ARTICLE

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How should myelodysplastic neoplasms with isolated deletion 5q and *TP53* multihit alterations be classified?

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Myelodysplastic neoplasms (MDS) with *TP53* multihit alterations are associated with dismal outcomes. MDS with isolated del(5q) present favorable prognosis but is defined by the absence of *TP53* multihit alterations. However, whether *TP53* multihit alterations exert the same adverse impact in this genetic context remains uncertain. We retrospectively analyzed the characteristics and outcome of 43 patients with MDS with isolated del(5q) harboring *TP53* multihit alterations (MDS-del(5q) *TP53* multihit) and compared with 68 patients with low-blast MDS with *TP53* multihit and without isolated del(5q) (MDS-LB *TP53* multihit). Patients with MDS-del(5q) *TP53* multihit showed significantly higher platelet counts, more frequent *SF3B1* mutations, were less often classified as high-risk by IPSS-R or IPSS-M, and had significantly better outcomes than patients with MDS-LB *TP53* multihit: overall survival of 70.2 vs 13.9 months, and time to acute myeloid leukemia progression (AML) of 31.9 vs 7.2 months, respectively. Moreover, the superior outcomes of MDS-del(5q) *TP53* multihit patients persisted significant even when compared with MDS-LB *TP53* multihit cases without complex karyotype (survival of 70.2 vs 39.9 months; time to AML progression of 31.9 vs 11.4 months). These findings indicate that, in MDS-del(5q) the adverse impact of *TP53* multihit alterations may be less important than in other MDS subtypes.

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INTRODUCTION

Advances in high-resolution genomics have led to the classification of hematologic neoplasms, including myelodysplastic neoplasms (MDS), according to molecular markers when available. Both the World Health Organization (WHO) and the International Consensus Classification (ICC) currently define three genetically characterized entities: MDS with isolated del(5q) (MDS-del(5q)), MDS with *SF3B1* mutation, and MDS with *TP53* multihit mutation [1, 2].

MDS with isolated del(5q) are defined by bone marrow (BM) blasts <5%, peripheral blood blasts <2%, and deletion of chromosome 5q, either alone or with one additional cytogenetic

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abnormality, excluding monosomy 7 or del(7q), and importantly, *TP53* multihit alterations must be absent [1, 2]. These patients usually respond well to lenalidomide and are associated with favorable long-term outcomes [3, 4]. MDS with *TP53* multihit alterations are defined as the presence of two or more *TP53* lesions, including multiple mutations, mutation plus deletion, or mutation with copy-neutral loss of heterozygosity (cnLOH), resulting in biallelic inactivation of *TP53* [1]. These patients generally present increased marrow blasts, complex karyotypes (CK), and have dismal prognosis [5]. The recently proposed harmonization classification introduces a hierarchical framework that prioritizes the assessment of *TP53* multihit alterations, whereby cases with *TP53* multihit alterations are classified as such, and MDS with isolated del(5q) is considered only in their absence [6], similar to the WHO and ICC approach [1, 2].

Our group recently found that, in patients with MDS-del(5q), *TP53* multihit alterations were associated with shorter overall survival (OS) compared with single-hit mutations or wild-type *TP53* (median OS 56.9 months, 73.2 months, and 77.3 months, respectively) [7], but significantly longer than in *TP53* multihit cases across other MDS subtypes [5]. Interestingly, only female sex was more prevalent in the single-hit *TP53* group than in the multihit *TP53* group (81.6% vs 54.8%, respectively), with no other significant differences found in the main clinical variables between patients with *TP53* wild-type, single-hit and multihit alterations [7].

Accordingly, we hypothesized that *TP53* multihit alterations may not exert per se the same adverse biological and clinical impact in MDS-del(5q) as in other MDS subtypes. Therefore, current MDS classifications may underestimate the distinct pathogenic and prognostic significance of isolated deletion 5q in the setting of *TP53* multihit alterations.

To address this, we analyzed the clinical and biological features and outcomes of *TP53* multihit status in MDS-del(5q) (MDS-del(5q) *TP53* multihit) and compared them with other MDS subtypes with <5% blasts and non-isolated del(5q) karyotypes (MDS-LB *TP53* multihit).

METHODS

Patients

For the MDS-del(5q) *TP53* multihit cohort, patients diagnosed with de novo MDS-del(5q) according to the WHO 2017 classification [8], and having *TP53* multihit abnormalities, were included from 21 international institutions (Supplemental Data). Of these, 31 of 43 patients were reported in our previous study [7]. For the MDS-LB *TP53* multihit cohort, patients with low bone marrow blast counts (< 5%) and *TP53* multihit alterations who did not meet diagnostic criteria for MDS-del(5q) were retrieved from the study of Bernard et al. [5].

Clinical and hematological data

Clinical characteristics and laboratory parameters, including sex, age, hemoglobin level, platelet count, differential white blood cell count, and bone marrow blast percentage, were recorded at diagnosis. Risk stratification was performed according to the Revised International Prognostic Scoring System (IPSS-R) and its molecular version, the IPSS-M [9, 10]. For analytical simplicity, patients with an IPSS-R of ≤3.5 were categorized as lower-risk, while those with IPSS > 3.5 were considered higher-risk. Likewise, patients categorized as very-low, low, or moderate-low IPSS-M were grouped as lower-risk, while those in the moderate-high, high, or very-high categories were considered higher-risk. Clinical outcomes included OS and progression to acute myeloid leukemia (AML).

Genetic data

For the MDS-del(5q) *TP53* multihit cohort, cytogenetic and molecular data were obtained from all patients at diagnosis or prior to treatment initiation. Genetic profiling was performed at each institution and included conventional G-banding analyses in all cases. Additionally, and depending on the institution, the profiling included fluorescence in situ hybridization of 17p, single nucleotide polymorphism microarrays, Sanger sequencing of *TP53* gene, targeted Next-generation sequencing, whole exome sequencing (WES), and whole-genome sequencing (WGS), as previously described [5], in which only variants with a variant allele frequency (VAF) ≥ 2% were considered. Allelic imbalances, defined as deletions and copy number-neutral loss of heterozygosity (cnLOH) of chromosome 17p affecting the *TP53* locus, were evaluated by FISH, SNP-A, and various NGS techniques (WES, WGS, and targeted panels; Supplemental Data). For the MDS-LB *TP53* multihit cohort, cytogenetic and molecular data were similarly collected from all patients at diagnosis or before the initiation of therapy. To allow comparative analysis of the molecular landscapes between cohorts, a shared set of 33 genes commonly assessed across both datasets were analyzed. These genes included: *ASXL1, BCOR, BCORL1, CALR, CBL, CEBPA, CSF3R, DNMT3A, ETV6, EZH2, FLT3, GATA2, IDH1, IDH2, JAK2, KIT, KRAS, MPL, NPM1, NRAS, PHF6, PTPN11, RAD21, RUNX1, SETBP1, SF3B1, SRSF2, STAG2, TET2, TP53, U2AF1, WT1*, and *ZRSR2*. Variant filtering and categorization were performed as previously described [11].

Definition of TP53 multihit alterations

The biologically accurate definition of *TP53* multihit refers to the presence of *TP53* biallelic alterations. However, routine diagnostic workups often lack the resolution to determine whether both alleles are indeed affected. Consequently, the term 'multihit' is commonly used in the literature to describe cases in which multiple *TP53* mutations are detected. In this study, *TP53* multihit alterations were defined according to Bernard et al. and the 2022 WHO classification [1, 5], ie: presence of two or more *TP53* gene mutations, a single *TP53* mutation accompanied by a 17p deletion or cnLOH, or a single *TP53* mutation with a VAF of ≥50%, reflecting loss of the wildtype allele.

Statistical analysis

Clinical variables were summarized using descriptive statistics. A logistic model was used to calculate *p*-values and to identify significant differences between groups in the descriptive analysis. Overall survival, defined as the time from diagnosis to last follow-up or death of any cause, was calculated using the Kaplan-Meier method. A Cox proportional hazard model was used to detect differences in survival endpoints and hazard ratio (HR) with 95%CI and *p*-value were reported. The cumulative incidence of leukemic progression, defined as the time from diagnosis to disease progression, was estimated by Fine-Gray method with nonleukemic death as a competing risk. This model provides the derivation of HR with 95%CI and associated *p*-values. Patients were categorized into three groups: progression to AML (the event of interest), death without prior progression (the competing event), or censoring in the absence of these events. Multivariable analysis was adjusted for covariates selected a priori based on their established prognostic significance and potential confounding effect in MDS. All statistical tests were two-sided, and a p-value < 0.05 was considered statistically significant. No imputation for missing data was performed. All statistical analyses were conducted using R (version 4.2.2).

RESULTS

Characterization of TP53 multithit alterations in MDS-del(5q) TP53 multihit and MDS-LB TP53 multihit patients

A total of 43 patients with MDS-del(5q) *TP53* multihit from 21 international institutions were compared with 68 patients with MDS-LB *TP53* multihit derived from the study of Bernard et al. [5]. Their baseline characteristics are summarized in Table 1.

In MDS-del(5q) *TP53* multihit patients, 18 (41.9%) carried ≥2 *TP53* mutations, 12 (27.9%) had a single *TP53* mutation combined with either 17p deletion ($n = 8$, 66.7%) or cnLOH ($n = 4$, 33.3%), and 13 (30.2%) had a *TP53* VAF ≥ 50%. Notably, among patients with ≥2 *TP53* mutations, 94.5% (17/18) had a combined VAF < 50% (39.5% of the overall MDS-del(5q) *TP53* multihit cohort) suggesting the presence of small independent subclones rather than true biallelic *TP53* inactivation (Table 1; detailed mutation data in Supplementary Table 1). In MDS-LB *TP53* multihit patients, 32 (47.1%) carried ≥2 *TP53* mutations, while 36 (52.9%) had a single *TP53* mutation with 17p deletion ($n = 17$, 47.2%) or cnLOH ($n = 19$, 52.8%). In contrast with MDS-del(5q) patients, only 40.6% (13/32) patients with ≥2 *TP53* mutations showed a combined VAF < 50% (19.1% of the whole MDS-LB *TP53* multihit cohort), again consistent with the possible presence of minor subclones rather

Table 1. Main clinical characteristics of all the cohort and MDS-LB *TP53* multihit and MDS-del(5q) *TP53* multihit.

Variable	MDS-LB-*TP53* multihit $n = 68$	MDS-del(5q) *TP53* multihit $n = 43$	*P*
Age at diagnosis, y, median (IQR)	71 (64–76)	72 (62–79)	0.4
Sex, male %	33 (48.5)	17 (39.5)	0.5
Hemoglobin, g/dL, median (IQR)	9.3 (8.4–10.4)	9.6 (8.2–10.4)	0.7
Leukocytes, x10^9/L, median (IQR)	3.4 (2.6–5.0)	3.7 (3.0–5.8)	0.6
Neutrophils, x10^9/L, median (IQR)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.9
Platelets x10^9/L, median (IQR)	77 (50–121)	209 (146– 316)	<0.01
Bone marrow blasts, %	2.5 (1.0–4.0)	2.0 (1.0–3.0)	0.08
IPSS-R			
Low-risk	16 (24.6%)	36 (90.0%)	<0.01
High-risk	49 (75.4%)	4 (10.0%)	
IPSS-M			
Low-risk	7 (10.3%)	32 (74.4%)	<0.01
High-risk	61 (89.7%)	11 (25.6%)	
Karyotype			
Complex karyotype	53 (77.9%)	-	
Non complex karyotype*	15 (22.1%)	-	
TP53 multihit characterization			
≥2 *TP53* mutations	32 (47.1%)	18 (41.9%)	
1 TP53 mutation + 17p deletion	17 (47.2%)	8 (18.6%)	
1 *TP53* mutation + cnLOH	19 (52.8%)	4 (9.3%)	
TP53 VAF ≥ 50%	**	13 (30.2%)	

*MDS-del(5q) per definition can not harbor complex karyotype; ** All MDS-LB patients with 1*1 TP53* mutation + 17p deletion or cnLOH presented VAF > 50%.

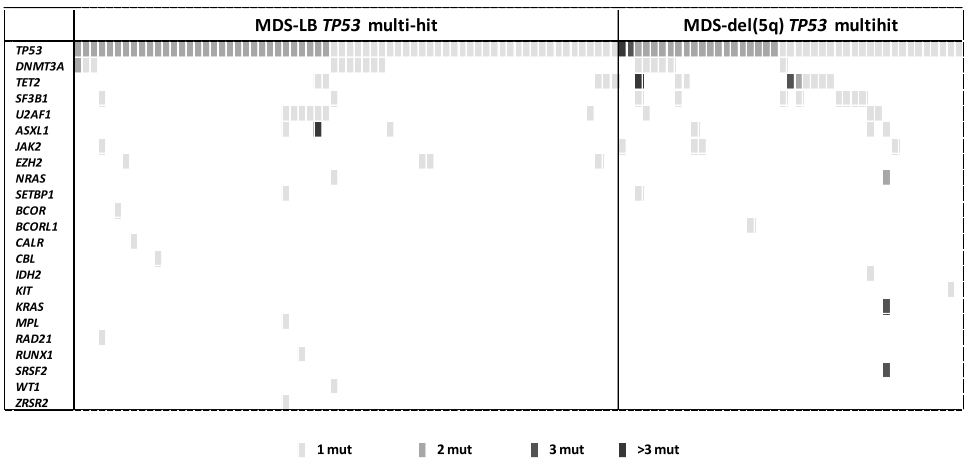

Fig. 1 Molecular profile observed in MDS-LB *TP53* multihit and MDS-del(5q) *TP53* multihit patients. mut mutation/s.

than definitive biallelic *TP53* inactivation (Table 1; detailed mutation data in Supplementary Table 2).

Comparison of clinical and genetic findings between MDS-del(5q) TP53 multihit and MDS-LB TP53 multihit patients

Patients with MDS-del(5q) *TP53* multihit showed significantly higher platelet counts compared to MDS-LB *TP53* multihit (median 209×10^9/L and 77×10^9/L, respectively; $p < 0.01$), while no other demographic or baseline laboratory differences were observed. Complex karyotypes were present in 77.9% of MDS-LB *TP53* multihit cases but, by definition, absent in MDS-del(5q) *TP53* multihit. This translated into marked disparities in risk stratification: by IPSS-R, 75.4% of MDS-LB *TP53* multihit patients were classified as high-risk compared with only 10.0% of MDS-del(5q) *TP53* multihit ($p < 0.01$). Similarly, by IPSS-M, 89.7% of *TP53* multihit patients were classified as high-risk compared with only MDS-LB and 25.6% of MDS-del(5q) patients were assigned to higher-risk categories ($p < 0.01$). The median number of additional mutations per patient (excluding *TP53*) was one in both groups. Mutations in *SF3B1* gene were significantly more frequent in patients with MDS-del(5q) *TP53* multihit compared with MDS-LB *TP53* multihit (20.5% vs 2.9%; $p < 0.01$) (Fig. 1 and Supplementary Fig. 1). No other recurrent gene mutations differed significantly between groups (Supplementary Table 4).

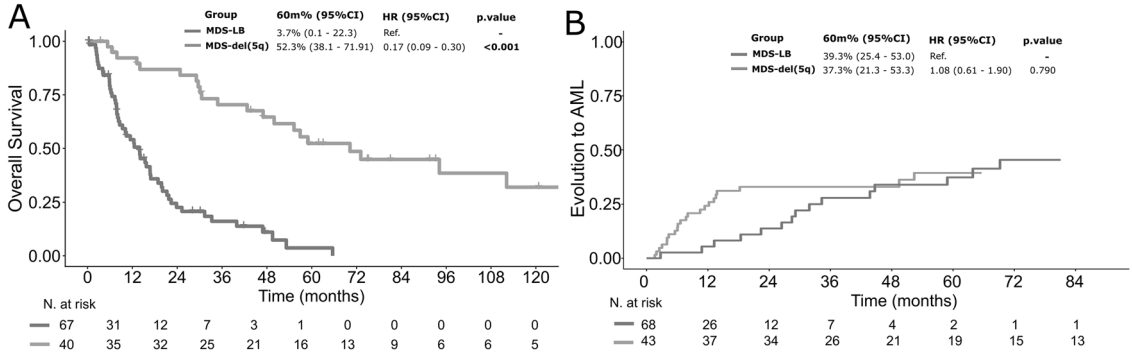

Fig. 2 Comparison of outcomes among patients with MDS-LB *TP53* multihit and MDS-del(5q) *TP53* multihit. A Overall survival. **B** Progression to acute myeloid leukemia (AML).

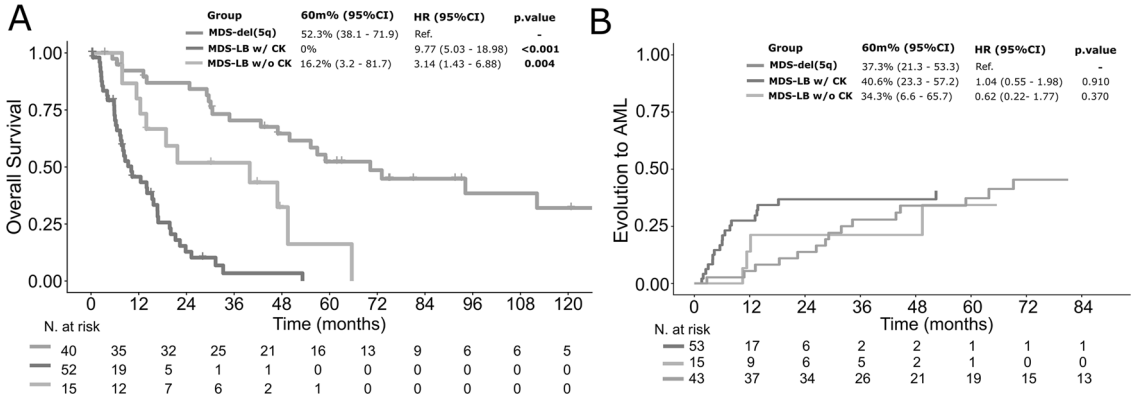

Fig. 3 Comparison of outcomes among patients with MDS-LB and *TP53* multihit according to karyotype status (with vs without complex karyotype), and those with MDS-del(5q) and *TP53* multihit. A Overall survival. **B** Progression to acute myeloid leukemia (AML). w/ with, w/o without.

Comparison of outcomes between MDS-del(5q) TP53 multihit and MDS-LB TP53 multihit patients

Overall survival was significantly longer in patients with MDS-del(5q) *TP53* multihit compared with MDS-LB *TP53* multihit (median 70.2 months (95% CI, 49.9–NR) vs 13.9 months (95% CI, 8.6–18.9), $p < 0.01$; Fig. 2A). The cumulative incidence of AML progression at 48 months was comparable between groups (34.0% for MDS-del(5q) *TP53* multihit and 33.0% for MDS-LB *TP53* multihit; HR 1.1; $p = 0.8$). However, the kinetics of progression differed markedly: median time to AML evolution was 31.9 months (IQR, 22.4–58.9) in MDS-del(5q) *TP53* multihit and 7.2 months (IQR, 4.1–12.9) in MDS-LB *TP53* multihit (IQR, 22.4–58.9) ($p < 0.01$; Fig. 2B).

As *TP53* multihit status does not invariably equate to biallelic inactivation, we examined whether the more favorable outcomes observed in MDS-del(5q) *TP53* multihit patients were related to a lower prevalence of likely biallelic *TP53* inactivation. Thus, MDS-del(5q) with likely *TP53* biallelic alterations (defined as a single *TP53* mutation with concomitant 17p deletion or cnLOH, or a *TP53* VAF ≥ 50%) (60.5%) were compared with MDS-LB *TP53* multihit patients (80.9%). Importantly, outcomes remained superior in MDS-del(5q) *TP53* multihit cases compared with MDS-LB *TP53* multihit, even when restricted to patients with likely *TP53* inactivation: median OS was 60.0 months (95% CI, 47.0–NR) vs 8.3 months (95% CI, 5.9–16.7; $p < 0.01$), and median time to AML progression was 33.1 months (IQR, 25.4–61.5) vs 6.1 months (IQR, 4.0–7.9; $p < 0.01$), respectively (Supplementary Fig. 2A, B). Moreover, these differences were also observed when MDS-del(5q) *TP53* multihit patients were compared with MDS-LB *TP53* multihit patients without CK. Median survival was 70.2 months in MDS-del(5q) *TP53* multihit and 39.9 months (95% CI, 13.9–NR) in MDS-LB *TP53* multihit without CK ($p < 0.01$). Median time to AML evolution was 31.9 months (IQR, 22.4–58.9) in MDS-del(5q) *TP53* multihit and 11.4 months (IQR, 10.5–12.2) in MDS-LB *TP53* multihit without CK ($p = 0.05$) (Fig. 3A, B).

Finally, in a multivariate analysis including platelet counts ($\leq 100 \times 10^9$/L vs $>100 \times 10^9$/L), IPSS-M risk category (lower vs higher), *SF3B1* mutation status (mutated vs wild-type), and the type of disease (MDS-del(5q) *TP53* multihit, MDS-LB *TP53* multihit without CK and MDS-LB *TP53* multihit with CK), the only two factors significantly associated with shorter OS were platelet counts $\leq 100 \times 10^9$/L (HR 3.1, 95% CI 1.7–5.9; $p < 0.01$), and having MDS-LB *TP53* multihit with CK (HR 6.6, 95% CI 2.7–16.1; $p < 0.01$), while MDS-LB *TP53* multihit without CK showed a trend toward inferior survival (HR 2.2, 95% CI 0.9–5.3; $p = 0.08$), compared to MDS-del(5q) *TP53* multihit. These findings further support that *TP53* multihit alterations in MDS-del(5q) do not confer the same adverse prognostic impact observed in other MDS subtypes.

Comparison of likely versus unlikely biallelic TP53 inactivation patterns in MDS-del(5q) TP53 multihit and MDS-LB TP53 multihit patients

We next compared outcomes between patients with likely biallelic *TP53* inactivation and those with an unlikely biallelic *TP53* inactivation pattern (defined as ≥2 *TP53* mutations with a combined VAF < 50%) in both disease subgroups. In MDS-del(5q) *TP53* multihit cases, no significant differences in outcomes were observed between these two patterns. Median overall survival (OS) was 70 months (95% CI, 47–NR) in the likely biallelic subgroup and 73 months (95% CI, 43–NR) in the unlikely biallelic subgroup

($p > 0.8$). The 48-month cumulative incidence of AML progression was 36.1% and 30.4%, respectively ($p = 0.5$) (Supplementary Fig. 3A, B). Similar findings were observed in the MDS-LB *TP53* multihit cohort. Median survival was 8.3 months (95% CI, 5.9–17.0) in patients with likely biallelic *TP53* inactivation and 16.0 months (95% CI, 7.5–24.0) in those with unlikely biallelic *TP53* inactivation ($p = 0.6$), with comparable 48-month AML progression rates (35.9% vs 37.9%, respectively; $p = 0.8$) (Supplementary Fig. 4A, B).

DISCUSSION

Our study shows that the prognostic impact of *TP53* multihit alterations is less severe in patients with MDS-del(5q) compared to other MDS subtypes with low blasts.

In a previous paper, we had shown that in MDS-del(5q) patients *TP53* mutations were detected in 19% of patients, of whom only 24% harbored multihit alterations. Moreover, median survival of patients with MDS-del(5q) *TP53* multihit alterations approached 5 years, close to that of MDS-del(5q) with no or single *TP53* single-hit mutations [7]. This finding is confirmed in the present cohort, which includes twelve additional MDS-del(5q) *TP53* multihit patients, showing a median survival of 70 months. Notably, the characteristics and clinical impact of *TP53* mutations in MDS-del(5q) sharply contrasted with those seen in the broader MDS population, in which *TP53* mutations occur in ~10% of patients, more than two-thirds are multihit alterations, and median survival is less than 1 year [5]. Consistent with this, in our analysis restricted to MDS with <5% blasts and *TP53* multihit alterations, median OS was only 14 months. Furthermore, although the cumulative incidence of AML progression was similar between MDS-del(5q) *TP53* multihit and MDS-LB *TP53* multihit patients, the kinetics of evolution differed markedly: median time to AML transformation was more than fourfold longer in MDS-del(5q) *TP53* multihit (31.9 months) than in MDS-LB *TP53* multihit patients (7.2 months). These findings highlight that the clinical impact of *TP53* multihit alterations is not uniform across MDS subtypes with significant differences in outcomes.

We used the definition proposed by Bernard et al. and adopted by the WHO classification for *TP53* multihit alterations [1, 5]. Using this definition, *TP53* multihit status does not always correspond to true biallelic *TP53* inactivation which requires functional loss of both alleles, typically through a combination of mutation and 17p deletion or cnLOH, or through multiple mutations affecting both alleles. In contrast, multihit status may occasionally result from independent *TP53* mutations arising in separate minor subclones derived from one allele, rather than affecting both alleles. In this line, the ICC requires the presence of two distinct *TP53* mutations each with a VAF > 10% to support *TP53* biallelic targeting [2]. Applying this criterion to our cohort, only 5 of the 18 MDS-del(5q) patients initially classified as *TP53* multihit based on ≥2 mutations fulfilled the ICC requirement. Thus, 30.2% of MDS-del(5q) cases would not be considered *TP53* multihit under the ICC definition.

In our study, the majority of MDS-LB *TP53* multihit cases (80.9%) showed clear inactivation of both *TP53* alleles, compared with 60.5% of MDS-del(5q) *TP53* multihit patients. This divergent biological configuration of *TP53* multihit alterations could partly account for the differences in outcomes observed between the two groups. In addition, most MDS-LB *TP53* multihit patients harbored a CK, which likely further contributed to their poorer prognosis. Nevertheless, the more favorable outcomes of MDS-del(5q) *TP53* multihit patients persisted even when the analysis was restricted to cases with likely biallelic *TP53* inactivation in both MDS-del(5q) and MDS-LB, and also when compared with MDS-LB *TP53* multihit cases lacking CK. Taken together, these observations reinforce the notion that MDS-del(5q) represents a biologically distinct entity. These data point out that in MDS-del(5q), the del(5q) clone itself remains the primary pathogenic driver, shaping disease phenotype and clinical outcome, and that *TP53* multihit status may not act as dominant driver of genomic instability or disease progression. We observed a higher incidence of *SB3B1* mutation in MDS-del(5q) *TP53* multihit compared with MDS-LB *TP53* multihit cases. A correlation between *TP53* mutations and *SF3B1* mutation had previously been reported in MDS-del(5q) where, in contrast to the general MDS population, *SF3B1* mutation is associated with poorer outcomes [12, 13]. In our prior work, we observed that the incidence of *SF3B1* mutation was increased in MDS-del(5q) irrespective of *TP53* mutational and allelic status [7]. Further studies are warranted to clarify the impact of *TP53* multihit alterations in MDS-del(5q) patients harboring *SF3B1* mutations.

Limitations of this study are inherent to its retrospective design. Treatment exposure was not uniformly captured across cohorts; therefore, differences in therapeutic pathways may have partially contributed to the outcome disparities observed between MDS-del(5q) *TP53* multihit and MDS-LB *TP53* multihit patients. Lenalidomide represents the standard treatment for transfusion-dependent patients with MDS-del(5q). In this setting, *TP53*-mutated BM progenitors have been associated with initial sensitivity to lenalidomide, characterized by transient suppression of the *TP53*-mutant clone, followed by subsequent clonal expansion and disease progression [14, 15]. Notably, a recent study evaluating earlier introduction of lenalidomide in MDS-del(5q) demonstrated that patients harboring *TP53* mutations (exclusively single-hit cases) achieved a reduction in VAF across all detected mutations, supporting the hypothesis that lenalidomide may favorably modify the natural history of MDS-del(5q) in selected patients [16]. In addition, the MDS-LB *TP53* multihit comparator cohort derived from Bernard et al. was externally assembled, and differences in sequencing workflows together with limited cohort size precluded full genomic harmonization. Finally, the distinction between *TP53* multihit status and true biallelic inactivation was not established through direct clonality assessment; instead, we performed comparative analyses of cases with likely *TP53* biallelic involvement versus those in whom *TP53* biallelic inactivation was less certain. While this approach provides indirect insight, confirmation using single-cell genomic techniques is warranted.

Our results provide evidence that the prognostic impact of *TP53* multihit alterations are not uniform across MDS, but is modulated by the presence of karyotype, especially isolated del(5q). Even in the context of high-risk molecular features, MDS-del(5q) retain a distinct biological and clinical behavior, with longer survival and slower disease evolution than other low-blast MDS carrying *TP53* multihit alterations.

Based on our data, a more refined classification could be suggested in MDS with <5% blasts, whereby isolated del(5q) should take diagnostic precedence when both isolated del(5q) and *TP53* multihit abnormalities are present. Conversely, in the presence of *TP53* multihit alterations without evidence of isolated MDS with del(5q), a diagnosis of MDS with *TP53* multihit should be favored. Those findings suggest that isolated del(5q) should continue to be recognized as a primary nosologic entity.

DATA AVAILABILITY

Data have been deposited in European Genome-Phenome Archive (EGA) at https://ega-archive.org/studies/EGAS50000000649 (accession number EGAS50000000649).

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AUTHOR CONTRIBUTIONS

MJM and DV designed the study, analyzed the data and wrote the manuscript. VN performed statistical analysis. TG, TB, FL, BX, NDV and AJ collected clinical data and contributed to patient management. PA, LP, CH, MMg, FSol, FS, ES, BB, and TH performed molecular and genomic analyses. OC, NHA, TK, AMZ, RSK, CG, JM, AAK, MS, RB, YW, DHW, AK, UP, DH, UG, and PF contributed to data acquisition, interpretation, and critical revision of the manuscript. YK, AC, FB, VS, AP, ED, MM, CZ, MDC, MGDP, and GGM contributed to data interpretation and manuscript revision. DV supervised the study and critically revised the manuscript. All authors reviewed and approved the final manuscript.

COMPETING INTERESTS

MJM: Received honoraria for consulting and scientific support from Jazz Pharmaceuticals; AA-K: Received honoraria from Celgene-BMS/Novartis/Astex/ALX Oncology/Aprea/Medimmune-AstraZeneca/H3B-Hemavant: research support. Novartis: scientific steering committee membership; AMZ participated in advisory boards, consulted, participated in clinical trial committees, and/or received honoraria from AbbVie, Akesobio, Agios, Amgen, Astellas, BioCryst, Beigene, Boehringer-Ingelheim, Celgene/BMS, Chiesi/Cornerstone biopharma, Daiichi Sankyo, Dr Reddy, Epizyme, Faron, Fibrogen, GSK, Glycomimetics, Genentech, Gilead, Geron, Janssen, Jasper, Karyopharm, Kyowa Kirin, Keros, Kura, Novartis, Notable, Orum, Otsuka, Pfizer, Regeneron, Rigel, Seattle Genetics, Shattuck labs, Schrodinger, Syros, Syndax, Servier, Takeda, Treadwell, Taiho, Vincerx, and Zentalis; DV: participated in advisory boards, consulted, participated in clinical trial committees, and/or received honoraria from AbbVie, Agios, Amgen, Asofarma, Astellas, Celgene/BMS, Grifols, Janssen, Jazz, MSD, Novartis, Pfizer, Sanofy, Servier, Sobi, Syros and Takeda.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Clinical Research Ethics Committee of Vall d'Hebron University Hospital (PR(AG)497/2018). All patients provided written informed consent. Additional approvals were obtained from the local ethics committees of participating centers when required.

ADDITIONAL INFORMATION

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