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Prognostic value of serum free light chain at diagnosis of multiple myeloma

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ABSTRACT

Purposes: To determine the prognostic value of serum free light chain (sFLC) at the diagnosis for patients with multiple myeloma at Ho Chi Minh City Hospital of Hematology and Blood Transfusion. *Methods:* A retrospective study was carried out on 74 patients who were diagnosed with multiple myeloma at Ho Chi Minh City Hospital of Hematology and Blood Transfusion from January 2019 to December 2021. *Results:* Three-year OS of patients in the low sFLCR group was higher than that in the high sFLCR group (96.7% vs. 74.7%, respectively). Median survival time of patient with low sFLCR was 21.5 months while 16.5 months in the high sFLCR group. Three-year PFS of the low sFLCR group was higher than that in the high sFLCR group (87.2% vs. 64.2%, respectively). The median progression-free survival time in the high sFLCR group and low sFLCR group was 16.5 months and 19 months, respectively. The difference of OS and PFS among 3 groups NSS1, 2 and 3 was not significant. However, the 3-year PFS among the NSS-1 and NSS-3 groups was significant when considering each group separately. *Conclusion:* Serum free light chain at diagnosis is a good marker to predict the outcomes of myeloma patients.

Keywords: sFLC, multiple myeloma, OS, PFS

1. INTRODUCTION

Multiple myeloma is a proliferative malignancy of the plasma cells in the bone marrow, and some other organs, accounting for 1% of all cancers and 10% of hematologic cancers in particular (Rajkumar et al., 2014; Rajkumar, 2014). Diagnosis and assessment of disease response were determined based on the criteria of the International Myeloma Working Group - IMWG (Kyle and Rajkumar, 2014). The prognosis of multiple myeloma is highly variable due to the biological heterogeneity of multiple myeloma cells, host factors and bone marrow microenvironment. Patient prognostic clustering is important, as it helps to optimize and initiate appropriate treatment to avoid irreversible organ damage as early as possible. Up to now, the serum-free light chain (sFLC) measurement test has been developed and widely used in clinical practice. In the vast majority of patients with monoclonal gammaglobulinemia, plasma cells secrete excess amounts of one of the two light chains, thereby disrupting the normal ratio between serum κ and λ light

chains. Approximately 15% of patients with plasma cells that secrete only free light chains without any identifiable heavy chains are referred to as multiple light chain myeloma (DTC) (Rafae et al., 2018).

The IMWG recommends sFLC quantification as part of the standard investigation in diagnosed patients newly with plasmacytic cytoplasmic disturbances (Dimopoulos et al., 2011) and sFLC is of great importance in the diagnosis of patients with CRC, multiple myeloma, CRC amyloidosis, and early detection of multiple myeloma nephropathy (Jenner, 2014). Furthermore, the prognostic value of the serum-free light chain ratio (sFLCR), defined as the ratio of related/unrelated light chain retention at diagnosis and after treatment, were demonstrated in patients with multiple myeloma. Because of the shorter serum half-life of sFLCs (2-4 hours) than that of heavy chains (17-21 days), they are valuable as flow markers and sFLC concentration monitoring allows for more accurate assessment compared with the heavy chain in the assessment of treatment response (Iwama et al., 2013).

More importantly, in multiple myeloma, measurement of sFLC aids in the assessment of treatment response and has been included in the IMWG recommendation in the strict complete response criteria (sCR), which requires serum sFLCR. Normal bars add to the complete response criterion without the presence of plasma cells in the bone marrow (Kapoor et al., 2013). Achieving sCR is associated with improved overall survival and reduced malignant cell load. The puposes of the our study was to determine the value of serum-free light chain in the prediction of the outcomes of patients who were diagnosed with multiple myeloma.

2. METHODS

We conducted a retrospective study on 74 patients with multiple myeloma who were treated at Ho Chi Minh City Hospital of Hematology and Blood Transfusion from January 2019 to December 2021. Inclusion criteria were: Adult patients > 18 years old; Diagnosis of multiple myeloma according to the criteria of IMWG; Be treated according to the regimen with bortezomib at the hospital; Newly diagnosed and untreated disease. Exclusion criteria were patients who had incomplete medical records (patients who did not have a quantitative sFLC test at the time of diagnosis).

Treatment protocol

In our study, the majority of patients were treated with a 3-drug regimen of VCD (bortezomib, cyclophosphamide and dexamethasone). Other regimens include VRD (bortezomib, lenalidomide and dexamethasone), VTD (bortezomib, thalidomide and dexamethasone), VD (bortezomib and dexamethasone), DTPACE (dexamethasone; thalidomide; cisplatin; doxorubicin; cyclophosphamide and etoposide) and BRD (bendamustine, lenalidomide and dexamethasone). The treatment response according to IMWG is shown in Table 1.

Table 1 Treatment response of multiple myeloma according to IMWG

Response classification	Treatment results
Molecular complete remission	Complete remission + ASO-PCR is 10^{-5}
Strictly Response (sCR)	Complete remission + Absence of aberrant phenotypical plasma cell lines in bone marrow with at least 1 million cells in the marrow as analyzed by multiparameter flow cytometry (with >4 colors) and sFLCR normal
Complete response (CR)	All three of the following criteria: Immunofixation electrophoresis of serum and urine was negative Loss of plasmacytoma and all soft tissue damage <5% of plasma cells (in bone marrow).
Very good partial response (VGPR)	Either of the following two criteria: Monoclonal protein is also detected on serum and urine IFE, but negative on blood protein electrophoresis. Serum M-protein decreased by ≥ 90% and urine M-protein to < 100 mg/24 h.
Partial response (PR)	The following two standards: Serum M-protein decreased by 50% and 24h urinary M-protein decreased by ≥90% or less than 200mg/24h.
Stable disease (SD)	Does not meet the criteria of CR, VGPR, PR and has no criteria for advanced disease

Progressive disease (PD) Used to calculate progression-free or progression-free survival and as an indicator for all patients including those with CR	At least 1 of the following criteria: Increase ≥ 25% of initial value: Serum M-protein and/or 0.5g/dl Urine M-protein and/or 200 mg/dl Bone marrow plasma cells 10% Record the presence of a new bone lesion or soft tissue plasmacytoma, or identify an increase size of previous bone lesion or soft tissue plasmacytoma. Aggravated hypercalcemia is defined by the cause of plasma cell proliferation alone.
Clinical recurrence	At least 1 of the following criteria: Direct markers of increased disease and/or target organ damage. Not used in the calculation of progression-free or progression-free survival, however, the following markers can be used selectively in clinical practice. Development of soft tissue plasmacytoma or new bone lesions. Identify increased size (≥ 50% of diameters and ≥1 cm) of plasmacytoma or existing bone lesions. Hypercalcemia (>2.65 mmol/L). Decrease Hemoglobin 2 g/dL [1.25 mmol/L] Increase in serum creatinine 2 mg/dL [from 177 mmol/L]
Recurrence after complete response (Only used if the end goal of the study is DFS)	One of the following criteria: Re-appearance of M-protein in serum or urine by IFE. Development of ≥ 5% PC in the bone marrow. Appearance of other signs of disease progression (new plasmacytoma, bone lesions, hypercalcemia...)

sFLC testing was performed with whole blood without anticoagulant or with anticoagulant (Heparin). Centrifuge to separate serum or plasma at 3000 rpm in 10 minutes. Put in NEPH 630_Siemens machine to run according to the process. Reference value: sFLC κ: 6.7 – 22.4 (mg/L); sFLC λ: 8.3 – 27 (mg/L); sFLC κ/λ: 0.31 -1.56. sFLCR in our study is defined as the light chain ratio κ/λ. Normal sFLCR values range from 0.26 to 1.65. Outside this range is abnormal sFLCR. Except for one case, when examining the rate of patients with sFLCR 100 according to the IMWG diagnostic criteria, we used the definition of sFLCR as the ratio between related light chains to unrelated light chains according to the criteria, recommended by the IMWG. That is, if the patient has a monoclonal increase in , then sFLCR = κ/λ, whereas if the patient has a monoclonal increase in λ, then sFLCR = λ/κ.

Because sFLCR values are different based on the type of light chain that secretes or, patients with sFLCR values above or below the median for multiple myeloma and are classified as high sFLCR group or low sFLCR group. Therefore, based on 2 parameters sFLCR and β2M, the new classification system (NSS) based on high and low sFLCR consists of 3 stages: Stage 1 (NSS-1) is defined as β2M < 3.5 mg/L and low sFLCR (less than median sFLCR value κ or λ); Stage 2 (NSS-2) when β2M > 3.5 mg/L or high sFLCR (higher than median sFLCR value κ or λ); Stage 3 (NSS-3) is when β2M > 3.5 mg/L and sFLCR is high.

Data processing with Stata IC 10 software. Use descriptive statistics, univariate analysis and multivariate analysis to control for confounding factors.

Descriptive statistics

Qualitative variables: use frequency and percentage tables. Use the chi-square test to test for qualitative variables.

Quantitative variables: are represented by two parameters: mean and standard deviation if normally distributed or median (interquartile range) if the variable has no normal distribution. Pearson's Chi-squared test was used to evaluate the correlation between sFLCR and patient characteristics, as well as parameters related to multiple myeloma. Kruskal-Wallis test to compare median sFLCR between different treatment response groups. OS, PFS were calculated by Kaplan Meier method and Log-Rank test. The different tests have statistical significance when p-value < 0.05.

3. RESULTS

The study followed 74 patients for 3 years. The median OS was 19.5 months, the shortest was 3 months, the longest was 36 months, 8 patients died, and 66 patients were alive. 1-year and 3-year OS are 95% and 85.5% respectively. Same and 1 and 3-year PFS are 89% and 75% respectively. Figure 1 shows 3-year OS in the low sFLCR group and the high group was 96.7% and 74.7%, this difference was statistically significant with p = 0.03. Median survival in the low sFLCR group was 21.5 months compared with 16.5 months in the high sFLCR group. Figure 2 shows the 3-year PFS of the low sFLCR group and the high sFLCR group was 87.2% and 64.2%, respectively, which were significantly different with p = 0.03, corresponding to the median progression-free survival time, respectively. in the high sFLCR group was 16.5 months and 19 months compared with the low sFLCR group.

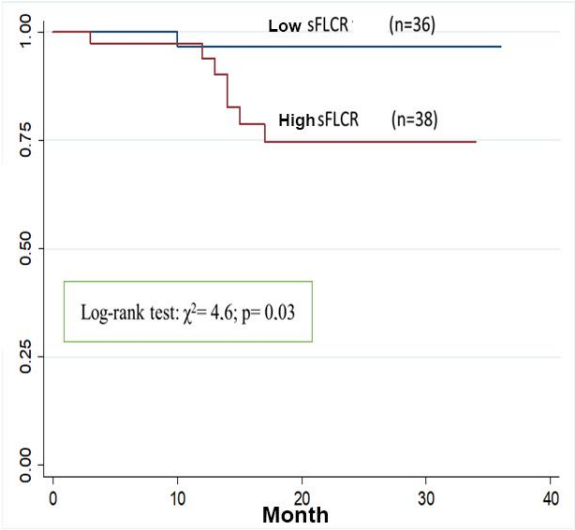

Figure 1 Overall survival between high and low sFLCR groups

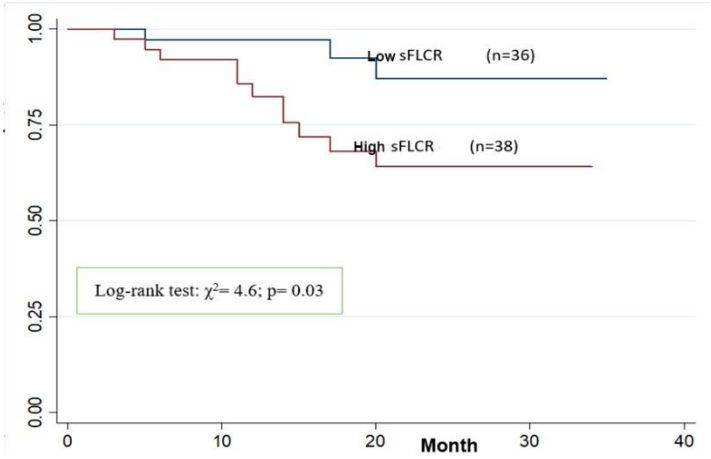

Figure 2 Progression-free survival between the low and high sFLCR groups

There was not difference between sFLCR versus different treatment levels across treatment courses (Table 2). Table 3 shows the new grade system based on sFLCR and β2M. OS difference of 3 groups NSS1, NSS 2 and NSS 3 was not significant (p > 0.05) (Figure 3). The difference in PFS among 3 groups NSS 1, NSS 2 and NSS 3 was not seen (p > 0.05). However, when considering each group separately, the 3-year PFS between the NSS-1 and NSS-3 groups was statistically significant with p < 0.05 (Figure 4).

Table 2 Differences in sFLCR with treatment response levels across treatment courses

Response / Treatment course	VGPR	PR	SD	PD	p-value
sFLCR 2 courses (n=74)	24	52.5	38	-	0.6
sFLCR 3 or 4 courses (n = 74)	21	88.4	34.1	158	0.25
sFLCR 6 courses (n = 68)	27	96.4	60.7	-	0.23

Table 3 Prognostic value of survival based on the new classification system (NSS)

Group of risk	n	Number of death	3-year OS (%)	Mean OS (month)
NSS-1 (β2M < 3.5 mg/L and low sFLCR)	15	0	100	22.6
NSS-2 (β2M > 3.5 mg/L or high sFLCR)	34	3	89	17.5
NSS-3 (β2M > 3.5 mg/L and sFLCR cao)	25	5	72.5	18
Group of risk	n	Number of event	3-year PFS (%)	Mean PFS (month)
NSS-1 (β2M < 3.5 mg/L and low sFLCR)	15	0	-	21
NSS-2 (β2M > 3.5 mg/L or high sFLCR)	34	7	72.3	16
NSS-3 (β2M > 3.5 mg/L and high sFLCR)	25	7	63.8	17

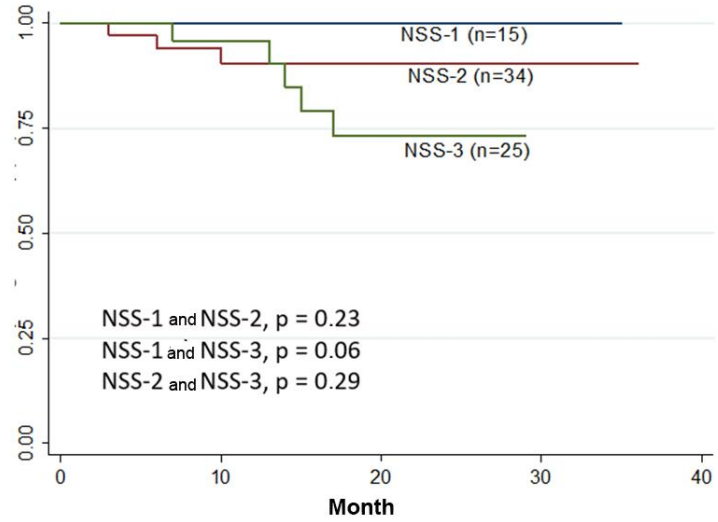

Figure 3 OS of all patients according to the new classification system

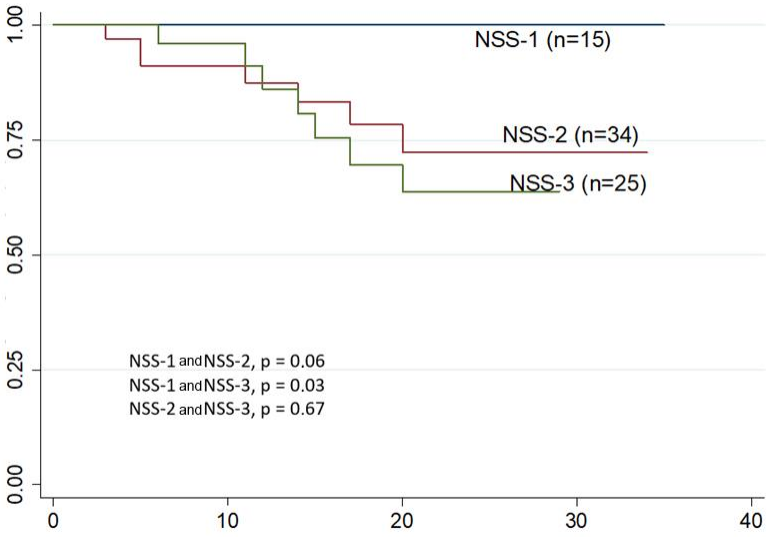

Figure 4 PFS of all patients based on the new classification system.

4. DISCUSSION

According to statistics from previous studies, when comparing sFLC quantification with IFE, serum protein electrophoresis, sFLC quantification gives more sensitive results in the confirmation of multiple myeloma, with serum quantification and calculation sFLCR algorithm detected 97.5% and 99.2% (Xu et al., 2013). In our study, all patients had 3 tests, so this role could not be investigated. According to many previous studies, there are many different cut-offs to classify high and low sFLCR, thereby assessing the prognosis of patients based on this cut-off. Continuing with previous studies, because our retrospective time was not long enough, we did not rely on overall survival to determine the cut-off point of sFLCR. An example is that of El Naggar based on response and non-response to treatment (El Naggar et al., 2015). Other studies based on differences in overall survival and progression-free time to select the most sensitive and specific cut-off point with a number of cut-off points such as author Snozek et al., (2008) (sFLCR < 0.03 or >) 32), by Xu et al., (2013) (sFLCR < 0.04, or sFLCR > 25), and more recently by Silva (sFLCR ≥ 47). In addition, Tacchetii's study is based on different sFLCR milestones (beyond the normal value, it is slightly increased, greater than 100 is elevated) or calculates the median sFLCR, from which that milestone is used to divide the patient group above and below the median are high and low sFLCR (Kyrtsonis et al., 2007). Because our study period is quite short, we chose to divide according to author Kyrtsonis et al., (2007) that is, based on the median sFLCR of 2 groups of light chain secretions κ and λ.

The relationship between sFLCR at diagnosis and the outcomes of this diseas has been evaluated in many prior studies. Kyrtsonis et al., (2007) firstly demonstrated that high sFLCR, defined as related/unrelated, was highly correlated with ISS-independent survival. Specific 5-year survival rates were 82.0% and 30.0%, respectively in patients with associated/unrelated sFLCR ≤ mean. Similarly, in a Mayo Clinic study (Snozek et al., 2008), abnormal sFLCR was an independent prognostic marker. They concluded that patients with sFLCR < 0.03 or sFLCR > 32 had a worse prognosis with a median survival of 30 months. The authors suggested that sFLCR could be added to the ISS to improve the risk of multiple myeloma. My study also found the difference of OS, 3-year survival and survival rates of 96.7%, 21.5 months and 74.7%, 16.5 months, respectively in the low sFLCR group compared with the high sFLCR group (P = 0.0385). PFS and the mean time without disease progression of 3 years were 87.2% and 19 months, compared with 64.2% and 16.5 months (p = 0.03) in the 2 groups of low and high sFLCR.

5. CONCLUSION

The 3-year OS and PFS of the low sFLCR group and high sFLCR group had statistically significant differences. Similarities between the two sFLCR groups in terms of post-treatment normality with 3-year OS and 3-year PFS were statistically significantly better than OS and PFS of the group whose sFLCR did not return to normal after treatment.

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Author Contributions

PNTV and CTL contributed equally to this work

Ethical approval

The study was approved by the Medical Ethics Committee of Ho Chi Minh City Hospital of Hematology and Blood Transfusion (Ethical approval code: 012/HBT)

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Conflicts of interest

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

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