

RESEARCH ARTICLE

Amp 1q21 is more predictable with dismal survival than gain 1q21 of newly diagnosed multiple myeloma in real-world analysis

Yu-tong Wang | Li Bao  | Bin Chu | Xiao-huan Chen | Min-qiu Lu | Lei Shi | Shan Gao | Li-juan Fang | Qiu-qing Xiang | Yue-hua Ding

Department of Hematology, Beijing Jishuitan Hospital, 4th Clinical Medical College of Peking University, Beijing, China

Correspondence

Li Bao, Department of Hematology, Beijing Jishuitan Hospital, 4th Clinical Medical College of Peking University, Beijing 100035, China.
Email: baolilq909@sina.com

Funding information

This work was supported by the Beijing Municipal Excellent Talents Foundation (grant no. 2018000021469G223) and the Beijing JST Research Funding (grant no. ZR-201909 & QN-201908)

Abstract

Introduction: The gain/amplification (amp) of 1q21 is one of the most common high-risk chromosome abnormality (HRCA) in multiple myeloma (MM). The prognostic value of 1q21+ remains to be controversial on the status of gain or amp and the combination of other HRCAs.

Methods: In this retrospective study, we included 318 newly diagnosed MM (NDMM) patients who had fluorescence in situ hybridization (FISH) data and treated with novel agents in our department.

Results: Our study noted MM patients with amp 1q21 were more likely accompanied with t(4;14), t(14;16), and t(14;20). Patients with amp 1q21 presented with elder age, advanced Revised International Staging System (R-ISS) stages, anemia, and more plasma cells in bone marrow compared to patients with gain 1q21 alone and no 1q21+. Moreover, amp 1q21 alone correlated with shorter progression-free survival (PFS) (22.8m vs. 40.5m vs. 39.6m) and overall survival (OS) (45.2m vs. NA vs. 83.5m) compared with gain 1q21 alone and no FISH abnormalities. Although the high ratio of proteasome inhibitor and immunomodulatory drugs used in patients with amp 1q21, the overall response (ORR) was the lowest compared with no 1q21+ and gain 1q21. Multivariate analysis defined amp 1q21 as an independent prognostic marker for NDMM patients, rather than gain 1q21.

Conclusion: The amp 1q21 predict inferior treatment response and survival, especially coexisted with high-risk IgH translocation.

KEYWORDS

Amp 1q21, FISH, high-risk cytogenetic abnormality, multiple myeloma

Yu-tong Wang and Li Bao were the co-first author for this article.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 The Authors. *Journal of Clinical Laboratory Analysis* published by Wiley Periodicals LLC.

1 | INTRODUCTION

Multiple myeloma (MM) is a highly heterogeneous disease.¹ Prognostic factors have been reported, including tumor burden (International Staging System (ISS) stage, lactate dehydrogenase (LDH), etc.),² patient characteristics (age, Eastern Cooperative Oncology Group (ECOG) status, etc.)³ and biological characteristics of the disease (genetics, extramedullary plasmacytoma, etc.).⁴ Above all, cytogenetic and molecular indicators represent biologic underpinnings of MM and have been reported to be significantly associated with treatment response and survival.⁴ The chromosomal 1 abnormality, gain (3 copy numbers) 1q21, or amplification (at least 4 copy numbers) 1q21 were demonstrated occurred in 30%–50% of patients with newly diagnosed MM (NDMM)⁵ and brought about dispute on its prognostic value. A lot of studies found the gain 1q21 was an independent adverse prognosis marker for overall survival (OS), even in the era of proteasome inhibitor (PIs) and immunomodulatory drugs (IMiDs).^{6–8} In contrast, some researches demonstrated that gain 1q21 had adverse effect on survival but not an independent parameter.^{9,10} The disparate conclusion maybe due to the status of gain 1q21 or amp 1q21, high-risk chromosome abnormality (HRCA) accompanied and diverse clinical trials relied on.

The amp 1q21 had profound adverse effect compared with gain 1q21,⁷ while other researches have shown the similar characteristic and survival of patients with gain 1q21 and amp 1q21.¹¹ According to the clone heterogeneity of MM, 1q21+ were more likely accompanied with other HRCAs, including t(4;14), t(14;16), t(14;20), del(1p), and del(13q).^{11,12} Previous studies have demonstrated that only amp 1q21 with additional HRCAs was negative predictor for newly diagnosed MM (NDMM) treated with thalidomide.^{13,14} Recent research also defined amp 1q21 as a parameter of double hit in era of new drugs.¹⁵ The converse prognostic significance of gain 1q21 and the various combination remains ambiguity. Moreover, The Revised International Staging System (R-ISS) excluded gain 1q21 of HRCAs,² while the consensus of the International Myeloma Working Group (IMWG)¹⁶ and the Mayo Clinic enlarged the HRCAs with gain 1q21,^{4,17} highlighting the need to elucidate the values of copy number, delineate the optimal combination for prognosis, and validate its adverse survival impact in real life.

In the present study, we retrospectively analyzed 318 patients with FISH results who had been hospitalized at our department in the past 7 years. We tried to illustrate the impact of gain 1q21, amp 1q21, and the combination of other HRCAs in NDMM treated with bortezomib-based regimen.

2 | MATERIALS AND METHODS

2.1 | Clinical data of patients

A total of 318 consecutive patients with newly diagnosed MM (NDMM) at the Department of Hematology, Beijing Jishuitan Hospital from March 2013 to March 2021 were enrolled in this

retrospective study. The clinical data in this study were obtained through our electronic medical record system. All of these study procedures were performed in accordance with the Declaration of Helsinki and approved by the ethics committee of our hospital (202005-18). Written informed consent was obtained from each patient prior to data collection and analysis. The diagnosis, ISS stage, R-ISS stage, and treatment and response evaluation of MM patients were performed according to the International Myeloma Working Group (IMWG) consensus.¹ The overall response (ORR) was included complete response (CR), very good partial response (VGPR), and partial response (PR). The other response included minor response (MR), stable disease (SD), and progression disease (PD). Patients who get PR and above response might underwent the upfront autologous stem cell transplantation (ASCT). The general and disease information of these patients is described in Table 1. We followed these patients from diagnosis until the end of this study, unless death or withdrawal occurred. The median follow-up was 27.8 m.

2.2 | Interphase fluorescence in situ hybridization (iFISH) analysis and HRCA definition

iFISH was performed according to standard protocols according to the manufacturer's instructions using CD38 positive selected bone marrow samples.¹⁸ The probes used in this study included GSP P53/CSP17(17p13), GSP D13S319(13q14), GSP RB1(13q14), GSP 1q21, GSP CCND1/IGH(11q22/14q32), GSP FGFR3/IGH (4p16/14q32), GSP MAF/IGH (14q32/16q23), and GSP MAFB/IGH (14q32/20q21) (LBP Medicine Science and Technology) to detect del(17p), del(13q), gain or amp 1q21, t(11;14), t(4;14), t(14;16), and t(14;20), respectively. Two hundred nuclei were analyzed for each probe with a 100× objective fluorescence microscope (BX51, Olympus) with single and triple emission filters. iFISH results were described according to the standards of the International System for Human Cytogenetic Nomenclature (ISCN) 2016.¹⁸ We considered patients who had three signals more than the threshold of 1q21 as having gain 1q21 and four or more signals as amp 1q21. The cutoff points were 8.0% for del(17p) and 5.0% for the remaining positive values (established by our laboratory based on the mean of 15 normal controls \pm 3 standard deviations).

The R-ISS combined the ISS and HRCAs by FISH, including del(17p), t(4;14), t(14;16), and elevated LDH levels. In addition to the HRCAs defined by the R-ISS, gain 1q21 and t(14;20) were also classified as HRCAs by the latest IMWG guidelines for risk stratification in NDMM.¹⁶ Moreover, the copy number of 1q21 was used to define the gain 1q21 (3 copies) and amp 1q21 (>3 copies). As some reports confirmed that del(17p) frequently cooccurred with *TP53* mutations,^{19,20} we defined patients with both del(17p) and *TP53* mutations as having one HRCA. The *TP53* mutation was detected by next-generation DNA sequencing (NGS). Translocation t(11;14) was not identified as a poor prognostic factor by IMWG.¹⁶

2.3 | Statistical analysis

The primary end point was progression-free survival (PFS), defined as the period from initial diagnosis to disease progression or death prior to progression that was related to the disease. The period from the initial diagnosis to the last follow-up date or death was defined as OS. The median values and ranges are reported for continuous variables, and proportions are reported for categorical variables. Although 75 years was defined as the cutoff for elderly MM by the IMWG,²¹ patients ≥ 65 years old were not candidates for autologous hematopoietic stem transplantation and showed poor PFS and OS compared with patients younger than 65.²² Accordingly, an arbitrary age cutoff of 65 years was used to define the elderly patient population. Shapiro–Wilk tests were used to estimate the normality of the distribution of parameters. Variables with a normal distribution were analyzed with a two-sided t test. Neither the values of LDH nor plasma cells in BM were normally distributed. The comparison of different cytogenetic abnormality (CA) risk groups was conducted by Mann–Whitney *U* nonparametric tests. Stepwise Cox regression was performed to select significant covariates for PFS and OS and estimate hazard ratios (HRs) and 95% confidence intervals (CIs). All procedures were performed using a statistical package (SPSS 20.0, SPSS, Inc.), with a two-sided *P* value less than 0.05 regarded as significant.

3 | RESULTS

3.1 | Baseline characteristics of patients with gain 1q21 or amp 1q21

According to whether accompanied with gain or amp 1q21, the clinical feature of three groups is shown in Table 1. There was no difference among the three groups in regard to sex, ISS stage, LDH, renal function, treatment modality in first-line therapy, and upfront ASCT. Compared to patients with no gain/amp 1q21, patients with gain/amp 1q21 were older and had more advanced clinical stages based on R-ISS ($p = 0.003$) and significantly higher level of BM plasma cells ($p = 0.002$). The results showed that gain/amp 1q21 was related to the advanced age and progressive disease. Notably, patients with amp 1q21 were more likely accompanied with anemia (81.7%) and few had chance to receive ASCT post first remission (4.2%). The advanced age, couldnot achieve deeper response and suffered early progress disease (PD) of this group, are the probably limits of upfront ASCT.

3.2 | Amp 1q21 more likely combined with HRCAs

As shown in Table 1, amp 1q21 more likely combined with t(14;16), t(14;20), and t(4;14) compared with gain 1q21 and no 1q21+ while the t(11;14) and del 17p/TP53 mutation were comparable. The MAF/IGH and MAFB/IGH were only detected companied with

amp 1q21 ($p = 0.00$). The details of accompanied parameters are depicted in Figure 1. In contrast with no 1q21+ group, we found patients with gain and amp 1q21 more tended to have other CAs (26.94% vs. 42.86% vs. 39.44%, $p = 0.043$). The subgroup analysis of HRCAs showed that amp 1q21 more likely accompanied with HRCAs including t(4;14), del 17p/TP53 mutation, t(14;16), and t(14;20) compared with gain 1q21 and no 1q21+ patients (32.41% vs. 28.57% vs. 18.26%, $p = 0.025$). Patients with two or three HRCAs except 1q21+ were more common in amp 1q21 groups than gain 1q21 and no 1q21+ (4.23% vs. 0 vs. 0.46%, $p = 0.039$).

3.3 | Amp 1q21 correlated with short survival in NDMM patients

The median PFS of patients without 1q21+, gain 1q21 and amp 1q21 were 38.2 months, 19.5 months, and 20.9 months ($p = 0.004$), while the OS of these three subgroups were 71.3 months, 32.6 months, and 45.2 months ($p = 0.008$), respectively (Table 1). The further analysis eliminated patients cooccurrence with other CA and presented in Figure 2. Patients with amp 1q21 alone encountered significantly shorter PFS compared with gain 1q21 and negative group (22.8m vs. 40.5m vs. 39.6m). There was a trend of poor prognostic of amp 1q21 on OS (45.2m vs. NA vs. 83.5m). The survival analysis revealed amp 1q21 alone significant affect survival, rather than gain 1q21 alone. The shorter survival of gain 1q21 group may related to the coexist of del 17p/ TP53 mutation.

Multivariate analysis showed only the ASCT ($p = 0.003$), amp 1q21 ($p = 0.002$) and del 17p/TP53 mutation ($p = 0.005$) were identified as independent adverse prognostic factors for PFS, suggesting the amp 1q21 was more powerful in recognized early relapse in the era of PI and IMiDs. For OS, the remaining prognostic variates after multivariate Cox regression analysis included age ≥ 65 ($p = 0.023$), elevated LDH ($p = 0.001$), ASCT ($p = 0.023$), amp 1q21 ($p = 0.038$) and del(17p)/TP53 mutation ($p < 0.001$). Above all, amp 1q21 was a negative predictor for NDMM patients (Table 2).

3.4 | Amp 1q21 coexisted with other HRCAs predicted inferior survival

The further explorations of amp 1q21 with or without other CAs were displayed in Figure 3. There was no difference between amp 1q21, t(11;14) and amp 1q21 with t(11;14). The amp 1q21 combined with del 17p/TP53 mutation exhibited shorter OS compared with amp 1q21 alone ($p = 0.007$). Meanwhile, The analysis of amp 1q21 and high-risk (HR) IgH translocation including t(4;14), t(14;16), and t(14;20) showed negative effect on PFS compared with amp 1q21 ($p = 0.0427$) and HR IgH translocation (0.0453) alone. The OS were comparable between amp 1q21 alone and combined with HR IgH translocation while both shorter than HR IgH translocation alone ($p = 0.0386$ and $p = 0.0085$, respectively).

TABLE 1 Demographic and MM clinical characteristics of patients

	No Gain/Amp 1q21 (N = 219)	Gain 1q21 (N = 28)	Amp 1q21 (N = 71)	<i>p</i> value
Age (years)	60 (27–85)	63 (46–88)	64 (37–79)	0.005
Gender (male/female)	122/97	11/17	35/36	0.209
ISS stage				
Stage I	83 (37.9%)	8 (28.6%)	19 (26.8%)	0.260
Stage II	57 (26%)	8 (28.6%)	25 (35.2%)	
Stage III	79 (36.1%)	12 (42.8%)	27 (38%)	
RISS stage				
Stage I	66 (30.1%)	7 (25%)	12 (16.9%)	0.003
Stage II	123 (56.2%)	16 (57.1%)	45 (63.4%)	
Stage III	30 (13.7%)	5 (17.9%)	14 (19.7%)	
LDH (IU/L)	172(78–797)	175 (77–346)	179 (83–2048)	0.425
Anemia	134 (61.2%)	18 (64.3%)	58 (81.7%)	0.037
Renal insufficiency	32 (14.6%)	2 (7.1%)	5 (7%)	0.368
Plasma cells in BM (%)	22 (0–98)	39 (4–80)	35 (3–90)	0.002
First line treatment				
PI and IM	9 (4.1%)	3 (10.7%)	13 (18.3%)	0.962
PI-based	167 (76.3%)	21 (75%)	51 (71.8%)	
IM-based	26 (11.9%)	2 (7.2%)	4 (5.6%)	
Traditional chemotherapy	14 (6.4%)	1 (3.6%)	2 (2.8%)	
Upfront ASCT	45 (20.5%)	7 (25%)	3 (4.2%)	0.057
PFS (months)	38.2 (29.8–46.7)	19.5 (15.7–23.2)	20.9 (14.1–27.6)	0.004
OS (months)	71.3 (52.3–90.4)	32.6 (26.8–38.4)	45.2 (30.2–60.2)	0.008
FISH (percentage)				
CCND1/IGH	24 (10.9%)	5 (17.8%)	8 (11.3%)	0.561
Del 17p/ P53 mutation	32 (14.6%)	8 (28.6%)	11 (15.5%)	0.165
MAF/IGH, MAFB/ IGH	0	0	4 (5.6%)	0.0001
FGFR3/IGH	8 (3.7%)	0	11 (15.5%)	<0.0001

Abbreviations: ASCT, autologous peripheral stem cell transplantation; BD-PACE, bortezomib, dexamethasone, platinum, adriamycin, cyclophosphamide, etoposide; BM, bone marrow; IM, immune-modulator; ISS, international staging system; LDH, lactate dehydrogenase; MM, multiple myeloma; OS, overall survival; PFS, progression free survival; PI, proteasome inhibitor; RISS, revised international staging system.

Bold indicates *P* values less than 0.05.

3.5 | Decreased effectiveness of treatment in NDMM with Amp 1q21

In regard to treatment, the first-line therapy was mainly proteasome inhibitors. For economic reasons, sixteen patients accepted a traditional regimen of melphalan-based. More patients received PI and IMiD-based therapy in NDMM with amp 1q21 compared with no 1q21 and gain 1q21 (18.3% vs. 10.7% vs. 4.1%). As shown in Figure 4, patients with amp 1q21 received lower ORR (75.8% vs. 80.9% vs. 100%), although the differences in changes were not always statistically significant. Only three patients with amp 1q21 received upfront ASCT, according to the elder age and poor response to therapy.

4 | DISCUSSION

This cross-sectional study was conducted to explore the predictive values of gain 1q21, amp 1q21, and the combination of 1q21+ with other CAs of NDMM patients in a real-world sample in China. Sixty-four NDMM patients also received NGS detection in this cohort. Our findings suggested that only amp 1q21 was an independent prognostic marker for NDMM patients. The long-term follow-up indicated combination of amp 1q21 with other HRCAs conferred worst prognosis on survival, while other single HRCAs none but del 17p/TP53 mutation appeared adverse effect on outcomes.

The gain/amp 1q21 was detected in 31.1% (99/318) NDMM patients in our cohort, in accordance with previous study.^{5,23}

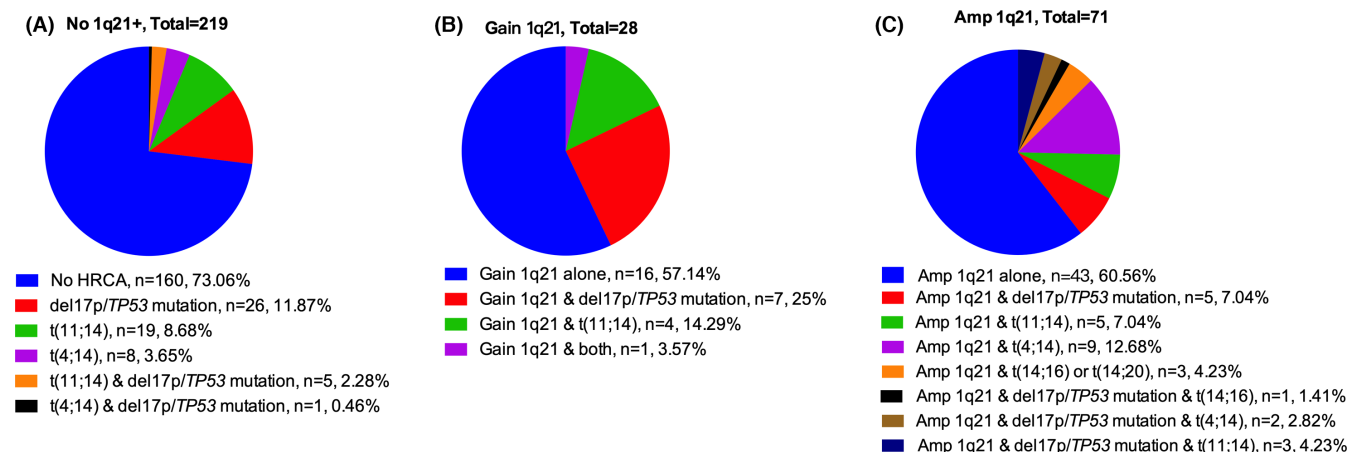


FIGURE 1 Coexisted of HRCA in no 1q21+ (A), gain 1q21 (B) and amp 1q21 (C)

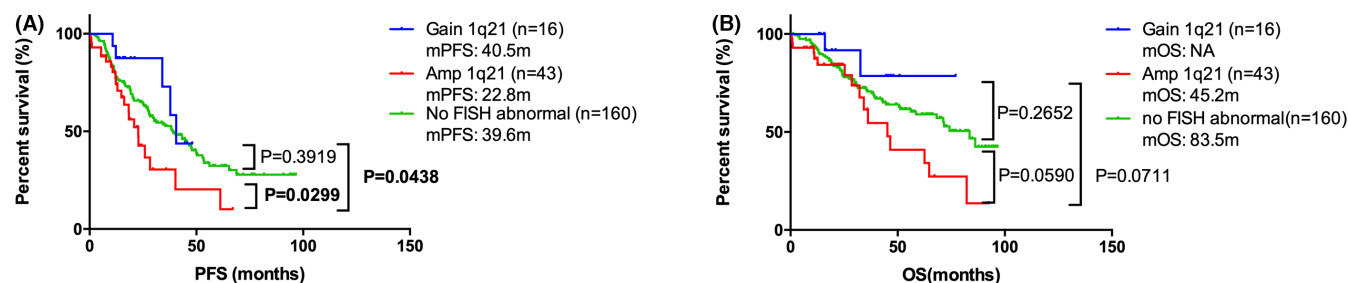


FIGURE 2 Kaplan-Meier analysis of no FISH abnormal, only gain 1q21 and only amp 1q21 for PFS (A) and OS (B)

Additionally, the amp 1q21 was more common with unfavorable IgH translocation. It worth noting that t(14;16) and t(14;20) were only existed in patients with amp 1q21. Meanwhile, gain 1q21 was more likely combined with del 17p. This clinical finding supported Arkansas's conclusion which 1q21+ had impact on secondary chromosomal abnormalities of del 17p.²⁴ Recent cohort study from Mayo Clinic including 1376 patients reported 28% with 1q21+ and associated with t(4;14), t(14;16), and t(14;20), none of del 17p.⁶ Report from China identified a significant relationship of gain 1q21 with del 13, t(4;14), and complex karyotype.²⁵ Our data were in line with Mayo which only displayed in amp 1q21. The relationship between amp 1q21 and other HRCA revealed the complicated genetic alteration and discriminated clearly unfavorable prognosis. Meanwhile, we showed that amp 1q21 was no surprisingly associated with aggressive disease, including elder age, advanced RISS stage, anemia, and high ratio of plasma in BM. The other meta-analysis of 2596 trial patients also came to the same result.²⁶

The adverse prognostic of gain/amp 1q21 for NDMM was first reported in the Total Therapy 2 (TT2) trail (tandem ASCT +/- thalidomide), whether adding thalidomide or not.²⁷ We found the amp 1q21 alone correlated with shorter PFS compared with gain 1q21 and no HRCA, while be an independent biomarker in multivariate analysis. The gain 1q21 failed to be a predictor of survival. The prognostic value remains controversial of gain 1q21 and amp 1q21. Recent studies reported the poor prognosis of gain/amp 1q21 on survival.^{5,6} Patients with gain 1q21 and amp 1q21 showed similar

survivals as reported in the real-world study from China.^{11,25} The other study with 201 NDMM patients received VRD induction, suggested the shorter survival of amp 1q21 compared with gain 1q21.⁷ A well-known double-hit model defined by Walker et al including amp 1q21 on the background of ISS-IIIand bi-allelic TP53 inactivated mutation which predicted poor PFS (15.4 months) and OS (20.6 months).¹⁵ The gain 1q21 was excluded in this definition as they found no difference survival with 1q21+ negative.¹⁵ The paradox results of 1q21 status might due to the different cohort and treatment regimens. Another possible explanation might be the copy numbers of oncogene on 1q21, including CKS1B, ILF2, MCL1, and IL-6R.^{28,29} Meanwhile, the combination of amp 1q21 and HR IgH translocation might enhance the risk predictable than amp 1q21 alone.

The analysis of amp 1q21 combined with other CAs showed t(11;14) not improved the shorter survival of amp 1q21, while del 17p/TP53 and HR IgH translocation means inferior survival of amp 1q21. The Mayo Clinic involved gain 1q21 in double-hit model of two HRCA with a shorter OS compared with that of one HRCA and no HRCA NDMM (median 2.7 years vs. 4.9 years vs. 8.3 years).³⁰ Rare report concerned independent 1q21+ combined with other HRCA before as Mayo accounted del 17p and other HRCA despite 1q21+.³⁰ The other study from An et al confessed gain 1q21 and/or del 17p as a high-risk cytogenetic profile while not t(4;14) as PIs overcome its adverse effects.²⁵ The prognostic values of gain/amp 1q21 with various parameters need more clinical data and validated practice.

TABLE 2 Cox regression analysis for PFS and OS

Variables	PFS				OS							
	Univariate		Multivariate		Univariate		Multivariate					
	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value			
Sex	0.96	0.67-1.33	0.821				0.69	0.48-0.98	0.040	0.82	1.07-2.36	0.320
Age ≥ 65	1.33	0.94-1.87	0.104				2.16	1.50-3.11	<0.001	1.59	1.07-2.36	0.023
Anemia	1.87	1.31-2.67	0.001	1.33	0.88-2.00	0.172	2.66	1.62-4.37	<0.001	1.66	0.94-2.54	0.089
ISS II/III	1.34	1.12-1.62	0.001	1.18	0.85-1.63	0.323	1.48	1.19-1.84	<0.001	1.54	0.94-1.59	0.194
Hypercalcemia	1.65	1.09-2.49	0.019	1.34	0.85-2.12	0.213	1.58	1.01-2.50	0.048	1.21	0.73-2.00	0.458
LDH elevated	1.47	0.96-2.45	0.079				2.49	1.63-3.81	<0.001	2.22	1.37-3.59	0.001
Renal insufficiency	1.65	1.09-2.51	0.019	1.01	0.63-1.64	0.953	1.45	0.90-2.32	0.123			
ASCT	0.44	0.27-0.71	0.001	0.46	0.27-0.76	0.003	0.30	0.15-0.59	<0.001	0.42	0.20-0.89	0.023
RB1/DIS319	1.09	0.71-1.69	0.688				1.28	0.79-2.08	0.324			
CCND1/IGH	1.07	0.63-1.83	0.811				0.94	0.50-1.74	0.834			
Gain 1q21	1.41	0.84-2.36	0.198				1.40	0.75-2.61	0.289			
Amp 1q21	1.82	1.28-2.59	0.001	1.78	1.24-2.56	0.002	1.76	1.20-2.59	0.004	1.55	1.02-2.35	0.038
del(17p)/TP53 mutation	1.95	1.29-2.95	0.002	1.82	1.20-2.78	0.005	2.95	1.96-4.43	<0.001	2.83	1.72-4.68	<0.001
MAF/IGH or MAFB/IGH	2.88	1.71-11.71	0.140				3.93	0.96-16.19	0.058			
FGFR3/IGH	1.85	0.97-3.54	0.063				1.57	0.73-3.39	0.252			

Abbreviations: CI, confidence interval; HR, high risk; ISS, international staging system; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression free survival; RISS, revised international staging system.

Bold indicates P values less than 0.05.

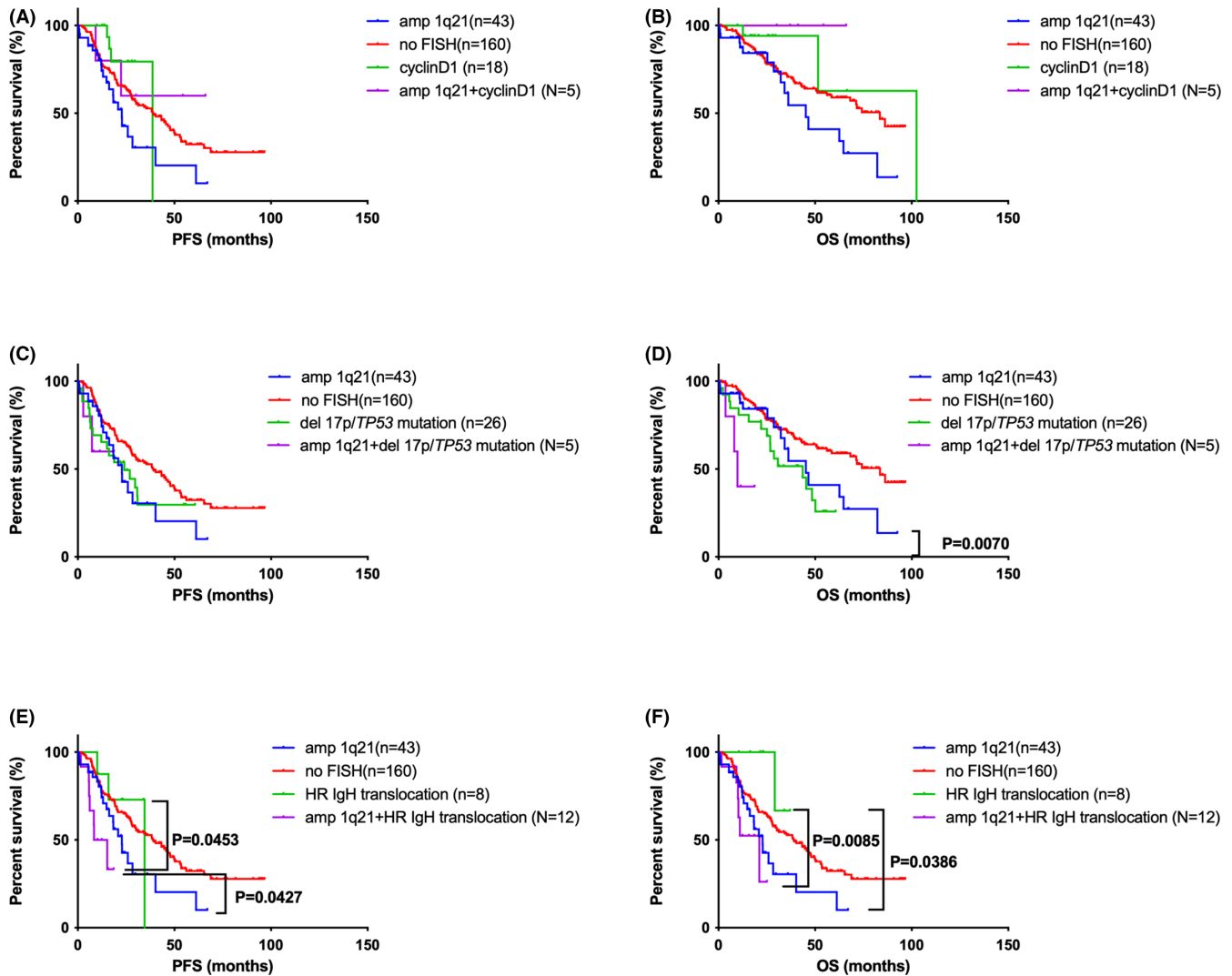


FIGURE 3 Subgroup survival analysis. Comparison of amp 1q21 with or without cyclinD1 for PFS (A) and OS (B), del 17p/TP53 mutation for PFS (C) and OS (D), high-risk (HR) IgH translocation for PFS (E) and OS (F). The p values >0.05 were not displayed in figures

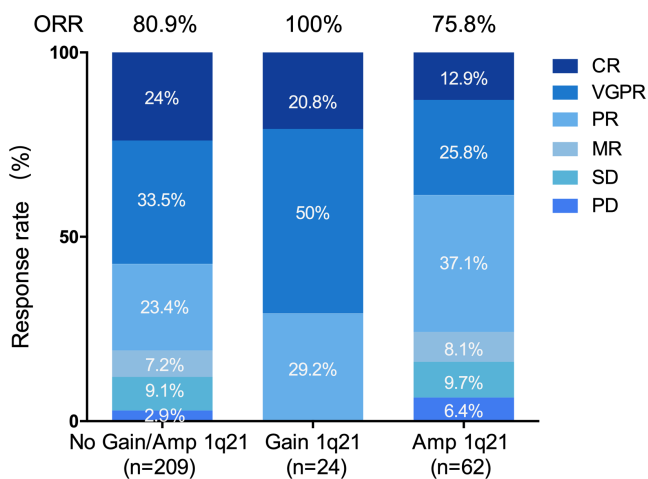


FIGURE 4 Treatment response of patients with no 1q21+, gain 1q21 and amp 1q21

Although the high ratio of PIs plus IMiD-based induction therapy used in patients with Amp 1q21, the ORR was lowest compare with no 1q21+ and gain 1q21. Some prior studies demonstrated that PIs or IMiDs³¹ and even ASCT³² could not overcome the adverse effect of 1q21+. There were no effect of gain 1q21 on the treatment response according to our research. Per the detail of patients with amp 1q21, we found these patients suffered drug resistance and early progression which resulted less opportunity for ASCT. The elder age and combined HRCA might also be the causes of poor response in amp 1q21. Our data came from the era before bortezomib (Velcade, V)+ lenalidomide (Revlimid, R)+ dexamethasone (VRD) induction which demonstrated the PI-based regimen had limitation to conquer the amp 1q21. The new drugs brought ahead in induction treatment might improve the remission and rate of ASCT. A study of another new anti-CD38 monoclonal antibody isatuximab combined with carfilzomib (Kyprolis, K) + RD (KRD) for high-risk NDMM (GMMG-CONCEPT study) enrolled 50 patients and reported a

100% ORR and deep response.³³ The effectiveness of other new drugs, including belantamab mafodotin, iberdomide, venetoclax, and molecular-targeted drugs,³⁴ in patients with amp 1q21 to be validated in further clinical trials.

The limitation of our study was a single-center retrospective analysis. The small numbers of ASCT patients and some subgroup analysis (amp 1q21+cyclinD1, $n = 5$). The regimens of patients were almost PI based as none compared of treatment.

In conclusion, amp 1q21 was characterized with advanced disease and more likely combined with HR IgH translocation. We confirmed the amp 1q21 as an independent adverse predictor for NDMM patients and inferior survival combined with del 17p/TP53 mutation and HR IgH translocation in the era of novel agents.

CONFLICT OF INTEREST

The authors have no conflict of interest.

AUTHOR CONTRIBUTIONS

L.B. designed the study; Y.-T.W. and L.B. analyzed the data and wrote the manuscript; and all authors contributed to the interpretation of the data, prepared the manuscript, and approved the final version.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants, but some of them are available from Li Bao (baolilq909@sina.com).

ORCID

Li Bao  <https://orcid.org/0000-0002-6436-1492>

REFERENCES

- Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol*. 2014;15(12):e538-e548.
- Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised international staging system for multiple myeloma: a report from international myeloma working group. *J Clin Oncol*. 2015;33(26):2863-2869.
- Engelhardt M, Dold SM, Ihorst G, et al. Geriatric assessment in multiple myeloma patients: validation of the International Myeloma Working Group (IMWG) score and comparison with other common comorbidity scores. *Haematologica*. 2016;101(9):1110-1119.
- Rajkumar SV. Multiple myeloma: 2020 update on diagnosis, risk-stratification and management. *Am J Hematol*. 2020;95(5):548-567.
- Hanamura I. Gain/amplification of chromosome arm 1q21 in multiple myeloma. *Cancers*. 2021;13(2).
- Abdallah N, Greipp P, Kapoor P, et al. Clinical characteristics and treatment outcomes of newly diagnosed multiple myeloma with chromosome 1q abnormalities. *Blood Adv*. 2020;4(15):3509-3519.
- Schmidt TM, Barwick BG, Joseph N, et al. Gain of chromosome 1q is associated with early progression in multiple myeloma patients treated with lenalidomide, bortezomib, and dexamethasone. *Blood Cancer J*. 2019;9(12):94.
- Shah V, Sherborne AL, Walker BA, et al. Prediction of outcome in newly diagnosed myeloma: a meta-analysis of the molecular profiles of 1905 trial patients. *Leukemia*. 2018;32(1):102-110.
- Fonseca R, Van Wier SA, Chng WJ, et al. Prognostic value of chromosome 1q21 gain by fluorescent in situ hybridization and increase CKS1B expression in myeloma. *Leukemia*. 2006;20(11):2034-2040.
- Shaughnessy JD, Haessler J, van Rhee F, et al. Testing standard and genetic parameters in 220 patients with multiple myeloma with complete data sets: superiority of molecular genetics. *Br J Haematol*. 2007;137(6):530-536.
- Xu J, Xu T, Yang Y, et al. The paradoxical prognostic role of 1q21 Gain/Amplification in multiple myeloma: every coin has two sides. *Leuk Lymphoma*. 2020;1-14.
- Walker BA, Boyle EM, Wardell CP, et al. Mutational spectrum, copy number changes, and outcome: results of a sequencing study of patients with newly diagnosed myeloma. *J Clin Oncol*. 2015;33(33):3911-3920.
- Grzasko N, Hus M, Chocholska S, Pluta A, Hajek R, Dmoszynska A. 1q21 amplification with additional genetic abnormalities but not isolated 1q21 gain is a negative prognostic factor in newly diagnosed patients with multiple myeloma treated with thalidomide-based regimens. *Leuk Lymphoma*. 2012;53(12):2500-2503.
- Grzasko N, Hus M, Pluta A, et al. Additional genetic abnormalities significantly worsen poor prognosis associated with 1q21 amplification in multiple myeloma patients. *Hematol Oncol*. 2013;31(1):41-48.
- Walker BA, Mavrommatis K, Wardell CP, et al. A high-risk, Double-Hit, group of newly diagnosed myeloma identified by genomic analysis. *Leukemia*. 2019;33(1):159-170.
- Sonneveld P, Avet-Loiseau H, Lonial S, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. *Blood*. 2016;127(24):2955-2962.
- Mikhael JR, Dingli D, Roy V, et al. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines 2013. *Mayo Clin Proc*. 2013;88(4):360-376.
- Daudignon A, Quilichini B, Ameye G, Poiriel H, Bastard C, Terre C. Cytogenetics in the management of multiple myeloma: an update by the Groupe francophone de cytogenetique hematologique (GFCH). *Ann Biol Clin*. 2016;74(5):588-595.
- Chin M, Sive JI, Allen C, et al. Prevalence and timing of TP53 mutations in del(17p) myeloma and effect on survival. *Blood Cancer J*. 2017;7(9):e610.
- Höllein A, Twardziok SO, Walter W, et al. The combination of WGS and RNA-Seq is superior to conventional diagnostic tests in multiple myeloma: ready for prime time? *Cancer Genet*. 2020;242:15-24.
- Palumbo A, Bringhen S, Mateos M-V, et al. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report. *Blood*. 2015;125(13):2068-2074.
- Zanwar S, Abeykoon JP, Kapoor P. Challenges and strategies in the management of multiple myeloma in the elderly population. *Curr Hematol Malig Rep*. 2019;14(2):70-82.
- Rajan AM, Rajkumar SV. Interpretation of cytogenetic results in multiple myeloma for clinical practice. *Blood Cancer J*. 2015;5:e365.
- Sawyer JR, Tian E, Heuck CJ, et al. Jumping translocations of 1q12 in multiple myeloma: a novel mechanism for deletion of 17p in cytogenetically defined high-risk disease. *Blood*. 2014;123(16):2504-2512.
- Du C, Mao X, Xu Y, et al. 1q21 gain but not t(4;14) indicates inferior outcomes in multiple myeloma treated with bortezomib. *Leuk Lymphoma*. 2020;61(5):1201-1210.
- Weinhold N, Salwender HJ, Cairns DA, et al. Chromosome 1q21 abnormalities refine outcome prediction in patients with multiple myeloma—a meta-analysis of 2,596 trial patients. *Haematologica*. 2021;106(10):2754-2758.
- Hanamura I, Stewart JP, Huang Y, et al. Frequent gain of chromosome band 1q21 in plasma-cell dyscrasias detected by fluorescence in situ hybridization: incidence increases from MGUS

- to relapsed myeloma and is related to prognosis and disease progression following tandem stem-cell transplantation. *Blood*. 2006;108(5):1724-1732.
28. Marchesini M, Ogoti Y, Fiorini E, et al. ILF2 Is a regulator of RNA splicing and DNA damage response in 1q21-amplified multiple myeloma. *Cancer Cell*. 2017;32(1):88-100 e106.
 29. Teoh PJ, Chung TH, Chng PYZ, Toh SHM, Chng WJ. IL6R-STAT3-ADAR1 (P150) interplay promotes oncogenicity in multiple myeloma with 1q21 amplification. *Haematologica*. 2020;105(5):1391-1404.
 30. Binder M, Rajkumar SV, Ketterling RP, et al. Prognostic implications of abnormalities of chromosome 13 and the presence of multiple cytogenetic high-risk abnormalities in newly diagnosed multiple myeloma. *Blood Cancer J*. 2017;7(9):e600.
 31. Nahi H, Våtsveen TK, Lund J, et al. Proteasome inhibitors and IMiDs can overcome some high-risk cytogenetics in multiple myeloma but not gain 1q21. *Eur J Haematol*. 2016;96(1):46-54.
 32. Shah GL, Landau H, Londono D, et al. Gain of chromosome 1q portends worse prognosis in multiple myeloma despite novel agent-based induction regimens and autologous transplantation. *Leuk Lymphoma*. 2017;58(8):1823-1831.
 33. Weisel K, Asemissen AM, Besemer B, et al. Depth of response to isatuximab, carfilzomib, lenalidomide, and dexamethasone (Isa-KRd) in front-line treatment of high-risk multiple myeloma: interim analysis of the GMMG-CONCEPT trial. *J Clin Oncol*. 2020;38(15_suppl):8508.
 34. Maples KT, Joseph NS, Harvey RD. Current developments in the combination therapy of relapsed/refractory multiple myeloma. *Expert Rev Anticancer Ther*. 2020;20(12):1021-1035.

How to cite this article: Wang Y-T, Bao L, Chu B, et al. Amp 1q21 is more predictable with dismal survival than gain 1q21 of newly diagnosed multiple myeloma in real-world analysis. *J Clin Lab Anal*. 2022;36:e24375. doi:[10.1002/jcla.24375](https://doi.org/10.1002/jcla.24375)