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.

The Cox proportional-hazard regression method was used to fit univariate and multivariate models for symptomatic HVS and overall survival. The time from WM diagnosis to development of symptomatic HVS, defined as the time in months between the diagnosis of WM and diagnosis of HVS, and the survival from WM diagnosis, defined as the time in months between WM diagnosis to last follow-up or death, were estimated using the Kaplan-Meier method; comparisons were made using the log-rank test. P-values<0.05 were considered statistically significant.

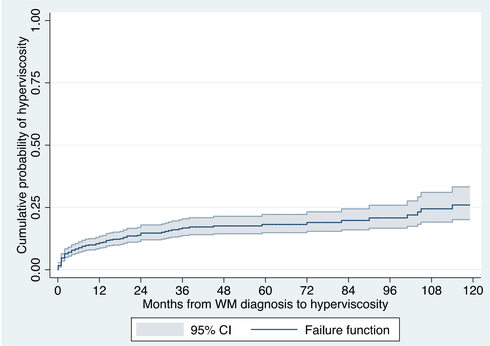
Results

Figure 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/dL	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

Results

Figure 1. Cumulative incidence of HVS from WM diagnosis.



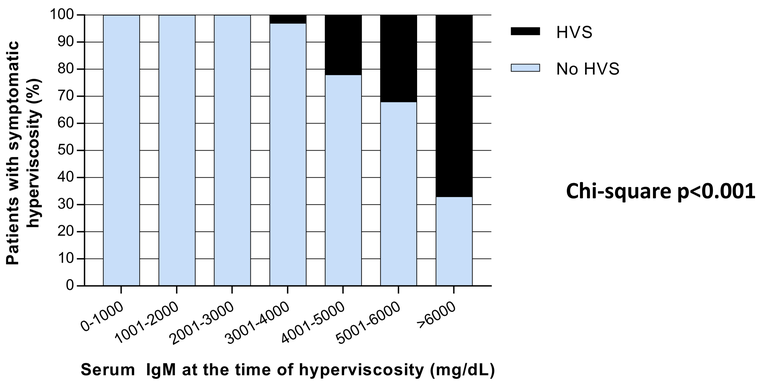
Time (Months)	Estimated Cumulative Incidence (95% CI)
12	10.8% (9.8-13.5%)
24	14.7% (12.0-18.0%)
36	16.8% (13.7-20.3%)
48	17.6% (14.4-21.4%)
60	18.2% (14.8-22.2%)
120	26.0% (20.1-33.2%)

Table 2. Predictive analysis for developing symptomatic HVS.

Risk Factor	Univariate		Multivariate	
	Hazard Ratio (95% CI)	P-value	Hazard 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/dL	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.

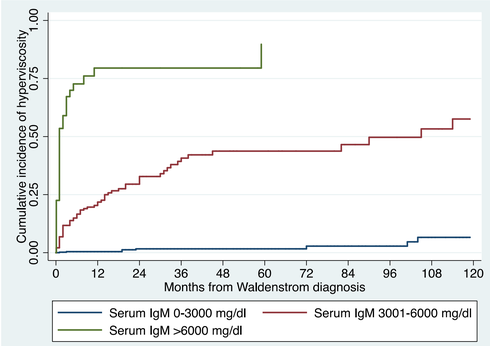
Figure 2. Serum IgM levels at the time of symptomatic hyperviscosity.



Chi-square p<0.001

Results

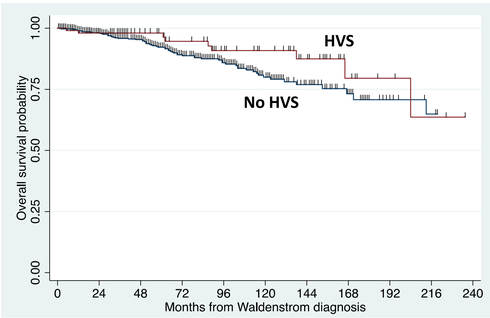
Figure 3. Cumulative incidence of HVS by serum IgM level at WM diagnosis.



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

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



Adjusted HR: 0.54 (95% CI 0.10-3.08)

Log-rank p=0.49

In the multivariate model, advanced age at WM diagnosis (>65 y.o.) was the only significant adverse prognostic factor for survival (Adjusted HR 3.98, 95% CI 1.56-10.2; log-rank p=0.004).

All but one patient with symptomatic HVS received WM-directed therapy in response to developing symptomatic HVS; one patient refused treatment. HVS patients with a serum IgM >6000 mg/dl were more likely to receive emergent plasmapheresis versus those HVS patients with a serum IgM ≤6000 mg/dL (77% vs. 58%; Fischer's exact p=0.04).

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.