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Prognostic nutritional index as a prognostic factor in lung cancer patients receiving chemotherapy: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: Lung cancer is one of the leading causes of morbidity and mortality in the world. In the past decade, numerous studies focus on the prognostic nutritional index (i.e., a measure of serum albumin and lymphocyte in peripheral circulation) as a possible biomarker to predict the survival outcomes in cancer patients undergoing chemotherapy. Prognostic nutritional index can reliably predict the survivability outcomes by effectively quantifying the nutritional and immunological status of cancer patients. To date, only one review has attempted to evaluate the impact of the prognostic nutritional index on the survival outcomes in lung cancer patients with certain limitations. The goal of the present systematic review and meta-analysis is to bridge the gap in the literature and evaluate the capacity of the prognostic nutritional index for predicting the survivability outcomes in lung cancer patients undergoing chemotherapy. The aim of the study is to evaluate the impact of prognostic nutritional index scoring on survival outcomes in lung cancer patients undergoing chemotherapy.

MATERIALS AND METHODS: A systematic academic literature search was performed based on the PRISMA guidelines across Web of Science, EMBASE, CENTRAL, Scopus, and MEDLINE databases. A random-effect meta-analysis was performed to evaluate the impact of prognostic nutritional index scoring (i.e., high/low) on survival outcomes (i.e., progression-free survival, overall survival) in lung cancer patients undergoing chemotherapy.

RESULTS: From 963 studies, 16 eligible studies with 4250 lung cancer patients (62.32 ± 5.08 years) undergoing chemotherapy were included. Our meta-analysis revealed worse mortality outcomes in terms of progression-free survival (HR: 1.31) and overall survival (1.21) for the group with a low prognostic nutritional index score as compared to the group with a high prognostic nutritional index score in lung cancer patients undergoing chemotherapy. Subsequent subgroup analyses further demonstrated markedly worse outcomes for progression-free survival (1.32) and overall survival (1.52) in non-small lung cancer patients with lower prognostic nutritional index scores.

CONCLUSIONS: We provide preliminary evidence suggesting that lower prognostic nutrition index scores are associated with worse survivability outcomes (progression-free survival and overall survival) in lung cancer patients undergoing chemotherapy. We also show that lower prognostic nutrition index scores correlate with even worse survival outcomes in patients with non-small lung cancer histological subtype of lung cancer. These findings should help clinicians to stratify the risks associated with the chemotherapeutic management of lung cancer patients.

Key Words:
Lung cancer, Prognostic nutrition index, Meta-analysis, Progression-free survival, Overall survival.

Introduction

Lung cancer is the third most common form of cancer across the world[1-3]. The prognostic outcomes of lung cancer, depending on its stage, is extremely poor[4]. Generally, lung cancer results in significantly higher morbidity and mortality as compared to cancers of other origins[5,6]. Accord-

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ing to the recent global burden of disease study, lung cancer accounts for almost 2 million deaths and 41 million disability-adjusted life years worldwide[6,7], and these numbers are expected to rise further. The study also projected an increase in the incidence of lung cancer in the upcoming years due to population growth and changes in the age-related incidence[7]. Despite recent advances[8,9] in treatment options, such as immune checkpoint inhibitors and tyrosine kinase inhibitors, patients with lung cancer still have poor morbidity- and mortality-related outcomes. As suggested by recent studies[10-12], there is a growing need for the development of more efficient individualized precision therapies with sensitive biomarkers.

In the past decade, studies have increasingly focused on evaluating the prognostic significance of a patient's immunological and nutritional status in general[10,13,14] and the prognostic nutritional index score in particular[13,15-17] in overall survival. As shown in numerous reports[18-20], prognostic nutritional index can reliably predict survivability outcomes in cancer patients. Typically, the prognostic nutritional index score tends to evaluate the impact of the nutritional, immunological status of a patient, as measured by quantifying the concentration of serum albumin and total lymphocyte count in the peripheral circulation, on the overall survival[21]. The reported benefits of using prognostic nutritional index include its prolonged stability, half-life, and cost-effectiveness[22-24]. Okada et al[25] (2018) suggested that the evaluation of prognostic nutritional index could be an integral component in establishing effective risk stratification guidelines that will contribute to developing personalized chemotherapeutic interventions for managing lung cancer.

To date, a few individual retrospective cohort studies[26-34] have attempted to evaluate the ability of the prognostic nutritional index to predict the survivability outcome in lung cancer patients undergoing chemotherapy. In the existing literature, however, a lack of consensus exists regarding the efficiency of lower/higher prognostic nutritional index scores in predicting overall survival in lung cancer patients undergoing chemotherapy. While some studies[26-29,34] indicated worse overall survival outcomes in lung cancer patients with lower prognostic nutritional index scores, other studies[19,30,32,35] have reported poorer overall survival outcomes in lung cancer patients with high prognostic nutritional index scores. Similarly, there is a lack of consensus regarding the prediction of progression-free survival. While some studies[28,33,34] reported superior capability of lower prognostic nutritional index score for predicting poorer progression-free survival outcome, other[30,35] reported only limited effect.

To the best of our knowledge, only one systematic review[36] has attempted to evaluate the predictive capacity of the prognostic nutritional index in lung cancer patients. However, the review included lung cancer patients with different treatment protocols (i.e., chemotherapy, radiotherapy, surgery), suggesting a possibility of bias. Moreover, since the publication of the review in 2018, several high-quality cohort studies[26-34] evaluating the impact of prognostic nutritional index scoring on survival outcomes in lung cancer patients undergoing chemotherapy were published. Therefore, an update of the existing state of evidence is strongly warranted.

The aim of this systematic review and meta-analysis is to attempt to bridge the gap in the current state of evidence by evaluating the capacity of prognostic nutritional index scoring for predicting the survival outcomes of lung cancer patients undergoing chemotherapy. The findings from this study will help deduce best practice guidelines for effectively reducing mortality-related outcomes in patients with lung cancer undergoing chemotherapeutic management.

Materials and methods

We adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[37] for performing this meta-analysis.

Data Search Strategy

Five scientific databases (Web of Science, MEDLINE, CENTRAL, EMBASE, and Scopus) were searched for relevant manuscripts from inception till April 2021 across a combination of the following MeSH keywords: "Cancer", "lung cancer", "pulmonary cancer", "PNI", "prognostic nutritional index", "DFS", "disease-free survival", "survival", "overall survival", and "progression-free survival". References of the included studies was manually searched to identify further relevant studies. The inclusion criteria were as follows:

- Studies reporting data from patients diagnosed with lung cancer undergoing chemotherapeutic treatment.
- Studies evaluating the impact of prognostic nutrition index on the outcome of overall

survival, disease-free survival, and progression-free survival.
- Studies of human participants.
- Case-control studies, prospective cohort trials, or retrospective cohort trials.
- Studies published in peer-reviewed scientific journals.
- Studies published in English.

The screening of the studies was performed independently by two reviewers. Cases of disagreements were resolved by discussion with a third independent reviewer.

Quality Assessment

Risk of bias of the included studies was assessed using the Newcastle Ottawa scale[38] that evaluates the outcomes for selective reporting, confounding bias, measurement of outcomes, and incomplete data availability as threats that can instigate instigating. Methodology quality assessment was performed independently by two reviewers. Cases of disagreement were resolved by discussion with the third reviewer.

Data Analysis

A within-group meta-analysis, based on the random-effects model[39], was performed using CMA, Comprehensive Meta-analysis version 2.0[40]. Hazard ratio was calculated to evaluate the outcomes of progression-free survival and overall survival in lung cancer patients undergoing chemotherapy with a variable level of prognostic nutrition index. Heterogeneity among the studies was assessed by computing I^2 statistics. I^2 statistics between 0-25% were considered indicative of negligible heterogeneity, 25%-75% of moderate heterogeneity, and ≥75% of substantial heterogeneity[41]. For the studies that provided the descriptive statistics as median and range, the method listed by Hozo et al[42] was used to convert it into mean and standard deviation. Publication bias was evaluated by Duval and Tweedy's trim and fill procedure[42]. This analysis of publication bias imputes studies from either side of the plotted graph to identify any unbiased effect. The significance level for this study was determined at 5%.

Results

A total of 950 studies were identified by searching the databases. Additional 13 studies were identified during the screening of the reference sections of the included studies. After applying inclusion criteria, a total of 16 studies remained and were included in the review. All of the included studies were retrospective cohort studies[19,26-35,] no studies have examined its prognostic role in small-cell lung cancer (SCLC[44-48] (Figure 1). The data was extracted in a tabular format and is summarized in Table I.

Participant Information

Data from a total of 4250 (1432F, 2817M) patients with lung cancer receiving chemotherapy were reported in the included 16 studies. A total of 1634 participants were in the low prognostic nutritional index group and 2337 in the higher prognostic nutritional index group. Four studies[30,31,33,46] did not report the sample distribution for the groups with low and high prognostic nutritional index. The average age of the patients included in this study was 62.32 ± 5.08 years. Two studies[31,34] did not report the age of their cohort.

Quality Assessment for Cohort Studies

Risk of bias of the cohort studies was assessed using the Newcastle Ottawa scale (Table II). The overall risk was found to be low in all the included studies (Figure 2).

Publication Bias

We used Duval and Tweedy's trim and fill method to determine missing studies according to the random effect model on either side of the mean effect of the funnel plot. There were no studies missing on either side of the mean effect. The overall random effect models determined the point estimates and the 95% confidence intervals for all the combined studies as 1.21 (0.89 to 1.66). The publication bias is reported in Figure 3.

Meta-Analysis Report

Progression-free survival

Progression-free survival outcome in lung cancer patients undergoing chemotherapy with low or high prognostic nutritional index were reported by nine studies. We observed an increased hazards ratio suggestive of worse progression-free survival for patients with lower levels of prognostic nutritional index as compared to patients with higher prognostic nutritional index (Figure 4) (Hazard ratio: 1.31, 95% C.I: 1.02 to 1.69, p=0.03), with moderate heterogeneity (I^2: 36.8%). Subgroup analyses were further conducted to eval-

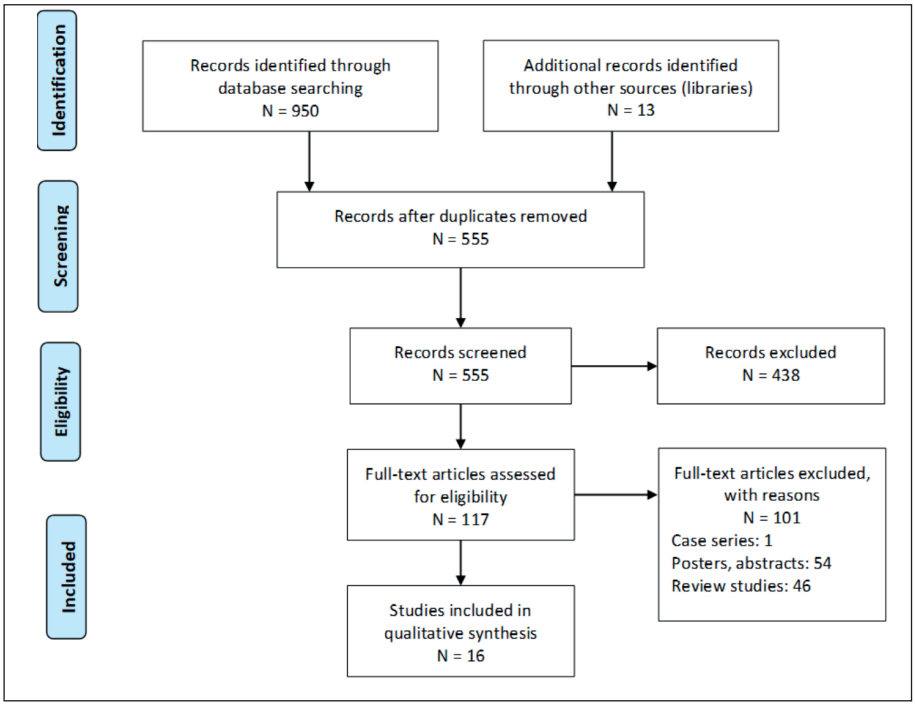

Figure 1. Illustrating the PRISMA flowchart.

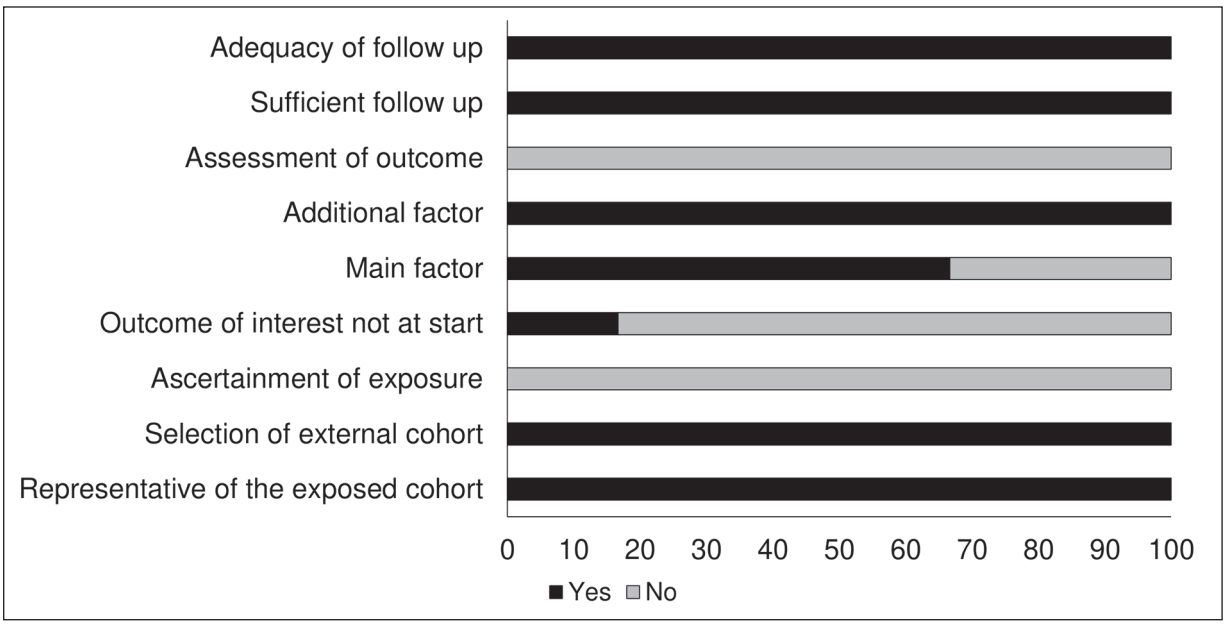

Figure 2. Demonstrates the risk of bias according to the Newcastle Ottawa scale for cohort studies.

uate the predictability of prognostic nutritional index in patients with non-small cell lung cancer histological subtype.

Small cell lung cancer

Progression-free survival outcomes of small lung cancer patients undergoing chemotherapy with low or high prognostic nutritional index were reported by two studies. We observed an increased hazards ratio suggesting worse outcome of progression-free survival for patients with lower levels of prognostic nutritional index as compared to patients with higher prognostic nutritional index (Figure 5) (Hazard ratio: 1.25, 95% C.I:

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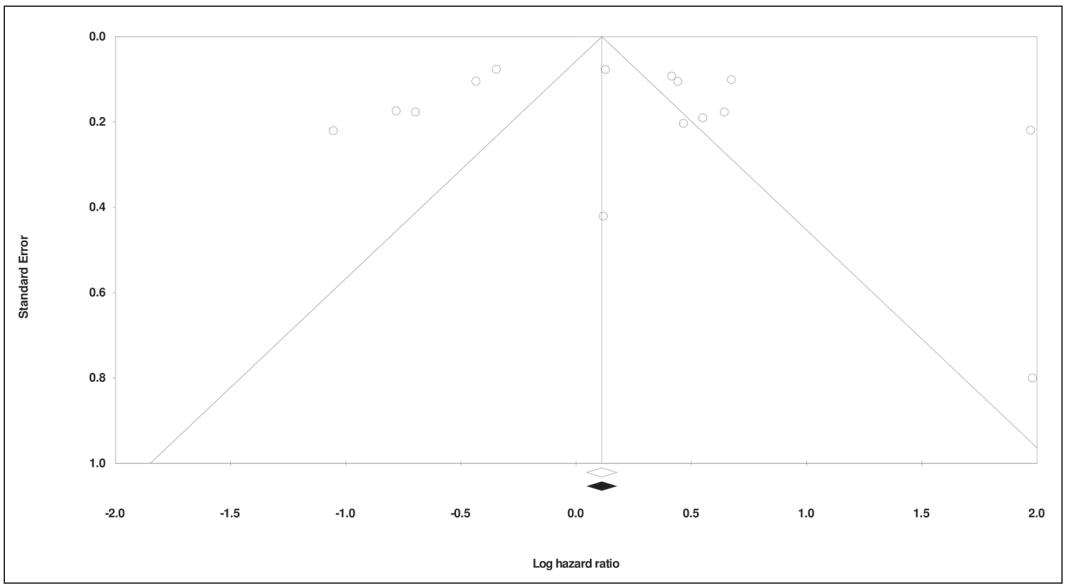

Figure 3. Demonstrates the publication bias by Duval & Tweedy's trim and fill method.

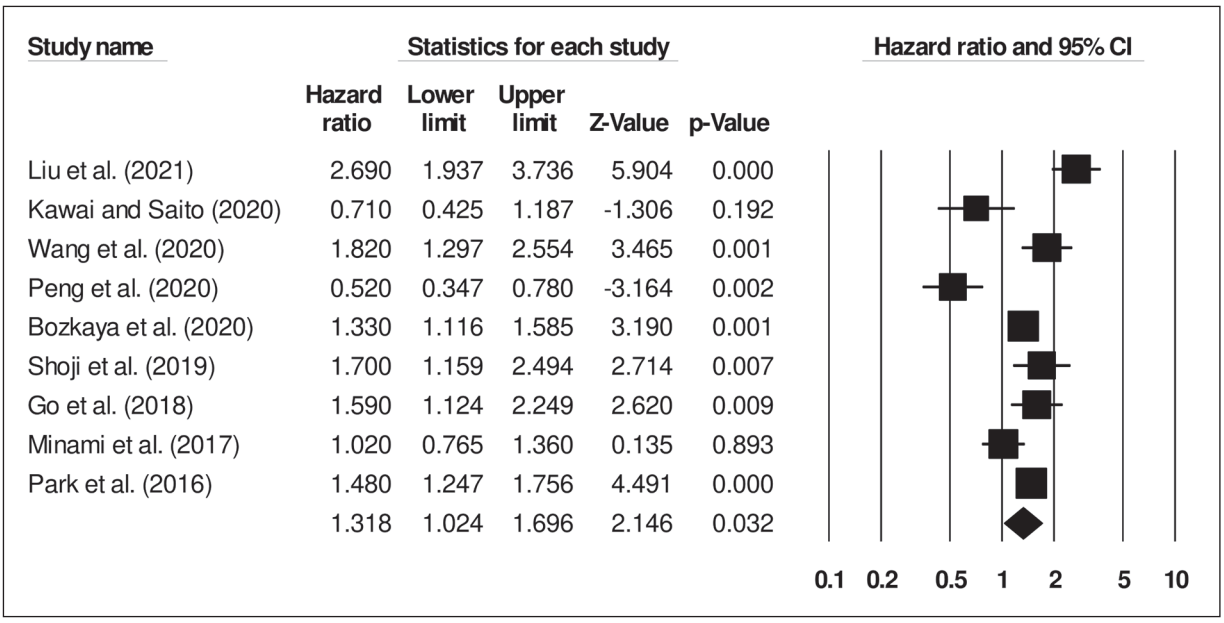

Figure 4. Demonstrates the forest plot for studies evaluating the comparative progression-free survival outcome between lung cancer patients undergoing chemotherapy with low or high prognostic nutritional index. The hazard ratios are presented as black boxes whereas 95% confidence intervals are presented as whiskers. A higher hazard ratio represents higher risks of low prognostic nutritional index on progression-free survival, a lower hazards ratio represents higher risks of high prognostic nutritional index on progression-free survival.

0.81 to 1.94, p=0.29), with negligible heterogeneity (I^2: 0%).

Non-small cell lung cancer

Progression-free survival outcomes of non-small lung cancer patients undergoing chemotherapy with low or high prognostic nutritional index were reported by 7 studies [26,28,30,33,34,46,47]. We observed an increased hazards ratio that suggests worse progression-free survival outcome for patients with lower levels of prognostic nutritional index as compared to patients with higher prognostic nutritional index (Figure 6) (Hazard ratio: 1.32, 95% C.I: 0.97 to

Table I. Demonstrates the details of the included studies.

Study	Country	Type of study	Sample descriptive	Age	Period	Histological type	Treatment	TNM stage	Follow-up	Prognostic nutritional index cut-off and (n)	Overall survival (months)	Survival outcome
Liu et al[28] (2021)	China	Retrospective cohort study	123 (25F, 98M)	59.9 ± 11.3	2018-2019	NSCLC	Programmed cell death protein 1 inhibitor	IIIB, IV	-	<46.05: 53 ≥46.05: 70	<46.05: 3 ≥46.05: 8.6	Progression-free survival 2.69 (1.75 to 4.15) Overall survival 7.22 (4.08 to 12.78)
C. Wang et al[48] (2021)	China	Retrospective cohort study	301 (96F, 205M)	56	2008-2009	SCLC	Platinum based chemotherapy	-	-	<53.85: 122 ≥53.85: 179	<53.85: 11 ≥53.85: 18	Overall survival 0.65 (0.49 to 0.85)
Qi et al[31] (2021)	China	Retrospective cohort study	53 (19F, 34M)	-	2015-2020	SCLC	Chemotherapy with atezolizumab	-	17.1-month	<48: - ≥48:-	<48: - ≥48: -	Overall survival 1.13 (0.38 to 3.36)
Kawai and Saito[46] (2020)	Japan	Retrospective cohort study	22 (3F, 19M)	68	-	NSCLC	Platinum based chemotherapy	I, II, III	-	<46.7: - ≥46.7:-	<46.7: - ≥46.7:-	Progression-free survival 0.71 (0.36 to 1.39)
J. Wang et al[34] (2020)	China	Retrospective cohort study	99 (33F, 66M)	-	2011-2019	NSCLC	Chemotherapy with cisplatin, carboplatin	-	3-month	<52.5: 54 ≥52.5: 45	<52.5: 10.81 ≥52.5: 20.45	Progression-free survival: 1.82 (1.17 to 2.85) Overall survival: 1.74 (1.06 to 2.86)
Peng et al[30] (2020)	China	Retrospective cohort study	102 (15F, 87M)	62	2017-2019	NSCLC	Programmed cell death protein 1 inhibitor	IIIB, IV	-	<45: - ≥45: -	<45: 4.2 ≥45: 11.5	Progression-free survival: 0.52 (0.30 to 0.87) Overall survival: 0.35 (0.20 to 0.63)
Bozkaya et al[26] (2020)	Turkey	Retrospective cohort study	333 (40F, 293M)	61	2008-2018	NSCLC	Chemotherapy Platinum doublets	-	3-month, 2 years	<46.7: 184 ≥46.7: 149	<46.7: 10.6 ≥46.7: 15.3	Progression-free survival 1.33 (1.06 to 1.68) Overall survival 1.56 (1.18 to 2.05)
Shen et al[32] (2020)	China	Retrospective cohort study	186 (48F, 137M)	56.1 ± 9.9	2014-2014	NSCLC	Platinum based chemotherapy	IIIB, IV	-	<50.45: 76 ≥50.45: 110	<50.45: 11.86 ≥50.45: 17.9	Overall survival 0.46 (0.29 to 0.72)
Matsubara et al[29] (2020)	Japan	Retrospective cohort study	24 (7F, 17M)	64.5	2018-2019	NSCLC	Programmed cell death protein 1 inhibitor	-	-	<40: 17 ≥40: 7	<40: - ≥40: -	Overall survival 7.28 (0.92 to 57.4)
Li et al[27] (2019)	China	Retrospective cohort study	315 (102F, 213M)	58.5	2010-2011	NSCLC	Chemotherapy, epidermal growth factor receptor-tyrosine kinase inhibitors	IIIB, IV	3-month, 2 years	<50: 179 ≥50: 136	<50: 14.4 ≥50: 17.95	Overall survival 1.52 (1.19 to 1.94)
Shoji et al[33] (2019)	Japan	Retrospective cohort study	102 (29F, 73M)	69	2015-2019	NSCLC	Chemotherapy with nivolumab, pembrolizumab, atezolizumab, pembrolizumab	IIIA, IIIB, IIIC, IVA, IVB	6.7-month	<40: - ≥40: -	<45.5: 7.2 ≥45.5: 17.4	Progression-free survival 1.70 (1.03 to 2.82) Overall survival 1.60 (0.95 to 2.74)
Go et al[44] (2018)	South Korea	Retrospective cohort study	220 (27F, 193M)	68	2006-2017	SCLC	Platinum based chemotherapy	-	4.1 years	≤45: 100 >45: 120	≤45: - >45: -	Progression free survival 1.59 (1.009 to 2.511) Overall survival 1.91 (1.20 to 3.02)
Minami et al[35] (2017)	Japan	Retrospective cohort study	97 (20F, 77M)	70.5 ± 8.7	2007-2016	SCLC	Chemotherapy with cisplatin, carboplatin, etoposide	IIIB, IV	-	<44.3: 46 ≥44.3: 51	<44.3: 7.6 ≥44.3: 12.4	Progression-free survival 1.02 (0.70 to 1.49) Overall survival 0.50 (0.31 to 0.78)
Park et al[47] (2016)	South Korea	Retrospective cohort study	630 (236F, 394M)	64	2002-2014	NSCLC	Chemotherapy with tyrosine kinase inhibitor	-	-	<45: 177 ≥45: 453	<45: - ≥45: -	Progression free survival 1.48 (1.18 to 1.85) Overall survival 1.97 (1.51 to 2.57)
S. Hong et al[19] (2015)	China	Retrospective cohort study	724 (97F, 627M)	59	2006-2013	SCLC	Chemotherapy with etoposide, irinotecan	-	39.4-month	<45: 162 ≥45: 757	<52.48: 15.9 ≥52.48: 25.2	Overall survival 0.71 (0.58 to 0.87)
X. Hong et al[45] (2015)	China	Retrospective cohort study	919 (635F, 284M)	56	2000-2012	SCLC	Chemotherapy	-	-	<45: 162 ≥45: 757	<45: 8.7 ≥45: 11	Overall survival 1.14 (0.93 to 1.40)

M: Male, F: Female, NSCLC: Non-small cell lung cancer, SCLC: Small cell lung cancer.

Table II. Risk of bias for individual studies based on the Newcastle Ottawa scale.

	Selection			Comparability			Outcome			Total
Study	Representative of the exposed cohort	Selection of external cohort	Ascertainment of exposure	Outcome of interest does not present at start	Main factor	Additional factor	Assessment of outcome	Sufficient follow up	Adequacy of follow up	(9/9)
Liu et al[28] (2021)	+	+	0	+	+	+	0	+	+	7
Wang et al[48] (2021)	+	+	0	0	0	+	0	+	+	5
Qi et al[31] (2021)	+	+	0	+	+	+	0	+	+	7
Kawai and Saito[46] (2020)	+	+	0	0	+	+	0	+	+	6
Wang et al[34] (2020)	+	+	0	+	+	+	0	+	+	7
Peng et al[30] (2020)	+	+	0	0	+	+	0	+	+	6
Bozkaya et al[26] (2020)	+	+	0	0	0	+	0	+	+	5
Shen et al[32] (2020)	+	+	0	0	+	+	0	+	+	6
Matsubara et al[29] (2020)	+	+	0	0	+	+	0	+	+	6
Li et al[27] (2019)	+	+	0	0	0	+	0	+	+	5
Shoji et al[33] (2019)	+	+	0	0	+	+	0	+	+	6
Go et al[44] (2018)	+	+	0	0	0	+	0	+	+	5
Minami et al[35] (2017)	+	+	0	0	+	+	0	+	+	6
Park et al[47] (2016)	+	+	0	0	0	+	0	+	+	5
Hong et al[19] (2015)	+	+	0	0	+	+	0	+	+	6
Hong et al[45] (2015)	+	+	0	0	0	+	0	+	+	5

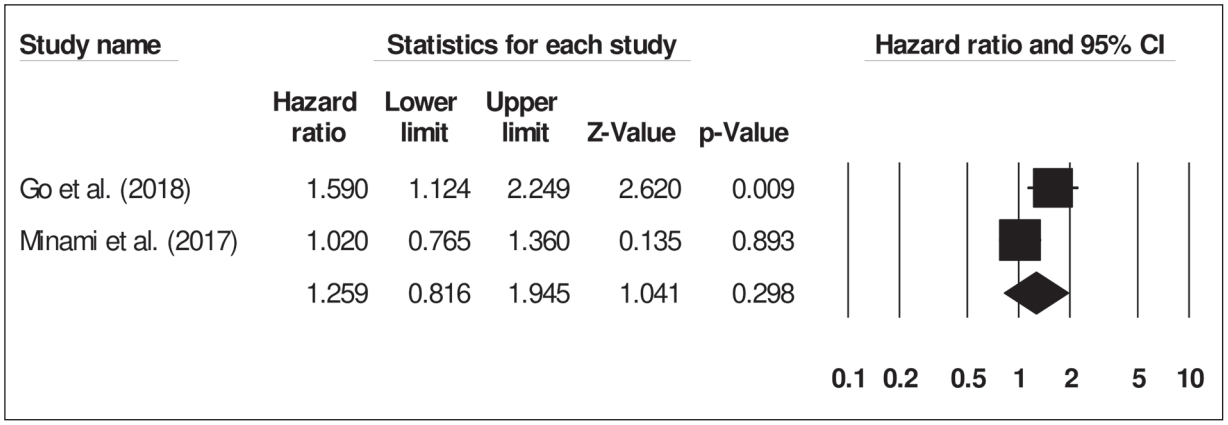

Figure 5. Demonstrates the forest plot for studies evaluating the comparative progression-free survival outcome between small lung cancer patients undergoing chemotherapy with low or high prognostic nutritional index. The hazard ratios are presented as black boxes whereas 95% confidence intervals are presented as whiskers. A higher hazard ratio represents higher risks of low prognostic nutritional index on progression-free survival, a lower hazards ratio represents higher risks of high prognostic nutritional index on progression-free survival.

1.81, p=0.07), with moderate heterogeneity (I^2: 42.17%).

Overall Survival

Overall survival of lung cancer patients undergoing chemotherapy with low or high prognostic nutritional index was reported by 15 studies [19,26-35,43,44,46,47]. We observed an increased hazards ratio indicative of worse overall survival for patients with lower levels of the prognostic nutritional index as compared to patients with higher prognostic nutritional index (Figure 7) (Hazard ratio: 1.21, 95% C.I: 0.89 to 1.66, p=0.21), with moderate heterogeneity (I^2: 43.06%). Additional subgroup analyses were carried out to evaluate the predictability of the prognostic nutritional index according to histological subtype and cut-off values.

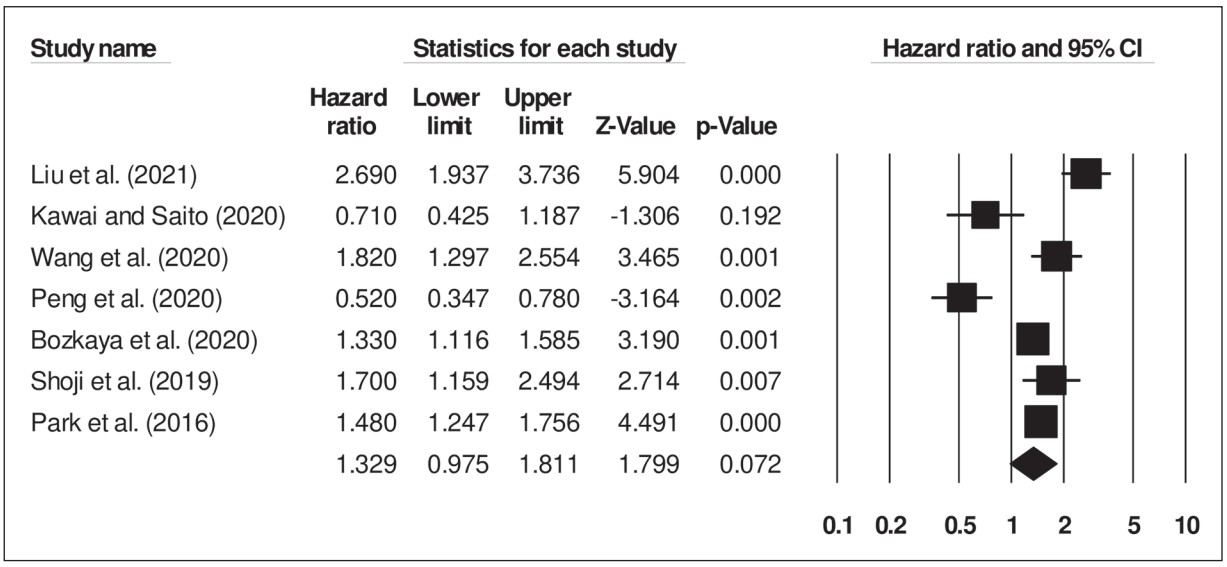

Figure 6. Demonstrates the forest plot for studies evaluating the comparative progression-free survival outcome between non-small lung cancer patients undergoing chemotherapy with low or high prognostic nutritional index. The hazard ratios are presented as black boxes whereas 95% confidence intervals are presented as whiskers. A higher hazard ratio represents higher risks of low prognostic nutritional index on progression-free survival, a lower hazards ratio represents higher risks of high prognostic nutritional index on progression-free survival.

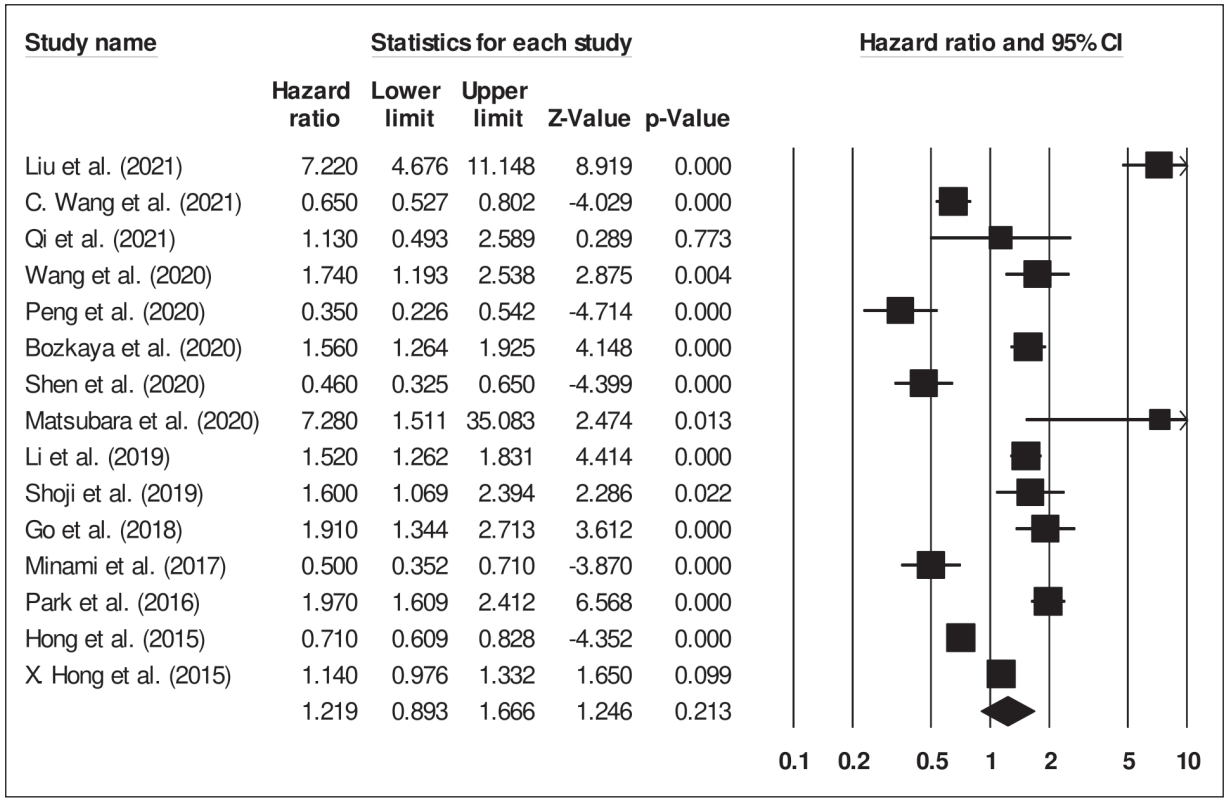

Figure 7. Demonstrates the forest plot for studies evaluating the comparative overall survival outcome between lung cancer patients undergoing chemotherapy with low or high prognostic nutritional index. The hazard ratios are presented as black boxes whereas 95% confidence intervals are presented as whiskers. A higher hazard ratio represents higher risks of a low prognostic nutritional index on overall survival, a lower hazards ratio represents higher risks of a high prognostic nutritional index on overall survival.

Small cell lung cancer

Overall survival of small lung cancer patients undergoing chemotherapy with low or high prognostic nutritional index was reported by six studies. We observed a reduced hazards ratio suggesting worse overall survival for patients with high levels of the prognostic nutritional index as compared to patients with lower prognostic nutritional index (Figure 8) (Hazard ratio: 0.88, 95% C.I: 0.63 to 1.24, p=0.48), with moderate heterogeneity (I^2: 26.3%).

Non-small cell lung cancer

The outcome of overall survival between non-small lung cancer patients undergoing chemotherapy with low or high prognostic nutritional index was reported by nine studies. We observed an increased hazards ratio suggesting worse overall survival for patients with low levels of the prognostic nutritional index as compared to patients with high prognostic nutritional index (Figure 9) (Hazard ratio: 1.52, 95% C.I: 0.97 to 2.39, p=0.06), with moderate heterogeneity (I^2: 48.6%).

Prognostic nutritional index cut-off value 40

The outcome of overall survival in lung cancer patients undergoing chemotherapy with low or high prognostic nutritional with an index cut-off value 40 was reported by two studies. We observed an increased hazards ratio suggesting worse overall survival for patients with low levels of the prognostic nutritional index as compared to patients with high prognostic nutritional index (Figure 10) (Hazard ratio: 2.79, 95% C.I: 0.66 to 11.72, p=0.15), with no heterogeneity (I^2: 0%).

Prognostic nutritional index cut-off value 45

Overall survival in lung cancer patients undergoing chemotherapy with low or high prognostic nutritional index with a cut-off value of 45 was reported by four studies. We observed an increased

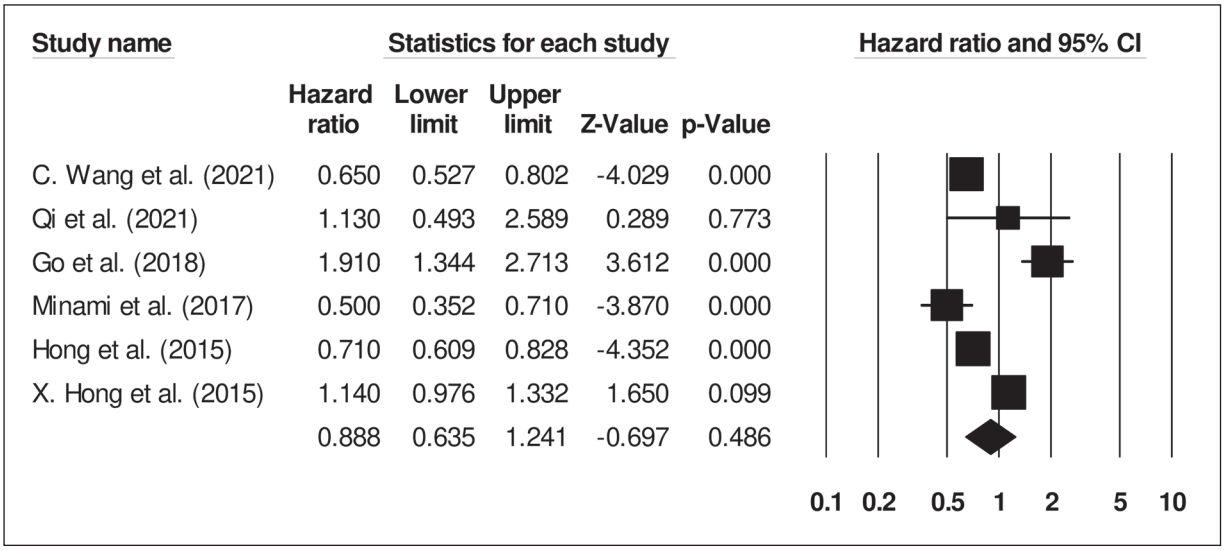

Figure 8. Demonstrates the forest plot for studies evaluating the comparative overall survival outcome between small lung cancer patients undergoing chemotherapy with low or high prognostic nutritional index. The hazard ratios are presented as black boxes whereas 95% confidence intervals are presented as whiskers. A higher hazard ratio represents higher risks of a low prognostic nutritional index on overall survival, a lower hazards ratio represents higher risks of a high prognostic nutritional index on overall survival.

hazards ratio indicative of worse overall survival for patients with low levels of the prognostic nutritional index as compared to patients with high prognostic nutritional index (Figure 11) (Hazard ratio: 1.13, 95% C.I: 0.65 to 1.97, p=0.65), with moderate heterogeneity (I^2: 48.6%).

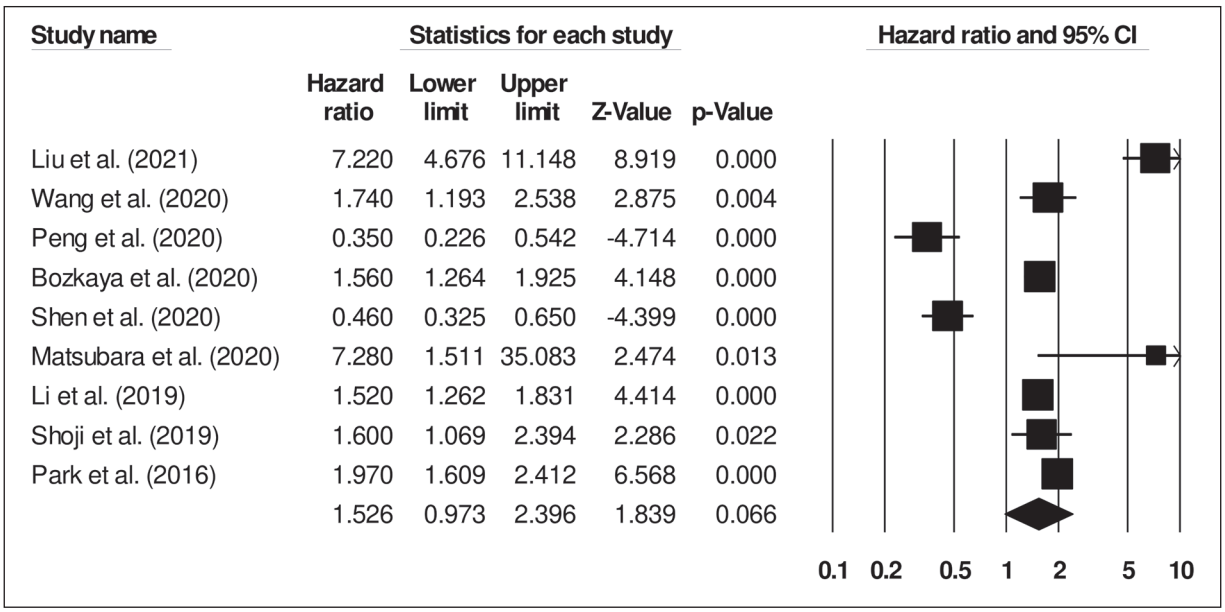

Figure 9. Demonstrates the forest plot for studies evaluating the comparative overall survival outcome between non-small lung cancer patients undergoing chemotherapy with low or high prognostic nutritional index. The hazard ratios are presented as black boxes whereas 95% confidence intervals are presented as whiskers. A higher hazard ratio represents higher risks of a low prognostic nutritional index on overall survival, a lower hazards ratio represents higher risks of a high prognostic nutritional index on overall survival.

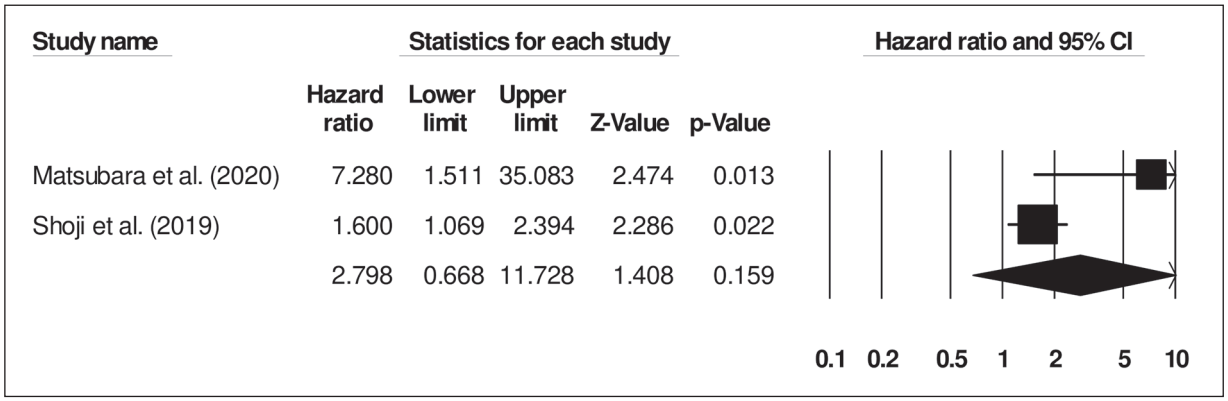

Figure 10. Demonstrates the forest plot for studies evaluating the comparative overall survival outcome between lung cancer patients undergoing chemotherapy with low or high prognostic nutritional index (cut-off value 40). The hazard ratios are presented as black boxes whereas 95% confidence intervals are presented as whiskers. A higher hazard ratio represents higher risks of a low prognostic nutritional index on overall survival, a lower hazards ratio represents higher risks of a high prognostic nutritional index on overall survival.

Discussion

This systematic review and meta-analysis provide preliminary evidence of the association between worse progression-free and overall survival and lower prognostic nutrition index scores in lung cancer patients undergoing chemotherapy. We also report that lower prognostic nutritional index scores are associated with worse overall survival outcomes in patients with non-small lung cancer histological subtypes and lower prognostic nutritional index cut-off values.

Management of lung cancer is considered one of the most challenging aspects for clinicians because of its poor prognostic outlook, and heterogeneous manifestations[49-51]. Recent studies[52-54] suggest that there is an ever-growing need for effective biomarkers that may enhance the efficacy of existing personalized oncologic interventions. The use of prognostic nutritional index has garnered a lot of attention in the past decade[55]. The prognostic nutritional index has been repeatedly identified as a biomarker that can predict survivability (i.e., overall, progression-free, dis-

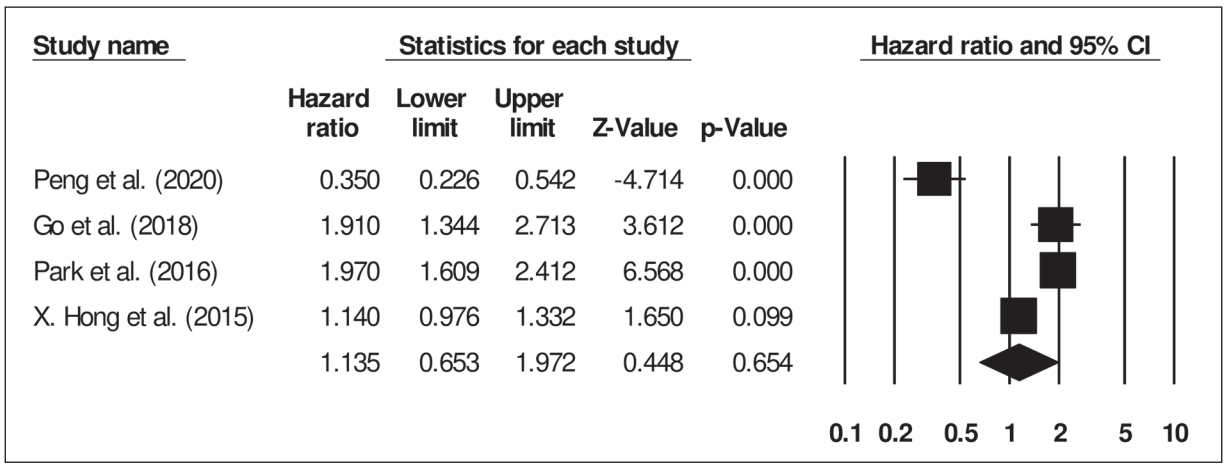

Figure 11. Demonstrates the forest plot for studies evaluating the comparative overall survival outcome between lung cancer patients undergoing chemotherapy with low or high prognostic nutritional index (cut-off value 45). The hazard ratios are presented as black boxes whereas 95% confidence intervals are presented as whiskers. A higher hazard ratio represents higher risks of a low prognostic nutritional index on overall survival, a lower hazards ratio represents higher risks of a high prognostic nutritional index on overall survival.

ease-free) in patients with cancer with a high levels of sensitivity and specificity[16-18,55-57]. Onodera et al[21] (1984) reported that prognostic nutritional index is a reliable indicator of the levels of serum albumin and the lymphocyte count, which eventually may help in the development of effective personalized oncologic interventions. For instance, evidence of poor pre-treatment nutritional, immunological status (i.e., lower prognostic nutritional index score) may allow clinicians to aptly modify the dosage of the chemotherapeutic agent or take additional precautionary steps to allow a better survivability outcome for patients.

In the present systematic review, we observed that most of the included studies reported a negative influence of lower prognostic nutritional index scores on the outcome of progression-free survival in lung cancer patients undergoing chemotherapy. For instance, in a cohort study of the Chinese population, Liu et al[28] (2021) reported significantly (p<0.001) poorer progression-free survival for the group with a lower prognostic nutritional index as compared to the group with a higher prognostic nutritional index (i.e., >46.05: 8.6 months *vs.* ≤46.05: 3 months). The authors also reported that the group with a lower prognostic nutritional index had almost 4-fold higher risk of early progression, possibly because of the poor innate immunity of the patients that limited the anti-tumor effect of programmed cell death protein 1 inhibitors. Similarly, J. Wang et al[34] (2020) reported worse progression-free survival outcomes in lower prognostic nutritional index scoring group. The authors additionally compared the prognostic influence of the prognostic nutritional index with that of the peripheral blood neutrophil to lymphocyte ratio. The study showed that the prognostic nutritional index was more efficient in predicting the survivability outcomes in non-small lung cancer patients receiving platinum-based chemotherapy. The authors, however, cautioned that the observed differences between the two scoring methodologies may be influenced by methodological limitations of the study (i.e., variable cases, tumor stages, and gene mutation status). In our present meta-analysis, we confirm these findings and report a significantly (p<0.05) higher impact of a lower prognostic nutritional index score (HR: 1.31) on progression-free survival in lung cancer patients undergoing chemotherapy. We also show that markedly worse outcomes were associated with an insignificantly (p>0.05) lower prognostic nutritional index score in patients with non-small lung cancer (1.32) and small cell lung cancer (1.25) undergoing chemotherapy.

In the present review we attempted to develop a consensus regarding the ability of the prognostic nutritional index to predict overall survival in lung cancer patients undergoing chemotherapy. Our meta-analysis indicated that although our findings were not statistically significant, studies reported poor overall survival outcomes in lung cancer patients with lower prognostic nutritional index scores (1.21) as compared to patients with a higher prognostic nutritional index score. We also observed that the outcomes differed in terms of histological subtypes of lung cancer. Worse overall survival outcomes were associated with insignificant lower prognostic nutritional index score in patients with non-small lung cancer (1.52), whereas an insignificant opposite effect (0.88) was noted for patients with small lung cancer. Matsubara et al[29] (2020) retrospectively evaluated the predictive capacity of the prognostic nutritional index in a Japanese cohort of lung cancer patients receiving atezolizumab and reported that prognostic nutritional index not only predicted the overall survival but that this biomarker was also successful in predicting time to treatment failure (i.e., duration between atezolizumab start and discontinuation). Similarly, Shoji et al[33] (2019) reported that lower levels of prognostic nutritional index reliably predicted the overall survival outcomes in non-small lung cancer patients receiving immune checkpoint inhibitors. The authors also demonstrated that the pretreatment evaluation of prognostic nutritional index was an effective measure to anticipate treatment response and dosage of the immune checkpoint inhibitors. For instance, significantly higher levels of the prognostic nutritional index were reported in patients with ≥5 cycles (i.e., 45.9 ± 0.9) as compared to patients with ≤4 cycles (i.e., 42.4 ± 1.0). While we did not report significant impact of the prognostic nutritional index on the overall survival outcome and progression-free survival, we recommend further evaluating these parameters for their importance based on existing literature[17,28].

Despite being a novel study, few limitations existed in the present systematic review and meta-analysis. Firstly, in our meta-analyses we observed scarce significance in the data we observed. We presume that the insignificance in our outcome could have primarily rooted from the limited number of studies in the sub-group analyses. Secondly, the studies included in this present meta-analysis used different cut-off ranges for the

prognostic nutritional index. Therefore, we could only carry out subgroup analyses for two cut-off ranges, i.e., 40 and 45. In the rest of the studies, different cut-off values have been reported and the data could not be pooled. Therefore, we recommend our readers to interpret our results with caution due to a possibility of incurring bias. Future studies are merited to address these limitations to determine uniform prognostic nutritional index cut-off values. This would allow clinicians to use this biomarker more reliably, and to better interpret the prognostic survival outcome of lung cancer patients undergoing chemotherapy.

Conclusions

We provide preliminary evidence of the association between worse survivability outcomes, such as progression-free and overall survival, and lower prognostic nutrition index scores in lung cancer patients undergoing chemotherapy. We also report worse overall survival outcomes with lower prognostic nutritional index scores in patients with non-small lung cancer as compared to patients with small lung cancer undergoing chemotherapy. These findings from this present systematic review and meta-analysis would allow researchers and clinicians to develop effective risk stratification tools that will effectively predict the survivability outcomes in lung cancer patients undergoing chemotherapy.

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Availability of Data and Materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions
QZ conceived and designed the study. JB and ZZ collected the data and performed the literature search. QZ was involved in the writing of the manuscript. MJ edited the manuscript. All authors have read and approved the final manuscript.

Ethical Approval
Not applicable.

Patients Consent
Not applicable.

Conflict of Interest
The authors declare that they have no competing interests.

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