Systematic Review and Meta-Analysis

Medicine

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Long-term effects of hematopoietic growth factors in aplastic anemia patients treated with immunosuppression

Meta-analysis of randomized controlled trials

Anzi Wang, MD[a], Dongyun Su, MD[b], Jingyuan Luo, MD[a], Yuhan Fu, MD[a], Qing Li, MD[a], Shu Chen, MD[a,*]

Abstract

Background and purpose: Immunosuppressive therapy is the frontline treatment for aplastic anemia patients ineligible for transplantation. The long-term effects of hematopoietic growth factors (HGF) added to standard immunosuppressive therapy are still unclear. We performed a systematic review and meta-analysis to clarify this issue.

Methods: A comprehensive search of databases was conducted including 5 international electronic databases (Cochrane, PubMed, Embase, Web of Science, and LILACS) and 4 Chinese electronic databases (Chinese Bio-medicine Database, Chinese National Knowledge Infrastructure, WanFang Data, and China Science and Technology Journal Database databases) from database inception until February, 2022. We included randomized controlled trials that assigned patients with acquired aplastic anemia treated with immunosuppressive therapy (IST), which compared between the addition of HGF and placebo or no treatment. The co-primary outcome were the overall survival (OS) and late clonal malignant evolution at the end of follow-up.

Results: Nine randomized controlled trials including 719 participants were identified. The addition of growth factors to immunosuppression yielded no difference in OS (relative risks [RR], 1.08, 95% confidence interval [CI] 0.99–1.18). HGF was not associated with higher occurrence of secondary myelodysplastic syndromes/acute myeloid leukemia (RR, 1.09, 95% CI 0.43–2.78) or paroxysmal nocturnal hemoglobulinemia (RR, 1.38, 95% CI 0.68–2.81) at the end of follow-up. No difference were found in overall response (RR, 1.16, 95% CI 0.98–1.37), infections occurrence (RR, 0.82; 95% CI, 0.51–1.31) or relapse (RR, 0.65; 95% CI, 0.37–1.13).

Conclusions: HGF as an adjunct to IST has no impact on long-term OS, late clonal malignant evolution, response rate, relapse or infections occurrence. HGF could be added to standard IST for high-risk patients with delayed neutrophil recovery without concern for long-term consequences but could not be recommended as routine clinical practice.

Trial registration number: PROSPERO CRD42021275188.

Abbreviations: AA = aplastic anemia, AML = acute myeloid leukemia, ATG = anti-thymocyte globulin, CI = confidence interval, CR = complete response, EBMT = European Group for Blood and Marrow Transplantation, EPO = erythropoietin, GM-CSF = granulocyte macrophage colony-stimulating factor, HGF = hematopoietic growth factor, IST = immunosuppressive therapy, MDS = myelodysplastic syndromes, OS = overall survival, PNH = paroxysmal nocturnal hemoglobulinemia, PR = partial response, RAs = receptor agonist, RCT = randomized controlled trial, RR = relative risks, TPO = thrombopoietin.

Keywords: aplastic anemia, hematopoietic growth factors, immunosuppressive therapy, meta-analysis

AW and DS contributed equally to this work.

The authors have completed the PRISMA reporting checklist.

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].

As this study did not involve patients or animals, no ethical approval was required.

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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1. Introduction

Aplastic anemia (AA) is a rare, immune-mediated and potentially fatal hematological disorder with an estimated incidence of 0.7 to 4.1 per million people per year.[1] Bone marrow transplantation from a human leukocyte antigen-identical sibling donor is the only potentially curative therapy for marrow failure while this approach is limited by patients' age, comorbidities, and available donors.[2] For transplant-ineligible patients, the other frontline treatment is immunosuppressive therapy (IST) with antithymocyte/antilymphocyte globulin and cyclosporine, which produces a hematologic response rate of approximately 60% to 70%. In contrast to stem cell transplantation, about 30% of patients receiving IST relapse and 10% to 15% predispose to late hematological clonal complications such as myelodysplastic syndrome and leukemia.[3,4] Despite various treatment modalities have been applied to potentiate the effects of IST, the outcome remains to be less optimistic.

Hematopoietic growth factors (HGF) are a class of cytokines that regulate proliferation, differentiation and functional activation of hematopoietic cells which include colony-stimulating factor, granulocyte macrophage colony-stimulating factor (GM-CSF), erythropoietin (EPO), and thrombopoietin (TPO).[5] The effect of HGF added to standard IST with anti-thymocyte globulin (ATG), and CSA, tested in several small prospective trials, was inconclusive.[6–11] A previous meta-analysis by Gurion et al,[12] published in 2008, reported that addition of HGF to IST could not decrease mortality or increase the risk of clonal events. However, the power of the analysis was limited by the small number of trials and relatively short-term follow-up data. Subsequently, several small randomized controlled trials (RCTs) from China suggested that HGF given as part of the initial standard immunosuppression to AA patients might produce encouraging results, namely improvement of overall survival (OS), enhancement of hematologic recovery and decrease of infectious complications.[13–18] Therefore, the role of HGF as an adjunct to IST was still not fully understood. All relevant data on the benefits and risks associated with various therapies for AA are not captured by a sole focus on initial hematologic response and short-term OS, longer follow-up data from the prospective research would allow for more precise and comprehensive understanding. In 2019, the results of a large, multicenter, long-term follow-up (15 years) trial regarding the effects of colony-stimulating factor in SAA from the European Group for Blood and Marrow Transplantation (EBMT) Working Party were published.[19] Thus, we undertook a systematic review and meta-analysis of the latest RCTs to elucidate the long-term effects of HGF as an adjunct to immunosuppression for the treatment of patients with AA.

2. Materials and Methods

This is a systematic review, and ethical approval was not necessary. The protocol of this review was registered in the International Prospective Register of Systematic Reviews, and the trial registration number was CRD42021275188.

2.1. Data sources and search strategy

We conducted a comprehensive literature search using 5 international electronic databases (Cochrane CENTRAL, PubMed, Embase, Web of Science, and LILACS) and 4 Chinese electronic databases (Chinese Bio-medicine Database, Chinese National Knowledge Infrastructure, WanFang Data, and China Science and Technology Journal Database databases) from database inception until February, 2022. We used the following specified search terms: "Aplastic Anemia" and "hematopoietic growth factor or colony stimulating factor or EPO or granulocyte colony stimulating factor or granulocyte macrophage colony stimulating factor or thrombopoietin" (see Table S1, Supplemental Digital Content, http://links.lww.com/MD/H606, which showed key terms for electronic database search). Searches were restricted to publications in the English and Chinese language. References of pertinent reviews and original articles were also manually searched to identify additional studies. This work was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[20] and was registered in PROSPERO (International Prospective Register of Systematic Reviews; reference number: CRD42021275188).

2.2. Study selection

Two individual reviewers (A.W. and D.S.) independently identified and reviewed articles that were deemed relevant by screening the list of titles and abstracts. In case of uncertainty, eligibility was determined through reading the full text. Disagreements between the 2 reviewers were resolved through arbitration by a third reviewer (S.C.) if consensus was not possible. Studies were eligible for inclusion if they fulfilled the following criteria: including patients with acquired AA treated with IST[21]; RCTs which compared between the addition of HGF and placebo or no treatment; no specific prior treatment for the disease; trials which had a follow-up longer than or equal to 12 months; be published in English or Chinese as a full-length publication. Patients were excluded if they had congenital AA, dyskeratosis congenita, severe uncontrolled infection, malignancies or paroxysmal nocturnal hemoglobinuria with positive findings on the Ham test/sucrose test. Basic research studies, review articles, case reports, retrospective studies, single-arm trials and nonrandomized trials were excluded.

2.3. Data extraction and quality assessment

For studies that met the eligibility criteria, 2 of the authors (A.W. and D.S.) independently extracted data from the full text and supplementary appendices and recorded them using a spreadsheet preformatted in Microsoft Excel. Data extraction forms were used to collect pertinent information about year/date of publication, study design, study population, details on treatment and comparator groups, length of follow-up, outcomes data and time points measured. If articles were based on the same trial, we selected the most recent one with the longest follow-up. We assessed the risk of bias in studies according to the Risk of Bias Assessment Tool from the Cochrane Handbook.[22]

2.4. Definition of outcomes

We used the OS and late clonal malignant evolution at the end of follow-up (≥12 months in each trial) as the primary outcomes. Late clonal malignant evolution included paroxysmal nocturnal hemoglobulinemia (PNH), myelodysplastic syndromes (MDS), and acute myeloid leukemia (AML).

Prespecified secondary analyses included the following: response to treatment [(overall response, complete response (CR), and partial response (PR)]; relapse; and infectious complications. We conducted some subgroup analyses for OS to examine whether effect estimates would be influenced by length of follow-up, region, sample size, study quality, type of HGF, and IST regimens.

2.5. Data synthesis and analysis

For each trial, results were expressed as relative risks (RR) with 95% confidence intervals (CI) for dichotomous data.

Heterogeneity across studies and subgroups was estimated using the I^2 statistic and the Cochran's Q (χ^2) statistic. When $I^2 > 40\%$ and P value < .1, the DerSimonian-Laird random-effects models were used to account for significant heterogeneity across studies. On the other hand, the fixed-effects (Mantel–Haenszel) models were used to obtain more precise estimates when no significant heterogeneity existed. Potential sources of heterogeneity were explored through stratifying subgroups and quality of trial. Publication bias was examined with the funnel plot method, the Begg–Mazumdar[23] test and the Egger test.[24] Sensitivity analyses by sequentially excluding 1 study at a time were carried out to check if the results were robust. All statistical analyses were performed using Review Manager 5.4.1 and Stata 12 software, with a P value of less than .05 considered statistically significant.

3. Results

3.1. Search results and characteristics of included studies

The initial literature search yielded a total of 7896 records, from which we removed 835 duplicates (see Table S2, Supplemental Digital Content, http://links.lww.com/MD/H607, which showed results of the electronic database search). After screening on title and abstract, 7013 citations were excluded. Forty-eight citations were selected to be potentially relevant and then reviewed by full text for details, which resulted in 9 RCTs published were identified.[6–11,13,14,19] The literature review and selection process were visualized in Figure 1.

Detailed characteristics of 9 articles included in this meta-analysis were listed in Table 1. There were a total of

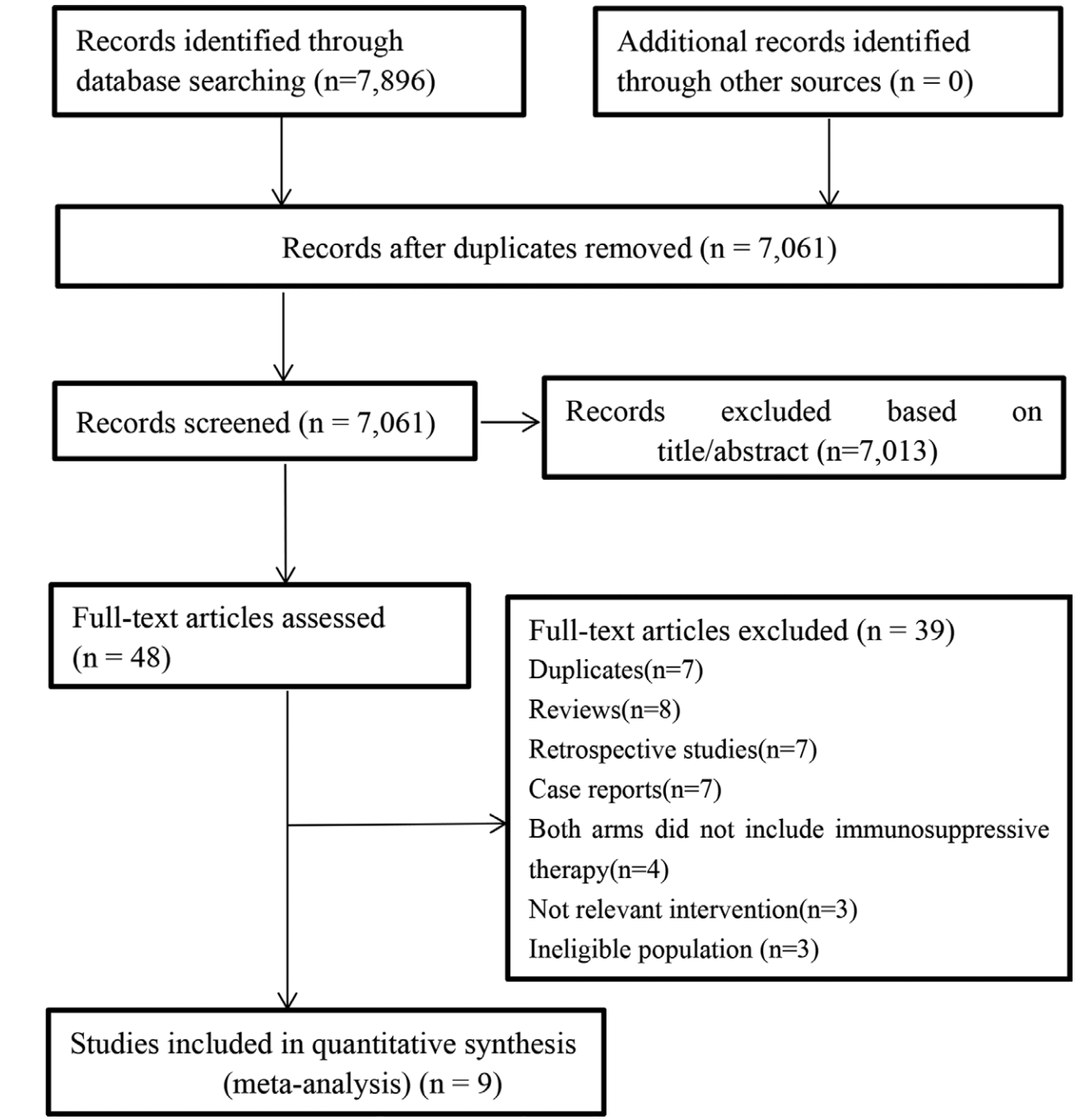

Figure 1. Flow diagram of literature search and study selection. RCT = randomized controlled trial.

Table 1

Characteristics of included randomized controlled trials (N = 9).

Reference, year	Country	Number recurited	Gender (female %)	Immunosuppressive therapy	Dose and duration (HGF)	Median age[a] (yr)	Disease Severity (NSAA/ SAA/ VSAA)	Neutrophil count at baseline[a] (×10^9)	Platelet count at baseline[a] (×10^9)	Reticulocyte count at baseline[a] (×10^9)	Lastfollow-up (yr)
Kojima, 2000[1]	Japan	69	44.9	Horse ATG + CsA + G-CSF	s.c./IV rhuG-CSF 400 μg/m^2/d for 90 d	8 (2–16)	15/18/0	0.48	13	32.0	4
				Horse ATG + CsA		9 (1–15)	13/18/0	0.46	14	29.0	
Zheng, 2006[1]	China	77	24.7	Horse ATG + CsA + GM-CSF + EPO Horse ATG + CsA	s.c. rhuGM-CSF 5 μg/kg/d +IV rhuEPO 100 U/kg/d, 3 d in a week for first months, 2 d in a week for second months and 1 d in a week for third months	36 (5–68)	0/19/11	0.43	11	6.9	5
						35 (8–71)	0/33/14	0.39	14	9.0	
Shao, 1998[1]	China	22	0	Horse ALG + GM-CSF + EPO Horse ALG CsA + GM-CSF + EPO CsA	s.c. rhuGM-CSF 300 μg/d + IV rhuEPO 6000 U/d in a week for first months, 2 d in a week for second months and 1 d in a week for third months	34 (23–63)	NA	NA	10	0.3	1
		16	25.0			32 (21–67)	NA	NA	14.6	3.2	
						28 (12–42)	NA	0.40	11	5.0	
						26 (9–45)	NA	0.41	14.7	9.6	
Tichelli, 2019[1]	Europe	192	51.0	Horse ATG + CsA + G-CSF	s.c. rhuG-CSF 150 μg/m^2/d for 240 d	50 (2–78)	0/66/3	NA	NA	NA	15
				Horse ATG + CsA		41 (9–80)	0/56/39	NA	NA	NA	
Gluckman, 2002[1]	Europe	102	50.0	Horse/rabbit ATG + CsA + G-CSF	s.c. lenograstim 5 μg/kg/d for 98 d	26 (2–71)	0/27/26	0.20	16	8.7	5
				Horse/rabbit ATG + CsA		22 (1–82)	0/30/19	0.20	15	10.7	
Teramura, 2007[1]	Japan	101	50.0	Horse ATG + CsA + G-CSF	IV filgrastim 400 μg/m^2/d or lenograstim 50 μg/m^2/d every other day till day 28 and then once or twice a week till day 84	53 (19–74)	0/29/19	0.30	9	19.0	4
				Horse ATG + CsA		54 (19–75)	0/36/11	0.32	9	11.0	
Gordon, 2008[1]	England	27	NA	Horse ALG + GM-CSF	s.c. 200 μg/d for 28 d	NA	NA	NA	NA	NA	1
				Horse ALG		NA	NA	NA	NA	NA	
Liu, 2010[1]	China	40	55.0	CsA + G-CSF CsA	s.c. G-CSF 5–10 μg/kg/d for 3 mo	NA	NA	NA	26	NA	2
						NA	NA	NA	25	NA	
He, 2001[1]	China	73	21.9	Horse ATG/ ALG + CsA + GM-CSF/G-CSF + EPO	s.c. rhuGM-CSF or rhG-CSF 300 μg/d + IV rhuEPO 6000 U/d	24 (2–63)	NA	0.36	1	4.8	1
				Horse ATG/ALG + CsA		24 (10–60)	NA	0.41	1	5.9	

ALG = anti-lymphocyte globulin, ATG = anti-thymocyte globulin, CsA = cyclosporine, CSF = granulocyte colony-stimulating factor, EPO = erythropoietin, GM-CSF = granulocyte-monocyte colony stimulating factor, HGF = hematopoietic growth factors, IST = immunosuppressive therapy, NA = not available, NSAA = non-severe aplastic anemia, SAA = severe aplastic anemia, VSAA = very severe aplastic anemia.

719 patients with acquired AA included in this study, 390 patients in HGF group and 398 in the control group, with a median age ranged from 8 to 54 years. The median study sample size was 77 patients (range, 27–192 patients). The observation time ranged from 1 to 15 years after treatment. G-SCF was used in 5 trials,[7,8,11,14,19] GM-CSF in 1 trial,[9] G-CSF plus EPO in 1 trial,[13] and GM-CSF plus EPO in 2 trials.[6,10,13] IST regimens consisted of the combination of ATG or ALG with CsA in 6 trials,[6–8,11,13,19] ATG or ALG alone in 2 trials,[9,10] and CsA alone in 2 trials.[10,14] It is important to mention that in a recent prospective, multicenter but open-label trial, the addition of the TOP receptor agonist (TPO-RAs) to IST resulted in improved hematologic response in comparison to those treated with IST alone.[25] However, structural differences between TPO-RAs and TPO may impart differential downstream effects on cell signaling pathways, potentially resulting in clinically relevant differences in outcome. Therefore, clinical trials that involved using TPO-RAs such as eltrombopag or avatrombopag were not included in our review.

3.2. Primary outcomes

OS was reported in all but one of the included trials. Pooled data showed that addition of HGF to IST could not significantly improve OS (RR = 1.08, 95% CI 0.99–1.18, P = .10, I^2 = 24%; Fig. 2A), as compared with the control group.

In terms of secondary MDS/AML, fixed effects meta-analysis found no difference between the HGF intervention group and control group (RR = 1.09, 95% CI, 0.43–2.78, P = .85; Fig. 2B) with low heterogeneity (I^2 = 0%). With regard to PNH, there was no statistically significant higher occurrence of PNH with HGF (RR, 1.38; 95% CI, 0.68–2.81; P = .38; I^2 = 0%; Fig. 2C).

3.3. Secondary outcomes

All 9 studies reported on overall response at the endpoint, and there was no difference between the groups (RR = 1.15, 95% CI 0.97–1.37, P = .12, I^2 = 51%; Fig. 3A). Similarly, there was no difference in CR (RR = 1.12, 95% CI 0.92–1.37, P = .28, I^2 = 27%; Fig. 3B) and PR (RR = 1.05, 95% CI 0.82–1.36, P = .68, I^2 = 0%;

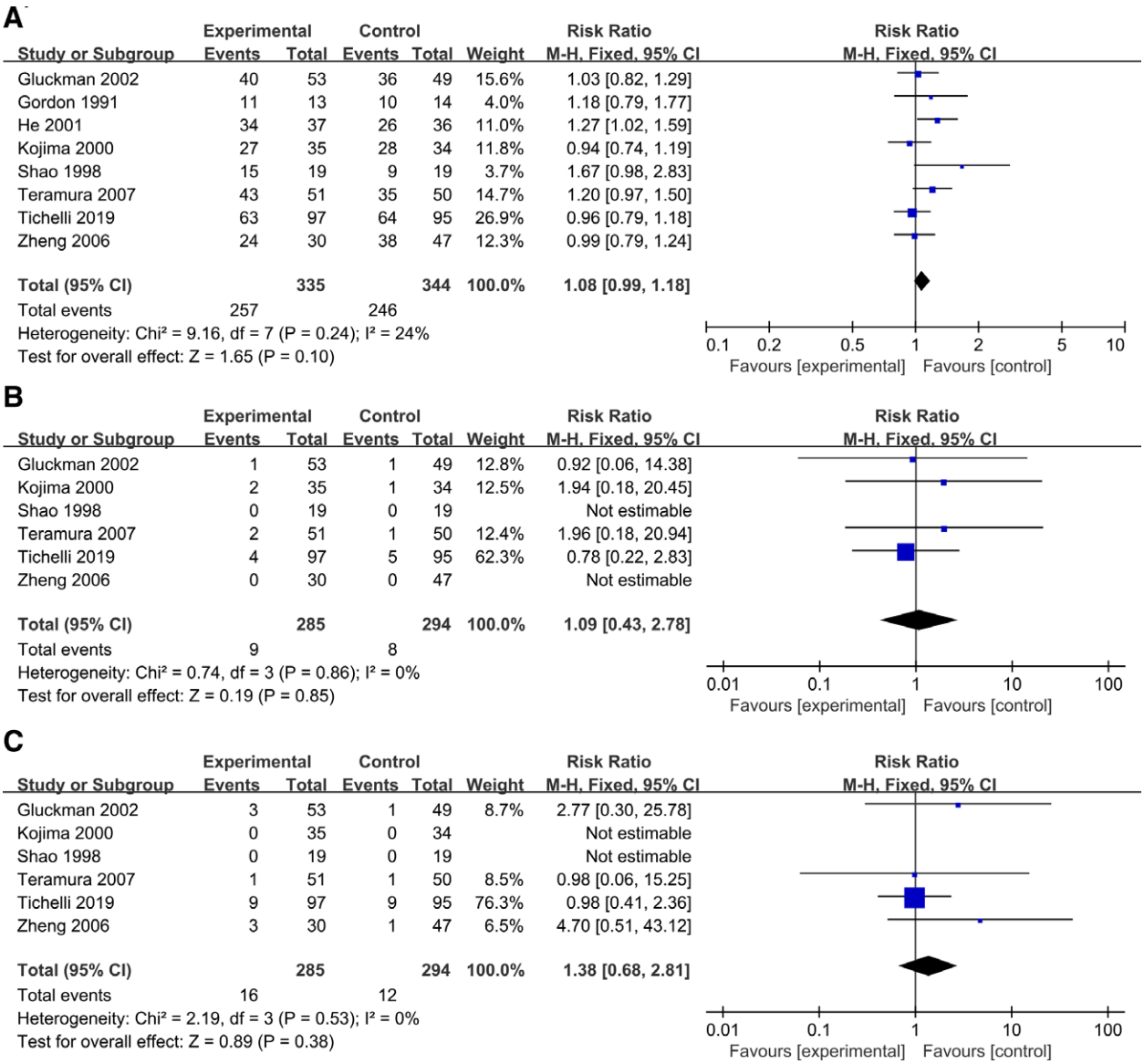

Figure 2. Forest plot of primary outcomes of adjuvant hematopoietic growth factors treatment compared with control. (A) Overall survival. (B) Myelodysplastic syndromes or acute myeloid leukemia. (C) Paroxysmal nocturnal hemoglobulinemia. CI = confidence interval, df = degrees of freedom, M-H = Mantel-Haenszel method.

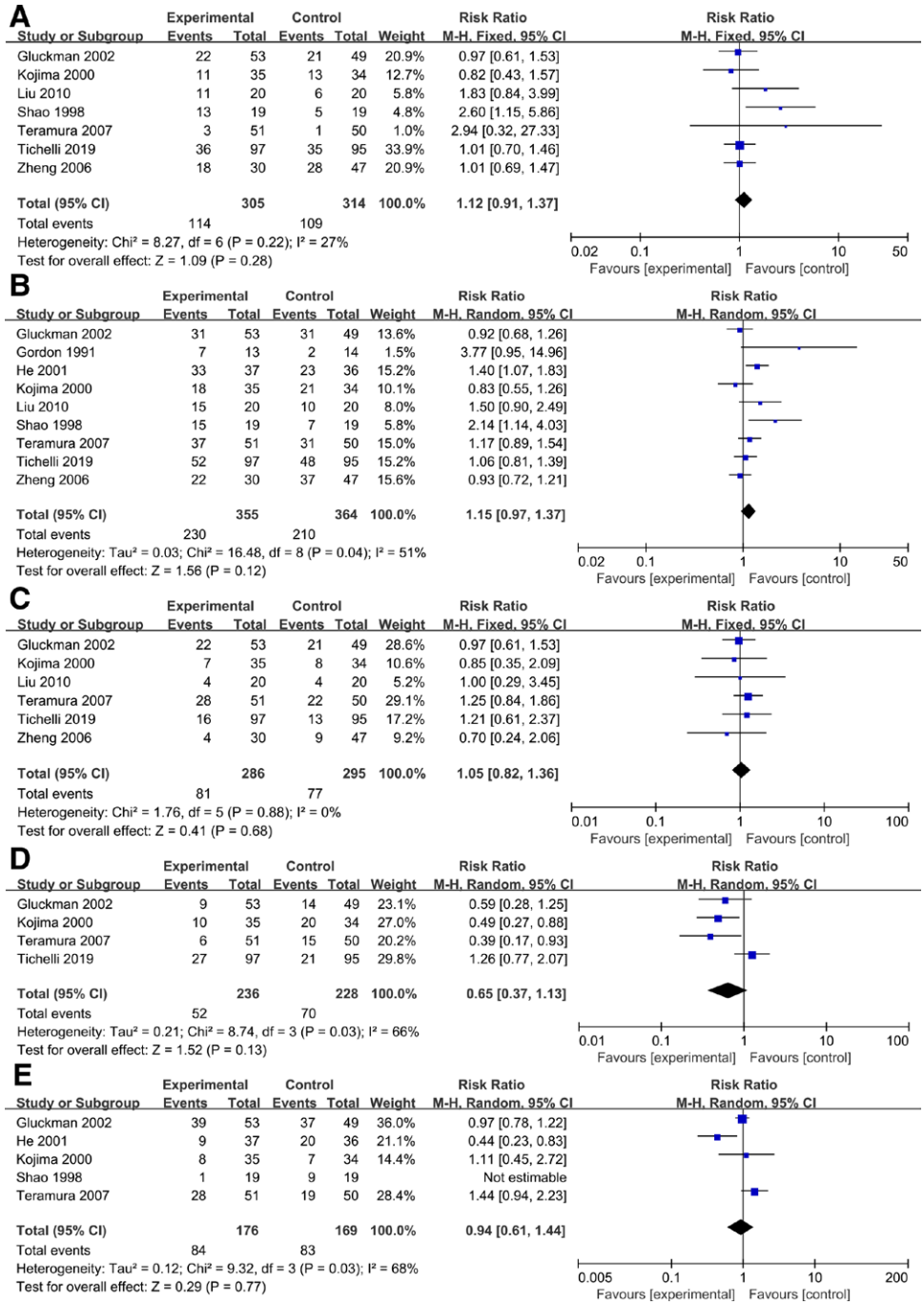

Figure 3. Forest plot of secondary outcomes of adjuvant hematopoietic growth factors treatment compared with control. (A) Overall response. (B) Complete response. (C) Partial response. (D) Relapse. (E) Infectious complications. CI = confidence interval, df = degrees of freedom, M-H = Mantel-Haenszel method.

Fig. 3C) between the groups with or without HGF. HGF administration compared with control did not significantly alter the occurrence of relapse (RR, 0.65; 95% CI, 0.37–1.13; $P = .13$; $I^2 = 66\%$; Fig. 3D) at the end of follow-up. In terms of the occurrence of clinically documented infections complications, random-effects model found no difference in the proportion of infectious patients (5 trials, n = 1261; RR, 0.83; 95% CI, 0.50–1.36; $P = .46$, $I^2 = 73\%$; Fig. 3E) between the HGF group and control group.

3.4. Subgroup analyses

We conducted 2 subgroup analyses according to type of HGF and IST regimens to examine the effect of the 2 key variables on OS. Neither drug species of growth factors (RR, 1.05; 95% CI, 0.96–1.15; P for interaction = .23; Fig. 4A) nor type of immunosuppressant regimens (RR, 1.08; 95% CI, 0.99–1.18; P for interaction = .20; Fig. 4B) showed significant statistic differences. In the subgroup analysis of length of follow-up, a significant effect was seen in studies with follow-up less than 5 years compared with control (RR, 1.08; 95% CI, 0.99–1.18; P for interaction = .04; Fig. 4C). Other subgroup analyses (Asia vs Europe; sample sizes ≥100 vs <100; high-risk vs others) showed no significant statistic difference (Fig. 4D–F).

3.5. Sensitivity analyses

Sensitivity analyses were conducted to examine the robustness of our results. In order to identify whether any research may

have a disproportionate influence on the summary treatment effect, we removed researches one at a time. For the primary outcome of OS, there was no statistical difference between HGF and the placebo group; however, in the sensitivity analysis after excluding the study of Tichelli et al,[19] overall effect reached significant values (RR, 1.12; 95% CI 1.02–1.24; $P = .02$; $I^2 = 23$), accompanied with low heterogeneity (see Fig. S1, Supplemental Digital Content, http://links.lww.com/MD/H603, which illustrated that overall effect reached significant values after excluding the study of Tichelli et al). For the primary outcome of late clonal evolution, sensitivity analysis achieved consistent results.

3.6. Quality assessment and publication bias

The Cochrane Collaboration's recommended tool for assessing risk of bias was used to assess the quality of the included RCTs. Overall, 4 studies were rated as being at high risk of bias and 5 as being unclear (see Fig. S2, Supplemental Digital Content, http://links.lww.com/MD/H604, which demonstrated the quality of the included RCTs). Begg's and Egger's tests indicated no significant evidence of publication bias (Egger test, 0.085; Begg test, 0.348) in our meta-analysis (see Fig. S3, Supplemental Digital Content, http://links.lww.com/MD/H605, which demonstrated no significant evidence of publication bias). No apparent publication bias was observed by visual inspection of the funnel plot (Fig. 5A–C).

4. Discussion

We performed a meta-analysis of 9 trials to evaluate the long-term effects of HGF as an adjunct to standard IST. Our findings indicated that prophylactic use of HGF had no impact on improving OS or increasing the risk of late clonal evolution. Likewise, there were also no effects on occurrence of infection episodes and hematological outcomes, including CR, PR, and relapse rate.

A previous meta-analysis summarizing the effect of HGF in patients with AA did not find statistically significant results

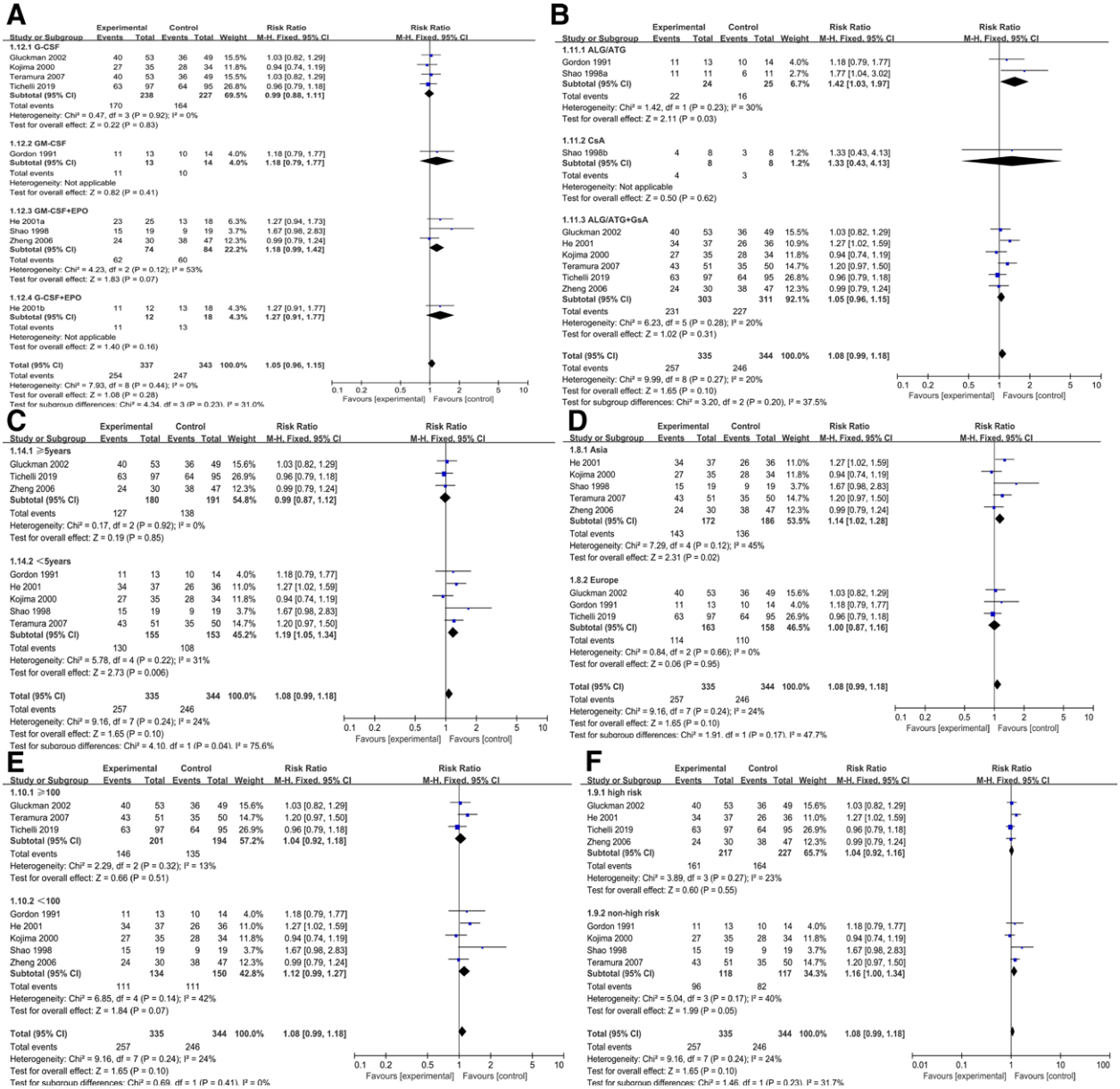

Figure 4. Forest plot of subgroup analyses for overall survival. (A) Type of hematopoietic growth factors. (B) Immunosuppressive therapy regimens. (C) Length of follow-up. (D) Region. (E) Sample size. (F) Study quality. CI = confidence interval, df = degrees of freedom, M-H = Mantel-Haenszel method.

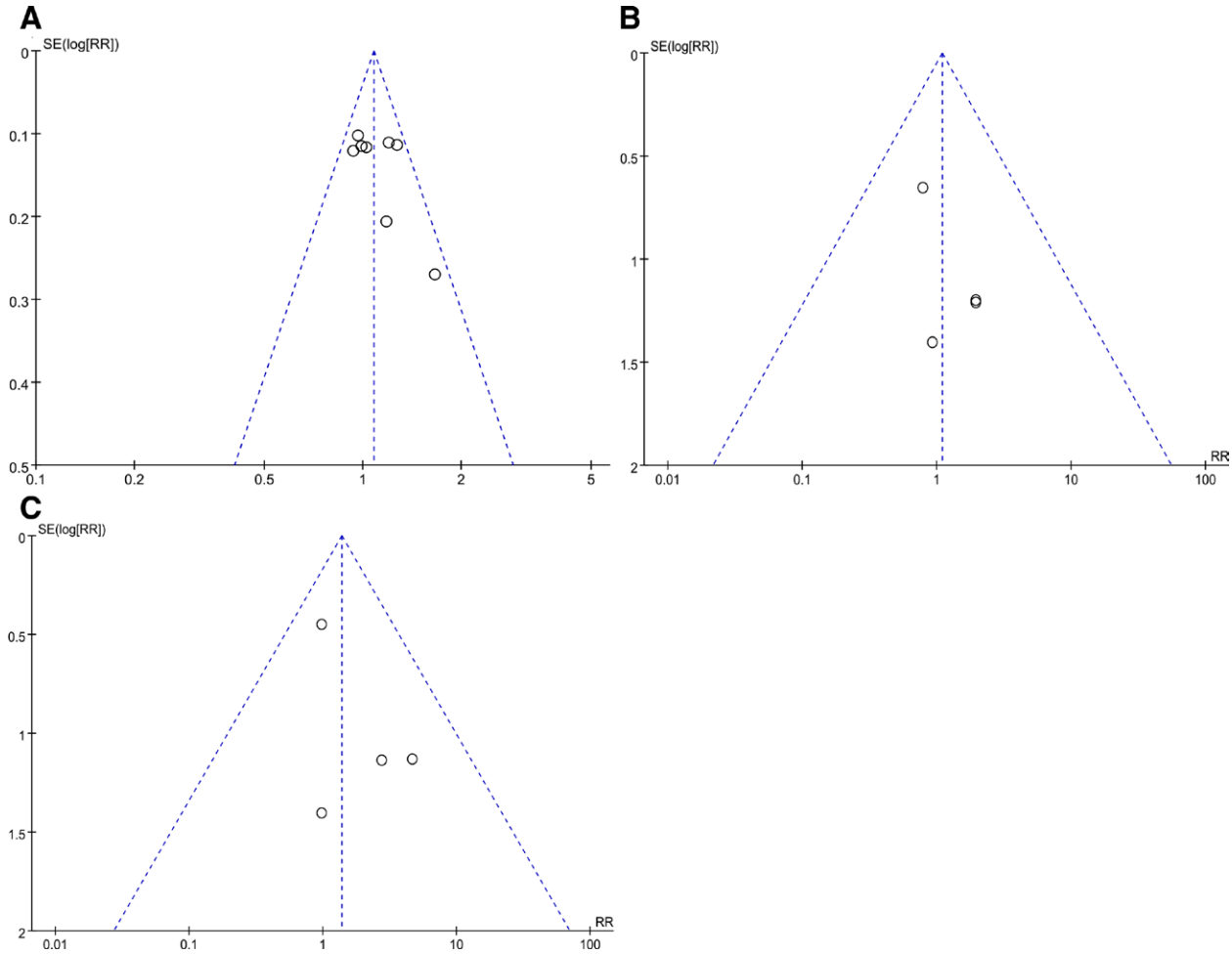

Figure 5. Funnel plots for publication bias for (A) overall survival, (B) myelodysplastic syndromes or acute myeloid leukemia, and (C) paroxysmal nocturnal hemoglobulinemia. RR = risk ratio.

regarding reduced mortality or increased clonal disorders.[12] However, due to the methodologic deficiencies and the short-term follow-up, the study was underpowered to show the effects of long-term stressed hematopoiesis and prolonged immunosuppression for the disease. Recently, the Aplastic Anemia Working Party of the EBMT[19] revisited the use of adjuvant growth factors AA treatment and provided the longest follow-up of AA patients treated with IST to date. However, it did not find improved long-term outcomes. Similarly, our meta-analysis found no effects of HGF on either OS or late clonal disease. These results were tested by sensitivity analyses and subgroup analyses. As for OS, the sensitivity analysis by excluding the study of Tichelli et al[19] displayed inconsistent result. We could not exclude the possibility that this result was biased by this large randomized, open-label, multicenter study. However, subgroup analyses stratified by sample size and study quality did not show significant statistic difference. Late events were common and eventually impacted on the prognosis of patients, but the follow-up periods of other studies were too short to definitively examine this risk. Given the follow-up of 15 years in this study,[19] it was speculated to be a potential influential parameter for OS. We demonstrated that length of follow-up was a powerful predictor of primary outcome of OS by subgroup analysis. However, the level of evidence seems to be quite shaky due to the small number of RCTs with long-term follow-up and heterogeneous designs. Thus, the current results should be cautiously interpreted, and future well-designed, long-term follow-up studies would be warranted.

AA results from an aberrant immune response involving the T-cell mediated destruction of hematopoietic stem cells. It was thought that the aberrant immune response initially eliminated abnormal cells at the cost of collateral damage to normal stem and progenitor cells. With time, the selection pressure would lead to the generation and escape of aberrant clones. One could theoretically deem that IST can significantly increase the OS, but in such prolonged survival there might be an increased risk of clonal evolution. In addition, early concerns arose that the addition of growth factors might stimulate and augment the aberrant clones during the course of the AA.

The role of growth factors added to IST in triggering clonal evolution to a hematological malignancy has been debated for years. The meta-analysis written by Gurion indicated higher occurrence of the secondary MDS/AML with the administration of HGF, which nearly approached a statistical significance. In contrast to the former meta-analysis,[12] our study included the large EBMT trial which offered strong evidence and demonstrated that HGF was unlikely associated with an increased risk of late clonal disease. Sensitivity analyses achieved consistent results with rare heterogeneity, proving the results robust. Moreover, relapse rate was not influenced by the use of adjuvant growth factors, which was inconsistence with the meta-analysis by Gurion et al.[12] Although relapse was common, the majority of relapsed patients responded to the reintroduction on immunosuppression and relapse did not affect survival. With regard to infections, the prophylactic use of HGF could not reduce infectious complications. In accordance with our meta-analysis, HGF could be added to standard IST

for high-risk patients with delayed neutrophil recovery or severe infections without concern for long-term consequences but could not be recommended as routine clinical practice.

There were several limitations of this meta-analysis. First, in addition to the RCT conducted by Tichelli et al, other included trials are relatively small, which may restrict the statistical power. This is probably due to the rarity of AA. Second, we are unable to evaluate if there was a dose-related response pattern of HGF owing to the paucity of data. Besides, disease severity and patients' age at first IST are important risk factors for survival but we could not perform subgroup analyses for those potential influential parameters owing to very few studies available for pooling data. Third, despite using well defined inclusion criteria, some level of heterogeneity was expected because of differences in study designs and populations.

5. Conclusion

In conclusion, the findings from this systematic review and meta-analysis of multiple studies indicate that HGF as an adjunct to immunosuppression has no impact on long-term OS or late clonal malignant evolution of patients with acquired AA. Since the administration of growth factors does not prolong survival, they should not be used on a routine basis but their use should be considered on an individual basis according to the clinical situation. Given the limitations of currently available clinical studies, further studies are required before generalizing the result of this study.

Author contributions

AW, DS, YF, and SC conceived and designed the study. AW, DS, JL, YF, and QL selected the articles and extracted the data. AW and DS analyzed the data. AW and DS wrote the first draft of the manuscript. AW, DS, YF, and SC interpreted the data and wrote the final version. All authors readed and approved the final submitted paper.

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Writing – original draft: Anzi Wang, Dongyun Su, Shu Chen.
Writing – review & editing: Anzi Wang, Dongyun Su, Shu Chen.

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