Association between patient-generated subjective global assessment and survival outcomes in patients with cancer: a systematic review and meta-analysis

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Running title: Poor overall survival correlated with PG-SGA

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ABSTRACT

Background and Objectives: Undernutrition is prevalent among patients with cancer and may be associated with survival. The Patient-Generated Subjective Global Assessment (PG-SGA) is a widely recognised scale for the nutritional assessment of patients with cancer. The relationship between undernutrition, as defined by the PG-SGA, and cancer prognosis has been somewhat controversial, and this meta-analysis sought to clarify this. This meta-analysis was performed to elucidate the association between undernutrition, as defined by the PG-SGA, and survival outcomes in patients with cancer. **Methods and Study Design:** Studies that investigated the association between undernutrition, defined by the PG-SGA, and survival outcomes in patients with cancer were included, and data were retrieved from PubMed, EMBASE, the Cochrane Library, and Web of Science until October 2023. **Results:** A total of 18 prospective and 14 retrospective studies with 27120 cancer patients were identified in this analysis. All studies had high methodological quality, with an average score of 7.66. The results showed that undernutrition, as defined by the PG-SGA, was significantly correlated with worse overall survival (Hazard Ratio (HR)=1.99, 95% Confidence Interval (CI): 1.62-2.45). Subgroup analyses further confirmed that the pooled HR was 1.64 (95% CI: 1.26-2.13) for moderate undernutrition, which increased gradually in cases of severe undernutrition (HR = 2.65, 95% CI: 2.45-2.87). The degree of undernutrition might be the source of the heterogeneity (p value for the test of subgroup differences was < 0.001). Sensitivity analyses confirmed the robustness and credibility of this meta-analysis. **Conclusions:** These results underscore the significant association between undernutrition, as defined by the PG-SGA, and reduced overall survival in patients with cancer. Detection of nutritional status using the PG-SGA may be beneficial for improving survival in patients with cancer.

Key Words: cancer, PG-SGA, undernutrition, survival, meta-analysis

INTRODUCTION

Cancer remains a significant public health challenge globally, marked by its rising incidence and mortality rates. According to GLOBOCAN 2020, an estimated 19.3 million new cancer cases and nearly 10.0 million cancer-related deaths were reported worldwide in 2020.[1, 2] Female breast, lung, colorectal, prostate, and stomach cancers were the most commonly diagnosed cancers.[2] Despite advances in cancer treatments, the prognosis for many patients remains unfavourable. Undernutrition, a complication resulting from cancer itself and its

treatments, can result in several negative consequences, such as decreased survival, reduced treatment tolerance and compliance, and diminished response to antineoplastic drugs.[3] Undernutrition is prevalent in patients with cancer, with studies reporting that between 4% and 87% of them experience undernutrition,[4, 5] therefore, early detection and active treatment of undernutrition are important for the treatment and prognosis of patients with cancer.

The PG-SGA, a modification of the original SGA, offers a subjective method that has been developed and validated for assessing undernutrition in cancer patients.[6-8] Its scope of evaluation includes multiple critical domains, including weight fluctuations, dietary intake patterns, presence and severity of clinical symptoms, level of physical activity, the relationship between the disease and nutritional requirements, metabolic state, and findings from physical examination. Undernutrition, as defined by the PG-SGA, has been associated with worse overall survival in patients with some types of cancer and cachexia.[9, 10] However, existing research findings on hepatocellular carcinoma (HCC) and nasopharyngeal carcinoma (NPC) differ from this, and such an association has not been observed.[11-13] Moreover, for patients with colorectal cancer, head and neck cancer, and gynaecologic cancer, severe undernutrition, rather than moderate undernutrition, was associated with a worse prognosis.[14-16] As such, the relationship between undernutrition, as defined by the PG-SGA, and cancer prognosis has not been entirely consistent. To address this controversy, the present study employed a meta-analysis to elucidate the association between undernutrition, as defined by the PG-SGA, and survival outcomes in patients with cancer.

MATERIALS AND METHODS

Publication search

Eligible publications were identified by searching PubMed, EMBASE, the Cochrane Library, and Web of Science up to October 2023. The search strategy used the following keywords: “patient generated subjective global assessment”, “PG-SGA”, “cancer”, “carcinoma”, “tumour”, “survival”, “mortality”, and “death”. Literature searches were conducted independently by two investigators. We obtained data by screening the titles and abstracts, and examined the full text. Reference lists were searched for additional relevant publications. No language restrictions were applied. Literature selection followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, as illustrated in Figure 1.

Inclusion and exclusion criteria

Studies were eligible if they satisfied the following conditions: (1) observational studies; (2) PG-SGA was used as a nutrition screening tool; (3) the primary outcome was death or survival; and (4) availability of HR with a corresponding 95% CI. Articles were excluded if they satisfied the following criteria: (1) non-human experiments; (2) reviews, editorials, letters, or conference abstracts; (3) follow-up duration < 3 months; (4) duplicate studies; and (5) incomplete data or data that could not be extracted.

Data extraction

For the included studies, the following basic information and characteristic data were recorded: author, year of publication, country, study design, cancer type, sample size, age and sex distribution, PG-SGA scores, follow-up duration, overall survival, progression-free survival, complication-free survival, event-free survival, quantity, HR with 95% CI, and adjusted variables. Data were independently extracted by two investigators.

Literature quality assessment

The Newcastle-Ottawa Quality Assessment Scale was used to estimate study quality. There were nine questions in total, and 1 point represented a satisfactory answer. The maximum score was 9. Scores of 6 or more indicated that the study had high methodological quality.

Statistical analysis

Depending on the heterogeneity, either fixed-effects or random-effects models were used to calculate the HR and 95% CI. Heterogeneity was assessed using the I^2 statistic (I^2 < 50% indicated acceptable heterogeneity), and a fixed effect-model was used when I^2 < 50%; otherwise, a random-effect model was applied. Sensitivity analysis was performed by sequentially deleting each study to determine the stability and reliability of the results. Subgroup and meta-regression analyses were conducted based on study design, cancer type, location, sample size, age, follow-up time, and degree of undernutrition to investigate heterogeneity sources, and differences between groups were assessed using an interaction test with a predetermined two-tailed α of 0.05.17 Egger's and Begg's tests were used to estimate publication bias (p < 0.05 indicated potential bias), and the impact of publication bias on the pooled risk estimate was investigated using trim-and-fill analysis. All statistical analyses were performed using Stata 12.0 software.

RESULTS

Characteristics of studies for meta-analysis

Thirty-two studies[9-16, 18-41] reported the relationship between undernutrition, as defined by the PG-SGA, and cancer survival; the characteristics of each study are shown in Supplementary Table 1. These studies, published between 2009 and 2023, comprised 18 prospective and 14 retrospective studies. Geographically, they included seventeen studies from Asia, seven from South America, four from Oceania, two from Europe, one from Africa and one from North America. The cancer types varied, with seven studies covering all cancer types, nine focusing on gastrointestinal cancers, and the others examining gynaecologic cancer, hepatocellular carcinoma, ampullary carcinoma, leukaemia, multiple myeloma, head and neck cancer, cachexia, pancreatic cancer, nasopharyngeal carcinoma, non-Hodgkin's lymphoma, and lung cancer. The sample size ranged from 41 to 8749, and a total of 27120 cancer cases were enrolled in this study. Among the 32 studies, the mean quality score was 7.66, indicating high methodological quality (Table 1).

Overall survival

All studies investigated the relationship between undernutrition, as defined by the PG-SGA, and overall survival in patients with cancer. As shown in Figure 2, undernutrition defined by the PG-SGA was associated with poor overall survival (HR = 1.99, 95% CI: 1.62-2.45) using a random-effects model, which showed high heterogeneity (I^2 = 94.8%, $p < 0.05$). Leave-one-out sensitivity analyses suggested that no significant change occurred, regardless of which study was excluded, using the random-effects model (Figure 3). To explore the source of heterogeneity, we performed subgroup analyses, and the results are shown in Table 2. The findings indicated that PG-SGA was effective in predicting poor overall survival in all examined subgroups. Significant subgroup differences were observed when stratified by the degree of undernutrition, that may be the source of heterogeneity (*p*-value for the test of subgroup differences was < 0.001). Meanwhile, the meta-regression analysis showed similar results. As presented in Table 3, the p-values for covariates such as study design, cancer type, location, sample size, age, and follow-up time were 0.802, 0.725, 0.788, 0.621, 0.353, and 0.521, respectively, but 0.035 for the degree of undernutrition. These results confirm the degree of undernutrition may be significantly associated with between-study heterogeneity.

Progression-free survival, complication-free survival, and event-free survival.

Regarding progression-free survival, undernutrition (PG-SGA ≥ 9) in patients with colorectal cancer showed no significant association after adjusting for covariates (HR = 1.50,

95% CI: 0.80-2.60). For patients with hepatocellular carcinoma, a prospective cohort study showed that baseline PG-SGA score did not correlate with complication-free survival (HR = 1.35, 95% CI: 0.55-3.33). Similarly, in patients with leukaemia, a PG-SGA score ≥9 did not predict poor event-free survival (HR = 1.24, 95% CI: 0.52-2.96).

Publication bias

To evaluate publication bias in the studies exploring the relationship between PG-SGA and overall survival, Egger's and Begg's tests were conducted. The result of Egger's test ($p < 0.001$), but not Begg's test ($p = 0.709$), indicated a potential publication bias. Furthermore, we employed a trim-and-fill analysis. The pooled HR for overall survival was 1.99 (95% CI: 1.62-2.45) after supplementing four possible missing studies using the random-effects model. The funnel plot is presented in Figure 4.

DISCUSSION

In this analysis, we collected 32 studies, involving 27120 cancer patients with cancer to explore the association between undernutrition, as defined by the PG-SGA, and survival outcomes in patients with cancer. Our meta-analysis indicated that undernutrition, as defined by the PG-SGA, was associated with poorer overall survival in patients with cancer, and patients with PG-SGA-defined undernutrition had a 99% increase in the risk of reduced overall survival. Furthermore, the value of the PG-SGA in predicting poor overall survival was consistently found in each subgroup, regardless of study design, cancer type, location, sample size, age, degree of undernutrition, and follow-up duration. Additionally, heterogeneity testing in this study found that the degree of undernutrition may be the source of heterogeneity, and the HR for severe malnutrition was greater (severe malnutrition: HR=2.65 and moderate malnutrition: HR=1.64). The reason for this may be that severely malnourished cancer patients have more impaired immune function, an increased risk of complications, and reduced tolerance to anti-cancer therapy.[10, 42, 43]

The relationship between undernutrition and survival of patients with cancer has also been explored in other meta-analyses. A meta-analysis involving older adults with cancer indicated that undernutrition, defined by the Prognostic Nutritional Index (PNI), was associated with poor overall survival (HR = 1.89, 95% CI: 1.03-3.48).[44] Another meta-analysis included eight studies and 3239 colorectal cancer patients, showing that when comparing the low with the high Geriatric Nutritional Risk Index (GNRI) group, the pooled HR was 2.40 for overall survival and 1.63 for disease-free survival.[45] A systematic review and meta-analysis in 2022

demonstrated that undernutrition, defined by the Global Leadership Initiative on Malnutrition (GLIM), was an independent prognostic factor for overall survival (HR = 1.90, 95% CI: 1.58-2.29) and disease-free survival (HR = 1.51, 95% CI: 1.27-1.79) in patients with cancer.[46] Despite these findings, our meta-analysis, using the PG-SGA as the assessment tool for undernutrition, emphasises that undernutrition was associated with overall survival (HR = 1.99, 95% CI: 1.62-2.45), but not with progression-free survival (HR = 1.50, 95% CI: 0.80-2.60), complication-free survival (HR = 1.35, 95% CI: 0.55-3.33), and event-free survival (HR = 1.24, 95% CI: 0.52-2.96). When compared with the PNI (calculated from serum albumin and total lymphocytes), GNRI (calculated from serum albumin, height, and body weight), and GLIM (derived from a measurement scale), the PG-SGA is a comprehensive index to evaluate nutritional status, which was adapted by Ottery specifically for cancer patients.[7] The PG-SGA includes a comprehensive assessment based on patient-provided information on weight, food intake, nutrition-related symptoms, activity, and physical function components, as well as a clinician-provided evaluation of the relationship between disease and nutritional requirements, metabolic needs, and physical indicators (including fat stores, muscle status and fluid status), which were derived from physical examination findings. Although it is not standardised, the PG-SGA is a widely accepted tool for the nutritional assessment of oncology patients. When compared with other screening tools such as Nutritional Risk Screening 2002, Mini Nutritional Assessment, Malnutrition Universal Screening Tool, or SGA, the PG-SGA has demonstrated the best diagnostic performance for assessing the nutritional status of patients with cancer.[47, 48] GLIM is a newer tool for nutritional diagnosis and has also shown a good predictive value for the prognosis of patients with cancer. However, muscle mass loss, one of its diagnostic indicators, while measurable using validated body composition techniques such as dual-energy X-ray absorptiometry, bioelectrical impedance analysis (BIA), computed tomography (CT), magnetic resonance imaging (MRI), hand-grip strength (HGS) and others, still lacks a universally accepted measurement standard.[49, 50] Therefore, the PG-SGA remains the more widely recommended scale for the nutritional assessment of cancer patients.

Although this meta-analysis showed that undernutrition defined by the PG-SGA was associated with overall survival, fewer studies were available for pooling data on progression-free survival, complication-free survival, and event-free survival. However, the original studies also indicated that PG-SGA-defined undernutrition was not significantly associated with these outcomes.[11, 23, 27] Event-free survival tended to be poorer in patients with acute leukaemia and severe undernutrition, although this was not statistically significant.[27]

Regarding progression-free survival, while undernutrition was not directly related, patients with decreased skeletal muscle index experienced shorter progression-free survival in metastatic colorectal cancer.[51] Reduced HGS was significantly associated with complication-free survival in hepatocellular carcinoma.[11] Since the reduction of skeletal muscle and HGS are key components of GLIM,[52] ongoing attention to the nutritional status of oncology patients remain essential.

Regarding the association between PG-SGA-defined malnutrition and overall survival across different cancer types, although no statistical heterogeneity was detected in the present study, as stated in the introduction, most studies on certain tumors (e.g. lung and colorectal cancers) have consistently shown a strong correlation between PG-SGA-defined malnutrition and poor overall survival. However, such an association remains elusive in HCC and NPC.[11-14, 22] In this study, we included one HCC and two NPC studies,11-13 with results showing a HR of 1.04 (95% CI: 0.38-2.86) for the HCC and a pooled HR of 1.46 (95% CI: 1.05-2.03) for NPC(pooled NPC results are presented in Supplementary Figure 1). These findings suggest that PG-SGA-defined malnutrition may be associated with overall survival in NPC patients, but not in HCC patients. In the HCC cohort, the original prospective study enrolled 56 patients, and the results revealed that only baseline HGS decline and Child-Pugh score deterioration were independently associated with shortened overall survival, whereas PG-SGA was solely correlated with impaired quality of life11. This discrepancy may be explained by the dominant role of muscle reserve and liver function in determining HCC prognosis, whereas PG-SGA is more sensitive to short-term quality of life changes than to long-term survival. Additionally, the potential for type II error due to the limited sample size (n = 56) and treatment heterogeneity warrants further validation in larger cohorts. The two included studies on NPC both demonstrated no association between PG-SGA-defined malnutrition and overall survival prior to data pooling; however, a correlation was observed after pooling, which may be related to the large sample sizes of the two studies (923 and 1365 cases, respectively). This finding is consistent with the conclusion from univariate analysis in NPC, where PG-SGA was associated with overall survival, whereas this association was attenuated in multivariate analysis, suggesting that NPC prognosis may be regulated by multiple factors. As noted in some studies, NPC is highly sensitive to chemoradiotherapy, and its survival outcomes are significantly influenced by treatment response (e.g. Epstein Barr virus-DNA clearance rate) and clinical staging.[53, 54] Therefore, the relationship between PG-SGA and tumour prognosis remains inconsistent, particularly showing significant differences

among various tumor types. Further high-quality studies with rigorous designs and sufficient sample sizes are required for further exploration.

In addition to the negative impact of PG-SGA-defined undernutrition on survival outcomes, undernutrition, as defined by the PG-SGA, also predicts clinical outcomes such as postoperative complications, length of hospital stay, and quality of life.[8, 55, 56] In clinical settings, the PG-SGA is a valuable tool for assessing the nutritional status of patients with cancer not only in the preoperative and postoperative periods, but also during rehabilitation. Its sensitivity to changes in patients' nutritional status over time is excellent, particularly following nutritional interventions.[59] Cancer patients should be regularly screened for undernutrition, and nutritional interventions should be provided in a timely manner to those affected.[60, 61]

Some limitations of this meta-analysis should be addressed. First, the inclusion of retrospective studies may have introduced a selection bias. Second, heterogeneity was observed in the pooled analysis of overall survival. Although this study suggests that the degree of undernutrition may contribute to heterogeneity, other factors, such as the type and stage of malignancy and variability in the criteria used to define undernutrition, may also exert an influence. Third, the Begg's test indicated the presence of publication bias. Publication bias stems from the tendency of researchers and editors to favour positive results. Thus, studies showing favourable outcomes are more likely to be published than those with neutral or negative findings, potentially leading to an overestimation of associations. However, we applied a trim-and-fill analysis, and undernutrition, as defined by the PG-SGA, remains strongly associated with overall survival.

Conclusions

This meta-analysis concludes that undernutrition, as defined by the PG-SGA, is significantly associated with worse overall survival in patients with cancer. Assessing nutritional status using the PG-SGA has the potential to improve the survival of patients with cancer.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare no conflict of interest.

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Table 1. Quality evaluation of all included studies

Studies	Selection				Comparability		Outcome			Score
	1	2	3	4	5A	5B	6	7	8	
Terefe et al. 2021	*	*	*	*	*	*	*	*	*	9
Katia et al. 2017	*	*	*	*	*	*	*	*	*	9
Derya et al. 2019	*	*	*	*	*	*	*	*		8
Kelcey et al. 2020	*	*	*		*	*	*	*		7
Lynette et al. 2020	*	*	*		*	*	*	*		7
Iasmin et al. 2021	*	*	*	*	*	*	*	*		8
Ding et al. 2021	*	*	*		*	*	*	*		7
Feng et al. 2022	*	*	*		*	*	*	*		7
Merran et al. 2021	*	*	*		*	*	*	*		7
Claire et al. 2019	*	*	*	*	*	*	*	*		8
Hsieh et al. 2016	*	*	*		*	*	*	*		7
Jin et al. 2021	*	*	*		*	*	*	*		7
Kim et al. 2017	*	*	*		*	*	*	*		7
Li et al. 2018	*	*	*		*	*	*	*		7
Zeinab et al. 2022	*	*	*	*	*	*	*	*		8
Rodrigues et al. 2015	*	*	*	*	*	*	*	*		8
Ruan et al. 2022	*	*	*		*	*	*	*		7
Marcela et al. 2018	*	*	*	*	*	*	*	*		8
Cindy et al. 2015	*	*	*	*	*	*	*	*		8
Dijk et al. 2022	*	*	*	*	*	*	*	*		8
Geldern et al. 2020	*	*	*	*	*	*	*	*		8
Wang et al. 2021	*	*	*		*	*	*	*	*	8
Zhang et al. 2021	*	*	*	*	*	*	*	*	*	9
Zhang et al. 2022	*	*	*		*	*	*	*		7
Balci et al. 2023	*	*	*	*			*	*	*	7
Couto et al. 2023	*	*	*		*	*	*	*	*	8
Fruchtenicht et al. 2018	*	*	*	*	*	*	*	*		8
Ge et al. 2019	*	*	*		*	*	*	*		7
Huo et al. 2023	*	*	*	*	*	*	*	*	*	9
Jia et al. 2023	*	*	*	*	*	*	*	*		8
Kubrak et al. 2009	*	*	*	*			*	*		6
Zou et al. 2022	*	*	*	*	*	*	*	*		8

√, The project was taken on that day.

Table 2. Results of subgroup analysis on the effect of PG-SGA on overall survival

Subgroup	No. of studies	Pooled HR	95% CI	Heterogeneity		*p*-value between subgroups
				I^2(%)	*p*	
Study design						0.951
Prospective	18	1.95	1.61-2.38	73.7	<0.001	
Retrospective	14	1.97	1.52-2.54	91.6	<0.001	
Cancer types						0.476
Gastrointestinal cancers	9	1.82	1.48-2.22	45.9	0.063	
Others	23	2.05	1.59-2.66	96.0	<0.001	
Location						0.637
Asia	17	1.89	1.58-2.27	81.7	<0.001	
Others	15	2.06	1.51-2.80	87.1	<0.001	
Sample size						0.883
<200 cases	12	2.00	1.61-2.49	27.2	0.177	
≥200 cases	20	1.95	1.51-2.52	96.6	<0.001	
Median/Mean age						0.219
<60 years	10	1.64	1.33-2.01	45.2	0.059	
≥60 years	16	2.01	1.57-2.59	88.9	<0.001	
Degree of undernutrition						<0.001
Moderate	6	1.64	1.26-2.13	53.1	0.058	
severe	12	2.65	2.45-2.87	52.0	0.015	
Median/Mean follow-up time						0.713
<20 months	14	1.97	1.61-2.41	52.1	0.012	
≥20 months	13	1.83	1.31-2.57	97.5	<0.001	

PG-SGA: Patient-Generated Subjective Global Assessment, HR: Hazard ratio, CI: Confidence interval.

Table 3. Meta-regression analysis of the effect of PG-SGA on overall survival

Covariates	β	SE	*t*	*p*	95%CI	Tau^2	Adjusted R^2(%)
Study design	0.96	0.14	-0.25	0.802	0.72-1.28	0.09	-3.23
Cancer types	1.06	1.17	0.36	0.725	0.77-1.45	0.09	-5.54
Location	1.04	0.15	0.27	0.788	0.78-1.39	0.09	-5.90
Sample size	0.92	0.15	-0.50	0.621	0.67-1.28	0.09	-2.54
Median/Mean age	1.17	0.19	0.95	0.353	0.83-1.63	0.09	-4.46
Degree of undernutrition	1.62	0.34	2.29	0.035	1.04-2.53	0.06	15.86
Median/Mean follow-up time	0.90	0.14	-0.65	0.521	0.66-1.25	0.09	-5.02

β: regression coefficient, SE: standard error, CI: confidence interval, Tau2: between-study variance, Adjusted R2 (%): percentage of heterogeneity explained by each covariate

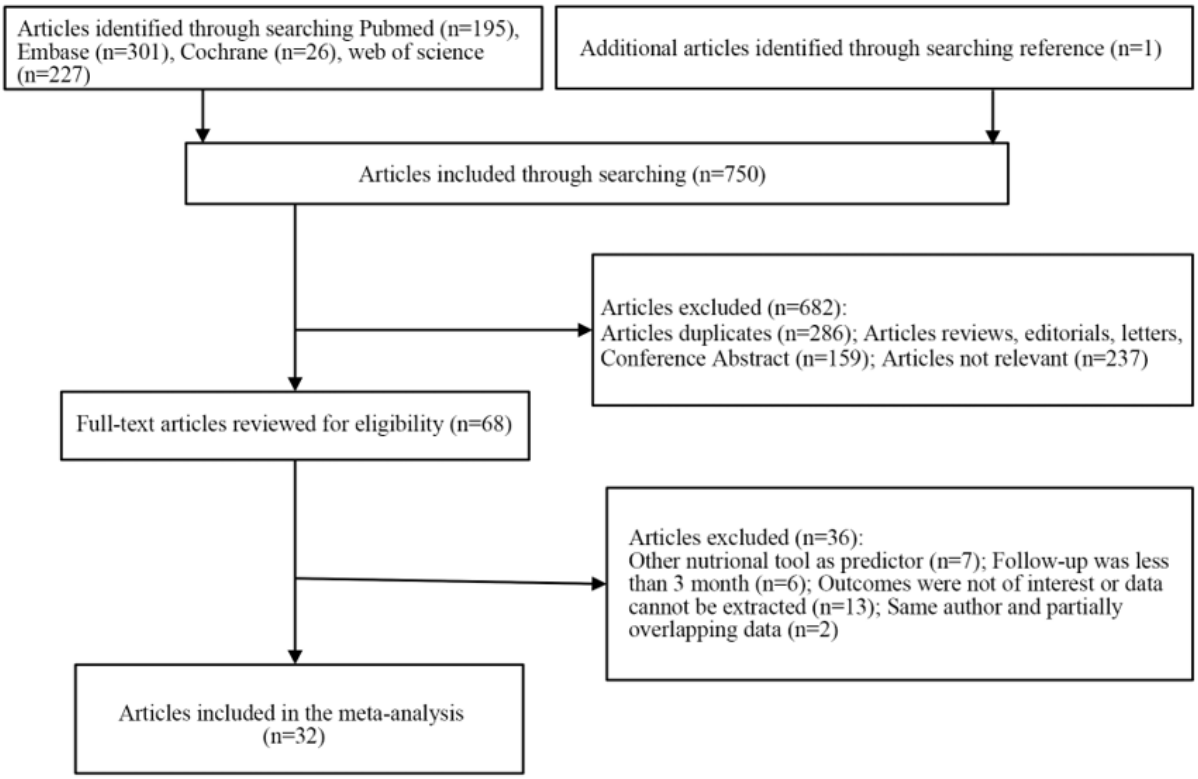

Figure 1. Flow diagram of literature selection for the meta-analysis.

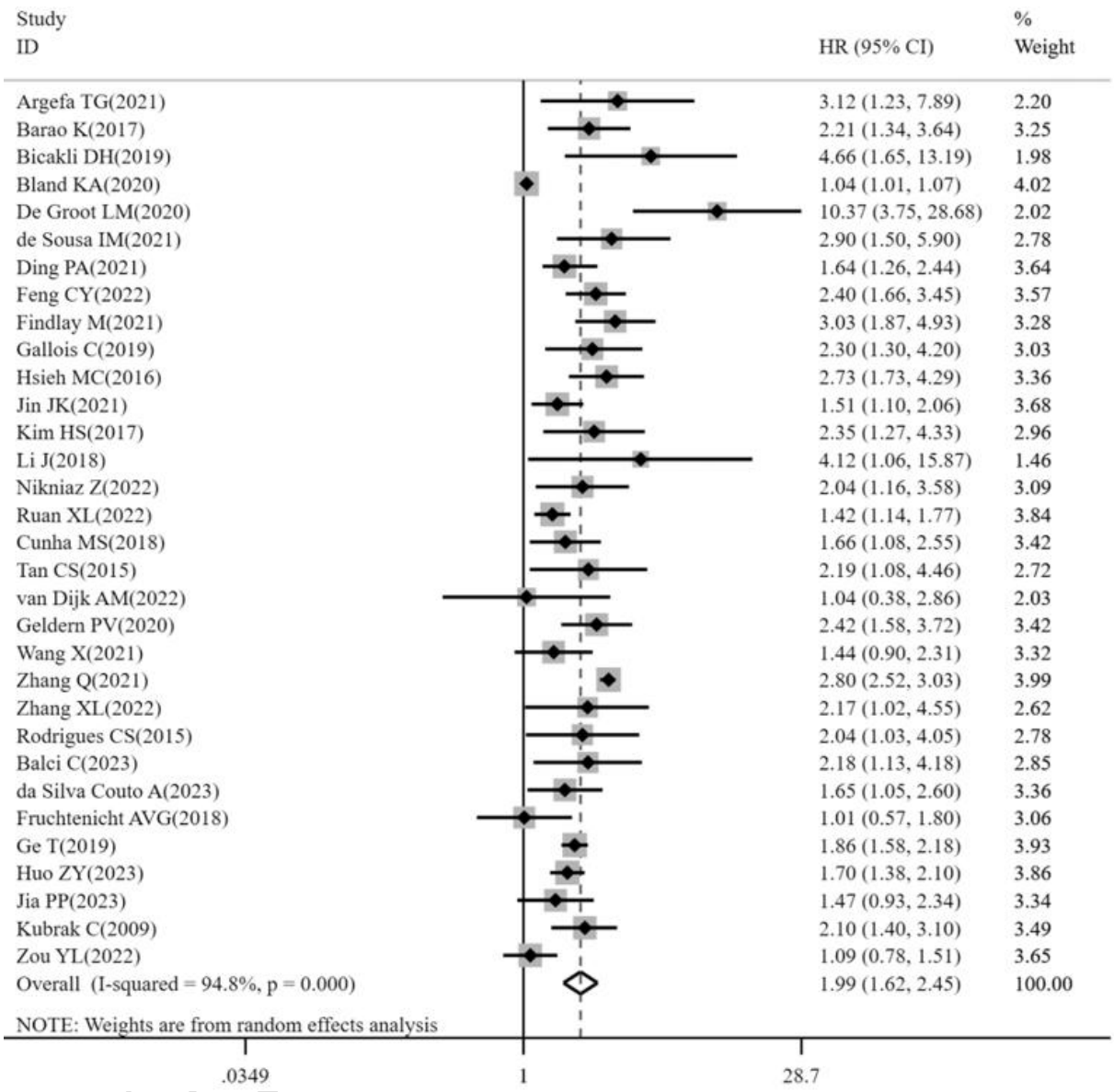

Figure 2. Forest plot of the association between PG-SGA-defined undernutrition and overall survival in a random-effect model. HR: hazard ratio, CI: confidence interval

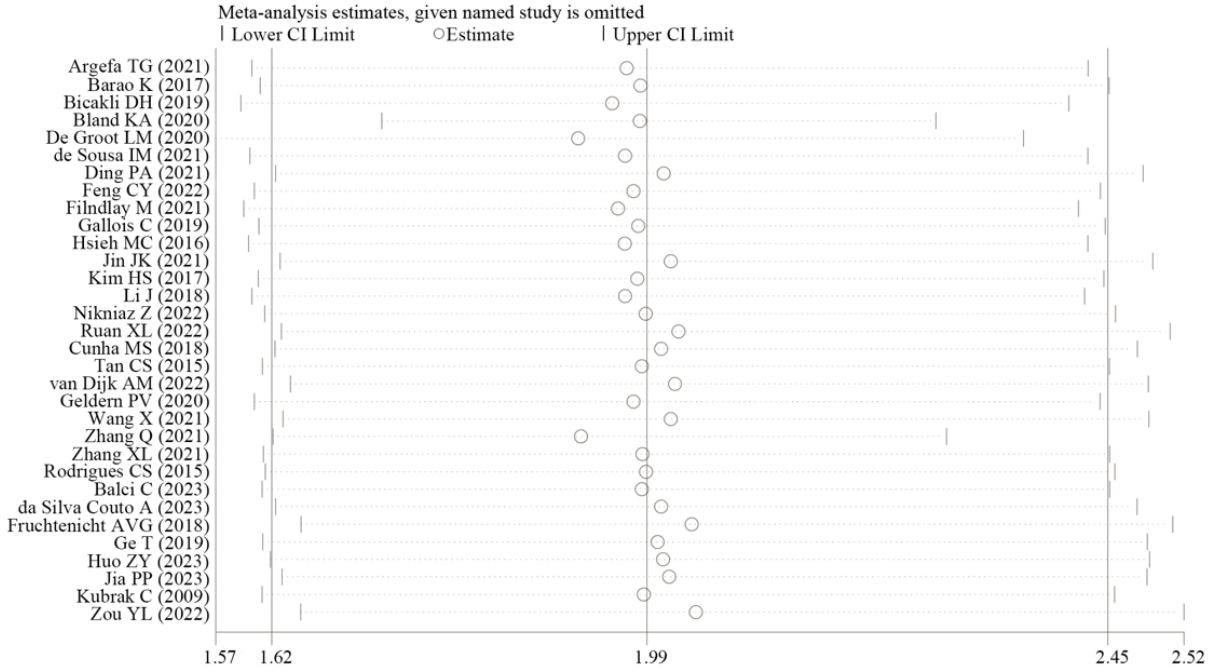

Figure 3. Sensitivity analysis of the association between PG-SGA-defined undernutrition and overall survival.
CI: confidence interval

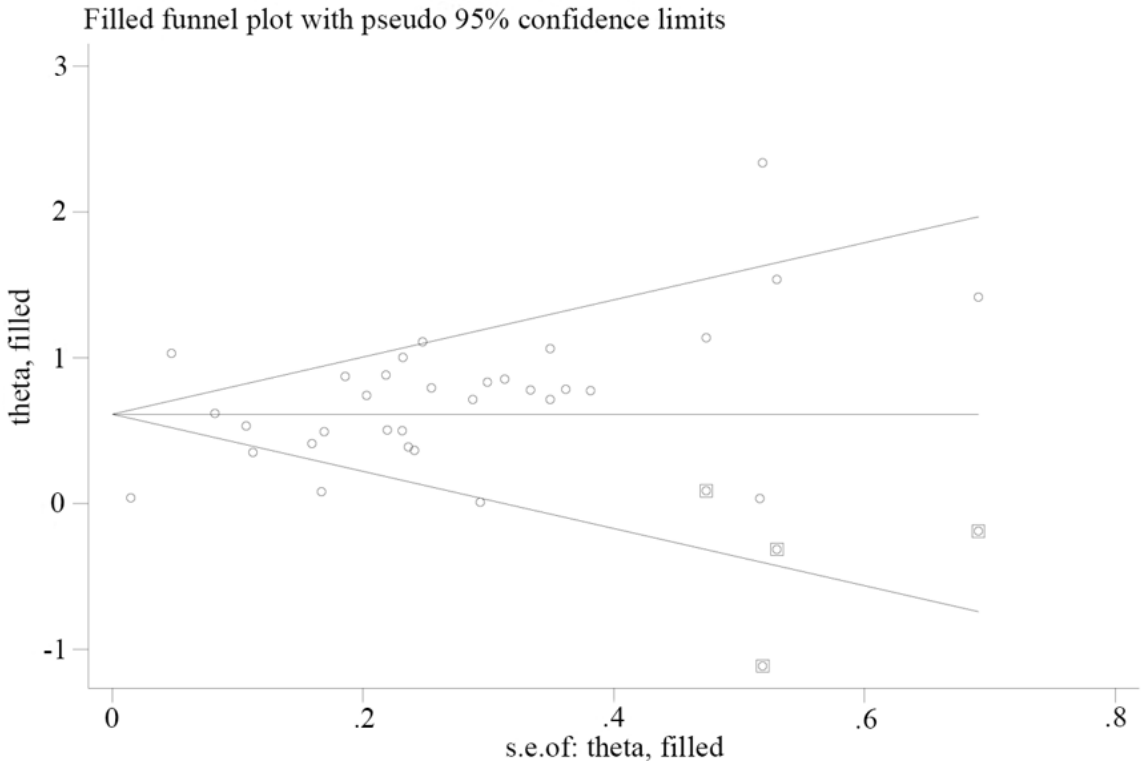

Figure 4. Funnel plot with trim-and-fill analysis illustrating the relationship between undernutrition, as defined by the PG-SGA, and overall survival