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Prognostic value of pretreatment anemia in patients with soft tissue sarcoma

A meta-analysis

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Abstract

Background: Anemia is one of the most common manifestations in patients with cancer. Recently, multiple studies have shown a positive correlation between pretreatment anemia and tumor prognosis. Yet, the relationship between pretreatment anemia and the prognosis of soft tissue sarcomas (STS) is unclear.

Methods: We searched the PubMed and EMBASE databases to identify relevant studies. Eligible studies were included according to the inclusion criteria to assess the relationship between pretreatment anemia and the prognosis of patients with STS. Prognostic significance was determined by studying hazard ratios (HR) and 95% confidence intervals (CIs).

Results: A total of 12 studies are included. If there is significant heterogeneity, a random-effects model is used. Pooled data indicated that pretreatment anemia is related to poor overall survival (HR = 2.13; 95%CI = 1.52–2.98), disease-specific survival (HR = 1.53; 95%CI = 1.20–1.96), and disease-free survival (HR = 1.55; 95%CI = 1.10–2.17). The results of the subgroup analysis also support this conclusion.

Conclusion: Our results suggest that pretreatment anemia may be a prognostic biomarker for STS.

Abbreviations: CI = confidence intervals, DFS = disease-free survival, DSS = disease-specific survival, HR = hazard ratios, LDH = lactate dehydrogenase, NLR = neutrophil-to-lymphocyte ratio, OS = overall survival, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, STS = soft tissue sarcomas.

Keywords: anemia, meta-analysis, prognosis, soft tissue sarcoma

1. Introduction

Soft tissue sarcoma (STS) mainly derived from embryonic mesoderm is a heterogeneous tumor that includes more than 50 subtypes.[1] STS is a rare tumor that accounts for about 1% of adult tumors. Different STS subtypes may have various degrees of biological behavior.[2] Primary tumors can be removed by surgery, however, metastatic or recurrent tumors usually require a systematic treatment.[3] Despite the development of new targeted therapies, approximately 50% of patients die due to recurrence or metastasis.[4] Therefore, the prognosis of STS is poor. To improve clinical treatment and prognosis attempts to find better biomarkers have been made in the mean time; results showed that many new markers such as MDM2, P53, and PD-1/PD-L1 may have a clinical significance.[5–8] Recently, hematological biomarkers are highly appreciated, due to their convenience and cost-effectiveness.[9,10] Hematological biomarkers such as the neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein have been introduced into the clinic to guide treatment. However, certain limitations remain. For example, the sampling size of STS tissues may cause changes in counting results, and the level of C-reactive protein does not always reflect the disease severity and treatment response. According to the clinical observation, anemia is one of the most common manifestations in patients with cancer, and ~40% of cancer patients suffer from anemia.[11] Hemoglobin, a hematological

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marker for anemia, has been widely used in the diagnosis of anemia in the clinic, as well as the prognosis of a variety of tumors. Anemia is related to the general type and pathological stage of gastric cancer and lung cancer. The pathological stage of gastric cancer and lung cancer can be roughly estimated based on the occurrence and degree of anemia.[12,13] Recently, studies have reported a positive relationship between anemia and the prognosis of STS.[14,15] A well-designed meta-analysis is a powerful weapon for obtaining comprehensive conclusions. Compared with reviewing different studies one by one, meta-analysis has obvious advantages, less subjective influence by the author, and less bias in conclusions. Therefore, we have performed this systematic review with meta-analysis to assess its prognostic value.

2. Materials and methods

2.1. Search strategies

A systematic review and meta-analysis were carried out according to the guidelines of "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) statement. Literature searches were performed in PubMed and EMBASE by the authors using the search terms "hemoglobin," "anemia," "soft tissue sarcoma," "survival," and "prognosis." We retrieved studies published before December 2020. After screening the abstracts, the articles deemed relevant were cross-referenced for additional manuscripts.

2.2. Inclusion and exclusion criteria

Inclusion criteria: (1) studies performed in humans; (2) the relationship between preoperative anemia or hemoglobin levels and prognosis of STS was studied using overall survival (OS), disease-specific survival (DSS), and/or disease-free survival (DFS); (3) studies that include the hazard ratio (HR) with a 95% confidence intervals (CI) or provides sufficient data to calculate it; (4) published in English; (5) full-text available; and (6) patient size >30.

Exclusion criteria: (1) animal research, case reports, letters, and comments; (2) subjects include patients with osteogenic tumors; (3) overlapping or duplicate studies; and (4) studies only published as abstract or not in English were excluded.

2.3. Data extraction and quality assessment

Two investigators independently reviewed each eligible study and extracted the following data: first author, published year, country, number of patients, treatment, sarcoma stage, cutoff value, and prognostic value. The quality of each study was assessed using the Newcastle–Ottawa scale, and studies with a score greater than 6 are considered high-quality studies.[16] Subsequently, the correspondent author checked all the data and resolved the discrepancies through discussion.

2.4. Statistical analysis

The meta-analysis was conducted by Stata software 15.0 (Stata Corp. LLC, College Station, TX, USA). The HR and the corresponding 95% CI were calculated to investigate the relationship between preoperative anemia and STS. Heterogeneity between studies was assessed by Cochran Q test and I^2 statistic, and random-effects models were used when significant heterogeneity existed.[17,18] Besides, we use subgroup analysis and sensitivity analysis to explore sources of heterogeneity. The publication bias was evaluated by funnel plots and Begg test.[19] A P value of less than .05 is considered statistically significant.

3. Results

3.1. Study selection and characteristics

Our search process is shown in PRISMA 2009 Flow Diagram. Initially, 341 potential kinds of literature are retrieved from PubMed and EMBASE. By removing duplicates, reading title and abstract, 317 articles that do not meet the inclusion criteria were further excluded. Then, 12 articles were excluded by reading the full text. Finally, 12 articles were included in our meta-research.[14,20–29]

The main characteristics of the 12 included studies are shown in Table 1. These studies were published between 2002 and 2020 with a total of 2445 patients. The median sample size of the study is 121, ranging from 47 to 403. Regarding the ethics of included studies, 8 are Caucasian, 3 are Asian, and 1 is mixed ethnic. Four studies are unable to get cutoff values, and 2 studies are treated with drugs. All studies are retrospective.

Table 1

Baseline characteristics of studies included in the meta-analysis.

References	Year	Country	Sample size	Treatment	Stage	Cutoff value	Outcome
Wang et al[14]	2016	USA	54	Mixed	Mixed	10	OS
Iqbal et al[27]	2016	India	110	Mixed	Metastatic	10	OS/DFS
Panotopoulos et al[21]	2015	Austria	85	Surgery	Mixed	13.1	OS/DSS
Szkandera et al[22]	2014	Austria	367	Surgery	Nonmetastatic	13/12*	OS/DSS
Kasper et al[29]	2013	Multi-country	343	Drug	Metastatic	NA	OS/DFS
Willegger et al[24]	2017	Austria	132	Surgery	Mixed	NA	OS/DSS/DFS
Stefanovski et al[28]	2012	Italy	376	Mixed	Mixed	10	OS
Nakamura et al[23]	2017	UK	376	Surgery	Nonmetastatic	13/12*	DSS
Nakamura et al[20]	2017	Japan	47	Mixed	Metastatic	13/12*	DSS
Maretty-Kongstad et al[25]	2017	Denmark	403	Mixed	Nonmetastatic	NA	DSS
de Nonneville et al[26]	2019	France	72	Drug	Metastatic	12	OS/DFS
Mahyudin et al[41]	2020	Indonesia	80	Surgery	Nonmetastatic	NA	OS

DFS = disease-free survival, DSS = disease-specific survival, NA = not available, OS = overall survival.
* 13 mg/L in male and 12 mg/L in female.

3.2. The prognostic value of pre-treatment anemia for OS/DSS/DFS

A total of 9 studies explored the relationship between pre-treatment anemia and the OS of patients with STS.[14,21,22,24,26–29,41] The pooled data shows that pre-treatment anemia is related to a poor OS (HR: 2.13, 95%CI: 1.52–2.98, $P < .00001$). A random-effect model was used due to the discovery of significant heterogeneity ($I^2 = 75.9\%$; Fig. 1).

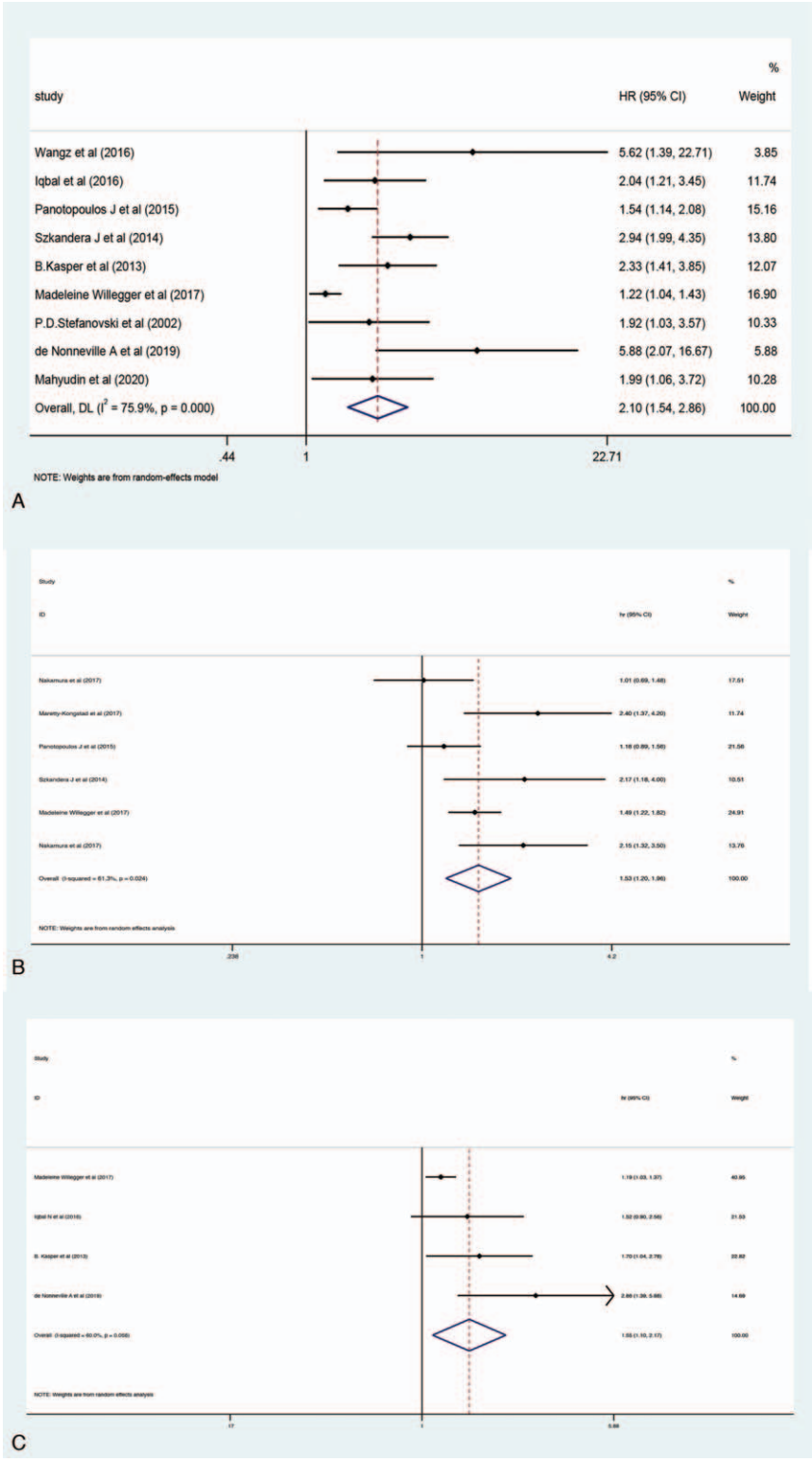

Figure 1. Forest plots of the prognostic effect of pretreatment anemia for (A) OS, (B) DSS, and (C) DFS. DFS = disease-free survival, DSS = disease-specific survival, OS = overall survival.

Six studies provide data on the relationship between pre-treatment anemia and DSS in patients with STS.[20–25] Our study shows that pre-treatment anemia also has a reliable prognostic value in DSS (HR: 1.53, 95%CI: 1.20–1.96, $P=.02$), and significant heterogeneity is detected between studies ($I^2=61\%$; Fig. 1).

Only 4 studies explored the prognostic significance of pre-treatment anemia in DFS.[24,26,27,29] The random-effects model shows that pretreatment anemia is related to poor DFS (HR: 1.55, 95%CI: 1.10–2.17, $P=.01$). Significant heterogeneity was observed ($I^2=60\%$; Fig. 1).

3.3. Subgroup analysis of pretreatment anemia

We conducted a large number of subgroup analysis and sensitivity analysis to find sources of heterogeneity. As shown in Table 2, each outcome had 3 subgroups including tumor stage, treatment, and ethnicity. Significant prognostic value was observed in most subgroup analyses, while the DSS mixed treatment group and several other subgroups did not show such prognostic value. Results of the sensitivity analysis are shown in Figure 2, and omitting each study, in turn, does not bring significant changes in the results.

3.4. Publication bias

Figure 3 shows results of publication bias. The Begg *P* for OS, DSS, and DFS are 0.251, 0.452, and 0.308, so the publication bias in this meta-analysis is not significant.

4. Discussion

For cancer patients, the cause of anemia may be multifaceted.[11] Studies have shown that anemia is mostly caused by the tumor itself and diverse therapies.[30] For example, surgery frequently causes blood loss, and radiotherapy and chemotherapy could induce bone marrow inhibition, etc. However, the anemia before treatment is more likely caused by the tumor itself.

Many recent studies have shown that pre-treatment anemia is associated with poor survival in a variety of cancer patients.[31,32] However, the relationship between preoperative anemia and the prognosis of STS remains controversial. Our current results

Table 2

Subgroup analysis of the prognostic value of HB.

Survival analysis	No. of studies	I^2 (%)	HR (95%CI)	*P*
OS				
Total	9	75.9%	2.13 (1.52–2.98)	$P<.00001$
Treatment				
Surgery	3	88%	1.72 (1.08–2.73)	$P=.02$
Mixed	3	0%	2.15 (1.46–3.16)	$P<.0001$
Drug	2	59%	3.29 (1.37–7.92)	$P=.008$
Stage				
Nonmetastatic	1	7%	2.63 (1.89–3.67)	$P<.00001$
Metastatic	3	38%	2.56 (1.61–4.06)	$P<.0001$
Mixed	4	0%	2.11 (1.52–2.92) $P<.00001$ I2=0%	$P<.00001$
Ethnicity				
Asian	1	0%	2.02 (1.35–3.01)	$P=.0006$
Caucasian	7	81%	2.16 (1.48–3.16)	$P<.0001$
DSS				
Total	6	61%	1.53 (1.20–1.96)	$P=.02$
Treatment				
Surgery	4	52%	1.55 (1.20–1.99)	$P=.0006$
Mixed	2	84%	1.52 (0.65–3.54)	$P=.33$
Stage				
Nonmetastatic	3	0%	2.23 (1.63–3.06)	$P<.00001$
Metastatic	1	NA	1.01 (0.69–1.48)	$P=.95$
Mixed	2	44%	1.35 (1.08–1.70)	$P=.008$
Ethnicity				
Asian	1	NA	1.01 (0.69–1.48)	P=0.95
Caucasian	5	56%	1.52 (1.32–1.76)	$P<.00001$
DFS				
Total	4	60%	1.55 (1.10–2.17)	$P=.01$
Treatment				
Surgery	1	NA	1.19 (1.03–1.37)	$P=.02$
Mixed	1	NA	1.52 (0.90–2.56)	$P=.12$
Drug	2	27%	2.01 (1.34–3.01)	$P=.0008$
Stage				
Metastatic	3	2%	1.81 (1.31–2.49)	$P=.0003$
Mixed	1	NA	1.19 (1.03–1.37)	$P=.02$
Ethnicity				
Asian	1	NA	1.52 (0.90–2.56)	$P=.12$
Caucasian	3	72%	1.62 (1.02–2.59)	$P=.04$

DFS = disease-free survival, DSS = disease-specific survival, OS = overall survival.

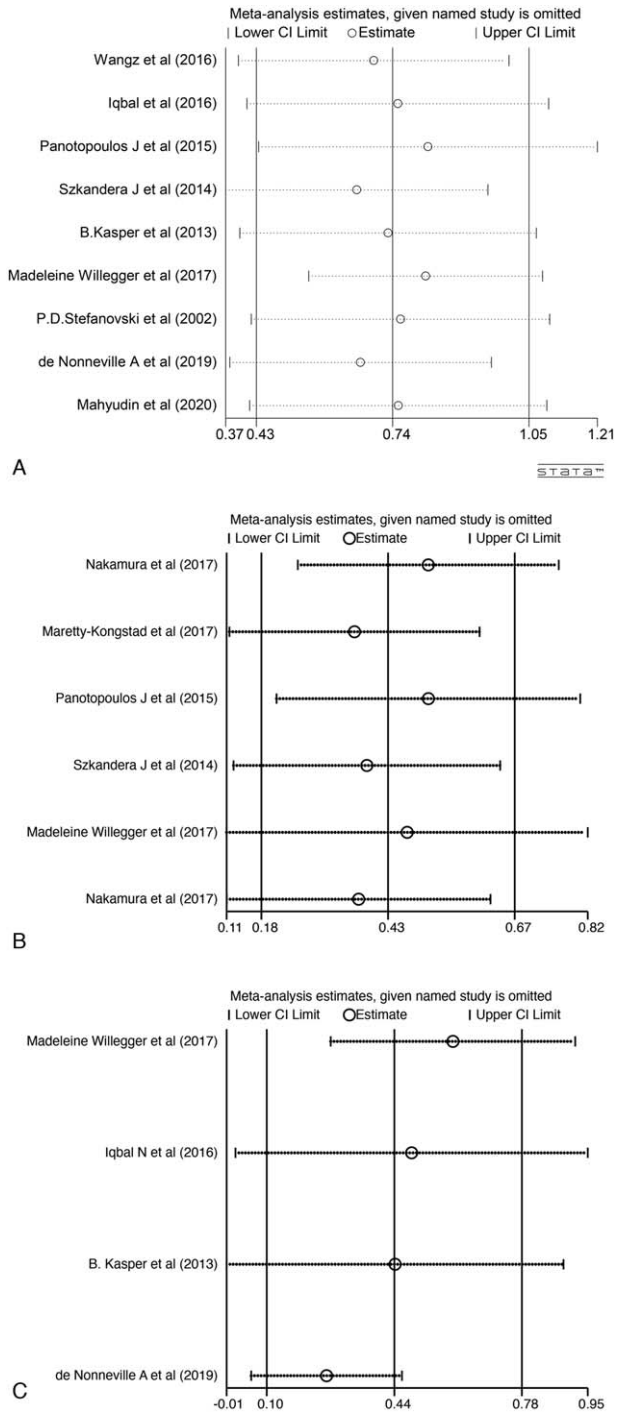

Figure 2. Sensitivity analysis of the prognostic effect of pretreatment anemia for (A) OS, (B) DSS, and (C) DFS. DFS = disease-free survival, DSS = disease-specific survival, OS = overall survival.

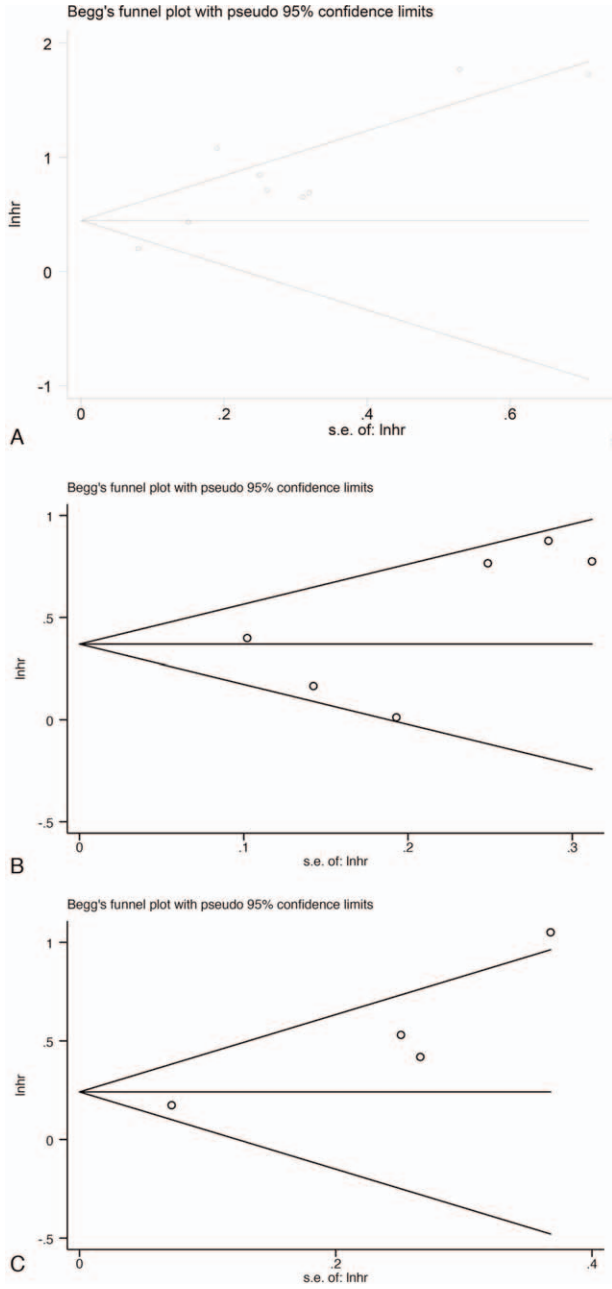

Figure 3. Begg' funnel plots of the prognostic effect of pretreatment anemia for (A) OS, (B) DSS, and (C) DFS. DFS = disease-free survival, DSS = disease-specific survival, OS = overall survival.

obtained from the meta-analysis of 12 studies including 2445 patients suggest that pre-treatment anemia is associated with the prognosis of STS. This conclusion is supported by the results of subgroup analysis. However, our results need to be interpreted with caution. In our study, the majority of patients had high-grade sarcomas. In addition, only a few patients have initial metastases. Therefore, the relationship between pretreatment anemia and the prognosis of patients with low-grade sarcoma and patients with primary metastases needs further study.

Although the exact mechanism between the treatment of anemia and survival of cancer patients is not clear, it might be explained by tumor hypoxia. As we know, anemia is the most important factor in tumor hypoxia, and tumor hypoxia will further lead to a series of adverse consequences.[33] First, tumor hypoxia increases tumor aggressiveness by stimulating angiogenesis.[11] Second, tumor hypoxia can slow down the cell cycle by reducing the formation of reactive oxygen species. This process promotes the resistance of tumors to radiation therapy. In addition, low blood flow in the tumor exacerbates the resistance

to chemotherapy.[34] Third, hypoxia stabilizes hypoxia-inducible factor 1α and dimerizes with HIF-1β, and then binds to hypoxia response elements.[35] This process will activate the transcription of a variety of oncogenes. In addition to promoting the survival, proliferation, invasion, and metastasis of tumor cells, this process will also promote the generation of tumors with undifferentiated phenotypes.[33]

Anemia is a lack of hemoglobin and red blood cells. The harm it causes is that the normal physiological functions of red blood cells and hemoglobin cannot be exerted, resulting in tissue hypoxia. Tissue hypoxia is damage at the organ level, and its performance in the body is a series of changes in the normal physiological functions of the organs. Although anemia is often only a systemic manifestation, it will affect all tissues, organs, and organs throughout the body. For cancer patients, the decrease in hemoglobin causes a decrease in the blood's oxygen-carrying capacity, thereby reducing the tumor's arterial oxygen supply. Severe anemia leads to a very poor oxygenation state and aggravates the original hypoxia of the tumor. Hypoxia has direct damage and impact on artificial hematopoietic stem cells, and affects the proliferation and differentiation of artificial hematopoietic stem cells. Under the hypoxic environment, the lactate dehydrogenase of artificial hematopoietic stem cells leaks out, and the adenosine triphosphate content in the cells decreases. Mitochondria are the body's aerobic oxidation sites. Hypoxia reduces the body's ATP, which first affects the normal function of the oxygen-dependent enzyme system and cell membrane structure, cell damage, cell proliferation, and differentiation are inhibited.

According to the state of preoperative anemia, a personalized treatment plan should be developed. Correcting anemia can make surgery safer and allows patients to better tolerate the side effects of radiation and chemotherapy. Blood transfusion and erythropoietin have been widely used to improve anemia in patients. Unfortunately, although blood transfusion or erythropoietin stimulator can improve the symptoms of anemia, it does not improve the outcome of patients.[36] Recent studies have shown that perioperative blood transfusion does not improve outcomes of STS patients and is associated with all-cause mortality, cancer-related mortality, and relapse.[37,38] Similarly, the use of erythropoietin preparations does not improve patient survival and increases the risk of venous thrombosis in patients.[39,40] Yet, there are few related studies in STS, so it is necessary to study the application of these measures in STS.

The findings should be taken into account. First, since STS is a group of heterogeneous tumors containing more than 50 subtypes, there is some heterogeneity in our findings, even though we conducted a subgroup analysis. Therefore, we communicated with the authors of included studies via email. The effect of hypoxia on different subtypes is inherently heterogeneous. Nakamura et al found that pretreatment anemia was not associated with the prognosis of liposarcoma, while malignant fibrous histiocytoma was the opposite.[23,42] Patients may differ from study to study, so heterogeneity is acceptable. Second, the cutoff values between different studies are different. Third, all the studies included are retrospective. Therefore, the validation of our current results in more randomized controlled trials and studies on specific subtypes of STS are needed. There is also a need to explore reasonable interventions of anemia to benefit STS patients.

To the best of our knowledge, this is the first meta-analysis of the relationship between pretreatment anemia and the prognosis of STS. Nakamura et al[23] described that anemia was an adverse prognostic factor for disease-specific survival for malignant fibrous histiocytoma and other sarcomas, but not for liposarcoma. The focus of Maretty-Kongstad et al[25] research is that a battery of serum biomarkers comprised of 5 proinflammatory biomarkers integrated into a prognostic score named Aarhus Composite Biomarker Score is prognostic for localized nonmetastatic bone sarcomas even after adjusting for various confounders including comorbidity. To the best of our knowledge, only 1 similar sized study in STS patients reported a poor prognostic value of Hb levels.[23] Therefore, this study aims to verify the prognostic significance of preoperative Hb level on OS, DSS, and DFS of STS patients. We included enough studies and excluded the confounding factor of osteogenic tumors. This reinforces the advantages of our research. Our results suggest that pretreatment anemia is associated with poor prognosis in patients with STS. Therefore, pre-treatment anemia may serve as a hematological biomarker to predict the prognosis of STS. Clinicians may be able to pay more attention to these hematological markers.

5. Conclusions

Preconditioning anemia may be an important marker for predicting the prognosis of STS. A well-designed randomized controlled trial is needed to validate our results.

Author contributions

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Dean Chou, Yao Zhao, Shuhao Zhang, Limin Wang, and Min Zhang. The first draft of the manuscript was written by Landa Shi, Longqing Li, Yilin Liu, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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