European Review for Medical and Pharmacological Sciences 2023; 27: 8144-8153

Naples prognostic score as a predictor of outcomes in lung cancer: a systematic review and meta-analysis

Y.-S. WANG, L. NIU, W.-X. SHI, X.-Y. LI, L. SHEN

Department of Oncology, Changxing County Hospital of Traditional Chinese Medicine, Changxing Country, Zhejiang Province, China

Abstract. – OBJECTIVE: The Naples prognostic score (NPS) is a newly developed indicator of inflammation and nutritional status. However, its role in predicting the prognosis of lung cancer is unclear. We hereby reviewed the association between NPS and outcomes of lung cancer.

MATERIALS AND METHODS: PubMed, Web of Science, Embase, and Google Scholar were searched up to 15th April 2023 for studies assessing the predictive role of NPS for overall survival (OS) and disease-free survival (DFS) in lung cancer.

RESULTS: Seven studies were included. All were from China. One study was on small cell lung cancer, while the rest were on non-small cell lung cancer. Meta-analysis demonstrated that a high NPS score was a significant predictor of OS (HR: 3.21 95% CI: 2.27, 4.54 I^2=62%) and disease-free survival (DFS) (HR: 3.81 95% CI: 2.57, 5.64 I^2=65%) in lung cancer patients. Subgroup analysis based on different NPS reference values also showed similar results. The results remained significant on sensitivity analysis.

CONCLUSIONS: The NPS is a strong and independent prognostic indicator of lung cancer patients. Higher NPS scores are associated with worse OS and DFS. Further studies from non-Chinese populations are needed to supplement the results.

Key Words:
Carcinoma, Tumor, Prognosis, Survival, Recurrence.

Introduction

Lung cancer is the commonest cause of cancer-related death across the globe and the second most common diagnosis amongst newly detected malignant cases[1]. The burden of the disease is indeed high, with around 2 million cases being detected every year, which represents 12% of all cancer cases seen worldwide[2]. Based on the pathological subtype, the majority of cases are of non-small cell lung cancer (NSCLC), while approximately 10-15% constitute small cell lung cancer (SCLC)[3,4]. Delayed diagnosis due to late presentation of symptoms is commonly seen in lung cancer, because of which a large number of patients are diagnosed with advanced disease and often with metastasis. Not surprisingly, as surgery is unfeasible in many advanced cases, lung cancer has one of the worst prognoses among solid malignancies[5]. In recent times, the use of immune checkpoint inhibitors has shown promising results. However, the 5-year survival rates are still poor[2]. Identifying lung cancer patients who are at a higher risk of recurrence and mortality has been difficult due to the many variables that can affect the outcome of the disease[3,4]. A reliable, accurate, and easy-to-use prognostic marker can aid in the identification of patients at risk, which can be targeted with personalized treatment plans and additional monitoring to improve outcomes.

Previous studies[6-8] have linked systemic inflammation with the development and progression of cancer. Studies[6,7] have found a link between inflammation and DNA mutations, the proliferation of blood vessels, cancer growth, invasion, and metastasis. It is postulated that markers representing systemic inflammation would therefore aid in predicting outcomes of cancer[8]. In this context, there have been several inflammation-based markers-based markers like neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio, systemic inflammation score (SIS), Glasgow prognostic score, etc., which have been advocated for prognostication of cancer patients[8-10]. However, no marker has demonstrated absolute accuracy in predicting outcomes, and the search for a more suitable one is still under research.

Recently, the Naples prognostic score (NPS) has generated significant interest as a marker of inflammation and the nutritional status of the patient. The score is generated from serum albumin

Corresponding Author: Lei Shen, MD; e-mail: Shenlei9216@163.com

concentration, total blood cholesterol, NLR, and LMR and is an independent prognostic indicator in colorectal cancer[11]. However, its ability to predict outcomes for lung cancer is unclear. We hereby systematically reviewed the evidence on the association between NPS and outcomes of lung cancer.

Materials and Methods

Search and Inclusion Criteria

The systematic review protocol was uploaded on PROSPERO before the commencement of the literature search (CRD42023414641). It was ensured that the PRISMA guidelines were followed[12]. An all-embracing literature search was carried out by two reviewers separately. The databases included PubMed, Web of Science, Embase, and Google Scholar. All articles available online, irrespective of the date of publication up to 15th April 2023, were eligible for inclusion. Due to limitations of translation, only English language publications were considered. The search was carried out using the following combination of keywords: "Naples prognostic score" AND "lung cancer".

Eligible studies were: 1. Studies conducted on lung cancer patients. 2. Assessing the prognostic ability of NPS by comparing patients with high *vs*. low NPS scores. 3. Outcomes reported were overall survival (OS) or disease-free survival (DFS). 4. Outcome reported in the form of multivariable-adjusted effect size. There was no restriction on the sample size, follow-up duration, or type of lung cancer.

Excluded studies were: 1. Studies not exclusively on lung cancer. 2. Studies not reporting adjusted ratios. 3. Studies with duplicate/overlapping data. If two or more articles used the same dataset from the same period, the study with the highest number of patients was included. Review articles and editorials were not considered for inclusion.

Duplicates from the search results were removed, and the remaining records were carefully inquired about based on the eligibility criteria by two reviewers separately. This was done first at the title/abstract level and then at the full-text level. Articles completing all eligibility criteria were included. Any disagreements were solved by consensus. The references list of eligible articles was hand searched for additional articles.

Data Management and Study Quality

Data on the author's last name, year of publication, location, inclusion criteria, sample size, age, gender, smokers, stage of cancer, poorly differentiated cancer, type of treatment, number of patients with NPS score of 1 or 2, follow-up duration, and outcome ratios were extracted by two reviewers independent of each other.

Two authors judged the study's quality based on Newcastle Ottawa Scale (NOS)[13]. The NOS has three domains: representativeness of the study cohort, comparability, and measurement of outcomes. Points are given based on the preformatted questions. The final score of a study can range from 0-9.

Statistical Analysis

Statistical analysis was done using "Review Manager" [RevMan, version 5.3; Nordic Cochrane Centre (Cochrane Collaboration), Copenhagen, Denmark; 2014]. We extracted data on the association between NPS and OS or DFS from the included studies. Data were combined to generate pooled outcomes as hazard ratio (HR) with 95% confidence intervals (CI) in a random-effects model. Due to limited data, funnel plots were not generated. The I^2 statistic was the tool to determine inter-study heterogeneity. I^2<50% meant low, and >50% meant substantial heterogeneity. A leave-one-out analysis was performed to check for any change in the results on the exclusion of any study. Subgroup analysis was done based on the score of NPS. p-value <0.05 was considered statistically significant.

Results

Search results at each step of the literature analysis are shown in Figure 1. At first, 167 studies were retrieved. Duplicates amongst those were removed, leaving 142 results. The reviewers examined these articles for primary eligibility, and 130 were excluded due to non-relevance. The 12 studies which were selected for full-text analysis underwent detailed examination, and seven[14-20] were found to be appropriate based on the inclusion criteria. The remaining five studies were excluded for reasons mentioned in Figure 1.

Table I represents the details extracted from included studies. The studies were published between 2021 to 2023, and all of them were from China. All included studies were designed as retrospective. One study[16] was on SCLC while all others[14,15,17-20] were on NSCLC. A total of 1,657 were included in the studies. The mean/median age of patients was more than 56 years in all studies. The percentage of male patients ranged

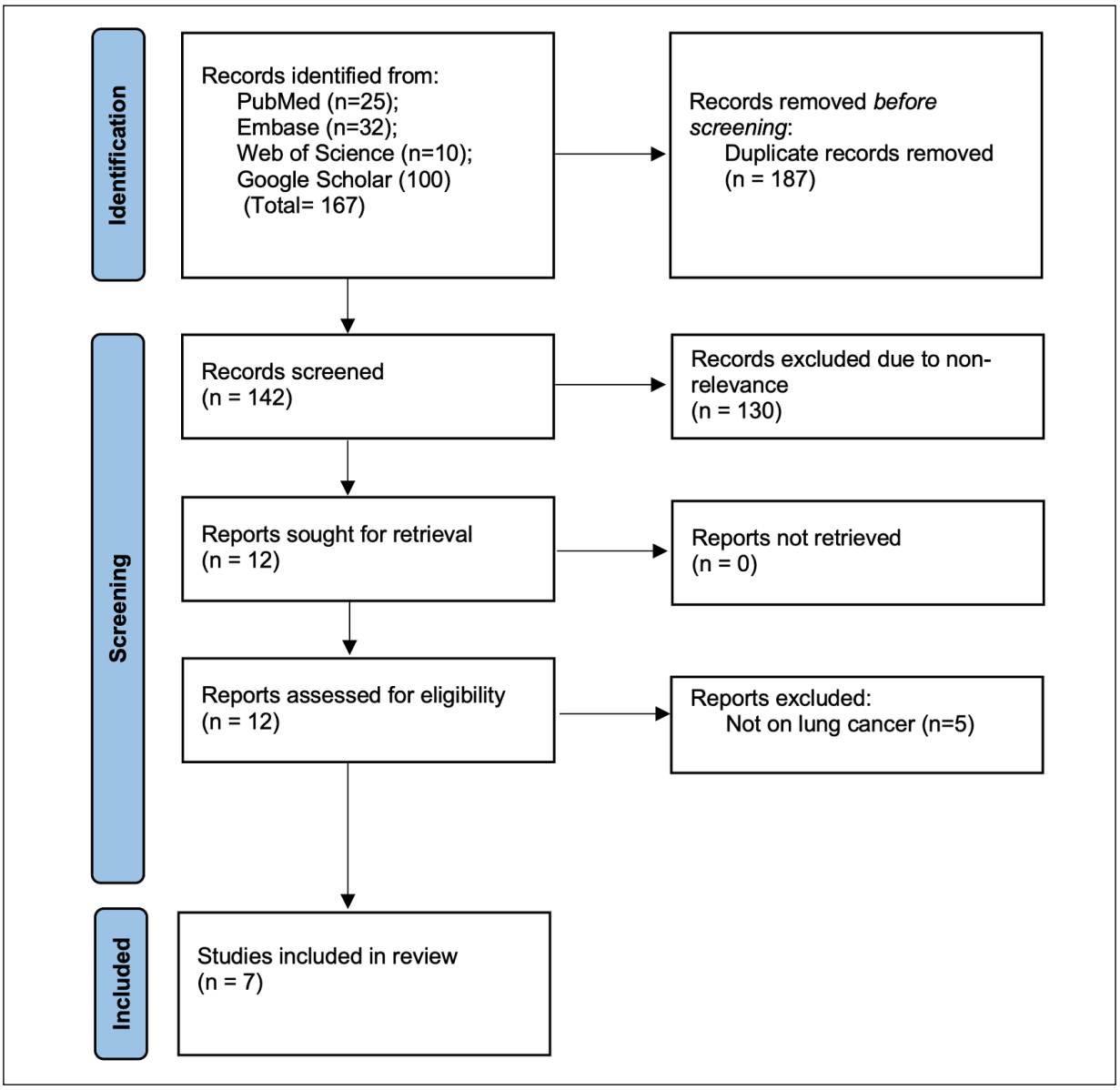

Figure 1. Study flowchart.

from 44.8 to 75.8%. About 29.5 to 60.9% of patients were smokers. The stage of cancer varied amongst studies. Overall, all stages of lung cancer were included in the review. Two studies[15,18] included only surgically treated patients, while one study[20] included patients under radiotherapy only. In the remaining studies, a mix of treatment options was provided to the patients. The median follow-up was more than two years across studies. On the risk of bias analysis, the studies were given a score of 7 or 8 on the NOS scale.

A meta-analysis of OS is shown in Figure 2. Separate meta-analyses were carried out based on the NPS group examined by the included studies. Overall, it was noted that a high NPS score was a significant predictor of OS in lung cancer patients (HR: 3.21 95% CI: 2.27, 4.54 I^2=62%). On subgroup analysis, NPS scores of 1 *vs.* 0 (HR: 7.46 95% CI: 4.03, 13.82 I^2=0%), 2 *vs.* 0 (HR: 7.46 95% CI: 4.03, 13.82 I^2=0%), 1-2 *vs.* 0 (HR: 2.07 95% CI: 1.64, 2.61 I^2=0%), and 3-4 *vs.* 0 (HR: 10.48 95% CI: 4.37, 25.14 I^2=0%) were all predictive of OS. The results of the analysis did not turn non-significant on the exclusion of any study.

A meta-analysis of DFS is shown in Figure 3. Overall, we found NPS to be a significant predictor of DFS in lung cancer patients (HR: 3.81 95% CI: 2.57, 5.64 I^2=65%). On subgroup analysis,

Table I. Study details.

Study	Location	Included patients	Sample size	Age (years)	Male gender (%)	Smokers (%)	Poorly differentiated (%)	Stage	Treatment	Patients with NPS score 1 (n)	Patients with NPS score 2 (n)	Follow-up	NOS score
Zou et al 2023[19]	China	Locally advanced NSCLC	165	NR	44.8	48.5	56.4	IIIA & B	Neoadjuvant chemotherapy and surgery	108	22	Median 34 months	8
Xuan et al 2022[20]	China	NSCLC with brain metastasis	186	57	45.7	53.2	55.9	I-III	Radiotherapy	NR	NR	Median 32 months	8
Ren et al 2022[18]	China	Surgically treated NSCLC	120	61	49.2	29.5	NR	I-III	Surgery	161	38	Median 32 months	8
Peng et al 2022[17]	China	NSCLC patients	395	63	63.8	49.4	NR	I-IV	Surgery, chemotherapy, radiotherapy	NR	NR	Median 32 months	8
Chen et al 2022[16]	China	SCLC patients	128	65	75.8	60.9	NR	NR	Surgery, chemotherapy radiotherapy	75	42	NR	7
Li et al 2021[15]	China	Early-stage NSCLC undergoing surgery	457	63.4	61.9	49	21	I-II	Surgery	122	86	Median 50 months	8
Guo et al 2021[14]	China	Unresectable NSCLC	206	62	58.3	46.1	61.6	III	Chemotherapy, radiotherapy ,	135 ,	39 ,	Median 37 months	8

NPS, Naples prognostic score; NOS, Newcastle Ottawa scale; n, number; NR, not reported; NSCLC non-small cell lung cancer; SCLC, Small cell lung cancer.

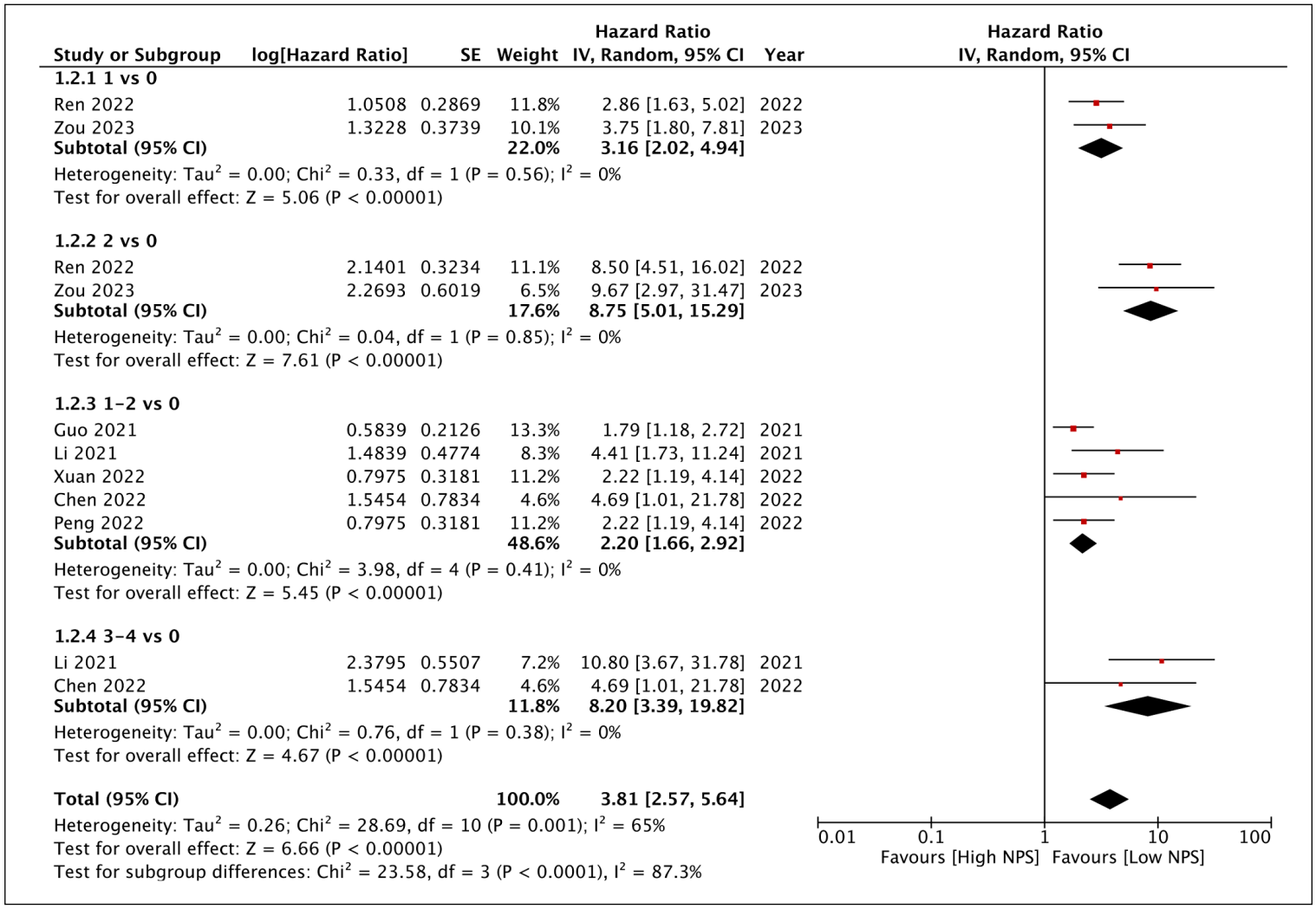

Figure 2. Meta-analysis of the association of NPS and OS in lung cancer.

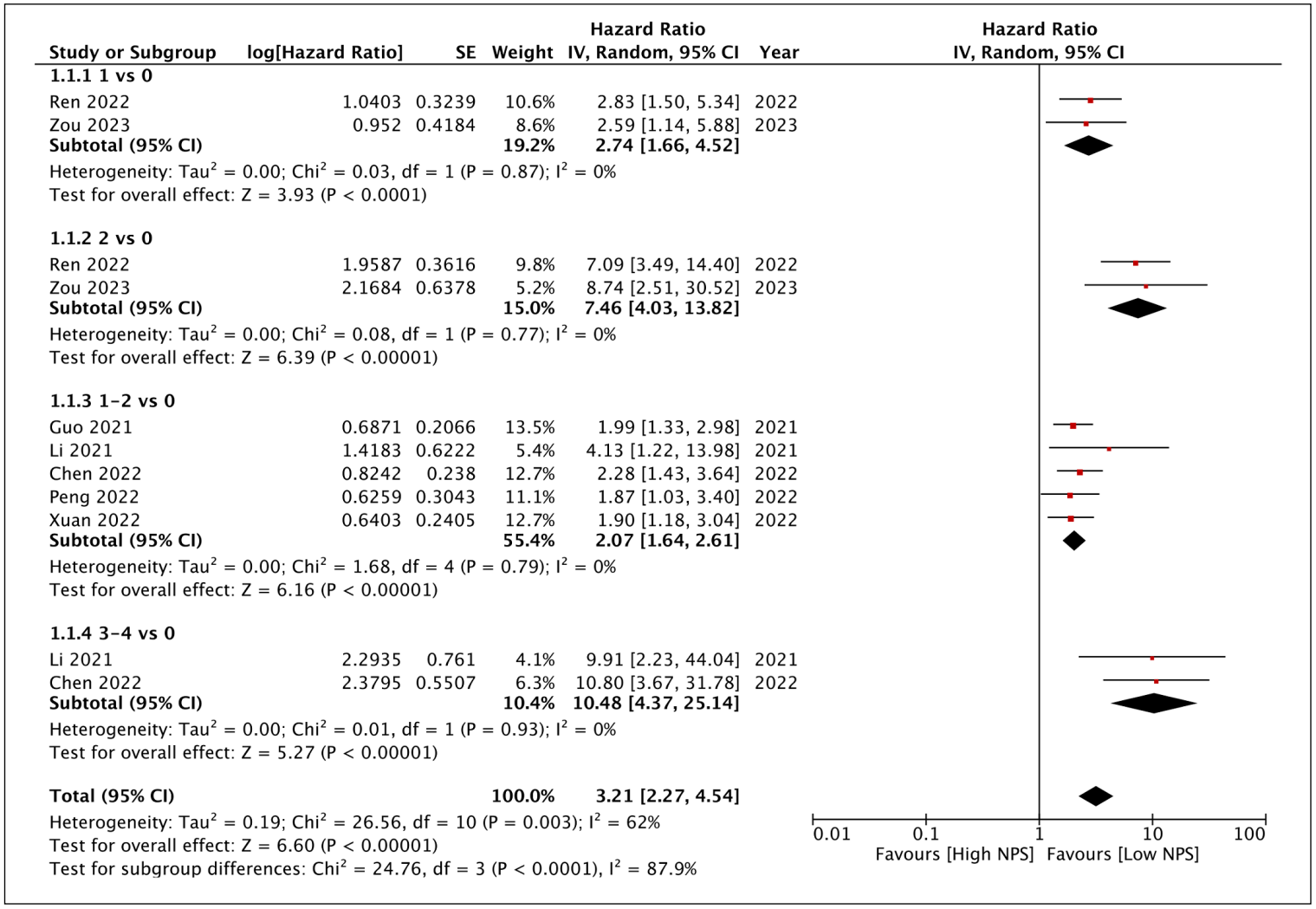

Figure 3. Meta-analysis of the association of NPS and DFS in lung cancer.

NPS scores of 1 *vs*. 0 (HR: 3.16 95% CI: 2.02, 4.94 I^2=0%), 2 *vs*. 0 (HR: 8.75 95% CI: 5.01, 15.29 I^2=0%), 1-2 *vs*. 0 (HR: 2.20 95% CI: 1.66, 2.92 I^2=0%), and 3-4 *vs*. 0 (HR: 8.20 95% CI: 3.39, 19.82 I^2=0%) were all predictive of DFS. The results of the analysis did not turn non-significant on the exclusion of any study.

Discussion

The NPS was first reported by Galizia et al[11] in 2017 to assess the prognosis of colorectal cancer. This was despite the availability of several other inflammatory and nutritional biomarkers like NLR, PLR, SIS, prognostic nutritional index (PNI), and controlling nutritional score (CONUT), which were extensively studied for the disease[11,21]. A major limitation of these markers is the lack of a common cut-off, with different studies[11,21] using variable values to assess the prognostic significance of cancer. In this context, the NPS was generated by combining four important variables i.e., NLR, LMR, cholesterol, and albumin, to overcome these limitations and generate a robust, accurate, easy-to-use marker. Unlike other markers[22,23], the NPS has a definite score ranging from 0 to 4 based on the values of individual components, which overcomes the limitation of variable cut-offs. In their study, Galizia et al[11] showed that patients with the NPS score of 1-2 and 3-4 had increasingly worse OS and DFS independent of other factors. Also, the NPS performed better compared to PNI, CONUT, and SIS. Subsequently, the NPS has generated much interest and has been reported as an independent prognostic factor for several cancers.

Li et al[24], in a retrospective analysis of 276 patients, have found NPS to be significantly associated with OS in glioblastoma, and it performed better than CONUT. Similarly, Chen et al[25] assessed the prognostic ability of NPS in a cohort of 173 HER2-positive breast cancer patients and found a significant association between NPS, OS, and DFS. Wang et al[26], in a group of renal cancer patients, have shown that high NPS scores are associated with older age, larger tumor size, worse pathological stage, higher tumor grade, and necrosis. However, NPS independently predicted OS and progression-free survival (PFS) and had the strongest discriminatory power compared to PNI and CONUT. Xiong et al[27] have noted NPS to be predictive of OS in a cohort of gastric cancer patients undergoing surgery. Similarly, Feng et al[28] found that cancer-specific survival worsened with increasing scores of NPS in esophageal cancer patients undergoing surgical resection. Furthermore, this relationship persisted even in different tumor stages. Jin et al[29] in a study on 404 patients with ampullary carcinoma undergoing pancreatoduodenectomy, have found that in addition to predicting OS and DFS, NPS was also associated with postoperative complications.

Considering the strong predictive power of NPS for various cancers, it would be interesting to know how the marker fare in cases of lung cancer. In this review, we combined data from seven different studies[14-20] to examine the prognostic value of NPS for OS and DFS in lung cancer. The analysis revealed that higher NPS scores were associated with around three times increased risk of poor OS and approximately four times higher risk of poor DFS. The results were consistent across studies which increases the validity of the results. Importantly, different NPS scores were compared with the reference score of 0 in the studies. Hence, a subgroup analysis was performed to compare NPS scores of 1 *vs*. 0, 2 *vs*. 0, 1-2 *vs*. 0, and 3-4 *vs*. 0. It was noted that NPS was predictive of OS and DFS in all subgroups and a tendency of worse outcomes was noted with higher NPS scores. For OS, a score of 2 resulted in a 7.5 times increased risk of mortality, while a score of 3-4 led to 10.48 times increased risk of death. Similarly, an NPS score of 1 was associated with 3.16 times poor DFS, while a score of 2 increased this risk by 8.75 times.

The relationship between inflammation, malnutrition, and tumor growth and progression is well-documented[8-10]. The four variables which form the NPS are all well-established markers of inflammation and malnutrition. Hypoalbuminemia directly correlates with malnutrition, with lower levels associated with postoperative complications and poor OS in different cancers[30]. Albumin levels are also congruous with systemic inflammation and immunity, with lower levels reducing macrophage activation and cancer-targeting cell-mediated immunity[31]. Nevertheless, albumin levels are influenced by diet and liver diseases which limits its use as a standalone marker. Cholesterol is an important component of cell membranes and immunity enabling immunocompetent cells to initiate an immune response against cancer[32]. Reduced cholesterol levels modify cell membrane fluidity and decrease the mobility of cell membrane receptors which limits transmembrane signals and the functionality of immune cells[11]. Lastly, the NPS score includes

two blood cellular ratios: NLR and LMR, both of which are independent predictors of OS in lung cancer[33]. Neutrophils secrete pro-inflammatory cytokines like interleukins, vascular endothelial growth factor, and tumor necrosis factor, which have tumor-promoting action[34]. Reprogramming of neutrophil function by the cancer microenvironment can aid in the influx of tumor cells in normal tissues causing tumor progression and metastasis[35]. Monocytes can also undergo similar reprogramming to aid in cancer progression by reducing the immune response and increasing angiogenesis and cancer cell infiltration[36]. On the other hand, lymphocytes have an anti-cancer role due to their immune-surveillance function. In breast cancer, lymphocytes have been shown to modulate treatment response with higher levels of tumor-infiltrating lymphocytes, improving survival[37].

There are some limitations to our meta-analysis. The number of included studies was not high, and only seven cohorts were eligible. There were differences in the studies based on the type of lung cancer, its stage, and the treatment offered. Limited data and high variability precluded a comprehensive subgroup analysis. Also, all studies were from China, and the prognostic significance of NPS for lung cancer is still unknown in other populations. The lack of studies from other regions significantly limits the generalization of results. Lastly, the groups of NPS compared by the studies were not similar. This reduced the number of studies in each subgroup, and further investigations are needed to examine the association between lung cancer outcomes and different scores of NPS.

Nevertheless, our review is the first to systematically examine the link between NPS and lung cancer outcomes. The strong association between the NPS and OS, and DFS suggests that this simple and rapid tool can aid in the routine prognostication of lung cancer patients.

Conclusions

The NPS is a strong and independent prognostic indicator of lung cancer patients. Higher NPS scores are associated with worse OS and DFS. Further studies from non-Chinese populations are needed to supplement the results.

Authors' Contributions

YW conceived and designed the study, LN, WS and XL collected data and performed data analysis. YW wrote the draft of this manuscript. LS edited the manuscript.

Funding

This study was supported by Huzhou Science and Technology Bureau (2019GY47).

Conflict of Interest

The authors declare that there is no conflict of interest.

Ethics Approval and Informed Consent

Not applicable.

ORCID ID

Y.-S. Wang: 0009000061730291
L. Niu: 000000032290744X
W.-Xia Shi: 0009000727668093
X.-Y. Li: 0009000953151615
L. Shen: 0009000358886553

References

1) Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394-424.
2) Schabath MB, Cote ML. Cancer Progress and Priorities: Lung Cancer. Cancer Epidemiol Biomarkers Prev 2019; 28:1 563.
3) Duma N, Santana-Davila R, Molina JR. Non-Small Cell Lung Cancer: Epidemiology, Screening, Diagnosis, and Treatment. Mayo Clin Proc 2019; 94: 1623-1640.
4) Van Meerbeeck JP, Fennell DA, De Ruysscher DKM. Small-cell lung cancer. Lancet (London, England)2011; 378: 1741-1755.
5) Siegel R, DeSantis C, Virgo K, Stein K, Mariotto A, Smith T, Cooper D, Gansler T, Lerro C, Fedewa S, Lin C, Leach C, Cannady RS, Cho H, Scoppa S, Hachey M, Kirch R, Jemal A, Ward E. Cancer treatment and survivorship statistics, 2012. CA Cancer J Clin 2012; 62: 220-241.
6) Hernández M, Martín R, García-Cubillas MD, Maeso-Hernández P, Nieto ML. Secreted PLA2 induces proliferation in astrocytoma through the EGF receptor: another inflammation-cancer link. Neuro Oncol 2010; 12: 1014-1023.
7) Wang Q, Zhu SR, Huang XP, Liu XQ, Liu JB, Tian G. Prognostic value of systemic immune-inflammation index in patients with urinary system cancers: A meta-analysis. Eur Rev Med Pharmacol Sci 2021; 25: 1302-1310.
8) Wu J, Wu XD, Gao Y. Correlation between preoperative systemic immune-inflammatory indexes and the prognosis of gastric cancer patients. Eur Rev Med Pharmacol Sci 2023; 27: 5706-5720.
9) Hirahara T, Arigami T, Yanagita S, Matsushita D, Uchikado Y, Kita Y, Mori S, Sasaki K, Omoto I,

Kurahara H, Maemura K, Okubo K, Uenosono Y, Ishigami S, Natsugoe S. Combined neutrophil-lymphocyte ratio and platelet-lymphocyte ratio predicts chemotherapy response and prognosis in patients with advanced gastric cancer. BMC Cancer 2019; 19: 672.

10) Jiang Y, Xu D, Song H, Qiu B, Tian D, Li Z, Ji Y, Wang J. Inflammation and nutrition-based biomarkers in the prognosis of oesophageal cancer: a systematic review and meta-analysis. BMJ Open 2021; 11: e048324.
11) Galizia G, Lieto E, Auricchio A, Cardella F, Mabilia A, Podzemny V, Castellano P, Orditura M, Napolitano V. Naples Prognostic Score, Based on Nutritional and Inflammatory Status, is an Independent Predictor of Long-term Outcome in Patients Undergoing Surgery for Colorectal Cancer. Dis Colon Rectum 2017; 60: 1273-1284.
12) Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. Int J Surg 2021; 88: 105906.
13) Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. (Accessed October 30, 2020).
14) Guo D, Liu J, Li Y, Li C, Liu Q, Ji S, Zhu S. Evaluation of Predictive Values of Naples Prognostic Score in Patients with Unresectable Stage III Non-Small Cell Lung Cancer. J Inflamm Res 2021; 14: 6129-6141.
15) Li S, Wang H, Yang Z, Zhao L, Lv W, Du H, Che G, Liu L. Naples Prognostic Score as a novel prognostic prediction tool in video-assisted thoracoscopic surgery for early-stage lung cancer: a propensity score matching study. Surg Endosc 2021; 35: 3679-3697.
16) Chen S, Liu S, Xu S, Cao S, Han Z, Kong L, Ren D, Duan G. Naples Prognostic Score is an Independent Prognostic Factor in Patients with Small Cell Lung Cancer and Nomogram Predictive Model Established. J Inflamm Res 2022; 15: 3719-3731.
17) Peng SM, Ren JJ, Yu N, Xu JY, Chen GC, Li X, Li DP, Yang J, Li ZN, Zhang YS, Qin LQ. The prognostic value of the Naples prognostic score for patients with non-small-cell lung cancer. Sci Rep 2022; 12: 5782.
18) Ren D, Wu W, Zhao Q, Zhang X, Duan G. Clinical Significance of Preoperative Naples Prognostic Score in Patients With Non-Small Cell Lung Cancer. Technol Cancer Res Treat 2022; 21: 15330338221129447.
19) Zou Z, Li J, Ji X, Wang T, Chen Q, Liu Z, Ji S. Naples Prognostic Score as an Independent Predictor of Survival Outcomes for Resected Locally Advanced Non-Small Cell Lung Cancer Patients After Neoadjuvant Treatment. J Inflamm Res 2023; 16: 793-807.
20) Xuan J, Peng J, Wang S, Cai Y. Prognostic significance of Naples prognostic score in non-small-cell lung cancer patients with brain metastases. Future Oncol 2022; 18: 1545-1555.
21) Yamamoto T, Kawada K, Obama K. Inflammation-Related Biomarkers for the Prediction of Prognosis in Colorectal Cancer Patients. Int J Mol Sci 2021; 22: 8002.
22) Wang Q, Zhu SR, Huang XP, Liu XQ, Liu JB, Tian G. Prognostic value of systemic immune-inflammation index in patients with urinary system cancers: A meta-analysis. Eur Rev Med Pharmacol Sci 2021; 25: 1302-1310.
23) Zhang Q, Bao J, Zhu ZY, Jin MX. Prognostic nutritional index as a prognostic factor in lung cancer patients receiving chemotherapy: A systematic review and meta-analysis. Eur Rev Med Pharmacol Sci 2021; 25: 5636-5652.
24) Li J, Yang W, Yuan Y, Zuo M, Li T, Wang Z, Liu Y. Preoperative Naples prognostic score is a reliable prognostic indicator for newly diagnosed glioblastoma patients. Front Oncol 2022; 12: 775430.
25) Chen Y, Guan Z, Shen G. Naples prognostic score: a novel predictor of survival in patients with HER2-positive breast cancer. Future Oncol 2022; 18: 2655-2665.
26) Wang Y, Hu X, Zheng D, Shao Y, Lia T, Li X. Prognostic significance of Naples prognostic score in operable renal cell carcinoma. Front Surg 2022; 9: 969798.
27) Xiong J, Hu H, Kang W, Liu H, Ma F, Ma S, Li Y, Jin P, Tian Y. Prognostic Impact of Preoperative Naples Prognostic Score in Gastric Cancer Patients Undergoing Surgery. Front Surg 2021; 8: 617744.
28) Feng JF, Zhao JM, Chen S, Chen QX. Naples Prognostic Score: A Novel Prognostic Score in Predicting Cancer-Specific Survival in Patients With Resected Esophageal Squamous Cell Carcinoma. Front Oncol 2021; 11: 652537.
29) Jin J, Wang H, Peng F, Wang X, Wang M, Zhu F, Xiong G, Qin R. Prognostic significance of preoperative Naples prognostic score on short- and long-term outcomes after pancreatoduodenectomy for ampullary carcinoma. Hepatobiliary Surg Nutr 2021; 10: 825-838.
30) Hu WH, Cajas-Monson LC, Eisenstein S, Parry L, Cosman B, Ramamoorthy S. Preoperative malnutrition assessments as predictors of postoperative mortality and morbidity in colorectal cancer: an analysis of ACS-NSQIP. Nutr J 2015; 14: 91.
31) Hu WH, Eisenstein S, Parry L, Ramamoorthy S. Preoperative malnutrition with mild hypoalbuminemia associated with postoperative mortality and morbidity of colorectal cancer: a propensity score matching study. Nutr J 2019; 18: 33.
32) Verstraeten SL, Albert M, Paquot A, Muccioli GG, Tyteca D, Mingeot-Leclercq MP. Membrane cholesterol delays cellular apoptosis induced by

ginsenoside Rh2, a steroid saponin. Toxicol Appl Pharmacol 2018; 352: 59-67.

33) Liu N, Mao J, Tao P, Chi H, Jia W, Dong C. The relationship between NLR/PLR/LMR levels and survival prognosis in patients with non-small cell lung carcinoma treated with immune checkpoint inhibitors. Medicine (Baltimore) 2022; 101: e28617.

34) Tan KW, Chong SZ, Wong FH, Evrard M, Tan SM, Keeble J, Kemeny DM, Ng LG, Abastado JP, Angeli V. Neutrophils contribute to inflammatory lymphangiogenesis by increasing VEGF-A bioavailability and secreting VEGF-D. Blood 2013; 122: 3666-3677.

35) Xiong S, Dong L, Cheng L. Neutrophils in cancer carcinogenesis and metastasis. J Hematol Oncol 2021; 14: 173.

36) Olingy CE, Dinh HQ, Hedrick CC. Monocyte heterogeneity and functions in cancer. J Leukoc Biol 2019; 106: 309-322.

37) Stanton SE, Disis ML. Clinical significance of tumor-infiltrating lymphocytes in breast cancer. J Immunother Cancer 2016; 4: 1354-1360.