


Serum IgM level as predictor of symptomatic hyperviscosity in patients with Waldenström macroglobulinaemia

Joshua N. Gustine, Kirsten Meid, Toni Dubeau, Zachary R. Hunter, Lian Xu, Guang Yang, Irene M. Ghobrial, Steven P. Treon and Jorge J. Castillo 

Bing Center for Waldenström Macroglobulinemia, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

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Correspondence: Jorge J. Castillo, Bing Center for Waldenström Macroglobulinemia, Dana-Farber Cancer Institute, Harvard Medical School, 450 Brookline Ave, M221, Boston, MA 02215, USA.

E-mail: jorgej_castillo@dfci.harvard.edu

Summary

Symptomatic hyperviscosity is a common clinical manifestation in patients with Waldenström macroglobulinaemia (WM) and high serum IgM levels. Prompt intervention is required to prevent catastrophic events, such as retinal or central nervous system bleeding. Identifying patients at high risk of symptomatic hyperviscosity might support the decision to treat asymptomatic patients before irreversible damage occurs. We carried out a large retrospective study in 825 newly diagnosed WM patients, of whom 113 (14%) developed symptomatic hyperviscosity. The median serum IgM level at the time of symptomatic hyperviscosity was 61.8 g/l (range 31–124 g/l). Forty-four patients (36%) had symptomatic hyperviscosity at the time of WM diagnosis. A serum IgM level >60 g/l at diagnosis was associated with a median time to symptomatic hyperviscosity of 3 months, whereas the median time for patients with serum IgM level of 50.01–60 g/l was approximately 3 years. Adjusting for other clinical factors, the odds of developing symptomatic hyperviscosity were 370-fold higher with serum IgM levels >60 g/l, and showed an association with *CXCR4* mutational status. Symptomatic hyperviscosity did not impact overall survival ($P = 0.12$). The findings support the use of serum IgM level >60 g/l as a criterion for initiation of therapy in an otherwise asymptomatic WM patient.

Keywords: Waldenström macroglobulinaemia, hyperviscosity, immunoglobulin M, *MYD88* mutation, *CXCR4* mutation.

Hyperviscosity syndrome is a common clinical manifestation of Waldenström macroglobulinaemia (WM), a malignant B-cell lymphoma characterized by the excessive secretion of monoclonal IgM (Owen *et al*, 2003). Accumulation of excess IgM in the bloodstream increases serum viscosity and may cause symptomatic hyperviscosity in up to 30% of patients with WM (Mehta & Singhal, 2003). Spontaneous epistaxis, new-onset headaches and visual disturbances often define the clinical presentation of hyperviscosity syndrome (Stone & Bogen, 2012). Prompt intervention is required to prevent catastrophic events such as central nervous system or retinal bleeding (Castillo *et al*, 2016).

Current consensus guidelines recommend the initiation of WM-directed therapy only for patients with symptomatic hyperviscosity, rather than when a specified serum IgM level is reached (Kyle *et al*, 2003). Individual patients can develop hyperviscosity-related symptoms at different serum IgM levels ('symptomatic threshold') (Fahey *et al*, 1965), and there are currently no data to justify early initiation of treatment for

asymptomatic patients with WM. However, asymptomatic patients with an elevated serum IgM level are often treated to pre-empt the development of symptomatic hyperviscosity. Given the risk of hyperviscosity-related injury, empiric treatment of high serum IgM levels irrespective of symptomatic status has been proposed as a reasonable criterion for treatment initiation in patients with WM (Treon, 2015).

We therefore set out as part of this retrospective study to determine the serum IgM threshold at which the risk of symptomatic hyperviscosity would outweigh continued observation and support the decision to initiate WM-directed therapy.

Methods

Cohort selection and variable identification

We performed a retrospective review of patients with a clinicopathological diagnosis of WM (Owen *et al*, 2003) who were seen in our WM clinic between 1 January 1999 and 31

May 2016. Patients who were untreated at the time of presentation were included in this study. Medical files were manually reviewed to identify cases of symptomatic hyperviscosity between the time of WM diagnosis and initiation of frontline therapy. Symptomatic hyperviscosity was defined by the presence of recurrent epistaxis, new-onset headaches, new-onset blurry vision, slowed mentation, and/or presence of retinal vessel engorgement, tortuosity, sausageing, and/or retinal haemorrhages that were attributed to WM. Pertinent clinical and pathological data were gathered. The presence of *MYD88* and *CXCR4* mutations were detected by allele-specific polymerase chain reaction (AS-PCR) and Sanger sequencing methods, respectively, as previously described (Xu *et al*, 2013, 2015).

Statistical analysis

Continuous variables were categorized to facilitate analysis. Univariate and multivariate logistic regression models were fit to evaluate the association between clinical variables and the risk of symptomatic hyperviscosity; the outcome measure was odds ratio (OR) with 95% confidence interval (CI). The time from WM diagnosis to development of symptomatic hyperviscosity was defined as the time in months between WM diagnosis and identification of symptomatic hyperviscosity. Patients with symptomatic hyperviscosity at initial presentation (i.e. within 30 days of WM diagnosis) were excluded from this analysis. The survival from WM diagnosis was defined as the time in months between WM diagnosis 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 univariate and multivariate models for overall survival; the outcome measure was hazard ratio (HR) with 95% CI. For both the regression and survival univariate models, only the variables with a *P*-value <0.05 were included in the multivariate analysis. *P*-values were two-sided and considered statistically significant if <0.05. All calculations and graphs were obtained using STATA/SE 13.1 (StataCorp, College Station, TX, USA).

Results

Patient characteristics

A total of 113 patients (14%) who developed symptomatic hyperviscosity were identified in a cohort of 825 treatment-naïve patients with WM. The epoch of WM diagnosis included: 1991–2000 (*n* = 49; 6%), 2001–2005 (*n* = 178; 22%), 2006–2010 (*n* = 310; 38%) and 2011–2016 (*n* = 288; 35%). The clinical characteristics of these patients at time of WM diagnosis are shown in Table I. WM patients who developed symptomatic hyperviscosity were more likely to have a haemoglobin level ≤ 115 g/l (57% vs. 31%), bone

marrow involvement $\geq 50\%$ (42% vs. 29%) and be younger than 65 years (78% vs. 59%) compared to patients who did not develop symptomatic hyperviscosity. WM patients who developed hyperviscosity were more likely to have serum IgM levels >30 g/l. No difference in the proportion of patients who had detectable cryoglobulins was observed between patients with and without symptomatic hyperviscosity (*P* = 0.67). The clinical presentation of symptomatic hyperviscosity included: blurry vision, retinal vessel sausageing, and/or retinal haemorrhages (*n* = 97; 86%), epistaxis (*n* = 85; 75%), headaches (*n* = 42; 37%) and slowed mentation (*n* = 12; 11%).

Risk of symptomatic hyperviscosity

The median serum IgM level at the time of symptomatic hyperviscosity was 61.8 g/l (range 31–124 g/l). The cumulative incidence of symptomatic hyperviscosity at 12, 24, 36, 48, 60 and 120 months from WM diagnosis was 10.8%, 14.7%, 16.8%, 17.6%, 18.2% and 26.0%, respectively (Fig 1A). No cases of symptomatic hyperviscosity were identified in patients with a serum IgM level <30 g/l (*n* = 431). Forty-one patients (36%) had symptomatic hyperviscosity at the time of initial presentation with WM. After excluding these patients, the median time from WM diagnosis to hyperviscosity was 3 months for patients with serum IgM level >60 g/l at diagnosis. The median time to hyperviscosity for patients with serum IgM levels 50.01–60, 40.01–50 and 30.01–40 g/l was 36, 32 and 156 months, respectively. The median time to hyperviscosity for patients with serum IgM levels of 30 g/l or lower was not reached (log-rank *P* < 0.001; Fig 1B).

The crude incidence of symptomatic hyperviscosity in patients with serum IgM levels ranging between 30.01–40, 40.01–50, 50.01–60 and >60 g/l was 3% (*n* = 3/120), 22% (*n* = 21/95), 32% (*n* = 28/88) and 67% (*n* = 61/91), respectively (*P* < 0.001; Fig 2A). The risk of symptomatic hyperviscosity increased exponentially with each increasing category of serum IgM level (R^2 = 0.98).

By univariate analysis, the odds of symptomatic hyperviscosity were significantly higher with a haemoglobin level ≤ 115 g/l and bone marrow involvement $\geq 50\%$ at the time of WM diagnosis, and with serum IgM levels >30 g/l. Age >65 years at WM diagnosis was associated with lower odds of hyperviscosity. Sex, platelet count, serum β_2 -microglobulin, cryoglobulins, or cold agglutinins were not associated with higher or lower odds of symptomatic hyperviscosity. In the multivariate analysis, serum IgM levels 30.01–40, 40.01–50, 50.01–60 and >60 g/l were independently associated with 20-, 50-, 40- and 370-fold higher odds of symptomatic hyperviscosity. Age >65 years at WM diagnosis (OR 0.45, 95% CI 0.24–0.81; *P* = 0.007) also remained associated with lower odds of symptomatic hyperviscosity. The univariate and multivariate models are shown in Table II.

Table I. Clinical characteristics at the time of Waldenström macroglobulinaemia diagnosis.

Characteristic	All patients (<i>N</i> = 825)	Developed symptomatic hyperviscosity		<i>P</i> -value*
		Yes (<i>N</i> = 113)	No (<i>N</i> = 712)	
Age				
>65 years	314 (38%)	25 (22%)	289 (41%)	<0.001
≤65 years	511 (62%)	88 (78%)	423 (59%)	
Sex				
Male	500 (61%)	70 (62%)	430 (60%)	0.75
Female	325 (39%)	43 (38%)	282 (40%)	
Serum IgM level				
0–10 g/l	180 (22%)	2 (1.8%)	178 (25%)	<0.001
10.01–20 g/l	198 (24%)	4 (3.5%)	194 (27%)	
20.01–30 g/l	164 (20%)	7 (6.2%)	157 (22%)	
30.01–40 g/l	125 (15%)	25 (22%)	100 (14%)	
40.01–50 g/l	74 (9.0%)	28 (25%)	46 (6.5%)	
50.01–60 g/l	44 (5.4%)	16 (14%)	28 (4.0%)	
>60 g/l	37 (4.5%)	31 (27%)	6 (0.9%)	
Haemoglobin level				
>115 g/l	538 (65%)	49 (43%)	489 (69%)	<0.001
≤115 g/l	287 (35%)	64 (57%)	223 (31%)	
Platelet count				
>100 × 10 ⁹ /l	801 (97%)	108 (96%)	693 (97%)	0.30
≤100 × 10 ⁹ /l	24 (3%)	5 (4%)	19 (3%)	
Serum β₂-microglobulin level				
>3.0 mg/l	330 (40%)	61 (54%)	434 (61%)	0.16
≤3.0 mg/l	495 (60%)	52 (46%)	278 (39%)	
Bone marrow involvement				
<50%	568 (69%)	65 (57%)	503 (71%)	0.003
≥50%	250 (31%)	48 (42%)	202 (29%)	
Cold agglutinins	75 (17%)	13 (22%)	62 (17%)	0.34
Cryoglobulins	69 (12%)	11 (14%)	58 (12%)	0.67

**P*-value denotes the comparison of clinical characteristics between patients who did and did not develop symptomatic hyperviscosity.

Management of patients with symptomatic hyperviscosity

Seventy-seven patients (68%) received emergent plasmapheresis for symptomatic hyperviscosity; 28 patients (36%) underwent plasmapheresis at our institution. The median serum IgM level before plasmapheresis was 63.8 g/l (IQR 54.6–75.4 g/l). Our protocol is to perform three sessions of plasmapheresis in 1 week followed by weekly plasmapheresis until WM-directed therapy takes effect, serum IgM level drops below 60 g/l, and the patient is free from hyperviscosity symptoms. Data on serum IgM levels during plasmapheresis were available in 53 patients (69%). The median serum IgM levels after 1, 2 and 3 sessions of plasmapheresis were 51.5 g/l (IQR 45.7–72 g/l), 38.1 g/l (IQR 28.9–46.1 g/l) and 25.8 g/l (IQR 21.67–32.3 g/l), respectively (Fig 2B). WM-directed therapy was initiated for all but one patient in response to developing symptomatic hyperviscosity; one patient refused treatment. Combination therapy with an anti-CD20 monoclonal antibody and a proteasome inhibitor (*n* = 71; 63%), alkylator (*n* = 13; 12%), nucleoside analogue (*n* = 12; 11%), or immunomodulator (*n* = 7; 6%) was

initiated for most patients. Ibrutinib (*n* = 5; 4%), everolimus (*n* = 2; 2%), and rituximab alone (*n* = 2; 2%) were also utilized. Resolution of hyperviscosity-related symptoms was observed for all patients who received intervention.

Survival analysis

With a median follow-up of 54 months (95% CI 51–60 months), 78 patients (10%) have died. No difference in overall survival was observed between patients with and without symptomatic hyperviscosity (Fig 3; *P* = 0.12). By univariate analysis, the risk of death significantly increased with age >65 years and serum β₂-microglobulin >3.0 mg/l at the time of WM diagnosis. Sex, haemoglobin level, platelet count, bone marrow involvement and serum IgM levels at the time of WM diagnosis, as well as presence of cryoglobulins or cold agglutinins, were not associated with risk of death. In the multivariate model, age >65 years (HR 2.46, 95% CI 1.56–3.88; *P* < 0.001) and serum β₂-microglobulin >3.0 mg/l (HR 1.74, 95% CI 1.11–2.73; *P* = 0.02) at WM

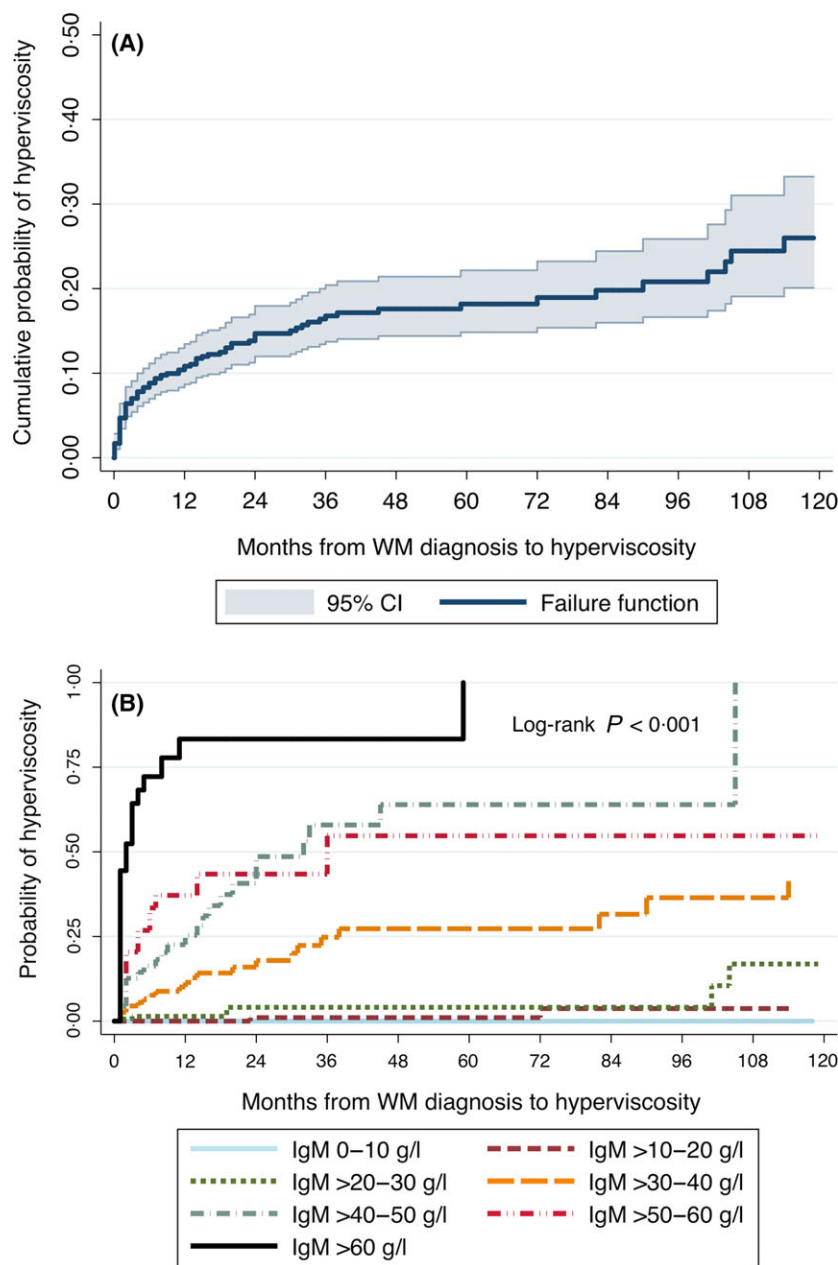


Fig 1. Estimated cumulative incidence of symptomatic hyperviscosity from Waldenström macroglobulinaemia diagnosis (A), and time to symptomatic hyperviscosity according to serum IgM level at Waldenström macroglobulinaemia diagnosis (B). 95% CI, 95% confidence interval; WM, Waldenström macroglobulinaemia. [Colour figure can be viewed at wileyonlinelibrary.com]

diagnosis were independently associated with an adverse prognosis. The univariate and multivariate models are shown in Table III.

Impact of tumour genotype

Tumour genotyping was performed in 224 patients. Among these patients, 216 (96%) carried the *MYD88* L265P mutation and 8 (4%) were wild-type for *MYD88*. Of the *MYD88* mutated patients, 106 (47%) carried at least one *CXCR4* mutation; 64 (60%) had a nonsense mutation, 37 (35%) had a frameshift mutation and 5 (5%) had both a nonsense and frameshift mutation. Patients who developed symptomatic

hyperviscosity had a similar rate of mutated *MYD88* (100% vs. 96%; $P = 0.21$) versus patients who did not develop symptomatic hyperviscosity. None of the patients with wild-type *MYD88* developed symptomatic hyperviscosity. Patients who developed symptomatic hyperviscosity were more likely to carry a *CXCR4* mutation (78% vs. 42%; $P < 0.001$) versus those who did not develop symptomatic hyperviscosity. For *CXCR4* mutated patients, the odds of presenting with symptomatic hyperviscosity were higher versus wild-type *CXCR4* patients (OR 4.94, 95% CI 2.14–11.4; $P < 0.001$). Moreover, symptomatic hyperviscosity was more likely with a *CXCR4* nonsense mutation than frameshift mutation (41% vs. 5%; $P < 0.001$). Patients with a *CXCR4* nonsense mutation had

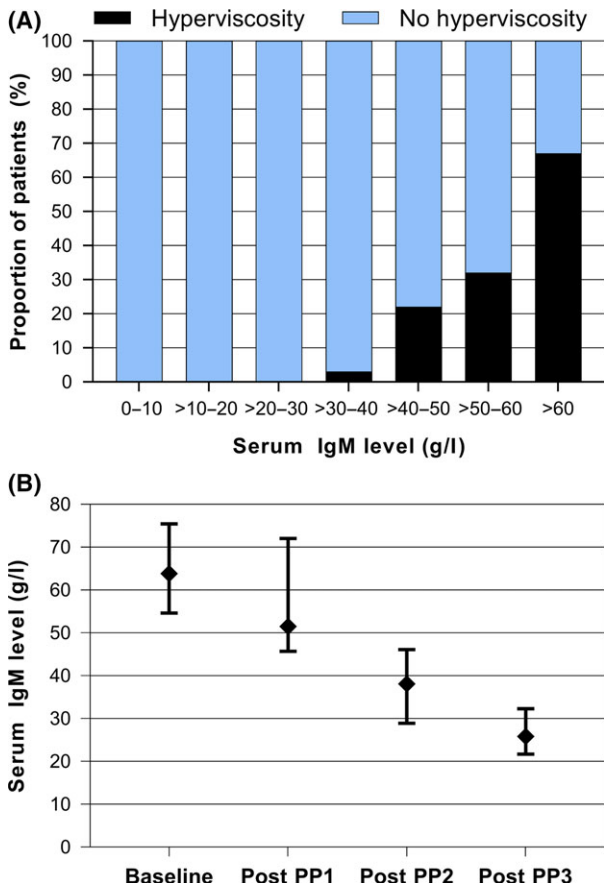


Fig 2. Incidence of symptomatic hyperviscosity according to serum IgM level (A), and serum IgM level reduction while undergoing plasmapheresis (B). PP, plasmapheresis. [Colour figure can be viewed at wileyonlinelibrary.com]

higher odds of symptomatic hyperviscosity (OR 9.41, 95% CI 2.93–22.5; $P < 0.001$) than patients with a *CXCR4* frame-shift mutation (OR 0.79, 95% CI 0.16–3.87; $P = 0.77$).

In an exploratory analysis, we evaluated the presence of *CXCR4* mutations against haemoglobin and serum IgM levels in a multivariate model ($n = 224$). In this model, *CXCR4* mutations remained associated with higher odds (OR 3.60, 95% CI 1.42–9.10; $P = 0.007$) of developing symptomatic hyperviscosity. Serum IgM levels 30.01–60 g/l (OR 14.6, 95% CI 4.14–51.7; $P < 0.001$) and >60 g/l (OR 66.2, 95% CI 11.4–385.4; $P < 0.001$) were also associated with higher odds of symptomatic hyperviscosity. Haemoglobin level was not associated with higher or lower odds of symptomatic hyperviscosity ($P = 0.89$).

Discussion

Symptomatic hyperviscosity may herald catastrophic events, such as central nervous system or retinal bleeding (Castillo *et al*, 2016). To prevent hyperviscosity-related injury, empiric treatment at high serum IgM levels has been proposed as a reasonable treatment criterion for patients with WM regardless of symptomatic status (Treon, 2015). However, a paucity of published data exists to suggest the serum IgM level for which the risk of symptomatic hyperviscosity would support initiation of WM-directed therapy. Current consensus criteria also do not address the role of treatment in asymptomatic WM patients with high serum IgM levels (Kyle *et al*, 2003). This prompted us to investigate the risk of symptomatic hyperviscosity in 825 treatment-naïve patients with WM to identify the serum IgM level at which treatment initiation could be reasonably considered.

Table II. Univariate and multivariate models for symptomatic hyperviscosity.

Variable	Univariate		Multivariate	
	OR (95% CI)	<i>P</i> -value	OR (95% CI)	<i>P</i> -value
Age >65 years	0.42 (0.26–0.66)	<0.001	0.45 (0.24–0.81)	0.007
Male sex	1.07 (0.71–1.60)	0.75		
Haemoglobin level ≤ 115 g/l	2.86 (1.91–4.29)	<0.001	1.13 (0.66–1.96)	0.65
Platelet count $\leq 100 \times 10^9/l$	1.69 (0.62–4.62)	0.31		
Serum β_2 -microglobulin >3.0 mg/l	1.33 (0.90–1.98)	0.16		
Cold agglutinins	1.39 (0.71–2.72)	0.34		
Cryoglobulins	1.16 (0.58–2.32)	0.68		
Bone marrow involvement $\geq 50\%$	1.84 (1.22–2.76)	0.003	0.95 (0.55–1.64)	0.84
Serum IgM level 0–10 g/l	Reference		Reference	
Serum IgM level 10.01–20 g/l	1.86 (0.34–10.3)	0.48	1.78 (0.32–9.88)	0.508
Serum IgM level 20.01–30 g/l	4.11 (0.84–20.1)	0.08	4.05 (0.83–19.9)	0.08
Serum IgM level 30.01–40 g/l	22.7 (5.25–98.2)	<0.001	20.6 (4.73–89.9)	<0.001
Serum IgM level 40.01–50 g/l	51.2 (11.7–224.4)	<0.001	49.1 (11.0–219.2)	<0.001
Serum IgM level 50.01–60 g/l	50.8 (11.0–234.9)	<0.001	44.0 (9.35–206.6)	<0.001
Serum IgM level >60 g/l	387.2 (70.8–2116.7)	<0.001	372.1 (65.2–2121.4)	<0.001

OR, odds ratio; CI, confidence interval.

Age, sex, haemoglobin level, platelet count, and serum β_2 -microglobulin level are at the time of Waldenström macroglobulinaemia diagnosis.

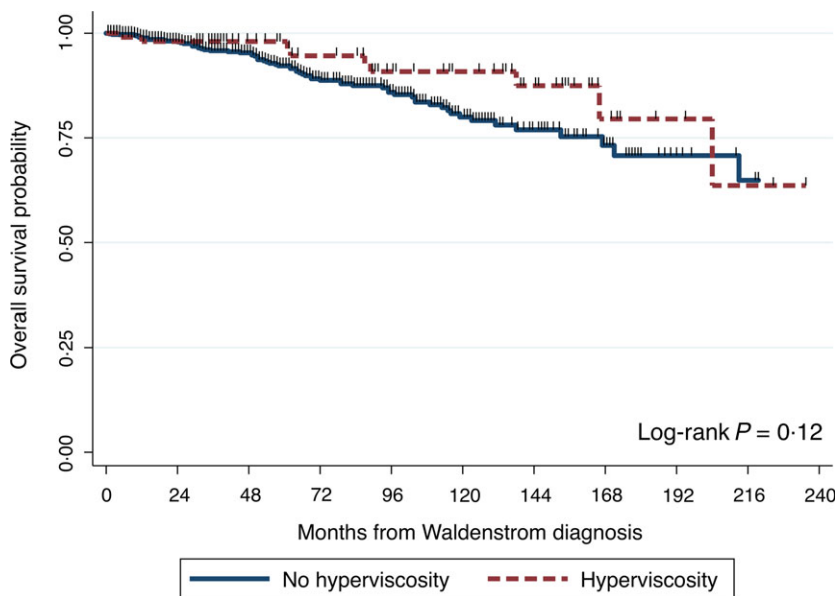


Fig 3. Kaplan–Meier overall survival curves according to the development of symptomatic hyperviscosity. [Colour figure can be viewed at wileyonlinelibrary.com]

Variable	Univariate		Multivariate	
	HR (95% CI)	<i>P</i> -value	HR (95% CI)	<i>P</i> -value
Age >65 years	2.55 (1.62–4.02)	<0.001	2.46 (1.56–3.88)	<0.001
Male sex	1.58 (0.97–2.58)	0.06		
Haemoglobin level ≤115 g/l	1.14 (0.71–1.84)	0.60		
Platelet count ≤100 × 10 ⁹ /l	0.88 (0.22–3.59)	0.86		
Serum β ₂ -microglobulin >3.0 mg/l	1.84 (1.18–2.88)	0.007	1.74 (1.11–2.73)	0.02
Cold agglutinins	1.49 (0.58–3.81)	0.41		
Cryoglobulins	1.05 (0.41–2.70)	0.92		
Bone marrow involvement ≥50%	1.48 (0.94–2.34)	0.10		
Symptomatic hyperviscosity	0.58 (0.29–1.17)	0.12		
Serum IgM level 0–10 g/l	Reference			
Serum IgM level 10.01–20 g/l	0.51 (0.26–1.01)	0.05		
Serum IgM level 20.01–30 g/l	0.53 (0.26–1.08)	0.08		
Serum IgM level 30.01–40 g/l	0.69 (0.35–1.39)	0.30		
Serum IgM level 40.01–50 g/l	0.86 (0.36–1.39)	0.74		
Serum IgM level 50.01–60 g/l	0.86 (0.32–2.30)	0.77		
Serum IgM level >60 g/l	0.80 (0.27–2.34)	0.68		

Table III. Univariate and multivariate models for overall survival.

HR, hazard ratio; CI, confidence interval.

Age, sex, haemoglobin level, platelet count, serum β₂-microglobulin level, and serum IgM level are at the time of Waldenström macroglobulinaemia diagnosis.

As part of these efforts, the cumulative incidence and timing of symptomatic hyperviscosity were examined. One in ten patients with WM develops symptomatic hyperviscosity within 1 year of WM diagnosis, and the risk continues to increase over time with a 10-year incidence of 26%. Symptomatic hyperviscosity has been previously reported in up to 30% of WM patients (Mehta & Singhal, 2003). Additionally, a shorter elapsed time to the development of symptomatic hyperviscosity was observed for patients with a high serum IgM level at the time of WM diagnosis. Patients with a

serum IgM level >60 g/l have a particularly acute risk of symptomatic hyperviscosity, occurring in more than half these patients within a few months of diagnosis. These results may be relevant to identify patients for whom increased monitoring is clinically indicated.

A serum IgM level of at least 30 g/l was identified as the threshold at which patients with WM are at risk for developing symptomatic hyperviscosity. Prior reports have described the occurrence of symptomatic hyperviscosity when the serum viscosity is >4.0 centipoise (Crawford *et al*, 1985;

Dimopoulos *et al*, 2000). Of importance, patients without complaints of visual disturbances can have evidence of hyperviscosity identified ('silent hyperviscosity'), particularly in the peripheral retina when a dilated fundoscopic examination is performed (Menke *et al*, 2009). Morphological changes in the retina attributable to hyperviscosity have been reported in WM patients with a serum IgM level as low as 29.5 g/l (Menke *et al*, 2006). Our data nonetheless support the recommendation of fundoscopic examination for WM patients with a serum IgM level >30 g/l to evaluate for signs of hyperviscosity and in all patients with suspected symptomatic hyperviscosity (Treon, 2015; Castillo *et al*, 2016).

To our knowledge, the risk of symptomatic hyperviscosity associated with a corresponding serum IgM level has not been previously evaluated. Our findings show the risk increases exponentially in response to increasing serum IgM level, consistent with the exponential increase in serum viscosity described when the serum IgM level rises above 30 g/l (Fahey *et al*, 1965). Modest increases in serum IgM level can therefore result in the rapid onset of symptomatic hyperviscosity. Importantly, patients with a serum IgM level >60 g/l are at high risk (370-fold) for symptomatic hyperviscosity. Two out of three patients with a serum IgM level >60 g/l developed symptomatic hyperviscosity in our cohort. Taken together, these findings support a serum IgM level >60 g/l as the serum IgM threshold for initiation of WM-directed therapy in otherwise asymptomatic patients.

The survival analysis demonstrates that the occurrence of symptomatic hyperviscosity does not affect the long-term prognosis of patients with WM. Two smaller retrospective studies have also reported similar results (Kyrtonis *et al*, 2001; Morel *et al*, 2009). A recent population-based study using the Surveillance, Epidemiology, and End Results (SEER) database reported the median survival of WM patients has increased over the last decade, despite an incurable disease course (Castillo *et al*, 2014, 2015). Some patients can have survival measured in decades, particularly those diagnosed at a younger age. In all, these data suggest patients with symptomatic hyperviscosity do not necessarily warrant more aggressive therapy, but rather appropriate and prompt control of serum IgM levels to prevent irreversible hyperviscosity-related injury.

Clinically, WM patients with symptomatic hyperviscosity or high serum IgM levels require careful management so as to not exacerbate serum viscosity. Plasmapheresis can rapidly reverse hyperviscosity-related symptoms and typically reduces the serum IgM level by 30–60% after 2–3 sessions (Menke *et al*, 2008; Stone & Bogen, 2012). Bortezomib-based regimens or ibrutinib (if available) may be appropriate therapeutic options in such a setting given the rapid reductions in serum IgM levels achieved with these agents (Treon *et al*, 2009, 2015). Rituximab should not be administered to patients with a serum IgM level >40 g/l due to the 'IgM flare' phenomenon (Ghobrial *et al*, 2004; Treon *et al*, 2004). Likewise, a similar effect can be seen with intravenous

immunoglobulin (IVIg) replacement, which may be indicated for WM patients with recurrent infections on the basis of IgG and IgA hypogammaglobulinaemia (Yang *et al*, 2009; Hunter *et al*, 2010). Furthermore, cryoglobulins can cause marked temperature-dependent elevation of serum viscosity (Stone, 2009), and may precipitate the occurrence of symptomatic hyperviscosity at lower serum IgM levels. Caution should also be exercised when transfusing red cells in patients with high serum IgM levels (Treon, 2009; Castillo *et al*, 2016).

MYD88 and *CXCR4* somatic mutations are present in 90–95% and 30–40% of WM patients, respectively, and have been shown to be determinants of disease presentation (Treon *et al*, 2012, 2014; Hunter *et al*, 2014; Schmidt *et al*, 2015). Our results demonstrate that the odds of symptomatic hyperviscosity are significantly higher for WM patients carrying a *CXCR4* nonsense mutation, whereas the *MYD88* mutation showed no association. These findings expand upon previous results, wherein higher serum IgM levels and rates of symptomatic disease requiring therapy, including symptomatic hyperviscosity, at the time of initial presentation were observed among WM patients carrying a *CXCR4* nonsense mutation (Treon *et al*, 2014). The *CXCR4* nonsense mutation that results from the introduction of a stop codon in the C-terminal domain showed more robust and prolonged AKT and ERK 1/2 signalling *versus* cells carrying *CXCR4* frameshift mutations in preclinical modelling (Cao *et al*, 2015a,b), and potentially could contribute to altered serum IgM production, thereby increasing the propensity for symptomatic hyperviscosity.

The present study, however, is not without limitations. Despite the large number of patients with WM included, our cohort may not be representative of the general population due to the inherent selection bias associated with patients seen at a tertiary referral centre. In addition, serum viscosity levels were not available for most patients, though serum viscosity levels are often not reproducible and may lack correlation to serum IgM levels (Castillo *et al*, 2016). Finally, tumour genotyping for *MYD88* and *CXCR4* somatic mutations was only available for approximately one-quarter of the cohort, probably reflecting the recent discovery of these genetic aberrations.

In summary, the findings of our study show that patients with a serum IgM level >60 g/l are at high risk for symptomatic hyperviscosity. Appropriate therapeutic intervention could be reasonable in this patient population regardless of symptomatic status to prevent hyperviscosity-related injury.

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Authors' contributions

JNG, SPT and JJC designed the study. JNG and KM performed the data gathering. TD, IMG, SPT and JJC took care of the patients. ZRH, LX and GY performed the tumour genotyping of patients. JNG and JJC performed the statistical analysis. JNG, SPT and JJC prepared the initial draft. The final manuscript was read and approved by all the authors.

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