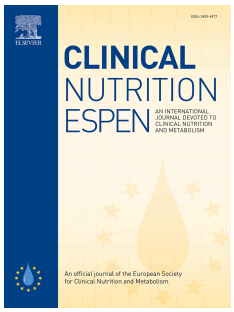

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Integrating Nutritional Status and Hematological Biomarkers for Enhanced Prognosis Prediction in Glioma Patients: A Systematic Review

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Integrating Nutritional Status and Hematological Biomarkers for Enhanced Prognosis Prediction in Glioma Patients: A Systematic Review

ABSTRACT

Purpose: Multiple inflammatory and nutritional biomarkers have been established as independent prognostic factors across various solid tumors, but their role in outcomes prediction for glioma is still under investigation. Aim of the present systematic review is to report the available evidence regarding the impact of nutritional assessment and intervention for glioma prognosis and patients' quality of life (QoL).

Materials and Methods: Our systematic review conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The PubMed and EMBASE databases were searched to identify studies assessing the impact of nutritional status and intervention and hematological biomarkers on survival outcomes and quality of life in patients with newly diagnosed gliomas. In the search strategy Medical Subject Headings (MeSH) terms were used. Search terms included ("nutritional status" or "nutritional assessment" or "nutritional intervention") AND ("glioma" or "glioblastoma" or "high-grade glioma" or "low-grade glioma" or "anaplastic astrocytoma" or "anaplastic oligodendroglioma") AND ("prognosis" or "survival outcomes"). The quality of each study was investigated based on the Newcastle-Ottawa Scale (NOS) criteria. Selected papers were in English and included publications in humans. This study was registered on PROSPERO (Registration No. CRD42024555442).

Results: Our search retrieved 20 papers published between 2015 and 2023, all aiming at investigating correlations between hematological biomarkers (albumin, prealbumin, fibrinogen) and/or nutritional tools (Controlling Nutritional Score, CONUT; Prognostic Nutritional Index, PNI) and survival outcomes and quality of life of glioma patients. Nutritional intervention as well was evaluated for outcomes prediction. Overall, most papers contributed to the evidence of how nutritional assessment and inflammatory biomarkers could play an independent prognostic role also in the management of glioma patients.

Conclusions: PNI, CONUT score and hematological biomarkers (e.g. albumin, globulin, neutrophils, lymphocytes) may serve as useful predictors in patients with gliomas, potentially influencing clinical decisions. Additional large-scale studies are required to validate these findings and determine the mechanisms by which nutritional status, systemic inflammation and immune status affect prognosis in glioma patients.

Keywords: Glioma, nutritional assessment, PNI, CONUT score, survival outcomes

Introduction

Among Central Nervous System (CNS) primary neoplasms, glioma is the most common. According to the new 2021 WHO classification system [1] adult gliomas can be divided into Astrocytoma, Isocitric Dehydrogenase (IDH) mutant; Oligodendroglioma, IDH mutant and 1p/19q co-deleted; Glioblastoma (GBM), IDH wildtype. The latter accounts for most adult gliomas (57.7%), with 2-3 cases per 100000 people [2], and the prognosis remains poor, with a median survival of 14.6 months following gross total resection (GTR) and subsequent adjuvant chemoradiation treatment [3] and a 5-year overall survival (OS) rate <5% [4].

Several inflammatory and nutritional markers have been identified as independent prognostic factors in many heterogeneous solid tumors. As a matter of fact, malnutrition, considered as a combination of inadequate caloric intake, reduced physical activity, systemic inflammation and metabolic rearrangement, is a well-known but still underestimated aspect which may affect patients' functional status, quality of life (QOL) and lead to increased treatment-related toxicity and, consequently, mortality [5], [6], [7], [8].

Nutritional assessment and serum biomarkers have not been thoroughly assessed in gliomas. While some studies have proposed that nutritional screening tools may be considered as independent prognostic factors for prediction of OS and progression-free survival (PFS) [9], [10], [11], [12], other available literature evidence has not confirmed such a correlation in glioma patients [13], [14], [15].

Therefore, the aim of our systematic review is to report data present in literature regarding the impact of nutritional assessment and intervention for glioma prognosis and patients' quality of life (QoL).

Background

A wide array of serum markers has been investigated in the context of nutritional assessment of cancer patients. Among inflammatory indicators (**Figure 1**), the most validated are represented by:

- *Albumin* (ALB), the most abundant protein in human serum which has been used for decades as an indicator of malnutrition in patients in clinically stable conditions [16], [17], even if its lack of specificity and long half-life could alter its perception of a key player in nutritional assessment [18];
- *Serum prealbumin* (pALB), a transport protein for thyroid hormone, advocated as a nutritional marker with the advantage of shorter half-life if compared to serum albumin [19].

  Both ALB and pALB are mostly synthetized in the liver and a decrease in their release can be detected during inflammatory states and production of acute-phase proteins [19];
- *Globulin*, another major component of serum proteins whose increased levels may function as surrogate of chronic inflammation. Therefore, an index combining both serum albumin and globulin such as *Albumin-to-globulin Ratio* (AGR, calculated as ALB/ (total protein-ALB)) can reflect nutritional status and systemic inflammation [20];
- *Fibrinogen*, a classic acute phase reactant linked to inflammatory states which promotes leukocytes' migration and function [21];
- *Neutrophil-to-lymphocyte Ratio* (NLR), calculated as a simple ratio between the neutrophil and lymphocyte count in peripheral blood, is a biomarker which combines two different faces of the

immune system: the innate immune response, mainly due to neutrophils, and the adaptive immunity, represented by lymphocytes [22]. An increase in NLR can be observed in every condition characterized by a neutrophil-induced proinflammatory state and it has been related to overall mortality [22], [23];

- *Lymphocyte-to-monocyte Ratio* (LMR) is calculated by dividing the absolute lymphocyte count by the absolute monocyte count from the blood test. Since lymphocytes are involved in cytotoxic cell death and inhibition of tumor cell proliferation and migration and monocytes can promote tumor progression and metastasis, a decreased LMR could generate a favorable immune microenvironment that promotes cancer development and which leads to poor prognosis in cancer patients [24];
- *Platelet-to-lymphocyte Ratio* (PLR) is a ratio between the absolute platelet count and absolute lymphocyte count which has been used as a marker of inflammation in cardiovascular and autoimmune diseases [25] and whose increased level has been related to an inflammatory state;
- The *Systemic Inflammatory Index* (SII) is a novel comprehensive inflammatory biomarker based on neutrophil, lymphocyte and platelet count which reflects both local immune responses and systemic inflammation and which can predict the prognosis of patients with different solid tumors [26], [27].

In addition to the afore-mentioned inflammatory markers, several nutritional indicators, including Prognostic Nutritional Index (PNI) score and Controlling Nutritional Status (CONUT) score, have been reported as independent predictors of OS in patients with miscellaneous primary tumors. PNI scores and CONUT scores indeed reflect the nutritional, inflammatory and immune status and have been related to the prognosis of patients with gastrointestinal tumors, hematological malignancies, urological and reproductive system neoplasms [28], [29], [30], [31], [32].

PNI, easily calculated using the formula *10 × serum albumin (g/dL) + 0.005 ×total lymphocyte count (per mm3)*, is an important biomarker linked to nutritional and immunological status that has been proven to affect survival in various cancer types [33]. Higher PNI scores correspond to higher functional status. CONUT score is instead an objective nutrition evaluation index based on serum albumin, total cholesterol and lymphocyte count which has shown critical importance in the evaluation of gastrointestinal and pulmonary patients [34] and with higher values corresponding to lower prognosis.

Nutritional Risk Index (NRI) is another malnutrition screening tool, assessed through serum albumin levels and weight variations, whose lower levels are related to severe malnourishment, especially in geriatric patients. NRI has been judged useful for prognosis prediction of patients with gastrointestinal and urological disease [35], [36], [37], [38].

Finally, the Naples Prognostic Score (NPS), based on inflammatory markers and nutritional assessment, was firstly evaluated in colo-rectal cancer patients [39] and hence its prognostic significance was validated in other cancer types [40], [41].

In **Table 1** the main nutritional status indicators and their corresponding definitions are presented.

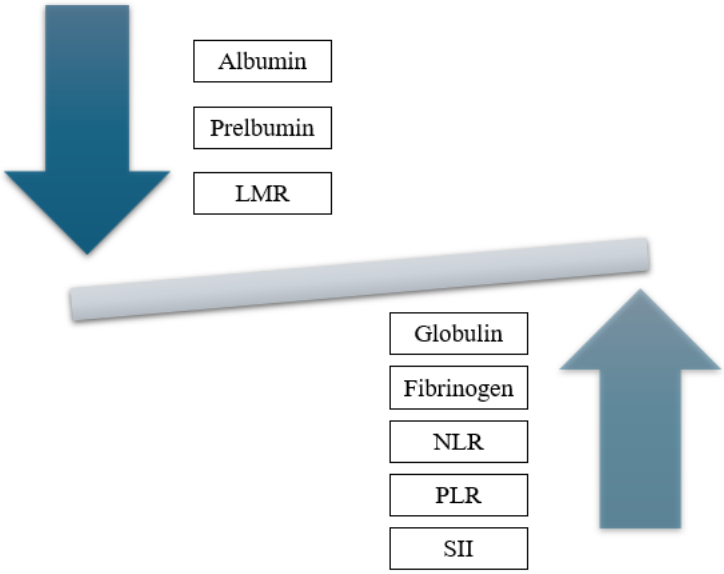

Figure 1. Variations of serum markers according to systemic inflammation: albumin and prealbumin, as well as LMR, show a decrease; on the other hand, globulin, fibrinogen, NLR, PLR and SII tend to progressively increase.

Nutritional Index	**Definition/formula**
Prognostic Nutritional Index (PNI)	*(10×serum albumin [g/dL]) +(0.005×lymphocytes/μL)*
Controlling Nutritional Status Score (CONUT)	*Based on lymphocyte count, serum albumin and cholesterol levels*
Nutritional Risk Index (NRI)	*Based on serum albumin, present weight and usual weight (stable for 6 months)*
Naples Prognostic Score (NPS)	*Based on serum albumin, total cholesterol (TC), NLR, LMR*

Table 1. Definition of the main tools for nutrition assessment

Materials and Methods

This systematic review conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [42]. The PubMed and EMBASE databases were comprehensively searched to identify published studies assessing the impact of nutritional status and/or intervention and hematological biomarkers on survival outcomes and quality of life in patients with newly diagnosed gliomas. In the search strategy Medical Subject Headings (MeSH) terms were used. Search terms included ("nutritional status" or "nutritional assessment" or "nutritional intervention") AND ("glioma" or "glioblastoma" or "high-grade glioma" or "low-grade glioma" or "anaplastic astrocytoma" or "anaplastic oligodendroglioma") AND ("prognosis" or "survival outcomes").

Following the literature search, all references were imported into a specific reference management software. The software's automatic duplicate detection feature was utilized to identify and remove duplicates, followed by additional manual screening to ensure all duplicates were accurately identified.

After duplicates removal, two independent reviewers (I.M. and I.D.) screened the remaining articles by titles and abstracts to exclude irrelevant content. The full texts of the eligible articles were then obtained and evaluated for potential inclusion by the same reviewers. Any discrepancies between the reviewers were resolved on a case-by-case basis with a discussion among co-authors.

Data extraction was performed by the same two reviewers and entered an electronic database specifically designed for this review. The database allowed for easy tracking, updates and data exportation for analysis. The final extracted data were reviewed by the entire research team to identify any discrepancies and ensure accuracy. After data extraction process, the research team synthesized and discussed the data. A standardized data extraction form was used to confirm the included studies and record key details, including authors, year of publication, sample size, nutritional status assessment and cut-off values, primary outcomes, results and main findings.

The quality of each study was investigated by the same authors based on the Newcastle-Ottawa Scale (NOS) criteria, which aims at assessing the quality of nonrandomized trials. The quality of the studies is based on three domains: the selection (maximum score 4), the comparability (maximum score 2) and the exposure (maximum score 3) assessment. The total score can reach up to a maximum of 9 and a score ≥ 7 is considered an indicator of high quality. In case of any discrepancies in the quality assessment process, another investigator had been consulted.

Selected papers were in English and included only publications in human subjects. Other inclusion criteria involved (a) Newly diagnosed glioma; (b) OS and/or PFS or QoL assessment as primary endpoints; (c) Univariate or multivariate hazard ratios/odds ratio (HRs/ORs) with 95% confidence intervals; (d) Retrievable English full text. Studies meeting any one of the following criteria were excluded: (a) Studies involving recurrent GBM; (b) Studies involving children (c) Studies focusing on different outcomes than survival and QoL; (d) Studies published as abstracts, case series, letters and reviews; (e) No relevant data for calculating the risk (i.e., HRs and 95% CIs).

PRISMA flow-chart illustrating the various phases of the review search and the study selection process is reported in **Figure 2.** A completed PRISMA checklist (**Figure 3**) is provided as a supplementary file.

This study was registered on PROSPERO (Registration No. CRD42024555442).

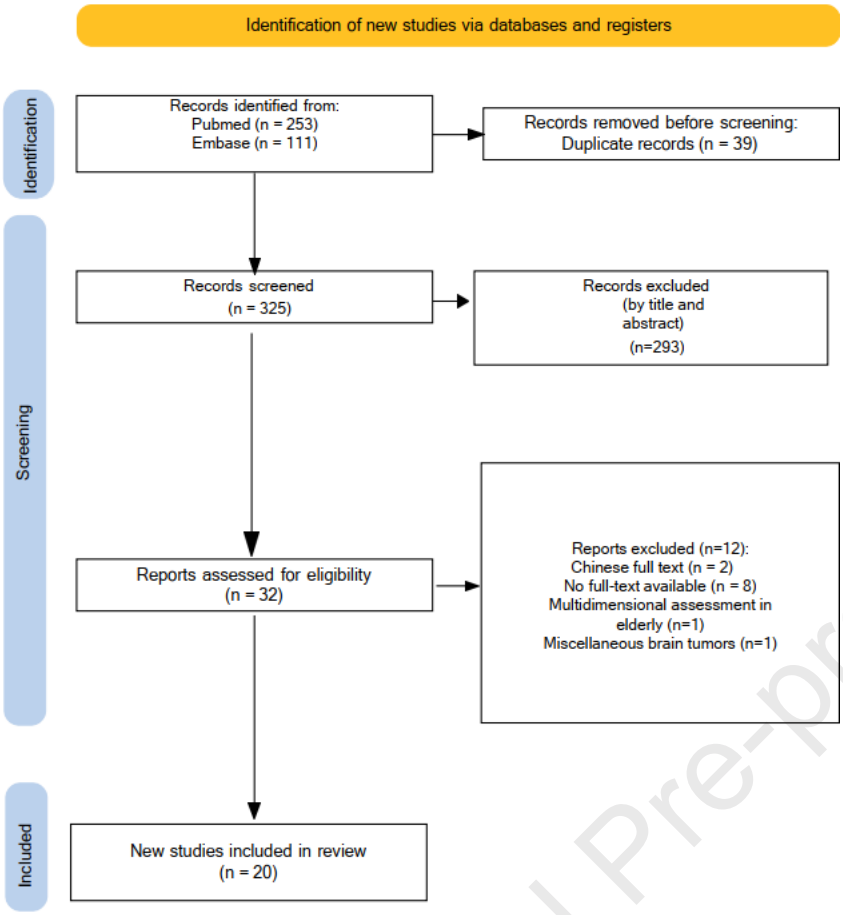

Figure 2. PRISMA flow diagram illustrating the various phases of the review search and the study selection process

Results

Our initial search retrieved 364 published papers between 1984 and 2024; after duplicates' removal (n=39), 325 works were firstly screened by title and abstract. Among 32 papers assessed for eligibility, 12 were further excluded (Chinese full-text n=2; evaluation of different outcomes than survival n=1; no full-text available n=8; multidimensional assessment in elderly n=1). In the end, 20 works were included in the present review and their main characteristics are reported in **Table 2.** The quality of studies assessed using NOS is revealed in **Table 3** with all the 20 studies considered at low risk of bias (NOS score range: 8-9).

Author, year	patients	period	Assessment				dings
Han S, 2015 [43]	214	2009-2012	Serum Albumin	ALB: 30 g/L	OS	Patients with low serum albumin levels (<30 g/L) had a significantly shorter OS. ALB is a prognostic factor for OS both at UVA (HR 0.938, p<0.001) and at MVA (HR 0.966, p=0.023)	Serum albumin level is associated with prognosis in glioblastoma patients
Zhou XW, 2016 [44]	84	2013-2014	PNI	PNI: 44.4	OS	At UVA age, PNI score was predictors of OS. At MVA a PNI≥44.4 (HR:0.479, p=0.042) remained an independent prognostic factor.	A PNI>44.4 was an independent prognostic parameter of OS and of efficacy of adjuvant treatment in GBM patients
He ZQ, 2017 [20]	188 (training set), 130 (validation cohort)	2001-2014	PNI	PNI: 52.55	OS, PFS	In the training set at MVA PNI was as an independent predictor for PFS (HR = 0.62, p=0.007) and OS (HR = 0.56, p=0.002). The PNI retained independent prognostic value in the validation set for both PFS (HR: 0.61, p = 0.013) and OS (HR: 0.55, p= 0.003)	PNI is a potentially valuable preoperative marker for the survival of patients following HGG resection
Xu WZ, 2017 [45]	166	2010-2015	AGR, PNI	AGR: 1.75 PNI: 48	OS	OS was enhanced with higher AGR (>1.75) and PNI (>48) (p<0.001 for both). At MVA, both AGR and PNI were independent predictors of OS (AGR, HR 0.785, p=0.04; PNI, HR 0.757, p=0.039)	Preoperative AGR and PNI may be useful for predicting OS in GBM patients, especially those undergoing adjuvant therapies
Ding JD, 2018 [13]	300	2008-2017	PNI	PNI: 44	OS	At UVA higher PNI levels were associated with favorable outcomes (HR1.59, p=0.031). The benefit was not confirmed at MVA	PNI is associated with age and sex in GBM patients but fails to provide independent prognostic values
Yang T, 2018 [46]	128	2008-2012	PNI, NLR	NLR: 2.8 PNI: 45	OS	NLR ≥2.8 and PNI <45 were significantly associated with decreased OS. At MVA NLR ≥2.8 (HR 2.037, p =0.003) was independent prognostic factors	The results of the present study indicated that high NLR was an independent risk factor for OS rates in patients with glioma
Rigamonti A, 2019 [15]	282	2004-2014	PNI	PNI: 45.9	OS	Median OS was 13 months with PNI-high vs 11.3 with PNI-low. Based on post-surgical treatment, no association between PNI and OS was confirmed	PNI is a controversial marker for prognosis in GBM patients and further prospective studies are necessary to elucidate its role
Hu C, 2020 [47]	94	2015-2018	CONUT	CONUT: 4	OS rate	At UVA, higher CONUT scores were closely associated with decreased OS (HR 2.581, p = 0.001). At MVA, this relationship remained significant (HR 3.110, p < 0.001)	Preoperative CONUT score has potential application as a predictor of prognosis in patients with GBM
Marini A, 2020 [48]	124	2013-2019	Hemoglobin, LDH, glycemia, ALB, NLR, PLR, AGR and PNI	Hemoglobin: 12 g/dL LDH: 240 U/L Glycemia: 137 g/dl ALB: 3 g/dl Neutrophils: 7 x 10^9/L Platelets: 350 x 10^9/L Lymphocytes: 1x10^9/L NLR: 4 PLR: 175 PNI 44.4 AGR 1.75	PFS, OS	Thrombocytosis (HR 1.83, p=0.006), lymphopenia (HR 1.66, p=0.006) and NLR > 4 (HR 3.15, p=0.044) were independently associated to a worse OS at MVA	Pre-operative blood markers, such as NLR, lymphocytes and platelets, could be predictable prognostic factors for OS in GBM patients

Yalikun K, 2020 [49]	126	2013-2017	ALB, AGR	ALB: 39.5 g/L AGR: 1.43	PFS, OS	Preoperative ALB (HR 0.342, p=0.040) was significantly related to PFS. Preoperative AGR (HR 0.280, p =0.013) was significant for OS and at Cox regression analysis AGR (HR 1.810, p =0.021) was independent predictor of OS	The ALB and AGR had significant predictive values for the prognosis of GBM
Zhao C, 2020[50]	228 (training set), 98 (validation cohort	2016-2019	HRS: (RDW, Hb, Glu, LDH, FIB, DD, NLR, PLR, MLR, PNI)	RDW: 12.8% Hb: 11.4 g/dl Glu:5.4 mmol/L LDH:179 U/L FIB:3.3 g/L DD:0.15 mg/L NLR: 2.3 PLR: 97.7 MLR: 0.59 PNI: 54.8	OS	The optimal cutoff value for the HRS was 0.839 and patients were classified into different prognostic groups based on their HRSs (p < 0.001). Based on both UVA and MVA, the HRS could predict OS in both the training set and validation set	The HRS is a powerful tool for accurate prognostic prediction in patients with newly diagnosed glioblastoma
Huq S, 2021 [12]	242	2007-2019	Albumin level, AGR, NRI, PNI	Albumin: 3.9 mg/dl AGR: 1.9 NRI: 100 and 97.5 PNI: 43.38	PS	On MVA, low albumin level (HR 2.09, p< 0.001), mild and moderate/severe NRI (HR 1.61, p = 0.032 and HR 2.51, p<0.001) and low PNI (HR 2.51, p< 0.001) predicted decreased PS	NS predicts PS in GBM. PNI may provide the best model for assessing NS
Garrett C, 2021 [14]	87	2013-2019	NLR, PNI	NLR 5.07 PNI 46.97	PFS, OS	Only at UVA, PNI and NLR were related to OS (HR 0.436, p=0.002; HR 1.832, p=0.032). PNI also was related to PFS at UVA (HR 0.501, p0.010)	Postoperative PNI was associated with PFS and OS but this did not remain significant on MVA. These findings highlighted the influence of systemic inflammation on GBM survival outcomes
Kim YJ, 2021 [35]	335	2010-2016	PNI	Pre-operative PNI: 50.1 Post-operative PNI: 50.2	OS	Median OS significantly longer in the high PNI group (24.0 vs. 15.0 months, p < 0.001). At MVA, high postoperative PNI was a significant predictor of OS (OR 2.17, p= 0.018)	High postoperative PNI is associated with improved OS and perioperative changes in PNI may provide additional important information for prognostic prediction in GBM patients
Yilmaz H, 2021 [9]	120	2010-2020	CONUT, SII, PNI, NLR	CONUT: 2.5 SII: 1111 PNI: 46.5 NLR: 4.48	PFS, OS	At UVA, CONUT score, SII, PNI, NLR were significant for both PFS and OS. In MVA, only age and CONUT score were independent prognostic factors for both PFS (HR 0.5135, p < 0,001) and OS (HR: 4.531, p < 0.001)	The CONUT score in the postoperative period in GBM patients is an independent prognostic parameter that predicts progression and survival
He Q, 2022 [11]	91	2013-2019	PNI	Grade IV: 44 Grade III: 47	OS	PNI was an independent prognostic factor for OS in grade III glioma only at UVA (HR 0.30, p=0.032). At MVA higher PNI was an independent prognostic factor only for grade IV glioma (HR 0.388, p = 0.040)	PNI is an independent prognostic factor for patients with grade IV glioma. A nomogram including preoperative PNI, age, EOR, number of gliomas and MGMT status could predict OS in patients with grade IV glioma well. The value of PNI in grade III glioma needs to be further evaluated
Hou S, 2022 [51]	219	2012-2017	ALB, pALB, FIB, AFR, PFR	ALB: 39 g/L pALB: 244 mg/L FIB: 2.37 g/L AFR: 15.2 PFR: 112.6	OS	At MVA PFR (HR 2.827; p = 0.006) was the only independent prognostic factor in patients with glioma along with clinicopathologic grade and age	Circulating preoperative PFR as a potential negative independent prognostic biomarker for individuals with glioma

Li J, 2022 [52]	276	2016-2019	NPS, CONUT	NPS score 0: group 0 NPS score 1-2: group 1 NPS score 3-4: group 2	OS	NPS ($p < 0.001$) and CONUT score ($p = 0.023$) were significantly associated with OS. At MVA both NPS and CONUT score were independent prognostic indicators (HR 2.274, p<0.001 and HR 2.086, p=0.003).	NPS is an independent prognostic indicator for patients with newly diagnosed GBM and the prognostic ability of NPS is superior to CONUT score
Duan X, 2023 [53]	281	2015-2018	NLR, SII, PLR	NLR: 2.12 SII: 537.50 PLR: 93.5	OS	High SII, NLR and PLR had shorter OS. At UVA NLR (HR = 1.456, p< 0.001), MLR (HR = 1.272, p < 0.001), FPR (HR = 1.183, p < 0.001), SII (HR = 0.218, p < 0.001) is related to OS. At MVA SII (HR = 1.64, p < 0.001) is also related to OS	High levels of NLR, PLR and SII before surgery are prognostic risk factors for GBM patients. A high preoperative SII level is an independent risk factor for GBM prognosis.
Liu C, 2023 [54]	100 (routing group=39; standard group=61)	2021-2022	ALB, pALB	NA	QoL and recurrence rate	14 days after surgery, ALB, PA and Hb of the standard group were significantly higher than those in the routing group (p< 0.05). PG-SGA scores were significantly lower in the standard group 30 and 60 days after the operation. Within 6 months, the tumor recurrence rate of the standard group was significantly lower than that in the routing group (p < 0.05)	Standard nutritional support based on nutritional risk screening can improve quality of life of post-operative glioma patients

174

175 **Table 2**. Main characteristics of the included studies

176 **ALB**, Albumin**; OS**, Overall Survival; **UVA**, Univariate Analysis; **HR**, Hazard Ratio; **MVA**, Multivariate Analysis; **PNI**, Prognostic
177 Nutritional Index; **GBM**, Glioblastoma; **PFS**, Progression-free Survival; **HGG**, High-grade Glioma; **AGR**, Albumin/globulin ratio;
178 **NLR**, Neutrophil/lymphocyte ratio; **CONUT**, Controlling Nutritional Status; **LDH**, Lactate Dehydrogenase; **PLR**,
179 Platelet/lymphocyte ratio; **HRS**, Hematological Risk Score; **RDW**, Red Distribution Cell Width; **Hb**, Hemoglobin; **Glu**, Glycemia;
180 **FIB**, Fibrinogen; **DD**, D-Dimer; **MLR**, Monocyte/lymphocyte ratio; **NRI**, Nutritional Risk Index; **NS**, Nutritional Status; **SII**, Systemic
181 Inflammatory Index; **EOR**, Extent of Resection; **MGMT**, O6-methylguanine-DNA methyltransferase; **pALB**, pre-albumin; **AFR**,
182 Albumin/Fibrinogen ratio; **PFR**, Prealbumin/fibrinogen ratio; **NPS**, Naples Prognostic Score; **NA**, Not Assessed; **QoL**, Quality of Life;
183 **PG-SGA**, Patient-Generated Subjective Global Assessment; **KPS**, Karnofsky Performance Status.

184

Author, year	Selection	Comparability	Outcome	NOS score
Han S, 2015	****	**	***	9
Zhou XW, 2016	****	**	**	8
He ZQ, 2017	****	**	**	8
Xu WZ, 2017	****	**	***	9
Ding JD, 2018	****	**	**	8
Yang T, 2018	****	**	**	8
Rigamonti A, 2019	****	**	***	9

Hu C, 2020	****	**	**	8
Marini A, 2020	****	**	***	9
Yalikun K, 2020	****	**	***	9
Zhao C, 2020	****	**	**	8
Huq S, 2021	****	**	**	8
Garrett C, 2021	****	**	**	8
Kim YJ, 2021	****	**	**	8
Yilmaz H, 2021	****	**	***	9
He Q, 2022	****	**	***	9
Hou S, 2022	****	**	***	9
Li J, 2022	****	**	***	9
Duan X, 2023	****	**	***	9
Liu C, 2023	****	**	**	8

Table 3. Quality evaluation of included studies using the Newcastle Ottawa Scale (NOS) for cohort studies

Clinical significance of CONUT score in GBM patients

Available evidence regarding GBM patients [9], [47], [52] shows that both preoperative and postoperative CONUT scores are independent prognostic parameters for survival.

Hu et al. [47] firstly evaluated the possible association between preoperative CONUT score and the OS of 257 GBM patients. In this series the cut-off value of the preoperative CONUT score was four and therefore patients were divided into either high-CONUT score (≥4, n = 16, 17.02 %) or low-CONUT score (< 4, n = 78, 82.98 %) groups. CONUT score was not related to age (< 60 years vs ≥ 60 years) nor to other clinical parameters such as sex, tumor location, preoperative epilepsy and LMR, while it was related to NLR and PLR ($p < 0.05$). Regarding OS, at univariate analysis (UVA) of the Cox proportional hazard regression model a high-CONUT score ($p = 0.001$) was associated with a lower OS, along with age ≥ 60 years, no adjuvant treatment and subtotal tumor resection. After multivariate analysis (MVA) by the Cox proportional hazards regression model, preoperative CONUT score ($p < 0.05$) remained an independent predictive factor for GBM patients, as well as age, adjuvant treatment and extent of resection. According to the Kaplan–Meier (KM) survival curve, the OS of patients in the high-CONUT score group ($p = 0.001$) was significantly lower than that of the low-CONUT score group.

Yilmaz and colleagues [9] on the other hand evaluated the prognostic significance of CONUT score in the postoperative setting in a group of 120 GBM patients. In this series the best cut-off point was found to be 2.5.

According to KM survival curves, in those with higher CONUT scores both OS (p<0.001) and PFS (p<0.001) were shorter. At UVA CONUT score was significant parameter for PFS (HR 3.427, p<0.001) and OS (HR 3.253, p<0.001). At MVA CONUT score remained significant for both PFS (HR 0.5135, p < 0.001) and OS (HR 4.531, p < 0.001), along with age (p=0.040 and p=0.041, respectively).

Li et al. [52] analyzed 276 newly diagnosed GBM patients, stratified into four groups according to their preoperative CONUT score (0-1, 2-4, 5-8, 9-12). As a result, the KM curve indicated that CONUT score (p = 0.023) was significantly associated with OS. At UVA Cox regression, CONUT score was significantly related to prognosis (HR 1.795, p=0.013); at MVA Cox regression CONUT score served as well as independent prognostic indicator (HR 2.086, p=0.003), along with age adjuvant therapy and IDH-1 status. The authors concluded that the prognostic model based on CONUT score had lower prognostic capability and less model-fitting than that based on Naples Prognostic Score (NPS, see below).

Clinical significance of PNI score in GBM patients

Many retrospective series evaluated the role of both preoperative and postoperative PNI score in GBM patients. Back to 2016, Zhou and colleagues [44] identified a PNI cut-off level of 44.4 and established a correlation with OS in a population of 84 patients. UVA showed that patients with a PNI < 44.4 had a median survival of 270 days vs 375 days for those patients with a PNI ≥ 44.4 (HR 0.470, p = 0.013). At MVA PNI≥44.4 (HR 0.479, p=0.042) remained an independent prognostic factor, along with age<60 years and completed adjuvant treatment.

He et al. [55] used a cut-off of 52.22 to stratify patients according to their PNI value and found that among 188 patients (training cohort) those with lower PNI values reported shorter OS and PFS (p<0.001 for both), with PNI being a prognostic independent factor for survival outcomes (HR 0.62, p=0.007 for PFS and HR 0.56, p=0.002 for OS). When validated in a proper matched-cohort (n=130), PNI retained independent prognostic value for both PFS (HR 0.61, p= 0.013) and OS (HR 0.55, p =0.003).

Preoperative PNI>48 reached statistical significance also in the series by Xu and colleagues [45], with an OS benefit at MVA (HR 0.757, p=0.039), especially in the subset of those undergoing adjuvant therapies.

Preoperative (3 weeks before surgery, cut-off 50.1) and postoperative (within one month after surgery, cut-off 50.2) PNI were both evaluated in 335 GBM patients by Kim et al. [56]. Patients were classified into four groups according to the cutoff values of the preoperative and postoperative PNIs: Group HH (both high PNIs, n = 92), Group HL (high preoperative and low postoperative PNI, n = 70), Group LH (low preoperative and high postoperative PNI, n = 37) and Group LL (both low PNIs, n = 136). As a significant difference in OS was reported between Group HH and Group LL (P < 0.001), OS was longer in Group HH than in Group HL (p = 0.029) and in Group LH than in Group LL (p=0.027). OS was not significantly different between Groups HH and LH or between Groups HL and LL.

It turned that OS was significantly longer in the high postoperative PNI group than in the low postoperative PNI group (median OS: 24.0 vs 15.0 months, p< 0.001) and longer in the high preoperative PNI group than in the low preoperative PNI group (median OS 22.0 vs. 17.0 months, p=0.008). At MVA significant predictive

factors for postoperative OS were age < 60 years, high postoperative PNI (OR 2.17, p= 0.018), MGMT promoter methylation and completion of the Stupp protocol.

He et al. [11] encompassed a wider range of high-grade gliomas, including also grade III, with the results that patients with higher PNI reported an OS benefit both for grade III (p=0.023) and grade IV (p=0.138). Nonetheless, Cox regression analysis showed that PNI was a prognostic independent factor only for grade IV glioma (HR 0.388, p =0.040), while in grade III glioma no statistical relationship between PNI levels and prognosis could be made.

PNI with a cut-off value of 43.38 was evaluated along with albumin level, AGR and NRI also in the series provided by Huq and colleagues [12] with the result that lower PNI predicted decreased OS (HR 2.51, p<0.001) at multivariate Cox regression. PNI also outperformed the other inflammatory markers in nutritional status assessment.

If the above-mentioned literature data have contributed to emphasize the prognostic influence of PNI for outcomes prediction in GBM patients, on the other hand some evidence stand against the trend.

In this regard, Ding et al [13] provided data about 300 GBM patients treated between 2008 and 2017 with an established PNI cut-off of 44 for nutritional evaluation. PNI ≥44 was associated with improved OS in younger patients and women with statistical significance at UVA (HR 1.59, p=0.031). Unfortunately, the benefit was not confirmed at MVA and PNI did not provide independent prognostic value.

Almost the same conclusion was reached in the analysis by Garrett and collaborators [14] who reported how postoperative PNI was associated with OS and PFS at UVA, without maintaining significancy at MVA.

The Italian experience by Rigamonti [15] reported that patients with PNI-high (cut-off 45.9) had undoubtedly longer OS than those with lower PNI values (13 months vs 11.3), but no association between PNI and OS was confirmed, thus establishing a controversial role of PNI itself.

Clinical significance of other nutritional tools in GBM patients

Naples Prognostic Score was firstly assessed in the Neuro-oncological setting by Li et al. [52]. Patients were stratified according to their NPS score in 3 different groups and retrospectively analyzed: the KM estimate showed that NPS (p < 0.001) was significantly associated with OS. At MVA NPS, as well as CONUT score, proved an independent prognostic indicator (HR 2.274, p<0.001). When comparing the prognostic ability of CONUT and NPS score, the latter resulted superior.

The Nutritional Risk Index was evaluated by Huq and colleagues [12] in 242 GBM patients for correlation between nutritional status and prognosis. In the results mild and moderate/severe NRI (HR 1.61, p = 0.032 and HR 2.51, p<0.001) predicted decreased survival; also, nutritional status was related with STUPP protocol completion.

Clinical significance of serum markers in GBM patients

In the series by Duan [53] and Yilmaz [9], NLR showed a correlation with OS at UVA, but it did not maintain statistical significancy at MVA. Marini et al. [48] on the other hand reported that preoperative NLR>4 was associated with worse OS at MVA (HR 3.15, p=0.044). NLR proved of independent prognostic value in patients with glioma also in the work by Yang [46], where a NLR ≥2.8 was significantly associated with decreased OS. At MVA NLR ≥2.8 continued to be significant for OS (HR 2.037, p =0.003).

AGR as well was explored in many series where it was shown to correlate with the prognosis of GBM patients. In this regard, Xu et al. [45] reported an AGR cut-off of 1.75 and found that AGR was independent predictor of OS (HR 0.785, p=0.04) at MVA. The benefit was observed especially among those undergoing adjuvant therapies. Yalikun and colleagues [49] showed that preoperative AGR (HR 0.280, p =0.013) was significant for OS and at Cox regression analysis was independent predictor of OS (HR 1.810, p =0.021).

Albumin levels alone were evaluated in the work by Han et al. [43] which reported how patients with low serum albumin levels (<30 g/L) had a significantly shorter OS than those with levels in the normal range. Albumin revealed a prognostic factor for OS both at UVA (HR 0.938, p<0.001) and at MVA (HR 0.966, p=0.023). Lower albumin level predicted worse survival also in GBM population analyzed by Huq and colleagues [12] (HR 2.09, p< 0.001).

Prealbumin in relation to fibrinogen concentrations (PFR) was the only independent prognostic factor in glioma patients, along with clinicopathological characteristics, as reported by Hou et al. [51].

For what concerns platelet count evaluation, thrombocytosis (HR 1.83, p=0.006) was independently associated to a worse OS at MVA in the series by Marini et al. [48].

Other circulating biomarkers potentially related to survival outcomes in the Neuro-oncological setting were platelet-to-lymphocyte ratio (PLR), with higher levels associated to worse OS [53], and the Systemic Inflammatory Index (SII), whose levels before surgery could predict prognosis [9], [53].

Zhao et al. [50] established a comprehensive scoring system, the hematological risk score (HRS), with proven prognostic efficacy. It included ten parameters and it was tested in a training set and then validated in an external validation cohort. In the results, the optimal cutoff value for the HRS turned out to be 0.839 and patients were successfully classified into different prognostic groups based on their HRSs (p < 0.001). Based on both univariate and multivariate analyses, the HRS possessed a strong ability to predict OS in both the training set and validation set.

Nutritional intervention in the management of glioma patients

Among the included papers, the only one regarding active nutritional intervention in the management of newly diagnosed glioma patients, and aiming at assessing their quality of life, was that by Liu et al. [54]. In their work, the authors retrospectively analyzed 100 glioma patients, 39 of which underwent routine nutritional support in the perioperative period (standard amounts of enteral/parenteral nutritional support). The remaining 61 underwent instead nutritional intervention according to a more personalized strategy. The two groups were

then compared according to their albumin, prealbumin and hemoglobin levels, patient-generated subjective global assessment (PG-SGA) score, Kanofsky performance score (KPS) and short-term prognosis. Fourteen days after surgery, the standard group reported higher levels of albumin, prealbumin and hemoglobin ($p < 0.05$). A benefit in the standard group was observed also for PG-SGA and KPS, if compared to routine group. For what concerns tumor recurrence at 6 months, the rate of the standard group was significantly lower than that in the routing group ($p < 0.05$). The results contributed to the evidence that standard nutritional support based on tailored nutritional risk screening can improve the quality-of-life of glioma patients and their survival outcomes.

Discussion

Our systematic review led to the identification of 20 different papers, mostly contributing to the evidence of how nutritional assessment and inflammatory biomarkers could play a prognostic role in the management of glioblastoma patients.

Recently, local immune responses and systemic inflammation have been deeply investigated in the setting of tumorigenesis, with chronic inflammatory processes affecting all stages of tumor development and, consequently, patients' survival [57]. Peripheral blood neutrophils, lymphocytes, monocytes and platelets are representative of individuals' inflammatory status and therefore have been evaluated for predicting prognosis and therapeutic response in different cancer specimens [58], [59], [60], [61], [62], [63].

Nutrition as well plays an essential role in cancer progression since it is responsible for oxidative stress, molecular reactions in cells and alterations in the metabolic state of tissues [64], [65]. Albumin, prealbumin, cholesterol and Body Mass Index (BMI) above all have shown to be effective predictors for disease progression and prognostic assessment. Over the years, the above-mentioned indices have been included into different nutritional tools, with Prognostic Nutritional Index (PNI) and Controlling Nutritional Status (CONUT) scores emerging as crucial factors for disease course and response to therapies in many different cancer types [28], [29], [30], [31], [32], [33], [34], [35].

Among CNS tumors, glioblastoma is the most common malignant primary neoplasm characterized by a dismal prognosis and a high risk of local recurrence despite the use of Stupp protocol (postoperative radiotherapy plus concomitant and adjuvant temozolomide chemotherapy) [3]. Among the most accounted prognostic factors in GBM patient population we can find age, preoperative Karnofsky performance status (KPS) score, genetic composition (i.e., isocitrate dehydrogenase [IDH] mutation, O6-methylguanine-DNA methyltransferase [MGMT] promoter methylation) and the extent of surgical resection [66], [67], [68].

Whether nutritional status can be included among the factors most commonly influencing prognosis, this remains underreported. In our systematic review of 20 retrospective studies published between 2015 and 2023 we analyzed the correlation between survival outcomes (OS and PFS) and QoL with nutritional intervention and hematological biomarkers assessment in glioma patients.

Our results showed overall significant association between PNI and CONUT and OS and PFS in 9 series, with higher PNI and lower CONUT scores relating to favorable survival outcomes. Similarly, Hung et al [69] conducted a metanalysis and systematic review involving 13 retrospective studies and 2712 glioma patients and reported that high PNI was linked to improved OS (HR 0.61, $p < 0.00001$, $I^2 = 25\%$). Patients with higher PNI had also better PFS than those with lower values (HR=0.71, p=0.001, $I^2 = 0\%$). Peng and colleagues [70] as well evaluated both PNI and CONUT scores in a metanalysis of 1506 glioblastoma patients. In line with our results, a high PNI score resulted predictor of greater OS (HR 0.50, I^2 0%) and progression free survival (HR 0.63, $I^2 = 0\%$), whereas a low CONUT score was associated with longer OS (HR 2.39; $I^2 = 25\%$). At MVA, PNI and CONUT benefit was confirmed for OS (HR 0.64; $I^2 = 24\%$ and HR 2.79, $I^2 = 39\%$, respectively), whereas PNI score was not significantly associated with PFS (HR 1.02, I^2 0%). The prognostic significance of PNI was also assessed in a metanalysis by Liu et al. [71] with promising results. Eleven studies with 2928 cases were included and showed that a high PNI (HR 0.56, $p<0.001$) could be a predictor of favorable OS for those with high-grade gliomas. A systematic review and metanalysis provided by Wang [72] reported that higher PNI was associated with better OS outcomes (HR 0.57, p= 0.0002).

Unlike our series, the above-mentioned systematic reviews and metanalyses did not include any studies exploiting the role of nutritional intervention on survival outcomes in glioma population. Furthermore, other systematic reviews included studies involving glioma patients at recurrence, whereas we deliberately decided not to focus on this patient population. As a matter of fact, we wanted to demonstrate the impact of nutritional assessment and hematological biomarkers only on newly diagnosed patients with a typical prognosis > 1 year where an early nutritional intervention might be more meaningful in providing a benefit for survival.

For what concerns serum biomarkers, most retrospective evidence in our review highlighted a correlation between NLR, AGR and serum albumin values and survival outcomes in glioma patients with statistical significance at MVA reached in 9 series.

In 2020 Linhares [73] reported many serum biomarkers with potential application in glioblastoma, distinguishing between those related to vascular proliferation and cell growth from those linked to the immune system, coagulation and inflammatory response. Among biomarkers connected to nutritional status, the authors identified IGFBP-2 and albumin with its derivatives (e.g. PNI and AGR) as significantly related to OS, with lower albumin levels associated with shorter OS values. Preoperative serum albumin levels and AGR were assessed also in the above-mentioned metanalysis by Liu [71]. Even though with premises that the prognostic values of albumin and AGR were limited for gliomas ($p>0.05$), nonetheless high preoperative serum albumin was significantly related with excellent OS (HR 0.95, p =0.018) in subgroup analysis and AGR (HR 0.57, p=0.034) was identified as a protective factor of favorable OS in the same setting. At MVA reduced preoperative serum albumin, AGR and PNI were all predictors of poor prognosis. In his metanalysis of 18 studies and 3261 patients, Wang et al. [72] reported NLR and red cell distribution width (RDW) as independent predictors of worse survival in patients with gliomas (HR 1.38, p= 0.008 and HR 1.40, p= 0.002, respectively). On the other hand, neither PLR nor LMR correlated with OS (p= 0.91 and p=0.21, respectively).

Nutritional intervention represents an established cornerstone in the diagnostic and therapeutic process for Head and Neck and Gastrointestinal neoplasms [74], [75], [76]. In the next future nutritional intervention will be of crucial importance for risk stratification and for the adoption of much more tailored treatment strategies also in glioma patients, as it has been already demonstrated in the series by Liu et al. [54]. Since glioblastoma is, among gliomas, characterized by the most dismal prognosis, the benefit of an early nutritional intervention based on patients' characteristics could be even greater.

Also, body fat distribution and composition and the assessment of muscle mass have recently been subjects of investigation in the setting of GBM. In this context, temporal muscle thickness (TMT), as representative of objective sarcopenia, has already emerged as independent predictor of survival in glioblastoma patients [77], [78]. In 2013 a completed early phase 1 study (NCT01770626) [79] was designed to evaluate how the body composition determined by bioelectrical impedance analysis, nutrition assessment by Subjective Global Assessment and serum albumin, the type of microbes present in the gut and the participant's DNA information could predict the progression and outcomes of GBM. The study started in April 2011 and concluded in June 2014; the results indicated significant correlations between hand grip strength, phase angle and skeletal muscle mass. However, there were no associations found between nutritional parameters and tumor progression or OS. This trial, although unpublished, provided valuable insights into the nutritional needs and challenges faced by GBM patients, suggesting the importance of comprehensive nutritional assessments in managing GBM.

Larger series are warranted for a more in-depth investigation. Some issues indeed may still raise some concerns regarding our analysis; first, the number of included studies, all retrospective, and patient sample sizes were relatively small. Secondly, even though our search strategy aimed at assessing all glioma subtypes, including those low-grade, most studies evaluated patients with glioblastoma. Thirdly, studies were extremely heterogeneous in terms of nutritional tools and biomarkers cut-offs, which vary among retrospective series. Fourth, other prognostic factors may have influenced the prognostic value of nutritional status. Also, the timing for nutritional status assessment is still debatable; if most series evaluated preoperative serum biomarkers, on the other hand other works investigated postoperative indices [9], [14] and even one [56] analyzed perioperative changes stratifying patients according to variations among preoperative and postoperative values. The exclusion of non-English papers, including those from Asian countries where substantial glioma research is conducted, represents a potential limitation of this review. This decision was primarily driven by practical and systemic challenges: linguistic barriers can prevent thorough evaluation by reviewers unfamiliar with the language, English-language papers typically garner more citations and journals often face resource constraints in translating or engaging multilingual reviewers. Consequently, relevant studies may have been inadvertently overlooked. Our analysis also did not deliberately include recurrencies; nonetheless, available retrospective evidence suggests PNI is an independent prognostic factor for OS in recurrent GBM patients [10].

Future Research

As previously outlined, the retrospective nature of the included studies represents a limitation of our work. Ideally, nutritional and hematological markers would be prospectively validated through randomized controlled trials (RCTs). However, conducting RCTs in rare tumors like gliomas is challenging due to the rarity of the disease and the heterogeneity of clinical presentation at diagnosis, which hinders the standardization of study protocols and the establishment of uniform inclusion criteria. Therefore, a viable alternative could be represented by prospective cohort studies, where a group of patients is followed over time to observe how specific biomarkers correlate with survival outcomes. This design could allow for the establishment of a correlation between biomarkers and clinical events and might enable patient stratification based on clinical characteristics.

Conclusions

The results of our systematic review overall suggested that PNI, CONUT score and hematological biomarkers (e.g. albumin, globulin, neutrophils, lymphocytes), all low-cost and easily applicable in daily practice, may serve as useful predictors in patients with gliomas, potentially influencing clinical decisions. Nonetheless, some studies present controversial results with specific mechanisms still unclear and warranted to be further investigated. Additional large-scale studies are therefore required to validate these findings and determine the mechanisms by which nutritional status, systemic inflammation and immune status affect prognosis in glioma patients.

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676 **SUPPLEMENTARY MATERIALS**

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Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Pages 5-6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 6

Section and Topic	Item #	Checklist item	Location where item is reported
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 6
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 6
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 6
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 7
Study characteristics	17	Cite each included study and present its characteristics.	Pages 8-10
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Pages 10-11
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Pages 11-15
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Pages 11-15
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Pages 11-15
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Pages 11-15
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Pages 11-15
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Pages 11-15
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Pages 11-15
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pages 15-17
	23b	Discuss any limitations of the evidence included in the review.	Page 17
	23c	Discuss any limitations of the review processes used.	Page 17
	23d	Discuss implications of the results for practice, policy, and future research.	Page 17
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 6
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 6
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 6
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 2
Competing interests	26	Declare any competing interests of review authors.	Page 2
Availability of data, code	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used	Page 5

Section and Topic	Item #	Checklist item	Location where item is reported
and other materials		for all analyses; analytic code; any other materials used in the review.	

Figure 3. PRISMA check-list.

From: 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 2021;372:n71. doi: 10.1136/bmj.n71