Systematic Review and Meta-Analysis

Medicine

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Association of systemic inflammatory and autoimmune manifestations with myelodysplastic syndromes

A systematic review and meta-analysis

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Abstract

Background: Systemic inflammatory and autoimmune manifestations (SIAMs) are frequently reported in Myelodysplastic syndromes (MDS). Studies focused on the impact of SIMAs on survival outcomes of MDS remains controversial. We performed this systematic review and meta-analysis to determine the association of SIAMs with overall survival, median survival, rate of acute myeloid leukemia transformation and mortality of MDS.

Materials and methods: An electronic search was conducted in 4 databases without any language restrictions, including PubMed, EMBASE, Medicine and Cochrane library up to April 30, 2021.

Results: The 18 studies included a total of 4603 MDS patients, of which 1175 (25.5%) patients had SIAMs. MDS patients with SIAMs had a statistically shorter overall survival compared with patient without SIAMs (Hazard ratio, 2.43; 95% confidence interval [CI], 1.34–4.41; $P < .01$). Our results were most compatible with no effect of SIAMs on median survival, rate of acute myeloid leukemia transformation and mortality (Median survival ratio, 1.16; 95% CI, 0.91–1.47; Odds ratio, 0.96; 95% CI, 0.63–1.45 and 1.2; 95% CI, 0.84–1.7, respectively).

Conclusion: In this systematic review and meta-analysis, SIAMs appeared to have an adverse effect on overall survival of MDS patients. This finding suggested that SIAMs may be a potential independent prognostic factor for MDS.

Abbreviations: AML = acute myeloid leukemia, HR = Hazard ratio, MDS = Myelodysplastic syndromes, MSR = Median survival ratio, OR = Odds ratio, SIAMs = systemic inflammatory and autoimmune manifestations, SLD = Single lineage dysplasia.

Keywords: autoimmune manifestations, meta-analysis, myelodysplastic syndromes, prognosis, systemic inflammatory

1. Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematologic stem cell diseases characterized by dysplasia in 1 or more myeloid cell lineages, ineffective hematopoiesis and a propensity for transformation to acute myeloid leukemia (AML). Systemic inflammatory and autoimmune manifestations (SIAMs) are frequently reported in MDS, and the prevalence is up to 30%.[1–6] Accumulating evidence suggests that dysregulation of innate immune and aberrant inflammatory signaling act as pivotal drivers of MDS pathogenesis.[7–9] More than 50% MDS patients were recorded overexpression of gene mutations involved in innate immune pathway.[10] In addition, research has shown MDS clone and innate immune pathway activation are critical to the development of SIAMs.[3,11] These findings demonstrate innate Immune dysregulation may be a potential common trigger force between MDS and SIAMs. Nevertheless, the

QL and JZ contributed equally to this work.

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The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files]; The datasets generated during and/or analyzed during the current study are publicly available.

This article does not contain any studies with human participants or animals performed by any of the authors Conflict of interest.

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Highlights

- This is the first meta-analysis to evaluate association of SIAMs with MDS.
- SIAMs appeared to have an adverse effect on overall survival of MDS patients.
- Our study may bring a new insight into prognostic assessment and potential treatment strategy in MDS.

association of SIAMs with the prognosis of MDS is still not well established.

Several observational studies revealed that MDS patients with SIAMs experienced the worse overall survival and higher mortality than those without SIAMs.[12–14] Conversely, some research indicated that SIAMs conferred a favorable impact on outcomes in MDS patients.[3,4] Moreover, a 4-year prospective cohort study and a large French multicenter retrospective study found SIAMs had no impact on the prognosis of MDS.[15,16] The heterogeneity and complexity of pathology, clinical manifestations and response to therapy make the prognosis of MDS with SIAMs a matter of debate.[17]

Currently, the association of SIAMs with MDS is not completely consistent, and the isolated observational studies were underpowered to answer this question. In addition, no research has been done specifically and quantitatively on their relationship. Hence, there is an urgent need for a pooled analysis to provide critical and clinically useful information concerning MDS prognosis.

2. Methods

2.1. Data source and search strategy

We followed the PRISMA guidelines to perform this meta-analysis. Literature search was conducted in 4 databases without any language restrictions, including PubMed, EMBASE, Medicine and Cochrane library (up to April 30, 2021). Additional search was conducted on Google Scholar for eligible studies. The main search terms were as follows: ((Myelodysplastic Syndrome) OR (Dysmyelopoietic Syndrome) OR (Hematopoietic Myelodysplasia) OR (MDS)) AND ((Autoimmune disease) OR (Autoimmunity) OR (Autoimmune disorder) OR (Autoimmune phenomena) OR (Autoimmune manifestations) OR (Immunologic abnormalities) OR (Autoimmune and inflammatory conditions) OR (Systemic and Immune Manifestations)). The review protocol has been registered in the PROSPERO International Prospective Register of Systematic Reviews (registration number: CRD42021229595).

2.2. Measured outcome and selection criteria

The primary outcome was to identify the impact of SIAMs on overall survival or median survival of MDS patients. The other 2 outcomes included AML transformation and mortality.

Studies were selected based on the following inclusion criteria: Comparative studies concentrated on the association of SIAMs with MDS patients; Studies reported sufficient data for at least 1 of the measured outcomes, including rate of AML transformation, mortality, median survival and overall survival. Literatures with overlapping data were excluded, only the latest or the highest quality 1 could be included in our meta-analysis.

2.3. Data extraction and quality assessment

Two reviewers (Qian Liang and Jingyu Zhao) independently extracted the data of interest from eligible studies. The extracted information for each study included: title and study details (name of the first author, study design, year of publications, country, MDS subtype, number of cases and controls), study population characteristics (gender, median or mean age, median follow-up, median survival, overall survival, rate of AML transformation and mortality) (Table 1). We also extracted more essential details of case and control arms in each study (WHO classification, blood cell counts, risk scoring, karyotype and the percentage of peripheral blood and bone marrow blasts) (Table 2). The quality of each study was evaluated based on the Newcastle-Ottawa Scale, and 7–9 scores was perceived as high quality (Table S1, Supplemental Digital Content, http://links.lww.com/MD/H827).

2.4. Statistical analysis

Overall survival and median survival were reported as hazard ratio (HR) and median survival ratio (MSR), respectively. The HR was extracted from the univariate cox-regression analysis provided by eligible studies. A MSR was the ratio of median survival time compared the SIAMs with non-SIAMs group. AML transformation and mortality were reported as odds ratio (OR). On condition that the result greater than 1.0, a HR or OR demonstrated SIAMs carried a poor prognosis in MDS, whereas a MSR favored a better survival outcome. The difference of the clinical features between MDS with and without SIAMs were detected by Pearson's chi-squared test, Cochran–Mantel–Haenszel test and Wilcoxon rank sum test.

Heterogeneity across studies was assessed by the Cochran's Q-test with a significance level at $P = .1$, and the I^2 was performed to estimate the extent of heterogeneity. The impact of SIAMs on MDS throughout meta-analysis was combined using a fixed-effects model ($P \geq .1$ and $I^2 \leq 0.25$) and a random- effects model ($P < .1$ or $I^2 > 0.25$). We also conducted the sensitivity analysis by the sequential omission of individual studies to investigate the validity of the overall results. Potential publication bias was examined by visual inspection of asymmetry in the funnel plot and estimated quantitatively using the Begg's and Egger's test. A P-value < .05 indicated publication bias was significant across studies. All analysis was conducted by using R software, Version 4.0.2.

2.5. Ethical consideration

Institutional review board approval was not necessary because all the data were retrieved from public databases.

3. Results

3.1. Description of studies

A total of 3515 publications were identified through database searching, of which 18 studies were eligible for inclusion (Fig. 1). All studies were published between 2002 and 2021. Most of the studies were retrospective case-control studies except for 2 prospective studies. The 18 studies included a total of 4603 MDS patients, of which 1175 (25.5%) patients had SIAMs (Table 1).[1,3,4,12–16,18–28] The most common SIAMs were hypothyroidism (17.7%), vasculitis (16.2%) and the immune cytopenia or coagulation disorder (10.7%) (Table S2, Supplemental Digital Content, http://links.lww.com/MD/H828).

3.2. Patient characteristics

According to the available data of included studies, clinical characteristics of MDS patients with or without SIAMs were detailed analyzed in Table 2. Median age of MDS with SIAMs were 70, with the majority of subjects being male (59.28%).

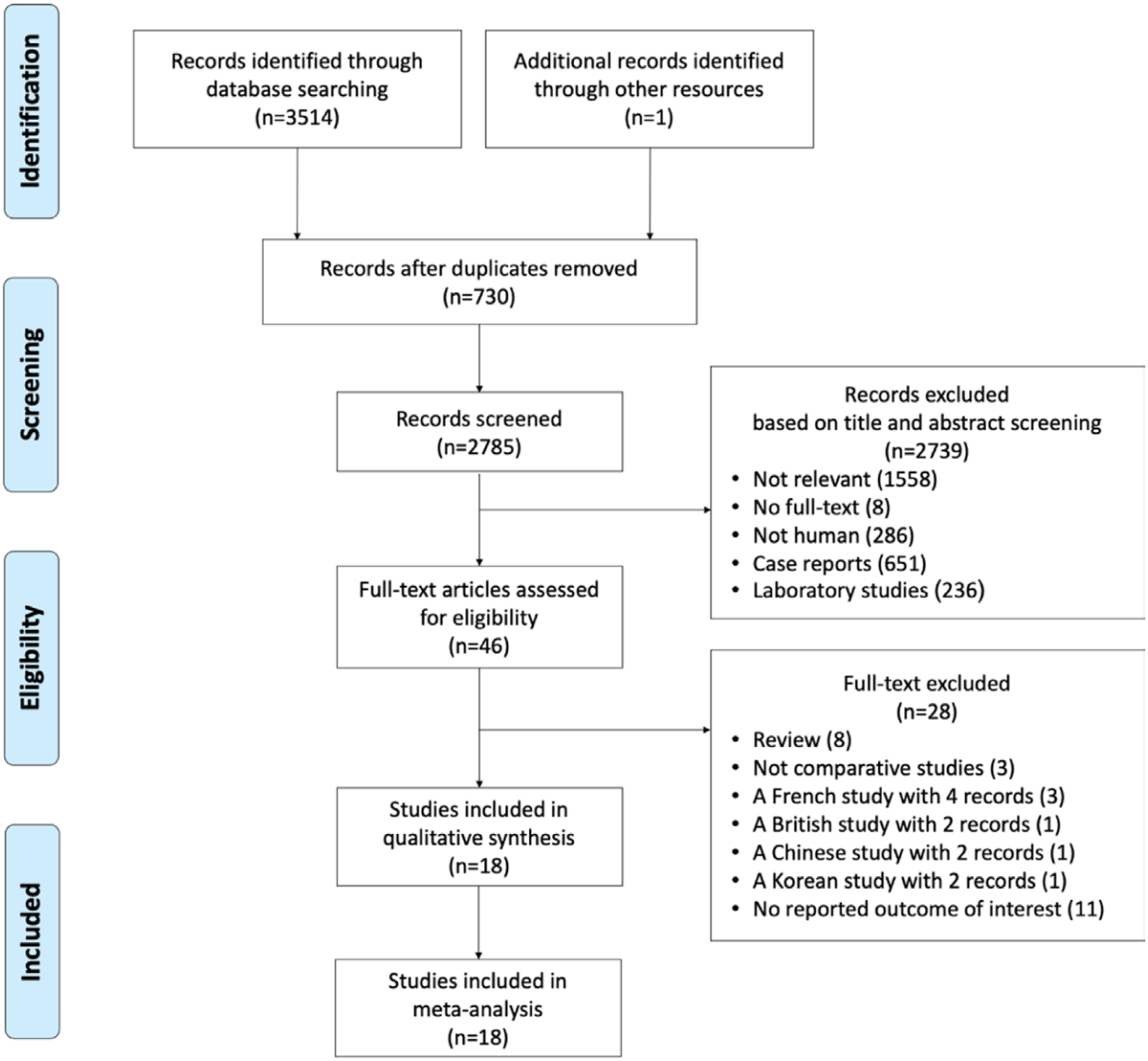

Figure 1. Flow-chart of literature search.

Similarly, 61.68% of male patients in the non-SIAMs group, and the median age ranged between 24 and 94.

Concerning clinical subtype, most MDS patients with SIAMs had multilineage dysplasia or ring sideroblasts with multilineage dysplasia (n = 388, 29.24%), followed by excess blasts (EB) (n = 284, 24.57%), and single lineage dysplasia (SLD) or ring sideroblasts with SLD (n = 199, 17.21%). The most common subtypes in the non-SIAMs group were EB (n = 982, 28.88%), followed by multilineage dysplasia or multilineage dysplasia (n = 790, 23.24%) and SLD or ring sideroblasts with SLD (n = 689, 20.26%).

According to the IPSS, most patients with or without SIAMs had an intermediate prognosis, with 64.89% and 60.63% respectively. Depending on the IPSS-R, most patients had lower risk in both arms.

Among MDS patients with or without SIAMs, 466 (73.73%) and 1318 (74.55%) presented favorable karyotype, 106 (16.77%) and 330 (18.67%) presented intermediate karyotype. More details regarding other clinical characteristics were reported in Table 2, (Table S3–S4, Supplemental Digital Content , http://links.lww.com/MD/H829).

Both MDS subtypes and IPSS-R were statistically significant in patients with SIAMs compared with the non-SIAMs group ($P < .01$). No differences in median age, gender, median of blood cell counts, IPSS, karyotype and the percentage of peripheral blood and bone marrow blasts.

3.3. Siams and MDS

Three retrospective studies reported univariate cox regression hazard ratios. MDS patients with SIAMs had a statistically shorter overall survival compared with patient without SIAMs (HR, 2.43; 95% CI, 1.34–4.41; $P < .01$). Meta-analysis of 11 studies showed SIAMs did not have a statistically significant effect on median survival (MSR, 1.16; 95% confidence interval [CI], 0.91–1.47; $P = .24$) (Fig. 2).

Of the 18 eligible publication, 12 and 13 studies reported data on AML transformation and death, respectively. Patients with SIAMs had similar rate of AML transformation and mortality compared with the non-SIAMs group (OR, 0.96; 95% CI, 0.63–1.45 and 1.20; 95% CI, 0.84–1.70, respectively) (Fig. 3).

Table 1

Characteristics of the included studies in meta-analysis.

Author/design	Year	Country	MDS subtype	Patient no.	MDS-SIAMs+ MDS-SIAMs-	Male/Female	Median/mean age, years (range)	Median follow-up, months (range)	Median survival, months (95% CI)	Overall survival, years (95% CI)	AML transformation (%)	Death (%)
Yojiro A, et al[13]	2021	Japan	RCUD/RARS/RCMD/RAEB1/RAEB2/U	61	12	9/3	62.9	NR	NR	NR	0 (0)	5 (47.1)
Single-center retrospective study			17/2/27/10/4/1		49	34/15	62.4				2 (16.7)	8 (16.3)
Abdulla W, et al[14]	2021	United Kingdom	ACML/CML/U/5q-/MMNU/RAEB/RARS/RCMD/RCUD	134	62	37/25	73.22	NR	23*	NR	17 (27.4)	44 (71.0)
Single-center retrospective study			2/27/1/3/4/36/10/50/1		72	48/24	76.74		55*		7 (9.7)	34 (47.2)
Anne LR, et al[19]	2020	France	MLD/ RS/ RS-SLD/ RS-MLD/5q-/EB1/EB2/ U	253	70	49/21	71.5 (21–90)	33.2 (1–162)	NR	NR	9 (12.9)	20 (28.6)
Multicenter retrospective study			70/27/11/13/6/37/29/6		183	103/80	70 (38–79)	28.5 (0–174)			59 (32.2)	47 (25.7)
Julie S, et al[3]	2019	France	SLD/MLD/ RS-SLD/ RS-MLD/5q-/EB1/EB2/ U/CMML1/CMML2	216	89	51/38	68.9	44.4	140.4*	10.3	13 (14.6)	36 (40.9)
Single-center retrospective study			25/39/16/8/4/39/31/3/46/5		127	86/41	69.9	46.8	62.4*	(6.2–12.9)	35 (27.6)	66 (52.0)
B. Kipfer, et al[17]	2018	Switzerland	RARS/RCMD/RAEB1/RAEB2/CMML/NC	93	30	20/10	71 (47–87)		21 (2–77)	4.8 (4.2–8.7), NR	9 (30.0)	23 (76.1)
Single-center retrospective study			6/31/14/17/18/7		63	36/27	75 (42–91)		18 (1–62)		17(27.0)	45 (71.4)
Julia M, et al[12]	2018	Spain	SLD/MLD/ RS/5q-/EB1/EB2/ CMML0/CMML1/CMML2	142	68	35/33	77 (44–95)	NR	38.5	NR	NR	21 (30.9)
Single-center retrospective study			22/42/27/10/18/9/10/3/1		74	54/20	76 (24–90)		NR			9 (12.2)
Praveen, et al[20]	2017	India	NR	117	52	28/24	NR	NR	NR	NR	8 (16.3)	15 (28.6)
Single-center retrospective study					65	NR					19(29.4)	16 (25.0)
JM Gómez, et al[21]	2017	Spain	RCUD/RARS/ RCMD/5q-/RAEB1/RAEB2/CMML1/CMML2	241	92	55/37	77 (44–95)	22 (0–69)	23 (17–29)	NR	NR	NR
Single-center retrospective study			26/3/113/13/29/24/29/4		149	95/54	76 (24–94)		45 (35-NA)			
Rami S, et al[4]	2016	United Kingdom	RA/RARS/RCMD/5q-/RAEB1/RAEB2/U/CMML/Other	1408	391	219/172	NR	74 (69–78)	60 (50–70)	NR	89 (22.8)	NR
Multicenter retrospective study			148/122/430/57/253/225/23/32/118		1017	712/305			45 (40–49)		301 (29.6)	
Arsene M, et al[16]	2016	France	RCUD/RARS/RCMD/5q-/RAEB1/RAEB2/U/CMML	788	123	82/41	70	25 (12–58)	72 (59–105)	NR	26 (21.1)	43 (35.0)
Multicenter retrospective study			84/58/167/31/148/126/33/127		665	374/291	73	25 (12–46)	75 (48–300)		83 (12.5)	154 (23.2)
Y Takeoka, et al[22]	2014	Japan	RCUD/RARS/RCMD/RAEB1/RAEB2/U	102	13	8/5	64	NR	20.4*	NR	6 (46.2)	NR
Single-center retrospective study			23/10/20/19/14/16		89	62/27	74		22.8*		18 (20.2)	
Li B, et al[23]	2012	China	RA/RARS/RCMD/5q-/RAEB1/RAEB2/U	173	16	6/10	46 (30–75)	14 (1–65)	NR	NR	NR	4 (25.0)
Single-center retrospective study			9/8/62/1/40/44/9		157	105/52	53 (7–81)					66 (42.0)
Ki-Jo KIM, et al[24]	2012	Korea	RA/RARS/RCMD/RCMD-RS/RAEB1/RAEB2/NC	129	27	NR	NR	NR	60.5 (45.6–75.3)	NR	NR	11 (40.7)
Single-center retrospective study			18/3/19/2/29/32/8		102				53.6 (46.0–61.2)			34 (33.3)
Hollanda, et al[25]	2011	France	RA&RARS/RCMD&RS/5q-/RAEB1/RAEB2	235	46	25/19	78 (68–93)	NR	NR	NR	8 (17.4)	31 (67.4)
Multicenter retrospective study			115/40/11/45/8		189	87/102	81 (65–89)				32 (16.9)	130 (68.8)
Dragmir, et al[26]	2006	Serbia	NR	284	32	23/9	64.5	NR	37	NR	NR	16 (50.0)
Single-center retrospective study					252	148/104	64		20			170 (67.5)
F. Bouali, et al[27]	2005	France	RA/RCMD/RAEB/RAEB-T†	40	20	6/14	49.5	NR	NR	NR	1 (5.0)	6 (30.0)
Single-center prospective study			2/21/16/2		20	13/7	61.5				NR	9 (45.0)
Giannouli, et al[15]	2004	Greece	NR	70	13	7/6	67 (51–80)	NR	39	NR	2 (15.4)	NR
Single-center prospective study					57	31/26	74 (43–89)		26		7 (12.3)	
Zhao S, et al[28]	2002	China	RA/RAS/RAEB/RAEB-T/CMML†	117	19	4/15	NR	NR	18.5 (6.3–77.4)	NR	5 (26.3)	NR
Single-center retrospective study			39/30/19/17/12		98	NR			29.7 (4.7–81.4)		20 (21.5)	

* Median survival was estimated from the Kaplan–Meier curve.

† MDS subtype was determined using the French-American-British (FAB) classification system.

5q- = MDS associated with isolated del (5q), ACML = atypical chronic myeloid leukemia, CML = chronic myeloid leukemia, CMML = chronic myelomonocytic leukemia, MLD = multilineage dysplasia, NC = not classified, NR = not reported, RA = refractory anemia, RAEB1 = refractory anemia with excess blasts-1, RAEB2 = refractory anemia with excess blasts-2, RAEB-T = refractory anemia with excess blasts in transformation, RARS = refractory anemia with excess blasts, RCMD = refractory anemia with multilineage dysplasia, RS-MLD = ring sideroblasts with multilineage dysplasia, RS-SLD = Ring sideroblasts with single lineage dysplasia, SLD = Single lineage dysplasia., U = MDS unclassifiable.

Table 2

Difference between MDS patients with or without SIAMs in the meta-analysis.

Characteristics	MDS/SIAMs+	MDS/SIAMs-	$\chi 2$ /W	P
Median age (range), years	70 (21–95)	74 (24–94)	68.0*	.41
Gender (%)				
Male	642 (59.28)	2039 (61.68)	1.87†	.17
Female	441(40.72)	1267 (38.32)		
WHO classification (%)				
MLD/RS-MLD	388 (29.24)	790 (23.24)	29.59†	<.01
SLD/RS-SLD	199 (17.21)	689 (20.26)		
EB	284 (24.57)	982 (28.88)		
CMML	78 (6.75)	197 (5.79)		
Del (5q)	36(3.11)	100 (2.94)		
MDS-U	33(2.85)	59 (1.74)		
Other	188 (16.26)	583 (17.15)		
Hemoglobin (range), g/L	92.5 (40–150)	92 (40–169)	29.00*	.79
Platelets (range), × 10^9 cells per L	124.5 (2–1780)	110.5 (1–897)	38.00*	.56
Neutrophils (range), × 10^9 cells per L	2.35 (0.02–23)	1.80 (0.07–23.67)	29.00*	.61
IPSS (%)				
Low	173 (25.63)	576 (26.28)	7.35‡	.06
INT-1	311 (46.07)	927 (42.29)		
INT-2	127 (18.82)	402 (18.34)		
High	64 (9.48)	287 (13.09)		
IPSS-R (%)				
Very low	100 (18.38)	190 (15.35)	31.32‡	<.01
Low	201 (36.95)	429 (34.65)		
INT	108 (19.85)	247 (19.95)		
High	72 (13.24)	193 (15.59)		
Very high	63 (11.58)	179 (14.46)		
Karyotype (%)				
Favorable	466 (73.73)	1318 (74.55)	0.67‡	.41
INT	106 (16.77)	330 (18.67)		
Poor	36 (5.70)	114 (6.45)		
Very poor	24 (3.80)	6 (0.34)		
Blood blasts (range), %	0.55 (0–1.1)	0.60 (0–1.2)	1.50*	1.00
Bone marrow blasts (range), %	3.6 (0–29)	3.0 (0–32)	15.50*	.60

*W derived from the Wilcoxon rank sum test.

† χ^2 derived from the Pearson's chi-squared test.

‡ χ^2 derived from the Cochran–Mantel–Haenszel test.

CI = confidence interval, CMML = chronic myelomonocytic leukemia, Del(5q) = MDS associated with isolated del (5q), EB = excess blasts, MDS-U = MDS unclassifiable, MLD = multilineage dysplasia, RS-MLD = ring sideroblasts with multilineage dysplasia, RS-SLD = Ring sideroblasts with single lineage dysplasia, SLD = Single lineage dysplasia.

3.4. Heterogeneity and sensitivity analysis

Significant heterogeneity was observed among the analysis of 3 survival outcomes, varied from 48% to 98%. Sensitivity analysis was conducted with leave-one-out meta-analysis by sequential omission of individual studies (Figure S1–S2, Supplemental Digital Content, http://links.lww.com/MD/H830). The changes in *P*-values and the heterogeneity of the combined results were shown in Table 3.

3.5. Publication bias

Visual inspection of the funnel plot did not identify substantial asymmetry (Fig. 4). Begg's rank correlation, Egger's weighted regression also indicated no evidence of publication bias.

4. Discussion

In this study, we demonstrated that MDS patients with SIAMs had inferior overall survival compared with the non-SIAMs group. Nevertheless, no strong evidence of the association of SIAMs with median survival, the rate of AML transformation or mortality.

Firstly, SIAMs negatively affected the overall survival of MDS. All 3 studies included in this meta reported the consistent result of the negative association of SIAMs and the survival of MDS. The heterogeneity was substantial due to the limited studies but was not explained by any individual study. It is worth mentioning that the multivariate survival analysis of these 3 studies suggested inconsistent results of the association of SIAMs with overall survival of MDS. Yojiro[13] and Julia[12] showed that patients with SIAMs had shorter overall survival. However, Abdulla[14] found SIAMs was not related to the survival of MDS after adjusting for age, gender, risk stratification and received treatment. Moreover, Lee's study[29] using the univariate analysis reported no association between SIAMs and the overall survival of MDS, was not included in the meta because the detailed data was unavailable.

Secondly, SIAMs did not have a statistically significant effect on median survival. MSR is an important statistic for use in survival data and helps us to better understand the clinical interpretation of the HR.[30,31] In this meta-analysis, the pooling HR and MSR presented a divergence in results. That may include the following reasons. First, the result of HR was susceptible for selection bias due to limited data. Second, MSR is not an indicator for time-to-event outcomes and may not accurately represent the entire observation period.[32]

Thirdly, our results were most compatible with no effect of SIAMs on the rate of AML transformation and mortality. In selected studies of Anne,[18] Rami[4] and Julie,[3] MDS patients with SIAMs had a lower risk to develop AML. However, contrary results were represented in the other 2 studies.[22,23] The finding of the remaining studies was consistent with ours. Meanwhile, there were 3 studies reported the presence of SIAMs increased the mortality of MDS in the included 13 studies. The finding of other

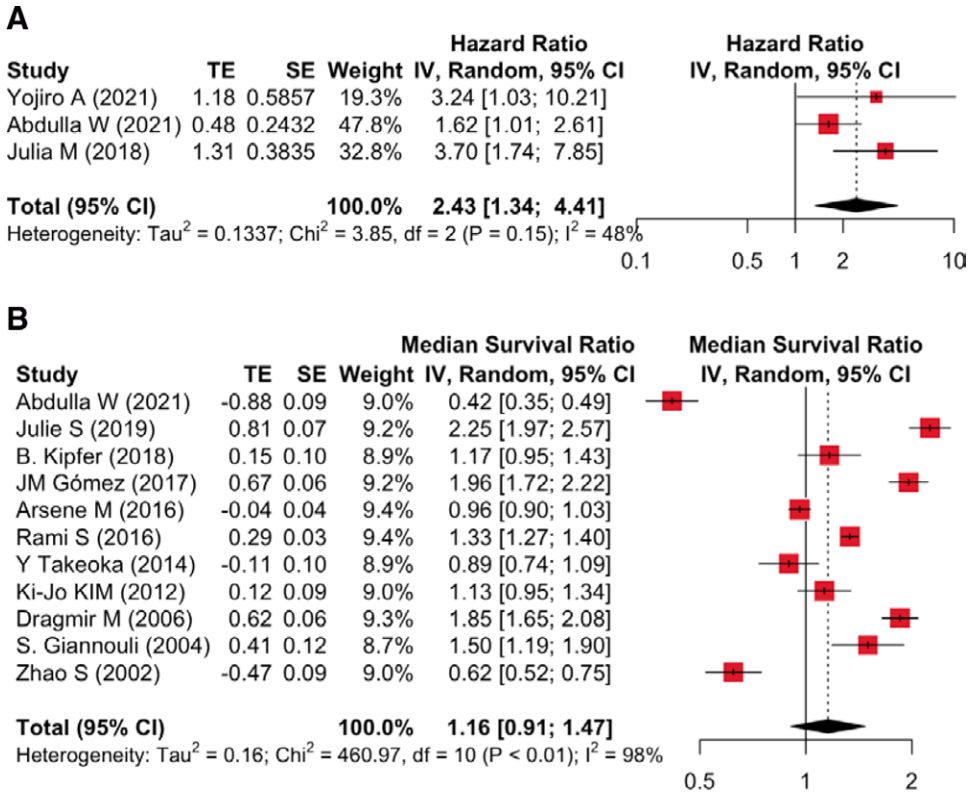

Figure 2. Forest plots of association between SIAMs and overall survival (A) and median survival (B) of MDS. MDS = Myelodysplastic syndromes, SIAM = systemic inflammatory and autoimmune manifestations.

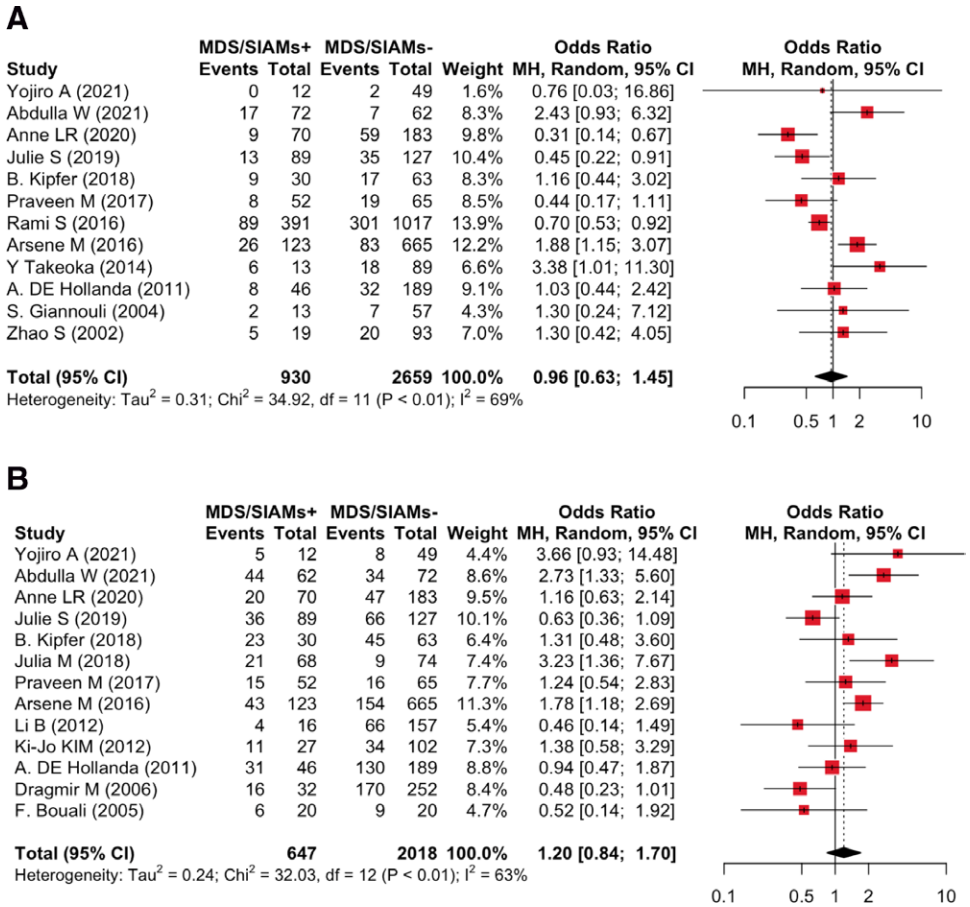

Figure 3. Forest plots of association between SIAMs and rate of AML transformation (A) and mortality (B) of MDS. AML = acute myeloid leukemia, MDS = Myelodysplastic syndromes, SIAM = systemic inflammatory and autoimmune manifestations.

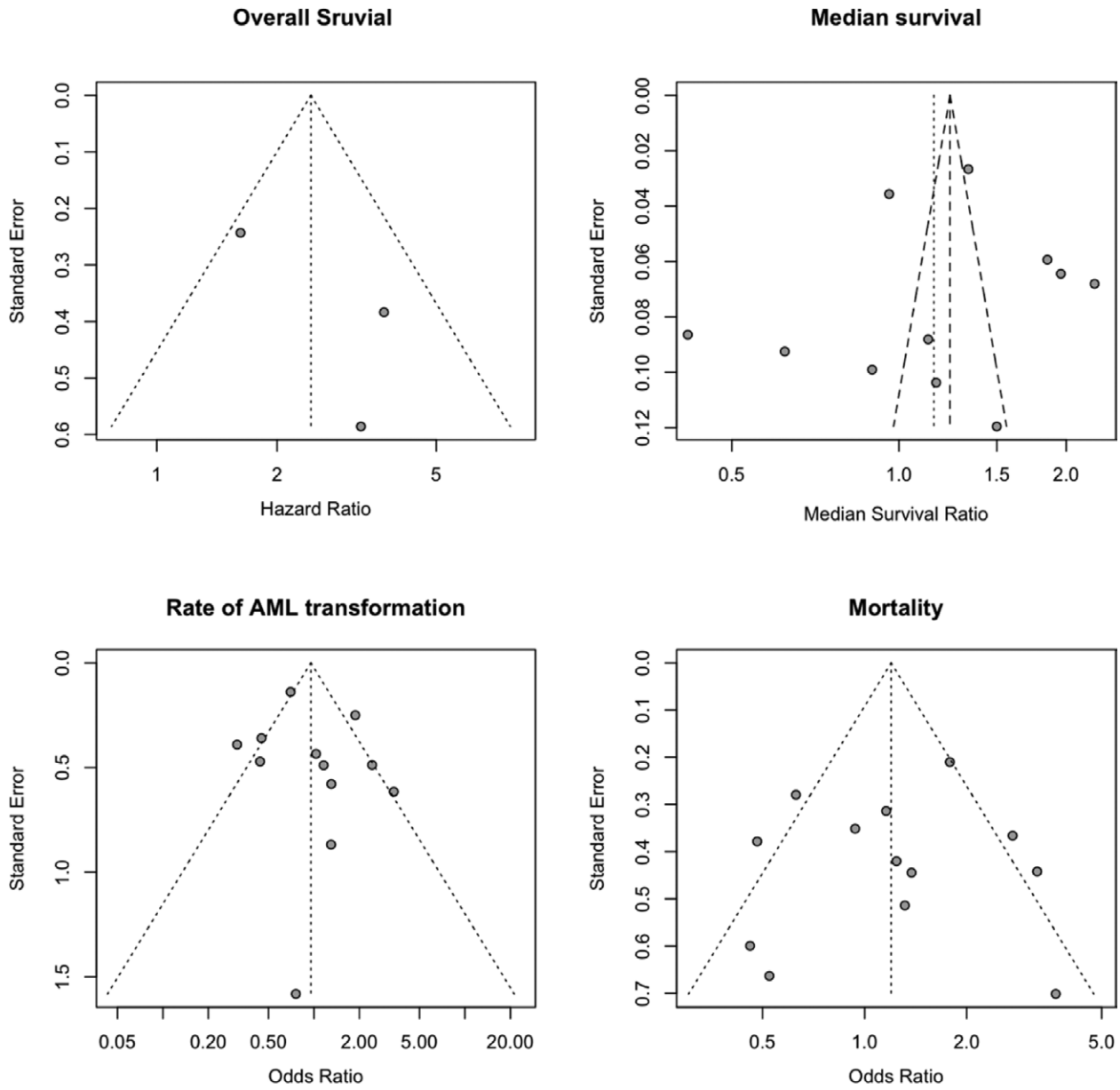

Figure 4. Funnel plot analysis to examine publication bias.

Table 3

Overall meta-analysis of the impact of SIAMs on survival outcomes.

Survival outcomes	Studies Number	Type of Indicators	95% CI	*P*	Heterogeneity			Publication bias	
					I^2 (%)	P_H	M	P_{Begg}	P_{Egger}
Overall survival	3	HR	2.43 (1.34,4,41)	<.01	48.0	.15	R	.60	.40
Median survival	11	MSR	1.16 (0.91, 1.47)	.24	97.8	<.01	R	.94	.68
Rate of AML transformation	12	OR	0.96 (0.63, 1.45)	.83	70.2	<.01	R	.27	.47
Mortality	13	OR	1.20 (0.84, 1.70)	.31	62.5	<.01	R	.81	.77

AML = acute myeloid leukemia, CI = confidence interval, HR = hazard ratio, OR = odds ratio; model for meta-analysis, P_{Begg} = *P*-value for Begg's test, P_{Egger} = *P*-value for Egger's test, P_H = *P*-value for heterogeneity test, P_{OR} = *P*-value for OR test, MSR = median survival ratio, R, Random-effects model.

9 studies were compatible with our result. The reason for these inconsistent results may potential due to the clinical heterogeneity of SIAMs and MDS.[5] SIAMs are not exactly certain type of autoimmune disorders. Hence, depends on types of SIAMs in each study, the impact on the survival outcomes could be different.

To the best of our knowledge, this is the first meta-analysis to evaluate the association of SIAMs with survival outcomes of MDS patients. The highlight of this study was that we comprehensively measured the relationship between SIAMs and MDS by using 4 survival outcomes with 3 indicators, including HR,

MSR and OR. However, the findings of this systematic review and meta-analysis were limited by several factors. Firstly, the study design included only case-control studies that were susceptible to biases. Hence, the casual relationship between SIAMs and MDS was unclear. Secondly, both SIAMs and MDS consist of a group of diseases, and lead to clinical heterogeneity. That probably effects the accuracy of our result. Thirdly, we were unable to perform detailed subgroup analysis due to paucity of data. There was still a great need for large, prospective and high methodological quality publications to verify our findings.

5. Conclusion

In this systematic review and meta-analysis, SIAMs appeared to have an adverse effect on overall survival of MDS patients. This finding suggested that SIAMs may be a potential independent prognostic factor for MDS.

Author contributions

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