MAF translocation remains a strong prognostic factor despite concurrent chromosomal abnormalities

Despite notable advancements in treatments of multiple myeloma (MM) contributing to enhanced overall survival (OS), this progress has not proven beneficial for high-risk patients, constituting an unmet medical need.[1] The t(14;16) and t(14;20), identified in approximately 6% of newly diagnosed MM patients, result in upregulation of the c-MAF and MAFB proto-oncogenes, respectively. The t(14;16) has been incorporated into the Revised International Staging System (R-ISS) as a high-risk chromosomal abnormality (HRCA).[2] However, the adverse prognostic significance of t(14;16) has been questioned due to its rarity and frequent co-existence with concurrent chromosomal abnormalities.[3-5] Moreover, the Second Revision of the International Staging System (R2-ISS) did not categorize t(14;16) as a stand-alone marker of high-risk disease.[6] Despite the lack of large databases, available studies support t(14;20) as an adverse factor with equal prognostic implication as the t(14;16).[7,8] The Arkansas group found that the MAF translocation group (defined as the MF group), which includes the t(14;16) and t(14;20), resulted in dysregulation of common downstream targets and was associated with early relapse.[9]

In order to evaluate the prognostic value of t(14;16)/t(14;20) and contribute valuable insights regarding its association with other chromosomal abnormalities, we conducted a retrospective analysis of 830 newly diagnosed multiple myeloma (NDMM) patients, diagnosed between January 2013 and June 2021 in China, comprising 34 with t(14;16), four with t(14;20) and 792 without t(14;16) or t(14;20). Patients were sourced from the MM database of the National Longitudinal Cohort of Hematological Diseases (NICHE; *clinicaltrials gov. Identifier: NCT04645199*). Written informed consent was obtained from all patients. The study was in compliance with the Declaration of Helsinki and was approved by the Ethics Committee of the Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Science & Peking Union Medical College.

The interphase fluorescence *in situ* hybridization (iFISH) and next-generation sequencing (NGS) in this study have been previously described.[10] Data on the immunophenotype were collected using a Cytomics FC 500 flow cytometer and FACSCanto flow cytometer and the CellQUEST program. We performed propensity score matching (PSM) to achieve balanced comparison groups. Each patient's propensity score was estimated using a multivariate logistic regression model, and a 1:4 group matching was conducted using the nearest-neighbor matching method without replacement. All *P* values were two-tailed, with a significance level of <0.05. SPSS 20.0 software and R program (version 3.6.3) were used for database construction and statistical analysis.

A total of 82.9% (29/35) of t(14;16)/t(14;20)-positive patients presented at diagnosis with at least one other HR-CA, including gain/amp(1q21) (73.0% *vs.* 40.9%; *P*<0.001), del(17p) (21.1% *vs.* 9.8%; *P*=0.048), del(1p32) (5.6% *vs.* 5.4%; *P*=1.000). Of note, among patients with t(14;16)/t(14;20), the combined presence of 1q21^{+} often had a copy number ≥4 (43.2% *vs.* 11.9%). In addition, the positive group had a slightly higher percentage of *TP53* mutation (22.2% *vs.* 7.3%; *P*=0.151). The incidence of *TP53* bi-allelic inactivation was also higher (11.1% *vs.* 3.2%; *P*=0.278), albeit constrained by a small sample size (*Online Supplementary Table S1*).

We delineate a specific immunophenotypic profile of t(14;16)/t(14;20)-positive MM cells. In the positive group, only five of 37 patients (13.5%) had positive expression of CD56, which was significantly lower than that in the negative group (*P*<0.001). The absence of CD56 is often observed in plasma cell leukemia and extramedullary disease.[11] These data suggest that MAF may confer a more aggressive biology to MM cells, potentially elucidating the slightly higher proportion of peripheral blood plasma cells and extramedullary disease observed in our study. In fact, it has been reported that extramedullary relapse appear to occur more frequently in patients with t(14;16).[12]

Five hundred sixty-seven patients undergoing standard treatment[10] with available follow-up status were selected for survival analysis. The median follow-up period was 29.5 months, ending on January 31, 2023. Patients with t(14;16)/t(14;20) had inferior progression-free survival (PFS) (median PFS 16.7, 95% confidence interval [CI]: 8.2-25.1 months *vs.* 55.0, 95% CI: 45.5-64.4; *P*<0.001) and OS (median OS 36.0, 95% CI: 15.5-56.5 *vs.* not reached [NR], 95% CI: NR-NR; *P*<0.001) compared to those without t(14;16)/t(14;20) (Figure 1A, B). After multivariate analysis, t(14;16)/t(14;20) retained its role as an independent adverse prognostic factor for PFS (hazard ratio [HR]= 2.38, 95% CI: 1.49-3.80; *P*<0.001) and OS (HR=2.09, 95% CI: 1.17-3.74; *P*=0.013) (*Online Supplementary Table S2*). After PSM, 109 patients (28 carrying with t(14;16)/t(14;20), and 81 without) were matched. All these features became well balanced and comparable between the two groups (all *P*>0.050) (*Online Supplementary Table S3*). As depicted in *Online Supplementary Table S3*, the matched cohort represents a population of high-risk MM. After PSM, the t(14;16)/t(14;20)-positive group still exhibited inferior PFS (median PFS 22.6 months *vs.* 48.0 months; *P*=0.011) and OS (median OS 36.0 *vs.* 65.8 months; *P*=0.002) compared to non-t(14;16)/t(14;20) group (Figure 1C, D). Similar conclusions were drawn from a multivariate analysis after PSM (*Online Supplementary Table S2*).

Subsequently, we evaluated the prognostic significance

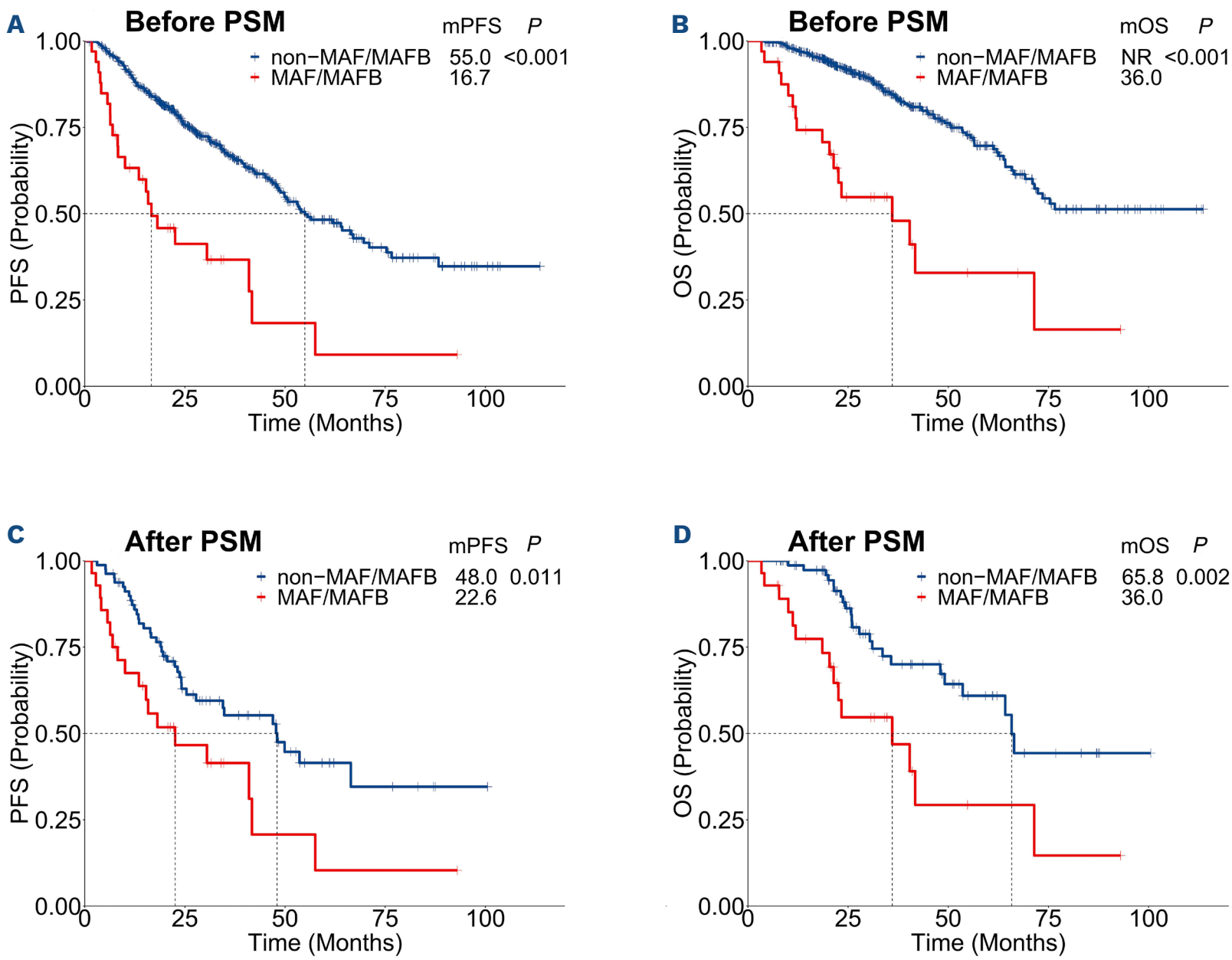

Figure 1. Prognostic significance of t(14;16)/t(14;20). Survival outcomes of newly diagnosed multiple myeloma (MM) patients according to the status of t(14;16)/t(14;20) before propensity score matching (PSM) (A, B) and after PSM (C, D). mPFS: median progression-free survival; mOS: median overall survival; MAF/MAFB: t(14;16)/t(14;20).

of t(14;16)/t(14;20) and additional HRCA. While only five patients in the cohort without HRCA had t(14;16)/t(14;20), they still had a lower OS (NR *vs.* 36.0 months; *P*=0.003). For patients with more than one HRCA, indicating a high-risk group, t(14;16)/t(14;20) conferred a significantly shorter median PFS (15.8 *vs.* 49.8 months; *P*<0.001) and inferior median OS (40.4 months *vs.* 71.5; *P*< 0.001) (Figure 2A, B). Even with more than two HRCA, t(14;16)-positive patients (N=5) had a significantly shorter median PFS (8.3 months *vs.* 47.0; *P*=0.031) and inferior median OS (12.2 months *vs.* 54.4; *P*=0.240) compared to negative group (N=37). For patients with del(17p), the presence of t(14;16)/t(14;20) would not worsen the survival outcome for both PFS and OS (*P*=0.434; *P*=0.838). But among gain/amp(1q21)-positive patients, the median PFS in patients with and without t(14;16)/t(14;20) was 15.3 and 49.8 months (*P*<0.001); and the median OS of the two subgroups was 23.4 and 72.3 months (*P*< 0.001), respectively (Figure 2C-F).

The R2-ISS staging did not incorporate t(14;16) because its rarity and non-significant for PFS in a multivariate analysis,[6] but our data show that the inclusion of t(14;16)/t(14;20) in the R2-ISS enables a more precise risk stratification and facilitates subsequent personalized therapeutic interventions. Particularly in the R2-ISS stage III, the presence of t(14;16)/t(14;20) resulted in a division of the survival curves of PFS and OS into two significantly distinct survival curves (*P*<0.001) (Figure 3).

Our study has several limitations. First, the limited number of t(14;16)/t(14;20) patients may introduce potential bias, especially in subgroup analysis. Second, our study is a real-world observational study, and treatments are not homogeneous. However, results obtained from real-world studies are more aligned with the practical application in clinical settings, potentially offering greater clinical value. Thirdly, the lack of data on new drugs related to CD38 monoclonal antibodies necessitates further exploration in the future.

Our data support that MAF translocation remains a strong prognostic factor despite concurrent chromosomal abnormalities, emphasizing the importance of incorporating it into the risk stratification system. A recent study identified 169 NDMM patients with t(14;16) among 5,141 patients

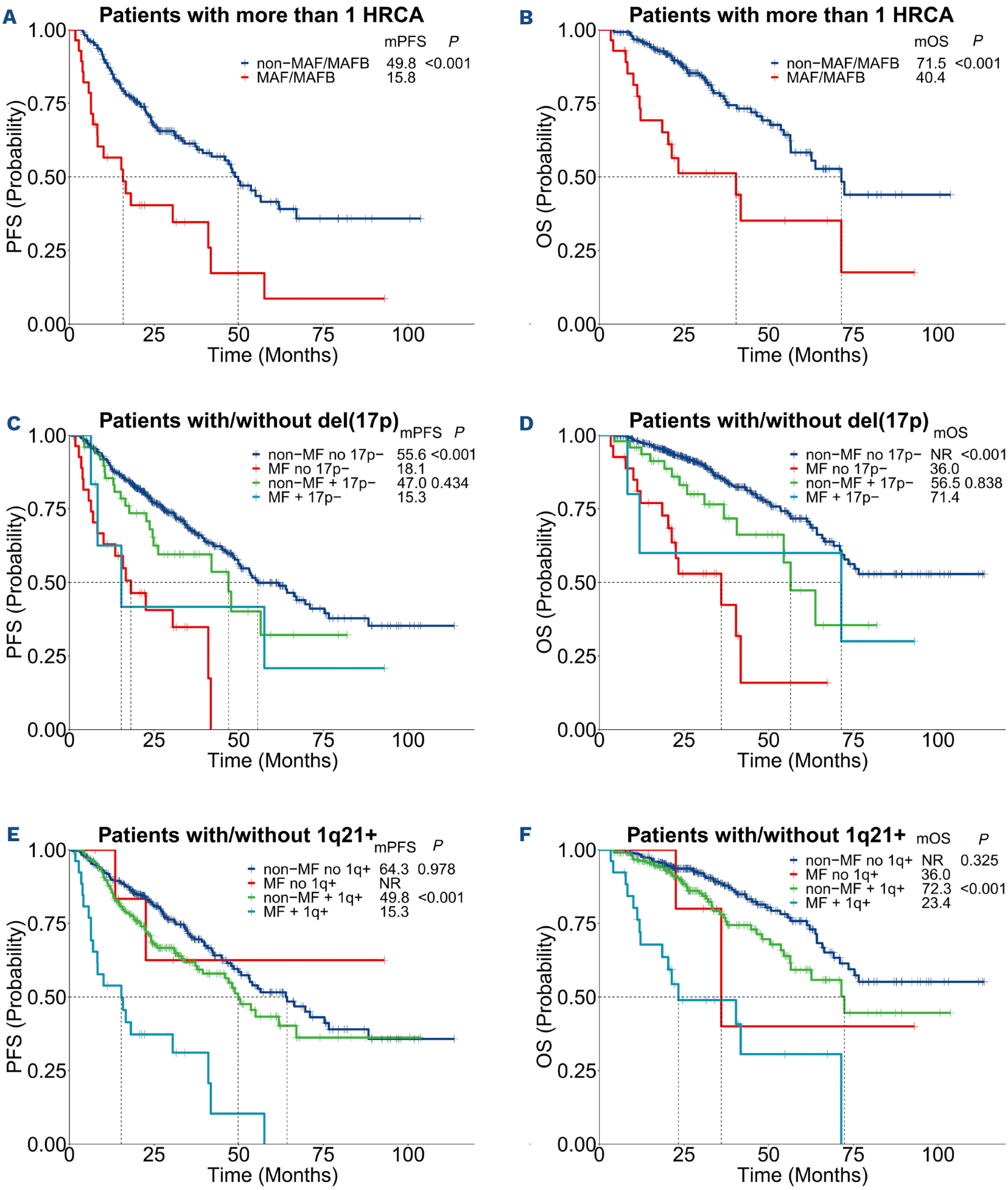

Figure 2. Prognostic significance of t(14;16)/t(14;20) and additional high-risk chromosomal abnormality. (A, B) Kaplan-Meier survival curves of progression-free survival (PFS) and overall survival (OS) of patients with more than 1 high-risk chromosomal abnormality (HRCA) according to the status of t(14;16)/t(14;20). (C, D) Patients were grouped according to the status of del(17p) and/or t(14;16)/t(14;20). (E, F) Patients were grouped according to the status of gain/amp(1q21) and/or t(14;16)/t(14;20). HRCA: high-risk chromosomal abnormality, including del(17p), del(1p32), gain/amp(1q21); MF, MAF/MAFB: t(14;16)/t(14;20); mPFS: median PFS; mOS: median OS.

and highlighted that the presence of t(14;16) exacerbated the prognosis in patients with del(17p) or gain/amp1q,[13] confirming its role in intensifying disease aggressiveness among other high-risk patients. Patients with MAF trans-

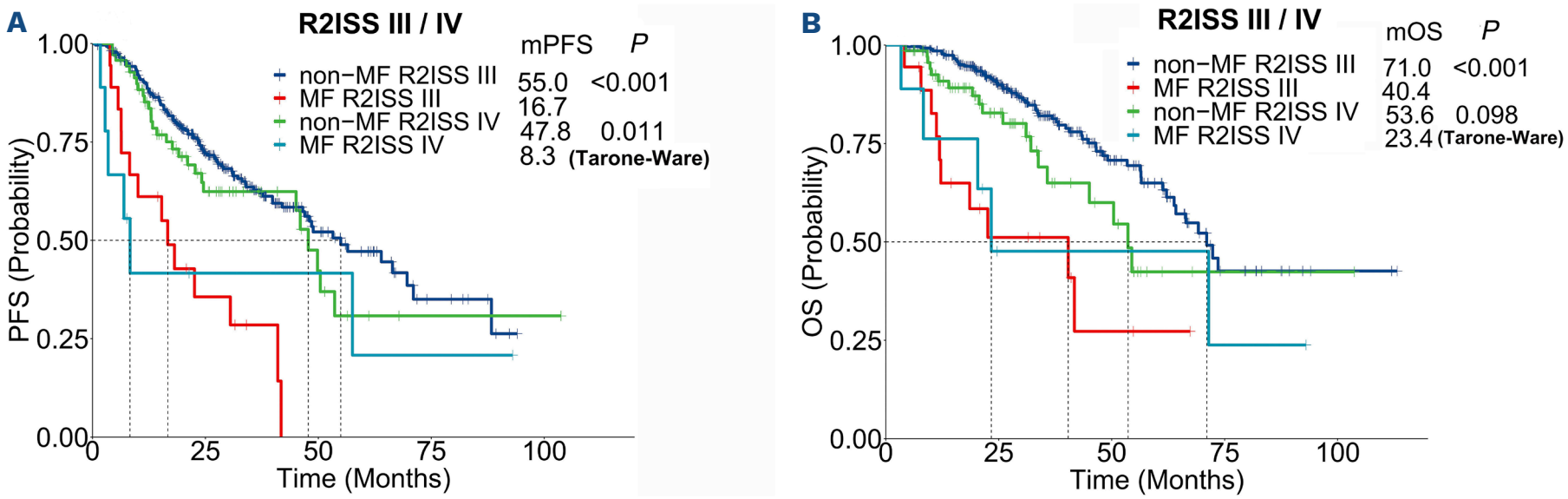

Figure 3. Addition of t(14;16)/t(14;20) to the Second Revision of the International Staging System staging. Kaplan-Meier survival curves of progression-free survival (PFS) (A, B) and overall survival (OS) (C, D) of patients with the Second Revision of the International Staging System (R2-ISS) stage III or IV according to the status of t(14;16)/t(14;20). MF, MAF/MAFB: t(14;16)/t(14;20);mPFS: median PFS; mOS: median OS.

location may represent an ultra high-risk population. The rapid progression precludes subsequent access to novel regimens, prompting us to consider highly active regimen to prolong disease remission.

Disclosures

No conflicts of interest to disclose.

Contributions

YL, RL and GA analyzed data, interpreted results, and drafted the manuscript. WY, HF, JX, LL, and JC collected data and performed patient follow-up. CD, SD, and YX acquired data and managed patients. SD, WS and YX suggested revisions. DZ, LQ, and GA designed the research and approved the final version.

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Data-sharing statement

The datasets generated and/or analyzed during the current study are available from the corresponding author at angang@ihcams.ac.cn upon reasonable request.

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