The prognostic role of myeloid-related gene mutations in adult acute lymphoblastic leukemia

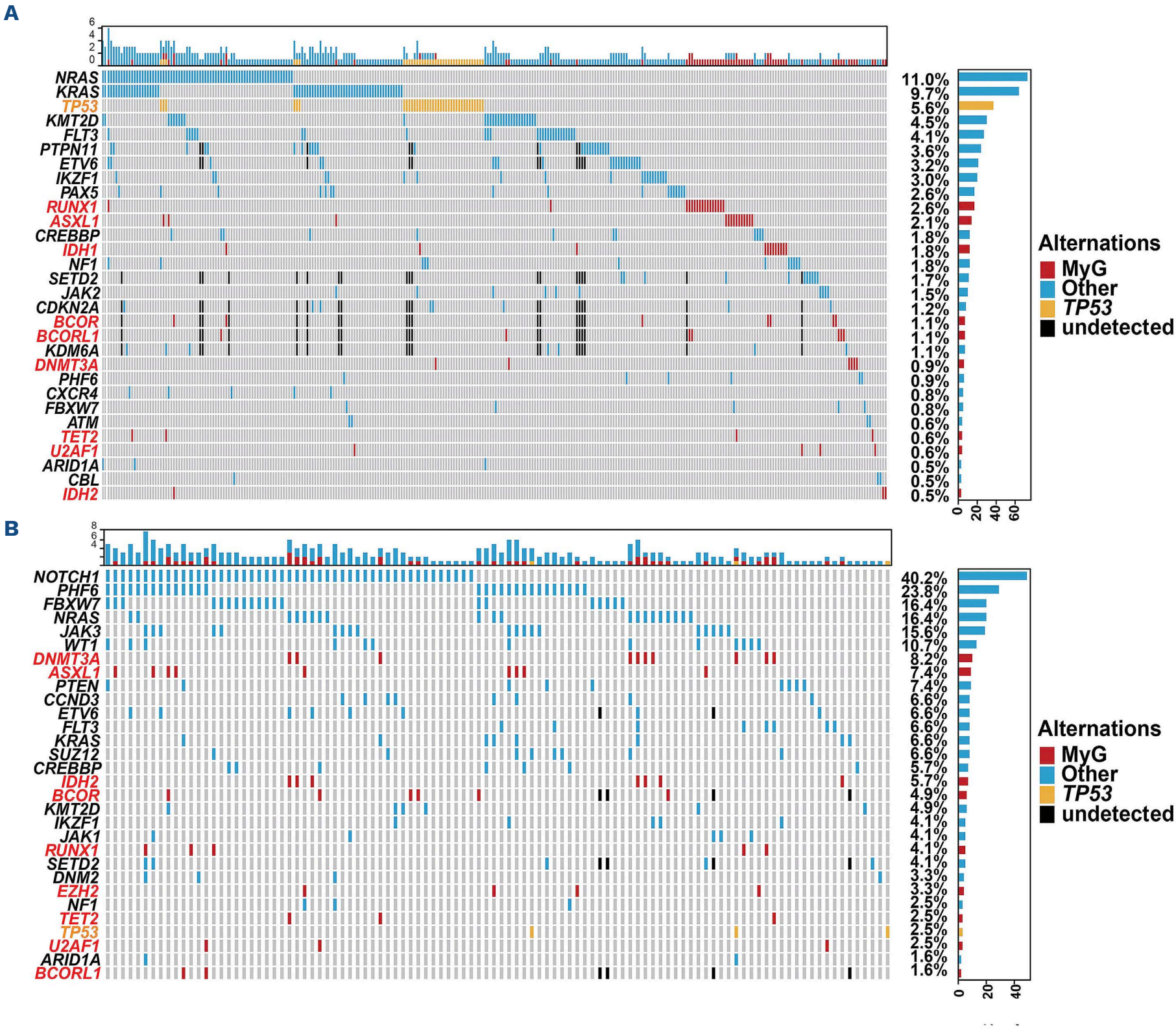
Acute lymphoblastic leukemia (ALL) is a highly heterogeneous hematologic malignancy with poor outcomes. The most frequent somatic mutations such as *DNMT3A*, *TET2*, *ASXL1*, *TP53*, and so on in clonal hematopoiesis are drivers of myeloid neoplasms.[1-3] However, the prognostic role of these myeloid gene mutations in ALL remains unclear. A recent study reported that myeloid mutations are frequent in adult ALL and are associated with adverse outcomes,[4] but this finding has not been widely validated. We defined a set of myeloid-related genes (MyG), which include DNA methylation regulators (*TET2, DNMT3A, IDH1/2*), histone modifiers (*ASXL1, EZH2*), RNA splicing factors (*SF3B1, SRSF2, ZRSR2, U2AF1/2*), transcriptional regulators (*RUNX1, BCOR, BCORL1, CEBPA, NPM1*), and cohesion complexes (*STAG2, SMC3, SMC1A, RAD21*).[5-7] We investigated the clinical characteristics and prognostic impact of MyG and *TP53* mutations in adult ALL. With approval from the ethical committee of the Institute of Hematology and Blood Diseases Hospital and in accordance with the Declaration of Helsinki, we screened 842 consecutive newly diagnosed adult ALL patients between 2016 and 2024, excluding acute leukemia of ambiguous lineage (ALAL) patients, with 783 adult ALL patients included in the final analysis, including 394 Philadelphia chromosome-negative (Ph-) B-cell ALL (B-ALL), 267 Ph-positive (Ph^+) B-ALL, and 122 T-cell ALL (T-ALL) patients. The median age was 35.6 years and 46.2% of patients were female. In total, 92.0% patients achieved complete remission (CR) after the first cycle of induction chemotherapy (Table 1).

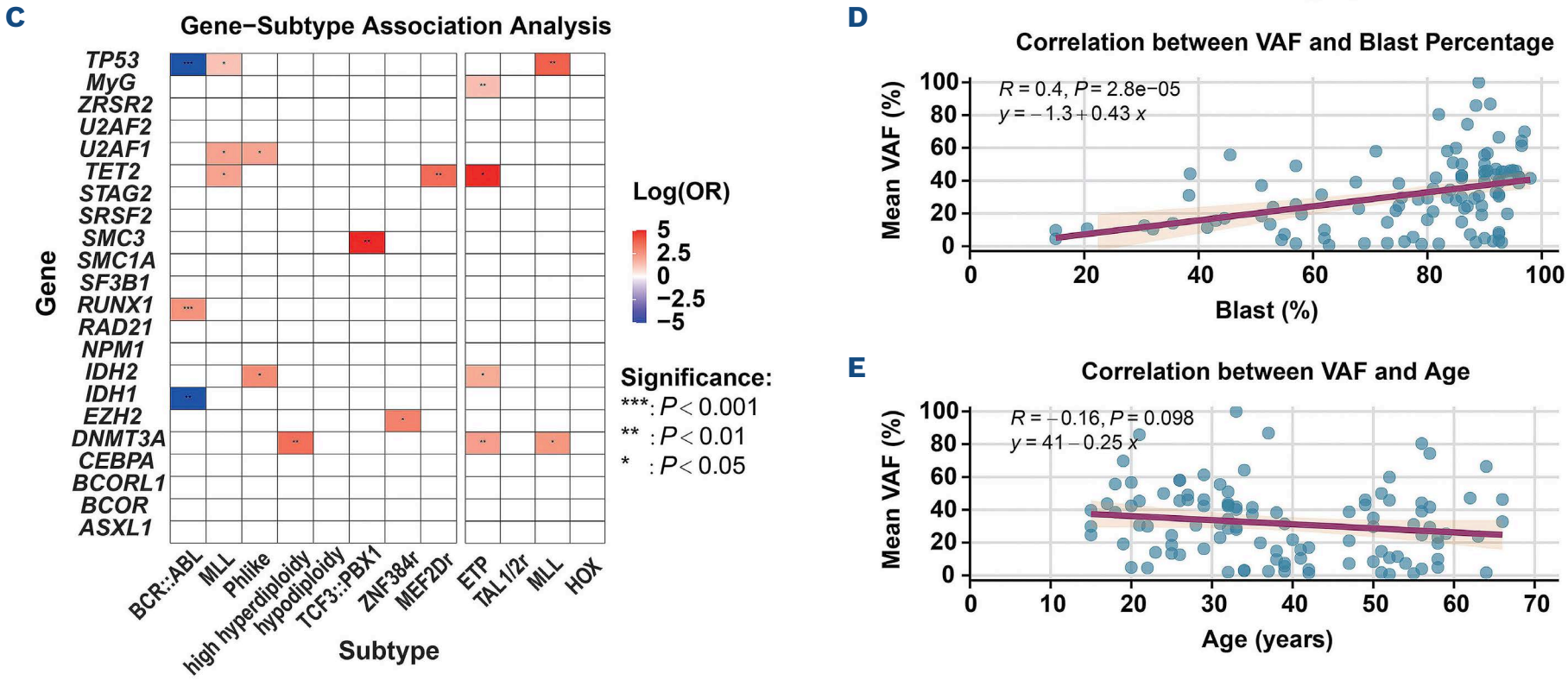
We identified 964 mutations in 453 of 783 individuals, averaging 2.13 mutations per patient. *TP53* mutations occurred in 5.1% (40/783) of patients, predominantly in Ph^- B-ALL (92.5%). MyG mutations occurred in 14.2% (111/783) of cases, with distinct subtype distributions: 10.4% in Ph^- B-ALL, 12.0% Ph^+ B-ALL, and 31.1% in T-ALL (P<0.001). Other subtype-associated mutations included *IDH1* in Ph^- B-ALL, *RUNX1* in Ph^+ B-ALL, and *DNMT3A/IDH2* in T-ALL. Within T-ALL, MyG mutations showed a strong correlation with early T-celll precursor (ETP). MyG mutations had a median variant allele frequency (VAF) of 30.2%. Analysis revealed a positive correlation between MyG VAF and blast count, but not with age, suggesting a leukemic rather than CHIP origin in this young adult cohort (Figure 1; *Online Supplementary Table S1*).

Table 1. Characteristics of patients with $MyG^{mut}/TP53^{wt}$, $MyG^{wt}/TP53^{wt}$, and $TP53^{mut}$.

Characteristic	ALL	$MyG^{mut}/TP53^{wt}$	$MyG^{wt}/TP53^{wt}$	$TP53^{mut}$	*P1*	*P2*	*P3*	*P* overall
	N=783	N=106	N=637	N=40				
Sex, N (%) Female Male	 363 (46.4) 420 (53.6)	 56 (52.8) 50 (47.2)	 292 (45.8) 345 (54.2)	 15 (37.5) 25 (62.5)	0.328	0.328	0.388	0.211
Age, years, median (range)	35.6 (15-74)	38.7 (15-66)	35.1 (15-74)	35.7 (15-74)	0.039	0.481	0.963	0.051
WBC, $\times 10^9$/L, median (IQR)	18 (4.7-55.8)	14.3 (3.0-47.6)	19.8 (5.1-58.5)	5.4 (2.9-16.7)	0.128	0.050	0.001	0.001
HB, g/L, median (IQR)	94 (71.0-119.0)	96 (73.0-120.0)	94 (71.0-119.0)	86 (70.8-115.0)	0.577	0.504	0.504	0.524
PLT, $\times 10^9$/L, median (IQR)	55 (28.0-119.0)	93 (48.0-150.0)	50 (26.0-112.0)	60 (32.8-101.0)	<0.001	0.020	0.677	<0.001
LDH, U/L, median (IQR)	483 (267-993)	368 (235-794)	495 (270-1,017)	619 (351-1,368)	0.014	0.008	0.072	0.004
Subtypes, N (%) Ph^- B-ALL Ph^+ B-ALL T-ALL	 394 267 122	 37 (34.9) 32 (30.2) 37 (34.9)	 320 (50.2) 235 (36.9) 82 (12.9)	 37 (92.5) 0 (0) 3 (7.5)	<0.001	<0.001	<0.001	<0.001
CR rate, N (%)	693 (90.1)	92 (90.2)	572 (91.2)	29 (72.5)	0.879	0.024	0.003	0.002
CR1 HSCT, N (%)	384 (49.0)	47 (44.3)	321 (50.4)	16 (40.0)	0.441	0.776	0.441	0.258

P1: $MyG^{mut}/TP53^{wt}$ *versus* $MyG^{wt}/TP53^{wt}$; *P2*: $MyG^{mut}/TP53^{wt}$ *versus* $TP53^{mut}$; *P3*: $My^{Gwt}/TP53^{wt}$ *versus* $TP53^{mut}$; *P* overall: $MyG^{mut}/TP53^{wt}$ *versus* $MyG^{wt}/TP53^{wt}$ *versus* $TP53^{mut}$. MyG: myeloid-related genes; ALL: acute lymphoblastic leukemia; WBC: white blodd cell count; IQR: interquartile range; HB: hemoglobin; PLT: platelet count; LDH: lactate dehydrogenase; Ph^-: Philadelphia chromosome-negative; Ph^+: Philadelphia chromosome-positive; CR: complete remission; CR1: first CR; HSCT: hematopoeitic stem cell transplant.





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Figure 1. Mutation spectrum and clinical correlations of myeloid related gene mutations in adult acute lymphoblastic leukemia. Oncoplots (A) and (B) show the mutation spectrum of adult B-cell acute lymphoblastic leukemia (B-ALL) and adult T-cell ALL (T-ALL), respectively. The top 30 genes with mutation frequencies are shown in the figures. Myeloid-related genes (MyG) are shown in red and *TP53* is shown in yellow. Plot (C) show associations between MyG mutations and B-ALL and T-ALL subtypes. The left panel represents the B-ALL subgroup, while the right panel represents the T-ALL subgroup. Only the color blocks with a *P* value less than 0.05 are displayed. The absolute value of Log (odds ratio [OR]) is capped at 5. Scatter plot (D) shows the relationship between the variant allele frequency (VAF) value of MyG mutation and the blast count. Scatter plot (E) showed the relationship between the VAF value of MyG mutation and age of corresponding patients.

Based on the status of *TP53* and MyG, ALL patients were categorized into *TP53*^{mut}, MyG^{mut}/*TP53*^{wt}, and MyG^{wt}/*TP53*^{wt} groups. In terms of clinical characteristics (Table 1), MyG^{mut}/*TP53*^{wt} patients were older than MyG^{wt}/*TP53*^{wt} patients (38.7 *vs*. 35.1 years; *P*=0.039), but not statistically older than *TP53*^{mut} patients (35.7 years; *P*=0.481). MyG^{mut}/*TP53*^{wt} had higher PLT (93.0×10^9/L *vs*. 50.0×10^9/L *vs*. 60.0×10^9/L; *P*<0.001) and lower LDH (368 U/L *vs*. 495 U/L *vs*. 619 U/L; *P*=0.004) compared with MyG^{wt}/*TP53*^{wt} and *TP53*^{mut} patients at diagnosis. Besides, *TP53*^{mut} patients showed lower CR rate (72.5%) after the first induction cycle compared with MyG^{mut}/*TP53*^{wt} (90.2%; *P*=0.024) and MyG^{wt}/*TP53*^{wt} (91.2%; *P*=0.003) patients.

Survival analysis across Ph$^-$ B-ALL, Ph$^+$ B-ALL and T-ALL patients showed T-ALL had the poorest outcomes (*Online Supplementary Figure S1*). Ph$^+$ B-ALL had better event-free survival (EFS) (hazard ratio [HR]=0.74; 95% confidence interval [CI]: 0.57-0.97; *P*=0.03), but similar overall survival (OS) (HR=0.91; 95% CI: 0.66-1.25; *P*=0.57) compared with Ph$^-$ B-ALL. After censoring at transplantation, T-ALL remained poorest outcomes *versus* Ph$^-$ (*P*<0.01) and Ph$^+$ (*P*<0.01) B-ALL. No differences were found in EFS (*P*=0.52) or OS (*P*=0.42) between Ph$^-$ and Ph$^+$ B-ALL.

Then, we explored the impact of *TP53* and MyG mutations on ALL outcomes. *TP53*-mutated (*TP53*^{mut}) patients exhibited inferior outcomes, whereas MyG mutations had no discernible effect. Specifically, the 3-year EFS for *TP53*^{mut} patients was 36.88%, significantly lower than those of MyG^{wt}/*TP53*^{wt} (48.15%; HR=1.65; 95% CI: 1.04-2.60; *P*=0.03) and MyG^{mut}/*TP53*^{wt} (64.58%; HR=2.30; 95% CI: 1.29-4.10; *P*<0.01) patients. A similar trend toward poorer OS was also observed for *TP53*^{mut} patients *versus* MyG^{wt}/*TP53*^{wt} (HR=1.52; 95% CI: 0.87-2.68; *P*=0.14) and MyG^{mut}/*TP53*^{wt} (HR=1.82; 95% CI: 0.91-3.67; *P*=0.09) groups, with 3-year OS at 51.70%, 58.38%, and 64.37%, respectively. In contrast, MyG^{wt}/*TP53*^{wt} and MyG^{mut}/*TP53*^{wt} patients exhibited similar EFS (HR=0.72; 95% CI: 0.48-1.07; *P*=0.10) and OS (HR=0.83; 95% CI: 0.53-1.33; *P*=0.44) (Figure 2A, B). Age-stratified analysis (≤35 *vs*. >35 years) confirmed MyG mutations lacked prognostic impact in both subgroups (*P*>0.05). Correspondingly, censoring at transplantation, *TP53*^{mut} patients exhibited the worst outcomes compared with MyG^{wt}/*TP53*^{wt} and MyG^{mut}/*TP53*^{wt}, and no significant differences were found in outcomes between MyG^{wt}/*TP53*^{wt} and MyG^{mut}/*TP53*^{wt} patients (*Online Supplementary Figure S1E, F*). Subsequently, we conducted a multivariate analysis of the overall cohort and demonstrated that *TP53* mutation was significantly associated with worse EFS and OS, but MyG mutation did not significantly affect EFS or OS in ALL (*Online Supplementary Table S2*).

We further analyzed the impact of MyG mutations on outcome in Ph$^+$ B-ALL, Ph$^-$ B-ALL, and T-ALL subgroups (Figure 2). In Ph$^-$ B-ALL, *TP53*^{mut} patients had a 3-year EFS of 38.35% inferior to MyG^{mut}/*TP53*^{wt} cases (65.17%; HR=2.33; 95% CI: 1.04-5.18; *P*=0.04), and also tended to be lower than MyG^{wt}/*TP53*^{wt} cases (47.34%; HR=1.49; 95% CI: 0.91-2.44; *P*=0.11). Additionally, we observed a trend toward poorer OS in *TP53*^{mut} patients (3-year OS 54.80%) compared with MyG^{mut}/*TP53*^{wt} (3-year OS 68.38 %; HR=1.84, 95% CI: 0.68-4.98; *P*=0.23) and MyG^{wt}/*TP53*^{wt} patients (60.16 %; HR=1.34; 95% CI: 0.72-2.51; *P*=0.36). In T-ALL and Ph$^+$ B-ALL subgroup, we did not analyzed effects of *TP53* mutations due to the low number of patients with *TP53* mutations. MyG mutation did not significantly impact EFS or OS in any subgroup. In Ph$^+$ B-ALL, MyG^{wt}/*TP53*^{wt} and MyG^{mut}/*TP53*^{wt} patients exhibited comparable EFS and OS, with a median EFS (mEFS) of 47.37 months *versus* not reached (HR=0.54; 95% CI: 0.23-1.24; *P*=0.14) and median OS (mOS) of 53.94 months *versus* 43.06 months (HR=0.67; 95% CI: 0.27-1.68; *P*=0.40). In Ph$^-$ B-ALL, the 3-year EFS was 47.34% for MyG^{wt}/*TP53*^{wt} patients and 65.17% for MyG^{mut}/*TP53*^{wt} patients (HR=0.64; 95% CI: 0.33-1.26; *P*=0.20), with 3-year OS rates of 60.16% and 68.38%, respectively (HR=0.73; 95% CI: 0.32-1.67; *P*=0.45). In T-ALL, no significant differences were observed, with an mEFS of 18.36 months for MyG^{wt}/*TP53*^{wt} *versus* not reached for MyG^{mut}/*TP53*^{wt} (HR=0.75; 95% CI: 0.40-1.43; *P*=0.39) and an mOS of 30.58 months *versus* not reached (HR=1.02; 95% CI: 0.48-2.14; *P*=0.96), and stratification by ETP and *NOTCH1/FBXW7/RAS/PTEN* genetic risk yielded consistent results (*P*>0.05). After censoring at transplantation (*Online Supplermentary Figure S1*), in Ph$^-$ B-ALL, *TP53*^{mut} patients had significantly worse EFS than MyG^{wt}/*TP53*^{wt} (*P*=0.02) and MyG^{mut}/*TP53*^{wt} (*P*=0.04). For OS, T*P53*^{mut} patients showed significantly worse OS than MyG^{wt}/*TP53*^{wt} (*P*=0.04) and a trend toward worse OS compared to MyG^{mut}/*TP53*^{wt} (*P*=0.10). However, MyG mutations did not affect outcomes in Ph$^+$ B-ALL, Ph$^-$ B-ALL, or T-ALL (all, *P*>0.05). Multivariate analysis in subgroups showed that *TP53* mutation was associated with inferior EFS but not OS in Ph$^-$ B-ALL, and no significant impact of MyG mutation on EFS or OS across the Ph$^+$ B-ALL, Ph$^-$ B-ALL, and T-ALL subgroups (*Online Supplementary Table S2*).

This study confirms *TP53* mutation as an independent ad-

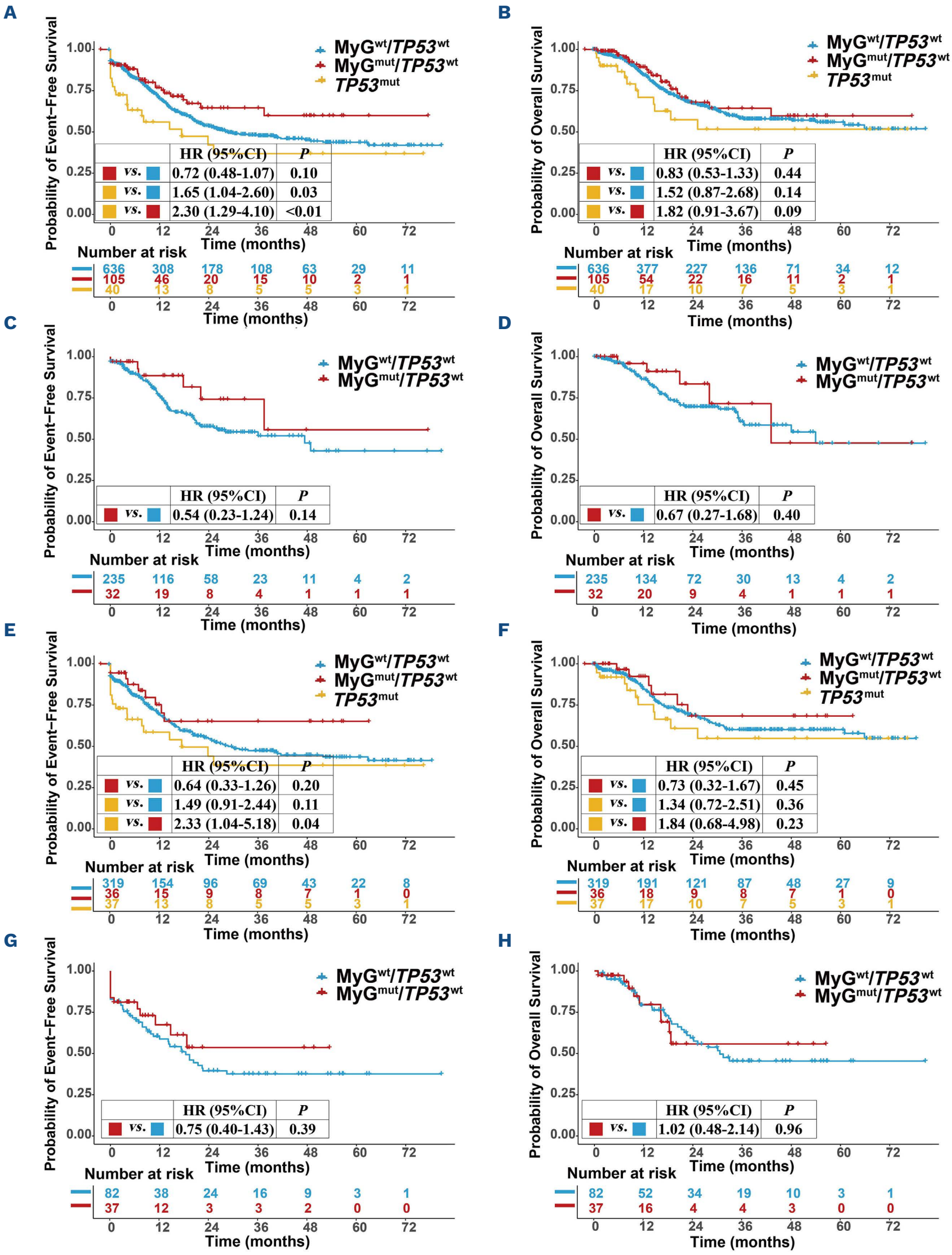


Figure 2. Kaplan-Meier survival analysis based on *TP53* and myeloid-related gene mutation status. Shown are event-free survial and overall survival for: (A, B) the overall acute lymphoblastic leukemia (ALL) cohort; (C, D) Philadephia chromosome-positive (Ph+) B-cell ALL (B-ALL); (E, F) Ph-negative (Ph-) B-ALL; and (G, H) T-cell ALL (T-ALL). MyG: myeloid-related gene mutations; HR: hazard ratio; CI: confidence interval, wt: wild-type; mut: mutated.

verse prognostic factor in adult ALL.[8-10] MyG mutations were more prevalent in T-ALL/ETP, with distinct gene-subtype associations: *IDH1* mutations in Ph$^-$ B-ALL, *RUNX1* mutations in Ph$^+$ B-ALL, and *DNMT3A/IDH2* mutations in T-ALL, but lacked independent prognostic impact.

Saygin *et al*. identified the adverse effect of myeloid mutation in ALL and attributed this to clonal hematopoiesis of indeterminate potential (CHIP). In our young-adult cohort, VAF correlated with blast count but not with age, supporting a leukemic rather than age-related CHIP origin. Specifically, VAF of *DNMT3A/TET2* mutations also showed no correlation with age, further arguing against a CHIP origin. Thus, prognostic impact depends on origin. Leukemic-derived mutations are passengers diluted by dominant drivers and intensive therapy. CHIP-derived mutations may show chemoresistance. This framework reconciles our negative findings with those of Saygin *et al*., and is further supported by Niroula *et al*., who showed that CHIP does not increase lymphatic malignancy risk.[11] Additional factors may contribute to the discrepancy between studies. Our Chinese cohort received Berlin-Frankfurt-Munic-based chemotherapy, combined with tyrosine kinase inhibitors for Ph$^+$ ALL, whereas Saygin *et al*. studied a diverse population treated with various regimens including hyper-CVAD and blinatumomab. Several limitations should be acknowledged. Our cohort is young (median 35.6 years) and exclusively Chinese, limiting generalizability to older or western populations. Future studies with single-cell genomic analyses at diagnosis are needed to map mutation ontogeny and distinguish drivers from passengers, and validation in older and Western cohorts is warranted.

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Disclosures

No conflicts of interest to disclose.

Contributions

HW, JW, and XG participated in concept design. WW was involved in data analysis, drafting and revising the manuscript. JC, YL, GZ, CZ, QF, SL, KL, DL, BG, and YL collected the data. CG, YH, YW, SQ, BL, YW, and YM were responsible for interpreting the results. All authors have read and approved the final manuscript.

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Data-sharing statement

The datasets from this study are available upon reasonable request from the corresponding author.

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