
















Review

# Overall and Progression-Free Survival of Patients With Malignant Neoplasm Following Intravenous Vitamin C: A Systematic Review and Meta-Analysis

Jinxu Qu<sup>1,†</sup>, Mingtao Yao<sup>1,†</sup>, Shijie Yu<sup>1</sup>, Yi Wang<sup>1</sup>, Shuai Lu<sup>1</sup>, Bing Wang<sup>1</sup>, Jia He<sup>1</sup>, Shiwan Wang<sup>1</sup>, Yuan Zhao<sup>1</sup>, Xin Wang<sup>1</sup>, Xiaomei Tao<sup>2</sup>, Xiaozhu Liu<sup>3</sup>, Yizhong Rao<sup>4</sup>, Yuru Li<sup>2</sup>, Benqiang Rao<sup>1,\*</sup>

<sup>1</sup>Center of Metabolism and Nutrition of Cancer, Beijing Shijitan Hospital, Capital Medical University, 100038 Beijing, China

<sup>2</sup>Department of Pharmacy, Beijing Shijitan Hospital, Capital Medical University, 100038 Beijing, China

<sup>3</sup>Department of Critical Care Medicine, Beijing Shijitan Hospital, Capital Medical University, 100038 Beijing, China

<sup>4</sup>School of Molecular Sciences, University of Western Australia, Perth, WA 6009, Australia

\*Correspondence: [raobenqiang@bjsjth.cn](mailto:raobenqiang@bjsjth.cn) (Benqiang Rao)

†These authors contributed equally.

Academic Editor: Torsten Bohn

Submitted: 23 January 2025 Revised: 2 April 2025 Accepted: 16 April 2025 Published: 1 July 2025

## Abstract

**Background:** This study aimed to determine whether administering intravenous vitamin C in patients with malignant neoplasm is associated with increased survival outcomes compared to no intravenous vitamin C administration. **Methods:** The primary search was conducted using MEDLINE (via PubMed), Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) databases from inception to October 13, 2024. Results were collected from randomized clinical trials and cohort studies that compared intravenous vitamin C and blank controls or placebo in patients with malignant neoplasm. Two reviewers independently assessed the data extraction process and the risk of bias, while the certainty of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation approach. A frequentist framework was used as the primary analysis approach. **Results:** A total of 8 studies with 2722 adult participants were included. The vitamin C dose ranged from 2.5 g/d to 1.5 g/kg of body weight per day, with the treatment duration ranging from 9 days to 1 year. The primary outcome was overall survival, with progression-free survival as a secondary measure. Intravenous vitamin C was associated with a significantly longer median overall survival (pooled estimated median survival ratio: 1.83; 95% confidence interval: 1.40–2.40;  $p < 0.001$ ; moderate certainty), and a trend towards improved progression-free survival (pooled estimated median survival ratio: 1.80; 95% confidence interval: 0.95–3.41;  $p = 0.073$ ). Subgroup analyses of overall survival showed higher median survival ratios with vitamin C doses  $< 1$  g/kg (vs.  $\geq 1$  g/kg), in non-Chinese regions (vs. Chinese regions), with non-chemotherapy combinations (vs. chemotherapy combinations), and in cohort studies (vs. randomized controlled trials). **Conclusions:** The administration of intravenous vitamin C to adults with malignant neoplasm was associated with a longer median overall survival compared to no vitamin C administration. The current evidence indicates a moderate degree of certainty for considering intravenous vitamin C as a standard of care in managing malignant neoplasms. **The PROSPERO Registration:** CRD42024600634, <https://www.crd.york.ac.uk/PROSPERO/view/CRD42024600634>.

**Keywords:** vitamin C; ascorbic acid; malignant neoplasms; survival; meta-analysis

## 1. Introduction

The concept that vitamin C could be utilized for the treatment of malignant neoplasms has been highly controversial over the past century [1,2]. However, an improved understanding of the pharmacokinetics of vitamin C has reignited interest in this therapeutic approach [1]. Specifically, mM levels of vitamin C, which are cytotoxic to cancer cells, can only be achieved via intravenous administration and not through oral dosing. In light of these findings, numerous clinical studies have been launched in recent years, with some already completed and reporting promising results.

The main mechanisms involving high-dose vitamin C in cancer therapy include: (1) exploitation of the redox imbalance in cancer cells to induce cell death by generating reactive oxygen species (ROS) and hydroxyl radicals ( $\bullet\text{OH}$ ); (2) epigenetic reprogramming of cancer cells to activate ten-eleven translocation (TET) enzymes, promote DNA demethylation, and restore the expression of tumor suppressor genes; and (3) inhibiting the hypoxia-inducible factor 1 (HIF1) signaling pathway to reduce the ability of tumor cells to adapt to hypoxia, thereby suppressing tumor growth [1].

Wang *et al.* [3] conducted the first randomized, multicenter, phase III clinical trial to investigate the efficacy and safety of high-dose vitamin C combined with



folinic acid, fluorouracil, and oxaliplatin (FOLFOX)  $\pm$  bevacizumab versus FOLFOX  $\pm$  bevacizumab alone as first-line treatment for metastatic colorectal cancer. Their results showed that intravenous vitamin C (IVC) combined with chemotherapy had no significant impact on progression-free survival (PFS) in the overall study cohort, although a potential benefit was observed in patients with rat sarcoma viral oncogene homolog (RAS) mutations. Ou *et al.* [4] conducted a retrospective cohort study involving 153 patients with non-small cell lung cancer. Patients who received high-dose IVC had significantly better overall survival (OS) and PFS compared to those receiving standard anticancer therapy alone. The median OS in the vitamin C group was approximately twice that of the control group (49.2 months vs. 25.6 months), while the median PFS was approximately 4.6 times longer (39.5 months vs. 8.5 months). Ma *et al.* [5] conducted a randomized phase I/IIa trial in ovarian cancer patients comparing high-dose IVC plus carboplatin and paclitaxel versus carboplatin and paclitaxel alone. The results demonstrated that the combination therapy group achieved significantly longer PFS and substantially reduced chemotherapy-related toxicities compared to the carboplatin-paclitaxel only group [5]. Similarly, Monti *et al.* [6] conducted a phase I study in metastatic pancreatic cancer, demonstrating that IVC combined with gemcitabine and erlotinib induced tumor shrinkage in 8 out of 9 patients. Additionally, Ou *et al.* [7] conducted a randomized phase II trial in patients with non-small cell lung cancer, showing that the combination of IVC and modulated electrohyperthermia was safe and significantly prolonged PFS, OS, and quality of life compared to best supportive care alone.

Vitamin C has also been found to alleviate chemotherapy-induced side-effects, such as nausea, vomiting, and fatigue, thereby improving the patients' quality of life [8,9]. However, these effects have yet to be confirmed in all patient groups. In contrast, oral vitamin C has more limited effects, with multiple studies finding that it has no significant impact on OS, disease progression, or symptom relief in cancer patients [10]. This may be related to the lower bioavailability of oral vitamin C, which makes it difficult to achieve pharmacological levels in the body. In addition, some studies have found that oral vitamin C may have a negative impact on the efficacy of certain chemotherapy drugs by reducing their effectiveness or increasing chemotherapy-related toxicity [10]. Despite this, vitamin C treatment is relatively safe, with no serious adverse effects reported [8–10]. Most studies have shown that patients tolerate vitamin C well, with only mild side-effects such as nausea, vomiting, and injection site discomfort being reported. These side-effects are usually related to the dose and administration method of vitamin C, and in most cases are quite manageable.

Despite numerous clinical studies [2] and several systematic reviews [8–10], no meta-analysis has yet been per-

formed to quantitatively evaluate the efficacy of IVC in the treatment of malignant neoplasms. The present study is the first meta-analysis aimed at assessing the OS and PFS of adult patients with malignant neoplasms who received IVC compared to those who did not. We included randomized controlled trials (RCTs) and cohort studies, and compared the outcomes following IVC with no treatment or placebo. Our analysis revealed that administration of IVC was associated with longer median overall survival compared to no IVC. The current evidence indicates there is a moderate degree of certainty with regard to the use of IVC as standard care for malignant neoplasms.

## 2. Materials and Methods

A systematic review and meta-analysis encompassing both RCTs and cohort studies was carried out following a prespecified protocol (**Supplementary Document 1**). The findings of this review were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [11], and the study was registered with the International Prospective Register of Systematic Reviews (registration number CRD42024600634).

### 2.1 Eligibility Criteria

The analysis included RCTs and cohort studies that targeted adult patients diagnosed with malignant neoplasms, and specifically those that compared the efficacy of IVC administration to a control group that did not receive any vitamin C treatment. Malignancy was strictly defined based on pathological diagnoses and other established standard diagnostic criteria applicable at the time of patient recruitment. The administration of vitamin C was characterized by a series of repeated intravenous infusions that followed predetermined doses and schedules, and which contrasted with the control group that received no vitamin C intervention at all.

### 2.2 Search Strategy

A thorough search was performed across MEDLINE (via PubMed), Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases up to October 13, 2024. This search included studies in all languages and was not restricted by publication date or status. The search strategy utilized a carefully crafted combination of keywords and Medical Subject Headings (MeSH) to locate studies related to “neoplasms”, “tumors”, “neoplasia”, “cancer”, “malignant neoplasm”, and various forms of vitamin C, including “ascorbic acid”, “L-ascorbic acid”, “ferrous ascorbate”, and “sodium ascorbate” among others. Additionally, the search focused on the term “survival”, and included both RCTs and cohort studies.

Additional studies were identified by manually reviewing references from the included studies and relevant systematic reviews. Further details regarding the electronic search strategy are given in **Supplementary Document 2**.

## 2.3 Study Selection

The titles and abstracts from the search were filtered using EndNote [12]. Duplicates and irrelevant studies were excluded. A minimum of two reviewers (JQ, MY, or SY) independently screened all identified references for inclusion. Reports that were deemed as possibly meeting the inclusion criteria, identified by either reviewer, were retrieved for full-text evaluation. A minimum of two reviewers (JQ, MY, or SY) independently evaluated the full text of potentially eligible studies for inclusion. When disagreements arose, these were resolved via discussion or by consulting with a third reviewer, if required (YW, SL, or BW). The selection process was recorded and reported in a PRISMA flow diagram.

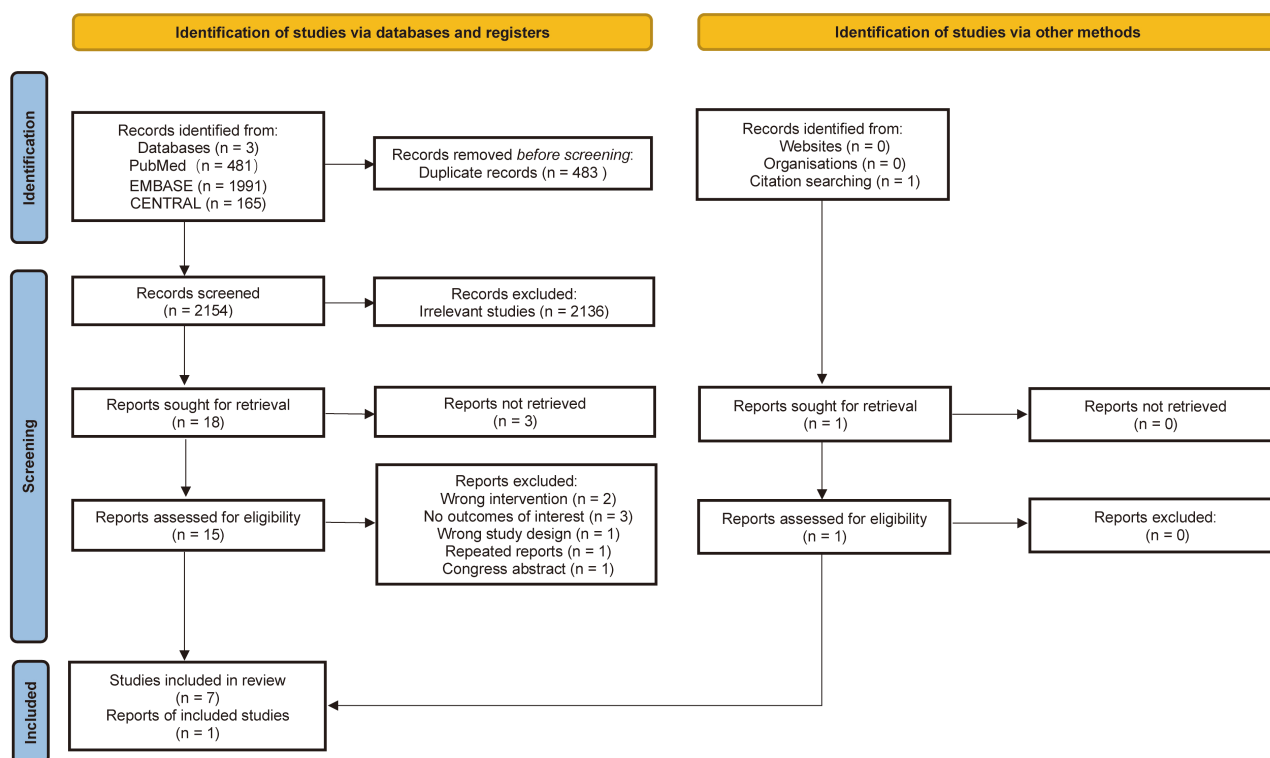
## 2.4 Data Collection

Two reviewers (JQ and MY) independently gathered information from each included study utilizing a standardized data extraction form. Inconsistencies were addressed through discussion, and if necessary advice was sought from a third reviewer (SY). Data extraction followed the established protocol (**Supplementary Document 1**) and included details on disease diagnosis, study region, outcomes, dosing and frequency of IVC, concurrent therapies, and study design. No imputation was performed for any missing data.

## 2.5 Risk of Bias Assessment

The Cochrane Risk of Bias Tool for randomized trials version 2 [13] was used to evaluate the risk of bias in each randomized trial included in the analysis. This tool examines various potential biases that could significantly affect the results of RCTs, focusing on five key areas: the randomization process, deviations from the intended interventions, missing outcome data, outcome measurement, and the selection of reported results. Each study was systematically assessed and categorized into one of three classifications: “low risk of bias”, “some concerns”, or “high risk of bias”. The proposed judgment for each study was generated using a detailed algorithm according to the responses to the signaling questions provided in the tool, thus ensuring comprehensive and objective evaluation.

The Newcastle-Ottawa Scale [14] was employed to evaluate potential bias in cohort studies, focusing on three key criteria that allow for a maximum score of 9 stars. The first criterion, “study selection”, can earn up to 4 stars. The second criterion, “group comparability”, contributes 2 stars, while the third, “outcome ascertainment”, can yield 3 stars. Based on their scores, the studies were subsequently categorized into quality levels. Those scoring 4 stars or fewer were considered low quality, those with scores between 5 and 7 stars were considered medium quality, while studies achieving 8 or 9 stars were recognized as high quality.



**Fig. 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart outlining the search strategy and included studies.**

**Table 1. Major details of the 8 studies included in this meta-analysis.**

Study	Diagnosis	N (vitamin C/controls)	Study region	IVC	Control	IVC	Control	IVC dose and frequency	Concurrent therapy	Design
				Median OS	Median OS	Median PFS	Median PFS			
Cameron and Campbell 1991 [22]	Incurable cancer	1826 (294/1532)	UK	11.4	6	NR	NR	10 g/day for 10 days and orally thereafter (10 g/day)	Conventional anti-cancer treatment	RCT
Ma <i>et al.</i> 2014 [5]	Stage III and IV ovarian cancer	22 (10/12)	USA	NR	NR	25.5	16.75	75/100 g, twice weekly for 12 months	Paclitaxel and carboplatin	RCT
Günes-Bayir and Kiziltan 2015 [23]	Radiotherapy-resistant bone metastatic cancer	39 (15/24)	Turkey	10	2	NR	NR	2.5 g/day	Palliative radiotherapy	Retrospective cohort
Zhao <i>et al.</i> 2018 [24]	Elderly acute myeloid leukemia	73 (39/34)	China	15.3	9.3	NR	NR	50–80 mg/kg/day, days 0–9	Decitabine, cytarabine and aclarubicin	RCT
Ou <i>et al.</i> 2020 [7]	Refractory advanced NSCLC	97 (49/48)	China	9.4	5.6	3	1.85	1 g/kg, three times per week for 25 treatments in total	Modulated electrohyperthermia and best supportive care	RCT
Ou <i>et al.</i> 2020 [25]	Advanced TNBC	70 (35/35)	China	27	18	7	4.5	1 g/kg/day, 25 treatments in total	Gemcitabine and carboplatin	Retrospective cohort
Wang <i>et al.</i> 2022 [3]	Metastatic colorectal cancer	442 (221/221)	China	20.7	19.7	8.6	8.3	1.5 g/kg/d for 3 hours from day 1 to day 3 for a maximum of 12 cycles	FOLFOX ± bevacizumab	RCT
Ou <i>et al.</i> 2023 [4]	NSCLC	153 (72/81)	China	49.2	25.6	39.5	8.5	1 g/kg/d, three times per week, 15 to 30 treatments in total	Standard anticancer treatments	Retrospective cohort

IVC, intravenous vitamin C; OS, overall survival; PFS, progression-free survival; NR, not reported; NSCLC, non-small cell lung cancer; TNBC, triple-negative breast cancer; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; RCT, randomized controlled trial.



The assessment of bias risk was conducted by two independent evaluators (JQ and MY) who were not involved in the selection of studies for this analysis. Any disagreements that arose during the assessment were resolved through discussions aimed at reaching a consensus. If necessary, advice from a third reviewer (SY or YW) was sought to finalize the assessment.

## 2.6 Outcomes

The main outcome of the study was OS, defined as the duration from the point of randomization until death due to any reason. The secondary outcome focused on PFS, defined as the period from randomization to the initial occurrence of disease progression or death due to any reason.

## 2.7 Data Synthesis

Pooled estimates of effect size, represented as median survival ratios (MSRs) for the median survival times, were accompanied by the corresponding 95% confidence interval (CI) to give a clear overview of the findings [15]. A random-effects model, utilizing DerSimonian-Laird estimates of the between-study variance, was selected in advance for all analyses due to anticipated differences in trial design and in the implementation of interventions across studies [16]. The heterogeneity between included studies was assessed using the Cochran Q test and the Higgins I<sup>2</sup> statistic, which offer important insights into the variability of study outcomes [17,18]. Additionally, publication bias was evaluated both qualitatively through visual inspection of the funnel plot, and quantitatively using the Egger test, enabling a comprehensive investigation of the potential impact of unpublished studies on the results [19]. All *p*-values were calculated as two-sided, with a threshold of *p* < 0.05 deemed as statistically significant. All statistical analyses were performed using STATA statistical software, version 18.0 (StataCorp LLC, College Station, TX, USA).

## 2.8 Subgroup Analyses

Five prespecified subgroups were analysed for the primary outcome: (1) non-small-cell lung cancer vs. other malignant neoplasms; (2) studies conducted in China vs. studies conducted outside China; (3) vitamin C dosage ≥ 1 g/kg vs. < 1 g/kg; (4) combination with chemotherapy vs. combination with standard care or other treatments; (5) RCTs vs. cohort studies.

## 2.9 Sensitivity Analyses

Sensitivity analyses were conducted by successively excluding individual studies to evaluate the influence on the pooled effect size [20].

## 2.10 Confidence in the Cumulative Evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) [21] approach was applied to evaluate the overall certainty of the evidence sup-

porting potential prolongation of survival following the administration of IVC. For each specific outcome assessed, the quality and certainty of the evidence were systematically judged using a scale that categorized them as “high”, “moderate”, “low”, or “very low”, thereby providing a comprehensive framework for understanding the reliability of the findings.

# 3. Results

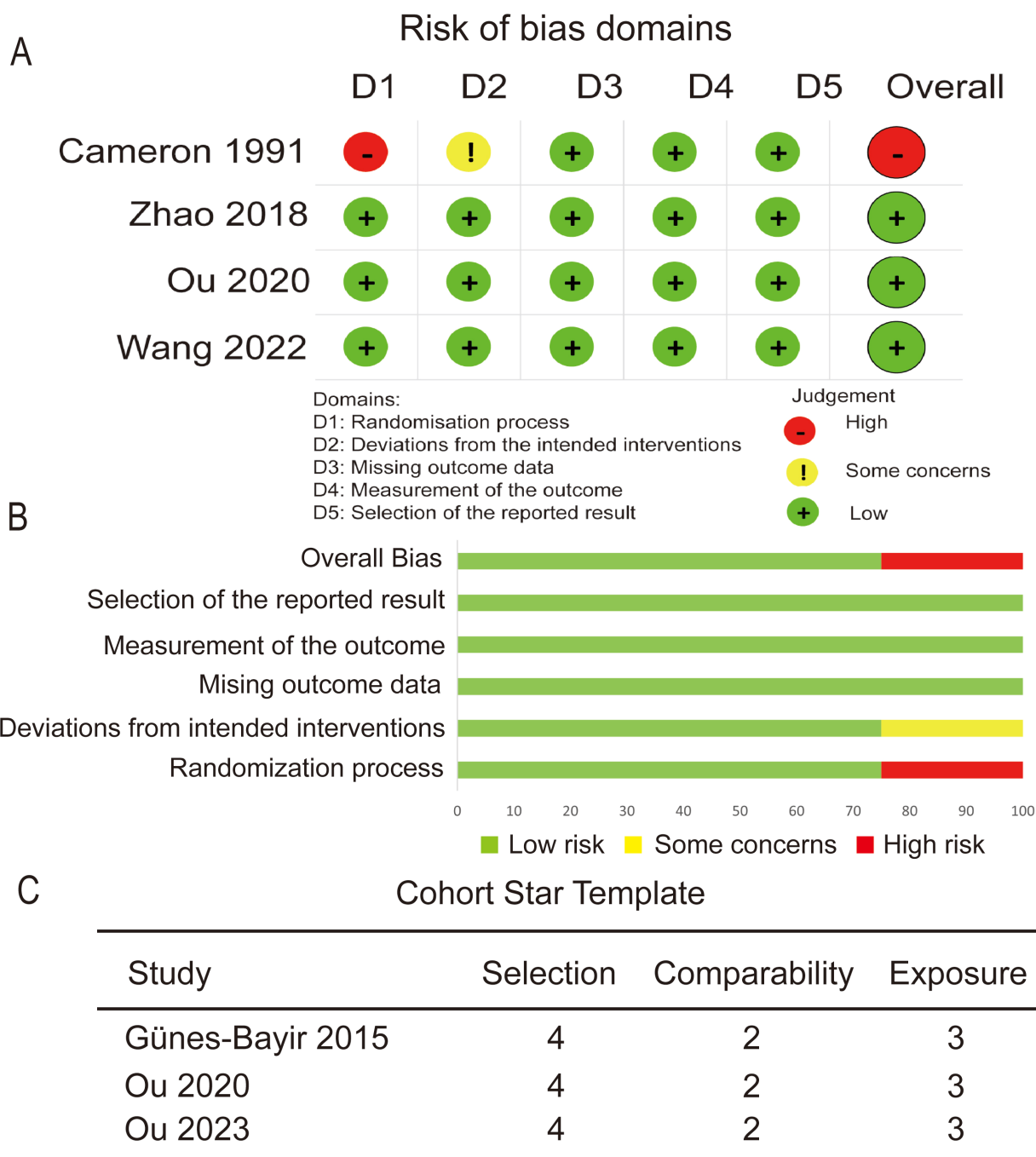
The findings derived from the extensive search, along with justifications for the exclusion of certain studies, are meticulously outlined in Fig. 1 and **Supplementary Table 1**. From an initial pool of 2637 records, a total of 8 eligible RCTs and cohort studies were identified, which collectively included 2722 adults diagnosed with malignant neoplasms [3–5,7,22–25]. Details of the included studies are shown in Table 1 (Ref. [3–5,7,22–25]). Notably, each study was published in reputable peer-reviewed journals, ensuring the credibility and reliability of findings. The median number of participants among the 8 studies was 85, with an interquartile range (IQR) of 47 to 370. Specifically, non-small cell lung cancer was the focus of two studies [4,7], while several types of malignancy were examined in two other studies [22,23]. Additionally, ovarian cancer [5], acute myeloid leukemia [24], triple-negative breast cancer [25], and colorectal cancer [3] were each the subject of one study. Geographically, 5 studies were conducted in China [3,4,7,24,25], and one each in the United States [5], the United Kingdom [22], and Turkey [23]. Seven studies [3,4,7,22–25] reported OS outcomes, and 5 [3–5,7,25] provided data on PFS outcomes, thereby contributing valuable insights into the effectiveness of various IVC treatments across different cancer types.

## 3.1 Risk of Bias

Fig. 2 is a visual representation of the potential biases in the studies analyzed here. Of the four RCTs that provided data on OS, three were deemed to have a minimal likelihood of bias throughout all assessed domains, indicating a high level of reliability in the findings [3,7,24]. Furthermore, each of the three cohort studies that contributed OS data had an impressive 9-star rating [4,23,25].

## 3.2 Primary Outcome

A total of four RCTs encompassing 2438 participants and three cohort studies involving 262 participants collectively contributed data to the primary outcome of this analysis. Random-effects model analysis revealed that patients with malignant neoplasms and who were treated with IVC experienced a significantly longer median OS compared to those who did not receive this treatment, with a median survival ratio of 1.83 (95% CI: 1.40–2.40, *p* < 0.001; I<sup>2</sup> = 96.5%; Fig. 3A). No significant sources of heterogeneity were identified by sensitivity analysis (Fig. 4A). Moreover, the Egger regression test yielded no evidence of publication

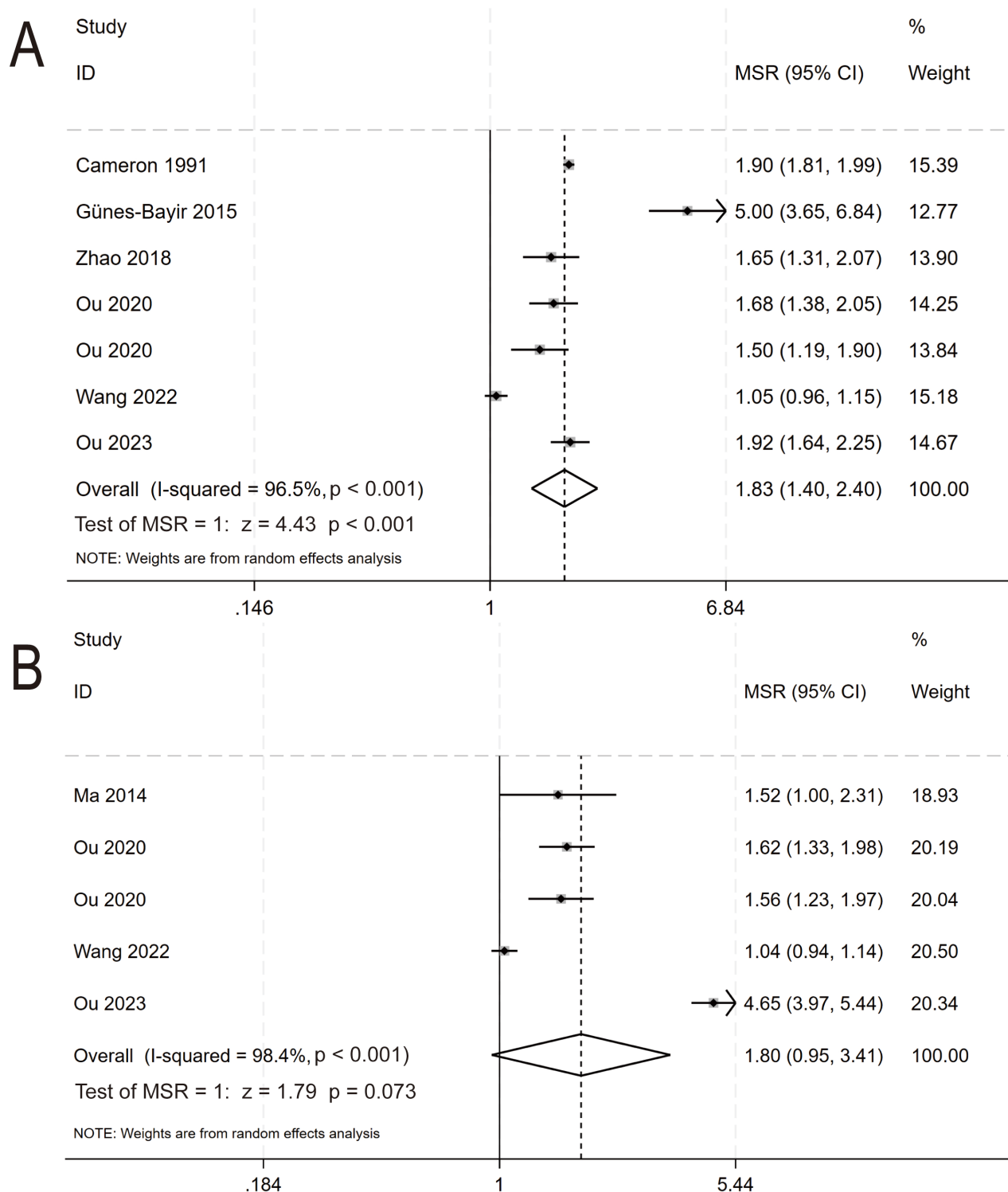


**Fig. 2. Risk of bias assessment for primary outcome.** (A) Traffic light plot of the RCTs. (B) Summary plot of the RCTs. (C) Assessment of the cohort studies.

bias, with a  $p$ -value of 0.989 (Fig. 4C). The overall certainty for the evidence derived from this analysis was adjudicated to be moderate.

The primary outcome was also evaluated in five pre-specified subgroups (Fig. 5). The pooled estimates were as follows: non-small-cell lung cancer (1.82, 95% CI: 1.60–2.07,  $p < 0.001$ ) vs. other malignant neoplasms (1.86, 95% CI: 1.29–2.69,  $p = 0.001$ ); studies conducted in China (1.52, 95% CI: 1.15–2.01,  $p = 0.003$ ) vs. studies conducted out-

side China (3.04, 95% CI: 1.18–7.85,  $p = 0.021$ ); vitamin C dosage  $\geq 1$  g/kg (1.49, 95% CI: 1.07–2.08,  $p = 0.017$ ) vs. vitamin C dosage  $< 1$  g/kg (2.45, 95% CI: 1.52–3.95,  $p < 0.001$ ); combination with chemotherapy (1.35, 95% CI: 0.99–1.86,  $p = 0.059$ ) vs. combination with standard care or other treatments (2.26, 95% CI: 1.72–2.96,  $p < 0.001$ ); RCTs (1.53, 95% CI: 1.07–2.18,  $p = 0.019$ ) vs. cohort studies (2.40, 95% CI: 1.35–4.29,  $p = 0.003$ ).

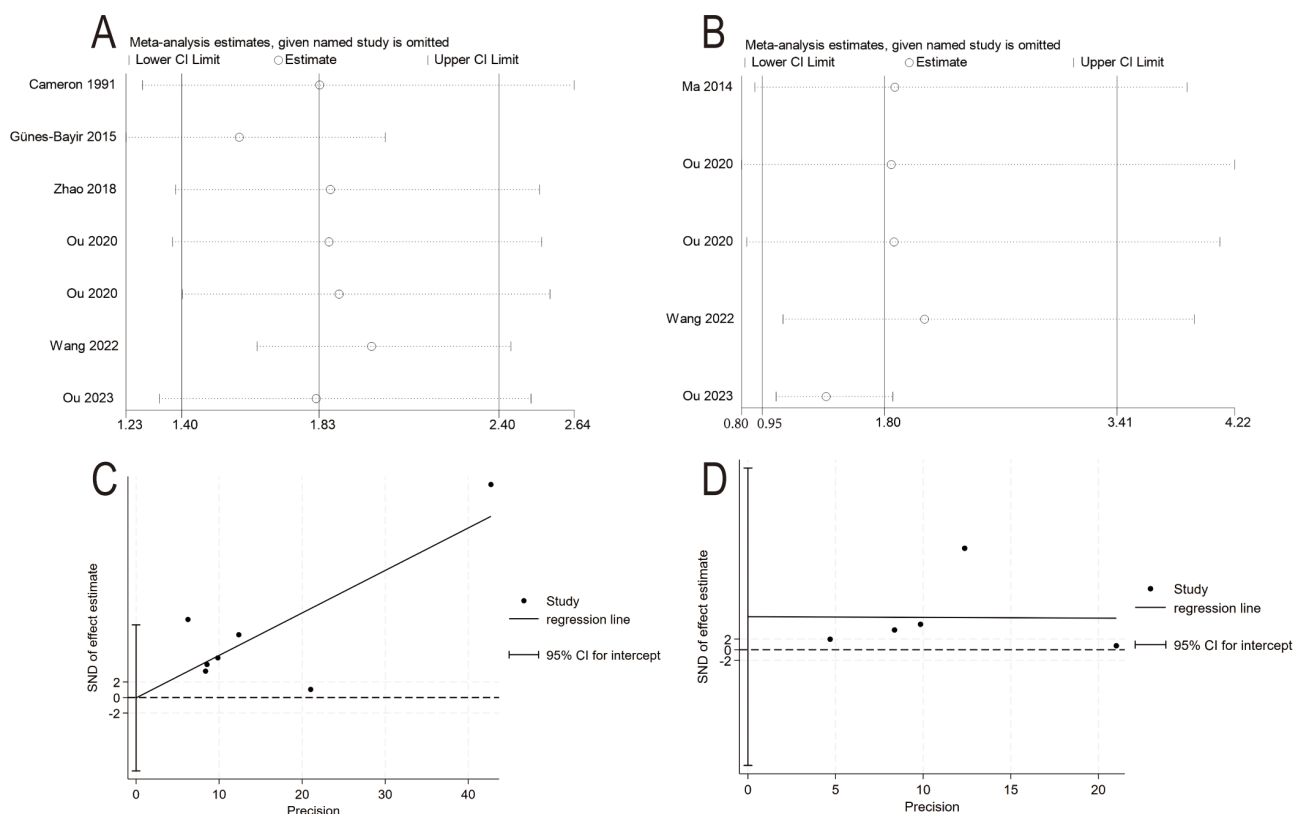


**Fig. 3. The overall survival (A) and progression-free survival (B) of cancer patients who received intravenous vitamin C were compared to those who received no intravenous vitamin C. MSR, median survival ratio; CI, confidence interval.**

### 3.3 Secondary Outcome

Three RCTs with a total of 561 participants, and two cohort studies with a total of 223 participants contributed data for analysis of the secondary outcome (PFS). Analysis with a random-effects model revealed a trend for longer

median PFS in patients with malignant neoplasms who received IVC, with a median survival ratio of 1.80 (95% CI: 0.95–3.41,  $p = 0.073$ ;  $I^2 = 98.4\%$ ; Fig. 3B). Furthermore, a sensitivity analysis revealed no significant sources of heterogeneity (Fig. 4B). The Egger regression test detected no trace of publication bias, with a  $p$ -value of 0.530 (Fig. 4D).



**Fig. 4. Sensitivity analyses and funnel plots.** (A) Sensitivity analysis for overall survival. (B) Sensitivity analysis for progression-free survival. (C) Egger test funnel plot for overall survival. (D) Egger test funnel plot for progression-free survival.

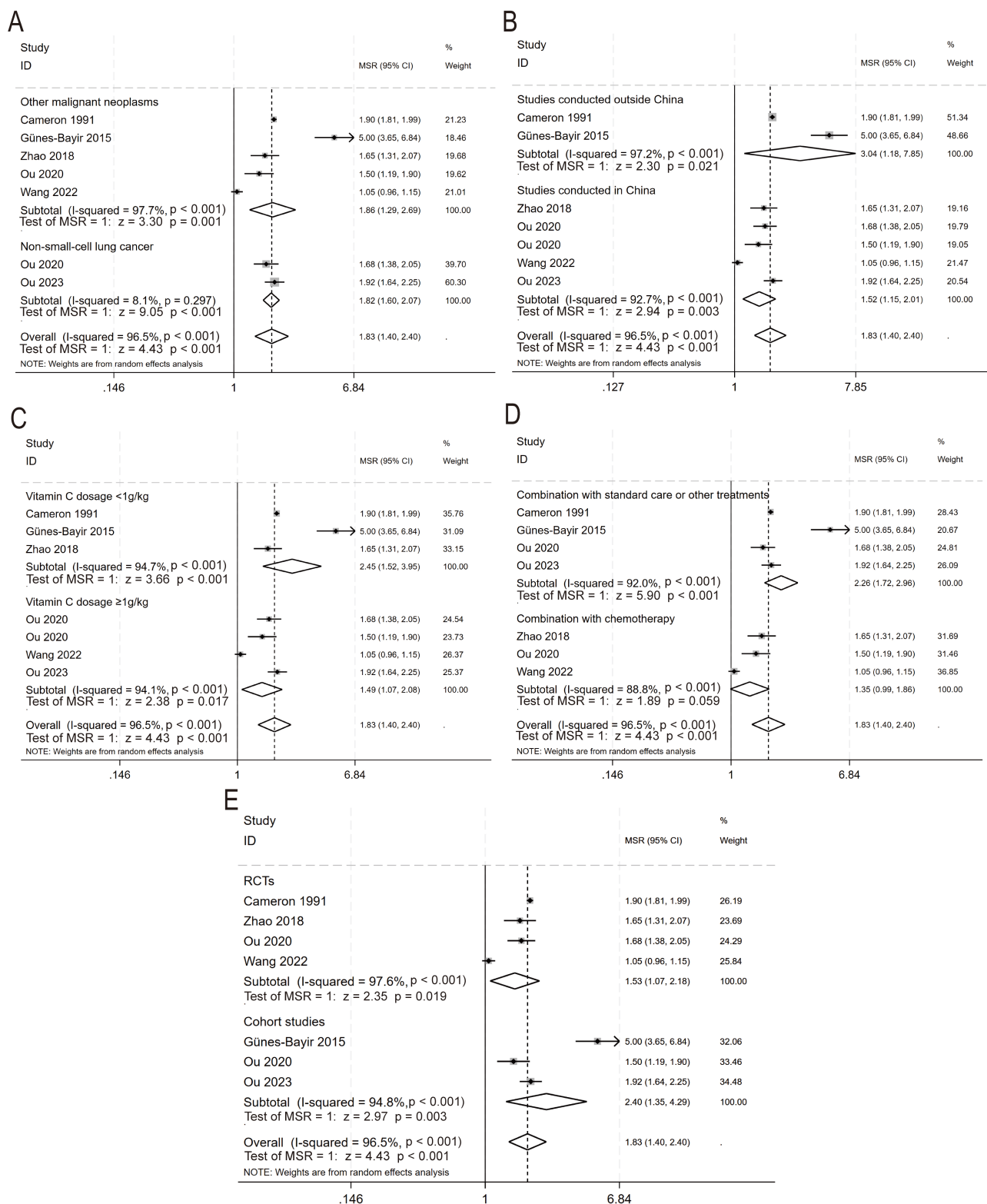
## 4. Discussion

This systematic review and meta-analysis found that administration of IVC was associated with a significant improvement in the OS rate among patients diagnosed with a malignant neoplasm. Specifically, the findings revealed the median OS for patients receiving this treatment was 1.83-fold longer than those who did not receive IVC. Our analysis revealed not only a significant improvement in OS, but also a notable trend towards increased median PFS in patients who received IVC compared to those who did not.

This study offers several innovative contributions to the field of oncology. It represents the first quantitative meta-analysis on the administration of IVC for the treatment of patients with malignant tumors, thus filling a gap in the current literature and providing a reference for future research and clinical decision-making. The subgroup analysis for OS revealed differences in the therapeutic efficacy of IVC according to the dose and geographical location. While subgroup analysis showed a numerically higher median survival ratio in the  $<1$  g/kg group (2.45 vs. 1.49), this finding should be interpreted with caution due to the limited sample size and wider confidence intervals in this subgroup. Notably, the  $\geq 1$  g/kg group demonstrated more consistent results across studies with tighter confidence intervals, suggesting better reproducibility of the treatment effect at higher doses. Additionally, studies conducted in

China [3,4,7,24,25] showed significantly different results compared to those from other countries [22,23]. These findings suggest that evaluation of the efficacy of IVC should consider both the dose level and contextual factors, highlighting the importance of personalized treatment strategies in clinical practice.

One of the main drawbacks of this research was the comparatively limited number of participants, which may affect the applicability of the findings to larger populations. The meta-analysis included eight studies with a total of 2722 participants. However, there were considerable differences in the sample size between different studies, which ranged from 22 to over 1000 participants. This heterogeneity in sample size may have contributed to the variability in observed treatment effects. Additionally, most studies were conducted in China [3,4,7,24,25], and differences in genetic background, environmental factors, and medical practice across regions may restrict the applicability of these findings across different populations. Another important limitation is the potential for confounding bias in observational studies [4,23,25], despite the use of various assessment tools to mitigate this impact. The current clinical studies on IVC lack unified standards, such as dosage, and the participants were often diverse, thereby limiting the interpretation and comparability of the study results. The subgroup analysis suggested that differences in study de-



**Fig. 5. Subgroup analyses for overall survival.** (A) Non-small-cell lung cancer vs. other malignant neoplasms. (B) Studies conducted in China vs. studies conducted outside China. (C) Vitamin C dosage <1 g/kg body weight vs. vitamin C dosage  $\geq 1$  g/kg body weight. (D) Combination with chemotherapy vs. combination with standard care or other treatments. (E) RCTs vs. cohort studies.

sign (RCTs vs. cohort studies) were an important source of heterogeneity in the results of this study. Most studies reported short- and medium-term outcomes, with limited

data on long-term survival. Additionally, the improvement in PFS with IVC did not reach statistical significance ( $p = 0.073$ ), possibly due to insufficient sample size or differ-



ences in follow-up time. To address these limitations, future studies should focus on conducting larger-scale, multicenter RCTs that include diverse populations. Moreover, standardized dosing and follow-up protocols should be employed to enhance the reliability, interpretability, and generalizability of the results, as well as helping to determine the optimal dosage range for efficacy and long-term effects.

IVC acts through multifaceted mechanisms in antitumor therapy, including the induction of oxidative stress, co-factor activity, epigenetic regulation, hypoxia sensing, and immune modulation. The redox capacity of vitamin C catalyzes the generation of hydrogen peroxide ( $H_2O_2$ ) by iron or copper ions [26–28]. This results in the production of ROS and subsequent induction of DNA, protein, and lipid damage in cancer cells, leading to apoptosis. Cancer cells are characterized by high iron content, high metabolic rates, mitochondrial defects, and low catalase activity. Hence, they are more susceptible to oxidative stress and more vulnerable to vitamin C-induced oxidative damage than normal cells [29,30]. Furthermore, when combined with chemotherapy or radiotherapy, vitamin C further increases oxidative stress and reduces antioxidant defenses, thereby significantly improving therapeutic efficacy [31,32]. With regard to co-factor activity, vitamin C reduces ferric ions ( $Fe^{3+}$ ) to ferrous ions ( $Fe^{2+}$ ), thus modulating the function of iron-dependent proteins and influencing various metabolic activities such as the mitochondrial respiratory chain, collagen synthesis, and oxidative stress regulation [2]. Vitamin C also promotes collagen synthesis to stabilize the extracellular matrix, thereby inhibiting tumor invasion and metastasis [33–35]. It also regulates the degradation of hypoxia-inducible factor 1 (HIF-1), thereby suppressing tumor growth and invasion in hypoxic environments [36–38]. In terms of epigenetic regulation, vitamin C modulates the function of TET enzymes to enhance DNA demethylation and reactivate the expression of tumor suppressor genes [39]. Moreover, vitamin C promotes the function of Jumonji C (JmjC) family histone demethylases to correct the aberrant epigenetic state of cancer cells and further disrupt tumor survival and proliferation [40]. Regarding immune modulation, vitamin C maintains high levels of immune cells and influences their differentiation, maturation, activation, and cytokine production through its antioxidant and co-factor activities [41]. Vitamin C also restores the epigenetic state of immune cells by modulating TET enzyme function [42]. Furthermore, vitamin C significantly enhances antitumor efficacy when combined with immune checkpoint inhibitors such as anti-programmed death-1 (anti-PD-1) and anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) [43,44]. A clinical study suggested the biomarkers SERPINE1 and SERPINB7 were associated with the benefits of IVC treatment in non-small-cell lung cancer [4]. The postulated mechanism is that IVC downregulates the expression of SERPINE1 and SERPINB7, thereby inhibiting the prolifer-

ation and invasiveness of tumor cells and enhancing the efficacy of chemotherapy or radiotherapy to improve patient outcomes [4]. Future research should integrate preclinical and clinical studies to further elucidate the mechanism of IVC in cancer therapy.

## 5. Conclusions

IVC has emerged as a potential therapeutic agent for human malignancies. This study found that IVC extended the median OS of patients with malignant tumors by 1.83-fold. Additionally, a trend towards longer median PFS was also observed for patients receiving IVC. Nevertheless, it is important to note that considerable heterogeneity was found amongst the studies in terms of design, dosing regimens, and the diverse patient populations. Any conclusions should therefore be drawn with caution. Future studies should focus on large-scale, multicenter RCTs to further assess the effectiveness and safety of IVC.

## Availability of Data and Materials

Data will be made available on reasonable request.

## Author Contributions

JQ, MY, and BR designed the research study. JQ, MY, and SY performed the literature search, study selection, and data extraction. YW, SL, and BW resolved discrepancies during the study selection and data extraction process. JQ, MY, SY, JH, SW, YZ, and XW contributed to the risk of bias assessment and data validation. XT, XL, YR, and YL provided critical insights into the interpretation of the results. JQ and MY conducted the statistical analysis. BR supervised the project and secured funding. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.

## Acknowledgment

Not applicable.

## Funding

This research was funded by the National Natural Science Foundation of China, grant number 82474333, the National Key Research and Development Program of China, grant number 2022YFC2009601, and the Beijing Shijitan Hospital Capital Medical University Talent Cultivation Program during the 14th Five-Year Plan, grant number 2024LJRCRBQ.

## Conflict of Interest

The authors declare no conflict of interest.

## Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.31083/IJVN37372>.

## References

- [1] Ngo B, Van Riper JM, Cantley LC, Yun J. Targeting cancer vulnerabilities with high-dose vitamin C. *Nature Reviews. Cancer*. 2019; 19: 271–282. <https://doi.org/10.1038/s41568-019-0135-7>.
- [2] Böttger F, Vallés-Martí A, Cahn L, Jimenez CR. High-dose intravenous vitamin C, a promising multi-targeting agent in the treatment of cancer. *Journal of Experimental & Clinical Cancer Research*. 2021; 40: 343. <https://doi.org/10.1186/s13046-021-02134-y>.
- [3] Wang F, He MM, Xiao J, Zhang YQ, Yuan XL, Fang WJ, *et al*. A Randomized, Open-Label, Multicenter, Phase 3 Study of High-Dose Vitamin C Plus FOLFOX ± Bevacizumab versus FOLFOX ± Bevacizumab in Unresectable Untreated Metastatic Colorectal Cancer (VITALITY Study). *Clinical Cancer Research: an Official Journal of the American Association for Cancer Research*. 2022; 28: 4232–4239. <https://doi.org/10.1158/1078-0432.CCR-22-0655>.
- [4] Ou J, Liao Q, Du Y, Xi W, Meng Q, Li K, *et al*. SERPINE1 and SERPINB7 as potential biomarkers for intravenous vitamin C treatment in non-small-cell lung cancer. *Free Radical Biology & Medicine*. 2023; 209: 96–107. <https://doi.org/10.1016/j.free-radbiomed.2023.10.391>.
- [5] Ma Y, Chapman J, Levine M, Polireddy K, Drisko J, Chen Q. High-dose parenteral ascorbate enhanced chemosensitivity of ovarian cancer and reduced toxicity of chemotherapy. *Science Translational Medicine*. 2014; 6: 222ra18. <https://doi.org/10.1126/scitranslmed.3007154>.
- [6] Monti DA, Mitchell E, Bazzan AJ, Littman S, Zabrecky G, Yeo CJ, *et al*. Phase I evaluation of intravenous ascorbic acid in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. *PloS One*. 2012; 7: e29794. <https://doi.org/10.1371/journal.pone.0029794>.
- [7] Ou J, Zhu X, Chen P, Du Y, Lu Y, Peng X, *et al*. A randomized phase II trial of best supportive care with or without hyperthermia and vitamin C for heavily pretreated, advanced, refractory non-small-cell lung cancer. *Journal of Advanced Research*. 2020; 24: 175–182. <https://doi.org/10.1016/j.jare.2020.03.004>.
- [8] van Gorkom GNY, Lookermans EL, Van Elssen CHMJ, Bos GMJ. The Effect of Vitamin C (Ascorbic Acid) in the Treatment of Patients with Cancer: A Systematic Review. *Nutrients*. 2019; 11: 977. <https://doi.org/10.3390/nu11050977>.
- [9] Nauman G, Gray JC, Parkinson R, Levine M, Paller CJ. Systematic Review of Intravenous Ascorbate in Cancer Clinical Trials. *Antioxidants (Basel, Switzerland)*. 2018; 7: 89. <https://doi.org/10.3390/antiox7070089>.
- [10] Hoppe C, Freuding M, Büntzel J, Münstedt K, Hübner J. Clinical efficacy and safety of oral and intravenous vitamin C use in patients with malignant diseases. *Journal of Cancer Research and Clinical Oncology*. 2021; 147: 3025–3042. <https://doi.org/10.1007/s00432-021-03759-4>.
- [11] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ (Clinical Research Ed.)*. 2021; 372: n71. <https://doi.org/10.1136/bmj.n71>.
- [12] Gotschall T. Resource Review: EndNote 21 desktop version. *Journal of the Medical Library Association: JMLA*. 2023; 111: 852–853. <https://doi.org/10.5195/jmla.2023.1803>.
- [13] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ (Clinical Research Ed.)*. 2019; 366: 14898. <https://doi.org/10.1136/bmj.14898>.
- [14] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *European Journal of Epidemiology*. 2010; 25: 603–605. <https://doi.org/10.1007/s10654-010-9491-z>.
- [15] Jin X, Xu XT, Tian MX, Dai Z. Omega-3 polyunsaturated fatty acids improve quality of life and survival, but not body weight in cancer cachexia: A systematic review and meta-analysis of controlled trials. *Nutrition Research*. 2022; 107: 165–178. <https://doi.org/10.1016/j.nutres.2022.09.009>.
- [16] Im YR, Jagdish R, Leith D, Kim JU, Yoshida K, Majid A, *et al*. Prevalence of occult hepatitis B virus infection in adults: a systematic review and meta-analysis. *The Lancet. Gastroenterology & Hepatology*. 2022; 7: 932–942. [https://doi.org/10.1016/S2468-1253\(22\)00201-1](https://doi.org/10.1016/S2468-1253(22)00201-1).
- [17] Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine*. 2002; 21: 1539–1558. <https://doi.org/10.1002/sim.1186>.
- [18] Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ (Clinical Research Ed.)*. 2003; 327: 557–560. <https://doi.org/10.1136/bmj.327.7414.557>.
- [19] Cai H, Jin Y, Liu R, Zhang Q, Su Z, Ungvari GS, *et al*. Global prevalence of depression in older adults: A systematic review and meta-analysis of epidemiological surveys. *Asian Journal of Psychiatry*. 2023; 80: 103417. <https://doi.org/10.1016/j.ajp.2022.103417>.
- [20] Ribeiro LM, Sasaki LMP, Silva AA, Souza ES, Oliveira Lyrio A, C M G Figueiredo A, *et al*. Overweight, obesity and assisted reproduction: A systematic review and meta-analysis. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*. 2022; 271: 117–127. <https://doi.org/10.1016/j.ejogrb.2022.01.019>.
- [21] Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, *et al*. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ (Clinical Research Ed.)*. 2008; 336: 924–926. <https://doi.org/10.1136/bmj.39489.470347.AD>.
- [22] Cameron E, Campbell A. Innovation vs. quality control: an 'unpublishable' clinical trial of supplemental ascorbate in incurable cancer. *Medical Hypotheses*. 1991; 36: 185–189. [https://doi.org/10.1016/0306-9877\(91\)90127-k](https://doi.org/10.1016/0306-9877(91)90127-k).
- [23] Günes-Bayir A, Kiziltan HS. Palliative Vitamin C Application in Patients with Radiotherapy-Resistant Bone Metastases: A Retrospective Study. *Nutrition and Cancer*. 2015; 67: 921–925. <https://doi.org/10.1080/01635581.2015.1055366>.
- [24] Zhao H, Zhu H, Huang J, Zhu Y, Hong M, Zhu H, *et al*. The synergy of Vitamin C with decitabine activates TET2 in leukemic cells and significantly improves overall survival in elderly patients with acute myeloid leukemia. *Leukemia Research*. 2018; 66: 1–7. <https://doi.org/10.1016/j.leukres.2017.12.009>.
- [25] Ou J, Zhu X, Zhang H, Du Y, Chen P, Wang J, *et al*. A Retrospective Study of Gemcitabine and Carboplatin With or Without Intravenous Vitamin C on Patients With Advanced Triple-Negative Breast Cancer. *Integrative Cancer Therapies*. 2020; 19: 1534735419895591. <https://doi.org/10.1177/1534735419895591>.
- [26] Pfeifhofer-Obermair C, Tymoszek P, Petzer V, Weiss G, Nairz M. Iron in the Tumor Microenvironment-Connecting the Dots. *Frontiers in Oncology*. 2018; 8: 549. <https://doi.org/10.3389/fo nc.2018.00549>.
- [27] Cao LL, Liu H, Yue Z, Liu L, Pei L, Gu J, *et al*. Iron chelation inhibits cancer cell growth and modulates global histone methylation status in colorectal cancer. *Biometals: an International Journal on the Role of Metal Ions in Biology, Bio-*

- chemistry, and Medicine. 2018; 31: 797–805. <https://doi.org/10.1007/s10534-018-0123-5>.
- [28] Jung M, Mertens C, Tomat E, Brüne B. Iron as a Central Player and Promising Target in Cancer Progression. *International Journal of Molecular Sciences*. 2019; 20: 273. <https://doi.org/10.3390/ijms20020273>.
- [29] Schoenfeld JD, Sibenaller ZA, Mapuskar KA, Wagner BA, Cramer-Morales KL, Furqan M, *et al.* O<sub>2</sub><sup>•−</sup> and H<sub>2</sub>O<sub>2</sub>-Mediated Disruption of Fe Metabolism Causes the Differential Susceptibility of NSCLC and GBM Cancer Cells to Pharmacological Ascorbate. *Cancer Cell*. 2017; 32: 268. <https://doi.org/10.1016/j.ccell.2017.07.008>.
- [30] Liberti MV, Locasale JW. The Warburg Effect: How Does it Benefit Cancer Cells? *Trends in Biochemical Sciences*. 2016; 41: 211–218. <https://doi.org/10.1016/j.tibs.2015.12.001>.
- [31] Sinha BK, van 't Erve TJ, Kumar A, Bortner CD, Motten AG, Mason RP. Synergistic enhancement of topotecan-induced cell death by ascorbic acid in human breast MCF-7 tumor cells. *Free Radical Biology & Medicine*. 2017; 113: 406–412. <https://doi.org/10.1016/j.freeradbiomed.2017.10.377>.
- [32] Pires AS, Marques CR, Encarnação JC, Abrantes AM, Marques IA, Laranjo M, *et al.* Ascorbic Acid Chemosensitizes Colorectal Cancer Cells and Synergistically Inhibits Tumor Growth. *Frontiers in Physiology*. 2018; 9: 911. <https://doi.org/10.3389/fphys.2018.00911>.
- [33] Cameron E, Rotman D. Ascorbic acid, cell proliferation, and cancer. *Lancet* (London, England). 1972; 1: 542. [https://doi.org/10.1016/s0140-6736\(72\)90215-2](https://doi.org/10.1016/s0140-6736(72)90215-2).
- [34] McCORMICK WJ. Cancer: a collagen disease, secondary to a nutritional deficiency. *Archives of Pediatrics*. 1959; 76: 166–171.
- [35] McCORMICK WJ. Cancer: the preconditioning factor in pathogenesis; a new etiologic approach. *Archives of Pediatrics*. 1954; 71: 313–322.
- [36] Fischer AP, Miles SL. Ascorbic acid, but not dehydroascorbic acid increases intracellular vitamin C content to decrease Hypoxia Inducible Factor -1 alpha activity and reduce malignant potential in human melanoma. *Biomedicine & Pharmacotherapy*. 2017; 86: 502–513. <https://doi.org/10.1016/j.biopha.2016.12.056>.
- [37] Józwiak P, Ciesielski P, Zaczek A, Lipińska A, Pomorski L, Wieczorek M, *et al.* Expression of hypoxia inducible factor 1 $\alpha$  and 2 $\alpha$  and its association with vitamin C level in thyroid lesions. *Journal of Biomedical Science*. 2017; 24: 83. <https://doi.org/10.1186/s12929-017-0388-y>.
- [38] Wohlrab C, Vissers MCM, Phillips E, Morrin H, Robinson BA, Dachs GU. The Association Between Ascorbate and the Hypoxia-Inducible Factors in Human Renal Cell Carcinoma Requires a Functional Von Hippel-Lindau Protein. *Frontiers in Oncology*. 2018; 8: 574. <https://doi.org/10.3389/fonc.2018.00574>.
- [39] Lv H, Zong Q, Chen C, Lv G, Xiang W, Xing F, *et al.* TET2-mediated tumor cGAS triggers endothelial STING activation to regulate vasculature remodeling and anti-tumor immunity in liver cancer. *Nature Communications*. 2024; 15: 6. <https://doi.org/10.1038/s41467-023-43743-9>.
- [40] Lee Chong T, Ahearn EL, Cimmino L. Reprogramming the Epigenome With Vitamin C. *Frontiers in Cell and Developmental Biology*. 2019; 7: 128. <https://doi.org/10.3389/fcell.2019.00128>.
- [41] van Gorkom GNY, Klein Wolterink RGJ, Van Elssen CHMJ, Wieten L, Germeraad WTV, Bos GMJ. Influence of Vitamin C on Lymphocytes: An Overview. *Antioxidants*. 2018; 7: 41. <https://doi.org/10.3390/antiox7030041>.
- [42] Yue X, Rao A. TET family dioxygenases and the TET activator vitamin C in immune responses and cancer. *Blood*. 2020; 136: 1394–1401. <https://doi.org/10.1182/blood.2019004158>.
- [43] Luchtel RA, Bhagat T, Pradhan K, Jacobs WR, Jr, Levine M, Verma A, *et al.* High-dose ascorbic acid synergizes with anti-PD1 in a lymphoma mouse model. *Proceedings of the National Academy of Sciences of the United States of America*. 2020; 117: 1666–1677. <https://doi.org/10.1073/pnas.1908158117>.
- [44] Magri A, Germano G, Lorenzato A, Lamba S, Chilà R, Montone M, *et al.* High-dose vitamin C enhances cancer immunotherapy. *Science Translational Medicine*. 2020; 12: eaay8707. <https://doi.org/10.1126/scitranslmed.aay8707>.