

ORIGINAL RESEARCH ARTICLE

Serum free immunoglobulin light chain fingerprint identifies a subset of newly diagnosed multiple myeloma patients with worse outcome

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Abstract

Multiple myeloma (MM) is a multi-subclonal malignancy with relatively high heterogeneity. Patients who initially presented with both monoclonal-protein (MP) and free light chain (FLC) secretion but then relapsed with a light chain escape pattern have been shown to reflect disease clonal evolution and to bare a worse prognosis. We hypothesized that a discordant MP/FLC pattern at diagnosis may reflect a similar clonal evolution that had occurred prior to diagnosis of active myeloma, conferring a worse outcome. We analyzed 255 consecutive newly diagnosed MM patients who received first line bortezomib-based therapy between 2007 and 2014, hypothesizing that their MP/FLC fingerprint at diagnosis reflects clonal heterogeneity and, therefore, affects outcome. An involved FLC level ≥ 700 mg/L and MP ≥ 2.5 g/L were used as cutoffs for low vs high FLC and MP levels, respectively. Patients were divided into 4 subgroups according to their involved FLC and MP blood levels at diagnosis: HiLC and HiMP for patients with either a predominant FLC or a predominant MP, respectively, and HiLC-MP and LoLC-MP when both FLC and MP were increased or decreased, respectively. There were 68 (27%) patients with HiLC, which presented more often with International Staging System-3 stage ($P < .0001$). Multivariate analysis showed that HiLC was associated with a 5.1-fold risk for mortality in a multivariate model (95% confidence interval [CI], 1.34-19.68). Both HiLC and HiLC-MP phenotypes were associated with shorter progression-free survival (hazard ratio of 2.66 [95% CI, 1.33-5.32] and 2.82 [95% CI, 1.37-5.83], respectively), independently of other prognostic factors, including the use of autograft. Thus, we identified an LC predominant secretory fingerprint (HiLC phenotype) at diagnosis as a potential independent risk factor that may affect disease control and survival in newly diagnosed MM patients treated with bortezomib-based induction therapy; this may represent increased subclonal heterogeneity.

KEYWORDS

light chain, myeloma, prognosis, secretory

1 | INTRODUCTION

Multiple myeloma (MM) has been recently recognized as a multi-subclonal malignancy with a relatively high intraclonal heterogeneity and clonal tides.^{1,2} In a recent study, Brioli et al³ suggested that in the clinical setting, clonal tides responsible for disease progression may be traced phenotypically by monitoring the evolution in the levels

of monoclonal protein (MP) vs involved free light chain (iFLC) during the disease course. By analyzing protein secretion pattern at relapse, they showed that patients who initially presented with both MP and FLC, but then relapsed with a light chain escape pattern, bare a worse prognosis.³

They hypothesized that this pattern, previously reported also by Kühnemund et al,⁴ may be due to clonal evolution in which a more aggressive FLC producing clone becomes predominant upon relapse.³ Recently, the International Myeloma Working Group proposed that

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high FLC ratio >100 attributed to high levels of iFLC is associated with a very high risk of development of symptomatic disease in patients with asymptomatic MM.⁵ Considering these data, we hypothesize that a discordant secretory pattern of light and heavy chains at diagnosis could serve as a surrogate for the presence of multiple subclones, of which a subclone with an increased production of FLCs has expanded, representing clonal evolution and increased subclonal heterogeneity, and this may affect disease response to therapy and outcome.

The aim of the current study was to evaluate the prognostic importance of an elevated involved FLC level, appearing as concordant vs discordant to the involved heavy chain level (ie, MP), in newly diagnosed MM (NDMM) patients treated with bortezomib-based induction.

2 | PATIENTS AND METHODS

The data of consecutive NDMM patients, treated in 3 participating centers (National and Kapodistrian, Athens, Greece; Tel-Aviv Sourasky Medical Center; and Rambam Medical Center, Israel), between January 1, 2007 and January 31, 2014, were retrospectively reviewed. Data on patients with NDMM who received bortezomib as part of their first-line therapy in combination with corticosteroids and/or alkylators were retrieved from the departmental myeloma databases and hospital pharmacy.

Patients with symptomatic MM, and measurable disease (defined as serum M-protein ≥ 1 g/dL [≥ 10 g/L], or urine M-protein ≥ 200 mg per 24 hours, or involved serum FLC level ≥ 10 mg/dL [≥ 100 mg/L], provided that the serum FLC ratio was abnormal),^{6,7} treated with a bortezomib-containing induction, were included. The study was conducted in accordance to the Declaration of Helsinki and was approved by the Institution's IEC/SC.

Data were collected from patient files, focusing on patient demographics, myeloma-related laboratory and clinical parameters (including immunoelectrophoresis, immunofixation, M-spike and FLC levels, Bence-Jones protein, International Staging System [ISS], chromosomal abnormalities determined by fluorescence in situ hybridization [FISH], renal failure, bone involvement, and anemia), details of induction therapy, response to induction, response duration, and current disease status. Triplet therapy included bortezomib, chemotherapy, and a steroid; doublet therapy included bortezomib with a steroid.

Monoclonal protein and iFLC levels were defined as "high levels" in the presence of MP > 2.5 g/dL and iFLC > 700 mg/L, respectively. Both cutoffs were chosen based on the corresponding median values for these laboratory tests in our cohort, and also in consensus with prior studies who detected this threshold as prognostically valuable,^{8,9} enabling patients categorization into 4 groups based on their FLC and MP values: high LC and low MP cohort (HiLC), high MP and low LC cohort (HiMP), high LC and high MP cohort (HiLC-MP), and low iFLC and low MP cohort (LoLC-MP). Table 1 presents patient categorization into 4 groups according to their LC and MP levels.

The 4 subgroups were compared, focusing on baseline characteristics and long-term outcome, determined by progression-free survival (PFS) and overall survival (OS) and factors predicting that outcome.

TABLE 1 Patient categories according to their LC and MP levels at diagnosis

	MP Level (g/dL)	iFLC Level (mg/L)
HiLC	<2.5	>700
HiMP	≥ 2.5	≤ 700
HiLC-MP	≥ 2.5	>700
LoLC-MP	<2.5	≤ 700

Abbreviations: iFLC, involved free light chain; LC, light chain; MP, monoclonal protein.

2.1 | Statistical analysis

Fisher exact and χ^2 tests were used to compare categorical variables. Student *t* and analysis of variance tests were used to assess continuous variables with a normal distribution, whereas Mann-Whitney and Wilcoxon rank sum tests were used to assess and compare continuous variables that were not normally distributed.

Overall survival was defined as the time from first treatment until death or censoring. Progression-free survival was defined as the time from first treatment to evidence of progression, death, or censoring. Survival curves were plotted using the Kaplan-Meier method with the log-rank test used to compare to survival differences between groups. The Cox proportional hazards method was used for univariate and multivariate survival analyses. To control for confounding differences between patients and treatment, multivariate analyses included, in addition to clonal type, age, sex, Eastern Cooperative Oncology Group performance status, bone marrow plasmacytosis, treatment type and bortezomib schedule, and performance of autologous stem cell transplantation (ASCT) at first remission. Analysis was performed using SPSS version 22 (IBM Inc, Chicago, Illinois).

3 | RESULTS

3.1 | Patient characteristics

3.1.1 | Characteristics of the entire cohort

The study population included 255 NDMM patients who received a bortezomib-based induction. The median age for the entire cohort, composed of equal proportions of males and females, was 62 years (range, 31-89 years). Approximately a third of the patients had ISS-3 (*n* = 82) features. The majority of patients (*n* = 212, 83%) were treated with a triplet combination chemotherapy, mainly VCD (*n* = 182, 71%). In most patients, treatment was administered on a biweekly schedule (*n* = 205, 80%). Approximately half of the patients underwent an upfront ASCT following induction (*n* = 122, 48%).

3.1.2 | Characteristics of patients according to the LC-MP phenotype

The HiLC cohort included 68 patients (27%) who presented with a dominating LC phenotype > 700 mg/dL (32 with no evidence of an accompanying heavy chain in immunofixation and 36 with an accompanying MP < 2.5 g/dL). The HiMP, HiLC-MP, and LoLC-MP cohorts included 82 (32%), 57 (22%), and 48 (19%) patients, respectively.

Characteristics of patient subgroups are presented in Table 2. There was a trend toward more elderly patients (>65 years) within

TABLE 2 Patient characteristics

	[All] N = 255	HiLC-MP N = 57	HiMP N = 82	HiLC N = 68	LoLC-MP N = 48	P Value	N (Evaluable Pts)
Patient features							
Median age, y [min-max]	62.0 [31.0; 89.0]	62.0 [41.0; 87.0]	61.0 [35.0; 89.0]	66.0 [31.0; 88.0]	61.5 [37.0; 84.6]	.256	255
Age > 65 y	96 (37.6%)	17 (29.8%)	26 (31.7%)	35 (51.5%)	18 (37.5%)	.041	255
Gender (female)	122 (47.8%)	29 (50.9%)	37 (45.1%)	35 (51.5%)	21 (43.8%)	.769	255
ECOG ≥ 2	91 (36.5%)	23 (43.4%)	24 (29.6%)	28 (41.8%)	16 (33.3%)	.29	249
Clinical/disease features							
ISS							
I	62 (27.2%)	6 (11.8%)	19 (25.7%)	15 (25.0%)	22 (51.2%)	<.001	228
II	84 (36.8%)	23 (45.1%)	35 (47.3%)	13 (21.7%)	13 (30.2%)		
III	82 (36.0%)	22 (43.1%)	20 (27.0%)	32 (53.3%)	8 (18.6%)		
M-spike level, mg/dL	3105 (2365)	5167 (2007)	4574 (1718)	820 (544)	1381 (641)	<.001	255
Light chain type (kappa)	154 (60.4%)	33 (57.9%)	55 (67.1%)	40 (58.8%)	26 (54.2%)	.471	255
Light chain level, mg/L, median (SD)	3087 (6642)	4164 (7982)	188 (180)	7677 (8691)	257 (230)	<.001	255
del17p	22 (14.9%)	9 (21.4%)	6 (13.6%)	4 (11.1%)	3 (11.5%)	.602	148
Any high-risk cytogenetics	64 (36.0%)	20 (44.4%)	24 (43.6%)	13 (31.0%)	7 (19.4%)	.057	178
BM plasma cells ≥ 60%	135 (51.6%)	37 (67.3%)	42 (52.5%)	39 (59.1%)	10 (21.3%)	<.001	248
Baseline Hb	10.7 (2.20)	9.55 (1.69)	10.9 (2.11)	10.3 (2.34)	12.1 (1.80)	<.001	231
Hb ≤ 10 g/dL	96 (41.6%)	33 (63.5%)	28 (37.3%)	30 (49.2%)	5 (11.6%)	<.001	231
Baseline creatinine (mg/dL)	1.90 (2.22)	2.00 (2.14)	1.25 (1.30)	3.00 (3.14)	1.29 (1.10)	<.001	235
Creatinine > 2 mg/dL	53 (22.6%)	13 (24.1%)	5 (6.7%)	29 (46.0%)	6 (14.0%)	<.001	235
Osteolytic lesions	177 (81.2%)	38 (77.6%)	61 (88.4%)	46 (79.3%)	32 (76.2%)	.308	218
Treatment features							
Any Velcade-based triplet							
	212 (83.1%)	50 (87.7%)	72 (87.8%)	52 (76.5%)	38 (79.2%)	.185	255
Biweekly Velcade							
	205 (80.4%)	47 (82.5%)	72 (87.8%)	53 (77.9%)	33 (68.8%)	.06	255
ASCT at 1st remission							
	122 (47.8%)	28 (49.1%)	49 (59.8%)	23 (33.8%)	22 (45.8%)	.017	255
No-ASCT total no. cycles							
	5 [1, 24]	4 [1, 10]	5 [1, 24]	5 [1, 20]	6 [1, 15]	.115	
Follow-up time							
	18.1 [0.26; 82.9]	17.6 [1.77; 82.9]	19.9 [0.59; 63.5]	15.5 [0.26; 73.6]	21.3 [3.44; 63.7]	.24	255

Abbreviations: ASCT, autologous stem cell transplantation; BM, bone marrow; ECOG, Eastern Cooperative Oncology Group; Hb, hemoglobin; ISS, International Staging System; LC, light chain; MP, monoclonal protein.

the HiLC group, and there were no statistically significant differences between the 4 categories in terms of sex and bone involvement.

The HiLC patients were older (51% were >65 years, compared with 38% in HiLC-MP, 32% in the HiMP, and 38% in LoLC-MP cohort, $P = .041$); they were more likely to present with a creatinine level > 2 mg/dL (46% HiLC, 24% HiLC-MP, 7% HiMP, and 14% LoLC-MP, $P < .0001$) and with ISS-3 staging (53% HiLC, 27% HiMP, 44% HiLC-MP, and 19% LoLC-MP, $P < .0001$).

The HiLC-MP phenotype was associated with greater bone marrow plasmacytosis (67%, $P < .0001$). Additionally, patients in this subgroup, as well as those presenting with HiLC, were more likely to present with hemoglobin level lower than 10 g/dL (64% and 49%, respectively, vs 37% in patients presenting with HiMP and 12% in the LoLC-MP category, $P < .0001$). There were no significant differences between the 4 categories in terms of type of induction treatment being used, considering the use of doublets vs triplets and the administration of intravenous vs subcutaneous bortezomib. The median number of induction cycles administered to nontransplanted patients was 5, compared with 4 in those treated with an upfront ASCT. Upfront ASCT was more commonly used in the treatment of patients in the HiMP cohort ($P = .02$).

3.2 | Progression-free survival and overall survival

After a median follow-up of 22 months, 218 patients (85%) were alive, 37 patients had died (29 because of disease progression), and 125 patients (49%) experienced disease progression, of which 17 occurred during induction. At 3 years, cumulative OS for the entire cohort was 80% (median not reached), and cumulative PFS was 32% (median 23.7 months).

Univariate analyses (Table 3) found age > 65 years, ISS-3, renal failure, anemia, increased lactic acid dehydrogenase level, lack of consolidative autograft, and both HiLC and HiLC-MP phenotypes to be associated with a significantly shorter PFS.

The HiLC subgroup had the worst PFS, although both HiLC and HiLC-MP patients had a significantly shorter PFS compared with their HiMP and LoLC-MP counterparts; median PFS in months were 14.6 for HiLC and 18.4 for HiLC-MP vs 27.6 for HiMP and 36.7 for the LoLC-MP groups ($P = .001$, Figure 1A). The impact of HiLC and HiLC-MP phenotype was most notable at 3 years post diagnosis (Table 4), where PFS in these cohorts were 19% and 25%, respectively, compared with 38% and 51% in patients presenting with HiMP or LoLC-MP phenotypes, respectively. Multivariate analysis confirmed both HiLC-MP and HiLC phenotypes and lack of upfront ASCT to be associated with a shorter PFS (Table 5).

Survival rate at 3 years was 66% in HiLC patients vs >80% in the other groups (Figure 1B; Table 4). Univariate analysis found poor performance status, advanced ISS (3 vs lower), renal failure, anemia, increased lactic acid dehydrogenase, extramedullary disease, nontriplet induction, lack of consolidative autograft, and HiLC phenotypes to be associated with significantly shorter OS (Table 3). All poor performance status, HiLC phenotype, and lack of consolidative autograft remained statistically significant predictors for shorter OS in a multivariate analysis (Table 5). Of note, patients in the HiLC cohort presenting with an accompanying low MP tended to have a shorter survival compared with their true HiLC counterparts presenting without an accompanying M protein (52 months vs not reached, $P = .14$). The HiLC patients tended to be older and, therefore, were less likely to undergo ASCT. Repeated analysis, looking separately at nontransplanted and transplanted patients, found HiLC phenotype to be significantly associated with shorter PFS and OS in nontransplanted ($P = .05$ and $P = .04$,

TABLE 3 Univariate analysis for factors affecting PFS and OS

	PFS			OS		
	HR	95% CI	P	HR	95% CI	P
Age > 65 y	2.06	1.45-2.96	<.0001	1.81	0.93-3.50	.08
Sex (M)	0.95	0.67-1.35	.79	0.87	0.45-1.66	.66
ECOG > 1	1.29	0.90-1.86	.17	5.22	2.52-10.79	<.0001
ISS 3 vs ISS 1/2	2.38	1.62-3.51	<.0001	4.95	2.20-11.14	<.0001
Cr > 2	1.34	1.10-1.64	.004	1.64	1.19-2.27	.003
Hb < 10	1.40	1.16-1.69	<.0001	1.54	1.09-2.17	.01
LDH > ULN	1.34	1.09-1.64	.006	1.57	1.10-2.24	.012
Lytic lesions	1.00	0.65-1.54	.99	1.31	0.54-3.19	.55
Extramedullary disease	1.39	0.73-2.67	.32	3.66	1.50-8.94	.004
BM plasmacytosis	1.08	0.75-1.54	.69	1.44	0.72-2.87	.30
HiLC-MP ^a	2.00	1.11-3.59	.021	1.88	0.48-7.27	.36
HiMP ^a	1.08	0.60-1.95	.795	1.88	0.52-6.83	.34
HiLC ^a	2.31	1.31-4.05	.004	4.51	1.32-15.43	.02
Triplet regimen	0.83	0.67-1.03	.09	0.66	0.47-0.93	.02
Once weekly	1.24	0.80-1.91	.34	1.86	0.95-3.63	.07
ASCT at 1st remission	0.31	0.21-0.46	<.0001	0.29	0.14-0.60	.001

Abbreviations: ASCT, autologous stem cell transplantation; BM, bone marrow; CI, confidence interval; Cr, creatinine; ECOG, Eastern Cooperative Oncology Group; Hb, hemoglobin; HR, hazard ratio; ISS, International Staging System; LDH, lactic acid dehydrogenase; OS, overall survival; PFS, progression-free survival; ULN, upper limit of normal.

^aIn reference to the Lo group.

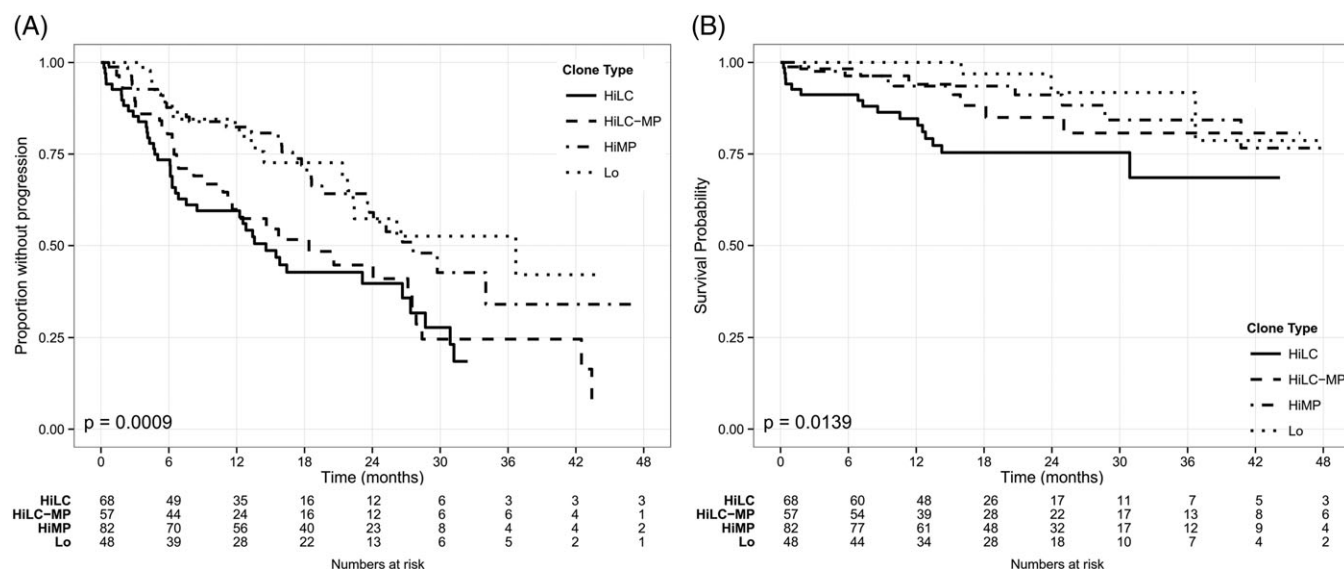


FIGURE 1 (A) Progression-free survival according to protein fingerprint at diagnosis. (B) Overall survival according to protein fingerprint at diagnosis. Abbreviations used: LC, light chain; MM, multiple myeloma

TABLE 4 Outcome of patients dependent on MM clonal subtype

	Entire Cohort	HiLC-MP	HiMP	HiLC	LoLC-MP	P ^a
PFS						
1 y	0.70 ± 0.03	0.59 ± 0.07	0.82 ± 0.04	0.58 ± 0.06	0.81 ± 0.06	.001
3 y	0.32 ± 0.04	0.25 ± 0.08	0.38 ± 0.08	0.19 ± 0.07	0.51 ± 0.10	.001
OS						
1 y	0.92 ± 0.02	0.94 ± 0.03	0.93 ± 0.03	0.84 ± 0.05	1.00 ± 0.00	.01
3 y	0.80 ± 0.04	0.80 ± 0.07	0.83 ± 0.06	0.66 ± 0.08	0.93 ± 0.05	.01

Abbreviations: LC, light chain; MM, multiple myeloma; MP, monoclonal protein; OS, overall survival; PFS, progression-free survival.

^aIn comparison with the LoLC-MP cohort.

TABLE 5 Multivariate analysis for factors affecting PFS and OS

	HR	OS 95% CI		P Value	HR	PFS 95% CI		P Value
		Lower	Upper			Lower	Upper	
Age > 65 y	1.63	0.57	4.60	.359	0.88	0.49	1.58	.667
Sex (female)	0.70	0.34	1.44	.330	0.74	0.49	1.13	.162
ECOG > 1	4.66	2.02	10.74	.000	1.16	0.76	1.78	.497
HiLC-MP	1.73	0.37	8.01	.481	2.82	1.37	5.83	.005
HiMP	3.87	0.95	15.77	.059	1.41	0.70	2.86	.337
HiLC	5.14	1.34	19.68	.017	2.66	1.33	5.32	.006
BM plasmacytosis	0.51	0.22	1.18	.116	0.85	0.67	1.07	.164
Lytic bone dis.	1.07	0.39	2.91	.894	0.82	0.48	1.40	.475
Twice weekly schedule	0.72	0.24	2.17	.563	0.77	0.42	1.42	.408
Any Velcade-based triplet	2.88	0.95	8.78	.062	1.23	0.67	2.23	.506
ASCT at 1st remission	4.70	1.62	13.66	.005	3.30	1.91	5.69	<.0001

Abbreviations: ASCT, autologous stem cell transplant; BM, bone marrow; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LC, light chain; MP, monoclonal protein; OS, overall survival; PFS, progression-free survival.

respectively) (Figure 2A and B) but not in transplanted patients ($P = .25$ and $P = .28$, respectively) (Figure 2C and D). Nontransplanted HiLC-MP patients also had a short PFS ($P = .01$). Yet another multivariate

analysis including also cytogenetic profiles (available in 178 patients) demonstrated that clonal subtype, in particular HiLC, retained its statistical significance in predicting OS ($P = .007$) and PFS ($P = .03$).

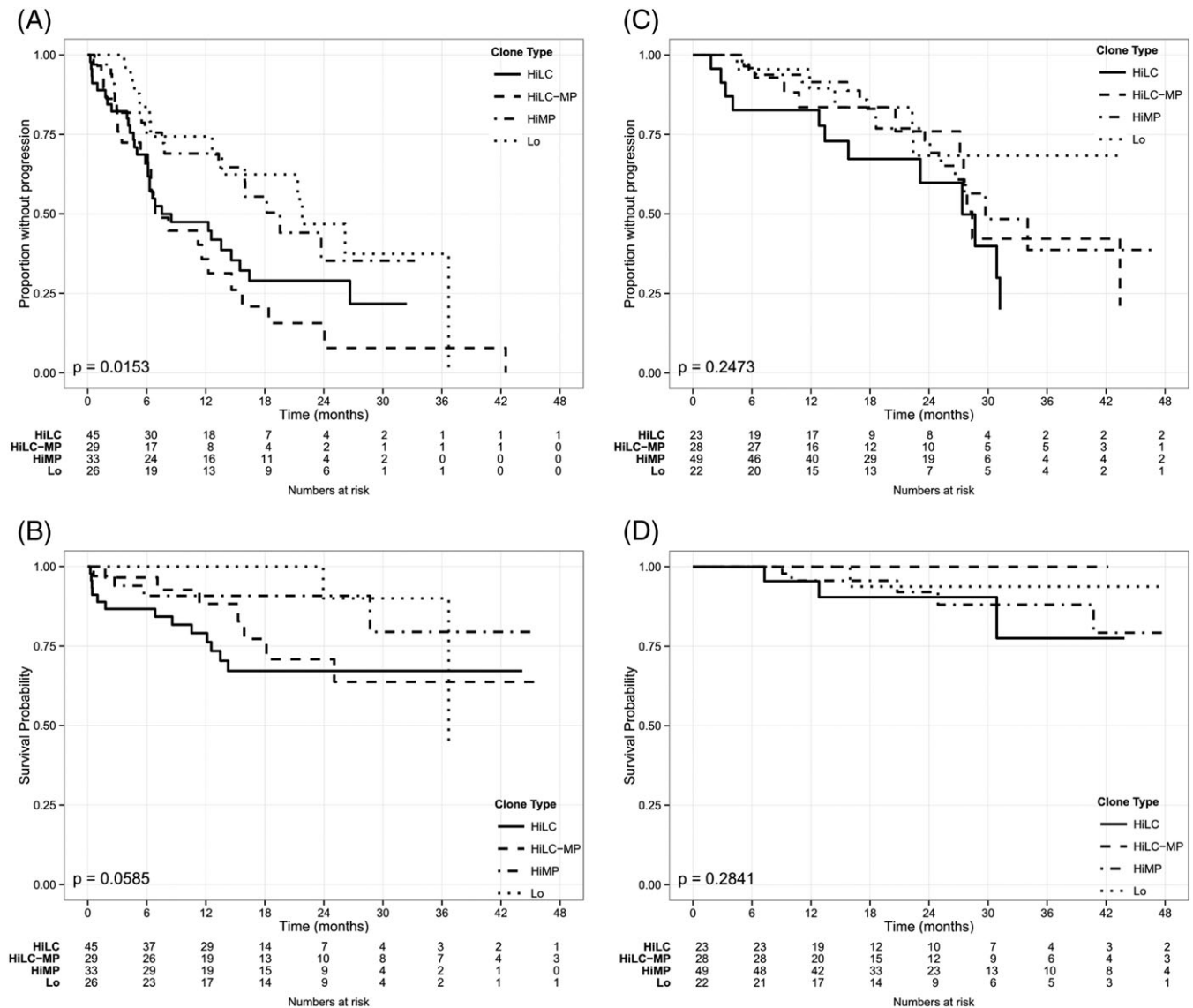


FIGURE 2 (A) Progression-free survival according to protein fingerprint at diagnosis, subgroup analysis: patients who did not undergo autologous stem cell transplantation (ASCT). (B) Overall survival according to protein fingerprint at diagnosis, subgroup analysis: patients who did not undergo ASCT. (C) Progression-free survival according to protein fingerprint at diagnosis, subgroup analysis: patients underwent ASCT. (D) Overall survival according to protein fingerprint at diagnosis, subgroup analysis: patients who underwent ASCT

4 | DISCUSSION

The LC predominance at relapse, known also as “LC escape,” was shown to be associated with a worse outcome, most probably reflecting an increased clonal heterogeneity with a selection of a more aggressive clone responsible for disease progression.⁹ While this phenotypic fingerprint may be observed at the relapse setting, we hypothesized that its appearance at diagnosis may also be due to clonal evolution with increased clonal heterogeneity, occurring prior diagnosis and contributing to the evolution from monoclonal gammopathy of undetermined significance (MGUS)/smoldering MM to active myeloma and, therefore, associated with a worse outcome.

The current study explored whether a predominant “LC fingerprint” at the time of initial diagnosis of symptomatic MM may also predict a worse outcome in NDMM patients. According to our data, LC/MP fingerprint at diagnosis was found to have an

independent impact on outcome. Patients presenting with a HiLC phenotype had the poorest prognosis, with a 2.7 hazard for progression ($P = .006$) and 5-fold hazard for mortality ($P = .017$) in multivariate models. Moreover, patients presenting with a predominant light-chain accompanied with a low MP tended to have an even worse outcome compared with “pure HiLC” (ie, no monoclonal heavy chain) patients, suggesting that the high “LC-tumor” burden itself, although shown to adversely affect patients outcome,^{8,9} may not entirely explain the worse prognosis observed in these patients; rather, the pattern of elevated light chain together with low levels of M-spike may actually reflect increased subclonal heterogeneity, which contributes to the inferior outcomes. Secondary genetic events,² potentially responsible for failure to secrete an intact immunoglobulin,^{10–13} or the emergence of a predominant subclone from a preexisting MGUS/smoldering MM phase, may explain this HiLC phenotypic fingerprint and its associated inferior outcome.

In consensus with this hypothesis, patients presenting with a HiLC-MP phenotype also had a relatively short PFS, much shorter than that reported in their HiMP counterparts, but have a PFS similar to that in their HiLC counterparts. This worse outcome may not be solely due to the high LC levels themselves, considering the fact that the median LC level in the HiLC-MP group was lower by 2-fold than that reported in the HiLC group, but due to a potentially increased subclonal heterogeneity leading to a HiLC-MP phenotype. The prognostic effect of HiLC and HiLC-MP phenotypes appeared to be most noticeable in nontransplant eligible patients in whom these phenotypes were associated with significantly shorter PFS and OS. Autologous stem cell transplantation, used in younger patients, appeared to overcome at least partly the risk related to this phenotype.

An alternative explanation for the observed phenotypic LC/MP patterns could be myeloma cells with discordant secretion of light vs heavy chains originating from the same subclone. However, considering the significant discrepancies in MP and LC levels characterizing the HiLC cohort, it is unlikely that these phenotypic features have no clonal patterns, which define the fate of the disease and its responsiveness to therapy.

It should be noted that our study has several limitations that extend beyond its retrospective nature; thus, cautious interpretation is advised. First, follow-up time was limited (range, 1–81 months, median 22) suggesting that differences in outcomes and in particular OS might become more pronounced with time. Second, FISH results were incomplete, available only for 167 (65%) of the patients, this may have precluded detection of their association with protein fingerprint. However, previous studies failed to detect an association between FLC levels and cytogenetics¹⁴; LC escape at relapse was found to be as an adverse risk factor independent of adverse FISH.³ Third, our cohort included patients who received a bortezomib-based induction, and further validation is required in independent series and in patients who received different frontline approaches. Last, we demonstrated a survival disadvantage for patients with HiLC; however, these patients, being generally older, also had lower rates of ASCT at first remission. Nevertheless, when evaluating the association between clonal type and survival in the subgroups of patients not receiving HDM, HiLC and HiLC-MP retained their prognostic significance for PFS, and HiLC was marginally significant for shorter OS.

In summary, we identified an LC predominant fingerprint at diagnosis as potential risk factor that may be associated with adverse outcome in NDMM patients treated with bortezomib-based induction therapy. We hypothesize that this pattern reflects clonal evolution, which occurred prior to myeloma clinical presentation and reflects greater clonal heterogeneity. Further studies assessing LC-MP phenotype and its clinical significance prospectively, from MGUS stage to MM development, and accounting fully for baseline and acquired cytogenetic aberrations could strengthen our data and confirm the importance of these findings in clinical practice, as would further studies

using deep sequencing to identify clonal pattern among these phenotypic subgroups.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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