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Lymphoma and Myeloma

Serum Free Light Chain Assay as a Prognostic Marker in Patients with Aggressive B-Cell Non-Hodgkin's Lymphoma: Impact on Survival Outcome

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Abstract

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Background The role of serum free light chain (FLC) as a prognostic biomarker in lymphoproliferative diseases is being increasingly studied. In this study we present the 5-year survival outcome for patients with aggressive B-cell non-Hodgkin's lymphoma (NHL) and their relation to FLC and other known prognostic markers.

Materials and Methods This is a prospective study conducted in patients diagnosed with aggressive B-cell NHL. Serum FLC level and ratio were estimated prior to initiation of treatment.

Results A total of 100 patients were included in the study from December 2013 to December 2015 with a median age of 53 years. Thirty-eight patients (38%) had elevated FLC level of which 26% were polyclonal and 12% were monoclonal elevations. Abnormal FLC ratio was noted in 12% patients. Median follow-up duration of the study was 75 months. Five-year relapse-free survival (RFS) for the study population was 54.4%. Five-year RFS was 64.1% for early stage and 48.2% for advanced stage diseases ($p = 0.05$). The RFS was significantly better in age less than 60 years (59.5% vs 43.8%, $p < 0.001$). Five-year overall survival (OS) was 61.3%. OS was significantly better in younger patients (73.6% vs 33.4%, $p < 0.001$), with International Prognosis Index score of 0 to 2 (87.4% vs 26.7%, $p < 0.001$). Patients with elevated FLC had inferior RFS (50% vs 71.4%, $p = 0.04$). Abnormal FLC ratio also strongly corresponded to inferior RFS (54.5% vs 66.2%, $p = 0.001$). OS was also significantly inferior in patients with abnormal FLC ratio (72.6% vs 63.6%, $p = 0.001$).

Conclusion In patients with newly diagnosed aggressive B-cell NHL, elevated FLC levels and abnormal FLC ratio were significantly associated with inferior survival.

Keywords

- free light chain
- non-Hodgkin's lymphoma
- survival
- aggressive B-cell NHL
- prognostic biomarker

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Introduction

The prognostic significance of elevation of free light chain (FLC) in predicting long-term outcome in non-Hodgkin's lymphoma (NHL) is still a matter of concern[1] and here we study the serum FLC and FLC ratio in patients with newly diagnosed aggressive B-cell NHL and its correlate with 5-year survival outcomes.

Methods

This prospective study was conducted in the Department of Medical Oncology at our institute during the period from December 2013 to December 2015. Patients with newly diagnosed aggressive B-cell NHL were prospectively enrolled in this study. This study was approved by the Institutional Review Board and Ethics Committee. All patients signed informed consent for participation in the study.

Baseline staging work-up was done as part of routine treatment protocol including routine blood examination; serum biochemistry; computed tomography of neck, chest, abdomen, and pelvis; and bone marrow studies.

Patients were staged according to Ann Arbor staging system. Stages I and II were considered as early stages and stages III and IV were considered as advanced stages. Patients with baseline serum creatinine $\geq$1.4 mg/dL were excluded. Serum FLC level and ratio were estimated prior to initiation of treatment. Elevated FLC was defined as κ >19.4 mg/L or λ >26.3 mg/L and abnormal κ/λ as ratio <0.26 or >1.65.

Monoclonal elevation of FLC was defined as an elevated FLC with the corresponding FLC ratio outside the reference range (0.26–1.65). Polyclonal elevation of FLC was defined as an elevation of either or both κ and λ light chain outside the laboratory normal range but with a normal ratio.

The patients were treated according to institute protocol and were followed up for assessing response to treatment. All patients were systematically followed up every 3 months for the first 2 years, then every 6 months till 5 years. Disease progression, retreatment, and deaths were noted. Impact on survival outcome at 5 year was analyzed.

Results

A total of 100 patients were included in the study with a median age of 53 years (range: 17–90 years). There were 57 male and 43 female patients with a male–female ratio of 1.3:1. The mean duration of symptoms was 4 months. B symptoms were present in 26% patients. Palpable lymphadenopathy was present in 71% patients. Twenty-nine patients had extra nodal involvement with gastrointestinal tract being the most common site. Diffuse large B-cell lymphoma was the most common histology in 59% patients followed by follicular lymphoma (grade 3) in 30% and primary mediastinal B-cell lymphoma in 2%. Thirteen patients had stage 1 disease, 27 had stage II, 37 had stage III, and 23 patients had stage IV disease (►**Supplementary Table S1**, available online only). International Prognosis Index (IPI) was calculated as good risk in 56 patients and high risk in 44 patients. Thirty-eight patients (38%) had elevated FLC level of which 26% were polyclonal elevation and 12% were monoclonal elevation. Abnormal FLC ratio was noted in 12% patients. All patients received chemotherapy. RCHOP—rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisolone—was the most common primary chemotherapy regimen used in 79% patients followed by RCOP—rituximab, cyclophosphamide, vincristine, and prednisolone—in 10%, CHOP—cyclophosphamide, vincristine, doxorubicin, and prednisolone—in 8%, and LP—chlorambucil and prednisolone—in 3% of patients (►**Supplementary Fig. S1**, available online only). Median follow-up duration of the study was 75 months. Twenty-four patients received radiotherapy in addition to chemotherapy as consolidation radiation dose ranging from 20 to 30 Gy. Twenty-eight patients relapsed and 26 patients received salvage chemotherapy. The salvage chemotherapy regimens were RICE—rituximab, ifosfamide, carboplatin, and etoposide—RDHAP—rituximab, cisplatin, cytarabine, and dexamethasone—RGDP, rituximab, gemcitabine, dexamethasone, and cisplatin—RGEMOX—rituximab, gemcitabine, and oxaliplatin—and LP (►**Supplementary Fig. S1**, available online only). Two patients underwent high-dose chemotherapy with stem

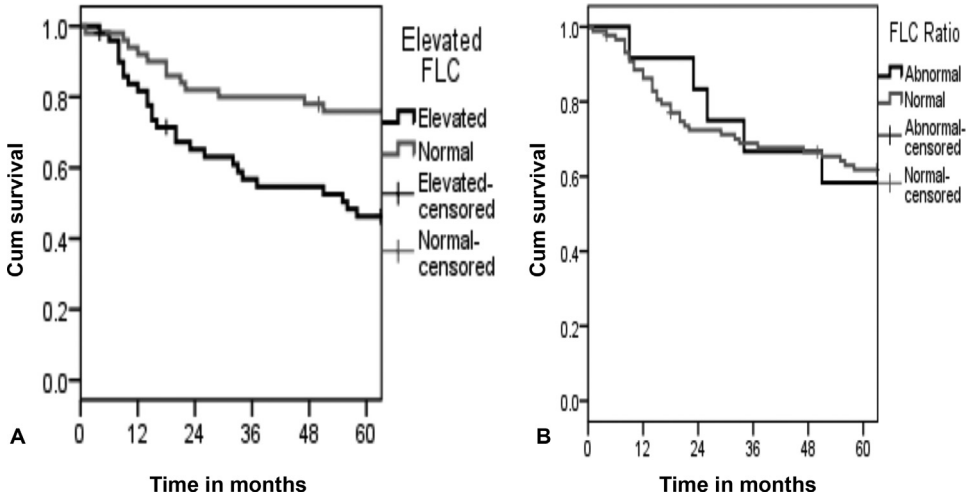

Fig. 1 Overall survival (OS) in elevated free light chain (FLC) and abnormal FLC ratio. (**A**) Elevated FLC for OS. (**B**) Elevated FLC ratio for OS.

cell transplantation. Serum FLC abnormalities in study population, logistic regression, and cox regression analysis in patients with elevated FLC and abnormal FLC ratio are listed in ►**Supplementary Tables S2-S6**, available online only.

Five-year relapse-free survival (RFS) for the study population was 54.4%. Five-year RFS was 64.1% for early stage and 48.2% for advanced stage disease ($p = 0.05$). The RFS was significantly better in patients with age less than 60 years (59.5% vs 43.8%, $p < 0.001$) (►**Supplementary Fig. S2**, available online only). Five-year overall survival (OS) was 61.3% with median follow-up 75 months. The OS was significantly better in younger patients (73.6% vs 33.4%, $p < 0.001$), with IPI score of 0 to 2 (87.4% vs 26.7%, $p < 0.001$). The survival was correlated with serum FLC and light chain ratio. Patients with elevated light chain had inferior RFS (50% vs 71.4%, $p = 0.04$). Abnormal FLC ratio also strongly corresponded to inferior RFS (54.5% vs 66.2%, $p = 0.001$). OS was also significantly inferior in patients with abnormal FLC ratio (72.6% vs 63.6%, $p = 0.001$; ►**Fig. 1**).

Age, IPI, and elevated FLC were found to be good independent prognostic indicators for RFS and OS. On multivariate analysis, age, IPI, and elevated FLC together predicted RFS with a concordance value of 0.771 whereas only age and IPI together predicted for OS with concordance value 0.677 (►**Table 1**). Higher the concordance, better was the predictability of the model.

Discussion

In this study, we provide 75 months of follow-up on the prognostic relevance of elevated serum FLC and abnormal FLC ratio in patients with aggressive NHL.

In the study by Witzig et al,[2] out of 453 patients with B-cell NHL, 27.8% had an elevated FLC with 17.4% polyclonal and 10.4% monoclonal in origin. In our study, 38% had elevated FLC of which 26% had polyclonal elevation and 12% had monoclonal elevation. The abnormal FLC ratio in our study population was 12%, which was similar to the study published by Maurer et al, which showed 14%. The abnormal FLC ratio ranged from 8 to 36% in various published studies.[3]

Moghimi et al reported a statistically significant relationship between the abnormal ratio of kappa chain to lambda with B symptoms ($p = 0.02$) and IPI ($p = 0.04$).[4] Our study clearly demonstrates that age, IPI, and elevated FLC were found to be good independent prognostic indicators for RFS and OS. None of the factors like sex, stage of NHL, performance status, or lactate dehydrogenase were found to be significant risk factors for abnormal FLC ratio in our study. Study by Kim et al described patients with an elevated FLC had significantly shorter OS and event-free survival compared with patients with normal FLC.[5] Similar to the previous studies published, survival analysis of our study also reveals that patient with elevated light chain and abnormal FLC ratio were associated with inferior RFS at 5 years. Five-year OS was also significantly inferior in patients with abnormal FLC ratio. The OS was significantly better in younger patients, with IPI score of 0 to 2.

Table 1 Cox regression analysis for RFS and OS

Variables	Univariate: RFS				Multivariate: RFS				Univariate: OS				Multivariate: OS			
	HR	95% CI for HR	*p*-Value	Concordance	HR	95% CI for HR	*p*-Value	Concordance	HR	95% CI for HR	*p*-Value	Concordance	HR	95% CI for HR	*p*-Value	Concordance
Sex (male vs female)	1.26	0.69–2.28	0.441	0.527					0.98	0.52–1.87	0.96	0.527				
Age (≤60 vs >60)	2.6	1.45–4.67	0.001*	0.617	1.16–2.24	4.31	0.016		3.62	1.91–6.85	0.001*	0.623	2.24	1.16–4.31	0.016	
IPI (poor vs good)	8.26	4.11–16.59	0.001*	0.744	3.78–7.69	15.64	0.001		10.01	4.37–22.91	0.001*	0.644	8.32	3.57–19.39	0.001	0.677
Stage (advanced vs early)	1.8	0.96–3.38	0.067	0.574					1.65	0.83–3.27	0.153	0.548				
PS (good vs others)	0.68	0.37–1.23	0.198	0.545					0.69	0.36–1.34	0.276	0.559				
LDH (<3 vs >5)	0.45	0.19–1.08	0.075	0.587				0.771	0.39	0.16–0.96	0.041	0.553				
LDH (3–5 vs >5)	0.86	0.31–2.38	0.775	0.612					**0.53**	0.18–1.58	0.254					
Elevated FLC (yes vs no)	2.63	1.41–4.88	0.002*		1.08–2.05	3.88	0.028		**2.70**	1.36–5.35	0.005*	0.602				
FLC ratio (Ab vs no)	1.24	0.55–2.77	0.603	0.500					1.02	0.40–2.62	0.963	0.537				

Abbreviations: CI, confidence interval; HR, hazard ratio; FLC, free light chain; IPI, International Prognosis Index; LDH, lactate dehydrogenase; OS, overall survival; PS, performance status; RFS, relapse-free survival.
Note: *p*-Values with asterisks indicate statistical significance.

Conclusion

In patients diagnosed with newly diagnosed aggressive B-cell NHL, elevated FLC and abnormal FLC ratio are significantly associated with inferior survival outcome.

Authors' Contributions

TMA and GN designed the study, collected the data, and wrote the article. SC, KMJK, and SGN also contributed to data collection, performed the analysis, and reviewed the final manuscript. All the authors equally contributed to this work.

Declaration

This manuscript has been read and approved by all the authors. Each author believes this manuscript represents honest work and the requirements of authorship have been met.

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Conflict of Interests

The authors declare no conflicts of interest.

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