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Molecular characteristics and clinical implications of *TP53* mutations in therapy-related myelodysplastic syndromes

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Dear editor,

TP53 mutations (*TP53*^{mut}) are observed in approximately 10% of patients with myelodysplastic syndromes (MDS) and associated with a high risk of acute myeloid leukemia (AML) transformation, poor response to conventional therapies, and dismal outcomes [1–4]. Recent updates by the World Health Organization (WHO) and International Consensus Classification (ICC) have incorporated *TP53*^{mut} into the classification of MDS [5, 6]. Despite critical differences in the definition of *TP53* allelic status, both classifications strongly emphasized the poor prognostic impact of multi-hit *TP53*^{mut}. However, these changes were driven by data predominantly came from primary MDS (p-MDS) [1–3], while studies focusing specifically on *TP53*^{mut} in therapy-related MDS (t-MDS) remain limited [7–9]. Here, we conducted a comprehensive analysis of the molecular characteristics and clinical implications of *TP53*^{mut} in the context of t-MDS and compared them with those of p-MDS.

A total of 138 consecutive patients ≥18 years with newly diagnosed t-MDS according to the 2016 revised WHO criteria at our hospital from February 2015 to June 2024 were enrolled. Additionally, 1 157 patients with newly diagnosed p-MDS were included as a control cohort. Details of the methods are provided in the supplementary material.

The clinical and laboratory details of 138 t-MDS patients, in comparison with p-MDS, are summarized in Table S1. The primary diseases and prior therapies are shown in Table S2. In line with previous studies [10], t-MDS exhibited a mutational profile distinct from p-MDS (Fig. 1A, Figure S1). Mutations in *TP53* and *PPM1D* were more prevalent in t-MDS, while spliceosome mutations were more frequently observed in p-MDS. Median overall survival (OS) was significantly shorter in t-MDS patients compared to p-MDS patients (14 vs. 47 months, $P < 0.001$) (Figure S2).

We identified 55 putative oncogenic *TP53*^{mut} at variant allele frequency (VAF) ≥ 1% in 45 (32.6%) t-MDS patients, a significantly higher frequency than in p-MDS (9.6%) ($P < 0.001$), which is consistent with the frequency of 20%-40% reported in previous t-MDS cohorts [7, 8, 10]. The distribution of multi-hit and single-hit *TP53*^{mut} was similar between t-MDS and p-MDS, following the 2022 WHO criteria [5] (Figure S3A). In both groups, most variants were single nucleotide changes, primarily transitions, with C:G to T:A substitutions being the most common (Figure S3B, C). As observed in p-MDS [1], missense mutations were the most frequent type and clustered in the *TP53* DNA-binding domain, with codon 248 being the most frequently mutated locus (Fig. 1B).

In contrast with prior study [11], *TP53*^{mut} in t-MDS were found in larger clone sizes, with a median VAF of 46.2% compared to 32.2% in p-MDS ($P = 0.002$) (Figure S3D). This difference was particularly pronounced in single-hit cases (33.0% vs. 14.6%, $P = 0.003$). Although multi-hit ones showed a similar trend, the difference did not reach statistical significance (57.7% vs. 45.0%, $P = 0.080$). Clonal hierarchy analysis based on VAF revealed that *TP53*^{mut} in t-MDS were predominantly (95.5%) found in ancestral clones, with fewer co-mutations but a higher frequency of mutations in *PPM1D* than p-MDS (11.9% vs.1.2%, $P = 0.028$) (Fig. 1C). *TP53*^{mut} were observed in ancestral clones in 77.6% (83/107) of p-MDS cases, including 89.9% (62/69) of multi-hit and 55.3% (21/38) of single-hit ones, often accompanied by mutations in *U2AF1* (12.0%), *DNMT3A* (8.4%) and *TET2* (6.0%). The remaining 22.4% of *TP53*^{mut} in p-MDS were secondary to other ancestral mutations such as those in *U2AF1*, *SF3B1* and *TET2*, and associated with better survival compared to those with ancestral *TP53*^{mut} clones (9 vs. 23 months, $P = 0.019$) (Figure S4). In both groups, no significant survival impact was observed with the presence of co-mutations (Figure S5A, B).

Similar to the findings in predominantly p-MDS [1–4], *TP53*^{mut} identified a unique subgroup in t-MDS with evident genomic instability and a significantly shorter median OS (6 vs. 23 months, $P < 0.001$) (Figure S6A, B, Table S3). The inferior outcomes persisted across all the bone marrow blast categories (< 5%, 5–10%, and ≥ 10%) (Figure S7A–C) and all treatment types for t-MDS (Figure S8A–D). Next, we evaluated the prognostic implications of clone size and allelic status of *TP53*^{mut} in different clinical contexts. In p-MDS, increasing *TP53*^{mut} VAF as a continuous variable was significantly associated with more chromosomal abnormalities ($P < 0.001$), complex karyotype (CK) ($P < 0.001$), fewer co-mutations ($P = 0.004$), and inferior survival ($P = 0.007$) (Fig. 2B). However, the genomic instability and dismal survival of *TP53*^{mut} t-MDS persisted across ranges of VAF (Figure S9 and Fig. 2A). There was no significant influence of *TP53*^{mut} VAF on OS when using cutoffs of < 20%, 20–40%, 40–60% and ≥60%, although the cases with *TP53*^{mut} at VAF < 20% were limited and requires further validation. In recent years, the prognostic impact of *TP53* allelic status remains an active area of research [1, 3, 4, 7–9]. Our data showed that single-hit and multi-hit *TP53*^{mut} t-MDS patients shared similar clinical parameters, cytogenetic profiles and co-mutation patterns (Table S4). Unlike p-MDS, no significant differences were observed in CK, del(5q)/-5, del(7q)/-7 between the two groups (Figure S10). Importantly, single-hit *TP53*^{mut} t-MDS cases had equally poor survival compared to multi-hit cases (median OS 6 vs. 5 months, $P = 0.784$) (Fig. 2C). Conversely, in p-MDS, OS differed significantly across all subgroups (multi-hit vs. single-hit, multi-hit vs. wild-type, single-hit vs. wild-type) (Fig. 2D).

As expected, *TP53*^{mut} was primarily observed in t-MDS patients with CK, a high-risk subset with a median OS of 9 months (Figure S11A). Even within the CK cohort, the presence of *TP53*^{mut} strongly predicted for adverse outcome (median OS 7 vs. 15 months, $P = 0.015$) (Fig. 2E, Figure S11B), consistent with previous reports in myeloid neoplasms (MN) [2, 4] and t-MN [8] cohorts. In contrast, CK failed to further stratify outcomes for *TP53*^{mut} or *TP53*^{wt} patients (Figure S11C, D), suggested that the poor prognosis of CK

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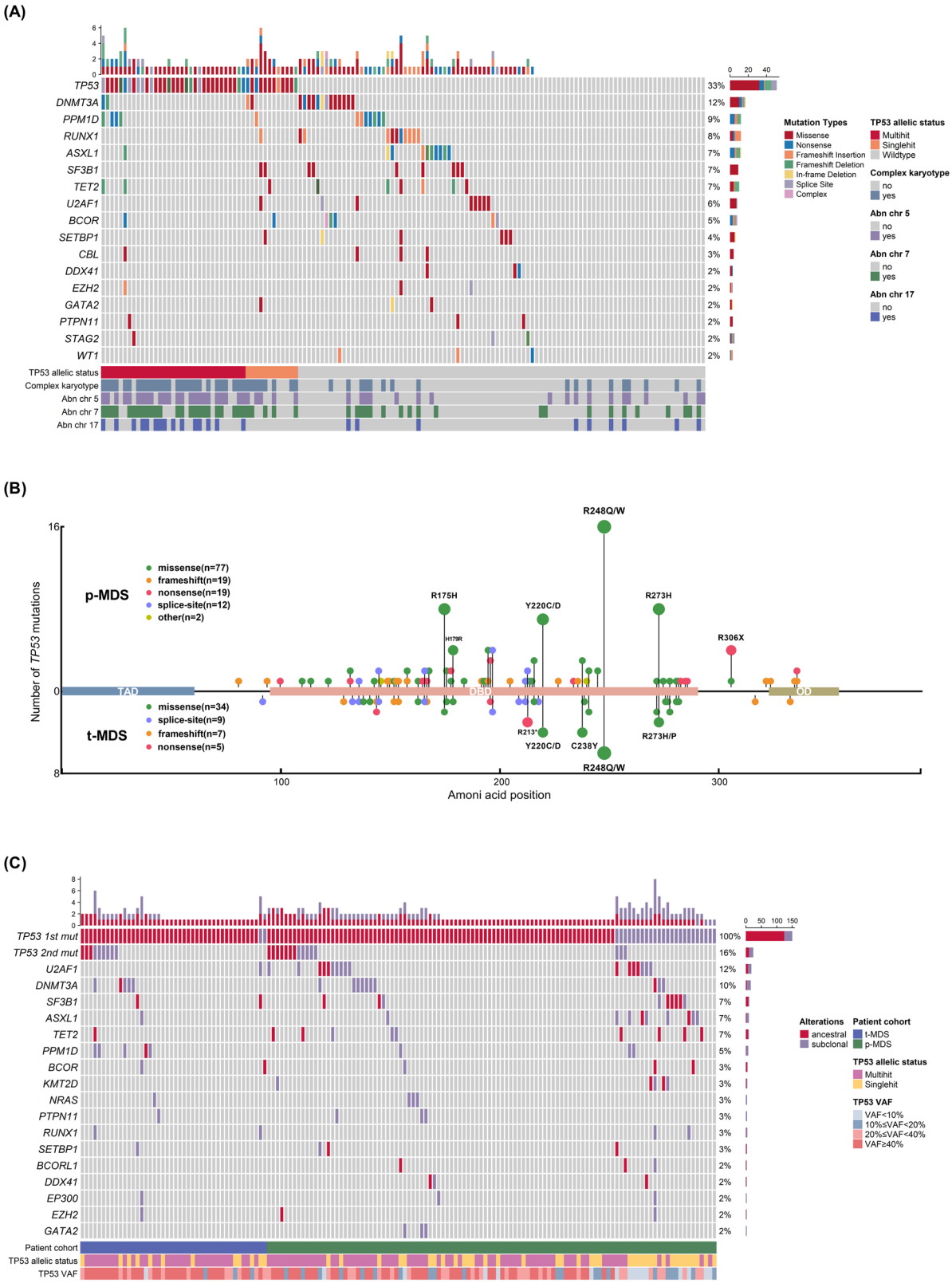

Fig. 1 Molecular characteristics of *TP53* mutations in t-MDS and p-MDS. A Molecular landscape of 138 t-MDS patients. Each column represents a patient. Mutations are colored according to mutation types as indicated above. *TP53* allelic status and recurrent cytogenetic abnormalities (complex karyotype, abnormalities of chromosomes 5, 7, and 17) are shown at the bottom. **B** Distribution of *TP53* mutations along the gene body. Mutations from t-MDS patients are shown at the bottom and those from p-MDS patients at the top, each variant is colored according to mutation type as indicated above. **C** Molecular landscape and clonal hierarchy of $TP53^{mut}$ t-MDS ($n = 43$) and p-MDS ($n = 107$). Each column represents a patient. Red depicts ancestral events and purple depicts subclonal events. Type of MDS, *TP53* allelic status and $TP53^{mut}$ VAF are shown at the bottom. t-MDS therapy-related myelodysplastic syndromes, p-MDS primary myelodysplastic syndromes, $TP53^{mut}$ *TP53*-mutated, VAF variant allele frequency.

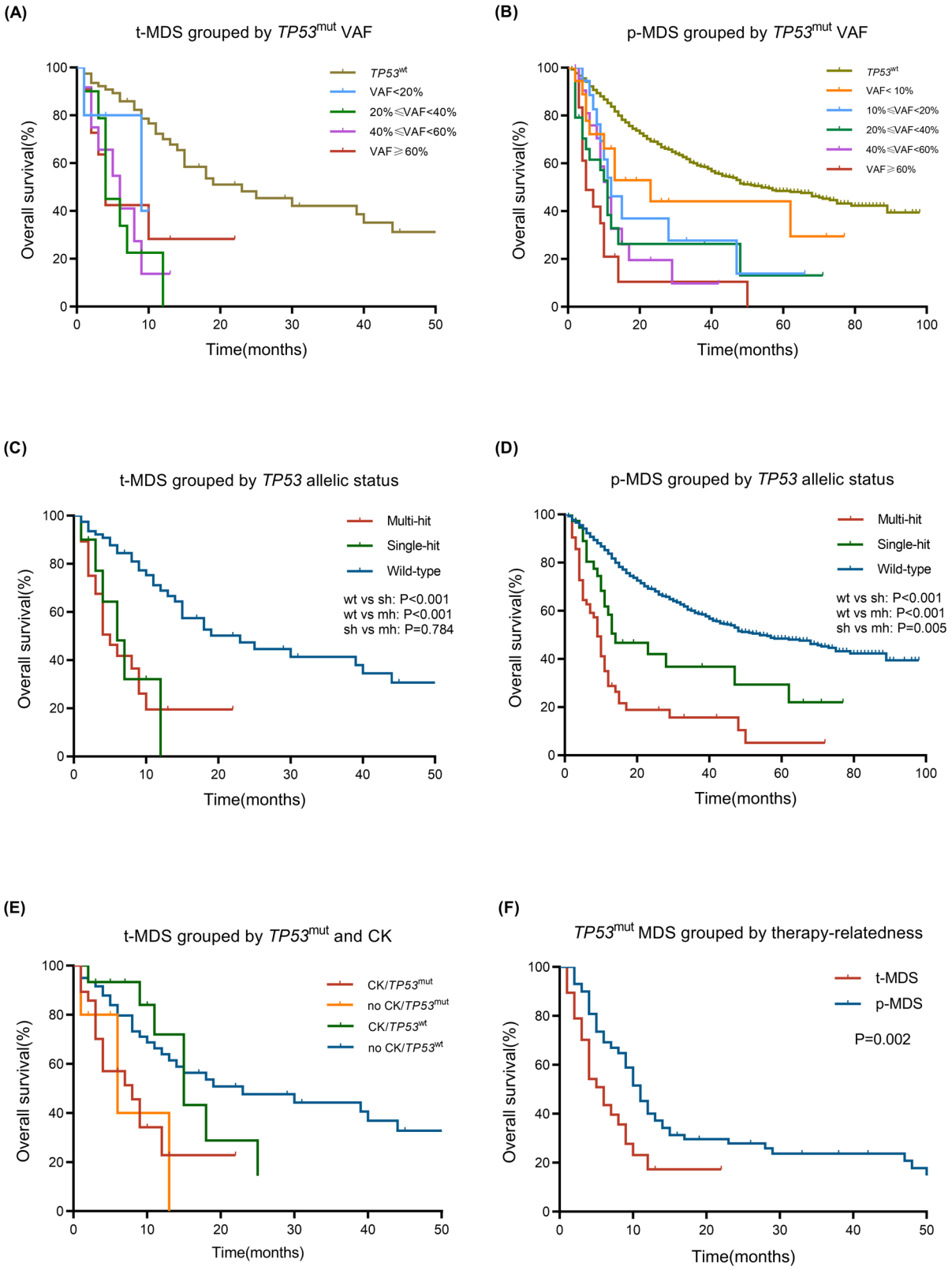

Fig. 2 Prognostic implications of *TP53* mutations in t-MDS and p-MDS. A, **B** Kaplan–Meier survival curves of OS in t-MDS and p-MDS patients stratified by *TP53*^{mut} VAF. **C**, **D** Kaplan–Meier survival curves of OS in t-MDS and p-MDS patients stratified by *TP53* allelic status. **E** Kaplan–Meier survival curves of OS in t-MDS patients stratified by *TP53* mutations and CK. **F** Kaplan–Meier survival curves of OS in *TP53*^{mut} patients stratified by t-MDS and p-MDS. t-MDS therapy-related myelodysplastic syndromes, p-MDS primary myelodysplastic syndromes, OS overall survival, *TP53*^{mut} *TP53*-mutated, VAF variant allele frequency, CK complex karyotype.

in t-MDS is largely driven by its co-occurrence with *TP53*^{mut}. A recent study reported that MDS patients with a single *TP53*^{mut} and CK exhibited clinicopathologic characteristics and survival similar to those with multi-hit *TP53*^{mut}, validating the ICC classification that treats CK as a surrogate for biallelic *TP53* inactivation [6, 12]. Our findings in this cohort with remarkably higher incidence of CK further supported the recommendation to consider single-hit *TP53*^{mut} cases with CK as equivalent to their multi-hit counterparts (Figure S12) [6, 12]. However, despite the small sample size, single-hit *TP53*^{mut} t-MDS patients without CK also showed extremely poor survival. Two patients died at 1 and 6 months after diagnosis, respectively. One patient died within 2 months of allogenic hematopoietic stem cell transplantation and one patient was lost to follow-up.

At last, we compared the clinical features and outcomes between *TP53*^{mut} t-MDS and p-MDS patients. Baseline characteristics were similar across both groups (Table S5). In disagreement with former study [11], *TP53*^{mut} t-MDS patients exhibited a significantly shorter median OS compared to p-MDS patients (6 vs. 11 months, $P = 0.002$) (Fig. 2F). Furthermore, multivariable Cox regression analysis confirmed therapy-related setting as independent predictor of OS in *TP53*^{mut} MDS patients (HR = 2.231, 95%CI: 1.289–3.862, $P = 0.004$) (Table S6). Considering only multi-hit *TP53*^{mut} patients, there was no significant difference between t-MDS (median OS, 5 months) and p-MDS (median OS, 9 months) patients ($P = 0.091$), while median OS was significantly shorter in single-hit *TP53*^{mut} t-MDS compared to p-MDS patients (6 vs. 13 months, $P = 0.004$) (Figure S13A, B).

Our current study compared the molecular and clinical landscapes of *TP53*^{mut} MDS in patients with or without prior exposure to cytotoxic therapies. *TP53*^{mut} were more prevalent in t-MDS than in p-MDS, irrespective of types of primary diseases or therapies. While *TP53* allelic status, mutation types and distribution of mutated loci were similar between t-MDS and p-MDS, *TP53*^{mut} in t-MDS were more frequently found in ancestral clones, with fewer co-mutations and higher VAF than in p-MDS. These findings supporting the model that *TP53*^{mut} may be age-related which could be detected as clonal hematopoiesis before exposure to any cytotoxic treatment and significantly increased the risk of t-MN [13–15]. The high frequency of *TP53* and *PPM1D* mutations in t-MDS likely reflect the preferential expansion of clones carrying mutant genes involved in DNA damage response pathway under the selective pressure of cytotoxic treatment [13–15]. Therefore, identifying individuals at high risk for developing t-MN may help optimize therapeutic decision-making.

Importantly, we indicated that *TP53*^{mut} in t-MDS defined a uniformly aggressive molecular subgroup, irrespective of CK, *TP53* allelic status or clone size. Of note, t-MDS patients with single-hit *TP53*^{mut} displayed equally aggressive biological features and survival to multi-hit cases [7–9], potentially linked to enhanced clonal dominance driven by the selective advantage under cytotoxic stress, as well as a higher co-occurrence of CK. Critically, there is no consensus on the optimal criteria to determine the *TP53* allelic status, which could contribute to apparent discrepancies among present studies. Given these findings, it is plausible to propose that the prognostic value of molecular characteristics of *TP53*^{mut} are context dependent. Undermining the prognostic significance of single-hit *TP53*^{mut} or smaller *TP53*^{mut} clones could negatively impact the management of these patients, potentially leading to their exclusion from clinical trials or consideration for allogenic hematopoietic stem cell transplantation.

In conclusion, *TP53*^{mut} t-MDS had unique biological and prognostic implications, and should be considered as a separate disease entity. As a single-center, retrospective study with a relatively small sample size, this research has important limitations, its conclusions warrant further validation in multicenter, prospective clinical trials.

Zefei Bao[1], Bing Li[1,2], Tiejun Qin[2], Zefeng Xu[1,2], Shiqiang Qu[1,2], Yujiao Jia[3], Chengwen Li[3], Lijuan Pan[2], Qingyan Gao[2], Meng Jiao[2], Huijun Wang[3], Qi Sun[3] and Zhijian Xiao[1,2,3] ✉

[1]*State Key Laboratory of Experimental Hematology, National Clinical Research Centre for Blood Diseases, Haihe Laboratory of Cell Ecosystem, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China.* [2]*MDS and MPN Centre, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China.* [3]*Hematologic Pathology Centre, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China.* ✉*email: zjxiao@ihcams.ac.cn*

DATA AVAILABILITY

Data are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

Z.J.X designed the study. Z.F.B collected and analyzed the data. B.L, T.J.Q, Z.F.X, S.Q.Q, Y.J.J, C.W.L, L.J.P, Q.Y.G, M.J, H.J.W and Q.S recruited subjects and collected the data. Z.F.B and Z.J.X prepared the typescript. All authors reviewed the typescript, approved this version and agreed to submit for publication.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Ethics Committees of the Institute of Hematology, Chinese Academy of Medical Science, and Peking Union Medical College (reference number IIT2021029-EC-1). All methods were performed in accordance with the relevant guidelines and regulations. Informed consent was obtained from all patients according to the Declaration of Helsinki.

ADDITIONAL INFORMATION

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Correspondence and requests for materials should be addressed to Zhijian Xiao.