The high risk of symptomatic hyperviscosity in patients with high serum IgM levels can be used to support initiation of treatment in Waldenström macroglobulinemia

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Background

Hyperviscosity syndrome (HVS) is a clinical feature that can be associated with Waldenström macroglobulinemia. Current consensus panel guidelines recommend initiating WM-directed therapy only for patients experiencing symptomatic HVS rather than when a specified serum IgM level is reached (Kyle *et al*, 2003). However, many clinicians initiate treatment for an elevated serum IgM in the absence of hyperviscosity-related symptoms to preempt the development of HVS. Empiric treatment for WM patients with high serum IgM levels has been proposed as a reasonable criterion for treatment initiation regardless of symptomatic status given the risk for hyperviscosity-related injury (Treon, 2015). We therefore sought to determine the serum IgM threshold for which the risk of HVS would be supportive of treatment initiation, as well as describe the risk factors and prognosis associated with developing HVS.

Patients and Methods

We identified 825 untreated patients who met the consensus diagnosis for WM (Owen *et al*, 2003), and who received care at our Institution between January 1999 and June 2016. Medical files were manually reviewed to identify cases of symptomatic HVS between the time of WM diagnosis and initiation of frontline therapy. Pertinent clinical data were gathered. Logistic regression models were fit to evaluate the association between clinical variables and the risk of symptomatic hyperviscosity. The time from WM diagnosis to development of symptomatic HVS was defined as the time in months between diagnosis of WM and identification of symptomatic HVS. The survival from WM diagnosis was defined as the time in months between diagnosis of WM and last follow-up or death. Time to events was estimated using the Kaplan-Meier method and comparisons between groups were made using the log-rank test. The Cox proportional-hazard regression method was used to fit a model for overall survival. For both the regression and survival univariate models, only the variables with a p-value <0.05 were included in the multivariate analysis.

Results

Table 1. Clinical characteristics at the time of WM diagnosis.

Characteristics	All Patients (N=825)	HVS (N=113)	No HVS (N=712)	P-value
Age	62 (29-91)	59 (29-81)	63 (31-91)	<0.0001
Male sex	500 (61%)	70 (62%)	430 (60%)	0.75
Serum IgM, mg/dL	2200 (94-12,400)	4750 (700-12,400)	1910 (94-6576)	<0.0001
Hemoglobin, g/dL	12.2 (4.0-17.8)	11.3 (4.0-15.1)	12.4 (5.0-17.8)	<0.0001
Platelets, K/uL	259 (2-890)	256 (29-575)	259 (2-890)	0.05
B2-microglobulin, mg/L	2.6 (0.9-13.9)	2.7 (1.3-8.8)	2.6 (0.9-13.9)	0.25
Bone marrow involvement (%)	30 (2-100)	40 (5-95)	25 (2-100)	<0.0001
Cold agglutinins	75 (17%)	13 (22%)	62 (17%)	0.34
Cryoglobulins	69 (12%)	11 (14%)	58 (12%)	0.67

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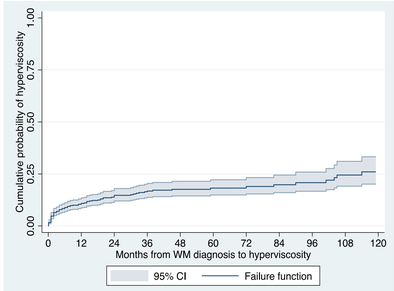
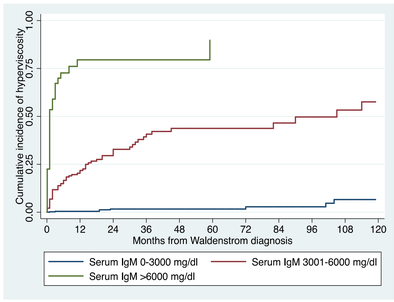
Results

Figure 1. Cumulative incidence of HVS from WM diagnosis.



Time (Months)	Estimated Cumulative Incidence (95% CI)
12	10.8% (9.8-13.5%)
24	14.7% (12.0-18.0%)
36	16.8% (13.7-20.3%)
48	17.6% (14.4-21.4%)
60	18.2% (14.8-22.2%)
120	26.0% (20.1-33.2%)

Figure 2. Cumulative incidence of HVS by serum IgM level at WM diagnosis.



Serum IgM (mg/dL)	Median Time to HVS (95% CI)
0-3000	Not reached
3001-6000	105 months (35-173)
>6000	1 month (1-3)

Log-rank p<0.001

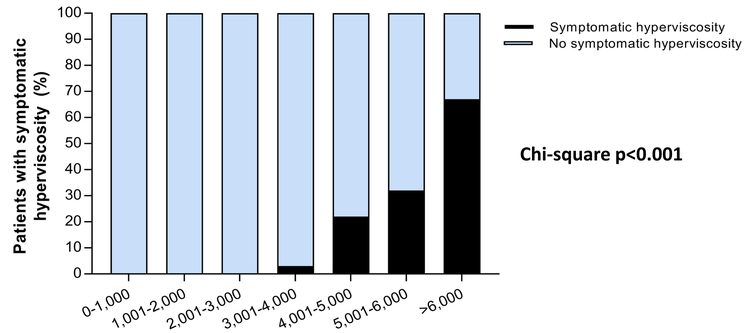
Table 2. Predictive analysis for developing symptomatic HVS.

Risk Factor	Univariate		Multivariate	
	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Age >65 years	0.50 (0.32-0.78)	0.002	0.61 (0.32-1.17)	0.14
Male sex	1.04 (0.71-1.53)	0.83	0.93 (0.52-1.64)	0.81
Hemoglobin ≤11.5 g/dL	4.57 (3.11-6.72)	<0.001	3.99 (2.13-7.46)	<0.001
Platelets ≤100 K/uL	2.94 (1.19-7.25)	0.02	2.87 (0.81-10.2)	0.10
β2-microglobulin >3.0 mg/L	1.54 (1.06-2.32)	0.02	0.69 (0.39-2.21)	0.19
Cold agglutinins	1.47 (0.79-2.72)	0.22	1.47 (0.75-2.87)	0.26
Cryoglobulins	1.22 (0.65-2.32)	0.53	1.60 (0.78-3.29)	0.20
Serum IgM 0-3000 mg/dL	Reference		Reference	
Serum IgM 3001-6000 mg/dL	14.4 (7.98-26.2)	<0.001	31.1 (9.56-102.4)	<0.001
Serum IgM >6000 mg/dL	65.5 (34.0-126.1)	<0.001	115.3 (32.4-411.1)	<0.001

*Age, sex, hemoglobin level, platelet count, and beta-2-microglobulin are at the time of WM diagnosis.

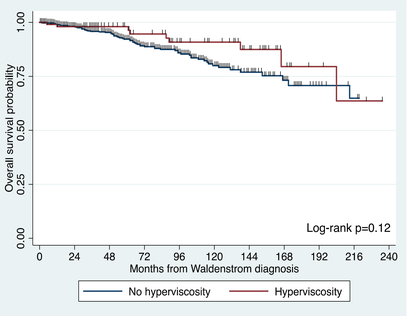
Results

Figure 3. Serum IgM levels at the time of symptomatic hyperviscosity.



Chi-square p<0.001

Figure 4. Kaplan-Meier survival curves according to hyperviscosity.



Advanced age at WM diagnosis (>65 years) was the only significant adverse prognostic factor independently associated with overall survival in the multivariate model (HR 3.98, 95% CI 1.56-10.2; log-rank p=0.004). 78 patients (10%) have died after a median follow-up of 54 months.

Conclusion

Patients with a serum IgM >6000 mg/dL are at a significantly increased risk for symptomatic HVS. However, development of symptomatic HVS does not adversely impact overall survival. Given the magnitude of the risk described herein for symptomatic HVS, a serum IgM >6000 mg/dL may reasonably be considered as a criterion for initiation of WM-directed therapy.

Disclosures: The authors have no conflicts of interest to disclose.