Original Article

Value of CD81 and CD117 in Multiple Myeloma and Its Relation to Remission State

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Abstract

Background: Plasma cell myeloma is a bone marrow malignancy characterized by the proliferation of monoclonal plasma cells associated with a serum M protein and symptoms linked to organ dysfunctions or lytic bone lesions. The flow cytometric immunophenotype plays a crucial role in the diagnosis, prognosis, and monitoring of plasma cell disorders. Two markers, CD117 and CD81, have been used in diagnosis and prognosis, with some studies showing good prognosis for CD117 expression and poor prognosis for CD81 expression. **Objectives:** This study aimed to detect CD81 and CD117 in multiple myeloma patients, determine their relationship to remission states, and identify other prognostic factors. **Materials and methods:** This cross-sectional study included 70 patients, with 50 newly diagnosed and 20 already deceased. Data was collected at diagnosis, including age, sex, serum protein electrophoresis, plasma cell number in bone marrow aspirate, Ca, urea, Hb, creatinine, albumin, and B2 microglobulin. A follow-up test assessed performance level based on the ECOG score, number of plasma cells in the bone marrow aspirate, serum protein electrophoresis, and an IMWG-based assessment of remission. **Results:** The study involved 58.26 male patients with a mean age of 58.26, with a mean disease duration of 15 months. Most patients had normal protein electrophoresis post-treatment, mostly in stage I, and most ended with complete remission. 71.4% tested positive for CD117, while 55.7% tested positive for CD81. **Conclusion:** The study found that CD117 and CD81 were positive in two-thirds of cases, but not in half due to factors like the sample size and the cost of flow cytometry in Iraq, and no significant relationship was found.

Keyword: Multiple myeloma, Plasma cell, CD81, CD117, flow cytometry

Introduction

Multiple myeloma is a haematologic malignancy that causes bone lesions due to abnormal bone marrow plasma cells [1]. This leads to high calcium levels, damage to bones, kidney problems, anemia, and painful fractures. Excessive monoclonal protein overproduction can cause end-organ damage, haemopoietic abnormalities, and bone destruction [2]. Multiple myeloma accounts for up to 10% of haematologic neoplasms [3,4]. Plasma cell disorders include MGUS, smouldering multiple myeloma (SMM), clinical multiple myeloma (MM), and infrequently plasma cell leukaemia [5]. Monoclonal antibodies, also known as light chains or Bence-Jones proteins, are a type of antibody that doesn't work properly [6]. The growth of cancerous cells in the bone marrow stops the production of blood cells and antibodies, causing osteolytic lesions and increasing the risk of osteopenia, osteoporosis, and fractures [7]. Factors such as genetics, environmental pollutants, radiotherapy, and long-term antigen activation contribute to the growth of this plasma cell neoplasm. Various strategies have been used in managing multiple myeloma, including chemotherapy, stem cell transplantation, and drug classes like corticoster-

oids, anti-cancer medications, proteasome inhibitors, and immunomodulatory drugs [8]. Novel treatments have been developed to make the disease curable [9]. The diagnosis of multiple myeloma requires ≥10% clonal bone marrow plasma cells or a biopsy-proven plasmacytoma plus evidence of one or more multiple myeloma defining events (MDE). The median survival rate is about 5-7 years, with variation depending on host factors, tumor burden, biology, and response to therapy [10]. Tumor burden in MM has traditionally been assessed by the International Staging System (ISS) [11, 12]. Disease biology is best reflected based on the molecular subtype of MM and the presence or absence of secondary cytogenetic abnormalities [13]. The Revised International Staging System (RISS) adds elements of tumor burden (ISS) and disease biology (presence of high-risk cytogenetic abnormalities or elevated lactate dehydrogenase level) to create a unified prognostic index that helps in follow-up as well as in comparison of clinical trial data [14]. Management steps include initial therapy, stem cell transplantation (if eligible), consolidation /maintenance therapy, and treatment of relapse. Patients eligible for transplant typically receive approximately 4 cycles of initial therapy followed by stem cell collection and autologous stem cell transplantation (ASCT) [15]. The presence or absence of high-risk cytogenetic factors often drives the choice of maintenance and duration of therapy.

Materials and Methods

Study design

This is an analytical cross section study performed on 70 diagnosed patients who had completed diagnostic criteria of multiple myeloma according to IMWG system. This study was done on patients attending consultant department at hematological center in medical city hospital. The study was done from November 2023 till June 2024 and has been approved by the ethical committee of scientific council of pathology at the Iraqi board for medical specialization. Of 70 patients, 50 patients newly diagnosed as multiple myeloma, (also patients that previously diagnosed and complete all courses of treatment included in this study), 20 patients were dead (their information was taken from archive of flow cytometry department in laboratory center for hematology in medical city), sex of patients randomly selected. At first, verbal permission has been taken from each patient (newly diagnosed patients), full medical history and thorough physical examination was done to them.

Blood and bone marrow sampling

A Venous blood sample of about 2.5 ml and /or bone marrow aspirate sample of 0.5 ml were obtained from each patient included in this study by venipuncture from antecubital fossa or bone marrow aspirate from posterior superior iliac crest under aseptic technique respectively, and the samples were collected in EDTA K2 tubes. In the teaching laboratory department of the medical city, the blood sample was examined for complete blood indices, a blood film and bone marrow slides was made by taking a drop of blood and /or bone marrow sample spreads it on a clean dry slide, and staining it by Leishman; the slides were examined by a specialist in the teaching laboratory department of medical city. Accordingly, sample of peripheral blood is prepared for analysis by automated device (CellDYN, RUBY list), and then in association with clinical suspicion, we recommend flow cytometric panel according to Euro Flow antibody panels [16].

Staining

It was prepared by adding 2 g of Leishman powder in 500 ml methanol, and then the container was put in water bath at 56c and shook every 15 minutes to make a homogenous mixture then the mixture filtered by filter paper. After the drop of blood sample was spread on a clean dry slide, it was covered with Leishman stain for about 4 min to fix, add the buffered solution (composed of 100 ml of 66 mmol/l buffer solution to 1000 ml of distal water at a PH of 6.8). Leave for 6 min then washed by tap water then left to dry by air and examined under light microscope [17].

low cytometry

By Four color flow cytometric analysis was performed using a BD FACS Calibur™ flow cytometer (Becton Dickinson, Bio) and FACS Canto II flow cytometer (Becton Dickinson Immunocytometry Systems, San José, CA, USA). Cell Quest software (Becton Dickinson, San Jose, CA) and FACS Diva software were used to analyze the data.

Statistical analysis

Statistical analysis was carried out using SPSS version 27. Categorical variables were presented as frequencies and percentages. Continuous variables were presented as (Means ± SD). Paired t-test was used to compare means between two periods of assessment (before and after course of therapy). Pearson Chi-Square test and Fisher Exact test were used to find the association between categorical variables. $P \leq 0.05$ was considered as significant.

Ethical Approval

The College of Medicine at the University of Babylon ethical committee approved this study's ethical approval, obtaining verbal consent from each specimen of this study.

Results

In this study which is done on patients who completed diagnostic criteria of MM at hematology center in Baghdad medical city .70 patients were selected, 50 patients were newly diagnosed also patients that previously diagnosed and complete all courses of treatment, 20 dead patients (in some parameter the dead patients not included). Distribution of patients with Multiple myeloma according to socio-demographic characteristics including (age and sex). Mean age of patients was (58.26 ± 10.02) with older patient was 80 year and younger patient was 40 years, less than three quarters of patients were less than 65 years (N=52,74.3%). Majority of patients (N=43, 61.4%) were males (Table 1).

Table 1: Distribution of patients with Multiple myeloma according to socio- demographic characteristics (N=70)

Socio- demographic characteristics	No.	%
Age (Year)		
< 65 Years	52	74.3%
≥ 65 Years	18	25.7%
Total	70	100%
Sex		
Male	43	61.4%
Female	27	38.6%
Total	70	100%

Distribution of patients with Multiple myeloma according to duration of the disease

Distribution of patients with Multiple myeloma according to duration (months) including (< 12 months, 12-18 months, 19-24 months and > 24 months). Mean duration was (15.94 ± 9.35) months with longer duration was 58 months and shorter duration was 6 months, more than one third of patients presented with duration between 12-18 months which Represent (N=17, 34.0%).

Table 2: Distribution of patients with Multiple myeloma according to duration of disease (months)

Duration (Months)	No.	%
< 12 Months	16	32%
12-18 Months	17	34%
19-24 Months	8	16%
>24 Months	9	18%
Total	50	100%

Distribution of patients with multiple myeloma according to laboratory investigations at diagnosis and after follow up The laboratorial investigations summed up in Table 3 below.

Table 3: The Distribution of patients with Multiple myeloma according to laboratory investigation (N=50)

laboratory investigation	No.	%	Mean±SD	Range
Hemoglobin (g/dl)				
< 8	6	12%	10.18±2.04	5.60±18.00
8-10	22	44%		
> 10	22	44%		
Total	50	100%		
Plasma cell number before treatment (%)				
< 10	2	4%	33.02±20.63	6.00±88.00
10-20	15	30%		
21-40	19	38%		
> 40	14	28%		
Total	50	100%		
Plasma cell after treatment (%)				
< 10	40	80%	7.00±12.34	1.00±88.00
10-20	8	16%		
21-40	1	2%		
> 40	1	2%		
Total	50	100%		
Serum calcium (mg/dl)				
< 8.5	14	28%	8.97±1.18	5.60±11.80
8.5-10.5	33	66%		
> 10.5	3	6%		
Total	50	100%		
Blood urea (mg/dl)				
< 20	3	6%	44.80±32.26	14.00±181.00
20-40	25	50%		
41-60	12	24%		
> 60	10	20%		
Total	50	100%		
Serum creatinine (mg/dl)				
< 1.2	39	78%	47.80±32.26	14 ± 181
1.2-2	8	16%		
> 2	3	6%		
Total	50	100%		
Albumin (g/l)				
< 35	18	36%	36.05±3.22	28 ± 42
≥ 35	32	64%		
Total	50	100%		
B2 microglobin				
Moderate	36	72%	-	-
Bright strong	13	26%		
Negative	1	2%		
Total	50	100%		

Distribution of patients with multiple myeloma according to serum protein Electrophoresis after treatment

Distribution of patients with Multiple myeloma according to serum protein electrophoresis after treatment including (Decrease, increase and normal). Normal serum protein electrophoresis represents (N=23, 46.0%). Those with decrease SPE represent (N=14, 28.0%) and those with increase SPE represent (N=13, 26.0%). Most of patients with normal SPE.

Table 4: Distribution of patients with Multiple myeloma according to serum protein electrophoresis after treatment (N=50)

Serum protein electrophoresis	No.	%
Decrease	14	28
Increase	13	26
Normal	23	46
Total	50	100

Distribution of patients with Multiple myeloma according to stage of disease at diagnosis:

Distribution of patients with Multiple myeloma according to stage of disease including (stage I, stage II and stage III). Stage I represent (N=24,

48.0%). Stage II represent (N=14, 28.0%) and stage III represent (N=12, 24.0%).

Table 5: Distribution of patients with Multiple myeloma according to stage of disease at diagnosis (N=50)

Stage of disease	No.	%
Stage I	24	48
Stage II	14	28
Stage III	12	24
Total	50	100

Detection of (CD117 and CD81) markers in Multiple myeloma patients

Regarding CD117, less than three quarters of patients (N=50, 71.4%) presented with positive results, while only 20 patients (28.6%) presented with negative CD117. Regarding CD81, more than half of patients (N=39, 55.7%) presented with positive results, while 31 patients (44.3%) presented with negative CD 81.

Table 6: Distribution of patients with Multiple myeloma according to CD 117 and CD 81 (N=70)

Study markers	No.	%
CD117		
Positive	50	71.4
Negative	20	28.6
Total	70	100
CD81		
Positive	39	55.7
Negative	31	44.3
Total	70	100

Remission state of multiple myeloma patients

According to IMWG including (complete remission, Partial remission, Relapse state and Death). Patients with complete remission represent 22 patients (31.4%). Those with partial remission represent 15 patients (21.4%). Relapse state represents 13 patients (18.6%). Twenty patients (28.6%) were dead.

Table 7: Distribution of patients with Multiple myeloma according to remission state (N=70)

Remission state	No.	%
Complete remission	22	31.4
Partial remission	15	21.4
Relapse state	13	18.6
Death	20	28.6
Total	70	100

The association between study markers including (CD117 and CD81) and clinical data

The association between study markers including (CD117 and CD81) and clinical data including (age, sex, performance and stage of disease). There was no significant association between CD117 and CD81 and clinical data.

Table 8: The association between CD117 and CD81 and clinical data (N=70)

Clinical data	Study markers					
	CD117		P value	CD81		P value
	+ (50)	- (20)		+ (39)	- (31)	
Age (years)						
< 65	36(72)	16(80)	0.489	28(71.8)	24(77.4)	0.593
≥ 65	14(28)	4(20)		11(28.2)	7(22.6)	
Total	50(100)	20(100)		39(100)	31(100)	
Sex						
Male	31(62)	12(60)	0.877	23(59)	20(64.5)	0.636
Female	19(38)	8(40)		16(41)	11(35.5)	
Total	50(100)	20(100)		39(100)	31(100)	
Performance						
Well	36(72)	10(50)	0.173	27(69.2)	19(61.3)	0.473
Ill	2(4)	2(10)		3(7.7)	1(3.2)	
Dead	12(24)	8(40)		9(23.1)	11(35.5)	
Total	50(100)	20(100)		39(100)	31(100)	
Stage of disease						
Stage I	21(55.3)	3(25)	0.058	12(40)	12(60)	0.371
Stage II	11(28.9)	3(25)		10(33.3)	4(20)	
Stage III	6(15.8)	6(50)		8(26.7)	4(20)	
Total	38(100)	12(100)		30(100)	31(100)	

The association between study markers including (CD117 and CD81) and duration of disease

The association between study markers including (CD117 and CD81) and duration of disease including (< 12 months, 12-18 months, 19-24 months and >24 months). There was no significant association between CD117 and CD81 and duration of disease.

Table 9: The association between CD117 and CD81 and duration of disease (N=50)

Duration of disease	Study markers					
	CD117		P value	CD81		P value
	+ (38)	- (12)		+ (30)	- (20)	
< 12 months	15(39.5)	1(8.4)	0.085	10(33.3)	6(30)	0.179
12-18 months	13(34.2)	4(33.3)		13(43.4)	4(20)	
19-24 months	4(10.5)	4(33.3)		4(13.3)	4(20)	
> 24 months	6(15.8)	3(25)		3(10)	6(30)	
Total	38(100)	12(100)		30(100)	20(100)	

The association between study markers including (CD117 and CD81) and serum protein electrophoresis after treatment

The association between study markers including (CD117 and CD81) and serum protein electrophoresis including (decrease, increase and normal). There was no significant association between CD117 and CD81 and serum protein electrophoresis.

Table 10: The association between CD117 and CD81 and serum protein electrophoresis after treatment (N=50)

Serum protein electrophoresis	Study markers					
	CD117		P value	CD81		P value
	+ (38)	- (12)		+ (30)	- (20)	
Decrease	9(23.7)	5(41.7)	0.274	9(30)	5(25)	0.192
Increase	12(31.6)	1(8.3)		6(20)	7(35)	
Normal	17(44.7)	6(50)		15(50)	8(40)	
Total	38(100)	12(100)		30(100)	20(100)	

The association between study markers including (CD117 and CD81) and laboratory investigation at diagnosis and at follow up.

The association between study markers including (CD117 and CD81) and laboratory investigation including (hemoglobin (g/dl), plasma before treatment (%), plasma after treatment (%), serum calcium (mg/dl), blood urea (mg/dl), serum creatinine (mg/dl), albumin (g/l) and B2 microglobin). There was no significance relationship between (CD117, CD81) and hb, Ca, urea, creatinine, albumin and B2 microglobin. However, there is positive significance relation between CD81 and plasma cell number after treatment (P value 0.033).

Table 11: The association between CD117 and CD81 and laboratory investigation (N=50)

Laboratory Investigation	Study markers					
	CD117		P value	CD81		P value
	+ (38)	- (12)		+ (30)	- (20)	
Hemoglobin (g/dl)						
< 8	4(10.5)	2(16.7)	0.342	4(13.3)	2(10)	0.214
8-10	15(39.5)	7(58.3)		16(53.4)	6(30)	
> 10	19(50)	3(25)		10(33.3)	12(60)	
Total	38(100)	12(100)		30(100)	20(100)	
Plasma cell number before treatment (%)						
< 10	2(5.3)	0(0)	0.952	1(3.3)	1(5)	0.855
10-20	12(31.6)	3(25)		10(33.3)	5(25)	
21-40	14(36.8)	5(41.7)		10(33.3)	9(45)	
> 40	10(26.3)	4(33.3)		9(30)	5(25)	
Total	38(100)	12(100)		30(100)	20(100)	
Plasma cell after treatment (%)						
< 10	29(76.3)	11(91.7)	0.127	27(90)	13(65)	0.033
10-20	8(21.1)	0(0)		2(6.7)	6(30)	
21-40	0(0)	1(8.3)		1(3.3)	0(0)	
> 40	1(2.6)	0(0)		0(0)	1(5)	
Total	38(100)	12(100)		30(100)	20(100)	
Serum calcium (mg/dl)						
< 8.5	10(26.3)	4(33.3)	0.759	10(33.3)	4(20)	0.568
8.5-10.5	25(65.8)	8(66.7)		18(60)	15(75)	
> 10.5	3(7.9)	0(0)		2(6.7)	1(5)	
Total	38(100)	12(100)		30(100)	20(100)	
Blood urea (mg/dl)						

< 20	3(7.9)	0(0)		3(10)	0(0)	
20-40	20(52.6)	5(41.7)		13(43.3)	12(60)	
41-60	9(15.8)	3(25)	0.581	7(23.3)	5(25)	0.441
> 60	6(15.8)	4(33.3)		7(23.3)	3(15)	
Total	38(100)	12(100)		30(100)	20(100)	
Serum creatinine (mg/dl)						
< 1.2	31(81.6)	8(66.7)		22(73.3)	17(85)	
1.2-2	5(13.1)	3(25)	0.373	6(20)	2(10)	0.754
> 2	2(5.3)	1(8.3)		2(6.7)	1(5)	
Total	38(100)	12(100)		30(100)	20(100)	
Albumin (g/l)						
< 35	14(36.8)	4(33.3)		10(33.3)	8(40)	
≥ 35	24(63.2)	8(66.7)	1.000	20(66.7)	12(60)	0.630
Total	38(100)	12(100)		30(100)	20(100)	
B2 microglobin						
Moderate	28(73.7)	8(66.7)		20(66.7)	16(80)	
Bright strong	9(23.7)	4(33.3)	0.778	10(33.3)	3(15)	0.145
Negative	1(2.6)	0(0)		0(0)	1(5)	
Total	38(100)	12(100)		30(100)	20(100)	

The association between study markers (CD117 and CD81) and remission state

The association between study markers including (CD117 and CD81) and remission state including (Complete remission, Partial remission, Relapse state and Death) among patients with Multiple myeloma. There was no significant association between (CD117, CD81) and remission state as Figure 1,2.

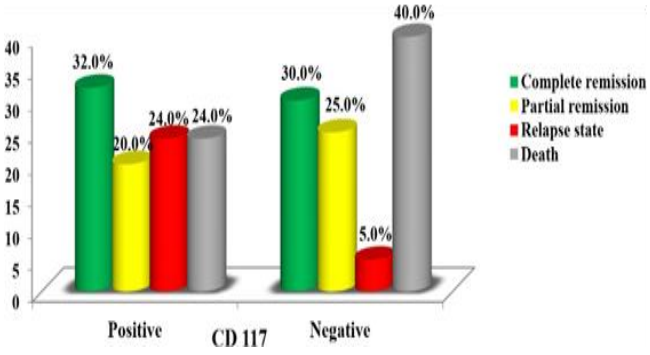

Figure 1: The association between CD117 and remission state (N=70)

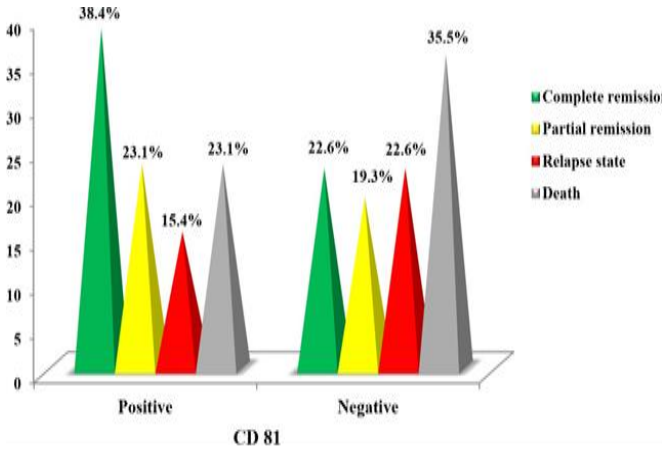

Figure 2: The association between CD81 and remission state (N=70)

Discussion

Multiple myeloma (MM) is a cancer of plasma cells (PC) with elevated calcium levels, renal dysfunction, anemia, osteolytic bone lesions, and impaired immune response. The mean age of patients with MM is 58, with less than three-quarters being under 65 years old. This study found a male preponderance over females, consistent with previous Iraqi investigations and a 2018 Chinese survey [18-20]. The majority of patients had a favorable performance status, corroborating findings from a 2017 study in China [21-23]. The mean illness duration in this research was 15.94 ± 9.35 months, with a maximum length of 58 months and a minimum of 6 months. About one-third of patients exhibited a duration between 12 and 18 months, which concurred with the Iraqi trial. The discrepancies between our study and others arise from several factors, including the quantity and availability of patients included and the geographical spread of the population [24]. The mean haemoglobin level was 10.18 ± 2.04, consistent with earlier Iraqi research [24]. A study revealed no statistically significant difference, and the mean plasma value before therapy and plasma cell post-treatment showed a

substantial disparity, suggesting a response to therapy and a favorable prognostic factor. The mean concentration of serum calcium was 8.97 ± 1.18, and the mean blood urea level was 47.80 ± 32.26. The mean blood creatinine level and average albumin level showed no significant difference compared to other studies conducted in Iraq [24] or China [23]. This study indicates a slight rise in B2 microglobulin values compared to other studies conducted in China in 2017 [23], which contradicts these findings. Additional Iraqi investigations indicated that the majority of patients exhibited elevated levels of B2 microglobulin at the time of diagnosis. Advanced illness correlates with a worse prognosis, while low levels signify a stable, non-progressive condition [26]. This study found that serum protein electrophoresis after treatment in most patients was normal, with some patients having increased or decreased levels. The normalization or reduction in serum protein indicates a response to treatment, while increased levels indicate no response or increased activity of the disease. This is consistent with other Iraqi and Spanish studies [27,25]. Most cases in this study were observed in stage 1, which differs from the study at China Medical University 2018, which showed most patients presented with stage II [21] or stage III [25]. There was a higher percentage of the CD117 marker being expressed in this study compared to other studies. CD117 acts as an adhesion molecule that favors the anchoring of plasma cells to precursor-associated bone marrow niches and homing of plasma cells to bone marrow microenvironments [28]. Over half of patients with positive results in this study had CD81 expression, while CD81 negative patients had a low percentage. No significant differences were found in baseline characteristics of CD81+ vs CD81-ve MM patients [29]. In this study, there was no significant association between CD117 and clinical data, sample size, time of diagnosis, and time of beginning treatment. The association between CD117, CD81, and duration of disease was an independent prognostic factor [21]. In vitro studies show that CD81 has an anti-tumorigenic effect on myeloid myeloma (MM) cells, lowering the rate of invasion and proliferation. It also increases protein synthesis by activating the unfolded protein response (UPR) [32], killing MM cells in a planned way. CD117 is occasionally expressed by plasma cells forming about a third of MM cases, as opposed to normal plasma cells that do not express it [21,33]. CD117+ MM patients were found to have more hyper diploid karyotype cases, less 14 chromosome translocations, and overall a better prognosis compared to CD117- MM patients [28,34]. There was no significant association between CD117 and serum protein electrophoresis after treatment, which was also supported by Chinese studies [21]. In this research, there was no significant link between CD117 and laboratory tests like haemoglobin, plasma before and after treatment, serum calcium, blood urea, serum creatinine, albumin, and B2 microglobulin. High levels of B2 microglobulin indicated an advanced stage of the disease [35]. CD117 may help PCM cells multiply and prevent normal haemophiliac cells from multiplying properly [36], but most studies have found that CD117 doesn't. Positivity predicts a favorable outcome, possibly because CD117(+) patients have normal plasma cells. This helps set the stage for a favourable prognosis. In our study, there was no significant link between CD81 expression and laboratory investigations, and the only instance where it did occur was in plasma cells following treatment [30]. CD81 might stop plasma cells from spreading, as some studies have shown that its

expression stops them from entering and moving around [31]. Lowering CD81 expression in these cells makes it easier for plasma cells to enter the peripheral circulation [37]. Other research has shown that CD81 expression by plasma cells predicts an adverse prognosis for patients with smouldering multiple myeloma or symptomatic MM [30]. Recent reports indicate that patients with CD81+ plasma cells, which are poorly differentiated clonal cells, are expected to have a poor prognosis [38]. There was a significant effect on plasma percent after treatment in this study (p-value 0.033). This is because CD81 expression is important for myeloma cells (39). In this study, there was no significant relationship between CD117 and remission state, but other studies have shown that CD117 has a favourable correlation with the disease response to treatment [21].

Conclusion

The result of this study showcase CD117 positive in one third of cases, while the result of CD81 was positive in half of cases. There was no significance relationship between of CD117 and CD81 with remission state because of some factors that may attributed to the causes such as sample size of the patients that included in this study. However, there was a significant effect on plasma after treatment in this study with (p-value 0.033), a further indication of CD81 expression importance for myeloma cells. Factors such as the number and availability of patients, location, diagnosis, treatment start time, medication availability, and management plan type may cause differences in the results of this study and other studies.Further study with larger number of cases may be recommended to confirm our results. Patients from other hematological center should be included in this study.

Interest Conflicts

None**.**

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