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REVIEW

GLIM-defined malnutrition and overall survival in cancer patients: A meta-analysis

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Abstract

Background: Malnutrition defined by the Global Leadership Initiative on Malnutrition (GLIM) has been associated with cancer mortality, but the effect is limited and inconsistent. We performed this meta-analysis aiming to assess this relationship in patients with cancer.

Methods: We systematically searched Embase, PubMed, Web of Science, Cochrane, CINAHL, CNKI, Wanfang, and VIP databases from January 1, 2019, to July 1, 2022. Studies evaluating the prognostic effect of GLIM-defined malnutrition on cancer survival were included. A fixed-effect model was fitted to estimate the combined hazard ratio (HR) with a 95% CI. Heterogeneity of studies was analyzed using the I^2 statistic. Quality assessment were performed using the Newcastle-Ottawa Scale (NOS) and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool.

Results: The search strategy identified 4378 articles in all databases combined. Nine studies (8829 patients) meeting the inclusion criteria were included for quantitative analysis. Meta-analysis revealed significant associations between GLIM-defined pooled malnutrition (HR = 1.75; 95% CI, 1.43–2.15), moderate malnutrition (HR = 1.44; 95% CI, 1.29–1.62), and severe malnutrition (HR = 1.79; 95% CI, 1.58–2.02) with all-cause mortality. Sensitivity analysis supported the robustness of these associations. The between-study heterogeneity was low (all $I^2 < 50\%$), and study quality assessed with NOS was high (all scores > 6). The evidence quality according to the GRADE tool was very low.

Conclusions: Our meta-analysis suggests a significant negative association of malnutrition, as defined by the GLIM, with overall survival in patients with cancer. However, definitive conclusions cannot be made, owing to the low quality of the source data.

KEYWORDS
cancer, GLIM, malnutrition, meta-analysis, survival

Liangyu Yin and Feifei Chong contributed equally to this study.

CLINICAL RELEVANCY STATEMENT

This article suggests a significant negative association of malnutrition, as defined by the Global Leadership Initiative on Malnutrition, with overall survival in patients with cancer. These findings are relevant for guiding clinicians in caring for these patients.

INTRODUCTION

Malnutrition is a major global public health problem affecting >1 billion of the world's population[1] and is a prevalent clinical condition in hospitalized patients.[2] Among all disease groups, cancer patients are at an especially high risk of developing malnutrition,[3] owing to the physical inactivity, metabolic disorders, and systemic inflammation induced by the tumor itself and/or side effects of anticancer therapies.[4–6] Cancer-related malnutrition can impede even the best anticancer treatments[7] and lead to an impaired quality of life,[8] increased risk of postoperative complications,[9] reduced treatment tolerance,[10] delayed rehabilitation of organ function,[11] and eventually shortened overall survival (OS).[5] However, malnutrition is often clinically underestimated,[12] misclassified,[13] or left untreated[14] in oncology populations. Previous studies estimate that approximately 10%–20% of cancer deaths can be attributed to malnutrition rather than to the cancer itself.[15] Thus, regular evaluation for the risk/presence of malnutrition is imperative in all cancer patients to guide intervention strategies as recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN) in its guidelines.[4,16]

However, the tools used to define malnutrition vary greatly across different institutions, regions, and/or countries,[2,17] and none of them has secured broad global acceptance.[18] Importantly, the need for diagnosis, severity grading, and phenotyping of malnutrition has emerged to support more individualized prevention and/or intervention strategies.[19] Thus, a diagnostic framework addressing these challenges and reflecting the latest evidence becomes imperative.

In view of this, the ESPEN proposed the Global Leadership Initiative on Malnutrition (GLIM) in 2019, a set of consensus-based guidelines aiming to unify the diagnosis of malnutrition in hospitalized patients,[18] which has been garnering increasing interest from clinical nutrition societies worldwide.[2,20–25] The GLIM framework has two modules—namely, the phenotypic criteria (including three components: unintentional weight loss, low body mass index, and reduced muscle mass) and the etiologic criteria (including two components: reduced food intake/assimilation and inflammation/disease burden).[18] A two-step scheme was recommended by the GLIM: First, patients should be screened for nutrition risk based on validated screening tools. Then, at least one phenotypic criterion and one etiologic criterion should be positive to establish the diagnosis of malnutrition in those patients positive for nutrition risk. In addition, the severity of malnutrition can be determined as per the different cutoffs noted in the three phenotypic criteria.[18]

Compared with its prototypic predecessor, proposed by the ESPEN in 2015,[26] two significant advances of the GLIM may be the addition of etiological criteria and the implementation of severity grading.[18] Indeed, the GLIM framework was proved effective in identifying malnutrition[6,27,28] and predicting postoperative complications.[9] Several cohort studies have also investigated the associations of GLIM-defined malnutrition with all-cause mortality and OS in cancer patients.[21–25,29–36] However, these studies had several limitations, including limited sample sizes, limited cancer types, or failure to control for cancer outcome–related confounders.

Previous systematic reviews and meta-analyses also indicate a positive relation between malnutrition and increased cancer mortality: A meta-analysis found that poorer nutrition status as indicated by the Geriatric Nutritional Risk Index at baseline was independently associated with poor survival in patients with colorectal cancer.[37] Another systematic review and meta-analysis reported similar association between the Prognostic Nutritional Index and mortality in older patients with cancer.[38] Zhang et al. also reported in their meta-analysis that malnutrition, as defined by various approaches, is negatively associated with OS in older patients with cancer. However, there are no prior meta-analyses assessing this relationship based on the novel GLIM framework. The study objective was to conduct a meta-analysis of published literature to investigate the effect of GLIM-defined malnutrition on OS in patients with cancer.

MATERIALS AND METHODS

Search strategy and included studies

This was a meta-analysis conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[39] Protocol of the present study was registered with the INPLASY platform (https://inplasy.com/, ID: 202270113, DOI: 10.37766/inplasy2022.7.0113). The PICO statement of the study was patient problem or population (patients with cancer), intervention or exposure (malnutrition with/without severity grading as defined by the GLIM), comparison or control (well-nourished status as defined by the GLIM), and outcome measure (OS/all-cause mortality). Two independent investigators (LY and FC) searched eight databases systematically for eligible studies published after 2019 (the GLIM framework was published in 2019), including Embase, PubMed, Web of Science, Cochrane, CINAHL, CNKI, Wanfang, and VIP. The two investigators were mutually masked to each other's results, and agreement on study selection was reached afterward. The search was completed on July 1, 2022, with a combined search term as ("GLIM" OR "GLIM criteria" OR "Scored-GLIM" OR "Global Leadership Initiative on Malnutrition" OR "Malnutrition" OR "Undernutrition" OR "Malnourishment") AND ("Tumor" OR "Neoplasm" OR "Malignancy" OR "Cancer") AND ("Mortality" OR "Survival" OR "Mortalities" OR "Case Fatality Rate" OR "Crude Death Rate" OR "Crude Mortality Rate" OR "Excess Mortality" OR "Mortality Declines" OR "Mortality Determinants" OR "Age-Specific Death Rate").

Study selection

We included retrospective and prospective cohort studies that met the following selection criteria: (1) observational design investigating the association between GLIM-defined malnutrition and all-cause mortality/OS in any type of solid malignancy; (2) follow-up of ≥1 year; (3) available data on hazard ratio (HR) with a 95% CI that support the calculation of effect size; and (4) availability of full text. The search was limited to original research articles without language restrictions. Reviews, case reports, conference abstracts, and nonpublished data were excluded. If several studies were conducted using data from an identical cohort (based on the consortium information in the author list, author affiliations, and study methodology), only the study with the largest sample size was selected. The workflow of study selection comprised three steps. First, we removed those duplicated studies; second, we reviewed the title and abstract to remove articles that were apparently irrelevant to nutrition status or prognosis of patients; finally, we thoroughly assessed the full text of the remaining articles for eligibility.

Data extraction

Two researchers (LY and FC) independently extracted data from the included studies: author, year of publication, study region, study design, sample size, mean/median age, cancer type, cancer treatment, length of follow-up, muscle parameter used in the GLIM, prevalence of malnutrition, and covariates. We selected the effect size from both the univariate and multivariate analyses in the study. We also separately selected the effect size from both the pooled GLIM diagnosis (without grading) and the graded GLIM diagnosis (moderate and severe malnutrition). HRs and CIs underwent logarithmic transformation, and standard errors were subsequently calculated as: (upper CI − lower CI)/(2 × 1.96).

Quality assessment

The quality assessment was performed using the Newcastle-Ottawa Scale (NOS) for cohort studies (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). The NOS-cohort scale has three domains: selection (including four components: representativeness of the exposed cohort, selection of the unexposed controls, ascertainment of exposure, and description that outcome was not present at the beginning of study), comparability (including one component: comparability of cohorts based on the study design or analysis), and outcome (including three components: outcome assessment, ascertainment of the sufficient length of follow-up for outcomes to occur, and adequacy of follow-up of cohort). All variables can be allotted 0–1 star except for comparability, which can be allotted 0–2 stars. LY and FC assessed the quality of all included full-text studies, and they agreed with the quality assessment results. The quality of the synthesized outcomes of this meta-analysis was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool.[40] Outcomes are allocated an initial score based on study design, which can be downgraded or upgraded if certain criteria are met. The final score of an outcome item refers to a GRADE assessment ranging from very low quality to high quality.

Data synthesis and statistical analysis

HRs were combined using an indirect variance estimation.[41] A fixed-effects model was used because the methodologies were highly homogeneous (considering that all included studies have employed the GLIM framework to define malnutrition) and effects were not expected to substantially vary between studies. Heterogeneity among studies was evaluated using the tau-squared statistic, I^2 statistic, and Cochran Q test. The I^2 statistic values of 0%–25%, 26%–50%, 51%–75%, and >75% indicate insignificant, low, moderate, and high heterogeneity, respectively.[42] Publication bias was assessed graphically using a funnel plot.[43] Sensitivity analysis was conducted using a "leave-one-out" approach—namely, excluding one study at a time to observe whether the results could have been influenced markedly. Another sensitivity analysis was performed by stratifying studies with or without adjusting patient sex in multivariable Cox regression models. $P < 0.05$ was considered statistically significant. All analyses were performed using an open-source software, R (version 3.6.3, http://www.rproject.org), with the package meta.

RESULTS

Study selection

A flowchart of study selection and detailed reasons for exclusion is shown in Figure 1. A total of 4378 records were identified after the initial search. After the automated removal of 3896 duplicates, 482 records were screened by two independent researchers (LY and FC). After screening of abstracts and titles, agreement was reached and 395 records were removed because of their irrelevance to nutrition status and prognosis of patients. Subsequently, 87 full-text articles were thoroughly assessed for eligibility. A total of 78 articles were removed for the following reasons: 19 studies for having an irrelevant population (such as patients with chronic obstructive pulmonary disease, cirrhosis, renal failure, heart failure, COVID-19, or trauma), 27 studies for being a repeated publication, 9 studies because they only reported relative risk or odds ratio, 14 studies for having an irrelevant outcome, 7 studies for being a review or meta-analysis, and 2 studies for being a case report. After full-text review of the 87 articles, 9 remained for quantitative analysis. We also manually reviewed the references of the included studies, which yielded no extra inclusions. Study characteristics are shown in Table 1.

Overview of the included studies

All studies were published between 2019 and 2022 and were conducted in Asia (eight studies) or Oceania (one study). They included

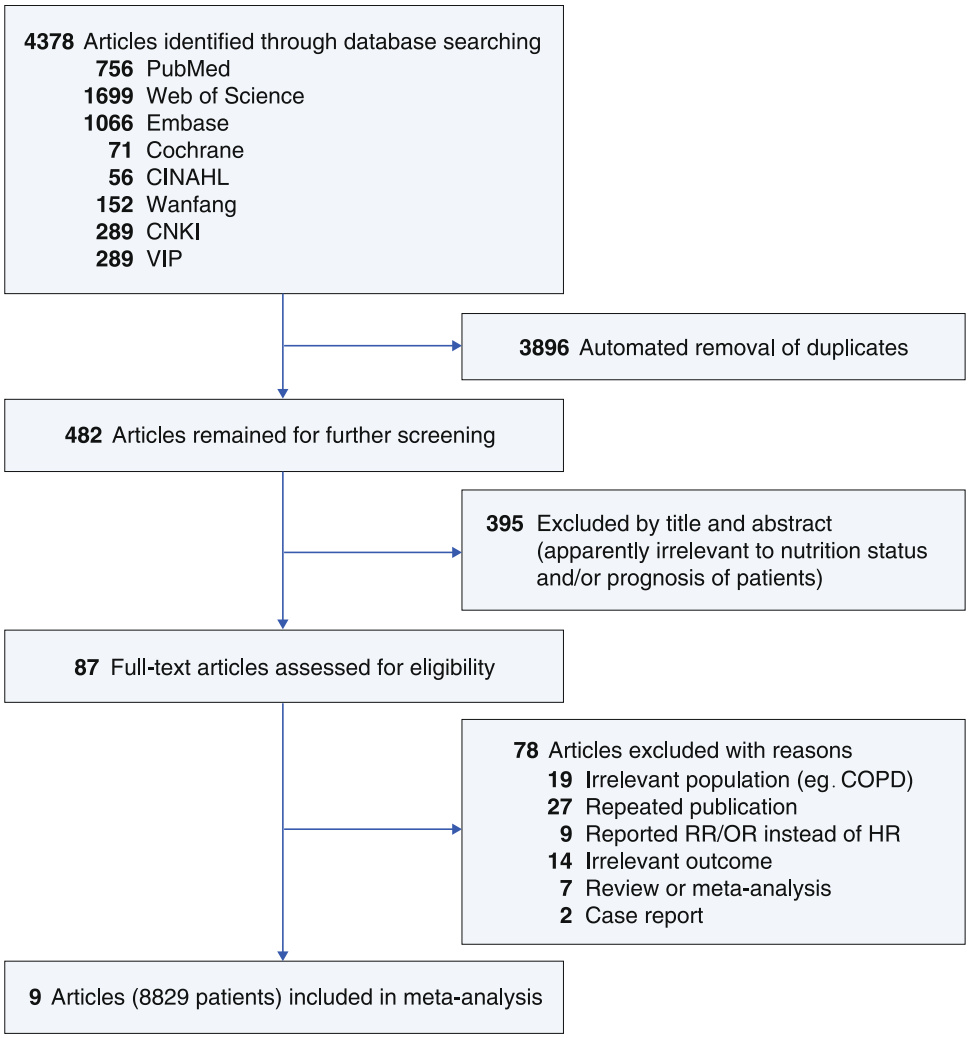

FIGURE 1 A flowchart of study selection. COPD, chronic obstructive pulmonary disease; HR, hazard ratio; OR, odds ratio; RR, relative risk

a total of 8829 patients with cancer who were observed for a range of 1–6 years. The mean or median age of patients ranged from 56.9 to 66 years. All included studies were of a retrospective nature,[21–25,29,30,35,36] and the GLIM diagnosis was retrospectively established using historical data. All studies were conducted in solid cancer,[21–25,29,30,35,36] including two comprising multiple cancers,[25,36] two esophageal cancer,[23,24] one nasopharyngeal cancer,[29] one colorectal cancer,[30] and three gastric cancer.[21,22,35] Regarding the muscle parameters for assessing muscle mass to establish the GLIM diagnosis, six studies used fat-free mass and/or skeletal muscle mass,[21–24,29,35] one study used calf circumference (CC),[36] one study used handgrip strength,[30] and one study did not assess muscle mass.[25] The length of patient follow-up ranged from 1 to 6 years. All studies used Cox regression models to analyze the associations between GLIM-diagnosed malnutrition and OS. One study reported univariate and multivariate associations of pooled and graded GLIM diagnosis with OS.[25] Two studies reported univariate and multivariate associations of pooled malnutrition with OS.[22,30] Three studies reported multivariate associations of graded malnutrition with OS.[24,35,36] Two studies reported univariate and multivariate associations of graded malnutrition with OS.[21,23] One study reported multivariate association of pooled malnutrition with OS.[29] The covariates were adjusted as confounders vary among the studies, as shown in Table 1. Eight studies were adjusted for age.[21,22,24,25,29,30,35,36] Five studies were further adjusted for sex and other clinical characteristics, such as cancer type, tumor stage, and anticancer treatment used.[22,24,25,29,36] Based on the availability of HRs as per the result type (univariate or multivariate) and diagnosis type (pooled malnutrition, moderate malnutrition, and severe malnutrition) in the included studies, six groups of studies were combined independently in subsequent meta-analyses: univariate-pooled, univariate-moderate, univariate-severe, multivariate-pooled, multivariate-moderate, and multivariate-severe.

Univariate: Moderate, severe, and pooled malnutrition and OS

The meta-analyses of the univariate associations of the GLIM-diagnosed malnutrition with OS are presented in Figure 2A–C. The

TABLE 1 Characteristics of the studies included for meta-analysis

First author	Year	Location	Study design	Sample size, *n*	Age,[a] years	Cancer type	Cancer stage	Cancer treatment	Follow-up, years	Muscle parameter	Malnutrition, *n* (%)	Adjusted factor
Groot[25]	2020	Australia	Retrospective	246	61.9	Multiple types	NR	Chemotherapy	1	Not assessed	77 (35)	Age, sex, BMI, cancer type
Okada[24]	2021	Japan	Retrospective	117	64	Esophageal cancer	0–IV	Multiple therapies	5	SMI	51 (43.6)	Age, sex, clinical stage, operative procedure
Yin[36]	2021	China	Retrospective	3998	56.9	Multiple types	I–IV	Multiple therapies	6	CC	1120 (28)	Age, sex, smoking, alcohol consumption, clinical stage, lymph node metastasis, radical resection, chemotherapy, nutrition support
Wan[29]	2022	China	Retrospective	113	NR	Nasopharyngeal cancer	II–IV	Multiple therapies	2	FFMI and ASMI	19 (16.8)	Age, sex, clinical stage, chemotherapy, the ECOG score
Huang[22]	2022	China	Retrospective	1359	66	Gastric cancer	I–III	Surgery	5	SMI	374 (27.5)	Age, sex, BMI, hypoproteinemia, anemia, the ASA grade, differentiation, tumor stage, surgery type, combined resection, laparoscopy-assisted surgery, type of reconstruction
Song[30]	2022	China	Retrospective	918	66	Colorectal cancer	I–III	Surgery	6	Handgrip strength	217 (23.6)	Age, BMI, handgrip strength, hypoalbuminemia, tumor stage, tumor differentiation grade
Xu[21]	2022	China	Retrospective	895	66	Gastric cancer	I–III	Surgery, adjuvant chemotherapy	5	SMI	343 (38.3)	Age, adjuvant chemotherapy
Wang[23]	2021	China	Retrospective	189	65.1	Esophageal cancer	0–IV	Surgery, adjuvant therapy	3	SMI	143 (75.7)	Karnofsky Performance Status score, tumor stage
Li[35]	2021	China	Retrospective	994	61	Gastric cancer	I–III	Surgery	5	SMI	312 (31.4)	Age, surgery, tumor stage

Abbreviations: ASA, American Society of Anesthesiologists; ASMI, appendicular skeletal muscle index; BMI, body mass index; CC, calf circumference; ECOG, Eastern Cooperative Oncology Group; FFMI, fat-free mass index; NR, not reported; SMI, skeletal muscle mass index.

[a]Mean or median as reported.

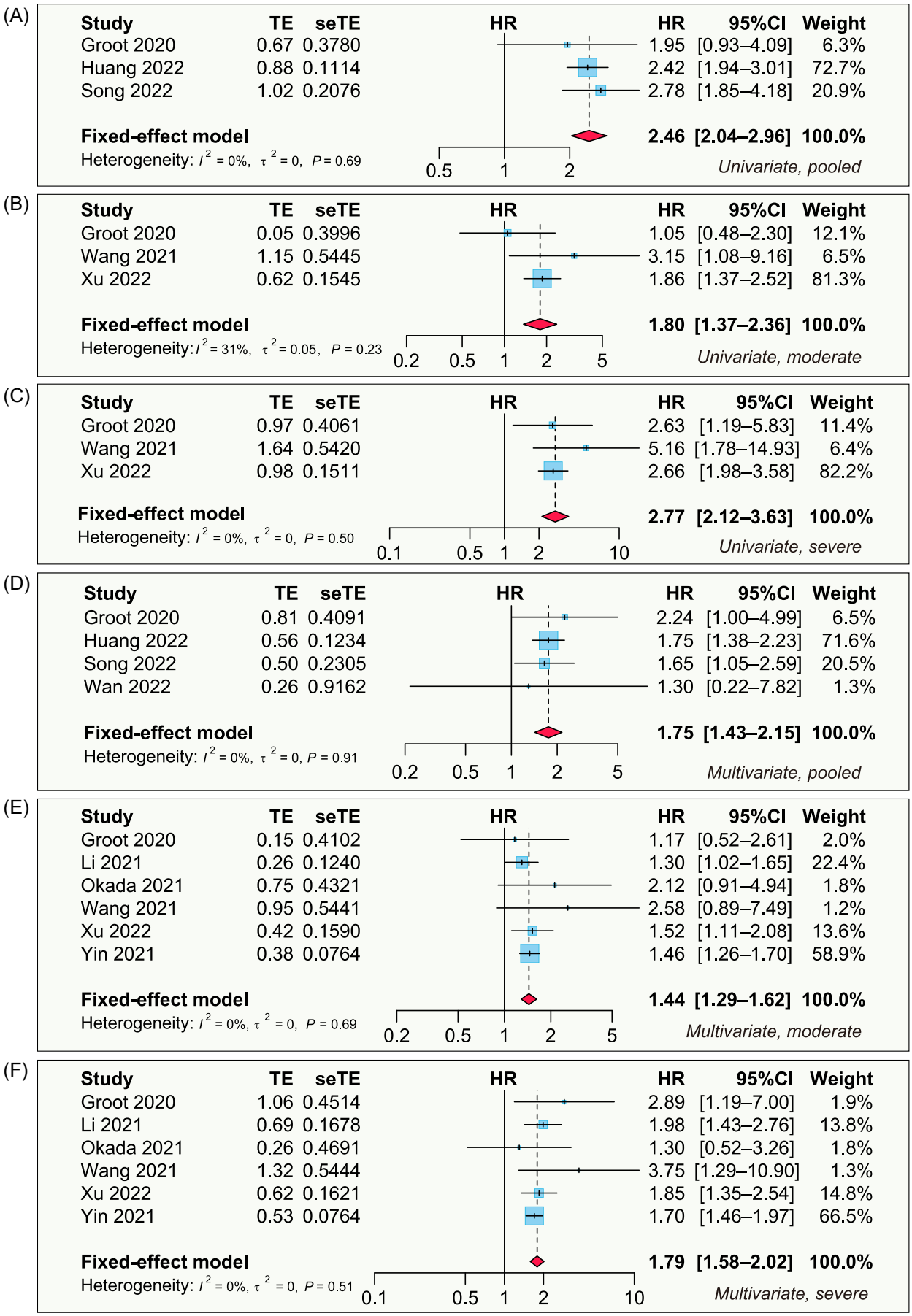

FIGURE 2 (See caption on next page)

overall effect of malnutrition on OS was significant (HR = 2.46; 95% CI, 2.04–2.96), as calculated by the fixed-effect model. The I^2 and tau-squared tests returned values of 0% and 0, respectively ($P = 0.69$), which indicates the methodological homogeneity between studies and supports the use of the fixed-effect model (Figure 2A). The overall effect of moderate malnutrition on OS was significant (HR = 1.80; 95% CI, 1.37–2.36) by the fixed-effect model. The I^2 and tau-squared statistics were 31% and 0, respectively ($P = 0.23$), indicating high homogeneity between studies (Figure 2B). Similarly, the overall effect of severe malnutrition on OS was significant (HR = 2.77; 95% CI, 2.12–3.63) by the fixed-effect model. The I^2 and tau-squared statistics were 0% and 0, respectively ($P = 0.50$, Figure 2C).

Multivariate: Moderate, severe, and pooled malnutrition and OS

The meta-analyses of the multivariate associations of the GLIM-diagnosed malnutrition with OS are presented in Figure 2D–F. The overall effect of pooled malnutrition on OS was significant (HR = 1.75; 95% CI, 1.43–2.15) by the fixed-effect model. The I^2 and tau-squared statistics were 0% and 0, respectively ($P = 0.91$, Figure 2D). The overall effect of moderate malnutrition on OS was also significant (HR = 1.44; 95% CI, 1.29–1.62) by the fixed-effect model. The I^2 and tau-squared statistics were 0% and 0, respectively ($P = 0.69$, Figure 2E). Similarly, the overall effect of severe malnutrition on OS was significant (HR = 1.79; 95% CI, 1.58–2.02) by the fixed-effect model. An I^2 of 0% and a tau-squared value of 0 ($P = 0.51$) indicated consistency.

Publication bias

The funnel plots in accordance with the six forest plots showed no obvious evidence of publication bias by visual assessment (Figure 3A–F). Because the number of included studies was <10 for all meta-analyses, a statistical test of the funnel plot asymmetry was not performed.

Sensitivity analysis

The results of the leave-one-out sensitivity analysis are shown in Figure 4. Among the six meta-analyses, only the univariate association between moderate malnutrition and OS became insignificant after omitting the meta-analysis by Xu et al. (HR = 1.55; 95% CI, 0.82–2.91). The other five meta-analyses were robust, and statistically significant effect modification was not observed in all sensitivity analyses (Figure 4A, C–F). For the three multivariate meta-analyses, we performed another type of sensitivity analysis by stratifying studies with or without adjusting sex in multivariable Cox regression models. The results consistently showed that the associations of pooled (Supporting Information: Figure S1A), moderate (Supporting Information: Figure S1B), and severe malnutrition (Supporting Information: Figure S1C) with OS were robust, and no significant effect modification was observed (tests for subgroup differences: $P = 0.76$, 0.73, and 0.30, respectively).

Quality assessment of included studies based on the NOS and GRADE assessment

Generally, the included studies were of apparently good quality, as indicated by the NOS scores. The mean (range) of the quality score was 6.9 (6–8). Most studies lost points mainly owing to a lack of description in the representativeness domain (representativeness: five studies; selection: one study; outcome not present: four studies; comparability: two studies; assessment of outcome: three studies, follow-up length: one study; adequacy of follow-up: three studies). More detailed scoring results are shown in Table 2. According to the GRADE rating, quality of the outcome was considered "very low" for the reliability of all associations. More details on the GRADE scoring are presented in Table 3, and the scoring criteria are shown in the corresponding footnotes. All associations were downgraded in the indirectness item. The reason for downgrading indirectness was because of the use of different approaches for assessing muscle mass to establish the GLIM diagnosis. The publication bias was not assessed, owing to the limited number of studies synthesized for each meta-analysis (<10).

DISCUSSION

Lacking a universally endorsed criteria to diagnose malnutrition in clinical settings has been a long-standing challenge to the nutrition society.[18] The GLIM framework was proposed to address this urgent need, and >200 studies have been conducted using the GLIM since its publication in 2019, indicating its huge potential for wide acceptance.[2,5,6,9,21-25,27-30,36,44,45] The present meta-analysis of 8829 patients suggests that GLIM-defined malnutrition is associated with increased all-cause mortality in the oncology population in both

FIGURE 2 Fixed-effect model forest plots in meta-analyses on the associations of the Global Leadership Initiative on Malnutrition (GLIM)–defined malnutrition and overall survival (OS) in cancer patients. (A) GLIM-defined malnutrition and OS, univariate. (B) GLIM-defined moderate malnutrition and OS, univariate. (C) GLIM-defined severe malnutrition and OS, univariate. (D) GLIM-defined malnutrition and OS, multivariate. (E) GLIM-defined moderate malnutrition and OS, multivariate. (F) GLIM-defined severe malnutrition and OS, multivariate. HR, hazard ratio; seTE, standard error of treatment effect (HR); TE, treatment effect (HR)

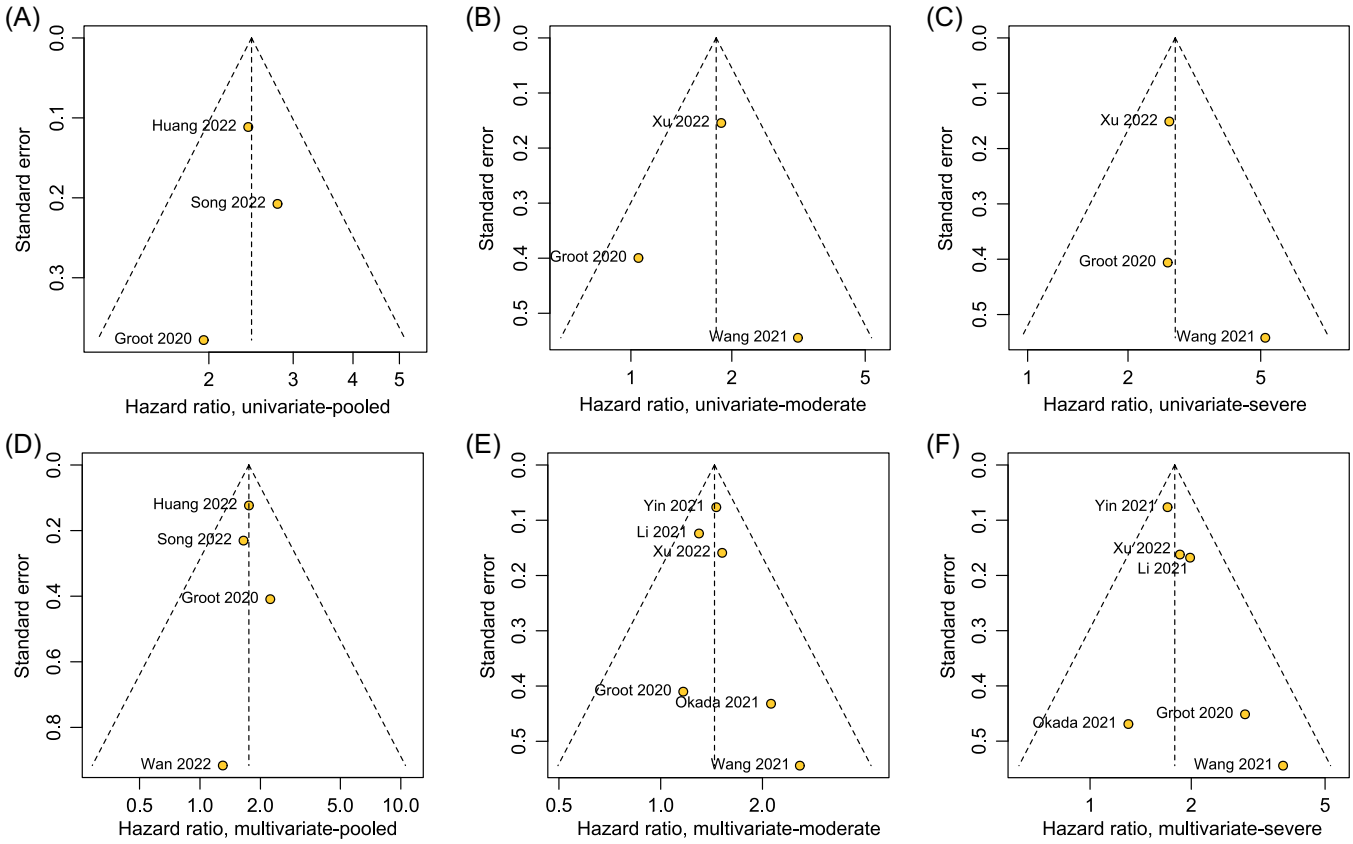

FIGURE 3 Funnel plots for publication bias on the associations of the Global Leadership Initiative on Malnutrition (GLIM)–defined malnutrition and overall survival (OS) in cancer patients. (A) GLIM-defined malnutrition and OS, univariate. (B) GLIM-defined moderate malnutrition and OS, univariate. (C) GLIM-defined severe malnutrition and OS, univariate. (D) GLIM-defined malnutrition and OS, multivariate. (E) GLIM-defined moderate malnutrition and OS, multivariate. (F) GLIM-defined severe malnutrition and OS, multivariate

univariate and multivariate analyses. The magnitude of the observed effect in this meta-analysis associated with pooled, moderate, and severe malnutrition was substantial, corresponding to a 75%, 44%, and 79% elevation, respectively, of death hazard in cancer patients. This may be the first meta-analysis to assess risk of all-cause mortality associated with GLIM-defined malnutrition in patients with cancer. The results of this meta-analysis thus provide quantitative support for clinical application of the GLIM framework in stratifying patients with different prognostic risks to help guide management strategies of patients. In addition, the results support the development of consensus guidelines that consider inclusion of the GLIM framework as a component of multidisciplinary cancer care.

The prevalence of malnutrition was 16.8%–75.7% in the included studies. This result was consistent with our previous studies showing that the prevalence of GLIM-defined malnutrition varied greatly across different cancer types.[2,5] The GLIM-defined malnutrition may have different prognostic roles in different cancer types. Among the nine studies included, Okada et al.[24] did not report a significant association between GLIM-defined malnutrition and mortality in patients with esophageal cancer. However, this was probably due to its small sample size (n = 117). In a previous study by us, we observed effect modifications on the associations between GLIM-defined malnutrition and different cancer types,[44] showing that the association between GLIM-defined malnutrition and OS was significant in lung cancer but not in colorectal cancer. Because of the limited cancer types included in the present study, more research in different malignancies is imperative to provide greater insights in this regard.

The assessment of muscle mass is an less straightforward phenotypic criterion under the GLIM framework.[46] Because different muscle parameters were used to indicate reduced muscle mass to establish the GLIM diagnosis (Table 1), the various approaches used for assessing reduced muscle mass might also influence the prevalence GLIM-defined malnutrition.[6] We have shown in our previous study that using CC plus handgrip strength rather than CC alone can lead to a risk of misdiagnosis of malnutrition under the GLIM framework.[36] However, similar to the cancer type, the impact of the various muscle mass assessment approaches on the OS was minimal.[36] Recently, the GLIM team recommended in its guideline to assess muscle mass using muscle indices or anthropometric measurements derived from dual-energy x-ray absorptiometry, computed tomography, or bioelectrical impedance analysis.[46] For the present study, seven of nine studies followed the recommendations from the GLIM team, using either fat-free mass index, skeletal muscle index, or anthropometric measurements to assess muscle mass, which should

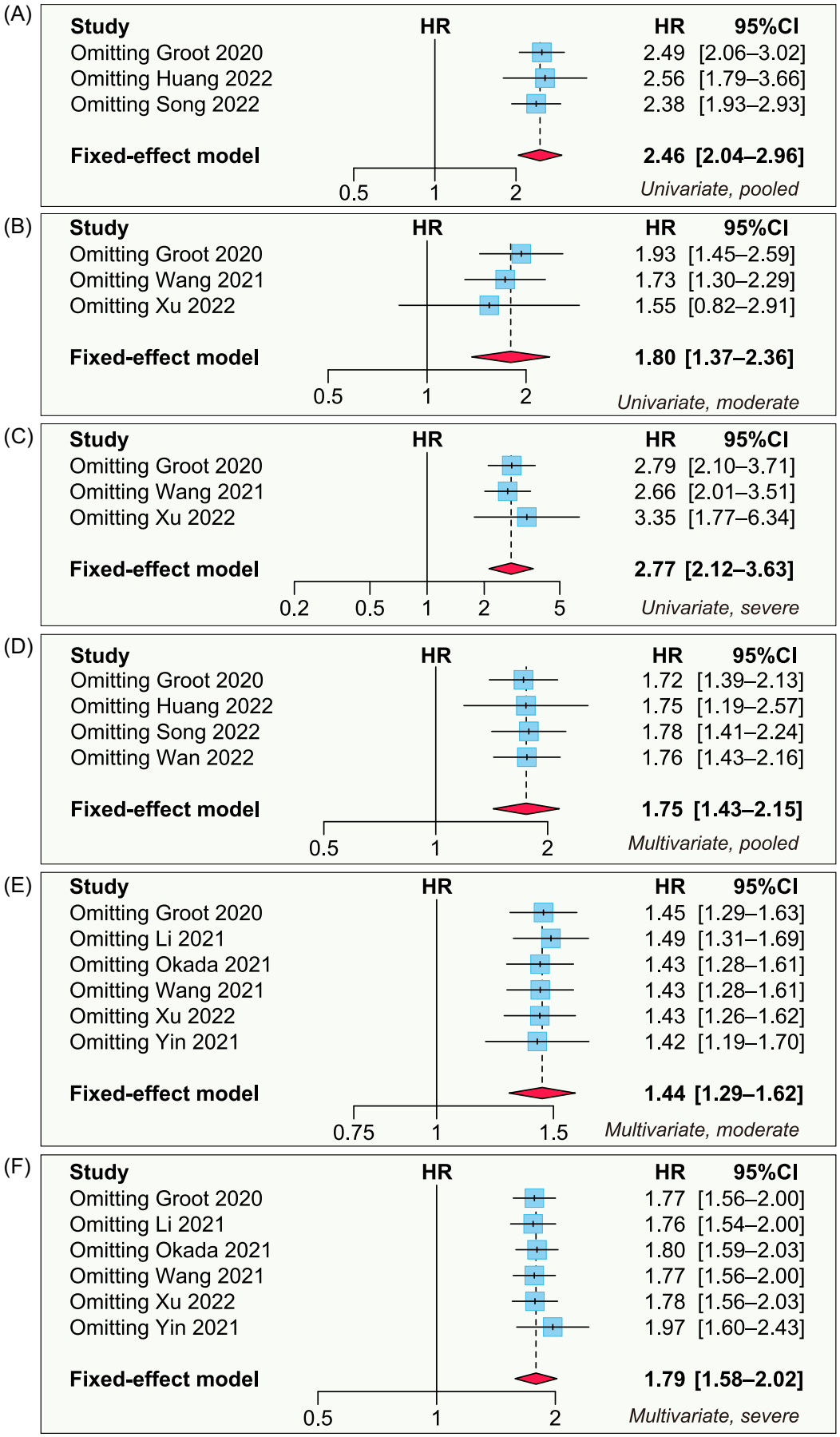

FIGURE 4 (See caption on next page)

TABLE 2 Quality assessment of selected studies using the Newcastle-Ottawa Scale

First author	Representativeness (0–1)	Selection (0–1)	Ascertainment (0–1)	Outcome not present (0–1)	Comparability (0–2)	Assessment of outcome (0–1)	Follow-up length (0–1)	Adequacy of follow-up (0–1)	Total
Groot[25]	1	1	1	1	2	0	1	0	7
Okada[24]	0	0	1	1	2	1	1	1	7
Yin[36]	1	1	1	1	2	1	0	1	8
Wan[29]	1	1	1	1	2	0	1	1	8
Huang[22]	1	1	1	1	2	0	1	0	7
Song[30]	0	1	1	0	1	1	1	1	6
Xu[21]	0	1	1	0	2	1	1	1	7
Wang[23]	0	1	1	0	1	1	1	1	6
Li[35]	0	1	1	0	2	1	1	0	6

support the accuracy of the overall malnutrition identified.[21-24,29,35,36] For the remaining two studies, Groot et al.[25] did not assess muscle mass, and Song et al.[30] used handgrip strength to assess muscle mass. Because handgrip strength is essentially an index reflecting muscle function, the GLIM team does not recommend it for assessing muscle mass independently.[46] Owing to the limited number of studies included, we were unable to perform subgroup analysis to evaluate the impact of different muscle assessment approaches on the synthesized results. However, all meta-analyses showed a low heterogeneity. Our previous study conducted in patients with lung cancer also showed that the GLIM diagnoses established using different combinations of muscle parameters had almost the same prognostic performance.[6] Nevertheless, it should be kept in mind that more accurate muscle parameters are recommended,[18,47] and anthropometric measurements sometimes can be an alternative approach to establish the GLIM diagnosis[9,45] in real-world clinical scenarios.

Most of the studies included for meta-analysis (eight of nine) were conducted in Asian populations.[21–24,29,30,35,36] Because of the limited number of non-Asian studies (only one), sensitivity analysis was not performed to evaluate the impact of ethnicity on the synthesized associations. However, all associations in the present study showed low heterogeneity (Figure 2). In addition, Kakavas et al.[33] and Contreras-Bolívar et al.[34] also reported positive independent associations between GLIM-defined malnutrition and cancer mortality in Western populations. Although the two studies were not included for meta-analysis because they only reported odds ratios and relative risks, their results might partially support the generalizability of our results in non-Asian populations. Nevertheless, the results should be interpreted with caution in non-Asian populations.

Consistent with our findings, a previous systematic review and meta-analysis also found the positive association of malnutrition, as defined by various assessment tools, with all-cause mortality in older patients with cancer.[48] Because the approaches for defining malnutrition in this meta-analysis were various, it has relatively high heterogeneity among different studies ($I^2 = 73.7\%$, $P < 0.01$). By contrast, we observed high homogeneity between studies in our meta-analyses. This was probably due to the unified GLIM criteria used to define malnutrition in the present study.

Although the heterogeneity of the meta-analyses in the present study was low (Figure 2A–F, all $I^2 < 50\%$ and $P > 0.05$), the I^2 (31%) of the model on the univariate association between moderate malnutrition and OS was apparently higher than that of other models (all $I^2 = 0$). A possible explanation for this phenomenon is that this study conducted by Groot et al.[25] had the shortest follow-up period (1 year) among all studies. Another possible explanation might be its limited sample size ($n = 246$), because this phenomenon disappeared when more studies were added in the multivariate meta-analysis (Figure 2E). Additionally, in the sensitivity analysis, the univariate association between GLIM-defined moderate malnutrition and OS (Figure 4B) was attenuated after omitting the study by Xu et al.[21] Because this omitted study had a relatively large sample size ($n = 895$), this effect modification was most likely attributed to the small sample size of the remaining two studies. Future studies with larger sample sizes are still needed to support the update of the present meta-analysis to address the above issues.

FIGURE 4 Forest plots of leave-one-out sensitivity analysis. (A) Global Leadership Initiative on Malnutrition (GLIM)–defined malnutrition and overall survival (OS), univariate. (B) GLIM-defined moderate malnutrition and OS, univariate. (C) GLIM-defined severe malnutrition and OS, univariate. (D) GLIM-defined malnutrition and OS, multivariate. (E) GLIM-defined moderate malnutrition and OS, multivariate. (F) GLIM-defined severe malnutrition and OS, multivariate. HR, hazard ratio

TABLE 3 GRADE score

			Certainty assessment									
Primary outcome	**Participants (studies)**	**Estimated effect size (95% CI)**	**Study design[a]**	**Risk of bias[b]**	**Inconsistency[c]**	**Indirectness[d]**	**Imprecision[e]**	**Publication bias[f]**	**Large effect**	**Plausible confounding**	**Dose response gradient**	**GRADE assessment**
Univariate												
OS, pooled	2523 (3)	2.43 (2.19–2.70)	++	0	0	−1	0	NA	0	0	0	Very low (+)
OS, moderate	1254 (3)	1.80 (1.37–2.36)	++	0	0	−1	0	NA	0	0	0	Very low (+)
OS, severe	1254 (3)	2.77 (2.12–3.63)	++	0	0	−1	0	NA	0	0	0	Very low (+)
Multivariate												
OS, pooled	2523 (3)	1.76 (1.43–2.16)	++	0	0	−1	0	NA	0	0	0	Very low (+)
OS, moderate	6363 (6)	1.44 (1.29–1.62)	++	0	0	−1	0	NA	0	0	0	Very low (+)
OS, severe	6363 (6)	1.79 (1.58–2.02)	++	0	0	−1	0	NA	0	0	0	Very low (+)

Note: 0, no serious limitation; −1, serious limitation; −2, very serious limitation. Outcome: +, very low; ++, low; +++, moderate; ++++, high.

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; NA, not applicable; OS, overall survival.

[a]Because all included studies were observational, each outcome starts with a low score of 2 points (++).

[b]Risk of bias was assessed with the Newcastle-Ottawa Scale.

[c]Inconsistency was defined by $I^2 \geq 65\%$ and $P < 0.10$ and by 95% CI and estimate points of effect found on both sides of null line.

[d]Indirectness was defined by the correspondence of the population of interest to the population included for analysis.

[e]Imprecision was defined by insufficient sample size and very wide CIs, crossing the null in ≥50% cases.

[f]Number of included studies was too low (<10 studies) for assessment of publication bias.

There are some limitations associated with this study. First, we may have overlooked some studies published in journals that are not indexed in the selected databases. Nevertheless, although the number of studies was limited, we did not observe significant publication bias that might have affected our findings. Second, despite the increasing popularity of the GLIM, there is no globally accepted standard to define malnutrition. The findings we gathered based on the GLIM framework may not be generalizable in settings using other tools for nutrition assessment. Third, the combined multivariate HRs we estimated from the selected studies were adjusted with different covariates, as shown in Table 1, which may have reduced the compatibility of the studies. Furthermore, because of the observational nature of the present study, large-scale randomized studies with intervention are needed to evaluate whether reducing the prevalence of malnutrition, as defined by the GLIM, in patients with cancer would reduce their death hazard. Finally, because of the limited number of studies that were included for data synthesis, a future update of the present study with more relevant literature is anticipated.

In conclusion, this meta-analysis suggests the adverse impact of GLIM-defined malnutrition on OS in patients with cancer. Assessment of malnutrition using the GLIM in cancer patients can provide important prognostic information to guide nutrition intervention and/or management strategies. The associations of malnutrition with OS were robust, and future studies are needed to provide more insights into these associations in diverse patient groups, such as those with different ethnicities or cancer types. Importantly, interventional studies are imperative to translate these findings into clinical evidence that can directly improve the survival outcomes of cancer patients.

AUTHOR CONTRIBUTIONS

Liangyu Yin, Feifei Chong, and Hongxia Xu designed the study. Liangyu Yin and Feifei Chong collected, analyzed, and interpreted the data. Zhenyu Huo, Na Li, and Jie Liu analyzed the data. Liangyu Yin drafted the manuscript. Feifei Chong and Hongxia Xu critically revised the manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

None declared.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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