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The inflammatory cytokine profile of myelodysplastic syndromes

A meta-analysis

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Abstract

Background: Accumulating evidence has indicated that the dysregulation of immunological environment has an important role in the pathogenesis of myelodysplastic syndromes (MDS). The previous studies about the levels of the inflammatory cytokines in MDS, such as TNF-α, IFN-γ, IL-6, IL-8, and IL-17, have yielded controversial results. Thus, we performed a meta-analysis to assess the levels of these inflammatory cytokines in MDS.

Methods: A systematic search in PubMed, MEDLINE, Cochrane Library, Web of Science, CNKI, and CBM was conducted to find eligible studies. Meta-analyses were performed using STATA 12.0 for Windows. Heterogeneity between included studies was assessed by I^2 test. We chose SMD as the summary statistic.

Results: A total of 697 individuals from 11 studies were included in this study. Our results suggest the levels of TNF-α, IL-6, IL-8 were significantly higher in MDS patients compared with controls, SMD and 95%CI was 1.48 (0.60, 2.36), 0.71 (0.16, 1.25) and 0.69 (0.28, 1.09), respectively. Moreover, the levels of IL-17 have decreased in the high-risk MDS, the SMD and 95% CI was 2.96 (0.78, 5.15).

Conclusion: A close association between immunological microenvironment disorders and the pathogenesis of MDS was revealed in this meta-analysis. More importantly, the profiles of inflammatory cytokines appear to change along the progression of the disease.

Abbreviations: AML = acute myeloid leukaemia, BM = bone marrow, CBA = cytometric bead array, CBM = China Biology Medicine database, CNKI = China National Knowledge Infrastructure, ELISA = enzyme-linked immunosorbent assay, FAB = French American British classification, HSC = hematopoietic stem cells, IBD = inflammatory bowel disease, IPSS = International Prognostic Scoring System, IST = immunosuppressive therapy, MDS = myelodysplastic syndromes, NOS = Newcastle–Ottawa scale, PB = peripheral blood, RA = refractory anemia, RAEB = RA with excess blasts, RAEB-t = RAEB in transformation, RARS = RA with ringed sideroblasts, RCMD = refractory cytopenia with multilineage dysplasia, SD = standard deviation, SMD = standardized mean difference, WHO = World Health Organization.

Keywords: IFN-γ, IL-17, IL-6, IL-8, meta-analysis, myelodysplastic syndromes, TNF-α

1. Introduction

Myelodysplastic syndromes (MDS) are clonal disorders involving hematopoietic stem cells (HSC) characterized by cytopenias caused by ineffective hematopoiesis and the potential to evolve into acute myeloid leukemia (AML). In recent years, more and more experimental results indicate that the dysregulation of the immunological environment has an important role in the pathogenesis of MDS, but the specific molecular mechanisms cause the pathogenesis of MDS have largely remained obscure. Much of the attention has been focused on the study of the pro-apoptotic or inflammatory cytokines such as TNF-α, IFN-γ, IL-6 or IL-8. In general, researchers found the levels of these cytokines were elevated in the samples from patients with MDS comparing with those in samples from healthy controls.[1–7] Another aspect the researchers have paid attention to is the immune regulatory cytokine such as IL-17, the secretion of which was also found increased in MDS patients by some researchers.[8]

However, the results remained controversial. The study conducted by Li et al[9] showed that when considered as a whole group, the levels of IL-17 and IL-6 in MDS patients did not elevate comparing with healthy controls. The research of Shao et al[10] indicated that both in peripheral blood and bone marrow samples, the levels of IL-17 has no significant difference between MDS patients and healthy controls either. A study attempted to comprehensively profile circulating cytokines levels in MDS patients included 72 individuals showed no significant difference in the levels of TNF-α between patients with MDS and healthy controls, and the levels of IFN-γ were even lower in MDS

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patients.[11] When analyzing the data derived from patients of different prognostic groups, the heterogeneity was even more significant. Therefore, we conduct this meta-analysis to investigate the immunological microenvironment of patients with MDS through evaluating the levels of inflammatory cytokines.

2. Methods

2.1. Ethics statement

Since this meta-analysis is conducted by the data from previously published studies, ethical approval and patient consent are not required.

2.2. Literature search

Two reviewers independently conducted a systematic search in PubMed, MEDLINE, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), and China Biology Medicine database (CBM). In order to maximize the ability to find eligible studies, we performed the search by using the following terms: ("MDS" or "myelodysplastic syndromes") and ("TNF" or "tumor necrosis factor" or "interleukins" or "IL" or "inflammatory cytokines" or "CXCL" or "IFN" or "interferon"). The publication date of literature was restricted before September 2018. Literature published in English or Chinese was both included in this study.

2.3. Eligible criteria

The included study should meet all of the following criteria: investigated the peripheral blood (PB) or bone marrow (BM) levels of one or more of following inflammatory cytokines: TNF-α, IFN-γ, IL-6, IL-8, IL-17; had detailed information about the concentration of target cytokine for analysis; MDS patients sample size should be more than 20; articles in Chinese should be published in Chinese core journals; if several studies reported the result from the same population, the one with more detailed information was included. Studies published in abstract form with no available data, case reports and letters were excluded.

2.4. Data extraction and quality assessment

Two reviewers independently collected the descriptive data from included studies: first author's name, year of publication, participants' country, number of patients and controls, the age of patients and controls, male-to-female ratio of the population, MDS subtype, IPSS score classification, the concentration of cytokines. If both peripheral blood and bone marrow concentrations of the cytokine were presented in the same study, the one with larger sample size was adopted. If the sample size was equal, we selected the data of peripheral blood concentration. The Newcastle–Ottawa scale (NOS) was used to assess the quality of the study.[12] The disagreements were resolved by discussion.

2.5. Statistical analyses

In this meta-analysis, the mean concentration and standard deviation (SD) of each cytokine were used in the comparison between patients with different prognostic categories, and between MDS patients and healthy controls. The data present by median and range were transferred to mean and SD by the methods proposed by Wen et al[13] and Luo et al[14] (http://www.comp.hkbu.edu.hk/~xwan/median2mean.html). If data needed for meta-analysis was only expressed graphically, we tried to reach the author for further information, and with no response, we measured the graphic for data using Engauge Digitizer (version 7.2, 2014 Mark Mitchell). The mean concentration and SD of subgroups were combined through the method provided by Zhang et al[15] for further analysis.

Heterogeneity between included studies was assessed by I^2 test. $I^2 > 50\%$ indicate substantial heterogeneity. Since the examination methods vary in included studies, we chose the standardized mean difference (SMD) as the summary statistic. The random-effects model, which is generally more conservative, was adopted in this meta-analysis. To further investigate the source of heterogeneity, we conducted stratified analysis according to examination method, study region, patients' mean age and diagnostic criteria during the comparison between MDS patients and healthy controls. For the analysis between different prognostic groups, we additionally divided the studies by risk-stratified criteria. Sensitivity tests were performed to assess the influence of each study on the stability of the meta-analysis by recalculating pooled SMD when omitting one study sequentially. We did not perform stratified analysis and sensitivity test for the comparison of IL-8 levels between low-risk and high-risk MDS patients, as there were only 2 studies included. Publication bias was statistically assessed via Egger's test.[16] Meta-analyses were performed using STATA 12.0 for Windows (Stata Corp LP, College Station, TX).

3. Results

3.1. Study selection and characteristics

Around 3849 Articles were found from 6 databases using the search terms described previously. A total of 78 articles were left when we screened through titles and abstracts after removed the duplicates. Among those, we cannot get access to the full text for 9 articles, and there are 24 articles were published in abstract form. A total of 69 articles were reviewed in detail, and 58 articles were excluded. Because 3 articles' sample size of patients was <20; 8 articles reported in duplication; 12 articles were not from Chinese core journals; 35 articles cannot provide the data needed for analysis. Finally, we included 11 studied in this meta-analysis (Fig. 1).

The characteristics of 11 eligible studies were summarized in Table 1. A total of 697 individuals were included in this study (511 patients with MDS and 186 healthy controls). These studies were published between 1998 and 2018. Five studies[1,4,8–10] were from China; 6 studies[2,3,5–7,11] were from the Western world. Two articles[1,4] published in Chinese; 9 articles[2,3,5–11] published in English. The NOS scores were all above 5.

3.2. Inflammatory cytokines levels have elevated in MDS patients

As shown in the Forest plots (Fig. 2), the levels of TNF-α, IL-6, IL-8 were significantly higher in MDS patients, the SMD and 95% confidence interval (CI) was 1.48 (0.60, 2.36), 0.71 (0.16, 1.25) and 0.69 (0.28, 1.09), respectively. The differences in levels of IFN-γ and IL-17 did not reach but have a strong tendency toward statistical significance, the SMD and 95%CI was 0.60 (−0.47, 1.66) and 0.63 (−0.06, 1.31), respectively.

3.3. The secretion of IL-17 has decreased in the high-risk MDS

We defined low-risk groups as those with a diagnosis of RA/RARS/RCMD, or IPSS score ≤ 1.0, whereas the high-risk groups

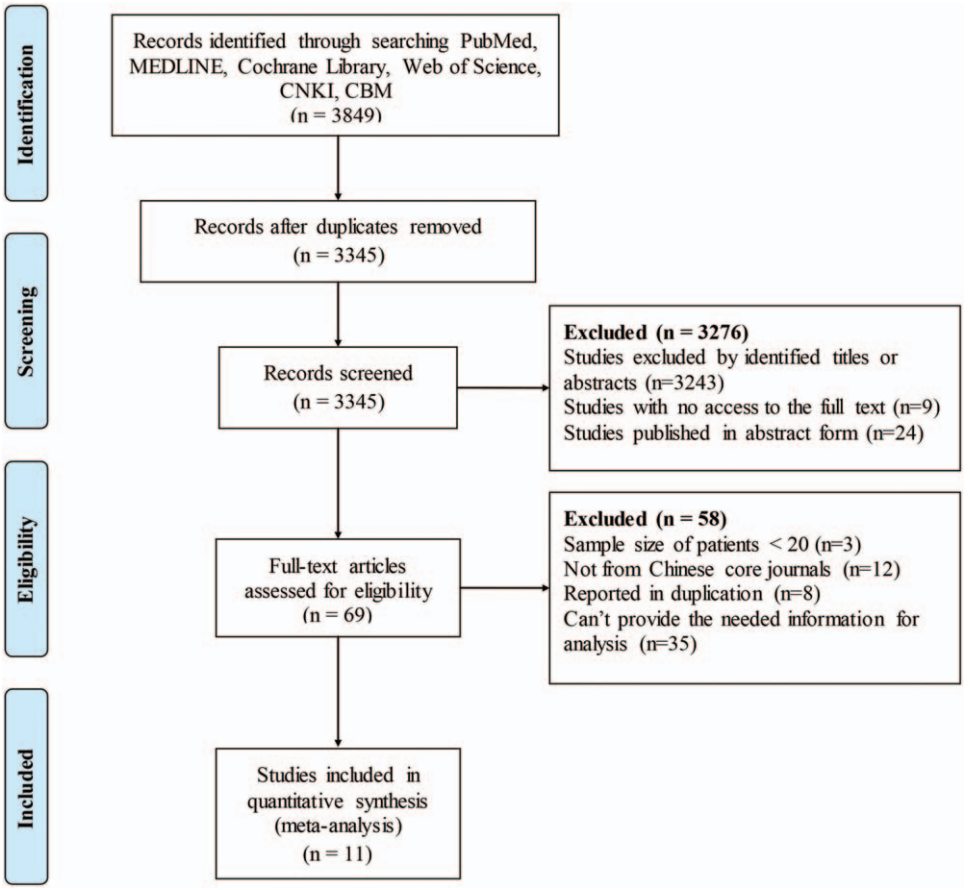

Figure 1. Flowchart for the process of selecting eligible studies.

Table 1

Main characteristics of included studies in the meta-analysis.

Study	Year	Country	Patients/Controls			Sample	Method	Cytokine	MDS subtype, n				Diagnosis Criteria	IPSS Low+Int-1/ Int-2+high, n	NOS
			No.	Age, mean (SD)	Male, %				RA/ -RS	RCMD	RAEB/ -1/-2/-t	CMML/ Others			
Guo et al[1]	2018	China	20/10	52.70 (12.31)/47.66 (16.16)	75/50	PB serum	CBA	TNF-α IFN-γ IL-6 IL-17	10	0	10	0	FAB	NA	6
Matos et al[2]	2017	Brazil	25/20	78.04 (8.95) /NA	44/NA	PB serum	ELISA	IL-8	4	16	5	0	WHO	11/6	7
Li et al[9]	2016	China	42/18	56.93 (14.48)/ 53.23 (14.72)	57.1/44.4	PB serum	ELISA	IL-6 IL-17	10	8	21	3	WHO	22/20	6
Kittang et al[11]	2016	Norway	49/23	73.91 (8.72)/ 40.48 (10.89)	75.6/37.5	PB serum	Luminex analyses	TNF-α IFN-γ IL-6 IL-8	NA	NA	NA	NA	NA	35/14	5
Zhang et al[8]	2013	China	47/10	51.73 (15.09) /NA	66/NA	BM plasma	ELISA	TNF-α IFN-γ IL-17	9	28	8	2	WHO	39/8	5
Pardanani et al[3]	2012	USA	78/35	71.27 (9.34) /NA	67/NA	PB serum	Luminex analyses	TNF-α IFN-γ IL-6 IL-8 IL-17	10	29	29	10	WHO	59/18	6
Shao et al[10]	2012	China	54/20	52.60 (15.4)/ 51.02 (15.9)	72/70	PB serum	ELISA	IL-17	14	2	19	19	WHO	29/25	6
Wu et al[4]	2007	China	34/13	56.03 (16.97) /NA	50/NA	BM serum	ELISA	TNF-α IFN-γ	4	18	12	0	WHO	23/11	5
Alexandrakis et al[5]	2005	Greece	51/15	73.43 (7.11)/ 65.83 (8.34)	68/NA	PB serum	ELISA	TNF-α	25	0	17	9	FAB	NA	5
Alexandrakis et al[6]	2004	Greece	67/15	72.92 (8.56) /NA	67/NA	PB serum	ELISA	IL-6	31	0	26	10	FAB	25/21	6
Gersuk et al[7]	1998	USA	44/12	45.72 (13.21) /NA	43/NA	BM plasma	ELISA	TNF-α	27	0	24	10	FAB	NA	5

CBA = cytometric bead array, ELISA = enzyme-linked immunosorbent assay, PB = peripheral blood, BM = bone marrow, MDS = myelodysplastic syndromes, WHO = World Health Organization, FAB = French American British classification, RA = refractory anemia, RARS = RA with ringed sideroblasts, RCMD = refractory cytopenia with multilineage dysplasia, RAEB = RA with excess blasts, RAEB-t = RAEB in transformation, IPSS = International Prognostic Scoring System, NOS = Newcastle–Ottawa scale score.

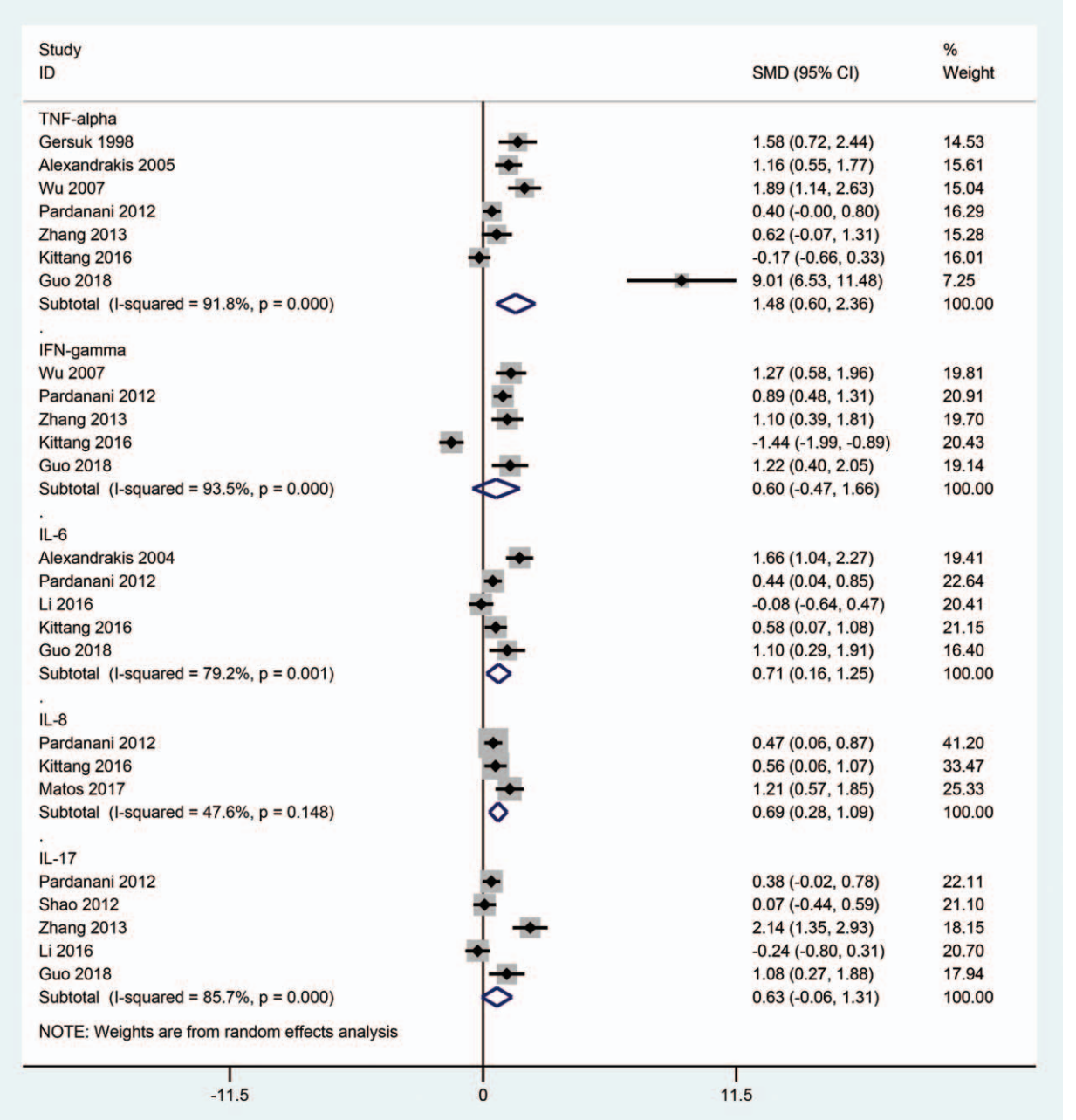

Figure 2. Forest plots of the pooled SMDs and 95% CIs of the cytokines levels in MDS patients and healthy controls. SMD > 0 implied higher cytokine concentration in MDS patients. MDS = myelodysplastic syndromes, SMD = standardized mean difference.

refer to those whose diagnosis was RAEB/RAEB-t/CMML or IPSS score > 1.0. The levels of IL-17 were significantly higher in patients with low-risk MDS, the SMD and 95% CI was 2.96 (0.78, 5.15). It seems that the levels of TNF-α and IFN-γ were also higher in low-risk patients, whereas the levels of IL-6 was higher in high-risk patients, but the differences both failed to reach conventional levels of statistical significance, the SMD and 95% CI was 0.78 (-0.39, 1.95), 0.92 (−0.34, 2.17) and −1.32 (−2.91, 0.27), respectively. We found no significant difference of levels of IL-8 between low-risk patients and high-risk patients, the SMD and 95% CI was 0.26 (−0.57, 1.10) (Fig. 3).

3.4. Stratified analysis and sensitivity tests

As shown in Table 2, in the stratified analysis for the difference of cytokine levels between MDS patients and healthy controls, we found the difference in examination method may be the main source of heterogeneity. When we divided studies by the examination method, the heterogeneity decreased in all endpoints except for the levels of IL-17. Interestingly, we found the heterogeneity almost disappeared when we did the stratified analysis for the difference of IL-6 levels between MDS patients and controls by the diagnostic criteria. The stratified analysis for the difference of cytokine levels from different prognostic groups

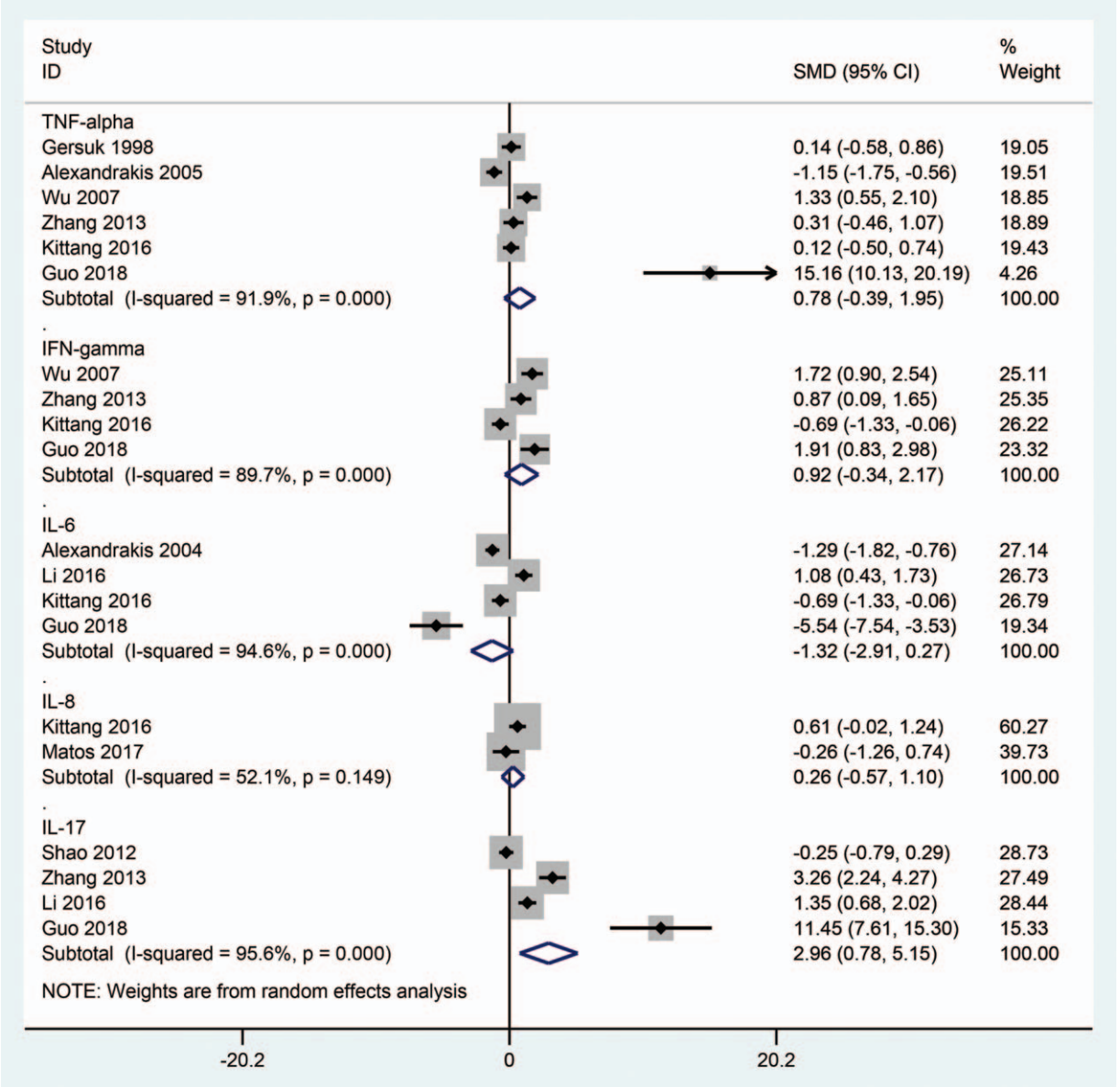

Figure 3. Forest plots of the pooled SMDs and 95% CIs of the cytokines levels in low-risk group and high-risk group. SMD > 0 implied higher cytokine concentration in the low-risk group. SMD = standardized mean difference.

showed that among the studies included for the levels of IL-6, those from the Western world had much less heterogeneity (Table 3).

The sensitivity tests showed that the result of the study conducted by Kittang et al[11] was the primary cause of heterogeneity in the meta-analysis for the levels of IFN-γ. When their study was omitted, both results of the comparison between patients and controls and the comparison between the low-risk group and the high-risk group reached statistical significance, and the heterogeneity was almost gone. Sensitivity tests also showed that the study of Li et al[9] caused instability in the meta-analysis for the levels of IL-17 between MDS patients and healthy controls and the levels of IL-6 between different prognostic groups. When their study was omitted from those 2 analyses, the results both showed significant differences. Moreover, the result was also significantly changed when the study of Guo et al[1] was excluded from the meta-analysis for the levels of IL-17 between different prognostic groups (Table 4). Sensitivity tests found no significant impact on the stability of meta-analysis at the rest endpoints.

3.5. Assessment of publication bias

In the meta-analysis for the difference of cytokine levels between MDS patients and healthy controls, Egger's test indicated there is publication bias in articles for TNF-α ($P < .01$), no publication bias was found for IFN-γ ($P = .76$), IL-17 ($P = .24$), IL-6 ($P = .41$), and IL-8 ($P = .23$). In the analysis for the difference of cytokine levels between the low-risk group and high-risk group, Egger's test showed publication bias in articles for TNF-α ($P = .02$) too,

Table 2

Heterogeneity of subgroups in the stratified analysis for the difference of cytokine levels between MDS patients and healthy controls.

	TNF-α			IFN-γ			IL-6			IL-8			IL-17		
Variable	**n**	***P***	I^2 **(%)**	**n**	***P***	I^2 **(%)**	**n**	***P***	I^2 **(%)**	**n**	***P***	I^2 **(%)**	**n**	***P***	I^2 **(%)**
method															
CBA	1	na	na	1	na	na	1	na	na	0	na	na	1	na	na
ELISA	4	.086	54.6	2	.742	0	2	< .001	94.1	1	na	na	3	< .001	92.1
Luminex	2	.08	67.3	2	< .001	97.7	2	.692	0	2	.762	0	1	na	na
region															
China	3	< .001	95.3	3	.945	0	2	.018	82	0	na	na	4	< .001	89.3
Western	4	< .001	83	2	< .001	97.7	3	.004	81.8	3	.148	47.6	1	na	na
diagnostic criteria															
FAB	3	< .001	94.5	1	na	na	2	.282	13.4	0	na	na	1	na	na
WHO	3	< .001	83	3	.64	0	3	.188	40.1	3	.148	47.6	4	< .001	88.1
NA	1	na	na	1	na	na	0	na	na	0	na	na	0	na	na
mean age															
<60	4	< .001	92.9	3	.945	0	2	.018	82	0	na	na	4	< .001	89.3
>60	3	.004	81.7	2	< .001	97.7	3	.004	81.8	3	.148	47.6	1	na	na

na = not available, n = number of studies in the subgroup.
The *P* value was calculated by *Q* test.

Table 3

Heterogeneity of subgroups in the stratified analysis for the difference of cytokine levels between the low-risk group and high-risk group.

	TNF-α			IFN-γ			IL-6			IL-17		
Variable	**n**	***P***	I^2 **(%)**	**n**	***P***	I^2 **(%)**	**n**	***P***	I^2 **(%)**	**n**	***P***	I^2 **(%)**
Method												
CBA	1	na	na	1	na	na	1	na	na	1	na	na
ELISA	4	< .001	88.7	2	.139	54.3	2	< .001	96.8	3	< .001	95
Luminex	1	na	na	1	na	na	1	na	na	0	na	na
region												
China	3	< .001	94.2	3	.199	38.1	2	< .001	97.3	4	< .001	95.6
Western	3	.004	81.8	1	na	na	2	.156	50.4	0	na	na
Diagnostic criteria												
FAB	2	< .001	95.5	1	na	na	2	< .001	93.8	1	na	na
WHO	3	.066	70.4	2	.139	54.3	2	< .001	93.2	3	< .001	95
NA	1	na	na	1	na	na	0	na	na	0	na	na
Mean age												
<60	4	< .001	92	3	.199	38.1	2	< .001	97.3	4	< .001	95.6
>60	2	.004	88.2	1	na	na	2	.156	50.4	0	na	na
Risk-stratified criteria												
subtype	4	< .001	95.1	2	.787	0	2	< .001	93.8	1	na	na
IPSS	2	.717	0	2	.002	89.1	2	< .001	93.2	3	< .001	95.6

na = not available, n = number of studies in the subgroup.
The *P* value was calculated by *Q* test.

Table 4

Sensitivity tests spotted several studies have influenced the stability of meta-analysis.

		Before omit the study		After omit the study	
Study	**Analysis**	**Pooled SMD**	**Heterogeneity**	**Pooled SMD**	**Heterogeneity**
Kittang et al[11]	IFN-γ P vs C	0.60 (−0.47, 1.66)	I^2= 93.5%, *P*< .001	1.04 (0.74, 1.34)	I^2= 0%, *P*= .775
Kittang et al[11]	IFN-γ L vs H	0.92 (−0.34, 2.17)	I^2= 89.7%, *P*< .001	1.44 (0.80, 2.09)	I^2= 38.1%, *P*= .199
Li et al[9]	IL-17 P vs C	0.63 (−0.06, 1.31)	I^2= 85.7%, *P*< .001	0.86 (0.07, 1.65)	I^2= 85.8%, *P*< .001
Li et al[9]	IL-6 L vs H	−2.07 (−3.57, 0.27)	I^2= 94.6%, *P*< .001	−2.07 (−3.57,-0.56)	I^2= 90.2%, *P*< .001
Guo et al[1]	IL-17 L vs H	2.96 (0.78, 5.15)	I^2= 95.6%, *P*< .001	1.41 (−0.43, 3.25)	I^2= 95%, *P*< .001

P vs C = patient vs control, L vs H = low-risk group vs High-risk group, SMD = standardized mean difference.
The *P* value was calculated by *Q* test.

revealed no publication bias for IFN-γ ($P = .13$), IL-17 ($P = .09$), and IL-6 ($P = .5$).

4. Discussion

Recent clinical and molecular studies of MDS have yielded accumulating evidence suggesting that abnormality of the immunological environment and associated inflammation contribute to the pathogenesis of this disease. Substantial evidence is that nearly 30% of patients treated with immunosuppressive therapy (IST), such as anti-thymocyte globulin or the immunomodulatory drug lenalidomide, become transfusion-independent and improve cell counts.[17] What's more, a new insight of the influence of a pro-inflammatory cytokine S100A9 on the pathogenesis of MDS had shown that the chronic inflammation status in patients' BM could induce DNA instability and promote the emergence of clonal expansion.[18] Thus, the importance to investigate the relation between the immunological environment and MDS is critical.

To the best of our knowledge, this is the first meta-analysis to assess the inflammatory cytokines levels of MDS patients. In our study, we found significant heterogeneity between included studies. One important cause of the heterogeneity probably is the difference in examination methods as we shown in the stratified analysis. Even in those studies using ELISA as the test method, ELISA kits from different manufacturers may still cause heterogeneity. An interesting signature that we found is the method tried to obtain the whole cytokines profile by one single test may induce the instability of the results. The 2 studies we spotted in sensitivity tests, which impaired the stability of meta-analysis, both used these kinds of technique. Another important potential cause of the heterogeneity is the possible autoimmune comorbidity of MDS. In the very early study of MDS, clinicians noticed its frequent association with rheumatic manifestations, especially rheumatoid arthritis. Although it is a common disease in the elderly, the observations suggested that this association was not fortuitous.[19] A recent review reported that arthritis preceded MDS in 55% of cases and that both the pathologies were concomitantly diagnosed in 27% of cases.[19] Similarly, MDS and inflammatory bowel disease (IBD) are frequently diagnosed simultaneously.[20] Other acute and chronic autoimmune disorders associated with MDS are diverse types of vasculitis, autoimmune anemias, several rheumatic and skin disorders, and certain thyroid diseases.[21,22] The autoimmune disorder like IBD could affect the levels of inflammatory cytokines in MDS patients. Unfortunately, none of the included studies had provided the status of MDS patients' comorbidities, so we cannot perform further analysis. When the inherent heterogeneity of the sampled population is considered, the limited sample size could also contribute to the significant heterogeneity between included studies.

Parallel profiling of 27 cytokines in the peripheral plasma of 114 MDS patients by Kornblau et al[23] revealed that the mean expression of some of the cytokines, such as IL-6 or IFN-γ, was significantly lower in MDS patients. In our study, the meta-analysis showed the levels of TNF-α, IL-6 and IL-8 were significantly elevated in the MDS patients compared with healthy controls. When the study by which caused instability and heterogeneity omitted from the analysis for the levels of IFN-γ, the pooled SMD also revealed significance. The summary statistic of IL-17 levels did not show a statistical difference between patients and controls in our meta-analysis. Noteworthy, all included studies with the data of IL-17 levels revealed no significant difference between high-risk patients and healthy controls,[1,8,10] the data of Li et al[9] even showed decreased IL-17 levels in high-risk patients. Thus, the composition of patient cohort could affect the outcome. In general, our results showed that the levels of inflammatory cytokines have elevated in the MDS patients, confirmed the clinical data previously collected by Feng et al[24] and Pardanani et al.[3] The overexpression of inflammatory cytokines reflects a profound dysregulation of the immunological environment in the pathogenesis of MDS.

Whereas low-risk MDS (or subtypes without excess blasts such as refractory anemia, RA) is characterized by an elevated apoptotic index, high-risk disease and the subtypes with high counts of clonal cells (RA with excess blasts, RAEB) are associated with more aggressive clonal expansion, and have higher chance to evolve into AML. The occurrence of apoptosis in the MDS BM is considered closely associated with the TNF-α levels.[25] Cytopenias in low-risk MDS could be the side effect caused by anti-tumor mechanisms which induced the apoptosis of clonal cells to keep a stable status of the disease.[26] The levels of these pro-apoptosis cytokines appeared to be significantly elevated in the specific subtype of MDS like RA diagnosed by FAB criteria, or refractory cytopenia with multiple dysplasias (RCMD) diagnosed by WHO criteria.[4,7] This might explain the reason we did not find a significant difference in the TNF-α levels between the low-risk group and high-risk group in the meta-analysis, as there is a different composition of the patient cohort in each study. We doubt the reliability of the result about IFN-γ levels presented by Kittang et al,[11] because it caused too much heterogeneity and the instability of meta-analysis. Thus, the secretion of TNF-α and other related pro-apoptosis cytokines, such as IFN-γ, probably elevate in some subtypes of low-risk MDS, whereas these cytokines are more likely to be down-regulated in high-risk cases.

Recent studies have yielded accumulating evidence indicate that the pro-inflammation cytokines like IL-6 and IL-8 are overexpressed by mutated stem cells in hematological malignancies, suggesting that these pro-inflammation cytokines may function as a regulatory factor within the tumor microenvironment promoting survival and proliferation of clonal cells.[27–29] The study performed by Pardanani et al[3] had shown that the levels of IL-6 were associated with inferior overall survival of MDS patients. Overexpression of IL-8 receptor CXCR2 was also identified in purified stem cells from MDS and was shown to be associated with worse prognosis.[30] Although there is an elevation tendency of IL-6 levels in the high-risk group, our meta-analysis found no statistical difference in the levels of IL-6 between different prognostic groups, nor for the IL-8 levels either. A potential reason is that those pro-inflammation cytokines do not only secrete by the malignant clone, but any acute or chronic inflammation status could also alter the levels of these cytokines. However, they do generally overexpress in MDS patients as mentioned above.

The immunomodulatory cytokine IL-17 is the signature cytokine of the newly found helper T cells named Th17 in recent year. The potential role of Th17 cells in the MDS pathogenesis has been intensively addressed. In some researchers' reports, Th17 cells and IL-17 were overrepresented in low-risk MDS compared with high-risk MDS.[31,32] In contrast, Bouchliou et al[33] believed that Th17 cells were significantly decreased and hypofunctional in low-risk MDS. Our meta-analysis had shown significant elevated IL-17 levels in the low-

risk group. Even in the only study with an inconsistent result, they also admitted that the Th17 cells in peripheral blood were overrepresented in low-risk MDS.[10] Downregulation of the levels of IL-17 indicates there is an impairment of the immune surveillance in high-risk MDS, which can lead to the expansion of the malignant clone.

To appreciate our study better, several limitations should be considered. First, although we used a comprehensive search strategy, the missing of relevant studies were hard to avoid, especially studies published in languages other than English and Chinese. Second, the access to the data of several studies was not available, and the missing data could affect the result of the meta-analysis. Third, we used several statistical methods to extract data from included studies, as it was not provided directly in the original article. Therefore, some degree of deviation could exist in the data adopted for our analysis.

In conclusion, our study revealed a close association between immunological microenvironment disorders and the pathogenesis of MDS. More importantly, the profiles of inflammatory cytokines appear to change along the progression of the disease. Fully comprehension of immune status in each stage of MDS can provide us with the new therapeutic target, diagnosis parameters, and prognostic markers. Thus, an adequately designed multicenter prospective study with a large population and standard examination methods is needed to verify these conclusions.

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