Serum free light-chain concentration and relationship with some characteristics of patients with multiple myeloma

Concentración de cadenas ligeras libres en el suero y relación con algunas características de pacientes con mieloma múltiple

Phan Nguyen Thanh Van[1]* https://orcid.org/0000-0002-9018-9075

Cao Thi Loc[2] https://orcid.org/0000-0002-6155-2648

Tong Duc Minh[3] https://orcid.org/0000-0001-5449-0832

Nguyen Hoang Trung[3] https://orcid.org/0000-0003-3527-7037

Tran Van Kha[3] https://orcid.org/0000-0002-9517-3304

Le Trong Dung[4] https://orcid.org/0000-0001-9581-3298

[1]Pham Ngoc Thach University of Medicine. Ho Chi Minh City, Vietnam.

[2]Department of Hematology. Blood Transfusion Hematology Hospital. Ho Chi Minh City, Vietnam.

[3]Department of Military Hygiene. Vietnam Military Medical University. Hanoi, Vietnam.

[4]Organization and Command of Military Medical Department. Vietnam Military Medical University. Hanoi, Vietnam.

*Author for correspondence. Email: pnthanhvan@pnt.edu.vn

ABSTRACT

Introduction: Quantifying serum free light-chain is a valuable test to determine the risk at the time of diagnosis, assess the response to treatment, and monitor the recurrence of multiple myeloma.

Objective: To investigate the characteristics of serum free light-chain concentration and its relationship with some clinical and subclinical characteristics in patients with multiple myeloma.

Methods: Descriptive, retrospective, non-controlled study was conducted, in 74 patients with multiple myeloma. All patients were completed with quantitative tests serum free light-chain κ, and serum free light-chain λ.

Results: Intact immunoglobulin multiple myeloma accounted for most patients (81%). Most patients had abnormal serum free light-chain at the time of diagnosis (98.6%). High serum free light-chain concentration was correlated with M protein concentration > 3 g/dL ($p < 0.05$) and there was no statistically significant correlation between high serum free light-chain and other clinical and subclinical features.

Conclusion: Most patients with multiple myeloma have an elevated serum free light-chain at admission time. Correlation of high serum free light-chain with increased serum M protein was noted.

Keywords: multiple myeloma; sFLC concentration; sFLCκ; sFLCλ.

RESUMEN

Introducción: La cuantificación de cadenas ligeras libres en el suero es una prueba valiosa para determinar el riesgo al momento del diagnóstico del mieloma múltiple, así como evaluar la respuesta al tratamiento y monitorear la recurrencia.

Objetivo: Determinar las características de la concentración de cadenas ligeras libres en el suero y su relación con algunas características clínicas y subclínicas en pacientes con mieloma múltiple.

Métodos: Se realizó un estudio descriptivo, retrospectivo, no controlado, en 74 pacientes con mieloma múltiple. Todos los pacientes completaron pruebas cuantitativas de cadena ligera libre en el suero κ y cadena ligera libre en suero λ.

Resultados: El mieloma múltiple de inmunoglobulina intacta representó a la mayoría de los pacientes (81 %). La mayoría de los pacientes tenían cadenas ligeras libres séricas anormales en el momento del diagnóstico (98,6 %). La concentración elevada de cadenas ligeras libres en el suero correlacionó con concentración de proteína M > 3 g/dL ($p < 0,05$) y no hubo correlación estadísticamente significativa entre cadenas ligeras libres en el suero elevadas y otras características clínicas y subclínicas.

Conclusión: La mayoría de los pacientes con mieloma múltiple tienen cadenas ligeras libres séricas elevadas en el momento del ingreso. Se observa correlación de cadenas ligeras libres séricas altas, con la proteína M sérica aumentada.

INTRODUCTION

Multiple myeloma is a malignant proliferative disease of plasma cells in the bone marrow and some other organs, accounting for 1% of all cancers and 10% of hematologic cancers in particular.[1] Diagnosis and response assessment of the disease was determined based on the criteria of the International Myeloma Working Group (IMWG).[2] The prognosis of multiple myeloma is highly variable due to the biological heterogeneity of multiple myeloma cells, the bone marrow microenvironment, and host factors. Patient prognostic clustering is important as it helps to optimize and initiate appropriate treatment as early as possible to avoid irreversible organ damage.

Serum free light chain (sFLC) quantification is a valuable risk-defined test at the time of diagnosis, assessment of response to therapy, and monitoring of recurrence; despite the role of it is not yet completely unified. The IMWG recommends quantifying sFLC as part of the standard investigation in newly diagnosed patients with plasmacytosis,[3] and sFLC is important in diagnosing patients with light chain myeloma, non-secretory myeloma, amyloidosis and early detection of multiple myeloma nephropathy.[4]

To evaluate the value of sFLC in patients with multiple myeloma, the study was conducted to test the role of sFLC in newly diagnosed multiple myeloma patients treated at Hematology and Blood Transfusion Hospital, Ho Chi Minh City, Vietnam with the objective of investigating the characteristics of sFLC concentration and its relationship with some clinical and subclinical characteristics in patients with multiple myeloma.

METHODS

Including 74 multiple myeloma patients hospitalized at Hematology and Blood Transfusion Hospital, Ho Chi Minh City, Vietnam, diagnosed and treated for multiple myeloma, completed quantitative tests sFLCκ, sFLC$_\lambda$ at the time of diagnosis, from January 2017 to December 2020. Selection criteria:

- Adult patients > 18-year-old
- Definitive diagnosis of multiple myeloma according to the IMWG criteria
- Be treated according to the regimen with bortezomib in the hospital
- Newly diagnosed and untreated disease

Research design: cross-sectional study, non-controlled study.

Research sample size: the following formula was used to calculate sample size to estimate 1 ratio:

$$n = \frac{Z^2_{1-\alpha/2} \times P \times (1-P)}{d^2}$$

- n is the minimum sample size
- α= 0.05 (probability of error type 1)
- p= 0.51 (*García De Veas Silva*'s study in 2016[5] with 51% of patients with high sFLCR with a statistically significant difference in survival prognosis compared with low sFLCR group)
- d= 0.1 (allowed error)

Was calculated n= 96. Thus, the minimum sample size was 96 people. Because the quantitative test for sFLC has just been deployed at the blood transfusion hospital from 2017 to present. Therefore, were collected all newly diagnosed multiple myeloma patients who met the sampling criteria and had a quantitative sFLC test at the time of diagnosis, for a total of 74 patients.

Research variables: mean age, proportion of age groups, sex, characteristics of sFLC concentration at the time of diagnosis, patient characteristics and association with high sFLCR.

Disease staging according to the International staging system (ISS):

- Stage I: β2-Microglobulin < 3.5 mg/L and serum albumin ≥ 3.5 g/dL

- Stage II: β2-Microglobulin: 3.5 mg/L - 5.5 mg/dL and/or Albumin < 3.5 g/dL
- Stage III: β2-Microglobulin ≥ 5.5 mg/L

Data management and analysis: data were analyzed with SPSS 22.0 software, using descriptive statistics algorithms, calculating the mean and standard deviation, using the Chi-square test and Fisher's exact test to compare the difference between clinical and laboratory characteristics of patients and the association with high sFLCR. Any variable with $p < 0.05$ was considered to be statistically significant.

From the ethical point of view, the confidentiality of the identity of the patients is maintained, only used for analysis as a group.

RESULTS

Demographic and other characteristics of patients

The proportion of male patients accounted for 48.7%, and female accounted for 51.3%, so the male/female ratio was approximately the same.

The average age of the study group of patients was 58.7 ± 11.1; in which the oldest age was 79 years old and the youngest age was 32 years old. The age group from 55-64 accounts for the highest percentage, followed by the age group 45-54; age group < 45 or > 84 accounted for low proportion (table 1).

Table 1 - Age distribution

Types (n= 74)	n	%
< 20	0	0.0
20-34	1	1.4
35-44	6	8.1
45-54	16	21.6
55-64	34	45.9
65-74	10	13.5
75-84	7	9.5
> 84	0	0.0
Total	74	100.0
$\overline{X} \pm$ SD	58.7 ± 11.1	
Max – Min	79 - 32	

The results in the table 2 show that, in this study, intact immunoglobulin multiple myeloma accounted for the majority of patients with a rate of 81%, in intact immunoglobulin multiple myeloma the majority of patients with heavy chain secretion was mainly IgG with 76.7% of patients, Kappa light chain in intact immunoglobulin multiple myeloma accounted for the majority of patients with 72%. For multiple light chain myeloma (19% of patients), Lambda light chain accounted for the majority with 9 patients (64%).

Table 2 - Types of multiple myeloma

Types (n= 74)		n	%
Intact immunoglobulin multiple myeloma		60	81
Heavy chain	IgG	46	76.7
	IgA	13	21.7
	IgM	1	1.6
Light chain	Kappa	43	72
	Lambda	17	28
Light chain multiple myeloma		14	19
Light chain	Kappa	5	36
	Lambda	9	64

Changes in sFLC and sFLCR across therapeutic stages of multiple myeloma

Most patients had abnormal sFLCR at the time of diagnosis (98.6%). A patient with sFLCR normally secretes IgG. The median value of sFLC in the 2 groups of intact immunoglobulin

multiple myeloma and light chain multiple myeloma differed considerably. In the group of light chain multiple myeloma, sFLC was very high, the median values of the two light chain types were equal (sFLC= 1500 mg/L). In contrast, in the intact immunoglobulin multiple myeloma group, the median value of light chain κ was higher than that of light chain λ. If calculating the rate of light chain secretion in general, λ tends to increase higher than κ (table 3).

Regarding the median sFLCR in the κ- secreting and λ-secreting groups, the λ-secreting group was higher than the κ-secreting group with values of 55.6 and 39.3 respectively, 38% of patients had a very high sFLCR rate (> 100). So, in this study, patients with multiple myeloma with λ light chain secretion, sFLCR > 55.6 is called high sFLCR group, similarly if sFLCR > 39.3 is called high sFLCR in κ secretory group. Lower than the above two corresponding values are called low sFLCR (Fig. 1).

Table 3 - sFLC characteristics at the time of diagnosis

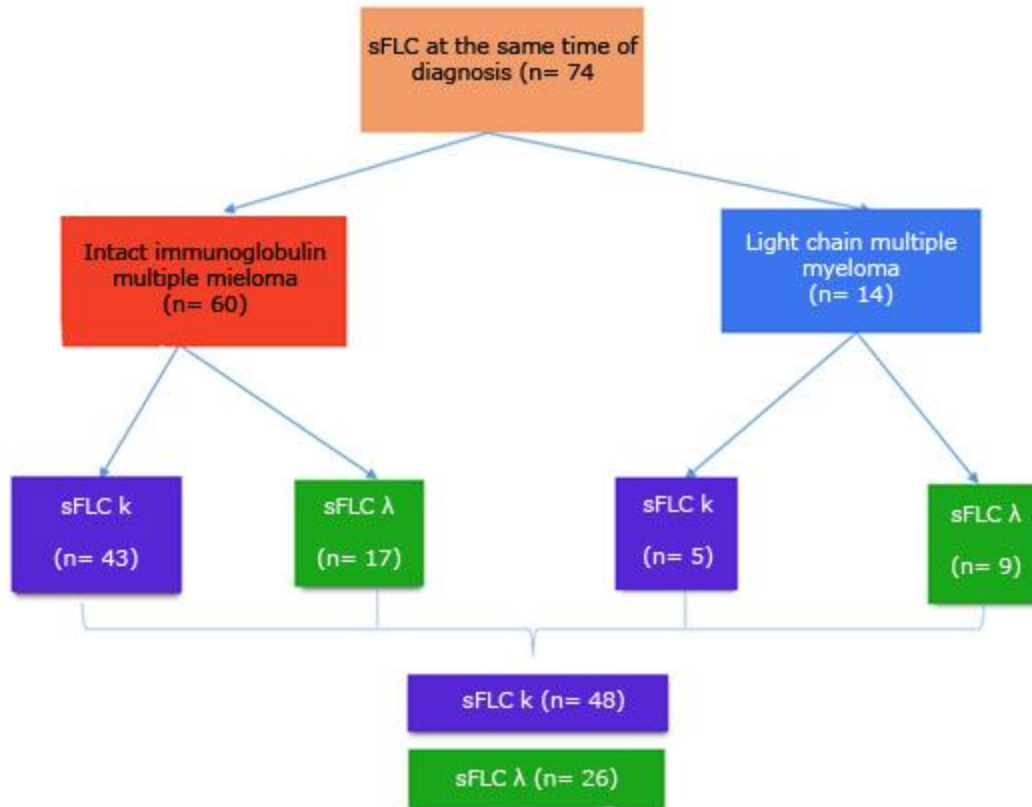| Characteristics		n	Median
Intact immunoglobulin multiple myeloma (n = 60)	sFLC κ (mg/L)	43	320 (30.7 - 1500)
	sFLC λ (mg/L)	17	127 (46.6 - 1500)
Light chain multiple myeloma (n = 14)	sFLC κ (mg/L)	5	1500 (1500 - 1500)
	sFLC λ (mg/L)	9	1500 (1500 - 1500)
General multiple myeloma	sFLC κ (mg/L)	48	390 (30.7 - 1500)
	sFLC λ (mg/L)	26	633.5 (46.6 - 1500)
	sFLCR (κ-secreting)	48	39.3 (1.2 - 306)
	sFLCR (λ-secreting)	26	55.6 (5.2 - 189)
	Number of patients with sFLCR > 1,65 or < 0.26 (%)	73 (98.6%)	
	Number of patients with sFLCR ≥ 100 (%)	28 (38%)	

Fig. 1 - sFLC subgroups.

Correlation of sFLCR with patient characteristics and parameters related to multiple myeloma

The study noted that high sFLCR was correlated with M protein concentration > 3 g/dL (p< 0.05) and there was no statistically significant correlation between high sFLCR and renal failure (p< 0.01), creatinine > 2 mg/dL), increase in β2M > 3.5 mg/L, anemia (HGB< 10 g/dL), hypercalcemia (Ca> 2.75 mmol/L), increase LDH> 460 U/L, Albumin < 3.5 g/dL as well as the presence of osteolytic lesions and plasma cell infiltration in the marrow. There was a larger proportion of patients classified as ISS stage 3 in the high sFLCR group, but the difference was not statistically significant.

Chromosomes recorded two high-risk mutations, del(17p), to belong to the low sFLCR group.

Table 4 - Patient characteristics and association with high sFLCR

Parameters	Low sFLCR (n = 37) n (%)	High sFLCR (n = 37) n (%)	Total (n = 74) n (%)	p- value*
Male/Female (%)	54.1/45.9	43.2/56.8	48.6/51.4	0.35
Age > 65	6 (16.2)	10 (27.0)	16 (21.6)	0.26
Intact immunoglobulin multiple myeloma	34 (91.9)	26 (70.3)	60 (81.1)	
IgG	25 (73.5)	21 (80.8)	46 (76.7)	0.33
IgA	9 (26.5)	4 (15.4)	13 (21.7)	
IgM	0 (0)	1 (3.8)	1 (1.7)	
Light chain multiple myeloma	3 (8.1)	11 (29.7)	14 (18.9)	
Kappa	1 (33.3)	4 (36.4)	5 (35.7)	0.92
Lambda	2 (66.7)	7 (63.6)	9 (64.3)	
Creatinine >177 μmol/L	3 (8.1)	7 (18.9)	10 (13.5)	0.17
HGB < 10 g/dL	34 (91.4)	31 (83.8)	65 (87.8)	0.29
Calcium > 2.75 mmol/L	(0)	2 (5.4)	2 (2.7)	0.15
β2M > 3.5 mg/L	24 (64.9)	21 (56.8)	45 (60.8)	0.47
Albumin < 3.5 g/dL	29 (78.4)	27 (73)	56 (75.7)	0.58
M-protein > 3 g/dL	19 (51.4)	29 (78.4)	48 (64.9)	0.015
LDH > 460 U/L	0 (0)	1 (2.7)	1 (1.4)	0.31
Percentage of bone marrow plasma cells > 20%	29 (78.4)	27 (73)	56 (75.7)	0.6
Presence of bone damage	33 (89.2)	35 (94.6)	68 (91.9)	0.39
Plasmacytoma	5 (13.5)	3 (8.1)	8 (10.8)	0.45
Translocation involving chromosome 14	13 (35.1)	9 (24.3)	22 (29.7)	0.31
Del(17p13)	2 (5.4)	0 (0)	2 (2.7)	0.15
Karyotype abnormalities	10 (27)	12 (32.4)	22 (39.7)	0.61
ISS stage				
ISS-1	4 (13)	7 (14)	11 (13.5)	
ISS-2 (so ISS-1)	19 (50)	16 (39)	35 (44.5)	0.58
ISS-3 (so ISS-1)	14 (39)	14 (44)	28 (42)	

* Chi- square test and Fisher exact test

DISCUSSION

About age, compared with other studies in Vietnam, for example, *Thanh Thanh*[6] at Cho Ray hospital was 62.5 years old, *Ngoc LB* et al.[7] at Cho Ray hospital was 53.4 years old, the results were quite similar. According to US statistics,[8] the median age of multiple myeloma was 70.28% from 65 to 74, and 35% was < 65 years. Similarly, the European study also found the mean age of

multiple myeloma to be 70 years, with 35-40% being older than 75 years.[9] The current study found that the average age was lower, and the age of high concentration was also younger, about 55 to 64 years old, accounting for 46%.

The older population pattern can explain it in European and American countries or it may be that in Vietnam people are perhaps more interested in health, so they should go to the doctor and detect diseases earlier. Another reason is that the hospital site of the study is a specialized one; elderly patients often have co-morbidities and weak health, they will choose general hospitals with Hematology Department for examination and treatment.

In most of the domestic and international studies, the male-female ratio is recorded (the ratio of male to female is 1.1/1 to 2:1), for example, 1.42:1 in the study of *Kaustubh Bora*[10] in India, and 1.18:1 in the study of *Lee BH* et al.[11] in Korea. However, also were recognized studies with the opposite ratio such as the study by author *García De Veas Silva*[5] in Spain, which recorded female dominance over men with a ratio of 1:1.2, or domestic studies such as in the hospital Cho Ray Institute with a male: female ratio of 0.73:1, and in the current study, the female ratio was also slightly dominant over male (1.1:1). The sex ratio also fluctuates widely across studies. This may be due to the different sample sizes across them.

In current study, IgG-type multiple myeloma accounted for the highest rate (76.7%), followed by IgA, IgM with the rate of 21.7%, and 1.6%, respectively, and light chain multiple myeloma accounting for 19%. No cases of IgD or IgE were recorded. This rate compared with previous studies on multiple myeloma in Vietnam by the authors *Suzanne MCB*[6] and *Khanh BQ*,[12] somewhat similar to IgG accounted for the highest percentage (78.26% and 73.8%). Compared with the world study of *García De Veas Silva*[5] also recorded the proportion of IgG, IgA, IgD and IgM respectively 64%, 34%, 2%, 1%, and other studies[13,14] also had similar results with IgG and IgA - dominant multiple myeloma.

Multiple myeloma has not been shown to be associated with disease prognosis, but one study found that IgA was often associated with high-risk genetic abnormalities and extramyeloid disease so it may be related to poor prognosis.[15] Observing 13 IgA patients in this study, 1 patient had a del(17p) mutation with poor prognosis, 6 patients had a t(4;14) translocation of intermediate risk. The study noted that 98.6% of patients had abnormal sFLCR at the time of diagnosis. Similar results with the ratio of 339/360 (94%) were reported by the author *Moustafa* et al.,[16] and 98% in the study of the author *García De Silva*.[5] This indicates that there was still a small percentage of

patients with normal sFLCR at the time of diagnosis, so that serum electrophoresis (protein electrophoresis and immunofixation electrophoresis) remains a more sensitive technique for diagnosing intact immunoglobulin multiple myeloma. However, serum FLC quantification was more sensitive than serum electrophoresis in diagnosing multiple light chain myeloma.[17]

Therefore, if multiple myeloma was suspected, the optimal test was still a combination of serum electrophoresis and quantitative serum FLC test. On the other hand, the incidence of urinary Bence Jones protein reported in previous studies in patients with intact immunoglobulin multiple myeloma was only 60%,[18] with a higher rate of serum FLC detection in urine was dependent on renal efficiency in FLC metabolism, so serum FLC levels remain a more accurate marker of tumor load. Related/unrelated SFLCR has been included in the diagnostic criteria of the IMWG.[1]

The study noted that the median sFLCR value was different at the time of diagnosis for the two light chain types. The median of sFLCR secretion λ was not significantly higher than κ were 55.6 and 39.3, sFLCR > 100 was seen in 38% of cases. The values are also similar to the world study, for example the common median value for all groups was 50.79 in the Spanish study[5] and sFLCR > 100 was seen in 42.5% of the study. *Tacchetti* et al.,[14] 43% by *Moustafa* et al.,[16] A threshold for related/unrelated sFLC >100 has been included in the IMWG's diagnostic criteria in other disqualifying cases,[1] so such a relatively high ratio (38%) also contributes value in the diagnosis of multiple myeloma.

On the other hand, in the current study, the median value of sFLC secretion κ was lower than λ with values of 390 and 633.5, respectively; this difference was also recorded in *García De Silva*'s study with a corresponding value of 254 and 453,[5] and 400.6 and 500 by *Dejoie T* et al.[19] Contrary to the above 2 studies, *Tacchetti* et al.[14] recorded a ratio of κ greater than λ, 720 and 480 respectively. This difference may be explained by differences in the study population with different numbers of patients with multiple light chain myeloma. In *Tacchetti's* study,[14] the rate of multiple light chain myeloma that secreted was more than (64% and 33%), in contrast in the current study with the rate of light chain myeloma that secreted κ less than λ, respectively, 36%-64% and 46%-54% by *García De Silva*.[5] It may be summarized that, in multiple light chain myeloma, very high secreted sFLC concentrations affect the overall ratio when combined with sFLC in intact immunoglobulin multiple myeloma. This is further confirmed when observed in the current study, the median of both light chains is 1500 which is much higher than the overall median. This is also evident in *Dejoie's* et al.[19] study with a median associated sFLC up to 1890

mg/L, who also highlighted multiple myeloma nephropathy caused by excessive accumulation of sFLC in the renal tubules. Therefore, it is necessary to take appropriate preventive measures for renal failure in these subjects, especially in light chain multiple myeloma.

The current study only correlated high sFLCR with increased M protein status. Many international studies also recorded a high correlation of sFLCR (sFLCR ≥ 47) with renal failure, increased β2M and osteolytic lesions, plasma cell concentrations in bone marrow, did not record the correlation of sFLCR with deficiency blood, increased calcium, decreased albumin, increased LDH and stage 3 ISS in *García De Silva's* study.[5] Previous studies also demonstrated results that correlated sFLCR at diagnosis with creatinine, HGB, calcium, β2M, DS and ISS stages, with no correlation with age, sex, and albumin of by *Sthaneshwar* et al.[20] Similar in this author's study showed that sFLCR level was significantly negatively correlated with HGB concentration, positively correlated with bone marrow plasma cell count, LDH level, C-reactive protein (CRP) level and β2M. The study further highlighted that, among patients with multiple myeloma, sFLC levels showed a significant negative correlation with PLT levels, for light chain λ, sFLC levels were strongly correlated with creatinine levels and 24-hour urine protein. Neither the κ nor the λ light chains were correlated with serum albumin levels. This difference may be due to the difference in the sFLCR cutoff points to separate the 2 groups of high and low sFLCR and the difference in sample size between studies.

Although the results of the studies are not uniform, the common point across the studies is that there is a correlation between sFLCR and β2M concentration, ISS, renal failure and plasma cell count in bone marrow. It is the correlation with these parameters that reinforces the prognostic value of sFLCR because they reflect a higher tumor burden (ISS, β2, bone marrow plasma cell count), worsening renal function and more advanced disease (LDH, CA).

Through a study on 74 patients who met the selection criteria for the study (including 60 intact immunoglobulin multiple myeloma and 14 light-chain multiple myeloma), the current study found that only a tiny percentage (1/74) of patients with multiple myeloma have a normal sFLCR at the time of diagnosis. Median sFLCR κ and λ were 39.3 and 55.6, respectively. Correlation of high sFLC with increased serum M protein was noted. No high correlation of sFLCR with creatinine, β2M and osteolytic lesions, anemia, percentage of plasma cells in bone marrow and ISS was observed.

BIBLIOGRAPHIC REFERENCES

1. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014 [access: 01/11/2014]; 15(12):e538-48. Available at: https://www.sciencedirect.com/science/article/abs/pii/S1470204514704425

2. Kyle RA, Rajkumar SV. Erratum: Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia. 2014 [access: 09/08/2014]; 28(4):980. Available at: https://www.nature.com/articles/leu201411

3. Dimopoulos M, Kyle R, Fermand JP, Rajkumar SV, San MJ, Chanan-Khan A, et al. Consensus recommendations for standard investigative workup: report of the International Myeloma Workshop Consensus Panel 3. Blood, The Journal of the American Society of Hematology. 2011 [access: 05/05/2011]; 117(18):4701-5. Available at: https://ashpublications.org/blood/article/117/18/4701/21362/Consensus-recommendations-for-standard

4. Jenner E. Serum free light chains in clinical laboratory diagnostics. Clinica Chimica Acta. 2014 [access: 01/01/2014]; 427:15-20. Available at: https://www.sciencedirect.com/science/article/pii/S0009898113003288

5. García de Veas Silva JL, Bermudo GC, Menéndez VP, Rojas Noboa JC, Kestler K, Duro MR. Prognostic value of serum free light chains measurements in multiple myeloma patients. PloS one. 2014 [access: 28/11/2016]; 11(11):e0166841. Available at: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0166841

6. Thanh Thanh S. Research for Clinical Features of Multiple myeloma at Hematology Department of Cho Ray Hospital. Medical Journal of Ho Chi Minh City. 2011 [access: 01/11/2011]; 15(4):259-66. Available at: https://yhoctphcm.ump.edu.vn/index.php?Content=ChiTietBai&idBai=6430

7. Ngoc LB, Monivong Cheanh BS. Treatment efficacy of Bortezomib, Cyclophosphamide and Dexamethasone (VCD) regimens in multiple myeloma patients with renal impairment. Vietnam Medical Journal. 2021 [access: 05/08/2021]; 505(2): 101-05. Available at: https://tapchiyhocvietnam.vn/index.php/vmj/article/view/1101/961

8. Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Altekruse SF, et al. SEER cancer statistics review, 1975-2009 (vintage 2009 populations). National Cancer Institute; 2012. [access: 05/08/2021]. Available at: https://seer.cancer.gov/archive/csr/1975_2009_pops09/

9. Palumbo A, Bringhen S, Ludwig H, Dimopoulos MA, Bladé J, Mateos MV, et al. Personalized therapy in multiple myeloma according to patient age and vulnerability: a report of the European Myeloma Network (EMN). Blood, The Journal of the American Society of Hematology. 2011 [access: 27/10/2011]; 118(17):4519-29. Available at: https://ashpublications.org/blood/article/118/17/4519/29031/Personalized-therapy-in-multiple-myeloma-according

10. Bora K. Distribution of multiple myeloma in India: Heterogeneity in incidence across age, sex and geography. Cancer epidemiology. 2019 [access: 01/04/2019]; 59:215-20. Available at: https://www.sciencedirect.com/science/article/abs/pii/S1877782118307173

11. Lee BH, Shin SH, Min CK, Yhim HY, Kwak JY, Kim JA. Role of high-dose melphalan with autologous stem cell transplantation in multiple myeloma patients receiving botezomib-containing induction therapy. International journal of hematology. 2013 [access: 20/04/2013]; 97(5):634-39. Available at: https://link.springer.com/article/10.1007/s12185-013-1311-2

12. Khanh BQ. Study on Autologous stem cell transplantation in treatment of Multiple Myeloma and non-Hodgkin Lymphoma. PhD thesis, Hanoi Medical University; 2014. [access: 20/01/2015]. Available at: https://sdh.hmu.edu.vn/news/cID97_nghien-cuu-hieu-qua-cua-ghep-te-bao-goc-tu-than-dieu-tri-benh-da-u-tuy-xuong-va-u-lympho-ac-tinh-khong-hodgkin.html

13. Mori S, Crawford BS, Roddy JV, Phillips G, Elder P, Hofmeister CC, et al. Serum free light chains in myeloma patients with an intact M protein by immunofixation: potential roles for response assessment and prognosis during induction therapy with novel agents. Hematological oncology. 2011 [access: 26/11/2011]; 30(3):156-162. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1002/hon.1019

14. Tacchetti P, Cavo M, Rocchi S, Pezzi A, Pantani L, Brioli A, et al. Prognostic impact of serial measurements of serum-free light chain assay throughout the course of newly diagnosed multiple myeloma treated with bortezomib-based regimens. Leukemia & lymphoma. 2016 [access: 23/01/2017]; 57(9):2058-64. Available at: https://www.tandfonline.com/doi/abs/10.3109/10428194.2015.1124994

15. Wang L, Jin FY, Li Y, Sun JN, Zhang JJ, Tang R, et al. IgA type multiple myeloma, clinical features, and prognosis. Chinese medical journal. 2018 [access: 28/05/2018]; 131(10):1249-50. Available at: https://mednexus.org/doi/full/10.4103/0366-6999.231513

16. Alhaj Moustafa M, Rajkumar SV, Dispenzieri A, Gertz MA, Lacy MQ, Buadi FK, et al. Utility of serum free light chain measurements in multiple myeloma patients not achieving complete response to therapy. Leukemia. 2015 [access: 12/05/2015]; 29(10):2033-38. Available at: https://www.nature.com/articles/leu2015118

17. Rafae A, Malik MN, Zar MA, Durer S, Durer C. An Overview of Light Chain Multiple Myeloma: Clinical Characteristics and Rarities, Management Strategies, and Disease Monitoring. Cureus. 2018 [access: 15/08/2018]; 10(8):[aprox. 17 scr.]. Available at: https://www.cureus.com/articles/13514-an-overview-of-light-chain-multiple-myeloma-clinical-characteristics-and-rarities-management-strategies-and-disease-monitoring

18. Ramakrishnan N, Jialal I. Bence-Jones Protein. Treasure Island: StatPearls Publishing; 2019. [access: 11/08/2019]. Available at: https://europepmc.org/article/NBK/nbk541035

19. Dejoie T, Corre J, Caillon H, Hulin C, Perrot A, Caillot D, et al. Serum free light chains, not urine specimens, should be used to evaluate response in light-chain multiple myeloma. Blood, The Journal of the American Society of Hematology. 2016 [access: 22/12/2016]; 128(25):2941-48. Available at: https://ashpublications.org/blood/article/128/25/2941/35690/Serum-free-light-chains-not-urine-specimens-should

20. Sthaneshwar P, Nadarajan V, Maniam JA, Nordin N, Gin GG. Serum free light chains: diagnostic and prognostic value in multiple myeloma. Clinical Chemistry and Laboratory Medicine. 2009 [access: 26/06/2009]; 47(9):1101-07. Available at: https://www.degruyter.com/document/doi/10.1515/CCLM.2009.260/html

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authorship contribution

Conceptualization: *Phan Nguyen Thanh Van, Cao Thi Loc.*