REVIEW

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Association of Somatic Gene Mutations with Risk of Transformation into Acute Myeloid Leukemia in Patients with Myelodysplastic Syndrome: A Systematic Review and Meta-Analysis

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Abstract

Objectives: we aim to conduct a systematic review and meta-analysis in population of adult MDS patients to elucidate the role of these genes in AML transformation risk. **Materials and Methods:** The protocol for this systematic review and meta-analysis was registered in the international prospective register of systematic reviews (PROSPERO) with ID number of CRD42020218581. Systematic literature search was conducted by all authors up to October 2021 on: (1) PubMed, (2) EBSCOhost, (3) Scopus, (4) JSTOR, and (5) grey literatures. Hand-searching for relevant articles was also conducted. The following keywords with their synonyms and combinations using Boolean operators were applied to all database: "myelodysplastic syndrome", SRSF2", "SF3B1", "U2AF1", "ASXL1", "DNMT3A", "TET2", "IDH1", "IDH2", "RUNX1", "acute myeloid leukemia progression", and "leukemia free survival". Outcome was measured using hazard ratio (HR). **Results:** We identified 14 articles to be used for this systematic review and meta-analysis. There was no statistically significant difference in AML transformation risk between U2AF1 mutant and U2AF1 wildtype MDS patients (HR: 1.41; 95% CI: 0.95–2.07, p=0.08, I^2=0%). Pooled HR showed that patients with SRSF2 mutation had higher risk of AML transformation (HR 2.62; 95% CI: 1.54-4.45; p= .0004; I^2= 55%). The pooled HR for SF3B1 was 0.48 (95% CI: 0.22–1.06, p=0.07, I^2=55%). Mutations of TET2, ASXL1, and EZH2 were not associated with AML transformation. Meanwhile, DNMT3A mutations were associated with AML transformation with pooled HR of 2.73 (95% CI: 1.43-5.21; p= 0.08; I^2: 67%). The pooled HR for IDH genes was smaller (HR: 2.92; 95%CI: 1.21-7.06; p=0.02; I^2:65%). Patients with RUNX1 mutation were associated with AML transformation (HR: 1.85; 95%CI: 1.11-3.09; p=0.02; I^2:38%). **Conclusion:** Based from our analyses, MDS patients with mutations of SRSF2, DNMT3A, IDH, and RUNX1 have higher hazard ratio for AML transformation.

Keywords: Myelodysplastic syndrome- mutation- leukemia progression

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Introduction

Myelodysplastic syndromes (MDS) is defined as a group of clonal hematopoietic stem cell (HSC) disorders with characteristics of ineffective hematopoiesis and dysmorphic bone marrow, which clinically presents with cytopenia(s) and an increased risk of transformation into acute myeloid leukemia (AML) (1982; Hong and He, 2017; Mohammad, 2018; Cazzola, 2020). Several epidemiologic studies have shown that MDS predominantly affects males and increases with age (Rådlund et al., 1995; Aul et al., 2001; Rollison et al., 2008; Neukirchen et al., 2011; Ma, 2012; Sultan and Irfan, 2016). For example, a study conducted by Sekeres et al. found that the median age of MDS diagnosis in United States is approximately 71 years (Sekeres et al., 2008). Additionally, according to Rollison et al., the prevalence of MDS is around 7 to 35 cases per 100,000 persons (Rollison et al., 2008). However, due to

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the heterogenous clinical presentations of MDS, ranging from asymptomatic to severe clinical phenotypes, a significant proportion of patients remain undiagnosed and there may be an underestimation or underreporting of the total global burden of MDS (Cogle et al., 2011; Pavlu et al., 2011; Zeidan et al., 2013; Cazzola, 2020).

The pathogenesis and pathophysiology of MDS is astoundingly very complex and currently remained incompletely understood. However, it is now widely accepted that the core of MDS pathophysiological process is self-renewal and selective growth advantage of a somatically mutated clonal HSC displacing normal HSC through clonal expansion (Zeidan et al., 2013; Cazzola, 2020; Fontenay et al., 2021). This process occurs through sequential accumulation of genetic and epigenetic mutations in the clonal HSC (Bejar et al., 2011; Fontenay et al., 2021). Indeed, somatic mutations in individual genes are observed to be very frequent in MDS with around 80% of MDS patients harboring at least 1 somatic mutation (Bejar et al., 2011; Malcovati et al., 2013; Papaemmanuil et al., 2013; Haferlach et al., 2014; Kwok et al., 2015). Cytogenetic abnormalities are also common in MDS but were only observed in around 50% of MDS patients (Kawankar and Rao Vundinti, 2011; Kwok et al., 2015). Thus, gene mutations may play a bigger role than cytogenetic abnormalities in MDS development and clinical presentations.

Some of the commonly mutated genes in MDS have role in RNA splicing machinery which excise introns to create mature messenger RNA transcripts such as serine/arginine-rich splicing factor 2 (SRSF2), splicing factor 3B subunit 1 (SF3B1), and U2 auxiliary factor protein 1 (U2AF1) (Wu et al., 2012; Dolatshad et al., 2015; Li et al., 2018; Hosono, 2019). Meanwhile, other genes such as additional DNA methyltransferases 3A (DNMT3A), sex combs-like 1 (ASXL1), tet methylcytosine dioxygenase 2 (TET2), enhancer of zeste 2 (EZH2), isocitrate dehydrogenases 1 (IDH1), and isocitrate dehydrogenases 2 (IDH2) are epigenetic regulators through DNA methylation and histone modification (Fontenay et al., 2021). Other mutated genes commonly observed in MDS is runt-related transcription factor 1 (RUNX1) that produces transcription factor protein. The majority of these genes (SF3B1, SRSF2, ASXL1, DNMT3A, TET2, and RUNX1) can be found mutated in more than 10% of MDS patients (Papaemmanuil et al., 2013; Haferlach et al., 2014).

Currently, the prognostic values of genetic mutations in MDS are still uncertain, resulting in genetic mutations not being used as a risk stratification criteria such as in International Prognostic Scoring System revised version (IPSS-R) or World Health Organization Classification-Based Prognostic Scoring System (Kantarjian et al., 2008; Greenberg et al., 2012; Arber et al., 2016).Several studies have been conducted in an attempt to elucidate the role of individual genetic mutations in MDS (Papaemmanuil et al., 2013; Bejar, 2017; Bejar, 2018). Nevertheless, it is actually difficult to determine which genetic mutations and their respective roles in pathogenesis of MDS, clinical phenotypes, and AML progression due to overlapping mutations in MDS and occurrence of these mutations in other malignancy such as de novo AML and myeloproliferative neoplasm (MPN) (Yoshida et al., 2011; Couronné et al., 2012; Kwok et al., 2015). Due to the uncertainties in the role of these genes in MDS, we aim to conduct a systematic review and meta-analysis in population of adult MDS patients to elucidate the role of these genes in AML transformation risk.

Materials and Methods

Method

The protocol for this systematic review and meta-analysis was registered in the international prospective register of systematic reviews (PROSPERO) with ID number of CRD42020218581. Furthermore, this systematic review and meta-analysis followed recommendations from Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).

Ethical Approval

As this study was a systematic review with meta-analysis using studies and grey literatures published on medical databases, no ethical approval was necessary for this study.

Search Strategy

Systematic literature search was conducted by all authors up to October 2021 on: (1) PubMed, (2) EBSCOhost, (3) Scopus, (4) JSTOR, and (5) grey literatures. Hand-searching for relevant articles was also conducted. Any difference in search results and opinions were resolved by consensus. The following keywords with their synonyms and combinations using Boolean operators were applied to all database: "myelodysplastic syndrome", SRSF2", "SF3B1", "U2AF1", "ASXL1", "DNMT3A", "TET2", "IDH1", "IDH2", "RUNX1", "acute myeloid leukemia progression", and "leukemia free survival".

Eligibility Criteria

The inclusion criteria were: (1) studies with design of prospective cohort or retrospective cohort; (2) studies with adult population aged ≥18 years diagnosed with MDS of any classification; (3) studies that include MDS patients with any gene mutations of "SRSF2", "SF3B1", "U2AF1", "ASXL1", "DNMT3A", "TET2", "IDH1", "IDH2", and "RUNX1"; (4) studies that have control group of MDS patients without the respective gene mutations; (5) studies that have acute myeloid leukemia transformation risk or leukemia free survival as outcomes; and (6); English or Indonesian language as primary language. The exclusion criteria were literature review, case report, non-human studies, and articles with inadequate data to calculate hazard ratio. No publication year restrictions were applied for the literature search.

Data Extraction

Data extracted from literatures include name of first author, year of publication, country of origin, MDS diagnosis criteria, sample size, median follow-up, proportion of male patients, median age, median hemoglobin, median leukocyte, median absolute

neutrophil count, median platelet, median blast, percentage of patients with aberrant karyotype, and type of gene mutations. Hazard ratios (HRs) with their 95% confidence intervals (Cis) for AML transformation outcome were extracted. If there is literature that reported the outcome with both univariate analysis and multivariate analysis, then multivariate analysis data will be preferred. Data extraction was conducted by two authors.

Quality Assessment

All selected literatures were independently assessed by two authors for risk of bias using Newcastle - Ottawa Quality Assessment (NOS).(Ottawa Hospital Research Institute, n.d.) Discrepancies in the judgement using NOS Scale was discussed between all authors of this review to reach a consensus.

Statistical Analysis

All statistical analysis was performed using Review Manager application version 5.4 (The Nordic Cochrane Center, Copenhagen). Generic inverse variance method was used to calculate combined HRs and their 95% CIs. All statistical analysis was conducted using random-effects model. Statistical significance was defined as p value of <0.05 and 95% CI not overlapping the value of 1. Slight differences may be observed between original numbers and forest plot results in some studies due to conversion towards Review Manager 5.4 format (Forero et al., 2019; Rinaldi et al., 2020).

Heterogeneity of the results was evaluated using the Cochrane standard statistical I^2. I^2 values of less than 25%, between 25% to 50%, and above 50% were considered as low, moderate, and high heterogeneity respectively.

Results

Study Selection

A total of 334 articles were initially retrieved from literature search (Figure 1). Out of these, a total of 51 duplicates were excluded, leaving a total of 283 unique articles. Subsequently, screenings of titles and abstracts excluded 259 irrelevant articles. Citation searching was also conducted which yielded 8 articles. Hence, only 32 articles were available for full-text review. However, 4 articles were not in English language, 2 articles were non-human studies, 6 articles did not have outcome of AML progression, and 6 articles did not have adequate data for hazard ratio calculation. Thus, we identified 14 articles to be used for this systematic review and meta-analysis (Dicker et al., 2010; Malcovati et al., 2011; Walter et al., 2011; Thol et al., 2012; Wu et al., 2013a; Lin et al., 2014; Hong et al., 2015; Kang et al., 2015; Jung et al., 2016; Tefferi et al., 2017; Xu et al., 2017; Gangat et al., 2018; Lin et al., 2018; Yan et al., 2021).

Characteristic of Selected Studies

The studies used were published between year 2010 and 2018 (Table 1). The studies were conducted in North America, Europe, and Asia. The majority of the studies diagnosed MDS based on WHO classification. The sample size ranged from 58 patients to 634 patients. Median duration of follow up ranged from 18.5 months to 66 months. All studies only included adult patients with mean or median age ranging from 54 to 74 years old.

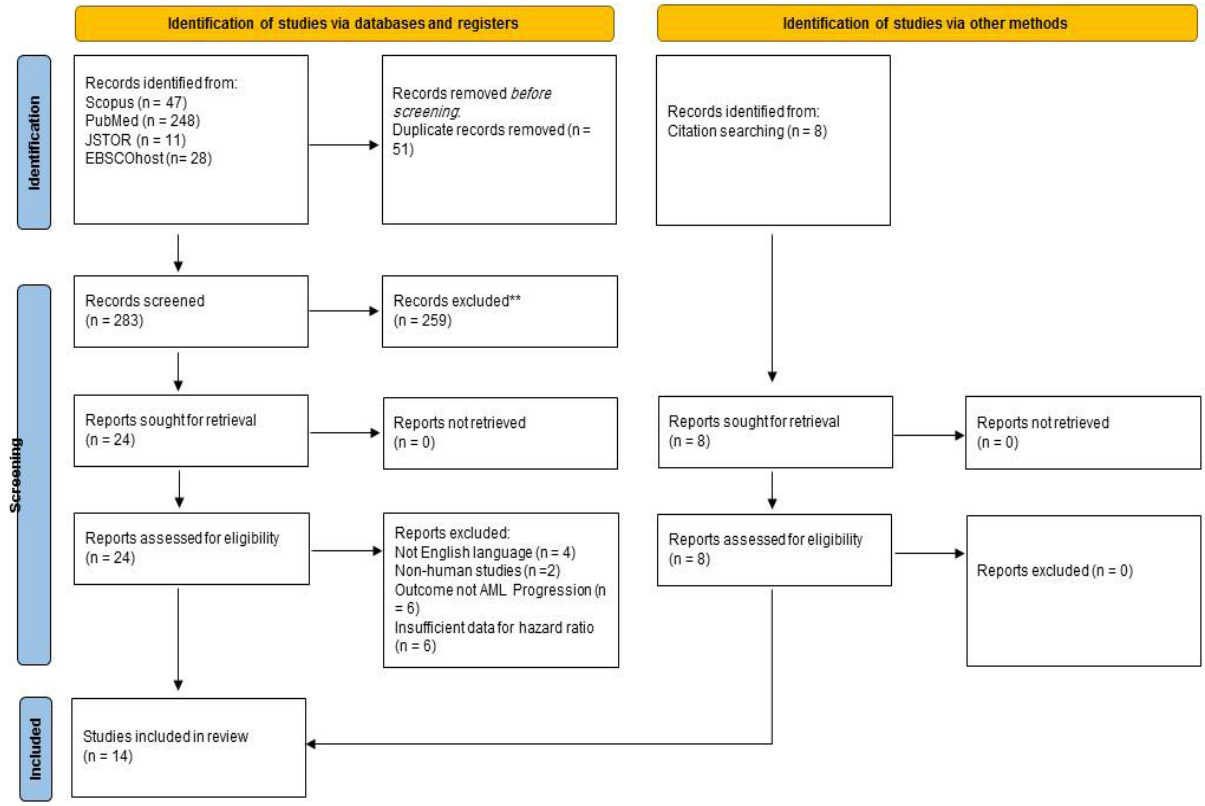

Figure 1. Study Selection Process Flowchart

Table 1. Summary of Included Studies

Author	Country	MDS Diagnosis Criteria	Sample Size	Median Follow-up (months)	Male (%)	Median Age (Years)	Median Hemoglobin (g/L)	Median Leukocyte ($\times 10^9$/L)	Median Absolute Neutrophil Count ($\times 10^9$/L)	Median Platelet ($\times 10^9$/L)	Median blast (%)	Aberrant karyotype (%)	Somatic Mutations Analyzed
Dicker et al.(2010)	Europe	WHO	188	NA	58.51%	69.4	NA	NA	NA	NA	NA	NA	RUNX1, FLT3-ITD, MLL-PTD, NRAS, NPM1
Gangat et al. (2018)	USA	WHO	300	18.5	70	73	96	3.8	1.8	119	0	NA	SF3B1, ASXL1, TET2, U2AF1, DNMT3A, SRSF2, TP53, RUNX1, IDH2, EZH2, SETBP1, IDH1, CSF3R, CEBPA
Hong et al.(2015)	Korea	FAB	58	40	79.3	67	NA	NA	NA	NA	NA	NA	SRSF2, U2AF1, ZRSR2, TET2, TP53, NRAS
Jung et al.(2016)	Korea	WHO	107	NA	62.6%	NA	NA	NA	NA	NA	NA	NA	U2AF1, ASXL1 TET2 TP53, RUNX1, SF3B1 EZH2, DNMT3A, NRAS, NF1, ATRX, ETTV6, JAK2, CBL, LAMB4, DNMT1, ZRSR2, SETBP1, KRAS, IDH1, STAG2, FLT3, PRPF8, NPM1, SRSF2, IDH2
Kang et al (2015)	Korea	WHO	129	NA	55.8%	63.4 (mean)	9.7 (mean)	5.6 (mean)	3.4 (mean)	95 (mean)	5.3 (mean)	27.5%	SF3B1, U2AF1, SRSF2
Lin et al (2018)	Taiwan	FAB and WHO	469	NA	67.2	65.5	8.3	3.84	NA	74	NA	NA	IDH1, IDH2, ASXL1, EZH2, TET2, FLT3, JAK2, NRAS, KRAS, PTPN11, WT1, MLL, RUNX1, U2AF1, SRSF2, SF3B1, SETBP1, TP53
Lin et al (2014)	Taiwan	WHO	168	NA	NA	NA	NA	NA	NA	NA	NA	NA	TET2, IDH1/2
Malcovati et al.(2011)	Italy	WHO	533	NA	NA	NA	NA	NA	NA	NA	NA	NA	SF3B1
Tefferi et al.(2017)	USA	NA	179	NA	68%	73	10	3.6	NA	91	2	60%	ASXL1, TET2, SF3B1, U2AF1, SRSF2, TP53, RUNX1, DNMT3A, IDH2, EZH2, CEBPA, SETBP1, IDH1, CSF3R, KIT, CBL, JAK2, CALR, FLT3
Thol et al. (2012)	Europe	WHO	193	36	119/74	>65	NA	NA	NA	NA	NA		
Walter et al (2011)	USA	FAB	150	NA	60	60	NA	NA	NA	NA	NA	38%	DNMT3A
Wu et al. (2013)	China	FAB	478	66	60.7	66	NA	NA	NA	NA	NA	43.3	
Xu et al. (2017)	China	WHO	320	NA	57	178/320	NA	NA	NA	NA	NA	NA	TP53, STAG2, EZH2, DNMT3A, RUNX1, SRSF2, ROBO1/2, WT1, U2AF1, ASXL1, BCOR, IDH1/2, UPF3A, SETBP1, GATA2, KIF20B, PTPRD, TET2, DHX9, ZRSR2, SF3B1, FZR1, ASIC2, ITIH3, CEBPA, ANKRD11
Yan et al. (2021)	China	WHO	634	26.1	58.2	57	76	NA	1.2	56	5	38.64%	TP53, EZH2, SF3B1, U2AF1, NRAS, DNMT3A, IDH1, IDH2, TET2, JAK2, CBL, ETV6, SRSF2, ASXL1, RUNX1

Table 2. Risk of Bias Assessment Based on Newcastle-Ottawa Scale

Study	Representativeness of Exposed Cohort	Selection of Non-Exposed Cohort	Ascertainment of Exposure	Outcome not Present at Start	Comparability	Assessment of Outcome	Follow-up Length	Follow-up Adequacy	Total Score
Dicker et al. (2010)	*	*	*	*		*		*	6
Gangat et al. (2018)	*	*	*	*	*	*	*	*	8
Hong et al. (2015)		*	*	*		*	*	*	6
Jung et al. (2016)	*	*	*	*		*	*	*	7
Kang et al. (2015)	*	*	*	*		*	*	*	7
Lin et al (2014)			*	*		*	*	*	5
Lin et al (2018)	*	*	*	*		*	*	*	7
Malcovati et al. (2011)	*	*	*	*		*	*		6
Tefferi et al. (2017)	*	*	*	*		*	*	*	7
Thol et al. (2012)	*	*	*	*		*	*	*	7
Walter et al. (2011)	*	*	*	*		*	*	*	7
Wu et al. (2013)	*	*	*	*		*	*	*	7
Xu et al. (2017)	*	*	*	*		*			5
Yan et al. (2021)	*	*	*	*		*	*	*	7

Risk of Bias Assessment

The risk of bias assessment was independently conducted in each study by two authors using Newcastle-Ottawa scale (Table 2).

Pooled Analysis of Splicing Factors Gene Mutations

Literature search for studies that include splicing factors gene mutation yielded 11 studies to be used. From these, 6 studies included U2AF1, 7 studies included SRSF2, 5 studies included SF3B1, and 2 studies included ZRSR2 (Figure 2).

From the 6 U2AF1 studies used for pooled analysis, there were no statistically significant difference between U2AF1 mutant and U2AF1 wildtype MDS patients (HR: 1.41; 95% CI: 0.95–2.07, p=0.08, I^2=0%). The majority of studies did not find any association between U2AF1 mutation with AML transformation except the study by Wu et al (Wu et al., 2013b).

The SRSF2 study by Tefferi et al. reported the highest HR for AML progression (HR, 6.90; 95% CI, 2.76–17.21) (Tefferi et al., 2017). In total, there are 5 studies indicating that SRSF2 mutation cause higher risk of AML transformation. Meanwhile, the studies by Hong et al. and Yan et al. did not find any association between SRSF2 and AML transformation (Hong et al., 2015; Yan et al., 2021). Pooled hazard ratio showed that patients with SRSF2 mutation had higher risk of leukemia transformation (HR 2.62; 95% CI: 1.54-4.45; p= .0004). However, there is high heterogeneity with I^2 of 55%.

The pooler HR for SF3B1 was 0.48 (95% CI: 0.22–1.06, p=0.07, I^2=55%). We then conducted an analysis excluding the study by lin et al. since the study contributed solely to the heterogeneity (Lin et al., 2018). Excluding the study resulted in HR of 0.35 (95% CI: 0.19-0.65; p= 0.0009; I^2= 0%).

Pooled Analysis of Epigenetic Regulator Mutations

Only mutations of DNMT3A and IDH genes were associated with risk of AML transformation (Figure 3). Mutations of TET2, ASXL1, and EZH2 were not associated with AML transformation. A total of 5 studies were available for DNMT3A with pooled HR of 2.73 (95% CI: 1.43-5.21; p= 0.08; I^2: 67%). Meanwhile, the pooled HR for IDH genes was smaller (HR: 2.92; 95%CI: 1.21-7.06; p=0.02; I^2:65%)

Pooled Analysis of RUNX1 Mutation

RUNX1 is a transcription factor gene which is commonly mutated in MDS. From our pooled analysis, patients with RUNX1 mutation were associated with AML transformation (HR: 1.85; 95%CI: 1.11-3.09; p=0.02; I^2:38%).

Funnel Plot

We use funnel plot to evaluate the publications bias of the studies qualitatively (Figure 5). From the funnel plots, there are low indication of publication bias due to symmetricalness of the funnel plots.

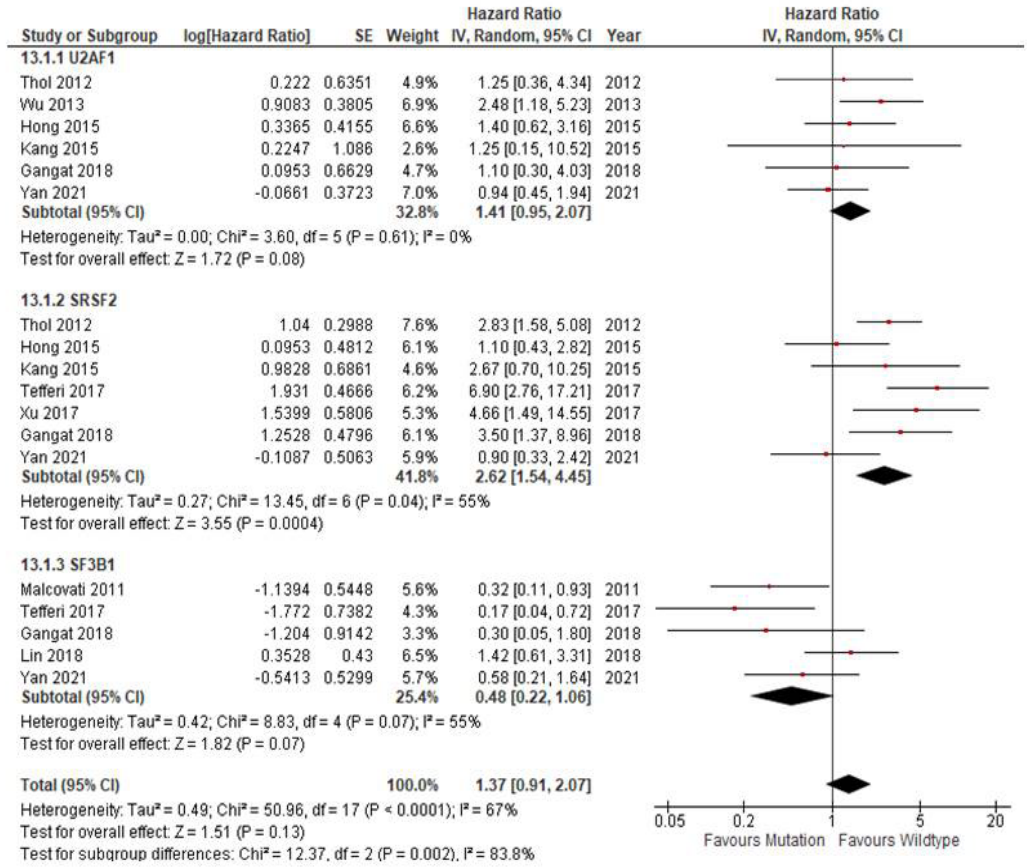

Figure 2. Forest Plot of the Association between RNA Splicing Machinery Gene Mutations and AML Transformation.

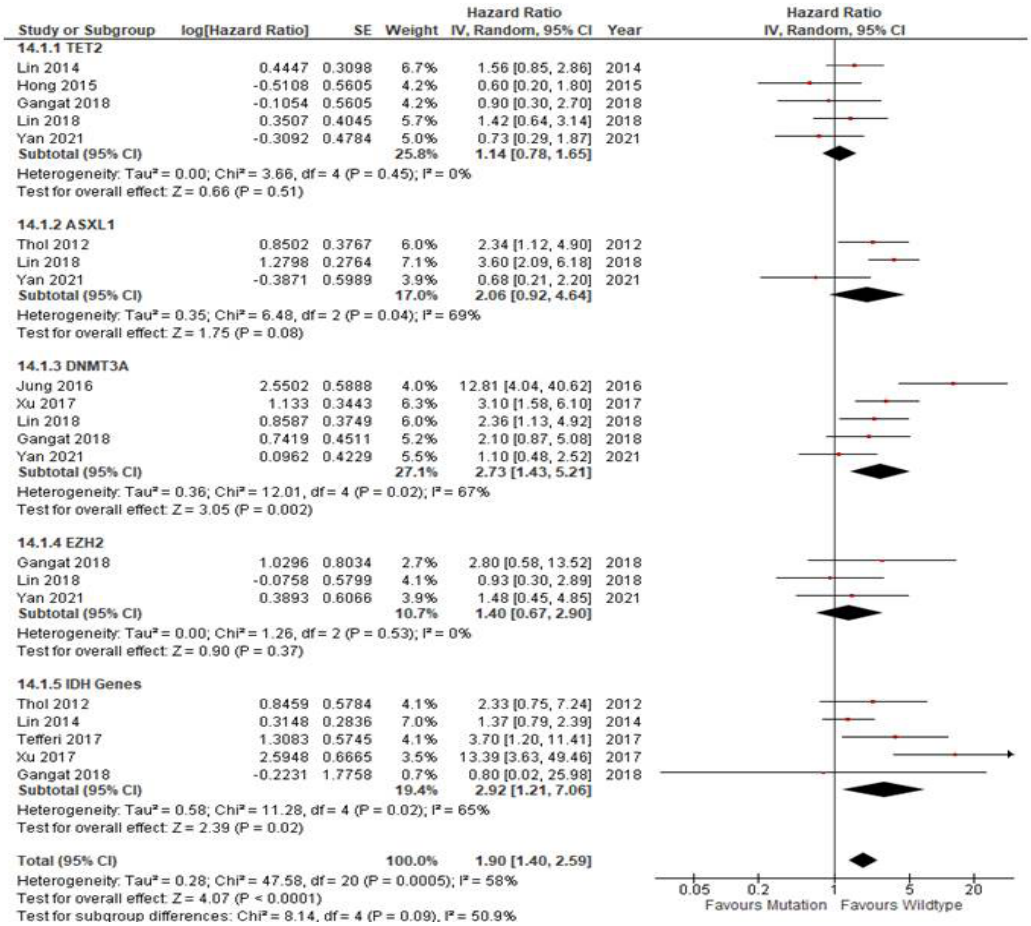

Figure 3. Forest Plot of the Association between DNA Methylation Gene Mutations and AML Transformation

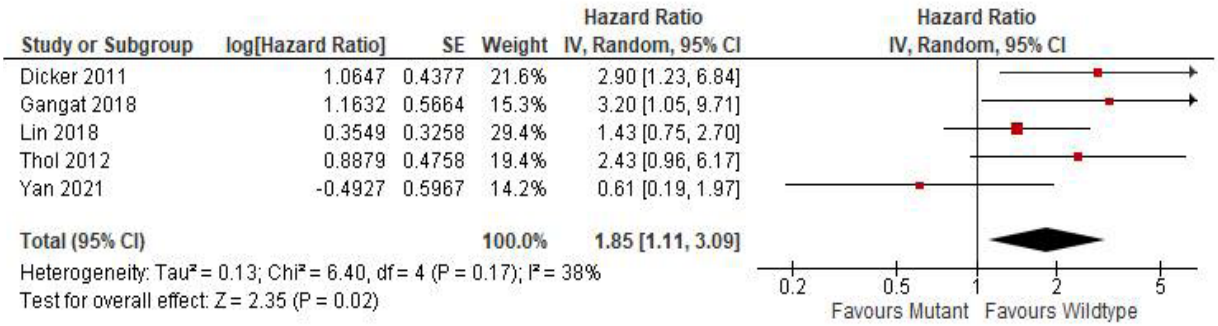

Figure 4. Forest Plot of the Association between RUNX1 Mutation and AML Transformation

Discussion

MDS has a heterogenous clinical course. Some patients are asymptomatic while others have MDS that can rapidly transform into leukemia. The heterogeneity of MDS shows that there is a complex pathogenesis and pathophysiology of MDS. Indeed, currently there are still many aspects of MDS which are not fully elucidated such as genetic mutations and bone marrow microenvironment.

Our first understanding of MDS comes from recognition of cytogenetic abnormalities which are present in at least 50% of MDS (Kelly et al., 2002). Recently, from genetic studies of MDS, it is observed that somatic mutations in individual genes are very frequent in MDS with around 80% of MDS patients harboring at least 1 somatic mutation (Bejar et al., 2011; Papaemmanuil et al., 2013; Haferlach et al., 2014; Kwok et al., 2015). Despite the explosion of information regarding mutation in MDS, determining which mutations that contribute to the disease itself is difficult since many mutations do not have pathogenic consequences (passenger mutations) such as due to aging hematopoietic stem cells (Welch et al., 2012; Vogelstein et al., 2013). Nevertheless, mutations with significant consequences tend to occur frequently in MDS. Currently, it is known that genes affecting RNA splicing (SRSF2, SF3B1, U2AF1) and affecting epigenetic regulation (TET2, ASXL1, EZH2, DNMT3A) are the most commonly mutated (Wu et al., 2012; Dolatshad et

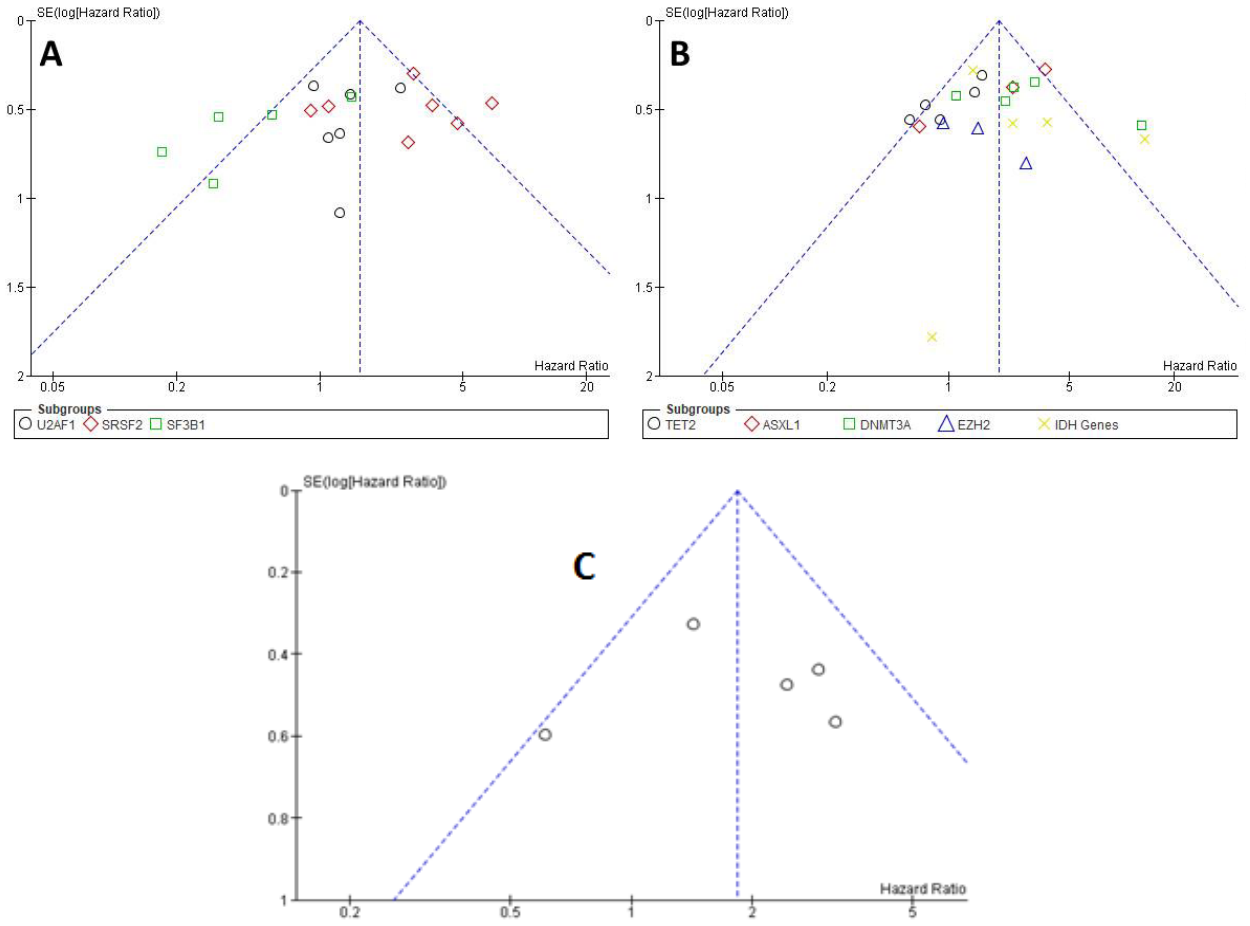

Figure 5. Funnel Plots for Publication Bias. A, Splicing Factors Gene Mutations; B, Epigenetic Regulators; C, RUNX1

al., 2015; Hosono, 2019). These mutations are likely to occur randomly.

Molecular genetic testing has now become a standard in many cancers to determine prognosis and treatments. For example, AML guideline from European LeukemiaNet incorporate genetic mutation testing such as ASXL1, TP53, FLT3, and RUNX1 as part of its prognosis stratification (Döhner et al., 2017). In contrast, the prognosis risk stratification of MDS such as from revised international prognostic scoring system (IPSS-R) which is used by many clinicians does not include molecular genetic testing despite the recurrently mutated genes shown above (Greenberg et al., 2012; Fenaux et al., 2021). The reason for this is mainly due to still unclear role of the genetic mutations for MDS. However, just like other malignancies, it is only a matter of time before molecular genetic testing is incorporated into prognosis.

RNA splicing machinery genes such as SRSF2, SF3B1, U2AF1 play an important role in messenger RNA maturation (Wang et al., 2019). In this study, forest plot in SRSF2 mutation has statistically significant result with overall HR is 2,57 (95% Cl: 1.57- 4.20, P .0002, I^2 =59%). Thus, this indicates that MDS patients with SRSF2 mutation have higher risk for AML transformation. However, the heterogeneity is moderate which may be caused by studies with different methodology and follow-up. SRSF2 mutation is present in approximately 15% of MDS patients (Thol et al., 2012). According to a study, MDS patients with SRSF2 mutation have higher dysplasia of the granulocytic lineage when compared with patients with SF3B1 mutations (Wu et al., 2012) . On the other hand, SF3B1 mutation is associated with ring sideroblast MDS type. In this study, we did not find an association between SF3B1 mutations with risk of AML transformation. Indeed, a study by Damm et al. showed that this mutation was not associated with poor prognosis (Damm et al., 2012). Of interest is that in the pooled analysis, the HR for SF3B1 almost crosses 1 which may indicate that SF3B1 mutation can lower risk of AML transformation but due to the heterogeneity in the pooled analysis, this effect was not evident. If the meta-analysis was conducted using fixed effect models, the pooled analysis would show that patients with SF3B1 mutation had lower HR for AML progression. However, due to differences in methodologies of the studies used, we decided to use random-effects model. For U2AF1 mutation, we did not find an association with AML transformation. Out of 6 studies used for pooled analysis, only the study by Wu et al. that showed association between U2AF1 mutation with AML transformation (Wu et al., 2013b).

DNA methylation can influence gene expression without DNA sequence alteration through methylation (Yang et al., 2015; Xu et al., 2017; Zhang et al., 2020). Current knowledge shows that DNA methylation is mediated by three DNA methylation enzymes, consisting of DNMT1, DNMT3A, and DNMT3B (Okano et al., 1998; Yang et al., 2015).

Based on numerous observations, DNA methylation is highly suspected to have important role in cancer and may have a role as future targeted therapies. Aberrant DNA methylation for example, were observed in many malignancies (Yang et al., 2015; Wong et al., 2019; Zhang et al., 2020). Furthermore, loss-of-function DNMT3A mutation is very commonly observed in hematological malignancies, including MDS (Yang et al., 2015; Brunetti et al., 2017). However, if DNMT3A loss-of-function is widely prevalent, which suggested hypomethylation state, why does many hematological malignancies can be treated by DNA hypomethylating agents (Garcia-Manero and Fenaux, 2011; Al-Ali et al., 2014; Yun et al., 2016). This discrepancy may suggest that there are still currently unknown molecular mechanisms.

DNMT3A is one of DNA methyltransferase that has role in DNA methylation process. Alterations in this gene have been implicated in the pathogenesis of MDS but underlying mechanism remains unknown. In this study, DNMT3A mutation has higher risk for AML progression with overall HR 6.87 (95% CI: 2.80–16.87, P <0.0001, I^2=55%). A study of aberrant DNA methylation in MDS showed a significant transformation to leukemia (Liang et al., 2019). However, it was not stated either the process was specifically caused by DNMT3A gene mutation or other related mutations. Meanwhile, other study showed about 20% of Total AML have somatic DNMT3A heterozygous mutation (Graubert and Walter, 2011). In consequence, there is an association that makes DNMT3A mutation act as a poor outcome indicator in MDS patients that could worsen into AML. For other epigenetic regulator genes (TET2, ASXL1, and EZH2), we did not find association with AML progression risk.

We also observed that patients with transcription factor RUNX1 mutation were associated AML transformation (HR: 1.85; 95%CI: 1.11-3.09; p=0.02; I^2:38%). RUNX1 mutation often occurs in the later stage of MDS (Menssen and Walter, 2020). It is possible that RUNX1 mutation is one of the mutations needed for AML transformation.

Based from the data of this systematic review and meta-analysis, MDS patients with mutations in SRSF2, DNMT3A, IDH, and RNX1 should be monitored more actively than those without mutations due to higher risk of AML transformation.

Study Limitations

Limitation of this study is that the interaction of gene mutations with each other was not assessed. It is unknown that the AML progression is due to combination of some mutations or independently certain mutation. Moreover, in this study, there were different definitions of outcome measured.

In conclusion,this study found that some of the MDS gene mutations may potentially be used as markers for predicting risk of AML transformation. Based from our analyses, MDS patients with mutation of SRSF2, DNMT3A, and RUNX1 have higher risk of AML transformation. Additional analysis of gene mutations interactions is urgently needed.

Author Contribution Statement

NS, IR, and KW conceived and designed the study; IR and KW searched the database, screened titles, abstracts,

and full text studies included. NS, IR, ML, and KW performed study quality assessments, data analyses, and data interpretations. IR, KW, and APK drafted the initial manuscript. All authors performed critical revisions of the manuscript and approval of the final version of the manuscript.

Protocol registration

The review protocol was registered prospectively with PROSPERO database (CRD42019122964).

Availability of data

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval

As this study was a systematic review with meta-analysis using studies and grey literatures published on medical databases, no ethical approval was necessary for this study.

Conflict of interest

The authors declare that no conflict of interests was present during the making of the study

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