RESEARCH ARTICLE

N-terminal fragment of the type-B natriuretic peptide (NT-proBNP) contributes to a simple new frailty score in patients with newly diagnosed multiple myeloma

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Multiple myeloma (MM) patient frailty has been delineated primarily by age and ECOG performance score (PS) and recently by the IMWG frailty score based on functional status [Activity of Daily Living (ADL) and Instrumental-ADL scores], comorbidities [Charlson-comorbidity-index (CCI)] and age. It was hypothesized that N-terminal natriuretic peptide type B (NT-proBNP) might be both a more convenient measure of frailty and a predictor of overall survival (OS). Three-hundred and fifty-one consecutive symptomatic MM patients who were seen at Mayo Clinic within 30 days of diagnosis and who had blood stored were eligible. Data from the first visit was abstracted and used to calculate an ADL, CCI, and measure the NT-proBNP level. The best cutoff of NT-proBNP predicting OS was 300 ng/L. Variables predictive for OS were ECOG-PS, age, CCI, ADL, ISS, revised-ISS, and NT-proBNP. On multivariate analysis age $\geq$70, PS $\geq$2, and NT-proBNP $\geq$300 were independent predictors of survival. Patients were assigned a score of 1 for each of these variables, creating stages I–IV with scores of 0–3 points, respectively. The median OS from diagnosis was not reached, 58, 28, and 18 months ($P < 0.0001$), respectively. This frailty risk schema was independent of initial therapy and the revised-ISS. NT-proBNP is a useful predictor of survival independent of age and PS. It is a widely available biomarker that could be added to the panel of laboratory tests of newly diagnosed MM patients and serve as a simple and objective tool of determining frailty in clinical practice.

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Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy, with a higher incidence in elderly subjects [1–3]. The introduction of immunomodulatory agents and proteasome inhibitors has improved the survival of patients with MM, including elderly subjects [4–6]. However, there is a subgroup of frail subjects, most of whom are elderly, who are susceptible to side effects of chemotherapy and are often unable to tolerate full dose treatment [7,8]. The well-known biologic and genetic prognostic factors, as well as age per se, are insufficient to explain this difference [5,9–11]. The International Myeloma Working Group (IMWG) showed that a frailty score that combined age, functional status, and comorbidities predicted survival and toxicity, and thus useful to determine the tolerability of treatment. This frailty profile was associated with increased risk of death, progression, non-hematologic adverse events and treatment discontinuation [12]. The determination of frailty adopted by Palumbo et al. consists of the Katz Activity of Daily Living (ADL) [13], the Lawton Instrumental Activity of Daily Living (IADL) [14] and the Charlson Comorbidity Index (CCI) [15,16]. These authors showed that patients' functional and health status have prognostic importance similar to that of myeloma-related risk factors, such as the International Staging System (ISS) [17] and chromosomal abnormalities [18–20]. In clinical practice, age, ECOG-PS, and comorbidities are widely used by clinicians to assess vulnerability and, consequently, to empirically tailor therapy for patients with MM, but it is a challenge in a busy clinical practice to incorporate all of the frailty assessments proposed by Palumbo [12].

Brain natriuretic peptide (BNP) and the N-amino terminal fragment of the prohormone BNP (NT-proBNP) [21] are released predominantly from the ventricular myocardium in response to increased ventricular wall stress [22]. They are measures of ventricular dysfunction and have a predictive utility for cardiovascular events and mortality [23–25], but because they are cleared by the kidney, and thus influenced by the glomerular filtration

Additional Supporting Information may be found in the online version of this article.

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rate [26–28], thereby capturing the two most common organ systems that contribute to a patients' frailty. Moreover, the prognostic value of NT-proBNP has been shown to be independent of traditional cardiovascular risk factors, prevalent cardiovascular disease, left ventricular dysfunction, and renal function [29].

Using this information, we tested the prognostic role of NT-proBNP in the context of other host and tumor clinical features in an unselected population of MM patients prospectively evaluated at Mayo Clinic, Rochester, MN.

Methods

Patient population and study design. The study included 351 patients who were seen at the Mayo Clinic, Rochester, MN within 30 days of their multiple myeloma diagnosis from 1/1/2007 to 12/31/2011. Patients, who had biopsy proven organ involvement with light-chain (AL) amyloidosis, at the time of NT-proBNP sample collections were excluded from the current analysis. All patients that during the follow-up had a subsequent biopsy proven diagnosis of AL amyloidosis were also excluded. Data were extracted from prospectively maintained databases and from review of medical records. Follow-up information was collected prospectively and entered at the time of each visit. For patients followed up at other institutions, annual follow-up letters were sent to patients to inquire about their disease status. All patients had consented to the use of their medical records. The study was conducted in accordance with the institutional guidelines with approval of the institutional review board (IRB) and in accordance with the principles of the Declaration of Helsinki.

Assessment. As part of the Mayo Clinic admission, all patients are required to complete a questionnaire about their past medical history, symptoms, and ADLs. Data from their first visit was abstracted and used to calculate the ADL score. The ADL score was adopted to assess self-care activities and independence status. It was composed of questions regarding independence in bathing, dressing, toileting, transferring, and feeding. The presence of incontinence was not prospectively collect with the questionnaires. Therefore, we retrospectively abstracted from the clinical report this information. Each of these tasks had a score of 1 (best score was 6). The CCI was calculated after a complete medical history of all patients prior and at the time of the diagnosis. This calculation was based on the original CCI scale proposed by Charlson et al. in 1987 [15,16]. Other prognostic systems considered were the Eastern Cooperative Oncology Group Performance status (ECOG-PS) [30] ISS [17], chromosomal abnormalities t(4:14), t(11:14), t(14:16), del13, del17p, trisomies [31,32], and the more recently defined R-ISS which is defined as: (a) R-ISS I, no high-risk chromosome abnormalities [del(17p) and/or t(4;14) and/or t(14;16)], and normal LDH levels); (b) R-ISS III: including ISS stage III and high-risk chromosome abnormalities or high LDH level; and (c) R-ISS II: including all the other possible combinations] [33].

NT-proBNP was measured on sera frozen at −20°C under a bio-bank IRB protocol. No indication of degradation of NT-proBNP during long term storage was previously reported [34]. The NT-proBNP assay was run on the E170 Modular analyzer (Roche Diagnostics, Penzberg, Germany). The reference limits (97.5 percentiles of healthy subjects) in men and women are 87 and 150 ng/L, respectively, in subjects less than 50 years of age and 220 and 331.5 ng/L, respectively, in individuals more than 50 years of age (data from Roche from 712 normal subjects). Precision with this assay is excellent, but substantial biologic variability exists, especially at higher values [35]. In particular, for subjects with more than 75 years of age, an NT-proBNP values less than 300 ng/L have a 99% negative predictive value for excluding acute congestive heart failure. A cutoff of 1,200 ng/L for patients with an eGFR less than 60 mL/min yields a diagnostic sensitivity and specificity of 89% and 72% for acute congestive heart failure. Finally, a cutoff of 1,800 ng/L has been suggested in adults over 75 years of age in absence of renal failure.

Statistical analysis. Continuous data were described with median and range. Fisher's exact test was used to test differences in nominal variables. Differences in continuous variables between groups were compared using Wilcoxon signed-rank test and correlations between them were compared using Spearman's rho. The best cutoff predicting survival of NT-proBNP was defined according to the maximum likelihood approach. Overall survival (OS) was calculated from the time of beginning treatment until the date of death for any cause or the date patients was last known to be alive. Kaplan–Meier analysis was used for analyzing overall survival, and the differences between the groups were tested for statistical significance by means of the log-rank test. Multivariate analysis of factors affecting survival was carried out using the Cox proportional hazards models. All analyses were performed using JMP 10.0 (SAS, Cary, NC).

Results

Baseline characteristics

The median age of the 351 patients was 65 years (interquartile range, IQR: 57–71). Table I details the clinical features and the baseline of NT-proBNP. The cut-point of NT-proBNP levels of 300 ng/L was obtained with a maximum likelihood approach. This cutoff was able to distinguish two groups with a significant difference in survival (Fig. 1). Median NT-proBNP in the overall cohort was 109 ng/L (IQR: 30–375 ng/L). The NT-proBNP low and high populations were significantly different by almost every clinical feature with the exceptions of sex, serum calcium, monoclonal component concentration, and likelihood of being clonal kappa or lambda and for having high-risk FISH (Table I).

Ninety-five (27%) patients had ADL $\geq$1 while CCI was $\geq$2 in 30%. The ADL tasks are listed in Supporting Information Table SI and the CCI score is listed in Supporting Information Table SII. The median (and IQR) NT-proBNP based on co-morbidities is shown in Supporting Information Table SII. As expected, patients with a history of myocardial infarction, congestive heart failure, atrial fibrillation, severe renal disease, or diabetes with organ damage had significantly elevated NT-proBNP values, but patients with cerebrovascular disease, chronic pulmonary disease, peptic ulcer, mild liver disease, diabetes with no organ damage, or other cancers did not have higher levels. There was a trend toward higher levels among patients with pulmonary hypertension, peripheral artery disease, hypertension and connective tissue diseases (Supporting Information Tables SII and SIII).

Overall survival

The median overall survival (OS) of the entire cohort was 5.7 years at a median follow-up of 5.4 years. On univariate analysis (Supporting Information Table SIV) the variables predicting survival were age [Relative risk (RR) 2.70 (1.97, 3.69)], ECOG-PS [RR 3.45 (2.45, 4.81)], CCI [RR 1.96 (1.42, 2.68)] all with $P < 0.0001$, ADL [RR 1.64 (1.17, 2.27), $P = 0.004$], history of hypertension [RR 1.44 (1.05–1.96), $P = 0.021$], LDH $\geq$222 U/L [RR 2.29 (1.50, 3.40), $P = 0.0002$], NT-proBNP $\geq$300 ng/L [RR 2.36 (1.71, 3.23)], and the ISS stages.

Despite relationships between NT-proBNP and other clinical variables, NT-proBNP retained independence as a prognostic marker for OS with each of these same variables (Supporting Information Table SV). In particular, all the proposed models were corrected by age and the prognostic ability of NT-proBNP outperformed CCI, ADL, traditional ISS, and eGFR. When further multivariate modeling was performed, factors retaining significance were age, revised ISS, and performance status (Table IIa and b). Interestingly, there was an interaction between performance status and revised ISS driving NT-proBNP off from the model (Table IIc). In contrast, when the traditional ISS and high-risk FISH were used in the model as independent variables along with NT-proBNP, ECOG-PS, and age, ISS was not significant, but NT-proBNP (Table IId) as well as LDH (Table IIe) remained prognostic.

Using this information, we devised a frailty risk system that incorporated age $\geq$70, ECOG-PS $\geq$2, and NT-proBNP $\geq$300 ng/L. This divided patients into four groups with median OS from diagnosis of not reached with no risk factors, 58 months with one risk factor, 28 months with two and 18 months ($P < 0.0001$) for those with all three risk factors (Fig. 2A), $P < 0.0001$. This frailty score was independent of high-risk cytogenetics (Table IIf) and of the revised ISS (Table IIg). As shown in Fig. 2B, there was excellent discrimination of the curves based on the new frailty score among the 220 standard risk FISH patients, $P < 0.0001$. For the 52 patients with high risk FISH, our new frailty score also performed well (Fig. 2C), $P < 0.0001$.

NT-proBNP is prognostic independent of treatment

NT-proBNP provided useful prognostic groupings in patients treated with lenalidomide-based first line regimens (Supporting Information Fig. S1A) and also divided patients treated with a proteasome-inhibitor as first line regimen (Supporting Information Fig. S1B), but this difference was not statistically significant, possibly

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TABLE I. Baseline patient characteristics [median (interquartile range) – number (%)].

Variable	All patients	NT-proBNP <300 ng/L 250 pts	NT-proBNP ≥300 ng/L 101 pts	*P*
Age (years)	65 (57–71)	62 (56–70)	70 (61–77)	<0.0001
Age ≥70	114 (33)	63 (25)	51 (50)	0.072
Sex: male	109 (56)	146 (58)	53 (51)	0.158
ECOG-PS				
0	155 (44)	126 (50)	29 (29)	0.0003
1	129 (36)	93 (37)	36 (36)	0.9026
≥2	66 (19)	31 (12)	35 (35)	<0.0001
CCI ≥2	104 (29)	57 (22)	47 (46)	<0.0001
ADL				
≥1	95 (27)	196 (78)	60 (59)	0.0005
≥4	10 (3)	4 (1)	6 (6)	0.036
Hemoglobin, g/dL	10.9 (9.6–12.6)	11.6 (10.1–13.4)	9.7 (8.8–10.8)	<0.0001
Calcium, mg/dL	9.7 (9.2–10.2)	9.7 (9.3–10.2)	9.6 (9–10.2)	0.4947
Creatinine, mg/dL	1 (0.8–1.3)	0.9 (0.8–1.2)	1.35 (0.9–2.62)	<0.0001
Creatinine >2 mg/dL	46 (13)	13 (4)	33 (9)	<0.0001
eGFR mL/min	72 (52–89)	76 (60–91)	52 (19–79)	<0.0001
eGFR <30 mL/min	43 (12)	10 (3)	33 (10)	<0.0001
Albumin, g/dL	3.5 (3.2–3.8)	3.6 (3.3–3.8)	3.4 (3.1–3.6)	0.0002
B2M, mg/dL	3.95 (2.7–6.5)	3.3 (2.5–4.8)	7.56 (4.4–11.6)	<0.0001
LDH ≥222 IU/L	45 (15)	25 (11)	20 (24)	0.01
NT-proBNP, ng/L	109 (30–375)	56 (0–123)	864 (459–2238)	<0.0001
BMPC, %	40 (20–65)	35 (20–55)	52 (40–75)	<0.0001
M-comp, g/dL	3 (1.8–4.1)	2.9 (1.7–4.1)	3.3 (1.9–4.4)	0.3943
Kappa: Lambda	215 (62):121 (35)	155 (63):85 (34)	60 (61):36 (37)	0.6239
High risk MM FISH	52 (19)	32 (11)	20 (7)	0.1603
ISS I	84 (27)	76 (33)	8 (9)	<0.0001
ISS 2	125 (40)	105 (47)	20 (23)	0.0002
ISS 3	101 (33)	43 (19)	58 (67)	<0.0001
R-ISS I	46 (17)	42 (22)	4 (5)	<0.0001
R-ISS II	177 (66)	133 (69)	44 (59)	<0.0001
R-ISS III	43 (16)	17 (8)	26 (35)	<0.0001
Therapy, first-line:				
Len-based	204 (63)	159 (68)	45 (49)	0.0014
Prot-inh-based	73 (22)	41 (18)	32 (35)	0.0011
ASCT, yes	138 (39)	105 (42)	33 (33)	0.05

ECOG-PS, Eastern Cooperative Oncology Group—Performance Status; CCI, Charlson comorbidity index; ADL, activity of daily leaving; eGFR, estimated glomerular filtration rate; B2M, beta-2-microglobulin; LDH, lactate dehydrogenase; NT-proBNP, N-amino terminal fragment of the B-type brain natriuretic peptide; BMPC, estimated bone marrow plasma cells infiltrate; M-comp, component where monoclonal protein migrates; FISH, fluorescent in situ hybridization; High risk MM by FISH, presence of del(17p) and/or translocation t(4,14) and/or translocation t(14,16); R-ISS, revised-international staging system, R-ISS I, ISS stage I and standard-risk MM by FISH and LDH <222 IU/L; R-ISS II, not R-ISS I or III; R-ISS III, ISS stage III and either high-risk MM by FISH or LDH ≥222 IU/L; Len-based, lenalidomide containing regimen; Prot-inh-based, proteasome inhibitor containing regimen, ASCT, autologous stem cell transplant.

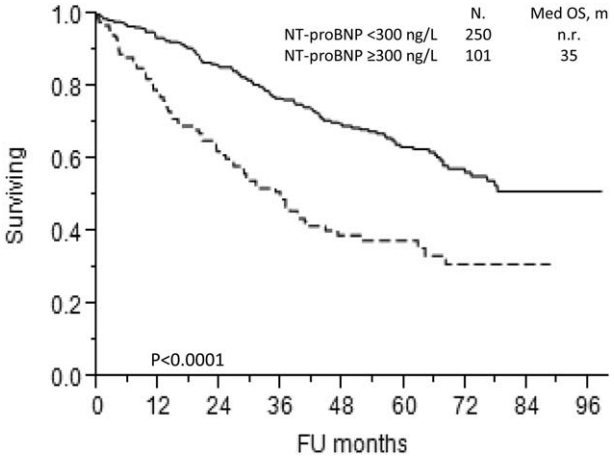

Figure 1. Kaplan–Meier curve for overall survival according to NT-proBNP ≥300 ng/L (Continuous line: patients with NT-proBNP <300 ng/L; dotted line: patients with NT-proBNP ≥300 ng/L).

because the limited number of patients. Amongst the 172 patients who did not undergo autologous stem cell transplant during the treatment course, NT-proBNP ≥300 ng/L sharply discriminated two different groups (Supporting Information Fig. S1C).

This new frailty system based on age, ECOG-PS and NT-proBNP was able to discriminate different groups of patients amongst all the subjects treated with lenalidomide-based and protasome-inhibitor first line regimens (Supporting Information Figs. S1D and S1E, respectively) and also amongst patients who did not undergo autologous stem cell transplant (Supporting Information Fig. S1F). In all the different subgroups, Stage IV patients (Age ≥70, PS ≥2 and NT-proBNP ≥300 ng/L) constituted only 6% of the patients.

Discussion

The present study demonstrates that NT-proBNP is a good indicator of prognosis in unselected patients with multiple myeloma seen at a tertiary referral center. Interactions between variables, especially age, ECOG-PS, NT-proBNP, and the revised ISS were striking (Table I). Any of these four variables when modeled with two other retained significance as predictors for OS, but when all four were included in a model, NT-proBNP was forced out; however, when the revised ISS was split into its components, LDH and high-risk FISH remained significant prognostic markers, NT-proBNP retained significance, and the traditional ISS was forced out of the model. Hence the combination of age, ECOG-PS, and NT-proBNP resulted in a simple but robust frailty model that is independent of other prognostic factors such as FISH and LDH.

TABLE II. Proportional hazards predicting for overall survival

a. Multivariate model		
Variable	RR (CI 95%)	*P*
ECOG-PS ≥2	2.60 (1.81, 3.70)	<0.0001
Age ≥70 years	2.17 (1.57, 2.99)	<0.0001
NT-proBNP ≥300 ng/L	1.62 (1.15, 2.28)	0.006
b. Multivariate model		
Variable	RR (CI 95%)	*P*
Revised ISS	2.51 (1.15, 2.19)	<0.0001
Age ≥70 years	2.36 (1.68, 3.30)	<0.0001
NT-proBNP ≥300 ng/L	1.67 (1.51, 2.39)	0.007
c. Multivariate model		
Variable	RR (CI 95%)	*P*
ECOG-PS ≥2	2.46 (1.66, 3.59)	<0.0001
Age ≥70 years	2.12 (1.50, 2.99)	<0.0001
Revised ISS	1.46 (1.06, 2.01)	0.02
NT-proBNP ≥300 ng/L	1.42 (0.97, 2.06)	0.07
d. Multivariate model[a]		
Variable	RR (CI 95%)	*P*
ECOG-PS ≥2	2.33 (1.54, 3.49)	<0.0001
Age ≥70 years	2.34 (1.60, 3.40)	<0.0001
High-risk FISH	1.88 (1.24, 2.78)	0.003
NT-proBNP ≥300 ng/L	1.72 (1.16, 2.55)	0.007
e. Multivariate model[a]		
Variable	RR (CI 95%)	*P*
ECOG-PS ≥2	2.34 (1.50, 3.62)	0.0003
High-risk FISH	2.28 (1.46, 3.48)	0.0005
Age ≥70 years	2.21 (1.48, 3.31)	0.0001
LDH ≥222	1.78 (1.08, 2.84)	0.03
NT-proBNP ≥300 ng/L	1.59 (1.05, 2.40)	0.03
f. Multivariate model		
Variable	RR (CI 95%)	*P*
ECOG-PS-Age-NT-proBNP (3a)[b]	2.10 (1.77, 2.50)	<0.0001
High-risk FISH	1.87 (1.23, 2.76)	0.004
g. Multivariate model		
Variable	RR (CI 95%)	*P*
ECOG-PS-Age-NT-proBNP (3a)[b]	1.95 (1.62, 2.34)	<0.0001
Revised ISS	1.40 (1.02, 1.92)	0.04

[a] Traditional ISS as ordinal variable or as a dichotomous variable of ISS = 3 is not significant.
[b] ECOG-PS-Age-NT-proBNP (3a) refers to PS ≥2, age ≥70, and NT-proBNP ≥300 ng/L each scoring 1 point for a score and creating a staging from 1 to 4.

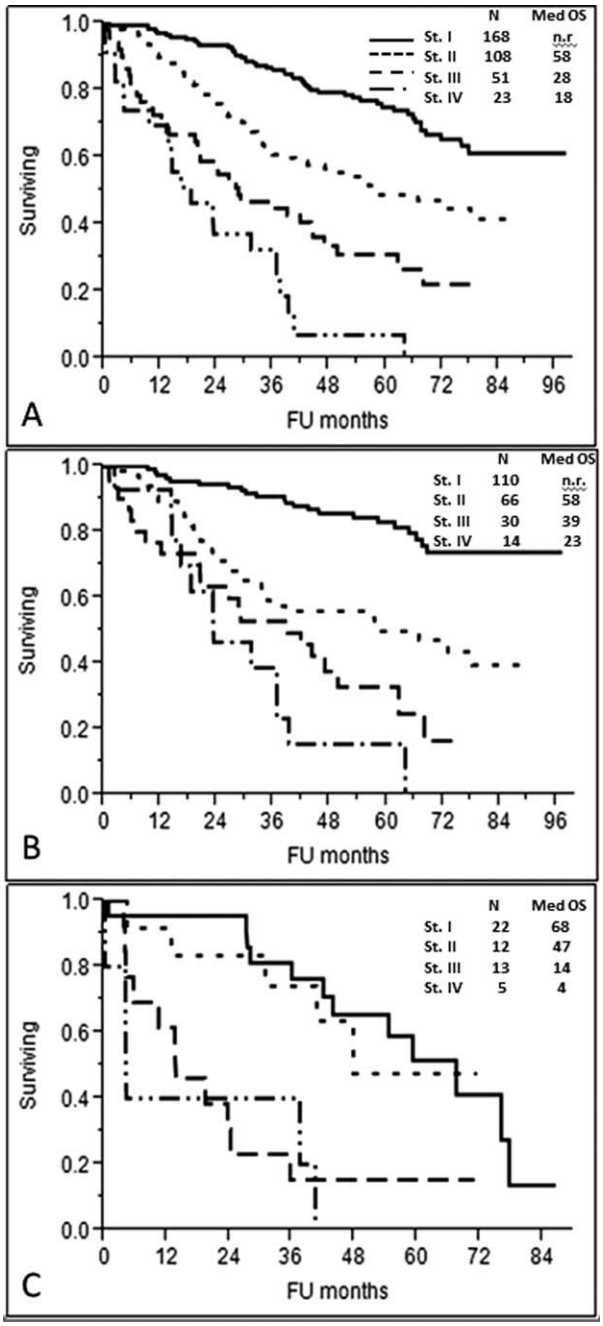

Figure 2. Kaplan–Meier curve for overall survival according to the frailty system based on Age ≥70, ECOG-PS ≥2, and NT-proBNP ≥300 ng/L ($P < 0.0001$) [different stages based on a score of 0 to 3 points, respectively]. A. Overall survival according to the frailty system in the entire cohort ($P < 0.0001$). B. Overall survival according to the frailty system in 220 patients with standard risk FISH (no high-risk chromosome abnormalities), ($P < 0.0001$). C. Overall survival according to the frailty system in 52 patients with high risk FISH [presence of del17p and/or translocation t(4;14) and/or translocation t(14;16)], ($P < 0.0001$).

The purpose of this study was to determine whether NT-proBNP could replace more complicated frailty scores despite an online tool (http://www.myelomafrailtyscorecalculator.net/). The identification of frail patients with an easily applicable, rapid and objective tool would be highly desirable to help identify specific tolerable but yet effective treatment approaches. Although direct comparisons cannot be made to the largest myeloma frailty study [12] our findings are compelling. As recommended by Palumbo et al, the combination of ADL, IADL and CCI scores resulted in a frailty score that identifies fit patients, "intermediate-fit" patients and un-fit ones. The ADL score includes one point each for not requiring assistance with any of the following: bathing, dressing, toileting, transferring, continence, and feeding (best score 6). The IADL score includes 1 point for each of the following abilities: use of telephone, shopping, food preparation, housekeeping, laundry, making transport, responsibility for own medications, and handle finances (best score 8). Finally, the CCI (worst score = 37) includes all the conditions reported in Supporting Information Table SII with different assigned weights. Using this very complex system of frailty, patients are deemed either fit, intermediately fit, or frail. Although these three categories were prognostic on univariate, the discriminatory ability between "fit" and "intermediate fitness"'when considered in the context of ISS, chromosome abnormalities, or therapy was not significant; only "frail" versus either intermediately fit or "fit" retained significance [12]. Moreover, the authors did not include the revised ISS or performance status when evaluating their frailty/geriatric assessment model. We would, therefore, suggest that our NT-proBNP risk system may perform as well as the geriatric assessment score and deserves further study. Due to the lack of the evaluation of the IADL score, the retrospective calculation of the CCI and of part of the ADL score, we were unable to do a direct comparison between the IMWG frailty index and our proposed frailty score.

The single blood test—NT-proBNP—captures infirmity due to cardiac [23–25] and renal disease [26–28] but not due to either central

or peripheral neurodegeneration; however, PS may compensate in part for these additional aspects of frailty. The NT-proBNP threshold of 300 ng/L corresponds to the well-established age-independent cut-off point for excluding acute heart failure [36] and provides information that is incremental to that obtained from established cardiovascular risk factors [37]. In addition, natriuretic peptide levels may be elevated before the onset of clinically apparent cardiovascular disease in patients with light chain (AL) amyloidosis [38,39]. Subtle elevation of NT-proBNP may predict existing cardiac amyloidosis which cannot be identified at echocardiography [38].

We demonstrated that the CCI $\geq$2 was forced out by NT-proBNP in our modeling, but the simple ECOG-PS was retained in every multivariate analysis constructed. An ECOG-PS $\geq$2 had a risk for death that was higher than any single variable. In clinical practice, ECOG-PS is widely used to assess fitness of cancer patients, and although more complex and time consuming scales are available [30,40], this simple and reliable measure, in most cases, accurately provides the grade of frailty and disability of patients. It is intuitive that patients who are not ambulatory or up and about more than 50% of walking hours (i.e., an ECOG PS $\geq$2) would have deficits in ADL's and IADL's, which are used in more complex scoring system. According to the Palumbo's geriatric assessment scoring system, age greater than 80 alone assigns the "unfit" designation on a patient as would the presence of any one or two comorbidities, like diabetes with retinopathy, regardless of performance status.

In our dataset, age was also important in determining outcome, and it is due to the physiological changes of organ function [11]. There is a definite relationship between age and natriuretic peptide levels which is likely consequent to age-related changes in left ventricular compliance [41], as well as decreasing eGFR [42]. In our cohort, the group of patients with elevated NT-proBNP had a higher median age and a higher incidence of renal dysfunction. However, the prognostic role of NT-proBNP was independent of age and outperformed eGFR. We chose the cutoff of age = 70 years because in clinical practice it is the cutoff for the consideration of autologous stem cell transplant as a treatment strategy in many centers. Currently, most European investigators choose a cutoff of 65 years in their clinical trial design, but this barrier can be increased to 70 years or even higher for fit patients [43]. The ability of NT-proBNP as prognostic marker was also confirmed in different models corrected by age with the different clinical variables. These data were in accordance with the assumption that biological age expressed by an individual performance status and, in our case by the combination of PS, NT-proBNP and age, despite only chronological age, should be a major determinant for the treatment approach.

There are some limitations of this study. First, it did not include an IADL score. Second, it is a single center study than on average contained participants approximately 10 years younger than the IMWG study. Third, there was no validation cohort. Finally, patients were not uniformly treated, and one could argue that they received a particular therapy according to their fitness. However, we demonstrated that our system of NT-proBNP, age, and performance status was an independent prognostic factor regardless of initial therapy. Also in balance, a potential advantage of the current study is that it included unselected newly diagnosed patients. All three studies included in the IMWG work had specific eligibility criteria that resulted in a lower percentage of patients with a CCI $\geq$2, only 17% as compared with our 30%.

In conclusion, we showed that patients with an NT-proBNP $\geq$300 ng/L, an ECOG-PS $\geq$2, and age $\geq$70 years should be considered as a "high risk" group. NT-proBNP could be easily added to the traditional workup for newly diagnosed myeloma patients as a means of both assigning frailty risk and guide us to a more specific workup in the exclusion of a concomitant cardiac amyloidosis. The true challenge will be to understand how to manage frail patients at diagnosis. Exactly how therapy should be tailored among these frail patients is yet to be determined and beyond the scope of this work. In curative diseases like lymphoma, dose-reductions are not recommended. In a disease that is not yet known to be curative, dose-adjustment is likely the best approach [1]. Regardless, further studies are needed to validate our findings regarding NT-proBNP before it can be considered standard in multiple myeloma, but we would suggest that it will be important moving forward in these patient populations with a better stratification of the possible confounding factors.

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