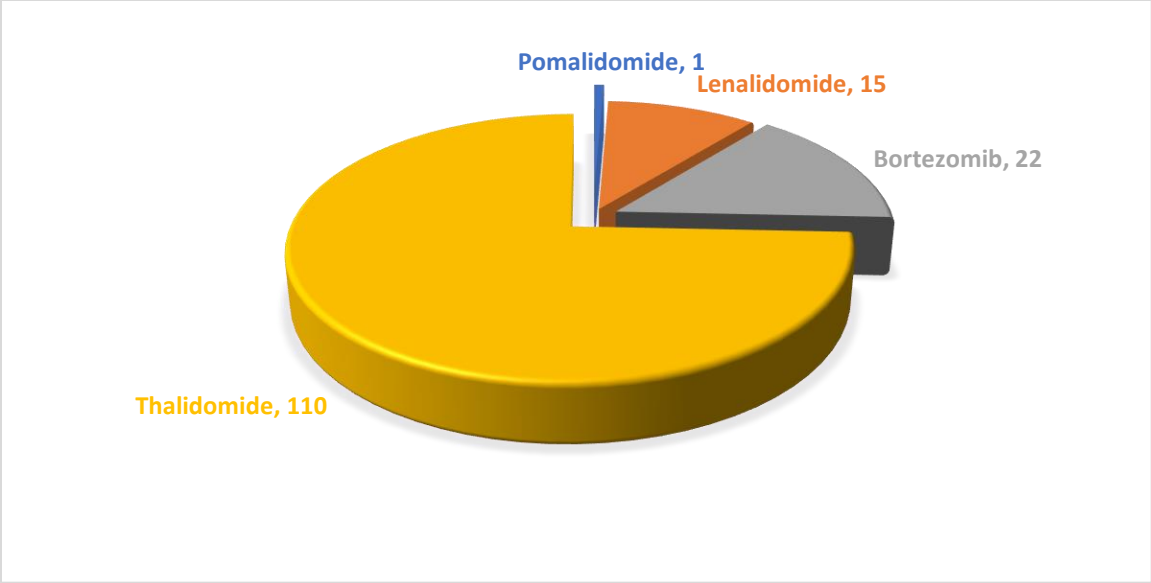

Figure 8: Frequency of Use of IMIDs and PIs in Multiple Myeloma Treatment at KNH

6.5.2 Supportive Treatment

Seventy-three patients (35.%) required transfusion of blood and blood products transfusions while 22 (10.6%) required dialysis. Bisphosphonates were prescribed in 82 patients (39.6%), most commonly an intravenous infusion of zoledronic acid. Radiotherapy was indicated in 83 patients (40%).

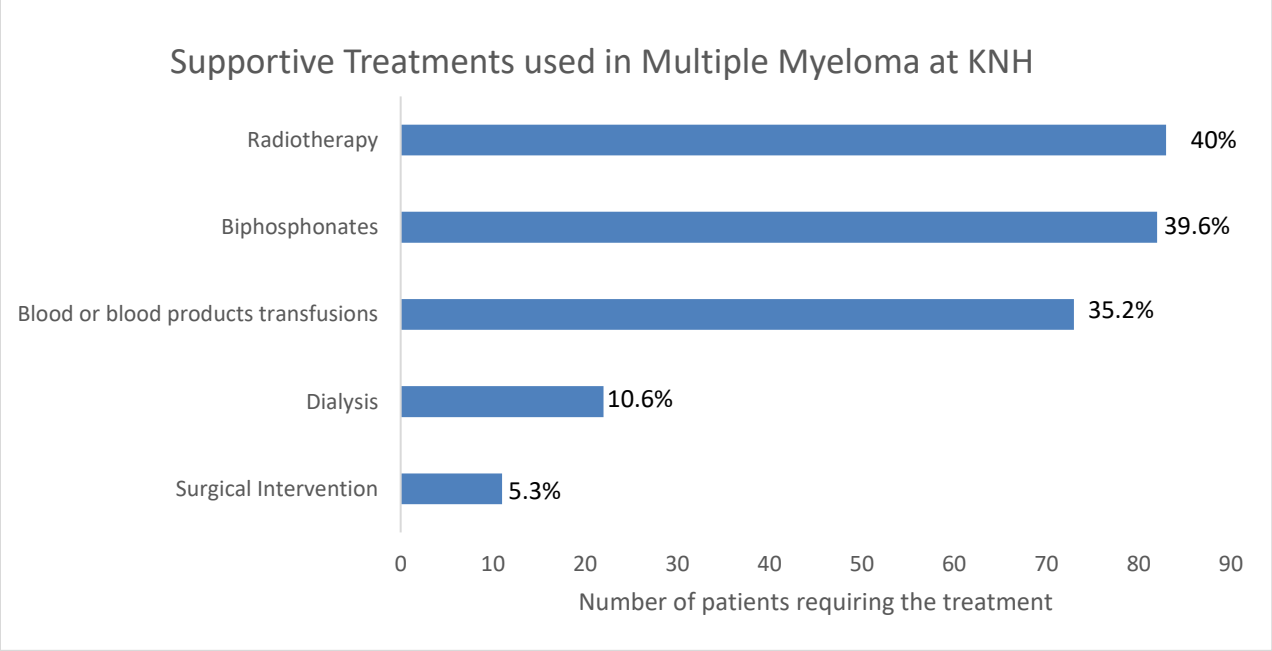

Figure 9: Frequency of Supportive Treatment requirements among Multiple Myeloma Patients

6.6 Outcome

The median duration of in-patient hospital stay among patients diagnosed with MM in their first admission was 23 days [IQR 10-43 days]. The mean stay was 38 days (SD; 67.6 days). Fifty-two (22%) patients had a non-chemotherapy related re-admission at KNH over the course of their management.

The median duration of follow-up was 52 weeks [range (IQR) 18 – 236 weeks]. There were 77 (33%) recorded deaths from the total study population at date of last known follow-up. However, the outcome in 130 patients (67%) at date of last-known follow-up could not be ascertained and censoring was done at date of last known follow-up.

On secondary exploratory analysis, several patient and clinical factors were analyzed for any increased risk of mortality. Presence of severe anaemia (Hb <7g/dl) was associated with increased risk of mortality [HR 3.38, 95% CI 1.7-6.7 (p=<0.0001]. Hypercalcemia was also significantly associated with increased risk of mortality [HR 1.93, 95% CI 1.14-3.26 (p=0.01]. Renal dysfunction (serum creatinine >177 uMol/l) at diagnosis was associated with an increased risk of mortality [HR 1.67, 95% CI 1.02-2.75 (p=0.04]. Age and sex did not show any significant association with increased risk of mortality.

Table 7: Factors Associated with Increased Risk of Mortality in Multiple Myeloma

Variable	Haz. Ratio	[95% Conf.	Interval]	P value
Age	1.01	0.99	1.04	0.23
Gender				
Female	1 (reference)			
Male	1.28	0.77	2.13	0.33
Severity of anaemia				
No anaemia	1.00 (reference)			
Mild	0.00	0.00		1.00
Moderate	1.60	0.82	3.09	0.17
Severe	3.38	1.71	6.70	<0.0001
Calcium levels at first admission				
No hypercalcemia	1.00 (reference)			
Hypercalcemia	1.93	1.14	3.26	0.01
Creatinine level at first admission				
Normal	1.00 (reference)			
Renal dysfunction	1.67	1.02	2.75	0.04

CHAPTER 7: DISCUSSION

A total of 207 MM patients were included retrospectively covering a five-year period, from January 2014 to December 2018. This was a higher number than that of a previous review at KNH covering ten years, from 1994 to 2004,which identified 173 cases[2]. A review of MM patients in Kenya at a private tertiary hospital captured 74 patients over a 12-year period[5]. The number of patients diagnosed and managed for multiple myeloma at KNH may have increased due to increased awareness of cancer in the general population, wider availability of diagnostic services as well as a general increase in the Kenyan population over the last two decades.

This being a retrospective review, we relied on the medical records as kept by the KNH registry. The digitisation of the file system coding using the ICD (International Classification of Disease) method assisted in quick and comprehensive identification of file numbers that were classified under C-90 Multiple Myeloma, and may have influenced the comparably higher number of cases identified by this study compared to the study done at KNH in 2004[2]. There was a general improvement in filing medical records that contributed to the completeness of data available for the study; evidenced by the availability in file of laboratory results, specifically, the full hemogram and renal function tests, for all study patients, where previously only 53% (92/173) of hemograms and 33.5% (58/173) of renal function tests were traced[2]. However, there were several challenges experienced. The actual retrieval of files was difficult due to the lack of a reliable file tracking system for the file once it is signed out of registry, which contributed to 41 files being untraceable and marked as "missing". Several retrieved files were misclassified under MM yet had a different diagnosis from the clinician notes. Verification of the diagnosis during transcription onto the digital platform would reduce the errors and loss of valuable information, as some MM files may have in turn been misclassified under a different ICD code.

The socio-demographic data showed a mean age of 58.5 years, with a median age of 60 years, with only 6.5% of patients being under 40 years. This was as not as expected, as MM is considered a disease of the aging population. An earlier local study by Othieno-Abinya *et al* (2004) described a median age of 53 years in Kenya, this difference may be attributed to an increased life expectancy in Kenya in the past two decades[2], with more people living to myeloma age. Our findings were consistent with more recent studies done locally by Kireka *et al* (2014)[5] and regionally, by Olaniyi and Fowodu (2015) in Nigeria[58] who also reported a median age of 57.9 and 60 years respectively. However, our findings are different from studies done in the West that reported a much higher age at diagnosis, for example, Kristinsson *et al* who looked at MM from 1973 to 2003 and reported a median age of 69.9 years (range 19 – 101)[14] and Kyle *et al* (1985 - 1998) found a median age of 66 years[4]. This may be attributable to their relatively longer life expectancy.

The male to female ratio of 1.2:1. This was consistent with cancer registry in Uganda by Wabinga *et al*[59] and Akinbami *et al* in Nigeria who reported a ratio of 1.4:1[60], a slight preponderance of MM among males. The regional distribution of patients managed for MM at KNH is skewed towards central and lower eastern counties which are in proximity of Nairobi county and can be attributed to proximity, healthcare seeking behaviour and not necessarily a higher incidence of disease in these regions.

Lifestyle factors such as cigarette smoking and alcohol intake have been linked to increased risk of several malignancies. Majority of the patients in this study had no history of smoking or alcohol use, which is not unexpected, as neither smoking nor alcohol use has been conclusively linked to an increased risk of MM. In a pooled analysis of 9 case-control studies on MM in the USA, Andreotti *et al* showed that ever smokers, current smokers and former smokers showed no increase in MM compared to non-smokers[62]. The relationship between alcohol and MM is also inconclusive. A meta-analysis of 5694 MM patients by Rota *et al* (2014), showed no strong association between alcohol and MM[63].

Information on lifestyle factors was not recorded for 39% of the study population, while information on co-morbidities was not recorded for 67% of patients. Although this was not an objective of the study, the amount of missing information suggests poor documentation and under-reporting of co-morbidities and lifestyle factors in the day-to-day clinical practice at the institution.

As expected, bone pain was a prominent complain, reported in as many as 59% of the patients on first presentation. This is comparable to findings by Mukiibi and Kyobe who in a previous study in KNH found a prevalence of 66.6%[64] but higher than that found by Othieno-Abinya of 27.4%[2]. Patel (1999), who did a prospective study, following up patients at a South African hospital for five years, found a much higher prevalence of bone pain at 94%[6]. This great variation may be due to the subjective way in which presenting complaints are usually recorded by clinicians. In retrospective studies such as this one, where the information is extracted from patient files, the clinician may not have deemed bone pain as a distinct clinical complaint whereas in prospective studies, the researchers may be more aware of the significance of bone pain and record it, resulting in much higher recorded prevalence.

Isolated lower back pain and paraparesis or paralysis, were the most common complaints at presentation. However, we also found a number of patients who presented with atypical symptoms. Several patients complained of chest pain and were evaluated for respiratory disease (11%), others presented with limb fractures (9%) and some had deep pain in other sites (4%), were subsequently diagnosed with MM. Some patients presented with symptomatic anaemia (8%), bleeding tendencies (2%) and fluid overload (3%) only to be later diagnosed with MM. Kishore *et al* (2019), described similar unusual and rare presentations, such as fluid overload, chest symptoms and limb fractures in MM patients[65]. It is important for first-line clinicians to recognise these atypical clinical presentations, which may occur in the absence of typical bone pain, and increase their index of suspicion for MM.

For this study, a case required a BMA report, tissue histology or SPEP report to confirm a diagnosis of MM. As per international guidelines by IMWG [Appendix 2], make a diagnosis of MM, a diagnostic report from positive bone marrow cytology or/and tissue histology with at least one myeloma-defining event are required for diagnosis. All 207 files included in this study met the IMWG criteria of diagnosis. Further analysis of pathology of the disease based on the bone marrow and serum paraprotein levels were therefore possible. Patients with plasmacytosis of >10% was 82%, which in addition to the presence of a myeloma defining event, fulfilled the 2014 IMWG diagnostic criteria for MM [Appendix 2].

Tissue biopsy confirming a plasmacytoma, in addition to the presence of a myeloma defining event was available for 12.6% of patients. Of those that had a BMA done, 30.7% of patients had high (>60%) plasmacytosis at diagnosis. High levels of plasma cells in the bone marrow may be associated with more severe disease. Kastritis *et al* (2013) looking at MM patients as part of the Greek Myeloma Working Group, found that patients with plasmacytosis of >60% have a much higher risk disease compared to those with less plasmacytosis. Their progression of disease is quite fast at 15 months, with severe anaemia and lytic bone lesions being the most prominent features of progressive disease[66]. The association between high plasmacytosis and severe disease could not be established in this study, nor whether having high plasmacytosis affected treatment regimen selected. Given that almost a third of patients at KNH may have MM associated with higher risk disease, it is advisable to identify and follow-up such patients closely as they may require more aggressive treatment to reduce disease progression.

Majority of MM patients (82%) of the patients had a confirmed secretory myeloma. While presence of M protein is not required in diagnosis of MM using the updated IMWG criteria, it assists in classifying MM as secretory on non-secretory. Secretory MM carries a poorer diagnosis than non-secretory MM. Circulating M protein (IgG) secreted in MM has been associated with progressive risk of renal disease specifically cast nephropathy (myeloma kidney), monoclonal Ig deposition disease (MIDD) and amyloidosis[33]. Acute renal injury from proximal tubule cell cytotoxicity and tubulointerstitial nephritis can also occur from serum free light chains[67]. Although not assessed in this study, peripheral neuropathy and life-threatening hyperviscosity syndrome are other systemic consequences of high levels of circulating M protein that require prompt clinician diagnosis and treatment[68].

There was generally a heavy burden of MM related end-organ disease (MDEs) in the study population. Although this was a retrospective records-based study, the results for laboratory investigations done to check on presence of anaemia and renal dysfunction were present in all eligible files. The presence of anaemia (71%) was higher than that of previous local studies[2,5]. This may be linked to the tendency of patients at KNH presenting in late stage disease with high plasma cell infiltration of bone marrow with reduced hematopoesis, as seen by 30% of patients having >60% plasmacytosis. However, the prevalence of renal dysfunction (38.2%) was comparable to other studies [Table 1]. Of note, the definition used in

this study of renal dysfunction was based on serum creatinine levels which may underestimate the disease burden in elderly populations and patients with low muscle mass[69].

Hypercalcemia was found in 55% of our patients which was higher than that reported in local and international studies. Serum calcium levels were not done at diagnosis for 29 patients. This is an oversight as all multiple myeloma patients should be worked up for hypercalcemia. Several factors could have led to the higher rate of hypercalcemia in our population. One could be increased bone destruction in patients presenting at KNH as evidenced by the high number of patients with multiple osteolytic lesions at diagnosis, which was 91% of our patients. A large multinational systematic review done by Mohty *et al* (2018) who only found presence of lytic lesions in 67.5%-71.5% of patients[70]. Hypercalcemia could also be related to the extensive bone destruction by the high plasma cell infiltration seen in almost a third of MM patients at KNH as described by Kastritis *et al* (2013)[66].

Presence of these MDEs confer an added burden in the management of these patients as seen in the need for supportive therapies such as bisphosphonates and blood transfusions in more than a third of patients, and renal replacement therapy in 10.6%. Hospitals that care for MM patients would require to facilitate the availability of supportive treatments to reduce morbidity of affected patients. There may also be an increased risk of mortality in patients who present with severe anaemia (haemoglobin <7 g/dl), hypercalcemia and renal dysfunction at diagnosis. However, the study not been powered to detect any associations and these findings are considered exploratory.

Staging information was available for those that had a serum beta-2 microglobulin level on file. It is noted that for those who did the test, most patients (52.4%) had ISS stage 3 that portends a lower overall survival. However, serum beta-2 microglobulin was not done in majority of patients; this may be due to unavailability of the test at KNH and the high cost in outside laboratories.

There were 27 combinations of drugs used in MM treatment at KNH with significant variations in the treatments prescribed by physicians which suggests a likely absence of standard treatment guidelines in the institution. The many different combinations mirror the findings of a large prospective multinational non-interventional study on MM treatment carried out in Africa, Europe and the Middle East by Mohty *et al* (2018) that revealed great diversity in current treatment regimens used in MM[70]. They attributed this to the evolution of treatment regimens as well as varied access to the increasing number of available MM treatments.

The 2019 Kenya national cancer treatment protocols recommend several bortezomib-based regimens as first line for both transplant eligible and non-transplant eligible patients[52]. However, only 11 (6%) of the patients at KNH were on triplet bortezomib-based regimen as a first-line regimen. For non-transplant eligible patients, the VISTA trial (2008), a multinational, open-label randomised trial with 683 patients,

reported a statistically significant difference in overall survival when bortezomib-based regimen was compared with a non-bortezomib-containing regimen (HR 0.65; $p < 0.001$)[12]. Bortezomib-based regimens have since become standard of care in both the European (ESMO) and American (NCCN) guidelines[49,50]. The national treatment protocols may be adopted for use by KNH to establish a standard of care for MM for the hospital. However, a prospective study of clinician, patient and institutional barriers may be required to elucidate the causes of low uptake of newer regimens. For example, although the drug is sold at a subsidized cost in the Kenyan market, it may still be unaffordable to most patients, even through NHIF. Accessibility to facilities that handle and administer bortezomib, which is given as a subcutaneous injection, may also be a factor. Further, several patients with MM suffer from debilitating back pain, paralysis and fractures that may hinder their mobility and therefore clinicians may opt to not prescribe an injectable preparation that requires a clinic visit.

CHAPTER 8: CONCLUSION

Multiple Myeloma in KNH is a disease of the middle aged, affecting men and women almost equally, and presenting mainly with bone pains and anaemia. Though there seems to be a general improvement in diagnosis and care, access to less-toxic novel agents for treatment is still wanting.

Recommendations

Development of standard printed checklists/proforma with a complete list of relevant clinical data and laboratory investigations to be attached to each MM patient file at diagnosis is recommended.

Standardization of treatment regimens for multiple myeloma at hospital to include evidence-based optimal drugs in the management of myeloma

A prospective registry of MM patients at KNH would be able to expand on the findings of this study and provide longitudinal data on the morbidity, treatment and survival of MM patients in Kenya

Study Limitations

As a retrospective records-based study, there was possibility of interviewer (recorder) bias during data extraction from the files. This was mitigated by use of standardised questionnaires with controlled data entry formats and training of the research assistant to subject each file to the same degree of scrutiny.

Confounding factors that may have influenced the findings of the study, for example, reasons for selection of diagnostic investigation used or treatment selected, were not collected. This may affect the contextual interpretation of the findings.

It was a single centre study and therefore cannot be generalised to other centres that may offer other diagnostic and treatment modalities in management of MM patients.

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APPENDIX 1: DATA EXTRACTION FORM

MULTIPLE MYELOMA KNH 2014 -2018

* Required

1. File No *

2. Unique Identifier Number *

3. Age *

4. Sex *

Mark only one oval.

- Female
- Male

5. County of Residence

6. Occupation

7. Ward/Clinic *

Mark only one oval.

- Medical Ward (7 or 8)
- Private Wing (9,10)
- Surgical Ward (4, 5, 6)
- Outpatient

CTC

8. Date of first admission or review *

Example: January 7, 2019

9. Date of discharge from the ward (for inpatients)

Example: January 7, 2019

10. Was the patient referred?

Mark only one oval.

- Yes
- No
- Unknown

11. If yes, please specify referring facility *Mark only one oval.*

- County Hospital
- Private Facility
- Outpatient Clinic at KNH
- Inpatient KNH
- Other: _____

Clinical and lab presentation

12. Major presenting complaint
please select the main presenting complaint

Check all that apply.

- Lower Back Pain
- Paralysis or Paraparesis
- Symptomatic anaemia
- Fluid overload e.g lower limb or facial swelling
- Dehydration
- Nausea, Vomiting

Other: _____

13. System affected by major presenting complaint * *Mark only one oval.*

- Genitourinary
- Gastrointestinal
- Musculoskeletal
- Central Nervous Sytem Respiratory

Hematological

Other cardiovascular

Asymptomatic

14. Co-morbidities

Check all that apply.

- [ ] Hypertension
- [ ] Diabetes Mellitus
- [ ] Heart Disease
- [ ] Retroviral Disease

Other: [ ] _____

15. Does the patient have a history of smoking?

Mark only one oval.

- ◯ Yes
- ◯ No

Not known

16. Does the patient have any history of alcohol intake?

Mark only one oval.

- ◯ Yes
- ◯ No

Not Known

17. Were any of the following tests done at presentation or within first admission? *

Check all that apply.

- [ ] Bone Marrow Cytology
- [ ] Urine for Bence Jones Proteins
- [ ] Serum Protein Electrophoresis
- [ ] Beta 2 microglobulin
- [ ] Tissue Histology
- [ ] Imaging

Other: [ ] _____

18. If there was a BMA report, kindly enter the percentage of plasma cells found in the bone marrow

_____

19. If there was a serum protein electrophoresis done, kindly enter the results in the space provided: alpha protein

_____

20. If there was a serum protein electrophoresis done, kindly enter the results in the space provided: beta 1 protein

21. If there was a serum protein electrophoresis done, kindly enter the results in the space provided: beta 2 protein

22. If there was a serum protein electrophoresis done, kindly enter the results in the space provided: gamma protein

23. If there was a serum protein electrophoresis done, kindly enter the results in the space provided: M protein

24. What was the patient's total white cell count at admission? *

25. What was the patient's hemoglobin (g/dl) level at admission? *

26. What was the patient's total platelet count at admission? *

27. What was the patient's serum urea in the first admission? number *

28. What was the patient's serum creatinine (in uMol/L) in the first admission? number *

29. What was the calcium level (in mMol/L)of the patient in the first admission? number *

30. What was the serum beta-2 microglobulin level at first admission?

31. What was the LDH level at first admission

_____

32. What was the serum total protein level?

_____

33. What was the serum total albumin level?

_____

34. What was the stage of Multiple Myeloma at presentation (according to ISS staging criteria)?

Mark only one oval.

- Stage 1
- Stage 2

Stage 3

35. Which of the following drugs were included in the first treatment regimen prescribed at the point of diagnosis of MM? (Tick all that apply)

Mark only one oval.

- Melphalan
- Prednisone
- Thalidomide
- Dexamethasone
- Bortezomib
- Lenalidomide
- Cyclophosphomide
- Vincristine
- Other: _____

36. Did the patient received any of the following novel agents during the course of their treatment? (Tick as many as applicable)

Check all that apply.

- None
- Thalidomide
- Lenalidomide
- Other IMID, please specify

Bortezomib

Other PI, please specify

37. What are other additional, if any, supportive treatments were requested? (Tick as many as applicable)

Check all that apply.

- [ ] Renal Replacement Therapy i.e. dialysis
- [ ] Blood or blood products transfusion
- [ ] Radiotherapy
- [ ] Biphosphonates
- [ ] Surgery
- [ ] Human recombinant erythropoetin

Other: [ ] _____

Outcomes

38. Has the patients had a second ward admission at KNH?

Mark only one oval.

- ◯ Yes
- ◯ No

39. If yes, to above, what was the major presenting complaint?

Check all that apply.

- [ ] For chemotherapy
- [ ] For post-chemotherapy side effects
- [ ] For non-chemotherapy related illness

40. What was the date of the second admission?

_____

Example: January 7, 2019

41. What was the date of discharge of the second admission?

_____

Example: January 7, 2019

42. What was the patient's total white cell count at second admission?

_____

43. What was the hemoglobin level (g/dl) on the second admission?

_____

44. What was the patient's total platelet count at admission?

45. What was the patient's serum urea level at second admission?

46. What was the patient's serum creatinine level at second admission?

47. What was the patient's serum calcium level at second admission?

48. Was the patient admitted for a third time at KNH?

Mark only one oval.

- Yes
- No

49. What is the date of the last known follow-up for the patient? *

Example: January 7, 2019

50. What was the last documented outcome of the patient at the date of last follow-up? *

Mark only one oval.

- Ongoing first chemotherapy
- Remission
- Relapse
- Death
- Unknown

APPENDIX 2: Revised International Myeloma Working Group Diagnostic Criteria for Multiple Myeloma 2014

(Lancet Oncol 2014; 15: e538–48)

Definition of Multiple Myeloma: Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

Myeloma defining events: Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:

- Hypercalcaemia: serum calcium >0·25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2·75 mmol/L (>11 mg/dL)
- Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 μmol/L (>2 mg/dL)
- Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
- Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT

Any one or more of the following biomarkers of malignancy:

- Clonal bone marrow plasma cell percentage ≥60%
- Involved: uninvolved serum free light chain ratio ≥100
- >1 focal lesions on MRI studies

APPENDIX 3: Diagnoses from Files Misclassified as Multiple Myeloma at KNH Registry

Diagnosis	Number
Cardiac disease	4
Acute Lymphocytic Leukemia	4
Allergic Rhinitis	1
Acute Myeloid Leukemia	2
Cancer of esophagus	1
Cancer of prostate	4
Chronic Myeloid Leukemia	2
Cerebrovascular accident	1
Dead before MM confirmed	4
Degloving Injury	1
Did not meet MM diagnosis	5
Eczema	1
Erythema Multiforme	1
Glioblastoma	5
Lacrimal Gland Tumor	1
Metastatic Bone disease	1
Neonatal Sepsis, prematurity	3
Osteosarcoma	2
Paraspinal mass	1
Perforated duodenal ulcer	1
Pregnancy	2
Squamous cell carcinoma	1
Solitary Plasmacytoma	4
Tuberculosis of the spine	2
Traumatic Spinal Injury	2
Total	**56**

APPENDIX 4: Comparison of Excluded Files due to no Documented Evidence and Included Files

Variable of Interest	Excluded files (n=22)	Included files (n=207)	Total
Anaemia (hemoglobin <10 g/dl)			
No anaemia	7	60	67
Anaemia	11	147	158
Total	18	207	225
Pearson chi2(1)	0.7767	P = 0.378	
Hypercalcemia (serum calcium >2.75mmol/l)			
No hypercalcemia	6	51	57
Hypercalcemia	12	127	139
Total	18	178	196
Pearson chi2(1)	0.9034	P = 0.342	
Renal Dysfunction (Serum Creatinine >177 umol/l)			
No renal dysfunction	12	128	140
Renal Dysfunction	6	79	85
Total	18	207	225
Pearson chi2(1)	0.1644	P= 0.6851	