



A Study of Clinical Profile and Biochemical Parameters in Multiple Myeloma

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Abstract

This study is to assess the clinical and biochemical profile of patients with multiple myeloma who presented to a tertiary health centre in northern kerala. This is a prospective observational study which started in January 2015 and was completed in December 2015. All patients more than 12years of age, diagnosed to have multiple myeloma as per the IMWG 2014 diagnostic criteria and who gave an informed consent were analysed in the study. A total of 65 patients were included who were evaluated using detailed clinical history, thorough clinical examination and relevant laboratory investigations including bone marrow study. The quality of life of the patients were assessed by the EORTC QLQ-C30 scoring system. The clinical profile of patients encountered in our setting is was studied, the average age of presentation of patients being 61.4 ± 7.6 yrs and 95.38% belonged to poor socioeconomic status, male to female ratio of patients with multiple myeloma was 0.97:1. The quality of life of the patients was 0.59. The most common associations of multiple myeloma were anemia $Hb < 10mg/dl$ (69.2%), elevated ESR $\geq 100mm/hr$ (73.8%), elevated serum creatinine $> 2mg/dl$ (43.1%), low albumin levels $< 3.5g/dl$ (70.8%). The most common type of immunoglobulin seen in multiple myeloma was IgG (75.4%) and bone marrow plasma cells between 20-29% was seen in a majority (46.2%) patients.

Keywords: Multiple myeloma; Clinicalprofile; Quality of life.

Introduction

Multiple myeloma is a malignant neoplasm of plasma cells that accumulate in bone marrow which leads to bone destruction and marrow failure¹. Multiple myeloma accounts for 1% of all malignancies and is the second most common hematologic malignancy with prevalence of around 10%. The mean age of affected individuals is 62 years for men (75% older than 70 years) and

61 years for women (79% older than 70 years)². The average incidence of myeloma is 3-4/100,000 in the US, representing approximately 1.3% of all types of cancer³. Samuel Solly described the first well documented case of myeloma in 1844. Otto Kahler in 1889 described a case involving a 46 year old physician and published a major review of this disease which still bears his name Kahlers disease^{4,5}. The major features of myeloma result

from the abnormal accumulation of myeloma cells in the bone marrow which causes disruption of normal bone marrow function reflected by anemia and/or low white counts or platelet counts, destruction and invasion of bone surrounding the bone marrow cavity, production and release of monoclonal protein from myeloma cells into the blood stream and/or into the urine and reduction of normal immune function, which causes reduced levels of normal immunoglobulins and increased susceptibility to infection. Infection is more likely if the white blood cell count is low^{6,7}. About 70% of patients with myeloma present with pain of varying intensity, often in the low back or ribs. Hypercalcemia, historically found in 30% of patients at diagnosis, causes tiredness, thirst, and nausea. Recently the incidence of hypercalcemia in newly diagnosed patients has dropped to 10-15% most likely because of the earlier diagnosis.⁸ The initial diagnostic workup in all patients should include a history and physical examination and the following baseline blood investigations and biological assessments to differentiate symptomatic myeloma from asymptomatic myeloma: a complete blood count with differential and platelet counts; Blood urea nitrogen (BUN); serum creatinine and serum electrolytes; serum calcium; albumin; lactate dehydrogenase (LDH); and β 2-microglobulin. Increased BUN and creatinine indicate decreased renal function, whereas LDH levels help assess the tumor cell burden. The level of β 2-microglobulin reflects the tumor mass and is now considered a standard measure of the tumor burden. The monoclonal protein (M-protein) component in serum and urine is detected and evaluated by various tests. Urine analysis as part of the initial diagnostic workup includes evaluating 24-hour urine for total protein, urine protein electrophoresis (UPEP), and urine immunofixation electrophoresis (UIFE). Serum analysis includes quantitative immunoglobulin levels of different types of antibodies (IgG, IgA, and IgM); serum protein electrophoresis (SPEP); and serum immunofixation electrophoresis (SIFE)

to obtain specific information about the type of abnormal antibodies seen.¹¹

To evaluate bone marrow plasma cell infiltration, bone marrow aspiration and biopsy are recommended to detect the quantitative and/or qualitative abnormalities of bone marrow plasma cells. To evaluate for lytic bone lesions, a full skeletal radiographic survey is recommended. There are five major classes of immunoglobulins synthesized by the normal B cells and plasma cells which includes IgG, IgA, IgM, IgD and IgE. The dysfunctional plasma cells secrete one of these immunoglobulins or in some instances produce only light chain immunoglobulins. Usually intact immunoglobulin molecules are secreted by plasma cells, however there may be a discrepancy in the production of heavy chain and light chains which leads to an imbalance with an excess of free light chain that is excreted in the urine (bence jones proteinuria). Occasionally cells do not secrete any paraproteins (non – secretory type myeloma), however they usually have cytoplasmic immunoglobulins and produce low levels of immunoglobulin which are undetectable by the current methods. The type of monoclonal protein produced varies in different patients. The most common is IgG and the least common is IgE.

Patients who present with active (symptomatic) myeloma are initially treated with primary therapy and in selected patients primary therapy is followed by high-dose chemotherapy with autologous stem cell transplant. Bortezomib-based regimens may be of value in patients with renal failure and those with certain adverse cytogenetic features^{12,13}. There is no single answer to the question of “the best” treatment options. The best choice for each patient depends upon the individual factors such as age, stage, genetic features, kidney status, and of course personal preference

Prognosis in multiple myeloma is determined by both the number and specific properties of myeloma cells in a given patient. These properties include the growth rate of myeloma cells, production rate of monoclonal proteins, and the

production or non-production of various cytokines and chemicals that damage or significantly impair other tissues, organs, or body functions. Serum β 2 microglobulin (S β 2M), serum albumin, platelet count, serum creatinine, and age have emerged as powerful predictors of survival¹⁴. The treatment of Multiple myeloma has dramatically improved over the past decade. The 5-year survival rate has increased from 25% in 1975 to 34% in 2003 as a result of newer and more effective treatment options.

Even though Multiple myeloma is the 2nd most common hematological malignancy there are only a few studies of multiple myeloma in our population. This study is to assess the clinical profile of multiple myeloma patients that is encountered in our setting which includes elderly patients mostly in the low socioeconomic status and with poor quality of life. This study also highlights the importance of clinical and biochemical parameters in myeloma which helps in early diagnosis and treatment of the disease.

Aims & Objectives

1. To study the selected biochemical parameters in patients with multiple myeloma.
2. To study the associations between the clinical profile and selected biochemical parameters in patients with multiple myeloma.

Materials & Methods

Study Design

This is a prospective observational study which started in January 2015 and completed in December 2015. All patients within the study period, who are diagnosed to have multiple myeloma as per the inclusion criteria of the study and who give an informed consent will be analysed in the present study.

Inclusion Criteria

Newly diagnosed cases of multiple myeloma of Age > 12yrs, who gave informed consent and

fulfill the Diagnostic criteria for multiple myeloma.

Exclusion Criteria

Patients who were < 12 yrs of age and patients who did not give consent.

Sample Size

A total of 65 patients were included in the study

Methodology

Those who were selected for the study were evaluated using detailed clinical history, thorough clinical examination and relevant laboratory investigations. The evaluation was done using the preset proforma. The quality of life of the patients were assessed and a bone marrow study was also done.

Operational Definitions

Diagnostic Criteria for Multiple Myeloma

International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma 2014

Clonal bone marrow plasma cells $\geq 10\%$ 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:
 - Hypercalcemia: 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 μ mol/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 $\geq 60\%$

- Involved: uninvolved serum free light chain ratio ≥ 100 (The involved free light chain being ≥ 100 mg/L)
- >1 focal lesions on MRI studies

Assessment of Quality of Life

Quality of life assessment was done at the beginning of the study and after 6 months of therapy. Questionnaire for quality of life assessment based on EORTC QLQ-C30-global health status / QoL - items 29, 30.

Table 1: Scoring the QLQ -C30 version 3.0

	Scale	Number of items	Item range	Version 3.0 Item numbers	Function scale
Global health status /QoL	QL2	2	6	29,30	

First calculate the raw score- raw score= $RS=(I_1 + I_2 + \dots + I_n)/n$
 Global health status/QoL: $S = \{(RS-1)/range\} \times 100$
 Range is the difference between the maximum possible value of RS and minimum possible value. The QLQ-C30 has been designed so that all the items in any scale take the same range of values. Therefore the range of RS equals the range of the item values. Most items are scored 1 to 4, giving range=3. The exceptions are the items contributing to the global health status/QoL, which are 7 point questions with range=6 and the initial yes /no items in the earlier versions of QLQ-C30 which have range=1.

Data Assessment

The information and investigation values of each patient were recorded using a proforma. All the statistical analysis was performed using SPSS statistical package (version 18) for windows. Chi-

square test was used to analyse the statistical significance of association between various factors. A p value <0.05 was considered statistically significant.

Results & Observations

The study group consisted of 65 patients.

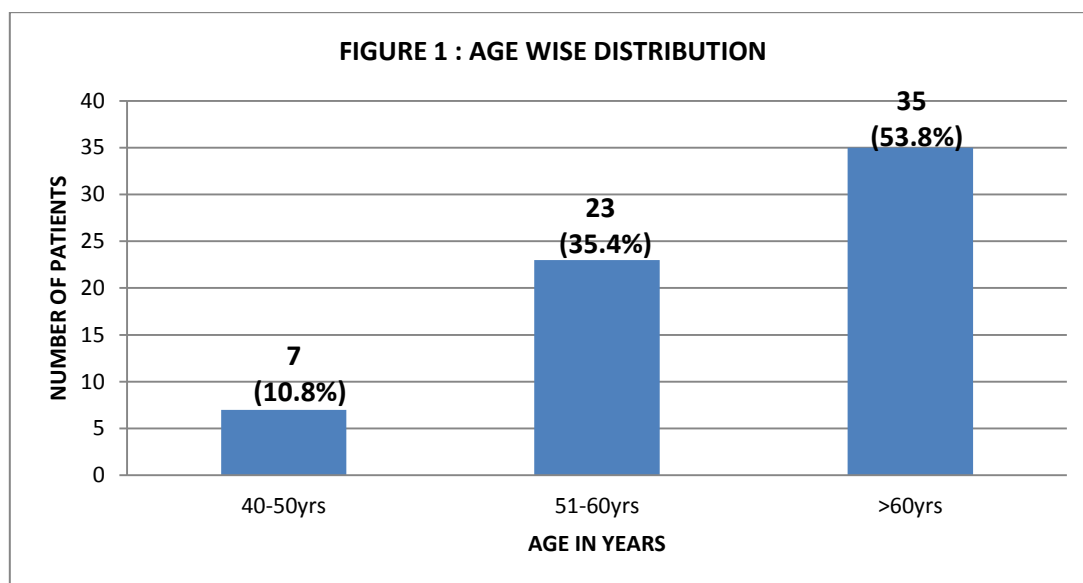
Baseline Characteristics of the Patients

Table 2: Baseline Characteristics of Study Population

Characteristics	Total (n=65)
Age (years)	61.4 \pm 7.6
Sex	Males=32; Females=33

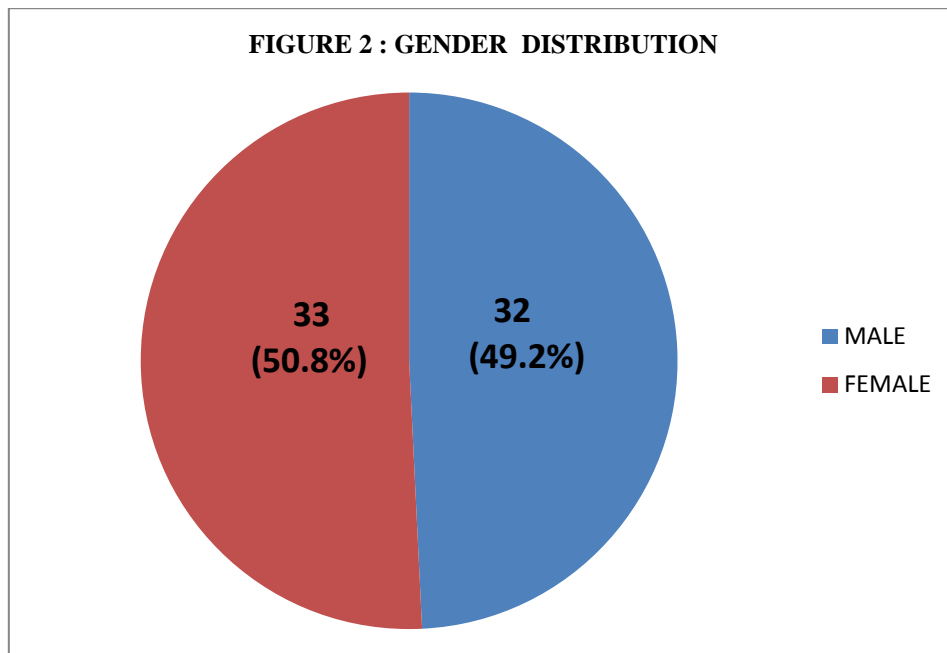
Age Wise Distribution

In this study group 7(10.8%) patients were between 40-50yrs, 23 (35.4%) patients were between 51 to 60 years and 35 (53.8%) patients were more than 60years of age and the mean age of the study group was 61.4 \pm 7.6years.



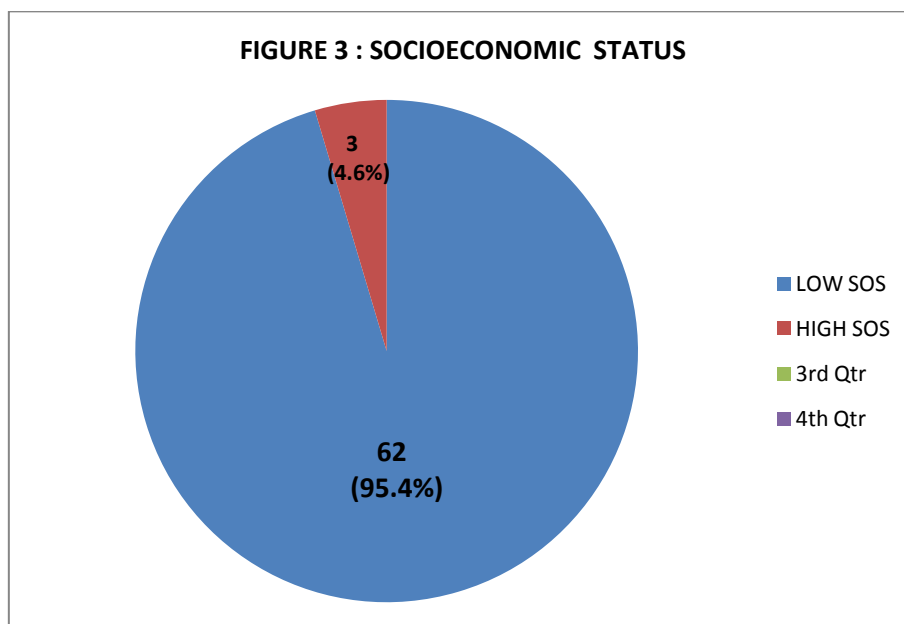
Gender Distribution

The study group consisted of 33 (50.8%) females and 32 (49.2%) males with a male to female ratio of 0.97:1.



Socioeconomic Status

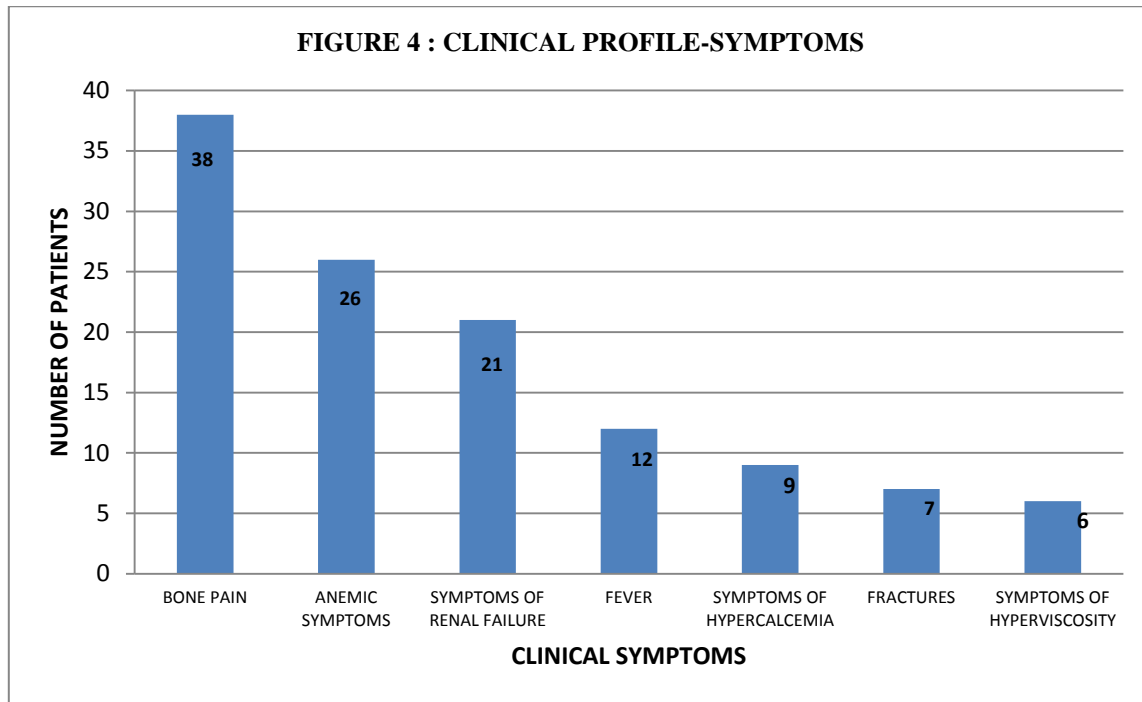
62 (95.4%) of patients in the study group were in the low socioeconomic status group.



Clinical Profile

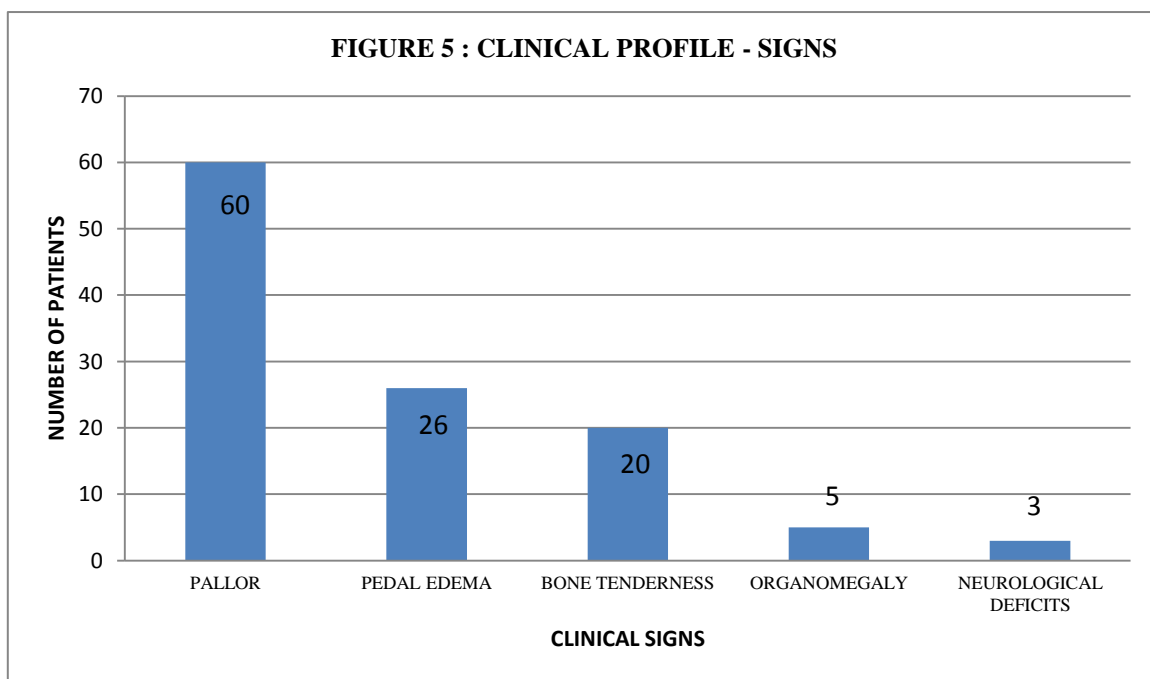
The most common presenting symptom of patients in this study was bone pain 38 (58.5%) followed by anemic symptoms in the form of lethargy, increased fatigue 26 (40%), symptoms of renal failure-pedal edema, decreased urine output

in 21 (32.3%), fever in 12 (18.5%), symptoms of hypercalcemia-increased thirst, vomiting in 9 (13.8%), and 7 (10.8%) patients presented with fractures, in the decreasing order of frequency.



The most common clinical sign elicited in the patients in the study group was pallor in 60 (92.3%) patients, followed by pedal edema in 26 (40%) patients, bone tenderness in 20 (30.8%)

patients, 5 (7.7%) patients had neurological manifestations and 3 (4.6%) patients had organomegaly.



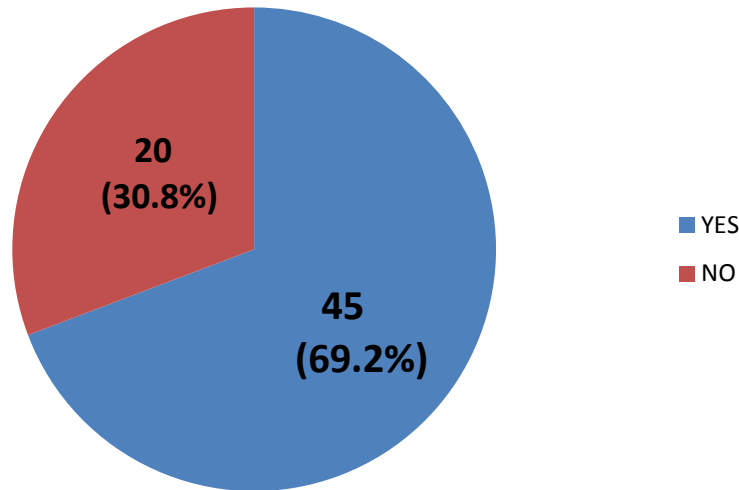
Investigations

Hemoglobin

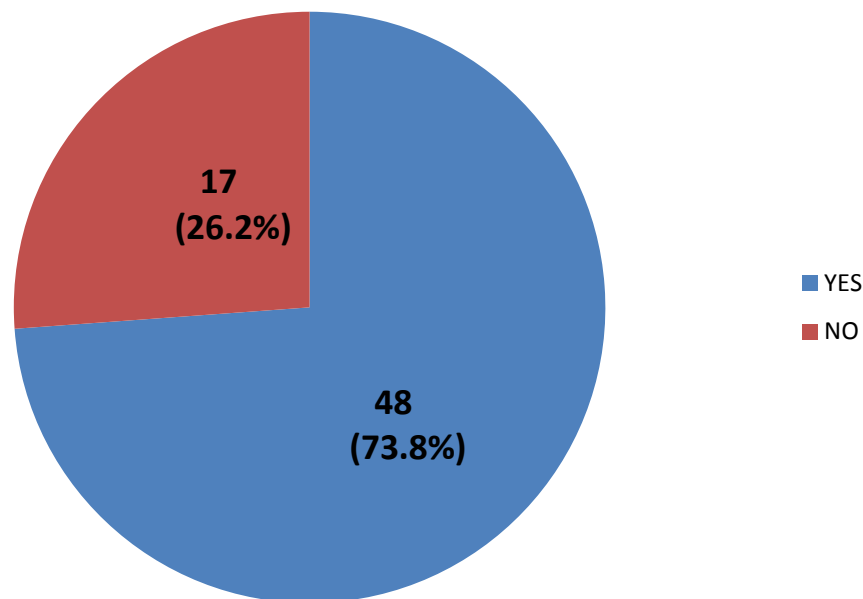
The mean hemoglobin value of the patients in the study group was 8.6±2.5g/dl. Hb<10g/dl was seen

in 45(69.2%) patients. MCV of 64 (98.5%) of the patients in the study group was normal (80-100fl).

FIGURE 6 : ANEMIA Hb < 10g/dl

**ESR**

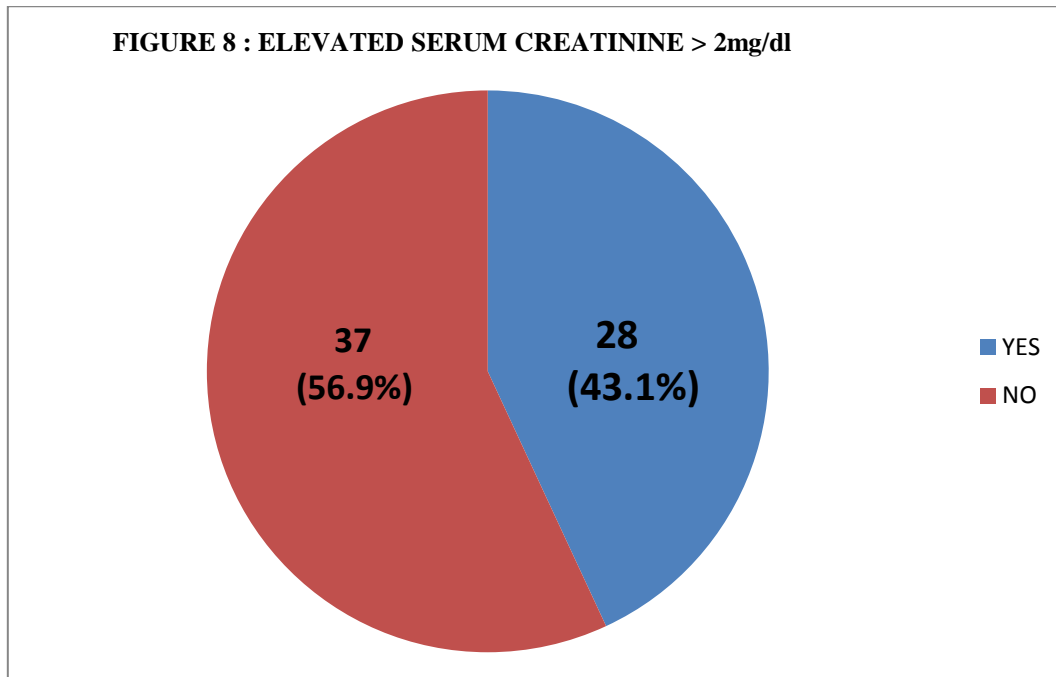
Mean ESR value of the study group was 103.2 ± 23.7 mm/hr. Elevated ESR of ≥ 100 mm/hr was seen in 48 (73.8%) patients.

FIGURE 7 : ELEVATED ESR ≥ 100 mm/hr**Bone Marrow Study**

Bone marrow plasma cells between 20-29% was seen in a majority 30 (46.2%) patients, bone marrow plasma cells $\geq 30\%$ was seen in 24 (36.9%) patients and 16 (24.6%) patients had a bone marrow plasma cell percentage $\geq 50\%$.

Serum Creatinine

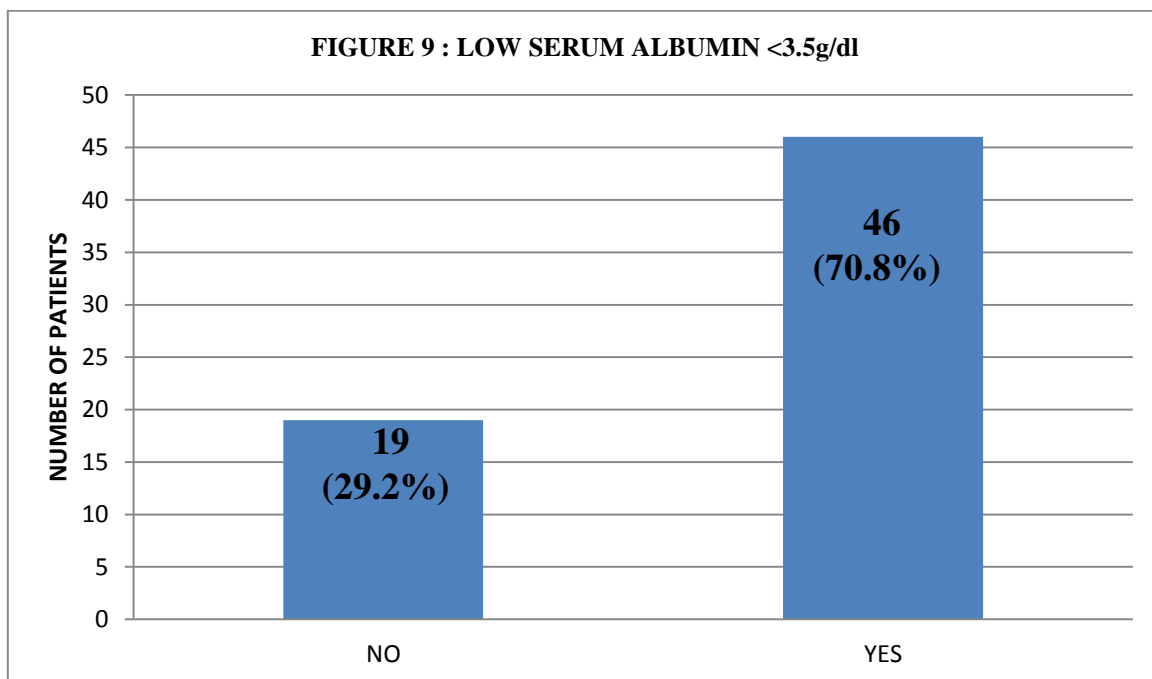
The mean value of serum creatinine in the study group of 1.8 ± 1.1 mg/dl. Elevated serum creatinine ≥ 2 mg/dl was seen in 28 (43.1%) patients in the study group.



Serum Albumin

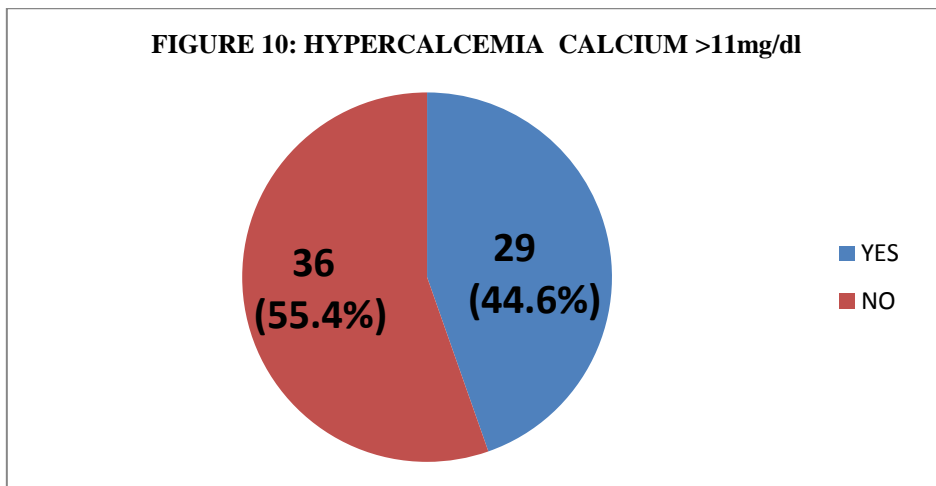
The mean value of serum albumin of the study population was 3.2±0.7g/dl. Low serum albumin

was seen in 46(70.8%) of the patients in the study group. Albumin globulin reversal was seen in 54 (84.6%) patients.



Serum Calcium

The mean value of serum calcium of the study group was 10.6±1.9mg/dl. Hypercalcemia as defined in the IMWG criteria >11mg/dl was seen in 29 (44.6%) patients.

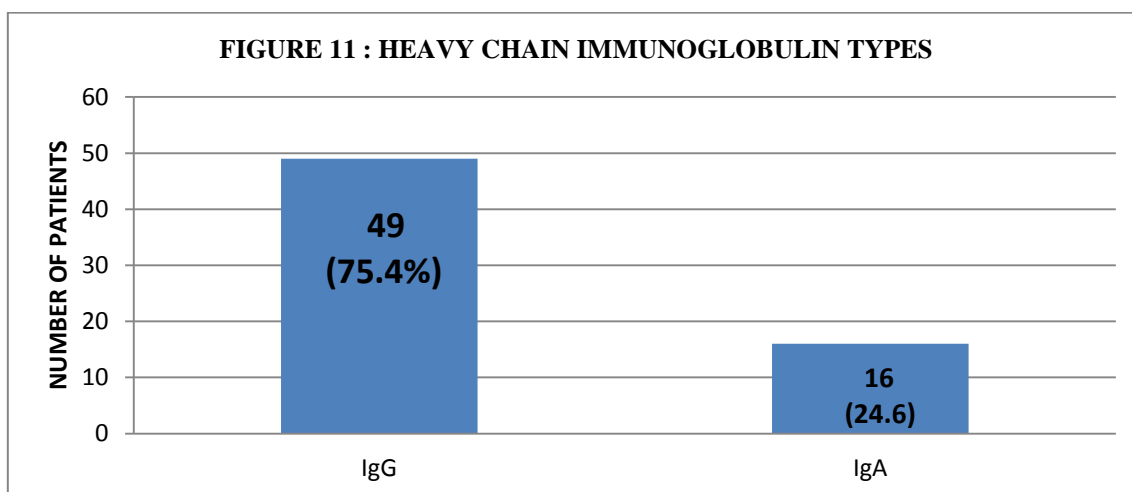


Serum electrophoresis showed presence of M band in all 65 of the study patients.

Immunoglobulin Levels

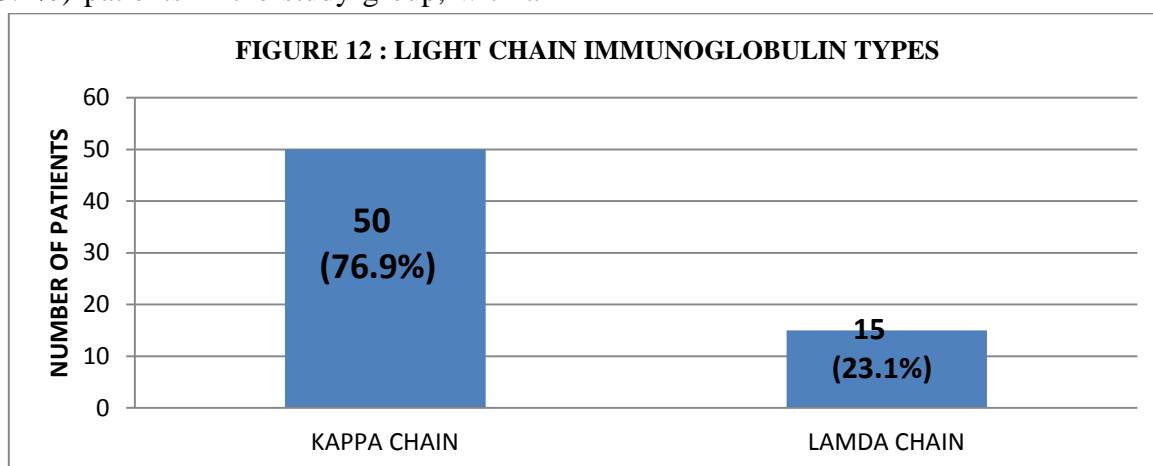
The most common immunoglobulin type of myeloma seen in the study population was IgG in 49 (75.4%), followed by elevated IgA in 16

(24.6%) patients, the mean value of IgG was 3223.1mg/dl and the mean value of IgA in the study population was 222.7mg/dl.



The most common light chain associated was kappa in 50 (76.9%) patients followed by lambda in 15 (23.1%) patients in the study group, with a

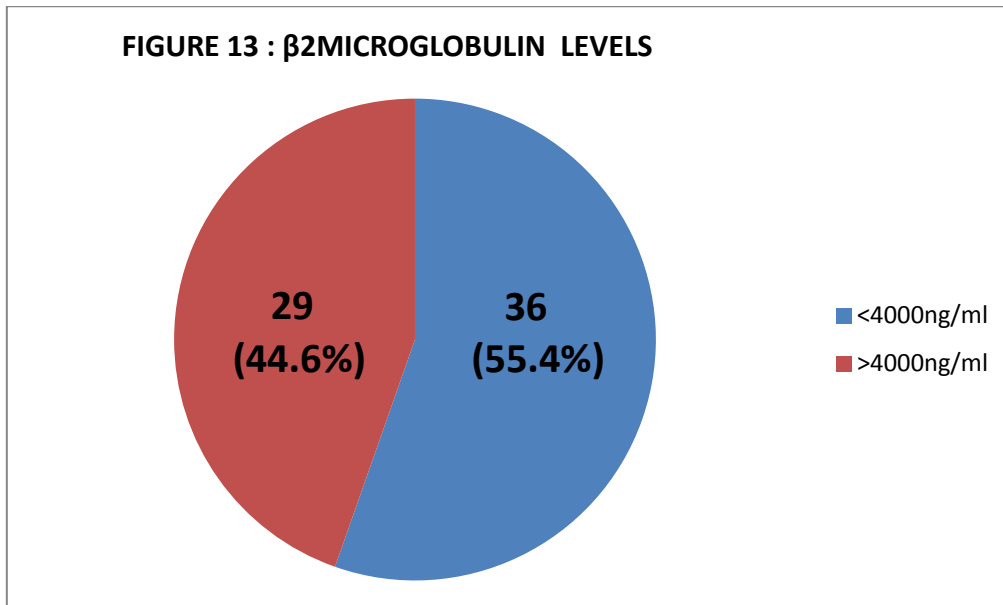
mean kappa value of 1763.77mg/dl and mean lambda value of 996.8mg/dl.



The most common type of myeloma was IgGκ type, immunoglobulin D, E or M elevation was not seen in any patients in the study group. Abnormal kappa/lambda ratio was seen in 20(30.8%) patients in the study group.

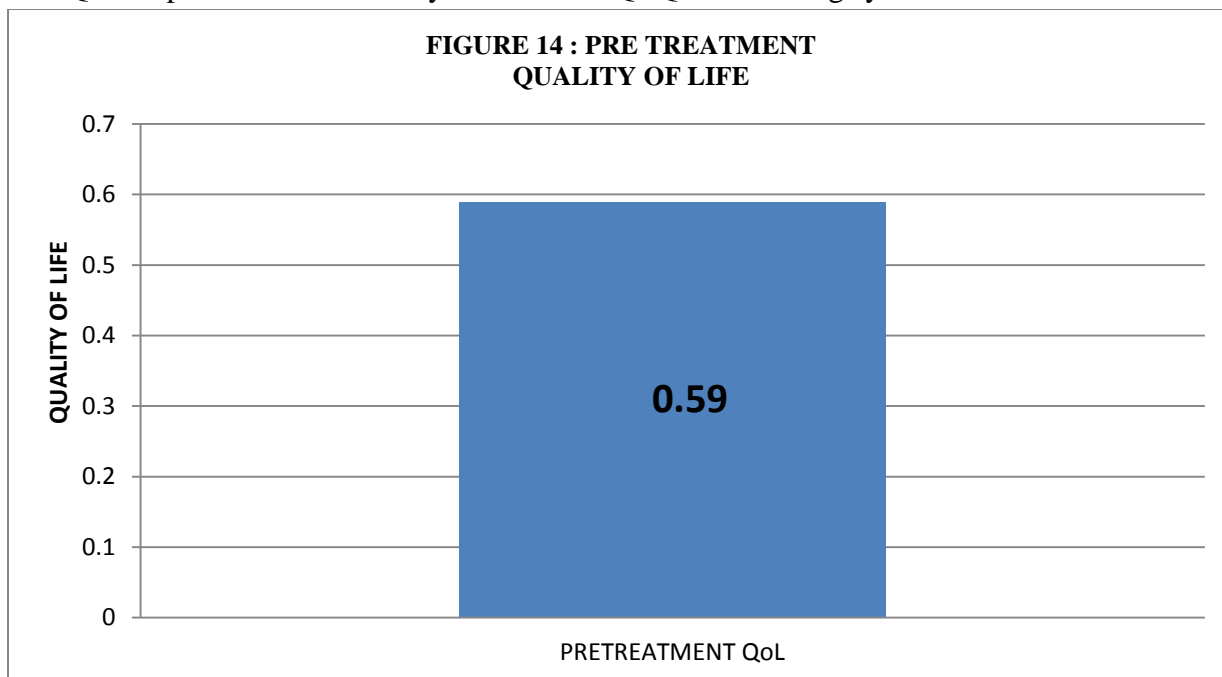
β2 Microglobulin

β2 microglobulin levels were seen to be less than 4000ng/ml in 36 (55.4%) patients in the study group with a mean value of 6039.7ng/ml.



Quality of Life (QoL)

The QoL of patients calculated by the EORTC QLQ-C30 scoring system was 0.59



Discussion

A prospective observational study was conducted during the period of January 2015 to December 2015 to assess the clinical profile and biochemical parameters in patients with multiple myeloma.⁶⁵

patients who were newly diagnosed to have the multiple myeloma and who fulfilled the diagnostic criteria of the disease were studied.

The mean age of the study group was 61.4±7.6 yrs with 35 (53.8%) patients in the age group of

>60yrs. The median age of diagnosis of multiple myeloma is 70 yrs and it is said to be uncommon <40yrs according to literature, in accordance with a study by Won Jin Chang et al the age group of > 60yrs included only 11.1% patients¹⁵. In a study by P.kaur et al the age range of patients with myeloma was from 27 to 81 years and the mean age was 57.8 years¹⁶. In the MRC myeloma IX trial by Gareth J. Morgan et al the median age of myeloma was 73 yrs and a study by Ping Wu et al had a median age of diagnosis of 57yrs¹⁷. The percentage of males and females were comparable in our study – 49.2% males and 50.8% females, this was in accordance with other similar studies. The polish myeloma group study by Anna Dmoszynska et al showed 46.2% males and 53.8% females¹⁸. The patients were predominantly in the low socioeconomic status group which includes 95.38% patients. So the patients that we encounter are mostly elderly with poor socioeconomic status. This becomes important because of the treatment we choose for the patient as there are several options of treatment including ASCT, but the patients that we encounter are mostly ineligible for ASCT and are to be started on chemotherapy. The chemotherapy should be chosen carefully and it should be affordable, well tolerated and should have a good response rate¹⁸. The clinical profile of the patients analysed showed that the most common symptom in these patients were bone pain - 38 (58.5%) patients, followed by anemic symptoms – 26 (40%) and symptoms of renal failure-21 (32.3%). In comparison to a study by Gupta et al 79% patients had bone pain at diagnosis¹⁹. The most common clinical sign elicited in the patients in the study group was pallor in 60 (92.3%) patients, followed by pedal edema in 26 (40%) patients, bone tenderness in 20 (30.8%) patients. Anemia (Hb value of <10mg/dl) was seen in 69.2% patients in our study group which is comparable to a study by Jyothi Wadhwa et al in which 59% patients had anemia¹⁶. The anemia was mostly normocytic anemia as reported in literature by Dispenzieri et al.

The mean ESR in our study group was 103.2 ± 23.7 mm/hr, Elevated ESR of ≥ 100 mm/hr was seen in 48 (73.8%) patients which was comparable to a study done by kaur et al in which ESR more than 100mm in the first hour is seen in 85.7% patients¹⁶. Bone marrow plasma cells between 20-29% was seen in a majority 30(46.2%) patients, bone marrow plasma cells $\geq 30\%$ was seen in 24 (36.9%) patients and 16 (24.6%) patients had a bone marrow plasma cell percentage $\geq 50\%$. The bone marrow plasma cells $\geq 30\%$ was seen in 48.4% patients in a study by Kihyun Kim et al²⁰. Elevated serum creatinine of >2mg/dl was seen in 43.1% patients which was higher when compared to a study by Kihyun Kim et al²⁰ in which only 23.4% patients had elevated serum creatinine but was significantly lower when compared to the study by kaur et al¹⁶ in which 77.3% had elevated serum creatinine >2mg/dl. Blood urea values of the patients in the study group ranged from 12 to 100mg/dl and the mean value was 41.4 ± 22.8 mg/dl. Serum albumin levels of the patients in the study group ranged from a minimum value of 1.6g/dl to a maximum value of 5.0g/dl with a mean value of 3.2 ± 0.7 g/dl. Low serum albumin was seen in 46(70.8%) of the patients in the study group. Albumin globulin reversal was seen in 54 (84.6%) patients. Low serum albumin was seen in 52% patients in a study by Kihyun Kim et al²⁰. Serum calcium values ranged from 6.8 to 14.5mg/dl with a mean value of the study group being 10.6 ± 1.9 mg/dl. Hypercalcemia as defined in the IMWG criteria >11mg/dl was seen in 29(44.6%) patients. This was similar to that of the study by P.Kaur et al¹⁶ in which 42.8% patients had hypercalcemia. The most common immunoglobulin type of myeloma seen in the study population was IgG in 49(75.4%), followed by elevated IgA in 16(24.6%) patients, the mean value of IgG was 3223.1mg/dl and the mean value of IgA in the study population was 222.7mg/dl. In a study by kihyunkim et al²⁰ 55.2% patients had IgG myeloma and 22% had IgA myeloma, 17.9% also showed light chain myeloma which was not seen

in our study population probably because these patients usually have renal failure as the presenting symptom and often end up with the nephrologist are started on bortezomib based chemotherapy. The most common light chain associated was kappa in 50 (76.9%) patients followed by lambda in 15 (23.1%) patients in the study group, with a mean kappa value of 1763.77mg/dl and mean lambda value of 996.8mg/dl. The most common type of myeloma was IgG κ type, immunoglobulin D, E or M elevation was not seen in any patients in the study group. Abnormal kappa/lambda ratio was seen in 20(30.8%) patients in the study group. β 2 microglobulin levels were seen to be <4000ng/ml in 36 (55.4%) patients in the study group with a mean value of 6039.7ng/ml. Raised serum β 2microglobulin was seen in 71.4% patients in the study by Kaur et al¹⁶ as compared to our study in which 44.6% had raised serum β 2microglobulin. Bone marrow plasma cells between 20-29% was seen in a majority 30(46.2%) patients, bone marrow plasma cells \geq 30% was seen in 24(36.9%) patients and 16 (24.6%) patients had a bone marrow plasma cell percentage \geq 50%.

Conclusions

- 1) Average age of presentation of patients with multiple myeloma is 61.4 \pm 7.6 yrs
- 2) Male to female ratio of patients with multiple myeloma was 0.97:1
- 3) Most common associations of multiple myeloma are anemia Hb<10mg/dl (69.2%), elevated ESR \geq 100mm/hr (73.8%), elevated serum creatinine >2mg/dl (43.1%), low albumin levels <3.5g/dl (70.8%)
- 4) Most common type of immunoglobulin seen in multiple myeloma was IgG (75.4%)
- 5) Bone marrow study showed plasma cells between 20-29% was seen in majority (46.2%) of patients.

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