

1q21 Gain Combined with High-Risk Factors Is a Heterogeneous Prognostic Factor in Newly Diagnosed Multiple Myeloma: A Multicenter Study in China

XIAOZHE LI,^{a,†} WENMING CHEN,^{b,†} YIN WU,^b JIANYONG LI,^c LIJUAN CHEN,^c BAIJUN FANG,^d YING FENG,^e JUNRU LIU,^a MEILAN CHEN,^a JINGLI GU,^a BEIHUI HUANG,^a JUAN LI[✉]

^aDepartment of Hematology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, People's Republic of China;

^bDepartment of Hematology, Beijing Chaoyang Hospital, Beijing, People's Republic of China; ^cDepartment of Hematology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, People's Republic of China; ^dDepartment of Hematology, Henan Cancer Hospital, Zhengzhou, People's Republic of China; ^eDepartment of Hematology, The Second Affiliated Hospital of Guangzhou Medical University, Guangzhou, People's Republic of China

[†]Contributed equally.

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Multiple myeloma • 1q21 gain • High-risk factors • Survival

ABSTRACT

Background. The prognostic value of 1q21 gain in newly diagnosed multiple myeloma (NDMM) remains controversial. Our aim was to investigate the prognostic value of 1q21 gain in a Chinese population.

Materials and Methods. We retrospectively identified 565 patients with NDMM from multiple centers in China.

Results. We detected 1q21 gain in 222 (39.3%) patients, among whom 144 had three copies of 1q21, 57 had four copies of 1q21, and 21 had at least five copies of 1q21. Copy number variation did not show any effect on the disease outcome. Multivariate analysis indicated that 1q21 gain was an independent factor for poor prognosis, but we found that 1q21 gain was strongly associated with other high-risk factors, such as del(17p), t(4;14), t(14;16), lactate dehydrogenase (LDH) level >300 U/L and International Scoring System (ISS) stage II–III ($p < .001$). Further analysis revealed that in

the absence of other high-risk factors, isolated 1q21 gain resulted in similar progression-free survival (PFS; 52.0 vs. 52.8 months, $p = .810$) and overall survival (OS; not reached vs. not reached, $p = .833$); additionally, when present with other high-risk cytogenetic abnormalities or increased LDH levels, 1q21 gain lost its prognostic power. However, the presence of 1q21 gain increased the adverse impact of ISS stage. Furthermore, 1q21 gain predicted poor PFS and OS in patients who received bortezomib-based regimens. Moreover, autologous stem cell transplantation reversed the poor prognosis in patients with 1q21 gain.

Conclusion. Our results show that heterogeneity exists among patients with 1q21 gain and suggest that we should assess the impact of 1q21 gain on prognosis according to different treatment regimens and accompanying high-risk factors. *The Oncologist* 2019;24:e1132–e1140

Implications for Practice: 1q21 gain is one of the most common chromosomal aberrations in multiple myeloma (MM); however, the prognostic value of 1q21 gain remains controversial. This study investigated the prognostic value of 1q21 gain in a Chinese population with newly diagnosed MM. The results showed that heterogeneity exists among patients with 1q21 gain and suggested that the impact of 1q21 gain on prognosis should be assessed according to different treatment regimens and accompanying high-risk factors. These results could help stratify risk in patients with MM and guide treatment decisions.

INTRODUCTION

Multiple myeloma (MM) is characterized by the expansion and accumulation of clonal plasma cells in the bone marrow,

secretion of monoclonal immunoglobulins (Igs), and the presence of osteolytic bone lesions [1]. MM remains an

Correspondence: Juan Li, Ph.D., Department of Hematology, The First Affiliated Hospital of Sun Yat-sen University, No. 58 Zhongshan Er Rd., Guangzhou, Guangdong 510000, People's Republic of China. Telephone: 8620-87332200; e-mail: 13719209240@163.com Received February 14, 2019; accepted for publication July 19, 2019 Received and accepted for publication July 19, 2019; published Online First on August 27, 2019. <http://dx.doi.org/10.1634/theoncologist.2019-0132>

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incurable disease. The course of the disease shows heterogeneity with widely diverging survival times ranging from months to years [2]. Therefore, the identification of prognostic factors of MM is very important. Prognostic factors that have been known for many years, such as lactate dehydrogenase (LDH) level and International Scoring System (ISS) stage, are very useful in predicting patient outcomes [3, 4]. Cytogenetic abnormalities are considered the major novel prognostic factors in patients with newly diagnosed MM (NDMM). The most important cytogenetic abnormalities indicative of poor prognosis are del(17p), t(4;14), and t(14;16) [5–7].

1q21 gain is one of the most common chromosomal aberrations in MM, especially in nonwhite patients [8–10]. 1q21 gain is detected in 30% to 50% of patients with NDMM [11–14]. However, the prognostic value of 1q21 gain in MM remains controversial. Several studies have shown that 1q21 gain is a significant and independent factor for poor prognosis [15], although other studies have failed to confirm this finding [13, 16, 17]. These apparently conflicting results might be explained by the fact that 1q21 gain is frequently accompanied by other classic biological and genetic prognostic factors. For example, del(13q) was previously considered to be an independent prognostic factor, but upon further research, its poor prognostic value was found to be strongly correlated with the presence of t(4;14) and del(17p) [18]. Various studies have shown associations between 1q21 gain and the presence of other abnormalities by fluorescence in situ hybridization (FISH) including t(4;14), as well as other markers of disease burden such as ISS stage III disease and LDH level [18–20]. Therefore, the significance of 1q21 gain in prognosis is heterogeneous, and the prognostic value of 1q21 gain alone and in combination with other high-risk factors needs further analysis. It is also unknown whether the discrepancies in terms of the prognostic value of 1q21 gain are related to the differences in the proportions of patients with more than three copies of 1q21 in each study. In addition, different therapeutic strategies may produce conflicting prognostic results in the presence of 1q21 gain. Treatment strategies for MM have improved in recent decades. Autologous stem cell transplantation (ASCT) and novel therapies, such as thalidomide, lenalidomide, and bortezomib, have reportedly overcome the adverse effects associated with high-risk chromosomal aberrations, such as t(4;14) [21, 22]. Thus, whether novel agents and ASCT affect outcomes for patients with MM with 1q21 gain in China remains unclear.

In the present study, we examined 1q21 gain by interphase FISH in Chinese patients with NDMM from multiple centers. We assessed the prognostic value of 1q21 gain and its impact on prognosis according to different treatment regimens and accompanying high-risk factors. The resultant data could provide useful information for the prognosis and treatment of patients with MM in China.

MATERIALS AND METHODS

Patients

Patients with NDMM treated at the First Affiliated Hospital of Sun Yat-sen University and 12 other hospitals in China between January 1, 2007, and August 1, 2017, were evaluated for inclusion in our retrospective study. All patients

were followed up for mortality and survival until December 31, 2017. Patients were included if FISH had been performed on a pretreatment bone marrow specimen. Demographic and disease characteristics and treatment regimens were extracted from the electronic medical records with approval from review boards from all centers.

Fluorescence in Situ Hybridization

Purity was confirmed by CD38+ and CD138+ phenotypes via flow cytometric analysis. Interphase FISH analysis was accomplished on CD138-purified plasma cells using probes for the detection of numerical aberrations in chromosomal regions 1q21, 17p13, t(4;14)(p16.3;q32), and t(14;16)(q32;q23). We scored 200 nuclei for each probe and estimated the positive results based on the following European Myeloma Network recommendations: more than 20% of nuclei with at least three copies of 1q21 represented a gain [23].

Response Evaluation

Patients were treated with different induction regimens, and some patients received ASCT. All MM treatments were classified as ASCT or non-ASCT or conventional; immunomodulator-based (thalidomide or lenalidomide); bortezomib-based; or bortezomib, thalidomide, and dexamethasone (VTD) or bortezomib, lenalidomide, and dexamethasone (VRD) regimens. Outcome measures included response to treatment, overall survival (OS), and progression-free survival (PFS). Response to treatment was defined according to the International Myeloma Working Group uniform response criteria [24]. OS was calculated from the beginning of treatment until death or last follow-up. PFS was defined as the time elapsed between treatment initiation and tumor progression or death from any cause.

Statistical Analysis

Statistical analysis was conducted using SPSS 22.0 software (SPSS, Chicago, IL). Differences in response rates and associations between 1q21 gain and other clinical characteristics were examined by Pearson's chi-square tests. PFS and OS analyses were performed using the Kaplan-Meier method, and the log-rank test was used to analyze the differences between survival curves. Multivariate Cox proportional hazards regression analyses were used to evaluate the prognostic impact based on hazard ratios and 95% confidence intervals. A value of $p < .05$ indicated statistical significance, and all tests were two-sided.

RESULTS

Patient Characteristics

The clinical data and biological characteristics of 565 patients with NDMM are summarized in Table 1. The median age was 59 (30–85) years, and the male-to-female ratio was 1.35 (325/240). The M-protein types found were IgG in 291, IgA in 118, IgD in 17, light chain in 132, and others including non-secretory and IgM in 7 patients. According to ISS stages, 143 patients had stage I disease, 195 had stage II disease, and 227 had stage III disease. Patients had a high disease burden with a median bone marrow plasmacytosis of 26% (range, 2%–95%), a median hemoglobin level of 89.0 g/L

Table 1. Patient characteristics

Characteristics	Number of patients, n (%) or median (range)
Sex, n (%)	
Male	325 (57.5)
Female	240 (42.5)
Age, median (range), years	59 (30–85)
Monoclonal protein type, n (%)	
IgG	291 (51.5)
IgA	118 (20.9)
IgD	17 (3.0)
Light chain disease	132 (23.4)
Others	7 (1.2)
ISS stage, n (%)	
I	143 (25.3)
II	195 (34.5)
III	227 (40.2)
Hemoglobin, median (range), g/L	89.0 (31.9–169.0)
Lactate dehydrogenase, median (range), U/L	172.0 (70.0–1,356.0)
Bone marrow plasmacytosis, median (range), %	26 (2–95)
Renal function stage, n (%)	
A	433 (76.6)
B	132 (23.4)
First-line therapy, n (%)	
Conventional	60 (10.6)
Immunomodulator-based	73 (12.9)
Bortezomib-based	414 (73.3)
VTD or VRD	18 (3.2)
ASCT, n (%)	
Yes	169 (29.9)
No	396 (70.1)
Incidence of 1q21 gain, n (%)	
All patients	222 (39.3)
Isolated	137 (24.2)
With del(17p)	29 (5.1)
With t(4;14)	58 (10.3)
With t(14;16)	19 (3.4)
Incidence of del(17p), n (%)	59 (10.4)
Incidence of t(4;14), n (%)	88 (15.6)
Incidence of t(14;16), n (%)	21 (3.7)

Abbreviations: ASCT, autologous stem cell transplantation; ISS, International Scoring System; VRD, bortezomib, lenalidomide, and dexamethasone; VTD, bortezomib, thalidomide, and dexamethasone.

(range, 31.9–169.0 g/L), and an LDH level of 172.0 U/L (range, 70.0–1,356.0 U/L; the upper limit of normal for LDH is 240 U/L).

Among all patients, 414 (73.3%) were treated with bortezomib-based regimens, 60 (10.6%) with conventional therapy, 73 (12.9%) with immunomodulator-based regimens,

18 (3.2%) with VTD/VRD regimens, and 169 (29.9%) with ASCT. All patients undergoing ASCT were treated with bortezomib-based inductions. The median follow-up duration for all patients was 23.8 (0.5–129.5) months.

Overall, 1q21 gain was detected in 39.3% (222/565) of patients with NDMM; 144 had three copies of 1q21 (25.5%), 57 had four copies of 1q21 (10.1%), and 21 had at least five copies of 1q21 (3.7%); del(17) was detected in 10.4% (59/565) of patients; and t(4;14) and t(14;16) were detected in 15.6% (88/565) and 3.7% (21/565) of patients, respectively. Furthermore, 1q21 gain was combined with del(17p) in 29 (5.1%) patients, with t(4;14) in 58 (10.3%) patients and with t(14;16) in 19 (3.4%) patients (Table 1).

Association Between 1q21 Gain and Clinical and Genetic Parameters

Patients were separated into two cohorts based on the presence or absence of 1q21 gain. The results are summarized in Table 2. The majority of 1q21 gain-positive patients had stage II or III disease (83.3%), in contrast to 1q21 gain-negative patients, who mostly had ISS stage I disease (30.9%; $p < .001$). LDH levels >300 U/L were more common in 1q21 gain-positive patients (15.8 vs. 7.6%, $p = .002$). There was a trend toward differences between 1q21 gain-positive and 1q21 gain-negative patients in bone marrow plasmacytosis (33 vs. 24%, $p < .001$). Patients with 1q21 gain had significantly lower hemoglobin levels (<100 g/L) than patients without 1q21 gain ($p = .006$). The other disease characteristics were similar between the two groups (Table 2). Some of the common high-risk cytogenetic abnormalities in MM are del(17p), t(4;14), and t(14;16). A significant correlation was observed between 1q21 gain and the presence of high-risk cytogenetic abnormalities. High-risk cytogenetic abnormalities were present in 38.3% (85/222) of patients with 1q21 gain and in 16.6% (57/343) of patients without 1q21 gain ($p < .001$). We identified the following as high-risk factors: increased LDH level, ISS stage II–III disease, and presence of high-risk cytogenetic abnormalities. The data showed that high-risk factors were strongly associated with 1q21 gain ($p < .001$).

Response to Treatment

Responses to initial therapy were similar between patients with and without 1q21 gain. For patients with 1q21 gain, the responses were complete response (CR) in 25.6% and very good partial response (VGPR) in 35.4% of patients, and for patients without 1q21 gain, the responses were CR 34.0% and VGPR 33.0%. No significant differences in response were observed between the groups ($p = .079$).

Survival

With a median follow-up of 23.8 months (range, 0.5–129.5 months), the median PFS estimated by the Kaplan-Meier method was 39.4 months for the group of 343 patients without 1q21 gain and 28.6 months for the group of 222 patients with 1q21 gain ($p < .001$; Fig. 1). Multivariate analysis was performed for the following six covariates: ISS stage, LDH level, 1q21 gain, t(14;16), del(17p), and t(4;14) (Table 3). The data confirmed 1q21 gain as being independently associated with shorter PFS ($p = .042$); 114 (20.2%) patients died by the time the final analysis was performed. The median OS

Table 2. Baseline clinical and biological characteristics of the analyzed patients with multiple myeloma

Characteristics	1q21 gain-positive (n = 222), n (%)	1q21 gain-negative (n = 343), n (%)	p value
Sex			.565
Male	131 (59.0)	194 (56.6)	
Female	91 (41.0)	149 (43.3)	
Age			.551
>65 years	58 (26.1)	82 (23.9)	
≤65 years	164 (73.9)	261 (76.1)	
Monoclonal protein type			.429
IgG	116 (52.3)	175 (51.0)	
IgA	53 (23.9)	65 (19.0)	
IgD	5 (2.3)	12 (3.5)	
Light chain disease	45 (20.3)	87 (25.4)	
Other	3 (1.4)	4 (1.2)	
ISS stage			<.001
I	37 (16.7)	106 (30.9)	
II–III	185 (83.3)	237 (69.1)	
Bone marrow plasmacytosis, mean (range), %	33 (2–92)	24 (2–95)	<.001
Renal function stage			.664
A	168 (75.7)	265 (77.3)	
B	54 (24.3)	78 (22.7)	
Hemoglobin			.006
>100 g/L	60 (27.0)	131 (38.2)	
≤100 g/L	162 (73.0)	212 (61.8)	
Lactate dehydrogenase			.002
>300 U/L	35 (15.8)	26 (7.6)	
≤300 U/L	187 (84.2)	317 (92.4)	
Calcium			.623
>2.8 μmol/L	31 (14.0)	43 (12.5)	
≤2.8 μmol/L	191 (86.0)	300 (87.5)	
HBsAg			.409
Negative	212 (95.5)	322 (93.9)	
Positive	10 (4.5)	21 (6.1)	
High-risk cytogenetic abnormalities (del(17p), t(4;14), or t(14;16))			<.001
Negative	137 (61.7)	286 (83.4)	
Positive	85 (38.3)	57 (16.6)	
Induction			.369
Bortezomib-based	156 (70.3)	258 (75.2)	
Immunomodulator-based	35 (15.8)	38 (11.1)	
Conventional	25 (11.3)	35 (10.2)	
VTD or VRD	6 (2.7)	12 (3.5)	
ASCT			.077
Yes	57 (25.7)	112 (32.7)	
No	165 (74.3)	231 (67.3)	

Abbreviations: ASCT, autologous stem cell transplantation; HBsAg, hepatitis B surface antigen; ISS, International Scoring System; VRD, bortezomib, lenalidomide, and dexamethasone; VTD, bortezomib, thalidomide, and dexamethasone.

estimated by the Kaplan-Meier method for the total group of 565 patients was 42.3 months. The median OS was not reached for the group of 343 patients without 1q21 gain and

was 53.0 months for the group of 222 patients with 1q21 gain ($p < .001$; Fig. 1). Similar to PFS, multivariate analysis was performed for the following five covariates: ISS stage,

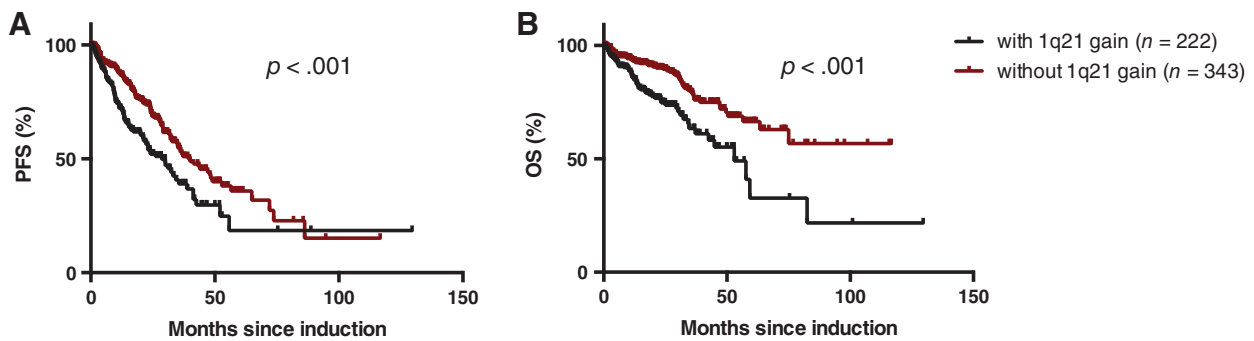


Figure 1. Impact of 1q21 gain on survival after induction therapy. **(A):** Progression-free survival. **(B):** Overall survival. Abbreviations: OS, overall survival; PFS, progression-free survival.

Table 3. Univariate and multivariate analyses of PFS and OS from induction

Covariates	Univariate		Multivariate	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
PFS				
ISS stage II–III disease	1.609 (1.168–2.216)	.004	1.413 (1.019–1.959)	.038
LDH level >300 U/L	1.833 (1.231–2.729)	.003	1.774 (1.180–2.668)	.006
With 1q21 gain	1.672 (1.282–2.183)	<.001	1.342 (1.010–1.783)	.042
With t(4;14)	2.222 (1.595–3.096)	<.001	1.795 (1.259–2.558)	.001
With t(14;16)	1.992 (1.082–3.663)	.045	1.264 (0.672–2.381)	.466
With del(17p)	2.469 (1.686–3.610)	<.001	2.092 (1.410–3.106)	<.001
OS				
ISS stage II–III disease	1.584 (1.012–2.481)	.044	1.288 (0.813–2.040)	.280
LDH level >300 U/L	2.379 (1.450–3.905)	.001	2.068 (1.243–3.442)	.005
With 1q21 gain	2.119 (1.462–3.067)	<.001	1.721 (1.163–2.551)	.007
With t(4;14)	2.283 (1.443–3.610)	<.001	1.613 (0.982–2.646)	.059
With del(17p)	3.125 (1.953–5.025)	<.001	1.065 (1.555–4.167)	<.001

Abbreviations: CI, confidence interval; HR, hazard ratio; ISS, International Scoring System; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival.

LDH level, 1q21 gain, del(17p), and t(4;14). Among these factors, 1q21 gain was significantly associated with OS by multivariate analysis ($p = .007$; Table 3).

Further investigation of the impact of copy number variation on survival indicated that the median PFS times of patients who had three, four, or at least five copies of 1q21 were 30.0 months, 26.0 months, and 21.1 months, respectively. The median OS of patients who had three copies of 1q21 was 53.0 months, whereas the OS times of patients with four copies or at least five copies were not obtained; no statistically significant differences were found (PFS, $p = .750$; OS, $p = .745$; Fig. 2). When the patients with four and at least five copies were analyzed as a whole, as one group of patients with at least four copies, patients with at least four copies of 1q21 also exhibited a comparable PFS (21.1 months vs. 30.0 months, $p = .673$) and OS (not reached vs. 53.0 months, $p = .800$), compared with patients harboring three copies of 1q21.

Prognostic Value of 1q21 Gain in Combination with Other High-Risk Factors

The median PFS for patients with 1q21 gain without other high-risk factors was 52.0 months and that for patients without 1q21 gain or other high-risk factors was 52.8 months

($p = .810$). Patients with 1q21 gain and high-risk cytogenetic abnormalities had a median PFS of 14.0 months, and patients without 1q21 gain or high-risk cytogenetic abnormalities had a median PFS of 23.5 months ($p = .108$); the difference was not statistically significant. The presence of high-risk cytogenetic abnormalities both with and without 1q21 gain resulted in shorter PFS than the presence of 1q21 gain without other high-risk factors ($p = .001$ and $p = .011$, respectively). Similar to PFS, the median OS was not reached either for patients with 1q21 gain without other high-risk factors or for patients without 1q21 gain without other high-risk factors (not reached vs. not reached, $p = .833$). Patients with 1q21 gain with high-risk cytogenetic abnormalities had a median OS of 59.3 months, and patients without 1q21 gain with high-risk cytogenetic abnormalities had a median OS of 36.6 months ($p = .117$); the difference was not statistically significant. Additionally, the presence of high-risk cytogenetic abnormalities both with and without 1q21 gain resulted in shorter OS than the presence of 1q21 gain without other high-risk factors ($p = .002$ and $p = .015$, respectively).

Similar results were observed for LDH levels. Patients with 1q21 gain with LDH levels >300 U/L had a median PFS of 20.0 months, and patients without 1q21 gain with LDH

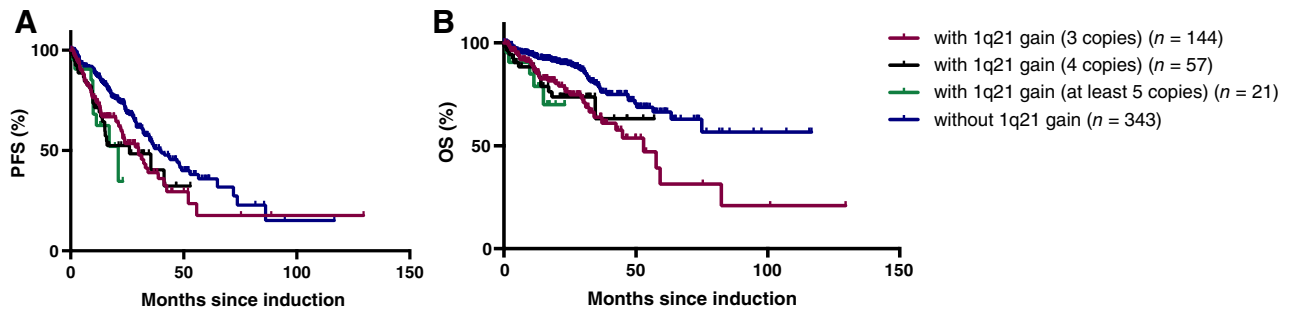


Figure 2. PFS and OS among patients with newly diagnosed multiple myeloma plotted against copy numbers of 1q21. **(A):** Progression-free survival. **(B):** Overall survival. No difference was seen among patients with three, four, or at least five copies of 1q21. Patients with three, four, or at least five copies of 1q21 resulted in shorter PFS and OS than the patients without 1q21 gain. Abbreviations: OS, overall survival; PFS, progression-free survival.

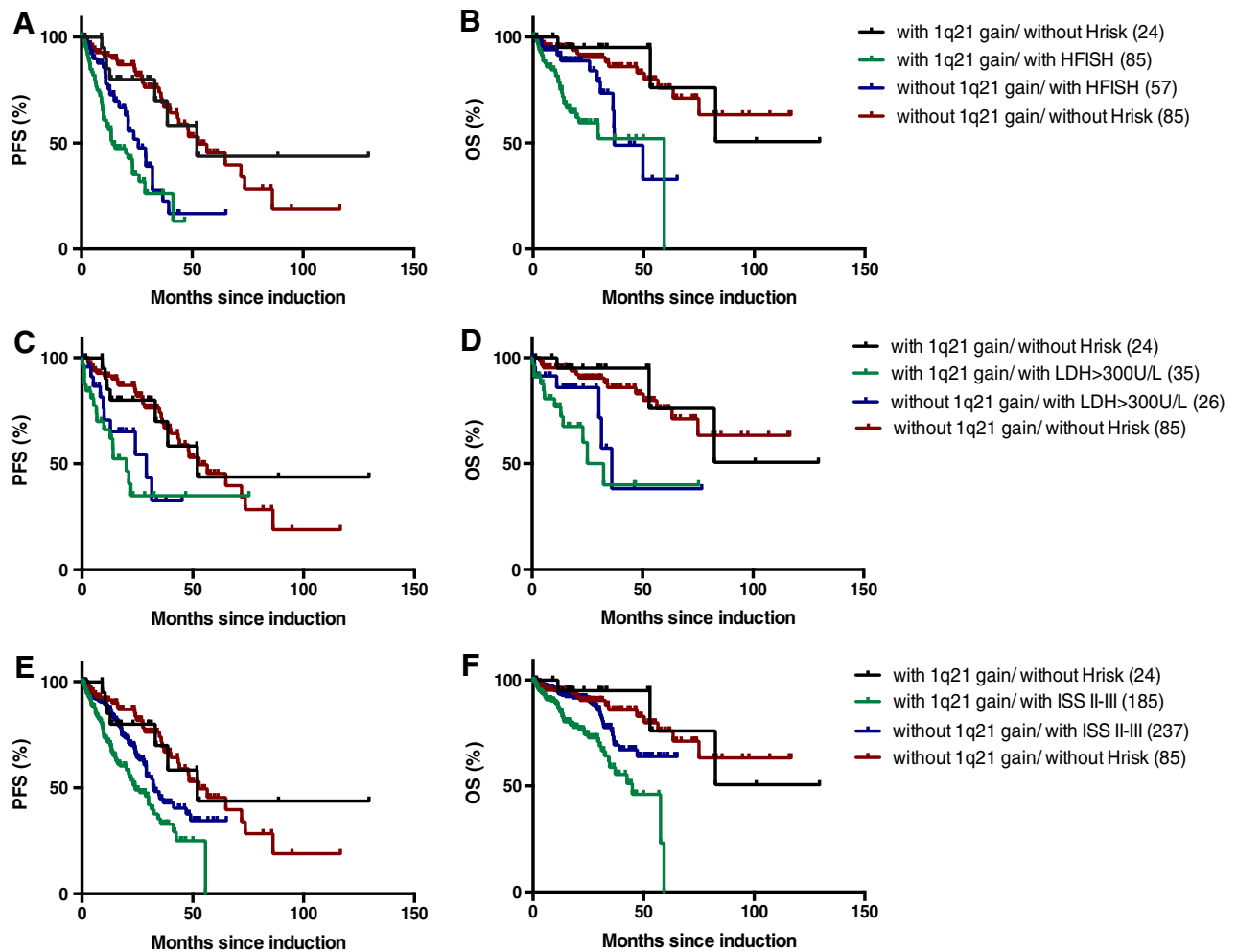


Figure 3. Impact of 1q21 gain accompanying other high-risk factors on PFS and OS in patients with multiple myeloma (MM). The differences in the median PFS (52.0 vs. 52.8 months, $p = .810$) and OS (not reached vs. not reached, $p = .833$) between 1q21 gain-positive and 1q21 gain-negative patients without Hrisk were not statistically significant. **(A–B):** Impact of 1q21 gain accompanying HFISH on PFS and OS in patients with MM. **(C–D):** Impact of 1q21 gain accompanying LDH levels >300 U/L on PFS and OS in patients with MM. **(E–F):** Impact of 1q21 gain accompanying ISS stages II–III on PFS and OS in patients with MM.

Abbreviations: HFISH, high-risk cytogenetic abnormalities (del(17p), t(4;14) or t(14;16)); Hrisk, high-risk factors including LDH levels >300 U/L, ISS stage II–III disease, del(17p), t(4;14) or t(14;16); ISS, International Scoring System; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival.

levels >300 U/L had a median PFS of 29.0 months ($p = .415$); the difference was not statistically significant. The presence of LDH levels >300 U/L both with and without 1q21 gain

resulted in shorter PFS than the presence of 1q21 gain without other high-risk factors ($p = .014$ and $p = .038$, respectively). Furthermore, patients with 1q21 gain with LDH levels

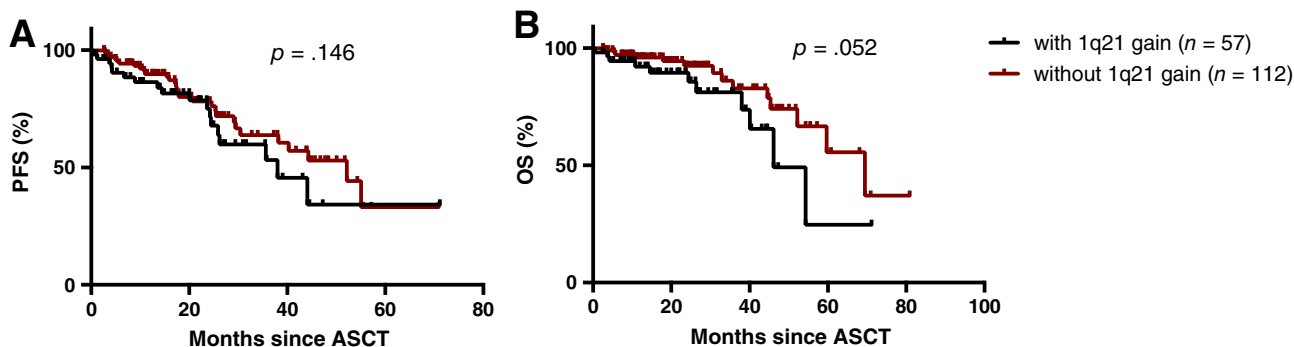


Figure 4. Impact of 1q21 gain on survival after ASCT. **(A):** Progression-free survival. **(B):** Overall survival. Abbreviations: ASCT, autologous stem cell transplantation; OS, overall survival; PFS, progression-free survival.

>300 U/L had a median OS of 25.0 months, and patients without 1q21 gain with LDH levels >300 U/L had a median OS of 36.100 months ($p = .415$); the difference was not statistically significant. The presence of LDH levels >300 U/L both with and without 1q21 gain resulted in shorter OS than the presence of 1q21 gain without other high-risk factors ($p = .003$ and $p = .019$, respectively).

Nevertheless, the presence of ISS stage II–III disease enhanced the negative effect of 1q21 gain on survival. Patients with 1q21 gain with ISS stage II–III disease had a median PFS of 23.9 months, whereas patients without 1q21 gain with ISS stage II–III disease had a median PFS of 32.1 months ($p < .001$). Patients with ISS stage II–III disease with 1q21 gain also had shorter PFS than patients with or without 1q21 gain in the absence of other high-risk factors ($p = .009$ and $p < .001$, respectively). Patients with 1q21 gain with ISS stage II–III disease had a median OS of 44.9 months, and the median OS of patients without 1q21 gain was not reached ($p < .001$). Moreover, patients with ISS stage II–III disease with 1q21 gain also had shorter OS than patients with and without 1q21 gain in the absence of other high-risk factors ($p = .004$ and $p < .001$, respectively; Fig. 3).

Prognostic Value of 1q21 Gain for Different Treatment Strategies

For patients treated with bortezomib, both PFS and OS in the presence of 1q21 gain were markedly shorter than those in the absence of 1q21 gain (PFS 30.0 vs. 43.9 months, $p = .001$; OS 57.7 months vs. not reached, $p = .002$). For patients treated with regimens not including ASCT, both PFS and OS in the presence of 1q21 gain were also markedly shorter than those in the absence of 1q21 gain (PFS 20.0 vs. 29.0 months, $p = .001$; OS 37.2 months vs. not reached, $p = .001$). To evaluate the potential benefit of ASCT, we measured PFS and OS from the date of transplantation. Median PFS from ASCT in patients with 1q21 gain was 38.0 months, and that in patients without 1q21 gain was 52.2 months ($p = .146$). Similarly, the median OS from ASCT in patients with 1q21 gain was 46.1 months, and that in patients without 1q21 gain was 69.5 months ($p = .052$; Fig. 4).

DISCUSSION

The present analysis, based on a large retrospective study including 13 centers in China, was performed to evaluate the prognostic value of 1q21 gain in Chinese patients with NDMM.

In recent years, with continuous advancements in MM treatment, novel agents such as bortezomib and lenalidomide, as well as ASCT, are being used in clinical practice. Although the survival of patients with MM has been significantly prolonged, MM remains an incurable, heterogeneous malignancy with survival ranging from a few months to a few decades [21, 22]. Thus, the identification of prognostic factors of MM is very important. Cytogenetic abnormalities are powerful prognostic factors in MM. The most important cytogenetic factors indicative of poor prognosis are del(17p), t(4;14), and t(14;16). In addition, LDH level and ISS stage have been described as adverse risk factors in MM [4].

One of the most common cytogenetic abnormalities in MM is 1q21 gain. This abnormality is not specific to MM and can be found in many hematological malignancies and solid tumors. However, it is highly prevalent in MM, and its frequency increases during the course of disease [25]. In our study, 1q21 gain was observed in 39.3% of patients with NDMM in a Chinese population, and this result was consistent with other findings [14] in which the incidence of 1q21 gain was 30%–50% of all NDMM cases. Thus, the prognostic significance of 1q21 gain, one of the most common cytogenetic abnormalities, deserves our attention.

The prognostic value of 1q21 gain in MM remains controversial, with some studies suggesting 1q21 gain as a major prognostic factor for MM and others showing the opposite. A long-term analysis of the Intergroupe Francophone du Myelome 99-02 and 99-04 trials for myeloma established that cytogenetic abnormalities such as 1q21 gain play a major role in defining long-term survival [16]. However, the Mayo Clinic showed that the importance of this parameter was not retained in multivariate analyses [13].

This discrepancy may be explained by the fact that 1q21 gain is frequently accompanied by other classic biological and genetic prognostic factors. In this study, for the entire group of 565 patients, the presence of 1q21 gain resulted in significantly short PFS and OS, and the results of multivariate analysis proved that 1q21 gain was an independent factor for poor prognosis without subgroup analysis. We also found that del(17p), t(4;14), t(14;16), ISS stage II–III disease, and LDH levels >300 U/L were linked to poor outcomes, as shown for PFS and OS in univariate analyses. After multivariate analysis, del(17), t(4;14), ISS stage II–III disease, and LDH levels >300 U/L were identified as independent

predictors for adverse PFS. Additionally, del(17), t(4;14), and LDH levels >300 U/L were identified as independent predictors for adverse OS.

Various studies have shown associations between 1q21 gain and the presence of other cytogenetic abnormalities including t(4;14) and del(17p) [26], as well as other markers of disease burden including beta-2-microglobulin, LDH level, anemia, bone marrow plasmacytosis, and ISS stage III disease [18–20]. In the present study, 1q21 gain was also found to be commonly associated with other high-risk factors. There were 222 patients with 1q21 gain, and among them, 85 also had other high-risk cytogenetic abnormalities, including del(17p), t(4;14), or t(14;16). There was a significant correlation between 1q21 gain and other high-risk cytogenetic abnormalities. The present study has also shown associations between 1q21 gain and the presence of other markers of disease burden, including ISS stage II–III disease, LDH level, bone marrow plasmacytosis, and hemoglobin level. We observed that 1q21 gain is frequently associated with these independent predictors.

Further analysis revealed that in the absence of other high-risk factors, the differences in PFS (52.0 vs. 52.8 months, $p = .810$) and OS (not reached vs. not reached, $p = .833$) between patients with and without 1q21 gain were not statistically significant. In addition, when coexisting with other high-risk cytogenetic abnormalities (del(17p), t(4;14) or t(14;16)) or LDH levels >300 U/L, the differences in PFS and OS between patients with and without 1q21 gain were not statistically significant. Furthermore, PFS and OS were significantly shorter in patients with high-risk cytogenetic abnormalities or increased LDH levels, both with and without 1q21 gain, than in patients with isolated 1q21 gain, which suggested that most of the prognostic power of 1q21 gain was related to other high-risk cytogenetic abnormalities or increased LDH levels. Additionally, the presence of ISS stage II–III disease in patients with 1q21 gain significantly shortened PFS and OS relative to those in the other three groups, which suggested that 1q21 gain coexisting with ISS stage II–III disease can worsen the adverse impact of ISS stage. Walker et al. [27] reported that patients with TP53 mutations and ISS stage III with 1q21 gain have a worse prognosis, which also supported our results. Therefore, the significance of 1q21 gain for prognosis needs to be analyzed according to other coexisting high-risk factors.

The impacts of copy number variation of 1q21 on the survival of MM also remains controversial. Walker et al. [27] reported that increased copy numbers of 1q21 gains are linked with adverse outcome in MM. Both gain (three copies) and amplification (at least four copies) of 1q21 detected by next generation sequencing were associated with decreased PFS and OS, but the effect was more pronounced in patients with amplification (18-month estimates, gain vs. amplification; PFS: 71 vs. 60%, $p = .06$; OS: 88 vs. 73%, $p = .08$). However, a group from Arkansas reported that patients with more than three copies of 1q21 at the time of diagnosis had similar 5-year event-free survival and OS times compared with those with three copies of 1q21 [25]. Our data are in agreement with the conclusion of group from Arkansas: although 1q21 gains were

linked to significantly inferior clinical outcomes in patients, the copy number variation had no additional prognostic value. The cause of the difference may be due to inconsistent follow-up and inconsistent testing methods, so further confirmation should be addressed in the future.

The discrepancy in the prognostic value of 1q21 gain could also be explained based on the different treatment strategies. Several research groups have reported that novel treatment strategies such as bortezomib and ASCT are able to overcome the unfavorable impact of cytogenetic abnormalities in patients with MM [21, 22, 28]. At present, no large sample study in China has estimated the impact of 1q21 gain on prognosis in response to different treatments. In our study, the response rate of patients with 1q21 gain remained high and similar to that of patients without 1q21 gain under initial treatment ($p = .079$). In the analysis of patients with NDMM treated with bortezomib, our results showed that patients with 1q21 gains had shorter PFS and OS than patients without 1q21 gains, suggesting that bortezomib could not overcome the adverse effect of 1q21 gain on PFS and OS. Similar findings have been reported by a study from An et al. [29] in which patients with 1q21 gain hardly benefited from regimens including bortezomib.

Although the timing of ASCT is currently being studied, upfront ASCT remains the standard of care for transplant-eligible patients with MM. When compared with patients without high-risk cytogenetic abnormalities, patients with MM with t(4;14) and del(17p) have similar responses but shorter PFS durations even after hematopoietic cell transplantation in the modern era [30]. Additionally, the adverse impact of 1q21 gain on the prognosis of patients with MM not undergoing ASCT has been confirmed by many authors, consistent with our results [29]. To further evaluate the potential benefit of ASCT, we measured PFS and OS from the date of transplantation. In our study, ASCT after bortezomib induction could change the poor prognosis since the date of transplantation in patients with MM with 1q21 gain, although the difference was not the same in all cohorts [31, 32].

There are several limitations of this study, including its retrospective nature. Furthermore, we did not compare the impact of different copy numbers of 1q21 gain. Additionally, no data are available concerning the role of other novel agents such as ixazomib or daratumumab in patients with 1q21 gain. We only analyzed the effect of 1q21 gain in NDMM and did not analyze its effect on relapsed/refractory myeloma.

CONCLUSION

In summary, although 1q21 gain has an adverse effect on survival, it is generally associated with other high-risk factors. In the absence of other high-risk factors, isolated 1q21 gain loses its prognostic power, and most of the prognostic power of 1q21 gain is related to the presence of other high-risk cytogenetic abnormalities or increased LDH levels. However, the presence of 1q21 gain with ISS stage II–III disease can worsen the adverse impact of ISS stage. Furthermore, ASCT can overcome the adverse effect of 1q21 gain on prognosis.

Our results also showed the presence of heterogeneity and variability among patients with 1q21 gain. Thus, we should assess the impact of 1q21 gain on prognosis according to different treatment regimens and accompanying high-risk factors.

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AUTHOR CONTRIBUTIONS

Conception/design: Xiaozhe Li, Juan Li

Provision of study material or patients: Wenming Chen, Yin Wu, Jianyong Li, Lijuan Chen, Baijun Fang, Ying Feng

Collection and/or assembly of data: Junru Liu, Meilan Chen

Data analysis and interpretation: Jingli Gu, Beihui Huang

Manuscript writing: Xiaozhe Li, Juan Li

Final approval of manuscript: Xiaozhe Li, Wenming Chen, Jianyong Li, Lijuan Chen, Baijun Fang, Ying Feng, Junru Liu, Meilan Chen, Jingli Gu, Beihui Huang, Juan Li

DISCLOSURES

The authors indicated no financial relationships.