

A comprehensive geriatric assessment to evaluate individual frailty status and quality of life in patients with Waldenström macroglobulinemia: A prospective Italian study

Alessandra Tedeschi¹, Arianna Zappaterra¹, Andrea Galitzia², Rita Rizzi³, Francesco Autore⁴, Concetta Conticello⁵, Silvia Ferrari⁶, Nicolo Danesin⁷, Raffaella Pasquale⁸, Chiara Borella⁹, Maura Nicolosi¹⁰, Emanuele Cencini¹¹, Elia Boccellato¹², Marzia Varettoni¹³, Alfredo Molteni¹⁴, Isacco Ferrarini¹⁵, Lorena Appio¹⁶, Massimo Gentile¹⁷, Filippo Bagnoli¹⁸, Vittorio Del Fabro¹⁹, Gloria Turri²⁰, Marina Motta²¹, Enrico Lista²², Giuseppe Amir Campanale³, Claudia Bellofiore⁵, Alessandro Noto¹, Marina Deodato¹, Luca Laurenti⁴, Francesco Piazza⁷, Roberta Murru², Anna Maria Frustaci¹

¹ASST Grande Ospedale Metropolitano Niguarda, Department of Hematology, Niguarda Cancer Center, Milan, Italy

²Hematology and Stem Cell Transplantation Unit, Ospedale Oncologico A. Businco, ARNAS G. Brotzu, Cagliari, Cagliari, Italy

³Haematology and Stem Cell Transplantation Unit, Department of Precision and Regenerative Medicine and Ionian Area (DiMePre-J), University of Bari 'Aldo Moro', Bari., Bari, Italy

⁴Institute of Hematology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Roma, Italy

⁵Hematology Unit with BMT A.O.U. Policlinico "G. Rodolico-San Marco", Catania, Catania, Italy

⁶Hematology and Bone Marrow Transplant Unit, ASST Papa Giovanni XXIII, Bergamo, Italy

⁷Hematology Unit, Azienda Ospedale Università Padova and Department of Medicine, University of Padova, Padova, Italy, Padova, Italy

⁸SOC Clinica Ematologica, Centro Trapianti e Terapie Cellulari, Azienda Sanitaria Universitaria Friuli Centrale (ASUFC), Presidio Ospedaliero Universitario "S. Maria della Misericordia", Udine, Udine, Italy

⁹Hematology Division, IRCCS San Gerardo dei Tintori Hospital, Monza, Monza, Italy

¹⁰Hematology Division, A.O.U. Città della Salute e della Scienza di Torino, Torino, Italy

¹¹UOC Ematologia Azienda Ospedaliera Universitaria Senese & University of Siena, Siena, Siena, Italy

¹²Department of Hematology, Santa Croce e Carle Hospital, Cuneo, Cuneo, Italy

¹³SC Ematologia 1, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

¹⁴Hematology, ASST Cremona, Cremona, Italy

¹⁵Hematology and Bone Marrow Transplant Unit, Section of Biomedicine of Innovation, Department of Engineering for Innovative Medicine, University of Verona, Verona, Italy

¹⁶SC Ematologia - ASST valle olona - Po Busto Arsizio, Italy

¹⁷Hematology Unit AO of Cosenza, Cosenza, Italy; Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Rende, Cosenza, Italy

¹⁸Department of Oncology and Hematology, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy

¹⁹Faculty of Medicine and Surgery, "Kore" University of Enna, Enna, Enna, Italy

²⁰Hematology and Bone Marrow Transplant Center, Central Hospital of Bolzano, Bolzano, Italy

²¹Hematology, ASST Spedali Civili di Brescia, Brescia, Italy

²²Hematology Unit, Santa Chiara Hospital, Azienda provinciale per i servizi sanitari, Trento, Italy.

Despite its impact on treatment access, tolerability, and outcomes, frailty in Waldenström's Macroglobulinemia (WM) lacks an objective definition. In WM, mainly affecting elderly, comorbid patients, first-line BTKi are EMA-approved only for chemoimmunotherapy-ineligible subjects, although no standardized definition of ineligibility exists. Based on this, we evaluated whether an integrated geriatric- and quality of life (QoL)-based approach could better define fitness and guide treatment in WM.

In this ongoing prospective, multicenter, observational cohort-study, consecutive WM patients regardless of age, disease stage or treatment status, completed Practical Geriatric Assessment (PGA) and EORTC QLQ-C30 questionnaires at enrollment (baseline), 6, 12, 18 months. PGA included physical, functional, psychological, cognitive, nutritional, social and comorbidity self-perception domains. Primary objective is PGA-based frailty definition. Secondary: PGA feasibility, associations between clinical characteristics and PGA domains, impact of PGA and EORTC QLQ-C30 on treatment choice, management, outcomes, non-cancer survival. Here we report interim-analysis from baseline and +6-months assessment.

From November 2024 to July 2026, 373 WM patients were enrolled: 131 on active treatment at any line (a-Tx); 113 previously treated and currently in watch and wait (t-ww); 129 untreated in watch and wait (u-ww). Table 1 reports patients characteristics. Compared to the other groups, a-Tx pts had at baseline higher IgM, lower hemoglobin and more concomitant medications. Overall, 95% had ≥ 1 impaired PGA domain (median 3, range 0–6), with no between-group differences in cumulative PGA burden or individual domains. Median EORTC QLQ-C30 global health status (GHS; 0–100, higher scores indicating better health) was 66.7 (67, 67 and 75 in a-Tx, t-ww, u-ww respectively, $p=.845$). Of 256 pts (68.6%) with no anamnestic severe comorbidities recorded, 88% reported self-perception of relevant coexisting conditions. Among baseline clinical characteristics, age, hemoglobin, bulky disease and vascular, respiratory, renal and neurologic CIRS items were independently associated with increased cumulative PGA burden; their impact on single PGA domains is shown in Figure 1. Patients classified as unfit by CIRS >6 and/or CrCl <70 mL/min had a significantly higher PGA burden than fit patients ($p=0.015$), despite a median PGA burden of 3 in fit patients, supporting the additional discriminatory value of the PGA. At multivariate analysis, neuropathy (–8 points), each additional concomitant medication (–1.8 points), and each 1 g/dL increase in hemoglobin (+2.2 points) were independently associated with QLQ-C30 GHS. While impairment in any individual PGA domain was associated with worse QLQ-C30 GHS, only impaired functional and psychological status retained their independent value, each conferring an 11.7 and 12.9-point lower GHS score, respectively ($p<.001$ for

both). At 6 months 201 pts (53.9%) were reassessed, with no changes in cumulative PGA burden or QLQ-C30 GHS overall or across groups.

Median PGA + QLQ30 completion time was 20 minutes (patients) and 5 minutes (physicians).

Preliminary data support the feasibility and potential value of this approach for fitness stratification. Baseline PGA and EORTC-QLQC30 GHS were comparable across the 3 groups. Impaired functional and psychological status, anemia, neuropathy and concomitant medications emerged as major detrimental factors for QoL. Ongoing enrollment will identify PGA-based fitness determinants, longitudinal changes and therapeutic implications.

Table 1. Patients' characteristics

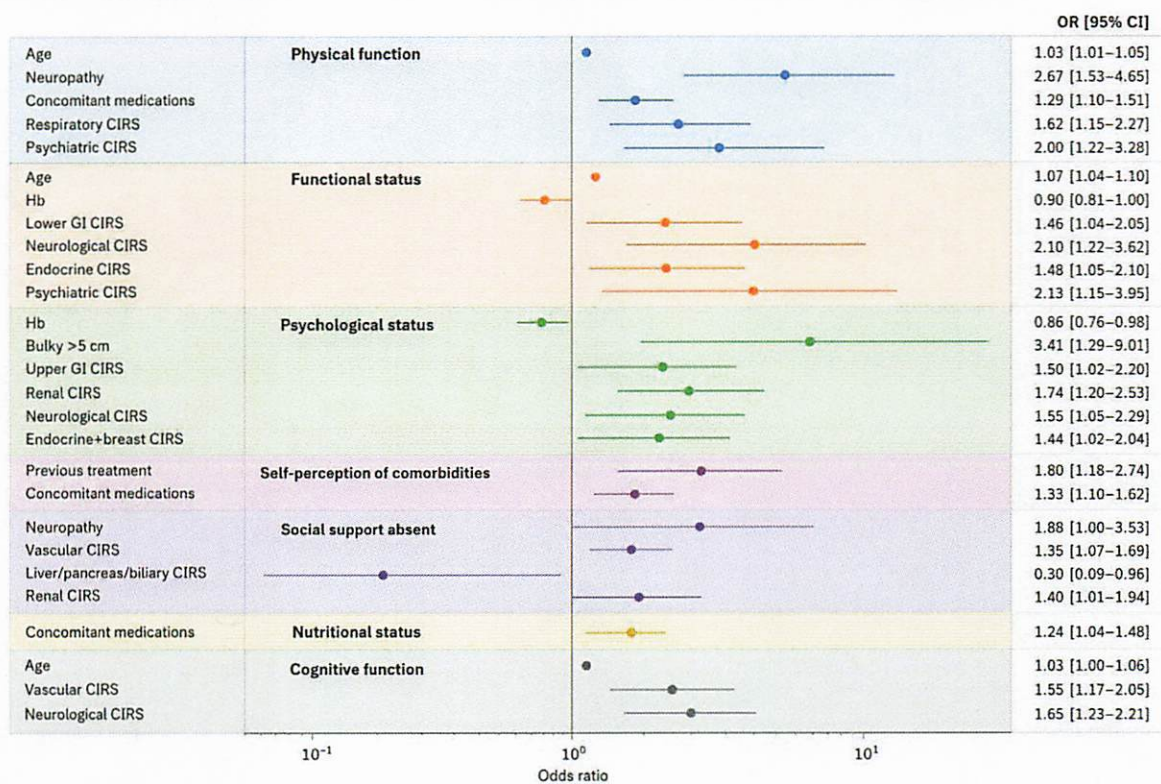
		a-Tx	t-WW	u-WW	Total	p
N (%)		131 (35.1)	113 (30.3)	129 (34.6)	373	
Gender	Female	37 (28.2)	35 (31.0)	39 (30.5)	111 (29.8)	0.881
	Male	94 (71.8)	78 (69.0)	89 (69.5)	261 (70.2)	
Age at PGA	Median (IQR)	73.9 (65.6-81.5)	72.5 (63.0-80.0)	73.0 (65.4-79.5)	73.4 (64.5-80.2)	0.307
IgM (g/L)	Median (IQR)	23.0 (9.3-34.98)	12.30 (5.69-30.40)	15.10 (9.89-26.92)	16.30 (8.61-31.82)	0.008
Hb (g/dl)	Median (IQR)	11.2 (9.7-13.0)	12.5 (10.6-13.9)	13.1 (11.2-14.4)	12.4 (10.6-13.9)	<0.001
Platelets (10⁹/L)	Median (IQR)	214 (169-281)	216 (174-265)	238 (185-297)	219 (172-281)	0.132
ClCr merged	Median (IQR)	70.9 (54.5-94.8)	74.8 (61.6-93.7)	79.2 (59.4-92.8)	74.8 (57.9-93.7)	0.500
Neuropathy		20 (15.6)	23 (20.4)	10 (7.9)	53 (14.4)	0.022
Bulky >5 cm		10 (7.9)	12 (10.6)	0 (0.0)	22 (6.0)	0.001
Splenomegaly >=18 cm		4 (3.2)	4 (3.5)	1 (0.8)	9 (2.5)	0.320
MYD88	WT	8 (7.1)	13 (15.1)	7 (7.6)	28 (9.7)	0.123
	Mutated	104 (92.9)	73 (84.9)	85 (92.4)	262 (90.3)	
CXCR4	WT	32 (71.1)	32 (78.0)	16 (64.0)	80 (72.1)	0.459
	Mutated	13 (28.9)	9 (22.0)	9 (36.0)	31 (27.9)	
N of treatment (if ongoing, current treatment included)	Median (IQR)	2.0 (1.0-3.0)	1.0 (1.0-1.0)	0.0	1.0 (1.0-2.0)	<0.001
N. of concomitant medications	Median (IQR)	3.0 (1.0-5.0)	2.0 (1.0-3.5)	3.0 (1.0-5.0)	2.0 (1.0-5.0)	0.004
Any anamnestic comorbidity	Yes	89 (84.0)	79 (78.2)	88 (87.1)	256 (83.1)	0.230

		a-Tx	t-WW	u-WW	Total	p
ECOG-PS>0	Yes	55 (42.0)	43 (38.1)	45 (34.9)	143 (38.3)	0.499
CIRS	Median (IQR)	3.0 (1.0-5.0)	2.0 (0.0-4.0)	2.0 (1.0-4.0)	2.0 (1.0-4.0)	0.129
CIRS>6 e/o CIRS3+ ^a	Yes	29 (22.1)	25 (22.1)	28 (21.7)	82 (22.0)	0.996
Fitness according to CIT traditional criteria	Fit	53 (40.5)	47 (41.6)	40 (31.0)	140 (37.5)	0.164
	Unfit	78 (59.5)	66 (58.4)	89 (69.0)	233 (62.5)	

^aCIRS>6: Cumulative Illness Rating Scale >6; CIRS3+: at least one individual CIRS system with a score ≥3

^bCIRS >6 and/or Creatine Clearance <70 mL/min

Figure 1. Impact of baseline characteristics on individual PGA domains





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Submitter operating system: win

First Name: Anna Maria

Last Name: Frustaci

Email: annamaria.frustaci@ospedaleniguarda.it

Phone Number (optional): +393471840497

Registration Type: Delegate

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