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COLLEGE OF HEALTH SCIENCE

SCHOOL OF MEDICINE

DEPARTMENT OF INTERNAL MEDICINE

Demographic, clinical characteristics, treatment outcome and determinant factors of patients with multiple myeloma at TASH from January 2015 to December 2019

A Five Years Retrospective Study

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December, 2020

Addis Ababa University

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December, 2020

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Abbreviations and Acronyms

ASCT	Autologous Stem cell Transplant
ASIR	Age-specific Incidence Rate
CVD	Cardio vascular disease
CyBorD	Cyclophosphamide – Bortezomib – Dexamethasone
DALYs	Disability-adjusted life years
DMX	Dexamethasone
D-S	Durie-Salmon
FISH	Fluorescence in situ hybridization
FMOH	Federal Ministry of Health
HDT	High dose chemotherapy
HMIS	Health Management Information System
IMIDs	Immunomodulatory drugs
IMWG	International Myeloma Working Group
ISS	International Staging System
MM	multiple myeloma
MPT	Melphalan – Prednisolone – Thalidomide
OS	Overall Survival
PFS	Progression-free Survival
PR	Partial Remission
RD	Lenalidomide plus Dexamethasone
SDI	Socio-Demographic Index
TASH	Tikur Anbessa Specialized Hospital
TD	Thalidomide plus Dexamethasone (high dose)
UNL	Upper normal limit
VAD	Vincristine – Doxorubicin – Dexamethasone
VRD	Bortezomib – Lenalidomide – Dexamethasone
VTE	Venous Thromboembolism

Abstract

Background of the study

Patients with multiple myeloma are being seen in increasing frequency in different hospitals of the country. However, local data regarding the demographic, clinical characteristics, treatment outcome, and risk stratification of patients is lacking. This study was designed to fill this existing gap in our setup. This will aid in the revision of treatment regimens based on a local data on the efficacy of treatment regimens and risk stratification of patients with a newly diagnosed Myeloma

Patients and Methods

A single centered Hospital-based retrospective Cohort study was conducted from January 2015 to December 2019. A total of 80 patients with newly diagnosed MM who received non Proteasome inhibitor based therapy at TASH, Addis Ababa, Ethiopia were analyzed in the study.

Results

In this cohort 63.8% of the patients were males (M:F ratio 1.76:1**)** and the median age at diagnosis was 52 years. The commonest complications identified were Anemia (56.3%) and pathologic fracture (55%). The commonest comorbid conditions were; systemic hypertension (24%), CKD (6.3%), and Diabetes (5%). The median PFS and OS of patients were found to be 17.5 and 20 months respectively. This study also identified factors like advanced DS stage, presence of Plasmacytoma, renal dysfunction, elevated serum LDH, high level of serum protein, and Monoclonal M protein to be significant contributors in negatively affecting OS and PFS of patients.

Conclusion

In our setup, Myeloma is more common in the male population group and our patients are younger than the western population. Myeloma treatment regimens like CP and CPT are found to perform less in our patients than in patients elsewhere. This is likely due to the advanced stage at presentation. In resource-limited areas, different clinical and laboratory parameters can still serve as of patient survival.

Keywords: multiple myeloma, clinical characteristics, PFS, OS, prognostic markers

1. Introduction

1.1 Background of the study

Multiple myeloma is a malignant hematologic disorder arising from the clonal expansion of mutated specialized mature B cells. It belongs to the group of hematologic disorders called Plasma cell neoplasms which encompasses conditions from the relatively stable plasma cell disorder with no identified organ dysfunction called essential monoclonal gammopathy to a rapidly advancing poor prognostic plasma cell leukemia. The prototype of plasma cell neoplasms, though, is multiple myeloma, which is marked by the development of end-organ dysfunction on top of the excessive proliferation of malignant plasma cells in the bone marrow and the formation or release of monoclonal M proteins.

With increasing life expectancy and aging of the population, the prevalence and incidence of multiple myeloma and related plasma cell disorders is currently rising to become an important public health problem worldwide.[(1)] Myeloma accounts for approximately 1 % of all malignant disorders and 10% of hematologic malignancies. In the western world, the age-standardized incidence is reported to be approximately 5 cases per 100,000 populations. [(2)] The Median age at diagnosis is reported to be 66 years with only 2% of patients being less than the age of 40 at diagnosis. Men are affected by multiple myeloma more frequently than women [(3)] and Individuals of African descent have twice the prevalence of MM as those of European descent. Though local national data on the magnitude of the disease is lacking, studies done in the indigenous African population suggested a progressively rising incidence and that MM accounts for around 13% of diagnosed cases of Hematologic malignancies[(4)].

Myeloma is characterized by multiple end-organ dysfunctions and the development of various complications that occur as a result of the expansion of malignant plasma cells in the marrow, tumor mass effect, the release of cytokines and other mediators by plasma cells, and deposition of myeloma proteins into target organs. Organ dysfunctions of the acronym CRAB (Elevated serum **C**alcium above normal limits, **R**enal dysfunction with Crcl >40ml/ml or Serum Cr >2mg/dl, **A**nemia with HgB <10gm/dl, One or more osteolytic **B**one lesions) attributed to the underlying plasma cell proliferative disorder defines the diagnosis of the disease.(5) Thrombogenesis and venous thromboembolism, recurrent bacterial infections, peripheral neuropathy, pathologic fracture, and hyperviscosity syndrome also occur either as a result of the underlying pathology or treatment agents used. The development of these complications contributes to the observed morbidity and mortality of patients with this particular disorder.

Multiple myeloma is a disease, which had been uniformly fatal within a few months of diagnosis. But following periods of dynamic change since the late 20th century, dramatic advances have been seen in the treatment of myeloma. With the introduction of new novel potent therapeutic agents and efficient stem cell transplant, significant major progress has been made in the treatment of patients with myeloma.(6) But still, due to the highly treatment-resistant myeloma stem cells and the supportive tumor microenvironment in the marrow, these patients will ultimately relapse, with some sooner than others, and will develop more aggressive and refractory disease.

Even though evolving treatment regimens through the years prolonged survival, they are un-satisfactory in giving a cure or a lasting treatment response. Therefore, the treatment of multiple myeloma is still continuously evolving and different international groups and treatment centers suggest variable combination regimens in the treatment of both newly diagnosed and relapsed patients with multiple myeloma.

Literature suggests various prognostic markers in the risk stratification of patients with multiple myeloma. These include; the presence of specific cytogenetic abnormalities, the extent of the disease by appropriate imaging techniques, the serum-free light-chain level, and the use of the International Staging System (ISS)**.**[(7)]But some studies also showed that complications and clinical presentations of myeloma like; severe anemia, infections, VTE, renal and Bone diseases can significantly compromise the quality of life of patients and could be important prognostic indicators determining survival and treatment outcome.[(8)] Hence, beside initiation of a selected appropriate treatment regimen in patients, follow-up, early identification and management of specific complications and organ dysfunctions associated with myeloma cannot be overemphasized for the sake of better treatment outcome.

1.2 Statement of the Problem

Though the Incidence of Myeloma is highly variable among different regions of the world, it has uniformly increased worldwide in the last few decades. The largest increase in incidence was seen in low and middle-income countries. [(1)] With the introduction of novel agents and the availability of ASCT, survival rates of cases of diagnosed MM improved significantly. However, access to effective care is very limited in low-income countries, particularly in sub-Saharan Africa.

Therefore, in the continuously evolving treatment of MM, it is always important to understand the treatment outcome of patients on a particular therapeutic regimen. Especially in developing countries like Ethiopia where potent novel agents of myeloma like Proteasome inhibitors were just recently introduced and standard stem cell transplant for eligible patients is not available, the extent

of treatment response and survival with the existing treatment regimens, mainly involving IMIDs, needs to be studied. Besides, in these resource-limited setups where internationally proven and accepted prognostic markers of multiple myeloma could not be applied into clinical practice, it would be reasonable to investigate and identify alternative clinical parameters determining treatment outcome and survival of patients.

1.3 Justification of the study

Hematologic malignancies are a group of non-communicable disorders that have a progressively rising incidence worldwide and in our country, Ethiopia. Out of these, multiple myeloma, which is a malignant neoplasm of Plasma cells, is seen in increased frequency in outpatient and inpatient departments of hospitals in the country. The disease burden is more predominantly seen in *Tikur Anbessa Specialized Hospital (TASH) located in Addis Ababa, Ethiopia,* as it has been the only tertiary referral treatment center for hemato oncologic disorders in the country.

The rise in incidence rate of MM in the country is assumed to be due to the improvement in disease awareness and better diagnostic services in health care setups. Nevertheless, local data regarding the magnitude, epidemiology, survival, and treatment outcome of patients with the disorder is lacking. Therefore, this study aims to provide a single-center experience regarding the demographic & clinical characteristics, treatment outcome, and important clinical prognostic factors determining the survival of patients managed at TASH in the five years of the study period specified. This study will aid in the revision of treatment regimens based on a local data on the efficacy of treatment agents and risk stratification of patients with a diagnosed Myeloma.

2. Literature Review

With the increasing life expectancy & aging of the population, the incidence and prevalence of patients with multiple myeloma is increasing worldwide with a tremendous impact on the economy of health. [(1)]

According to a report from a 13 years retrospective study done by the Mayo foundation for medical education & research, the median age at diagnosis of myeloma was 66 years with a M:F ratio of 1.4:1. Only 2% of the patients were less than the age of 40 years at diagnosis.[(3)] The study also showed that the prevalence of hypercalcemia, anemia, renal dysfunction, and bone disease (CRAB) was 13%, 19%, 73%, and 67% respectively. Twenty-six percent of patients encountered a pathologic fracture.[(3)]

Treatment and disease-related complications influence the quality of life and treatment outcome of patients with a diagnosed multiple myeloma. The appropriate prevention, diagnosis, and management of these complications are essential for improving patients' quality of life as well as improving survival.[(28)]

A significantly higher degree of occurrence of VTE as a treatment associated complication in patients taking Thalidomide as induction therapy compared with those given Dexamethasone as a monotherapy (17% Vs 3%) warrants the need for routine use of prophylactic anticoagulation in these group of patients especially in the first few months of therapy. In the absence of proper Prophylactic anticoagulation, the incidence of VTE can reach up to 70% in patients taking thalidomide in combination with dexamethasone.[(29)] With the initiation of therapy, appropriate risk stratification and use of one of the VTE prophylactic agents like ASA, LMWH or a full dose of warfarin is recommended.[(30)]

Polyclonal hypogammaglobinemia and suppressed CMI related immune deficiency has made recurrent infections to be a significant cause of morbidity and the leading cause of death in patients with myeloma.[(31)] The risk of infection is higher with high dose dexamethasone, melphalan, and lenalidomide and lower with thalidomide as it is not significantly myelotoxic.[(31)(32)]. Reactivation of viral infections like HSV and VZV are encountered with bortezomib therapy if not given appropriate viral prophylaxis.[(32)(33)(34)]

The management of multiple myeloma has continuously evolved through the years and the median OS of patients has been improving dramatically in the past few decades. The degree of initial disease control achieved with induction therapy, with or without a follow-up ASCT, is correlated

well with an improved outcome in terms of OS and PFS of patients.[15] The introduction of stem cell transplantation, wide use of novel anti-myeloma agents like proteasome inhibitors mainly bortezomib, and also immune modulators like thalidomide and lenalidomide contributed to this outcome.[16] The introduction of these new novel agents as front line therapy has improved response rates and also transplant outcomes by ensuring deeper and long-lasting responses.[16][17] HDT (usually with melphalan) with ASCT, following a successful induction therapy, is the current standard of care in eligible group of patients with MM.

In a multicenter randomized placebo controlled trial done to evaluate the efficacy of the immune-modulatory agent thalidomide, TD regimen used in newly diagnosed patients with MM showed overall treatment response (minimum PR) of 64%. Thrombosis, peripheral neuropathy, and constipation were the major reported treatment-related side effects.[18] Studies also proved a better survival with less toxicity by replacing high dose DMX with low dose (weekly dose of 40mg Prednisolone) when used with iMIDs in combination treatment of newly diagnosed patients with Myeloma.[19]

The triple combination therapy encompassing lenalidomide, bortezomib, and dexamethasone (VRD) was initially introduced as a salvage therapy in patients with relapsed or refractory disease at least after a single prior therapy.[20] In follow-up Prospective studies this regimen also showed a significant improvement in treatment outcome of newly diagnosed MM patients where participants achieved 18months OS of 97% and PFS of 75% with a favorable toxicity profile.[21] Another triple combination regimen, CyBorD, was also found to provide a rapid and profound overall response (>= PR) of 88% with tolerable and manageable Toxicities. [22]

These new highly efficacious treatment regimens also seem to abolish the previous treatment outcome difference in patients with adverse cytogenetics abnormalities.(22) Therefore, the triple combination therapy containing a Proteosome inhibitor and Immunomodulatory agents with the addition of low dose dexamethasone is regarded as the preferred front line induction therapy in newly diagnosed patients with MM.[22]

With the current advancement in therapy for myeloma and the introduction of newer agents, studies evaluating the efficacy of alternative regimens like CP, CPT, and MPT are derived only from older studies, few studies in resource-limited regions, and studies on fragile and elderly patients who remain ineligible for ASCT. According to these studies, the median OS and PFS of patients on these regimens is in the range of 33-50 months and 13-27 months respectively. [23][24]

Elderly and transplant-ineligible patients were able to achieve a median OS of 51.5 months with MPT as a standard front line therapy.[17] Bortezomib based treatment regimens appear to produce better and faster treatment response with less grade 3-4 toxicities when compared with IMIDs in the elderly population group.[25][26][27]

Monoclonal (M) Immunoglobulin, produced and detected in the serum of more than 95% of patients with multiple myeloma, is usually used for the diagnosis, prognostication, and treatment follow-up of these patients. B2 micro globulins are also other cell surface markers indicating tumor burden and survival time.[9] Serum level of free B2M alone is found to give an extremely reliable fit for predicting survival and treatment response both at diagnosis & follow-up. It is used as a vital component of the International staging scoring system (ISS) of Myeloma as it correlates well with the total body burden of myeloma cells.[10] Advanced ISS stages are proved to be associated with relatively poorer treatment response and shorter OS despite therapy.[7]

Few studies identified an elevated serum LDH level to be an important factor associated with a shortened period of survival.[11] High levels of serum LDH either at diagnosis or following high dose chemotherapy was shown to be associated with poor laboratory and clinical parameters like Hypercalcemia, high B2 microglobulin level, extraosseous disease, and renal failure.

Earlier studies done prior to the development of recent prognostic and staging systems have identified some clinical factors including Age>65 years of age, poor performance status, renal involvement, advanced *salmon Durie* stage, and severe anemia at presentation to have a statistically significant prognostic importance in predicting survival of patients with confirmed multiple myeloma.[8] The salmon Durie staging, put forward by Sydney E. Salmon (MD) & Brian G.M Durie first in 1975, tries to correlate the myeloma disease burden to treatment response and survival of patients.[12]

A retrospective study from the department of oncology in the university of Pretoria regarding prognostic factors in multiple myeloma identified laboratory markers like anemia (<11g/dl), hypercalcemia (>2.75mmol/l), elevated serum creatinine (> 150mmol/l), and ECOG performance status >= 3 to be associated with decreased survival. Age, sex, Durie-salmon staging, degree of lytic lesions, serum immune globulin concentration level, and percentage of plasma cells in the marrow were not significantly associated with survival of newly diagnosed white patients with MM.[13]

An African retrospective study conducted in a tertiary referral hospital in Ghana identified factors like severe anemia, hypercalcemia, deranged renal function, marrow plasmacytosis >20%, and advanced ISS stages were shown to be poor prognostic markers of survival.[5]

The treatment and survival outcome of patients with multiple myeloma is currently primarily dictated by cytogenetic abnormalities and the proliferative index of plasma cells. A study done by the Mayo clinic division of hematology showed that the presence of one of the poor cytogenetic markers including hypodiploidy, monoallelic deletion of chromosome 13 or translocations involving chromosome 14 (t(4,14),t(14,16)) by FISH or cytogenetics is associated with a statistically significant poor treatment outcome in terms of OS and PFS as compared to patients with standard risk.[14]

3. Objectives of the study

3.1 General Objective

- To assess the demographic, Clinical characteristics, treatment Outcome, and determinant factors of patients with multiple myeloma at TASH Hospital, Addis Ababa, Ethiopia

3.2 Specific Objectives

- To describe the demographic characteristics and major clinical presentations of patients with a newly diagnosed Myeloma
- To determine the major prognostic markers of survival of patients with a newly diagnosed multiple myeloma at TASH
- To identify the major disease and treatment-related complications encountered in patients with a newly diagnosed Myeloma in their treatment course
- To assess the median OS & PFS of patients treated at TASH for a newly diagnosed multiple myeloma

4. Methods and Materials

4.1 Study Setting

This study is conducted in the outpatient department of the unit of Hematology in *Tikur Anbessa specialized referral and teaching Hospital* located at *Lideta sub-city, Addis Ababa, Ethiopia*. The Hospital is the largest Tertiary referral Hospital in the Country accepting referrals from all over the country. The Outpatient department of the Hospital approximately manages an average of 400,000 patients yearly and out of these the outpatient unit of Hematology handles more than 15,000 patients every year.

4.2 Study Design

A single centered Hospital-based retrospective cross-sectional cohort study was conducted to assess the characteristics, treatment outcome, and major determinant factors in patients with a confirmed newly diagnosed multiple myeloma. Clinical records and laboratory data available for all illegible patients on follow up and treatment in the outpatient unit were reviewed.

4.3. Study Period

The study period for this retrospective study was from January 2015 to December 2019.

4.4 Study Population

4.4.1 Source Population

All patients who were on follow up at the outpatient department of the unit of Hematology at TASH in the specified study period.

4.4.2 Study population

All patients with a confirmed multiple myeloma, according to the IMWG diagnostic criteria, and on follow up at the outpatient hematology clinic of TASH in the specified study period were included in the study.

4.4.3 Sample size and Sampling Technique

Given the fact that multiple myeloma is a relatively uncommon hematologic disorder in the study setting specified and the study is institution-based, all observed cases in the study period were included in this retrospective cohort study.

4.5 Data collection tool and Procedures

4.5.1. Inclusion Criteria

- All patients with confirmed multiple myeloma, according to the IMWG diagnostic criteria, on follow up at the outpatient clinic in the study period specified

4.5.2. Exclusion criteria

- Patients with incomplete workup & laboratory data on diagnosis and follow up
- Those patients for whom specific chemotherapy was not initiated
- Patients for whom the period of follow up is less than 03 months.
- Patients who were managed with Proteasome inhibitor based combination chemotherapy

4.5.3. Study variables

Independent variables

- Age and Sex
- Stage of the Disease at presentation
- Degree of Anemia
- Renal dysfunction
- Development of Pathologic Fractures
- Treatment-related complications (VTE, infections)
- Serum Total calcium, LDH, and ESR level at diagnosis
- Total & Monoclonal M protein level at diagnosis

Outcome variables

- Overall survival rate
- Progression-free survival rate
- Rate of Hospitalization

4.5.4 Operational definition of study variables

- Disease Stage at presentation – clinical stage of Myeloma according to the revised Durie salmon staging system
- Anemia – hemoglobin level <10g/dl or >2g/dl below the lower limit of the normal range
- Renal insufficiency – serum creatinine level above 2mg/dl
- Pathologic fracture – bone fracture related to myeloma-related osteopenia and bone weakness

- PFS – duration of time from the start of treatment to disease progression, death or when lost to follow-up.
- OS - duration of time from the start of treatment to death or when lost to follow up.

4.5.5 Data collection process

4.5.5.1 Data Collection tool

A structured data collection questionnaire format prepared by the investigator in accordance with similar previous studies was used to fill in data obtained from patients' chart records. Some laboratory data was also obtained from electronic data recording of the hospital's Laboratory.

4.5.5.2 Data collector

Data, using the data collection tool, was collected and filled by the principal investigator of the study.

4.5.5.3 Data collection Procedure

All patients who were referred to, diagnosed, and on follow up at the outpatient hematology unit of the department of Internal Medicine of TASH from 1stof January 2015 to 31st of December 2019 were identified from the HMIS record of the clinic. Patients' chart was obtained and those fulfilling the inclusion criteria were enrolled and the rest were excluded from the study.

4.6 Data Management and Analysis Methods

Once data collection was completed, the data was edited and coded for processing and analysis. The principal investigator using the SPSS(v26) statistical software did data processing and analysis. Frequency tables and graphs were used to express the results. Descriptive statistics and odds ratio, with 95% confidence interval were used to show associations between the study variables. In all cases, a p-value of less than 0.05 was considered to depict a statistically significant association among study variables.

5. Ethical Consideration

Ethical clearance was obtained from the research ethical review committee at the College of Health Science, Addis Ababa University, Addis Ababa, Ethiopia.

6. Dissemination of study results

The final report of this study will be submitted and presented to the department of internal medicine, college of health science, Addis Ababa University. Results will also be sent to the FMOH and if possible to regional health bureaus Efforts will also be made to disseminate and publish research findings in national, regional, and international medical journals..

7. Results

7.1 Demographic characteristics of Study participants

A Five-year single centered Hospital-based retrospective cohort study was conducted on patients diagnosed and managed for multiple myeloma at TASH from January 2015 to December 2019. A total of 80 patients were identified in the study period specified. Out of these 51 (63.8%) were Males and 29 (36.2%) were females. The Median age of patients at diagnosis was 52 years. The mean age at diagnosis was 54 years (range 25 – 82). The majority of the patients (62.5%) were between the age of 40 years and 65 years. Extremes of age, less than the age of 40 years and greater than the age of 65 years, were each encompassing 18.8% of the study population.

Patients were seen from all regions of the Country except for the regions of Gambela and Afar. In this cohort, 35% of the patients were from Addis Ababa and 33.7% & 13.7% of the patients were from Oromia and Amhara regions respectively. The other 4 regions contribute to the remaining 19% of the patients.

Table 1 Demographic characteristics of patients

Demographic characteristics		Proportion of Patients
Total Number of patients		**80(100%)**
Age (Years)	**Median (M,F)**	**52 (52,52)**
	<40(Min)	**18.8 % (25)**
	>65(Max)	**18.8% (82)**
	40-65	**62.5%**
Sex		
	Males	**51 (63.8%)**
	Females	**29 (36.2%)**
Regions		
	Addis Ababa	**35%**
	Oromia	**33.7%**
	Amhara	**13.7%**
	Tigray	**5%**
	Others	**12.5%**

7.2 Clinical Characteristics of study participants

7.2.1 Clinical Features and Treatment of Patients

Patients in the study were managed with 3 major induction regimens; which include the CP (Cyclophosphamide – Prednisolone), CPT (Cyclophosphamide – Prednisolone- Thalidomide), MPT (Melphalan - Prednisolone- Thalidomide) regimens. 60% of patients were given the CP induction treatment regimen while 32.5% and 6.3% of patients were managed with CPT and MPT regimens respectively. Only a single patient was given a TP (Thalidomide-Prednisolone) combination Therapy. Apart from decisions from physicians in holding treatment for various treatment-related complications, 90% of the patients completed their induction treatment course with no discontinuation of therapy or follow up.

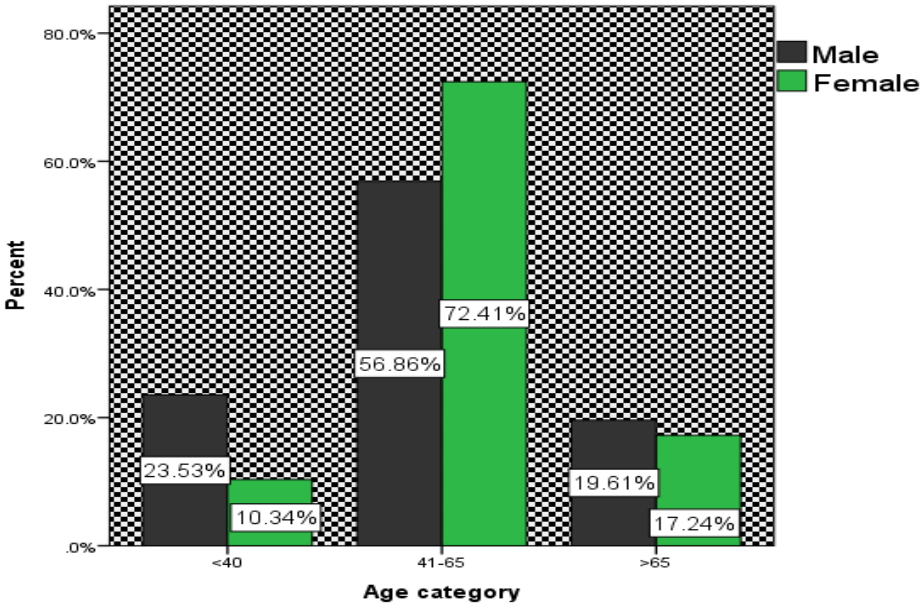

Figure 1 – The frequency distribution of Patients by Age category & sex

One or more major comorbidities were identified in 36% of the patients. These include Systemic Hypertension, which is the most common, seen in 24% of the study participants; chronic kidney disease in 6.3% and Diabetes mellitus in 5% of the cases. Only a single patient was found to have an underlying cardiac illness, IHD. Fifty-nine percent of patients had no known underlying comorbidity detected. Evaluation for the disease stage at diagnosis based on the DS (Durie-Salmon) clinical staging criteria was also made and the majority (61.3%) of the patients had a stage IIIA disease followed by a stage IIA accounting for 23.8% of the cases. Male patients in the study, as compared to females, tended to present at advanced stages but Mann Whitney test of medians didn't show a level of statistical significance (P= 0.13).

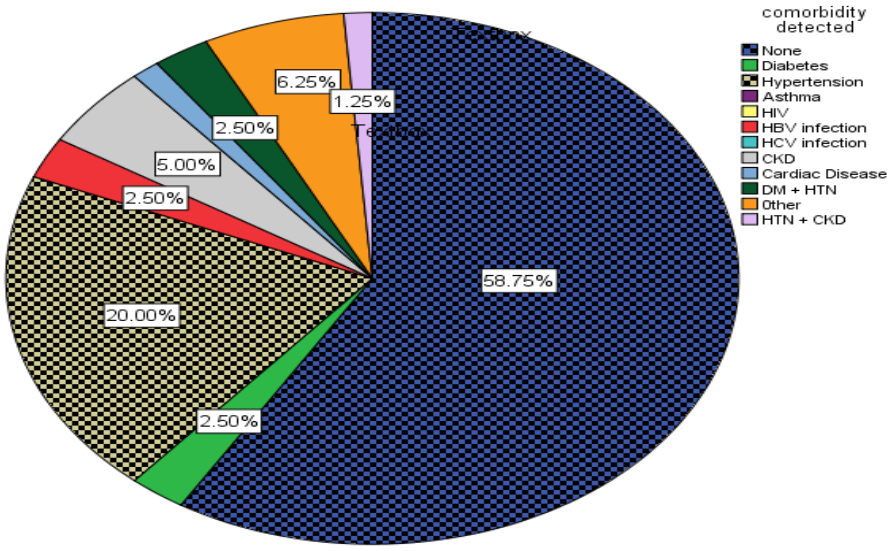

Figure 2 - The Proportion of different comorbidities seen in patients at diagnosis

Renal failure in the staging process was seen in 15% of study participants at presentation. Bone pain and Lytic lesions visualized on a plain x-ray were present in 93.8 % of diagnosed patients and only 5% of patients didn't develop this in the follow-up period.

7.2.2 Laboratory Features of Patients in the study

57.3% of the cases had **a**nemia of different degrees of severity at diagnosis and an additional 5.2% developed the condition in the follow-up period. The mean hemoglobin

Table 2 – Baseline Hematologic profile of Patients

	WBC at Diagnosis	PLT level at Diagnosis	Hemoglobin level at Diagnosis
Mean	10.899	242.25	10.155
Median	6.650	240.00	9.850
Mode	4.7	158	11.7
Std. Deviation	34.7768	101.529	3.0000
Variance	1209.424	10308.089	9.000
Skewness	8.850	.343	-.022
Std. Error of Skewness	.269	.269	.269
Range	315.8	526	12.4
Minimum	1.2	14	3.8
Maximum	317.0	540	16.2

level at diagnosis was 10.1 ± 3g/dl. Twenty-five and Thirty-one percent of patients had a severe and moderate anemia respectively. Sixteen percent of the patients required blood transfusion for anemia while only 2 patients were given EPO therapy for persistent and refractory anemia affecting patient management. Anemia was absent in 37.5% of the patients.

Hypercalcemia was another common laboratory parameter identified. 37.6 percent of patients had a serum calcium level, adjusted for the degree of hypoalbuminemia, above UNL with a mean value of 10.2 ± 2.4 mg/dl. Only a single patient developed a new-onset hypercalcemia after diagnosis in the study period

Renal failure was documented in 15% of the study participants at presentation and even more proportion (18.8%) of patients had a creatinine value above the laboratory **UNL**. Five patients with renal dysfunction required a RRT and none of these patients had a recovery in their kidney function. Close to 74 percent (73.8%) of the cases had a normal renal function determination throughout the follow-up period.

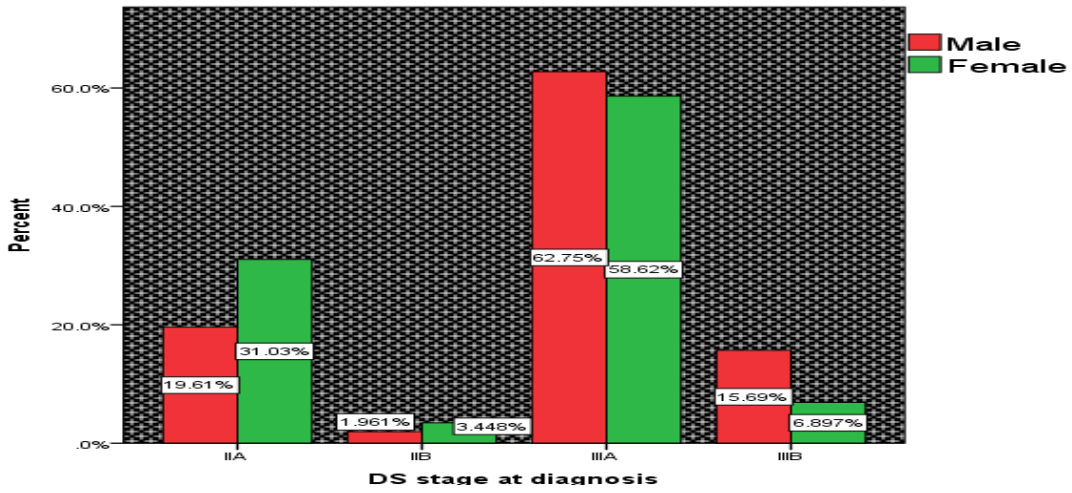

Figure 3 – D-S disease stage of patients at Presentation

From serum protein electrophoresis results, the mean value for monoclonal 'M' and also total proteins were 4.2 ± 2.3 g/dl and 9.6 ± 2.5g/dl respectively. Fifty-six percent of the patients had hypoalbuminemia and the mean serum albumin level was 3.1 ± 0.7g/dl. The mean bone marrow plasma cell percentage was 27 ± 20.5%

In this cohort, 56.3% of patients had an elevated ESR with a mean value of 97.3 ± 51.1 mm/hr at diagnosis. Another laboratory marker of disease activity considered was serum LDH. LDH level was elevated in 76.3 % of patients with a mean value of 373.4 ± 237.6 U/L at the time of disease diagnosis

Table 3 - Clinical characteristics and Treatment Outcome of patients

Measures	ESR at Diagnosis	Serum LDH at diagnosis	Cr level at Diagnosis	Total serum protein	M protein level	Serum Albumin level at Diagnosis	serum calcium level	Marrow Plasma cell %	OS of patients (In Months)	PFS duration (in Months)	Hospitalization rate
Mean	*97.29*	*373.36*	*1.614*	*9.559*	*4.247*	*3.132*	*10.233*	*26.96*	*27.75*	*22.03*	*.5019*
Median	*103.00*	*335.00*	*1.000*	*9.500*	*4.050*	*3.300*	*9.700*	*20.00*	*20.00*	*17.50*	*.3250*
Mode	*120*	*174[a]*	*.7*	*8.0*	*5.0*	*3.3*	*8.0*	*10*	*4*	*4*	*.00*
Std. Deviation	*51.218*	*238.047*	*2.1480*	*2.4922*	*2.3493*	*.7198*	*2.3704*	*20.524*	*24.178*	*20.406*	*.63223*
Variance	*2623.292*	*56666.341*	*4.614*	*6.211*	*5.519*	*.518*	*5.619*	*421.234*	*584.571*	*416.394*	*.400*
Range	*185*	*893*	*14.1*	*14.1*	*10.7*	*3.4*	*15.0*	*64*	*94*	*94*	*3.00*
Minimum	*5*	*107*	*.4*	*3.7*	*1.0*	*1.2*	*6.0*	*1*	*3*	3	*.00*
Maximum	*190*	*1000*	*14.5*	*17.8*	*11.7*	*4.6*	*21.0*	*65*	*96*	96	*3.00*

Peripheral neuropathy developed in 16.4% of the patients on follow up and patients who received a thalidomide containing regimen had a statistically significant more risk (P-value of 0.04) and Odds ratio of 3.4 (95% C.I,(1.01-11.2)) for the development of peripheral neuropathy during follow up.

A Significant number of patients had a major neurologic complication including neurologic weakness and bladder dysfunction. 31.3% of study participants developed one of these complications and out of these Para paresis was the most common encompassing 76.2 percent of the neurologic complications seen in patients. The development of neurologic weakness had a statistically significant correlation with the presence of pathologic fracture (P= 0.001) and plasmacytoma (P=0.02). 44(55%) and 25(31.3%) of patients had a documented pathologic fracture and an osseous or extramedullary plasmacytoma respectively.

7.3 Treatment and disease-related Complications

Venous thrombosis was seen only in 6.3% of the study participants. Eighty percent of the cases with venous thrombosis were females. Thrombotic episodes occurred in both Thalidomide and Non-Thalidomide containing regimens. The number of thrombotic events were few for determination of its possible association with the types of regimen and the use of a VTE prophylaxis.

Infections, which were all cases of pneumonia, were identified in 41.3% of patients on follow up. A Statistically significant variation was not detected in the risk of development of pneumonia among the different treatment regimens. Cases of pneumonia were seen more in females but the correlation was not statistically significant (P=0.35). Only a few (4) patients received antibiotic prophylaxis for a correlation to be made with its benefit of infection prevention. Spontaneous bleeding and also neutropenia were other infrequent hematologic complications each being reported in 7 (8.8%) patients.

It was difficult to determine common causes of death in patients managed for myeloma in this particular study as most of the patients died outside of the hospital and there was no tracking system for others who are lost to follow up after completion of their induction treatment. Out of the 20 (25%) patients for whom immediate cause of death is documented; disease relapse or refractor disease, renal failure, and severe pneumonia with related complications made up the 3 most common in Hospital causes of mortality; accounting for 35%, 30%, and 25% of the cases respectively.

7.4 Treatment Outcome and determinant Factors

The outcome of treatment for myeloma, in this particular study, was assessed through the overall Survival (OS) and Progression-free survival (PFS) of patients. The median OS of patients was 20.0 months. 25% of the patients had a survival period not exceeding 9 months and also, in the other end of the survival spectrum, a similar proportion of patients survived for more than 45 months. The 02 year and 03 year OS of patients was 50% and 28.6% respectively. The median PFS or period of a SD was 17.5 months. The 02 year and 03 year PFS of patients was 36.3% and 23.8% respectively.

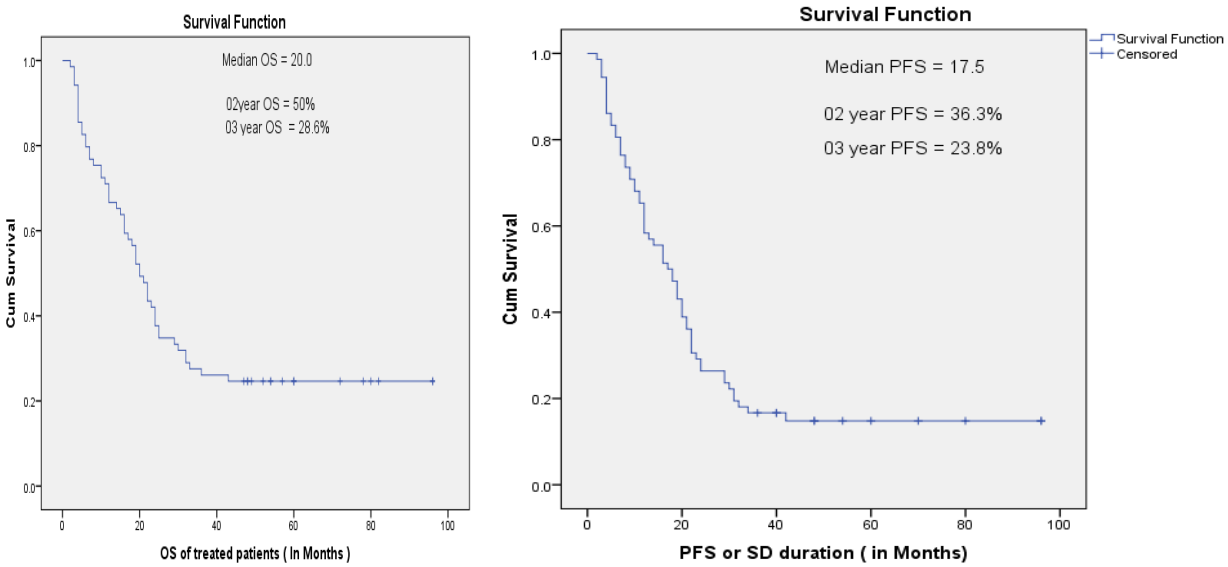

Figure 4 – Kaplan Meier Survival curve for OS and PFS of Newly diagnosed patients on first-line therapy for Myeloma

Different patient, disease, and treatment-related characteristics were assessed as a determinant factor for treatment outcome of patients. Demographic features like gender and age were assessed but survival didn't tend to differ, with statistical significance, by gender or across the different age groups. Pearson's method of correlation showed a negative correlation between age and survival but it was not statistically significant. The negative correlation between age and Survival is strong in the first 01 year of follow-up; and once patients survived past the first year, the contribution of age in survival lessens out.

Treatment-related factors like VTE prophylaxis usage, requirement for blood component transfusion, use of prophylactic antibiotic with chemotherapy were found to have no association with OS or PFS of patients.

D-S disease stage at presentation was significantly skewed as most patients presented with stage III disease As no patient was diagnosed with a stage I disease, patients were categorized into a stage II and a stage III disease at diagnosis. Non-parametric Spearman correlation coefficient between disease stage and survival showed a negative correlation. As compared to patients with a stage III disease, patients diagnosed with a stage II disease had a statistically significant better 01 year OS (P=0.03). The 01 year OS of patients with a stage II disease was 76.2% and this number significantly declines to 55.9% in patients with a stage III disease. This association was not found to be significant once patients survived past the first year of therapy. Kaplan Meier survival

analysis didn't show a statistically significant association between disease stage at diagnosis and PFS throughout the follow-up period.

Pathologic fracture, at presentation or encountered in the follow-up period, was more common in males but the association was not strong enough to reach a level of significance (P= 0.24). Though bisphosphonate therapy didn't have a survival benefit demonstrated in this study, its ability in preventing a new-onset lytic lesion or pathologic fracture was significant (P=0.01).

Total serum protein from the SPEP was found to have a statistically significant correlation with both OS and PFS with P values of 0.008, 95%C.I (-9.29, -1.56) and p=0.006,95%C.I (-4.71, -0.83) respectively. A 1g/dl rise in serum total protein was associated with a 5.4 and 2.8 months decline in OS and PFS respectively. These results were adjusted for multiple comparisons in multiple regression analysis. A similar degree of significant association was also shown between serum M protein levels and survival. (Table 4). A 1 g/dl rise in serum monoclonal M protein resulted in a 2.66 and a 2.93 months decline in PFS and OS of patients respectively.

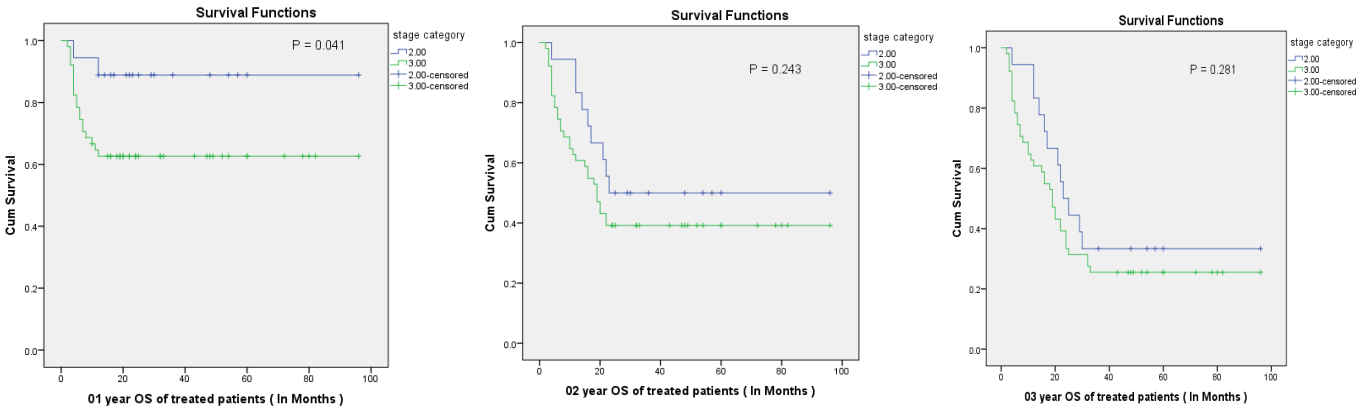

Figure 5 – Kaplan Meier survival curve for OS of patients with Myeloma compared with the stage at diagnosis

Treatment and disease-related complications were also assessed for their prognostic implications. Venous thrombosis, development of pathologic fracture & neurologic weakness, neutropenia, and also the development of pneumonia failed to demonstrate a statistically significant association with survival. Survival outcomes also tend not to differ in individuals with documented major comorbidities (hypertension, diabetes), assessed in the study, as compared to those with no such conditions.

The presence of Plasmacytoma in our patients with MM had a statistically significant negative association with OS (P= 0.046, 95% C.I (-21.47,-.211) of patients. The interaction between the presence of extramedullary disease and survival was not found to be significant in the first 02 years of follow up. But in the consequent period of follow-up, the OS of patients was significantly influenced by the presence of extramedullary disease at diagnosis. The three-year OS of patients with no coexisting plasmacytoma was 31% and this number significantly declines to 12% in patients with a plasmacytoma. The presence of plasmacytoma was not found to be related to gender (P=0.33) or affected by age of patients (P=0.26).

Serum LDH level was the other disease activity marker shown to have a prognostic impact on survival. seventy-six percent of the study participants had an elevated serum LDH value. A statistically significant level of negative correlation was seen between serum LDH level at diagnosis and OS of patients in the study (P= 0.02, 95%C.I (0.007-0.078). Based on the linear regression association between the variables, for every 100U/L rise in serum LDH, the OS of patients dropped by 4.3 months. A similar significant association was not demonstrated with the serum LDH level at diagnosis and PFS of patients.

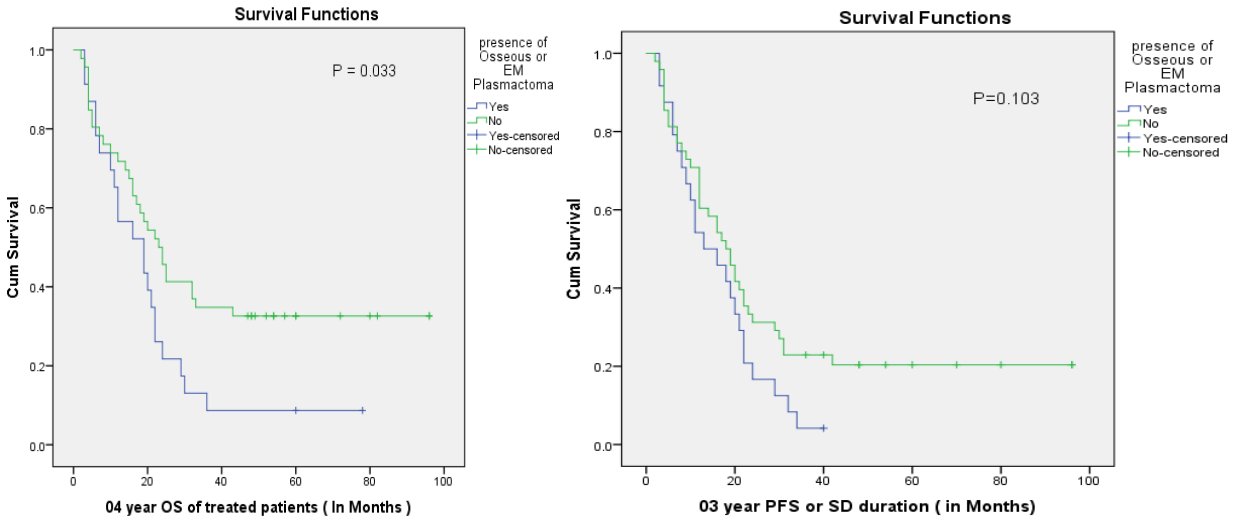

Figure 6 – Kaplan Meier survival curve comparing OS and PFS of patients in the presence of extramedullary disease

18.8% of patients had a deranged renal function test at presentation. Based on their baseline serum creatinine patients were divided into 3 groups; those with serum Cr within the laboratory normal range, UNL – 2mg/dl, and above 2mg/dl.

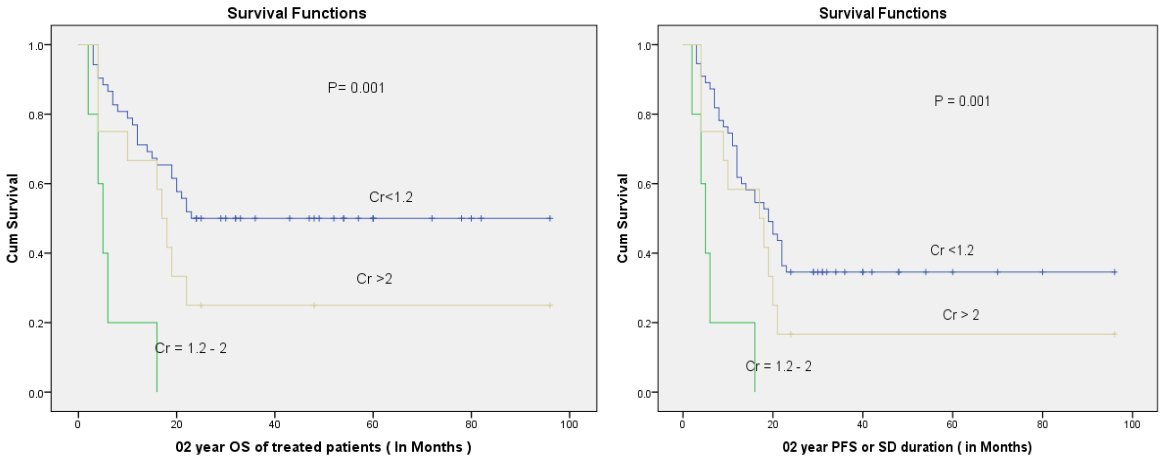

Figure 7 – Kaplan Meier survival curve (OS & PFS) of patients by the degree of renal dysfunction

Kaplan meier survival analysis showed a statistically significant negative correlation between derangement in renal function and both OS and PFS of patients. Patients with normal serum creatinine at presentation had a 01 year and 02 year OS of 62.3% and 57.4% respectively. This figure drops significantly in patients with serum creatinine in the range of 1.2 – 2mg/dl to a similar 28.6% 01 year and 02 years OS (P=0.01). Patients with serum creatinine more than 2mg/dl at presentation also had a significant drop in 02 year OS to 25%.

8. Discussion

This retrospective cohort study on multiple myeloma was conducted with the intention of providing a local data regarding the demographic characteristics of patients with the disease and also describe their clinical features, treatment outcome, and major clinical prognostic markers of survival. The progressively rising number of patients in our health care facilities motivated us to study this hematologic disorder which is once considered rare in this part of the world.

Out of the 80 patients identified in this five-year retrospective cohort, 63.8% of them were males (M:F ratio 1.76:1**)** , which is similar to the strong male preponderance of the disease reported from different studies.[(3)] Patients in our study were found to be younger (Median: 52 years) than the western population. The number of patients diagnosed before the age of 40 had a significantly higher proportion (18.7%) when compared to reports from other areas. [(3)]

Two-third of the patients were from the regions of Addis Ababa and Oromia, where each accounting for 35% and 33.7% of the cases respectively. This difference in epidemiology of the disease among the regions of the country is less likely due to a difference in incidence but could be due to lack of diagnostic modalities and access to health care service and remoteness of some of the regions from the Hospital in the study, which is located in Addis Ababa, Ethiopia.

The most common identified in the study were anemia (56.3%) & pathologic fracture (55%). The most common comorbid conditions identified were systemic hypertension (24%), CKD (6.3%), and Diabetes mellitus (5%). These conditions are also mentioned, in different studies, as the most prevalent complications & comorbidities with similar proportions.[(35)(36)] The higher prevalence of CVD at presentation mentioned in some studies in Myeloma, compromising long term Myeloma therapy, was not demonstrated in this study. Conforming to reports from other similar studies, results from our study also showed that some comorbidities like hypertension and diabetes are not significantly related to survival during the study period.[(36)]

It is not clear whether the reason for the high prevalence of systemic hypertension in these patients is to be related to the rise in the general prevalence of hypertension and older age of patients with myeloma or to be related to the disease process. Due to the small number of thrombotic incidents,

this study was unable to analyze its association with survival and also its prevention with a VTE prophylaxis.

The prevalence of disease-related complications like pneumonia, renal, and bone disease in our patients was significantly higher than other similar studies in the United States and Europe.[35][36] More than half of the patients (56.7%) in this study had anemia. This proportion is similar to reports from studies conducted in other similar African oncologic treatment centers.[23]

Despite the introduction of Proteasome inhibitor based regimens as the first-line treatment for newly diagnosed patients with myeloma, this study primarily intended to evaluate the treatment efficacy of earlier regimens (CP, CPT, MPT) which are still used in the country. With the high treatment-related cost of newer agents and lack of alternative regimens in treatment failure, alkylators like Cyclophosphamide, still widely used in resource-limited regions of the world, could still play a role in patient management. The median PFS and OS of patients in this study were 17.5 and 20 months respectively and is shorter than most other similar studies conducted in the western and also other African countries.[23][37]

This study showed a statistically significant negative correlation of survival with both renal dysfunction and disease stage at presentation. Patients with a D-S stage II disease, similar to other studies [10], were found to have a better 01-year survival (76.2%) as compared to a D-S **s**tage III disease (55.9%).

Renal dysfunction was also another factor identified in this study to negatively affect both OS and PFS. Patients with renal dysfunction at presentation had a significant drop in 01-year and 02 years OS from 62.3% to 28.6% (P=0.004) and from 57.4% to 25% (P=0.001) respectively. Acute kidney injury requiring RRT was a poor marker of prognosis. Out of the 5 patients (4%) who required RRT in the study period, none of the patients had a recovery in renal function and died of renal failure and associated complications.

The presence of osseous or extramedullary plasmacytoma also contributed to a significant decline in the 03 years and 04 years OS of patients from 31% to 12% (P=0.05) and from 27.3% to 8% (P=0.03). The effect of the presence of osseous or extramedullary plasmacytoma on survival was not significant in the first 02 years of treatment and follow up.

Total serum protein and serum monoclonal M protein levels were found to have a statistically significant correlation with both OS and PFS of patients. This is in contrary to reports from some other prognostic studies in myeloma which didn't find a statistically significant association between these markers and patients' survival.[13]

High levels of serum LDH either at diagnosis or following high dose chemotherapy was found, in some studies, to be an important factor associated with a shortened period of survival and poor laboratory and clinical variables. This study was also able to demonstrate that elevated serum LDH at diagnosis was associated with reduced OS and PFS of patients with myeloma.

In this retrospective cohort, the negative correlation found in univariate analysis between survival and factors like age, hypercalcemia, marrow plasma cell percentage, and degree of anemia was not found to be statistically significant. This finding is consistent with results from the oncology department of the University of Pretoria [13] and an African retrospective study conducted in a tertiary referral hospital in Ghana.[5]

9. Strength and Limitations

9.1 Strength of the study

The study was conducted in one of the largest and the well-recognized tertiary referral Hospitals in the country. The study included patients over 5 years of study period and efforts were made to include all patients managed in the study period. This study is also the first of its kind in the country and provides a new local practical knowledge for the management of patients with myeloma.

9.2 Limitations of the study

There was a difficulty in obtaining patients' medical records as the hospital's chart recording unit was not well organized. A significant number of patients didn't have a complete laboratory data at diagnosis and follow up. In some patients, it was difficult to determine the outcome of treatment and causes of mortality as most of the patients died outside of the hospital and there was no tracking system for others who are lost to follow up after completion of their induction treatment coarse.

10. Conclusion and Recommendations

Multiple myeloma is one of the hematologic malignancies currently rising among hematologic cases seen in our Hospital. This study provides physicians & other health care providers with a new knowledge regarding the demographic, clinical characteristics, treatment outcome and prognostic factors in patients managed for MM in our country. This will serve as a clinical framework for patient management, decision making and future researches to be done on new treatment regimens.

Our patients were found to present in advanced stages of the disease. The incidence of the disease below the age of 40 should also never be overlooked as patients in our country are younger than the western population. In this regard, a high index of suspicion, early diagnosis, and management of MM are important for ensuring survival. Therefore, decentralized oncologic diagnostic and treatment centers are needed in regions of the country if to address the growing need from the population at risk, achieve a better treatment outcome, and facilitate patient follow up.

Induction treatment regimens like CP and CPT were found to perform less in our patients than other oncologic treatment centers elsewhere. This could be due to the delayed presentation and the higher prevalence of comorbidities and disease-related complications. Close follow-up, identification, and treatment of these complications are also vital for a better treatment outcome.

This study also identified factors like advanced DS stage, co-existence of Plasmacytoma, elevated serum LDH, high level of serum total protein, and monoclonal M protein to be significant contributors in negatively affecting OS and PFS of patients. These factors can be utilized for risk stratification of patients in the absence of cytogenetic markers and other measures of disease burden like B2 microglobulin level.

Currently, Proteasome inhibitor based therapeutic regimens are the cornerstones of therapy in patients with newly diagnosed and treatment-resistant myeloma. The treatment outcome and contribution of different prognostic factors are shown to be different in many recent studies conducted on these regimens. To demonstrate this and compare results with this study, other follow-up studies are needed in our set up on patients who are and will be treated by these current regimens which have dramatically improved the treatment outcome of patients with multiple myeloma.

References

1. Cowan AJ, Allen C, Barac A, Basaleem H, Bensenor I, Curado MP, et al. Global burden of multiple myeloma: A systematic analysis for the global burden of disease study 2016. JAMA Oncol. 2018;4(9):1221–7.
2. Phekoo KJ, Schey SA, Richards MA, Bevan DH, Bell S, Gillett D, et al. A population study to define the incidence and survival of multiple myeloma in a National Health Service Region in UK. Br J Haematol. 2004;127(3):299–304.
3. Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc. 2003;78(1):21–33.
4. Oelofse D, Truter I. Incidence of haematological malignancies, Eastern Cape Province; South Africa, 2004–2013. Cancer Epidemiol [Internet]. 2018;53(January):166–71. Available from: https://doi.org/10.1016/j.canep.2018.01.016
5. Acquah ME, Hsing AW, McGuire V, Wang S, Birmann B, Dei-Adomakoh Y. Presentation and survival of multiple myeloma patients in Ghana: A review of 169 cases. Ghana Med J. 2019;53(1):52–8.
6. Srivastava G, Rana V, Lacy MQ, Buadi FK, Hayman SR, Dispenzieri A, et al. Long-term outcome with lenalidomide and dexamethasone therapy for newly diagnosed multiple myeloma. Leukemia. 2013;27(10):2062–6.
7. Chng WJ, Dispenzieri A, Chim CS, Fonseca R, Goldschmidt H, Lentzsch S, et al. IMWG consensus on risk stratification in multiple myeloma. Leukemia. 2014;28(2):269–77.
8. Rna HC V. From www.bloodjournal.org by guest on September 16, 2015. For personal use only. 4730. 2015;52(Riba Ii):4730–2. Available from: www.bloodjournal.org
9. Greipp PR, Lust JA, O'Fallon WM, Katzmann JA, Witzig TE, Kyle RA. Plasma cell labeling index and β2-microglobulin predict survival independent of thymidine kinase and C-reactive protein in multiple myeloma. Blood. 1993;81(12):3382–7.
10. Previous B, Grenier J, Sany J. Beta-2Microglobulin Prognosis, and Treatment-A. 2019;63(2):468–76.
11. Myeloma HL, Barlogie B, Smallwood L, Smith T, Alexanian R. High Serum Levels of Lactic Dehydrogenase Identify a. 2016;521–5.
12. Durie BGM, Salmon SE. A clinical staging system for multiple myeloma correlation of measured myeloma cell mass with presenting clinical features, response to

treatment, and survival. Cancer. 1975;36(3):842–54.

13. Walker E. With Multiple Myeloma. Race. 2006;91(10):1990–2.

14. Kapoor P, Kumar S, Fonseca R, Lacy MQ, Witzig TE, Hayman SR, et al. Impact of risk stratification on outcome among patients with multiple myeloma receiving initial therapy with lenalidomide and dexamethasone. Blood. 2009;114(3):518–21.

15. Van De Velde HJK, Liu X, Chen G, Cakana A, Deraedt W, Bayssas M. Complete response correlates with long-term survival and progression-free survival in high-dose therapy in multiple myeloma. Haematologica. 2007;92(10):1399–406.

16. Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood. 2008;111(5):2516–20.

17. Palumbo A, Attal M, Roussel M. Shifts in the therapeutic paradigm for patients newly diagnosed with multiple myeloma: Maintenance therapy and overall survival. Clin Cancer Res. 2011;17(6):1253–63.

18. Rajkumar SV, Hayman S, Gertz MA, Dispenzieri A, Lacy MQ, Greipp PR, et al. Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma. J Clin Oncol. 2002;20(21):4319–23.

19. Rajkumar SV, Jacobus S, Callander NS, Fonseca R, Vesole DH, Williams ME, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomized controlled trial. Lancet Oncol [Internet]. 2010;11(1):29–37. Available from: http://dx.doi.org/10.1016/S1470-2045(09)70284-0

20. Richardson PG, Weller E, Jagannath S, Avigan DE, Alsina M, Schlossman RL, et al. JOURNAL OF CLINICAL ONCOLOGY Multicenter, Phase I, Dose-Escalation Trial of Lenalidomide Plus Bortezomib for Relapsed and Relapsed / Refractory Multiple Myeloma. 2009;27(34):5713–9.

21. Richardson PG, Weller E, Lonial S, Jakubowiak AJ, Jagannath S, Raje NS, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. Blood. 2010;116(5):679–86.

22. Attal M, Moreau P, Charbonnel C, Hulin C, Leyvraz S, Michallet M, et al. Genetic abnormalities and survival in multiple myeloma : the experience of the Intergroupe Francophone du Mye ´ lome. 2016;109(8):3489–96.

23. Nwabuko Ogbonna Collins, Nnoli Martin Anazodo, Igbigbi Elizabeth Eneikido, Survival Outcomes of Double and Triple-Only Combination Anti-Myeloma Chemotherapeutic Regimens on 26 Multiple Myeloma Patients Seen In a Sub-Saharan African Country, 2013;

24. Morgan GJ, Davies FE, Gregory WM, Bell SE, Szubert AJ, Coy NN, et al. Articles and Brief Reports Cyclophosphamide, thalidomide, and dexamethasone as induction therapy for newly diagnosed multiple myeloma patients destined for autologous stem-cell transplantation : MRC Myeloma IX randomized trial results. 2012;97(3):442–50.

25. João C, Bergantim R, Neves M, Chacim S, Afonso C, Barradas J, et al. Multiple myeloma in elderly patients—a Portuguese multicentric real-life study. Ann Hematol. 2019;98(7):1689–701.

26. Garderet L, Beohou E, Caillot D, Stoppa AM, Touzeau C, Chretien ML, et al. Upfront autologous stem cell transplantation for newly diagnosed elderly multiple myeloma patients: A prospective multicenter study. Haematologica. 2016;101(11):1390–7.

27. Qazilbash MH, Saliba RM, Hosing C, Mendoza F, Qureshi SR, Weber DM, et al. Autologous stem cell transplantation is safe and feasible in elderly patients with multiple myeloma. Bone Marrow Transplant. 2007;39(5):279–83.

28. Terpos E, Kleber M, Engelhardt M, Zweegman S, Gay F, Kastritis E, et al. European myeloma network guidelines for the management of multiple myeloma-related complications. Haematologica. 2015;100(10):1254–66.

29. Rajkumar SV, Blood E, Vesole D, Fonseca R, Greipp PR. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: A clinical trial coordinated by the eastern cooperative oncology group. J Clin Oncol. 2006;24(3):431–6.

30. Palumbo A, Rajkumar S V, Dimopoulos MA, Richardson PG, Miguel JS, Barlogie B, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. 2008;(November 2007):414–23.

31. Zahid MF, Ali N, Nasir M, Baig MH, Iftikhar M, Bin Mahmood SU, et al. Infections in patients with multiple myeloma treated with conventional chemotherapy: a single-center, 10-year experience in Pakistan. Hematol Transfus Cell Ther [Internet].2019;41(4):292–7.Available from: https://doi.org/10.1016/j.htct.2019.02.005

32. Nucci M, Anaissie E. Infections in patients with multiple myeloma in the era of high-dose therapy and novel agents. Clin Infect Dis. 2009;49(8):1211–25.

33. Chanan-khan A, Sonneveld P, Schuster MW, Stadtmauer EA, Facon T, Harousseau J, et al. JOURNAL OF CLINICAL ONCOLOGY Analysis of Herpes Zoster Events Among Bortezomib-Treated Patients in the Phase III APEX Study. 2019;26(29).

34. Swaika A, Paulus A, Miller KC, Sher T, Almyroudis NG, Ball D, et al. Acyclovir Prophylaxis Against Varicella Zoster Virus Reactivation in Multiple Myeloma Patients Treated With Bortezomib-Based Therapies : A Retrospective Analysis of 100 Patients. SUPONC [Internet]. 2012;10(4):155–9. Available from:

http://dx.doi.org/10.1016/j.suponc.2011.10.006

35. Song X, Cong Z, Wilson K. multiple myeloma in the United States Original article Real-world treatment patterns, comorbidities, and disease-related complications in patients with multiple myeloma in the United States. 2016;7995(May 2017).

36. Kleber M, Ihorst G, Terhorst M, Koch B, Deschler B, Wa R. Comorbidity as a prognostic variable in multiple myeloma : comparative evaluation of common comorbidity scores and use of a novel MM – comorbidity score. 2011;

37. Morgan GJ, Davies FE, Gregory WM, Russell NH, Bell SE, Alexander J, et al. therapy for patients with multiple myeloma unsuitable for autologous transplantation Cyclophosphamide, thalidomide, and dexamethasone (CTD) as initial therapy for patients with multiple myeloma unsuitable for autologous transplantation. 2014;1231–8.

Annexes

Annex 1:

Declaration

I, the undersigned, declare that this postgraduate thesis is my original work, has not been presented for a degree in this or any other university and that all sources of material used for the thesis have been duly acknowledged.

Postgraduate Candidate: Ephrem Haile (MD, Internal Medicine Resident)

Signature: …….

Date of Submission: December 30, 2020

This thesis has been submitted with my approval as advisor.

Advisor: Amha Geberemedhin (MD, Consultant Internist, Hematologist, Associate Professor of Medicine)

Signature: …….

Date: …….

Place: Addis Ababa, Ethiopia

Annex 2

Revised International Staging System for Myeloma

Stage
Stage 1 • All of the following: • Serum albumin ≥3.5 g/dL • Serum beta-2-microglobulin <3.5 mg/L • No high risk cytogenetics • Normal serum lactate dehydrogenase level
Stage II • Not fitting Stage I or III
Stage III • Both of the following: • Serum beta-2-microglobulin >5.5 mg/L • High risk cytogenetics [t(4;14), t(14;16), or del(17p)] or Elevated serum lactate dehydrogenase level

Annex 3

Mayo clinic Risk Stratification for multiple myeloma (mSMART)

High risk	Intermediate risk	Standard risk
FISH	FISH	FISH
del(17p)	t(4;14)	t(4;14)
t(14;16)		t(6;14)
t(14;20)		
GEP	Cytogenetic del(13)	All other patients
High-risk signature		
	Hypodiploidy	
	Plasma cell labelling index ≥3%	

Annex 4

Revised IMWG Diagnostic Criteria of multiple myeloma

- Clonal plasma cells in bone marrow ≥ 10% or biopsy-confirmed bone plasmocytoma or an extramedullary manifestation and one of the following myeloma-defining events:
- **CRAB criteria**
  - Hypercalcemia: serum calcium >0.25 mmol/L above upper limit of normal range or >2.75 mmol/L (>11 mg/dL)
  - Renal insufficiency: GFR <40 mL/min or serum creatinine >177 µmol/L
  - Anemia: >2.0 g/dL under lower limit of normal range or <10 g/dL
  - Bone lesions: ≥ 1 lesion detected by radiography, computed tomography or positron emission tomography
- **Biomarkers**
  - Clonal plasma cells in bone marrow ≥ 60%
  - Ratio of involved/uninvolved free light chains (FLC) ≥ 100
  - >1 focal lesion >5 mm on MRI

GFR, glomular filtration rate; IMWG, International Myeloma Working Group;
MRI, magnetic resonance imaging
CRAB criteria: threshold values in multiple myeloma for assessment of disease consequences:
C, calcium elevation in blood, R, renal insufficiency; A, anemia; B, bony lesions

Annex 5

Revised Durie-Salmon Staging of multiple myeloma with Assessment of Tumor Mass

Stage	Criteria	Tumor mass
I	All the following:	Low tumor mass
	Hb > 10 g/dL	< 0.6 x $10^{12}/m^2$
	Normal calcium	
	IgG < 5 g/dL; IgA < 3 g/dL	
	Monoclonal urinary protein < 4 g/24h	
	No or single bone lesion	
II	Between Stages I and II	Intermediate tumor mass
III	Any of the following:	High tumor mass
	Hb < 8.5 g/dL	> 1.2 x $10^{12}/m^2$
	Calcium < 12 mg/dL	
	IgG > 7 g/dL; IgA > 5 g/dL	
	Monoclonal urinary protein > 12 g/24h	
	Multiple osteolytic lesions, fractures	
Subclass	A – creatinine < 2 mg/dL	
	B – creatinine ≥ 2 mg/dL	

Annex 6

Age-standardized Global Epidemiology of multiple myeloma