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Prognostic value and clinical feature of SF3B1 mutations in myelodysplastic syndromes: A meta-analysis

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ABSTRACT

SF3B1 gene mutations are the most frequent mutations found in myelodysplastic syndromes (MDS), and the prognostic implication of these mutations remains controversial. We conducted a meta-analysis of studies assessing the prognostic impact and clinical feature of SF3B1 mutations in MDS patients. The overall hazard ratio for overall survival (OS) was 0.90 (95% confidence interval 0.60–1.35, P = 0.61) in MDS patients with SF3B1 mutations compared to those without. Lower leukemia-free survival was associated with SF3B1 mutations. Subgroup analyses showed that Asian cohorts and Illumina HiSeq 2000 methods were significantly associated with OS. Furthermore, SF3B1 mutations were significantly correlated with a lower level of blast cells and a high level of platelet counts and bone marrow ring sideroblasts. Thus, the current meta-analysis suggests that SF3B1 mutations have no significant impact on the OS of MDS patients, and the hematologic parameters of SF3B1 mutations identify a distinct subset of MDS patients with homogeneous features.

1. Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of myeloid malignancies characterized by cytopenia, myelodysplasia, ineffective hematopoiesis, and propensity for progression to acute myeloid leukemia (Jhanwar, 2015; Pellagatti and Boultwood, 2015; Tefferi and Vardiman, 2009). Recent understanding of the impact of diversified pathway genes on MDS pathogenesis and its evolution to acute myeloid leukemia (AML) has provided molecular insight into MDS prognostication based on point mutations (Haferlach et al., 2014; Bejar et al., 2011). Splicing factor gene mutations, which occur in over half of all patients, are the most common molecular abnormalities found in this disorder (Haferlach et al., 2014; Graubert et al., 2011; Makishima et al., 2012; Papaemmanuil et al., 2011, 2013; Walter et al., 2013; Yoshida et al., 2011). Splicing factor gene mutations are found in other myeloid malignancies, including AML, but are strongly associated with the phenotypes of MDS and closely related conditions.

SF3B1 mutations are predominantly heterozygous missense mutations at residues K700, K666, R625, and H662, but the specific effects of these mutations on protein function remain unknown. It is hypothesized that mutations in SF3B1 alter branch points and the recognition of 30 splice sites, which contribute to changes in the mature mRNA pool. Indeed, a recent examination of the splicing of 81,564 exons in 9069 genes revealed that 423 exons in 350 genes were differentially used in mutants compared with their use in a representative healthy donor (Larsson et al., 2013).

SF3B1 mutations are found in approximately 20–28% of all MDS patients (Papaemmanuil et al., 2013; Yoshida et al., 2011; Malcovati et al., 2011) and in only 6% of patients with MDS without ring sideroblasts (RS), specifically implicating SF3B1 mutations in the pathogenesis of this subtype of MDS (Yoshida et al., 2011; Visconte et al., 2012). Importantly, it was recently shown that SF3B1 has a critical role in MDS by affecting the expression and splicing of genes involved in specific cellular processes, many of which are relevant to the pathophysiology of refractory anemia with ring sideroblasts (RARS) (Dolatshad et al., 2015).

SF3B1 mutations positively predict the RS phenotype in ~98% of MDS cases (Malcovati et al., 2011). Patients with MDS carrying SF3B1 mutations show homogeneous disease phenotypes characterized by a high prevalence of isolated erythroid dysplasia, high degree of

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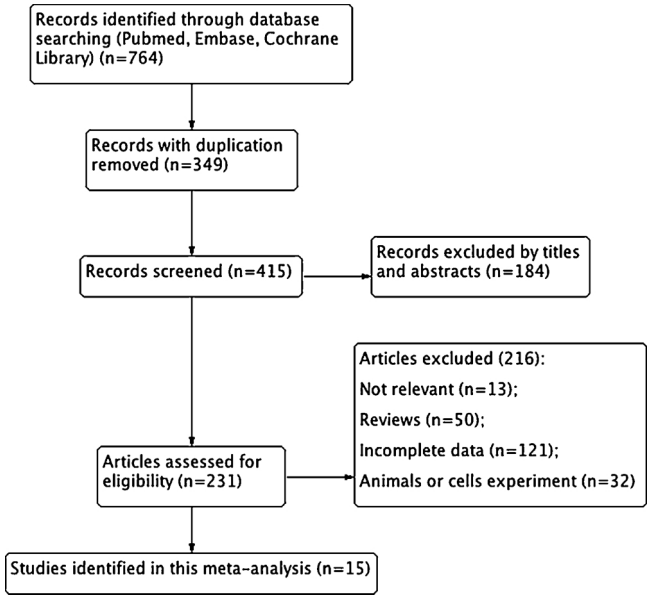

Fig. 1. Flow chart of the literature search and selection strategy.

erythroid dysplasia and high proportion of RS (Malcovati and Cazzola, 2016). Previous studies showed that SF3B1 mutations are able to identify a distinct subset of MDS patients with homogeneous genotypic and phenotypic features (Malcovati and Cazzola, 2016). However, the precise role of SF3B1 mutations in the prognosis of MDS patients remains controversial. Many studies have shown that SF3B1 mutations are predictive of better MDS patient survival and a reduced risk of AML transformation (Papaemmanuil et al., 2011; Malcovati et al., 2011, 2015), but other studies have not made this observation (Damm et al., 2012; Kang et al., 2015; Lin et al., 2014; Makishima et al., 2012; Thol et al., 2012). As a result, the exact implications of SF3B1 mutations on MDS are not well understood. Therefore, we performed a meta-analysis to exactly delineate the prognostic role of SF3B1 mutations in MDS patients.

2. Methods

2.1. Search strategy

The search for eligible studies was conducted in PubMed, Embase and the Cochrane Library with the following search terms: “myelodysplastic syndromes” or “myelodysplastic syndrome” or “syndrome, myelodysplastic” or “syndromes, myelodysplastic” or “dysmyelopoietic syndromes” or “dysmyelopoietic syndrome” or “syndrome, dysmyelopoietic” or “syndromes, dysmyelopoietic” or “hematopoietic myelodysplasia” or “hematopoietic myelodysplasias” or “myelodysplasia, hematopoietic” or “myelodysplasias, hematopoietic” and “SF3B1″. The search was restricted to human studies. Reference lists of relevant studies and review articles were also searched. If necessary, the corresponding authors were contacted to retrieve further information. The literature retrieval was performed by two independent reviewers (Y Tang and M Miao).

2.2. Selection criteria

Studies were included in this meta-analysis if they satisfied the following criteria: (1) primary studies; (2) assessed the association between SF3B1 mutation and prognosis in MDS patients; (3) offered detailed survival information from which we could calculate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) or sufficient data to calculate these estimates; (4) published before or during October 2017. We excluded studies that were published as review articles, case reports, re-analyses, editorials or commentaries. However, we included a meeting abstract in our meta-analysis because it met all of the inclusion criteria.

2.3. Data extraction and quality assessment

Information was carefully extracted from all eligible studies by two authors (Y Tang. and M Miao.). Disagreements were resolved by discussion until a consensus was achieved. The following data were extracted from the articles: the name of the first author, year of publication, journal, number of patients, age, sex, criteria for MDS classification, MDS classification, number of SF3B1 mutations, frequency and distribution of SF3B1 mutations, white blood cells, hemoglobin, platelet count, bone marrow blasts, RS, and HRs and 95% CIs for the overall survival (OS) based on SF3B1 mutation status. When outcomes published in the original articles were only survival curves, HRs and 95% CIs were calculated by methods proposed by Parmar et al (Parmar et al., 1998) and Hotta et al (Hotta et al., 2004). If HRs of the univariate analysis and multivariate analyses were reported, the results of the multivariate analyses including other variables were preferentially considered because they were likely more accurate.

2.4. Statistical analysis

All analyses were performed using STATA 14.0 (Stata Corporation, College Station, TX) and Review Manager (version 5.3, the Cochrane Collaboration, Oxford, UK). A bilateral P value < 0.05 indicated a significant difference. For the OS, progression-free survival (PFS) and leukemia-free survival (LFS), HRs and their 95% CIs were directly extracted from the included studies or indirectly calculated from the reported events, the P value in the log rank test or from the published Kaplan-Meier curves (Tierney et al., 2007; Higgins et al., 2003; DerSimonian and Laird, 1986). Subsequently, we assessed the heterogeneity among the studies based on the Q value and the I^2 statistic value (25%, 50%, and 75% correspond to the cut-off points for low, moderate, and high degrees of heterogeneity, respectively). Heterogeneity was considered to be statistically significant if I^2 was $> 50\%$; otherwise, no significant heterogeneity was observed. When the heterogeneity across studies was identified ($> 50\%$), the random effects model (the DerSimonian and Laird method) was used; otherwise, the fixed-effect model (the Mantel-Haenszel method) was used (Egge et al., 1997). Eventually, sensitivity analysis was conducted to investigate the influence of one single study on the overall HR, and Begg’s and Egger’s tests were conducted to detect possible publication bias. All the statistical analyses were done by Y Tang and M Miao.

3. Results

3.1. Characteristics of eligible studies

The initial literature search yielded 764 records (Fig. 1). After excluding 349 duplicates, 415 records remained for further screening. By reading the titles and reviewing abstracts, we excluded unrelated studies (n = 184). Thus, 231 records remained for full-text screening. After carefully reading the full texts, 216 studies were eliminated due to insufficient or irrelevant data, reviews, animals or cell experiments. Finally, we included 15 studies comprising 3568 patients in the meta-analysis. All 15 eligible studies were retrospective studies. The sample size ranged from 36 to 533, and the frequency of SF3B1 mutations in the included articles varied between 7.0 and 62.1%. Patients in 14 eligible studies (Makishima et al., 2012; Malcovati et al., 2011, 2015; Damm et al., 2012; Kang et al., 2015; Lin et al., 2014; Cui et al., 2012; Komrokji et al., 2015; Mian et al., 2013; Nazha et al., 2016; Seo et al., 2014; Tefferi et al., 2017; Traina et al., 2014; Wu et al., 2016) were classified by WHO criteria, and data from Bejar (Bejar et al., 2012) were not available. The basic characteristics and genotype distribution of the

Table 1
Summary of the data extracted from the 15 studies included.

Study, Year	Patients (No.)	Age (range)	No. Males (%)	Criterion	MDS classification	SF3B1 status (%)	Frequency and distribution of SF3B1 mutations
Bejar R, 2012	288	NA	NA	NA	NA	64(22.2)	NA
Cui R, 2012	104	16-81	70(67.3)	WHO	MDS-RS	55(52.9)	K700E(36), R625C/L(7), K666R/T(6), H662Q(3), G740E/V(2), E622D (1)
Damm F, 2012	317	36-95	189(59.6)	WHO	RA(63), RARS(38), RCMD(43), RCMD-RS(12), RAEB-1(55), RAEB-2(50), MDS-U(23), del(5q)(19)	47(14.8)	K700E(30), K666 N(6), H662Y(2), D781 G(2), K666Q(1), R625 L/C/H/G(1), E622D(1), H662Q(1)
Kang MG, 2015	129	NA	71(55.0)	WHO	RCUD(19), RCMD(56), RAEB-1(16), RAEB-2(30), del(5q)(2), Hypoplastic MDS(5), MDS-U(1)	9(7.0)	NA
Komrokji R S, 2015	144	NA	93(64.6)	WHO	RA(9), RARS(33), RARS-T(6), RCMD(25), RAEB-1(13), RAEB-2(12), MDS-U(5), MDS/MPN(11), CMML(9), del(5q)(7),	48(33.3)	NA
Lin CC, 2014	479	66(17-98)	318(66.4)	WHO	RARS(20), RCUD(76), RCMD(95), RCMD-RS(14), RAEB-1(79), RAEB-2(85), MDS-U(3)	48(10.0)	K700E(33), K666 N(5), R625C(2), K666Q/T/E(1), A672D(1), E622D (1), H662Q/D(1), I704 N(1)
Makishima H, 2012	58	NA	NA	WHO	Low-risk MDS (< 5% myeloblasts)	NA	NA
Malcovati L, 2011	533	NA	NA	WHO	RA(122), RARS(105), RCMD(96), RCMD-RS(52), RAEB-1(83), RAEB-2(53), MDSdel(5q)(22)	150(28.1)	K700E, H662Q, E662D, K666R, R625 L, K666 N, K666Q, R625C, D781 G, K666 T, E592 K, et al
Malcovati L, 2015	243	NA	NA	WHO	RARS(90), RCUD(7), RCMD(27), RCMD-RS(69), RAEB-1(20), RAEB-2(23), del(5q)(7)	151(62.1)	NA
Mian SA, 2013	154	65.5(17-85)	104(67.5)	WHO	RA/RCMD(40), RARS/RCMD-RS(24), RAEB-1/2(49), sAML(15), t-tMDS/AML(12), CMML&MPD/MDS-U(14)	24(15.6)	K700E(11), H662Q(4), K666Q/R(2), E622D(2), D781 G(1),R625C(1), others(3)
Nazha A, 2016	508	NA	NA	WHO	RARS(44), RCUD(24), RCMD(125), RAEB-1(74), RAEB-2(68), MDS-U(53), del(5q)(17), CMML(79), MDS/MPN-U(24)	73(14.4)	NA
Seo JY, 2014	36	14-84	26(72.2)	WHO	RA(2), RARS(3), RARS-T(4), RCMD(20), RAEB(5), MDS-U(2)	16(44.4)	K700E(10), H662Q(2), K666Q(2), R625C(1), G742D(1)
Tefferi A, 2017	179	73(28-96)	122(68.2)	WHO	NA	36(20.1)	NA
Traina F, 2014	92	NA	68(73.9)	WHO	NA	12(13.0)	NA
Wu L, 2016	304	57(11-89)	162(53.3)	WHO	RAS(9), RCUD(20), RCMD-RS(145), RAEB-1(52), RAEB-2(71), MDS-U(6), del(5q)(1)	25(8.2)	K700E(12), H662Y(1), E622D(2), K666E(1), R625 H(2), K666 N(3), E592 K(1), G605S(1), K666 T(2)

NA: not available.

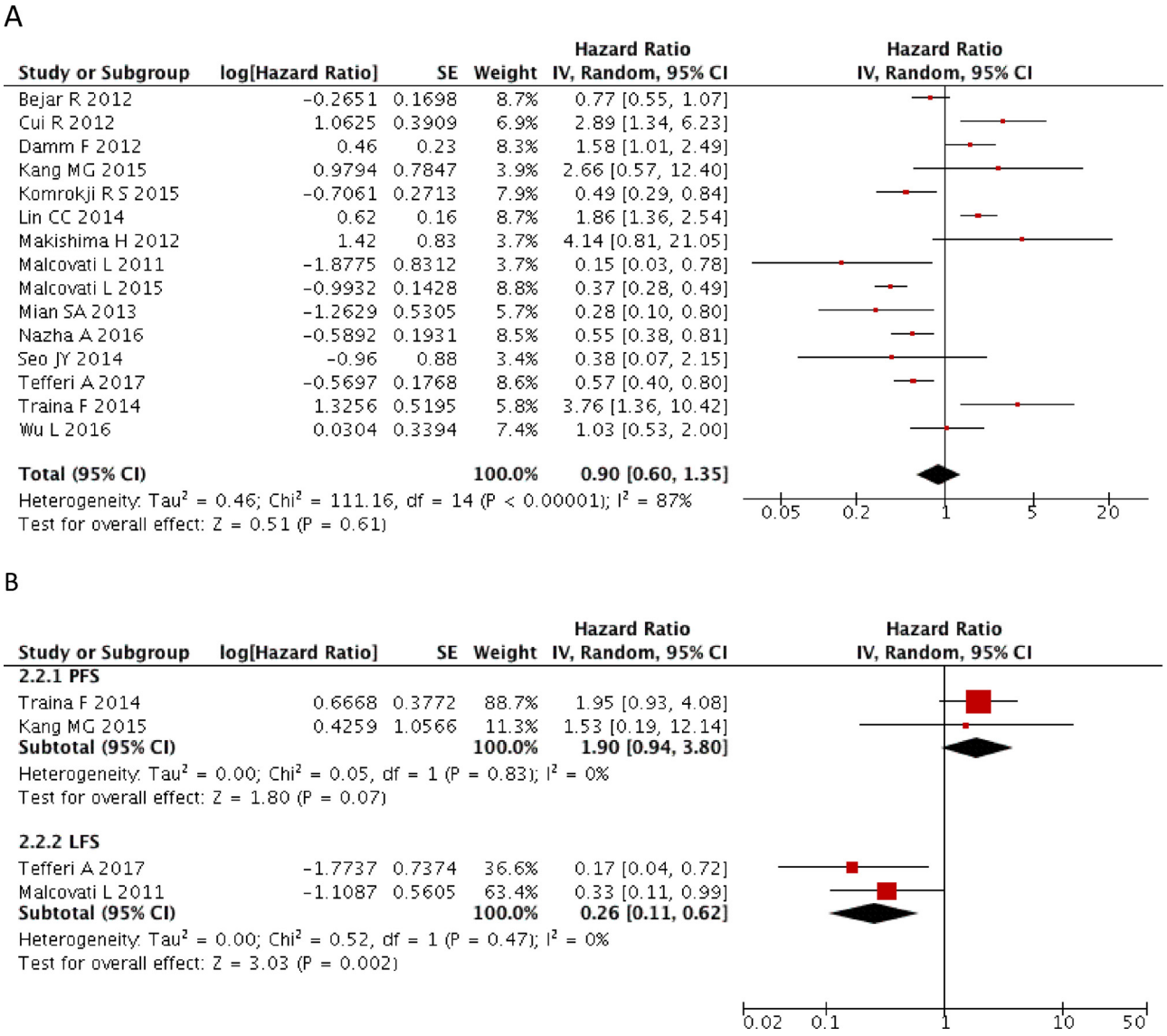

Fig. 2. Forest plots showing the association of survival with SF3B1 mutation. (A) No significant association was found between OS and SF3B1 mutation. (B) A significant association was found between LFS and SF3B1 mutation; no significant association was detected for PFS.

15 studies are listed in Table 1.

3.2. Prognostic impact of SF3B1 mutations in patients with MDS

We evaluated all eligible studies, with a total of 3568 patients. The overall HR for the OS was 0.90 (95% CI 0.60–1.35, I^2 = 87%, P = 0.61) in MDS patients with SF3B1 mutations compared to those without (Fig. 2). These data indicated that SF3B1 mutations did not significantly affect the OS in patients with MDS. The LFS and PFS between patients with and without TET2 mutations were analyzed, and the results showed that SF3B1 mutation significantly predicted LFS (HR 0.26, 95% CI 0.11–0.62, I^2 = 0%, P = 0.002), while no correlation was found between PFS and SF3B1 mutation (HR 1.9, 95% CI 0.94–3.8, I^2 = 0%, P = 0.07) (Fig. 2).

Furthermore, a subgroup analysis for race showed the pooled HR for Asian populations was 1.64 (95% CI 1.02–2.64, I^2 = 47%, P = 0.04); however, no significant association was found among Europeans and Americans (HR 0.46, 95% CI 0.17–1.25, I^2 = 91%, P = 0.13; HR 0.72, 95% CI 0.43–1.21, I^2 = 77%, P = 0.22, respectively) (Fig. 3). Additionally, the number of cases enrolled in studies did not alter the predictive value of SF3B1 mutation on the OS (cases number > 200: HR 0.78, 95% CI 0.45–1.35, I^2 = 92%, P = 0.37; cases number < 200: HR 1.10, 95% CI 0.55–2.19, I^2 = 81%, P = 0.79). For studies evaluating OS by using different methods for SF3B1 mutation detection, the results showed the pooled HR for Illumina HiSeq 2000 was 0.36 (95% CI 0.28–0.48, I^2 = 0%, P < 0.000), while there was no statistically significant correlation observed between detection by ABI 3730xl DNA analyzer and OS (HR 1.57, 95% CI 0.54–4.55, I^2 = 85%, P = 0.40) (Fig. 3).

3.3. Association between SF3B1 mutations and hematologic features of patients

A total of five studies reported peripheral blood cell counts between SF3B1-mutated and SF3B1 wild-type patients. Notably, our meta-analysis revealed that SF3B1 mutation was significantly correlated with a high platelet count (MD 82.11, 95% CI 53.81–110.41, I^2 = 0%, P < 0.000) (Fig. 4). No association was found between SF3B1 mutation and hemoglobin or white blood cells (MD -5.5, 95% CI -12.01–1.00, I^2 = 97%, P = 0.1; MD 0.63, 95% CI -0.21–1.47, I^2 = 7%, P = 0.14) (Fig. 4). The percentage of bone marrow RS for patients with SF3B1 mutations was significantly higher than that for SF3B1 wild-type

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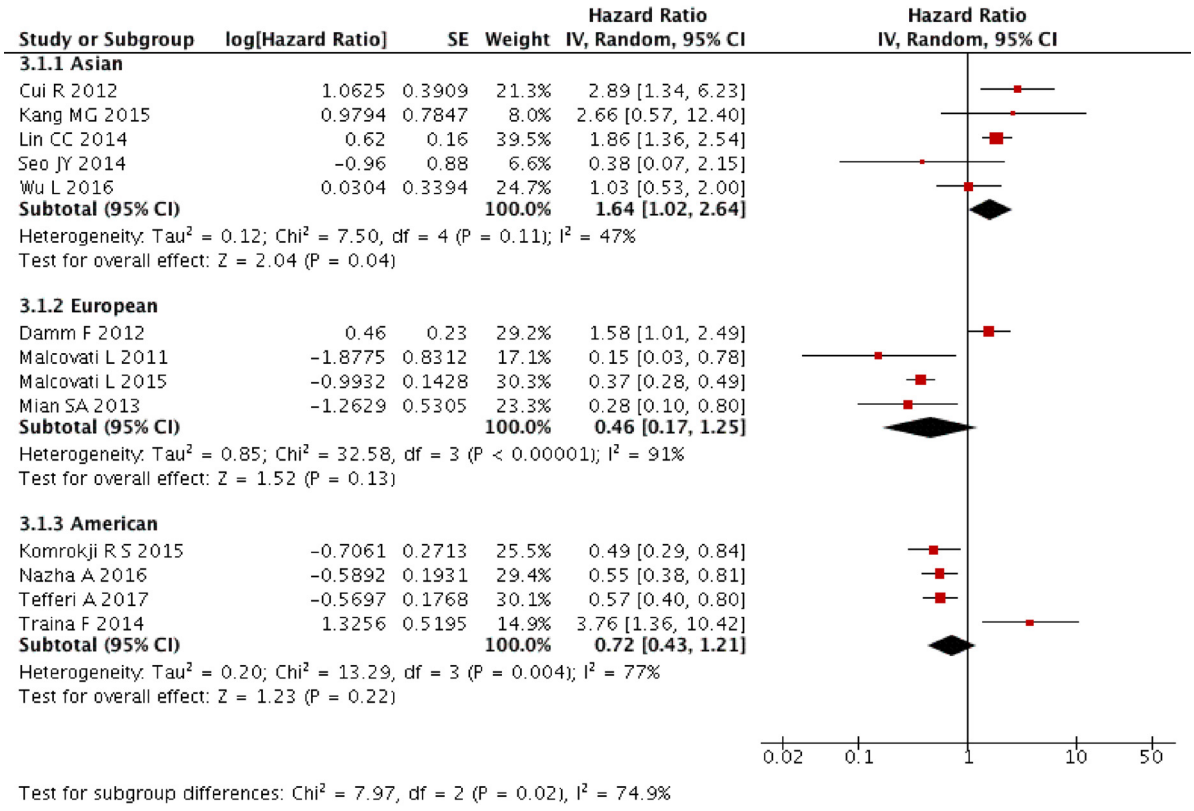

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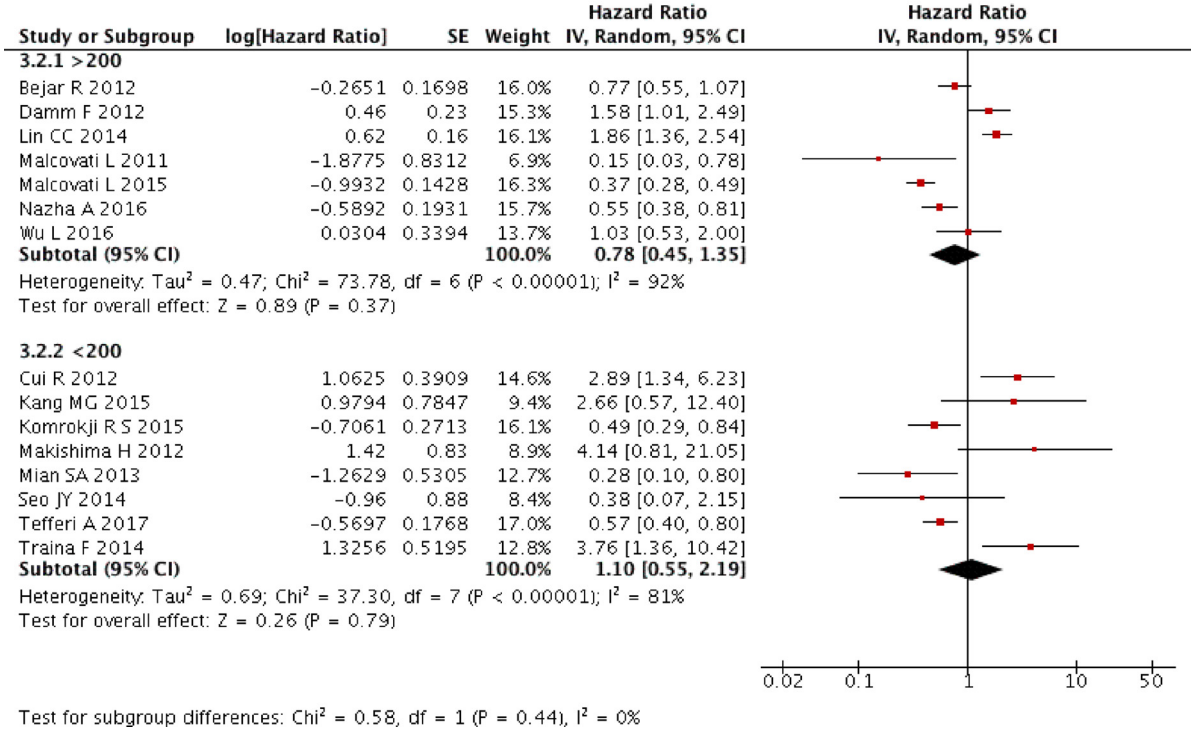


Fig. 3. Forest plot of different races. Cases included and mutation analyses were included in the subgroup analysis for OS. (A) Subgroup analysis of OS by race. (B) Subgroup analysis of OS by cases included. (C) Subgroup analysis of OS by mutation analysis methods.

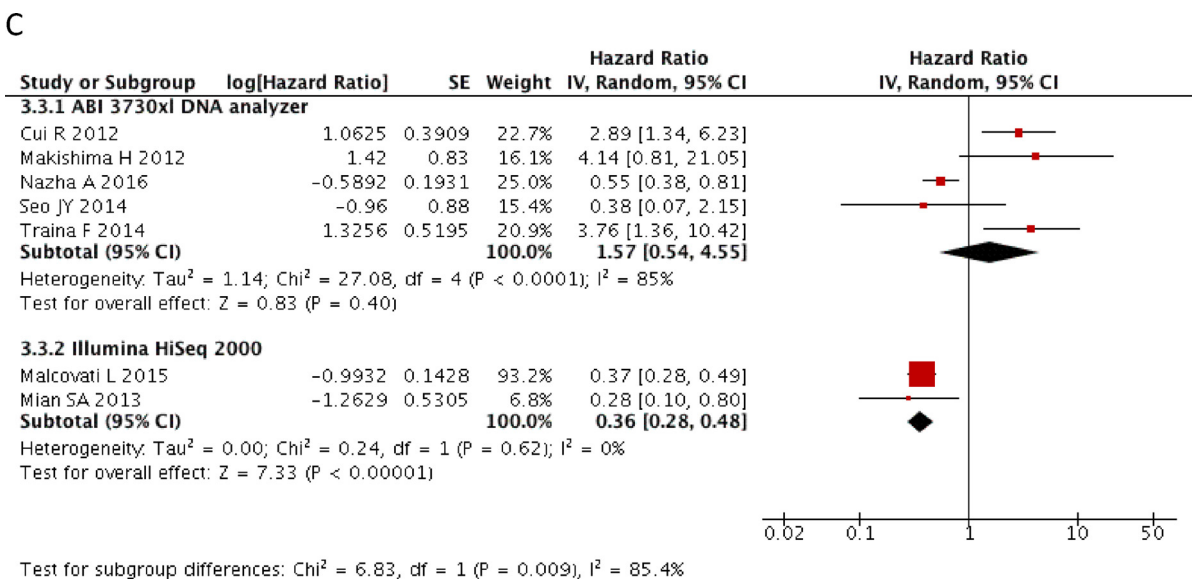


Fig. 3. (*continued*)

individuals (MD 16.34, 95% CI 10.93–21.74, $I^2 = 0\%$, $P < 0.000$) (Fig. 4), and lower levels of blast cells were observed in patients with SF3B1 mutations (MD -1.03, 95% CI -1.50– -0.56, $I^2 = 0\%$, $P < 0.000$) (Fig. 4).

As shown in Fig. 4, SF3B1 mutations significantly correlated with lower IPSS risk (OR 2.81, 95% CI 1.78–4.42, $I^2 = 33\%$, $P < 0.000$; OR 0.29, 95% CI 0.17–0.51, $I^2 = 39\%$, $P < 0.000$). Furthermore, a significant association was revealed between elderly age and SF3B1 mutation (MD 6.15, 95% CI 1.62–10.67, $I^2 = 72\%$, $P = 0.008$) (Fig. 4). However, there was no statistically significant correlation between gender and SF3B1 mutation (OR 1.17, 95% CI 0.82–1.66, $I^2 = 0\%$, $P = 0.38$) (Fig. 4).

3.4. Sensitivity analysis and publication bias

A sensitivity analysis was conducted to validate the certainty of our findings. As shown in Fig. 5, no individual study had a predominant influence on the overall HR. We constructed a funnel plot to detect the existence of publication bias, and the resulting figure indicates basic symmetry (Fig. 6). Indeed, no significant evidence of publication bias was found (P values for the Begg's test and Egger's test were 0.921 and 0.458, respectively).

4. Discussion

The SF3B1 gene encodes subunit 1 of the splicing factor 3b protein complex, which forms the U2 snRNP along with splicing factor 3a and a 12S RNA unit. This complex plays a critical role in the splicing machinery and regulates the diversity of splice variants (Wahl et al., 2009). SF3B1 is also involved in the alternative gene splicing program, which may explain the critical contribution of mutant SF3B1 in modulating the proliferation and survival of tumor cells (Rossi et al., 2011). Importantly, it was recently shown that SF3B1 mutations in MDS patients with RS can arise from the rare HSC compartment and are initiating events in this disorder (Mian et al., 2015).

The SF3B1 gene is one of the most frequently mutated genes in MDS. However, the prognostic value of OS in SF3B1-mutated patients with MDS remains controversial. This is the first time that such an estimation based on a quantitative summary of relative studies has been performed. Our meta-analysis showed that the overall HR for the OS was 0.90 (95% CI 0.60–1.35), which indicated that SF3B1 mutations did not significantly affect the OS in patients with MDS. Although the heterogeneity was large ($I^2 = 87\%$), the sensitivity analysis indicated the stability of our analysis, thus demonstrating that the results of the meta-analysis were reliable. Further analyses showed that the HR for LFS was 0.26 (95% CI 0.11–0.62), suggesting that lower LFS was associated with SF3B1 mutation. The pooled HR for PFS was 1.9 (95% CI 0.94–3.8), demonstrating that SF3B1 mutations had no significant impact on PFS in patients with MDS. Subgroup analyses showed that Asian cohorts and Illumina HiSeq 2000 methods were significantly associated with OS, suggesting the impact of ethnic variations on SF3B1 mutation. However, the Illumina HiSeq 2000 subgroup included only two studies, and the exact role of mutation detection in OS requires further investigation. Unfortunately, insufficient data were available regarding SF3B1 mutation to permit further subgroup analysis.

The association of hematologic features and SF3B1 mutation strongly supports the homogeneous disease phenotype. Platelet levels and the percentage of bone marrow RS were found to be significantly higher in patients with SF3B1 mutations, which is consistent with nearly all eligible studies. The study showed that SF3B1 mutations are strongly linked to the MDS-RS and lower IPSS risk scores, whereas no significant impact on the OS of MDS patients was found. A potential explanation for this discrepancy is that the SF3B1 mutation coexisted with other genetic alterations (for example, DNMT3A and RUNX1 mutations) related to unfavorable outcomes (Bejar et al., 2012, 2014; Lin et al., 2014), thereby mitigating the positive effect on survival. Furthermore, a significant association was revealed between elderly age and SF3B1 mutation in this analysis, and age has a marked prognostic impact on survival (Lin et al., 2014).

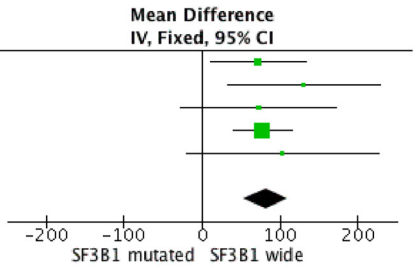
5. Conclusion

The results of this systematic review and meta-analysis clearly demonstrate that SF3B1 mutations have no significant impact on the OS of MDS patients. Subgroup analyses revealed that Asian cohorts and Illumina HiSeq 2000 methods were significantly associated with OS. Furthermore, SF3B1 mutations were associated with elderly age, higher platelet counts and RS in the bone marrow, lower levels of blast cells, lower IPSS risk and lower LFS. However, several limitations of this meta-analysis must be considered. First, we included only studies from selected databases, hence other relevant studies may have been left out. Second, some high-quality studies were excluded because detailed data were missing. Finally, the number of studies included was relatively small, which may affect the subgroup analyses. For example, only two studies investigated the impact of Illumina HiSeq 2000 methods, which reduced the statistical power of the subgroups. Thus, more

A

Study or Subgroup	SF3B1 mutated Mean	SD	Total	SF3B1 wide Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Cui R 2012	157	147	55	85	168.5	49	21.4%	72.00 [10.88, 133.12]
Damm F 2012	276	334.75	47	145	139.2	270	8.5%	131.00 [33.87, 228.13]
Kang MG 2015	168	151	9	95	91	120	8.0%	73.00 [-26.99, 172.99]
Lin CC 2014	149	122.25	48	71	154.8	431	56.8%	78.00 [40.45, 115.55]
Seo JY 2014	316.5	211	16	213.75	154.25	20	5.2%	102.75 [-20.78, 226.28]
Total (95% CI)			**175**			**890**	**100.0%**	**82.11 [53.81, 110.41]**

Heterogeneity: Chi² = 1.26, df = 4 (P = 0.87); I² = 0%
Test for overall effect: Z = 5.69 (P < 0.00001)



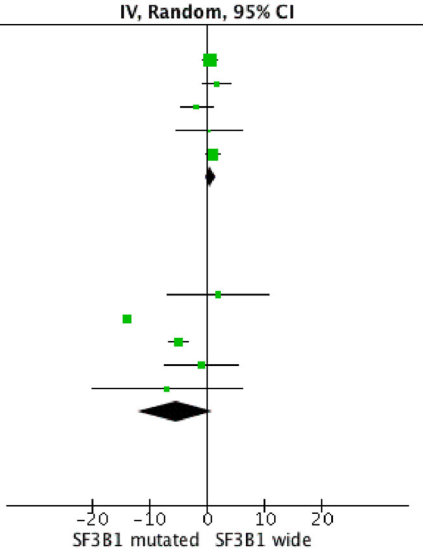
B

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
4.2.1 WBC								
Cui R 2012	3.4	3.125	55	2.9	2.95	49	42.3%	0.50 [-0.67, 1.67]
Damm F 2012	6.1	8.725	47	4.4	2.92	270	10.5%	1.70 [-0.82, 4.22]
Kang MG 2015	3.7	1.8	9	5.6	14.3	120	8.5%	-1.90 [-4.72, 0.92]
Lin CC 2014	4.175	4	48	3.745	59.14	431	2.1%	0.43 [-5.27, 6.13]
Seo JY 2014	4.775	2.175	16	3.7	1.6	20	36.5%	1.08 [-0.20, 2.35]
Subtotal (95% CI)			**175**			**890**	**100.0%**	**0.63 [-0.21, 1.47]**

Heterogeneity: Tau² = 0.08; Chi² = 4.31, df = 4 (P = 0.37); I² = 7%
Test for overall effect: Z = 1.48 (P = 0.14)

4.2.2 Hemoglobin								
Cui R 2012	70	20.25	55	68	25.25	49	17.2%	2.00 [-6.87, 10.87]
Damm F 2012	84	1.25	47	98	1.78	270	25.2%	-14.00 [-14.42, -13.58]
Kang MG 2015	92	2.3	9	97	2.2	120	24.9%	-5.00 [-6.55, -3.45]
Lin CC 2014	82	21.75	48	83	18.67	431	20.3%	-1.00 [-7.40, 5.40]
Seo JY 2014	85.5	19.5	16	92.5	20.5	20	12.5%	-7.00 [-20.12, 6.12]
Subtotal (95% CI)			**175**			**890**	**100.0%**	**-5.50 [-12.01, 1.00]**

Heterogeneity: Tau² = 43.63; Chi² = 147.08, df = 4 (P < 0.00001); I² = 97%
Test for overall effect: Z = 1.66 (P = 0.10)



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Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
4.3.1 RS								
Cui R 2012	42	18.25	55	26	16.25	49	66.5%	16.00 [9.37, 22.63]
Seo JY 2014	42.25	13.75	16	25.25	14.75	20	33.5%	17.00 [7.66, 26.34]
Subtotal (95% CI)			**71**			**69**	**100.0%**	**16.34 [10.93, 21.74]**

Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%
Test for overall effect: Z = 5.92 (P < 0.00001)

4.3.2 Blast								
Cui R 2012	0.5	2.125	55	1.5	4.625	49	11.0%	-1.00 [-2.41, 0.41]
Damm F 2012	0	1.25	47	1	3.17	270	81.2%	-1.00 [-1.52, -0.48]
Kang MG 2015	3.8	5	9	5.3	5.3	120	1.9%	-1.50 [-4.90, 1.90]
Mian SA 2013	5.25	4.75	24	6	12	130	2.8%	-0.75 [-3.55, 2.05]
Seo JY 2014	4.55	3.65	16	6.4	4.55	20	3.1%	-1.85 [-4.53, 0.83]
Subtotal (95% CI)			**151**			**589**	**100.0%**	**-1.03 [-1.50, -0.56]**

Heterogeneity: Tau² = 0.00; Chi² = 0.49, df = 4 (P = 0.97); I² = 0%
Test for overall effect: Z = 4.30 (P < 0.0001)

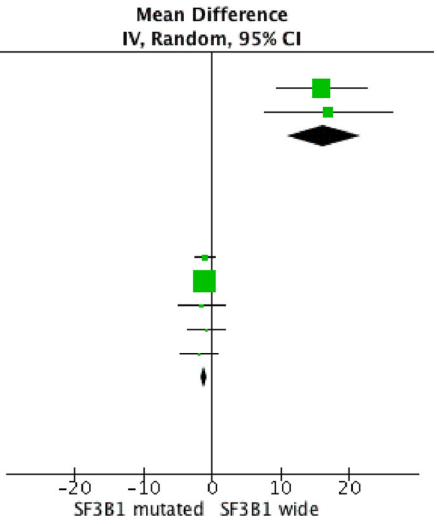
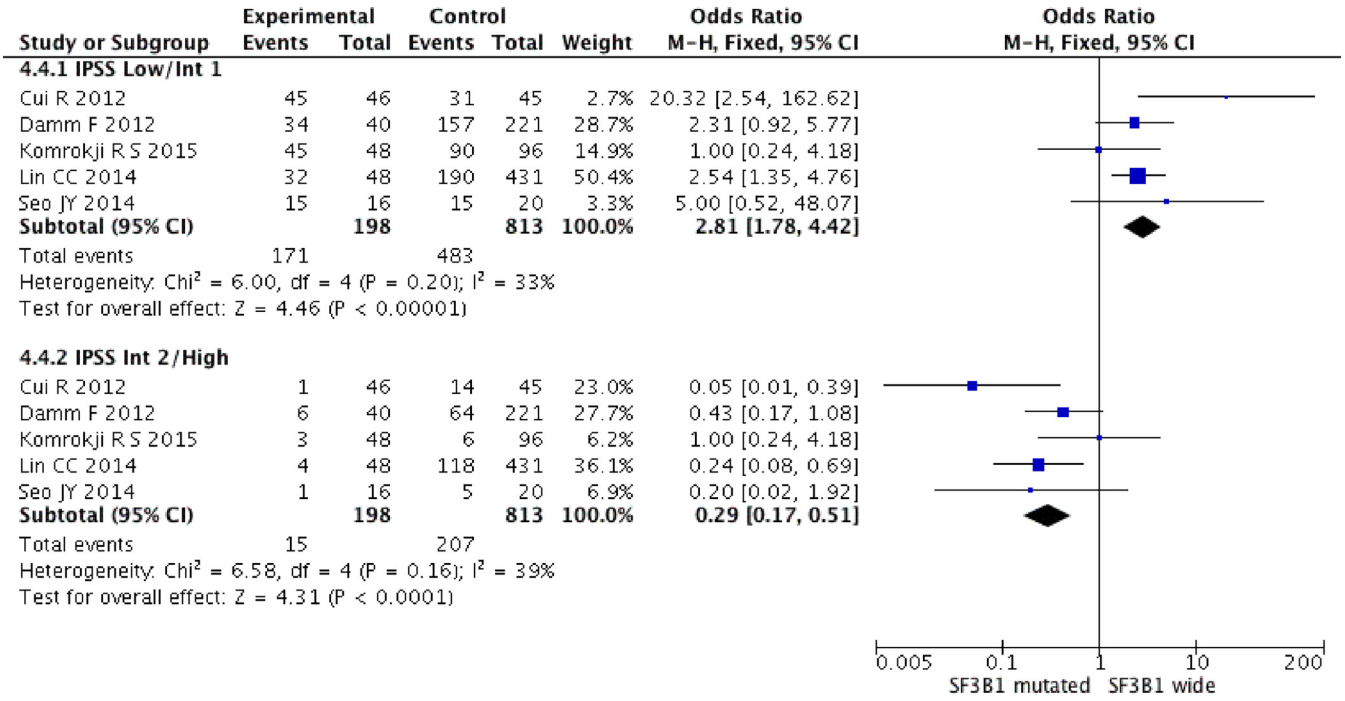
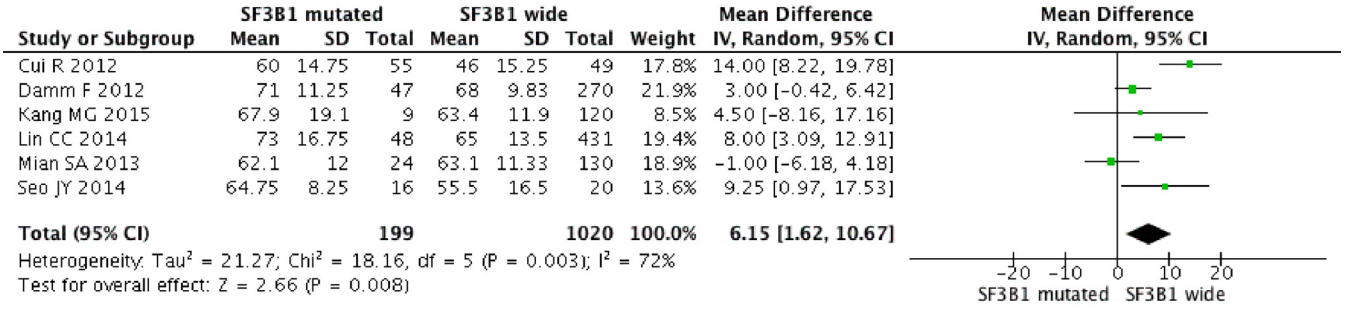


Fig. 4. Forest plots for the association of hematologic parameters, IPSS risk, age and gender with SF3B1 mutation. (A) A significant association was found between platelet count and SF3B1 mutation. (B) No significant association was detected for hemoglobin and white blood cells. (C) The percentage of bone marrow RS was significantly correlated with SF3B1 mutation, and no association was found between blast cells and SF3B1 mutation. (D) IPSS risk was significantly correlated with SF3B1 mutation. (E) A significant association was found between age and SF3B1 mutation. (F) No significant association was detected for gender.

D



E



F

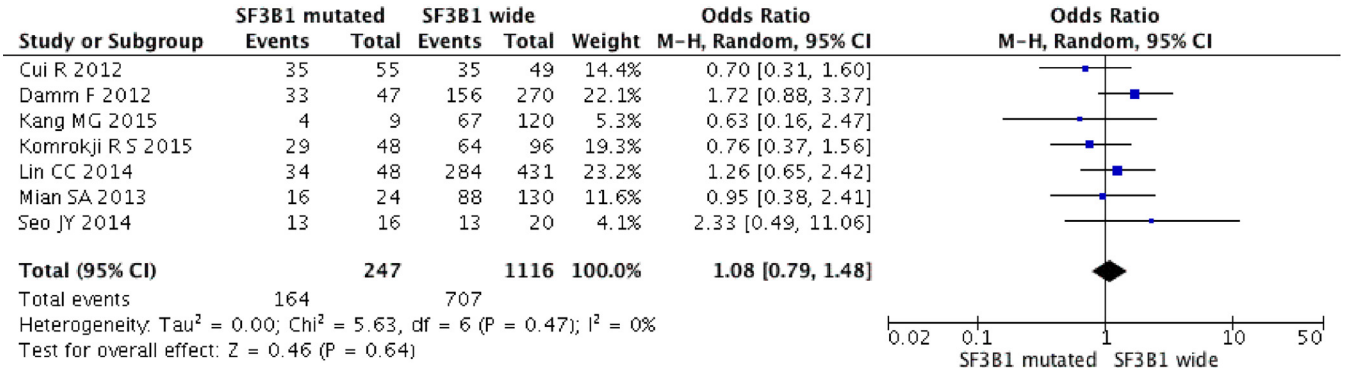


Fig. 4. (*continued*)

investigations with larger sample sizes are needed to reach a more convincing conclusion.

Authors' contributions

Y Tang and M Miao participated in the literature retrieval and performed the statistical analysis. S Han, J Qi and H Wang participated in data analysis and interpretation. C Ruan and D Wu participated in

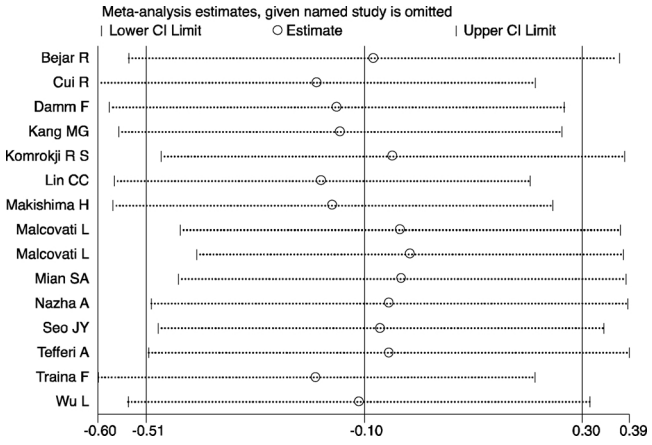


Fig. 5. Sensitivity analysis. The middle vertical axis represents the pooled HR, and the two vertical axes indicate the corresponding 95% CI. Each hollow circle represents the pooled HR when the left study was omitted in this meta-analysis, and the two ends of every broken line indicate the 95% CI.

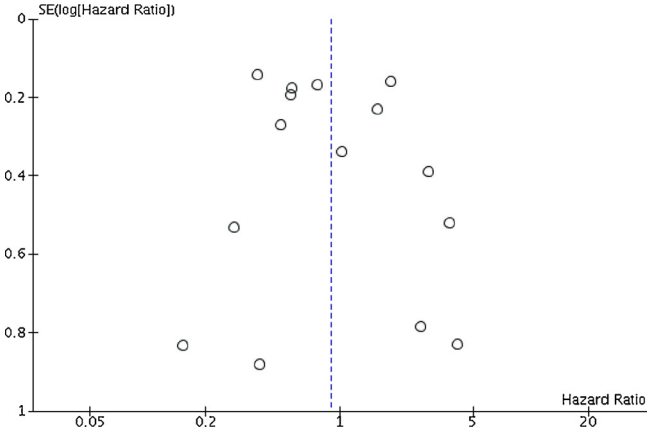


Fig. 6. Funnel plot for publication bias in terms of the association of SF3B1 mutation with OS.

study design. Y Han conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read, provided feedback, and approved the final manuscript. All authors had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflicts of interest

None.

Ethical approval

Not required.

Data sharing

No additional data available.

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