Prognostic impact of prognostic nutritional index on renal cell carcinoma: A meta-analysis of 7,629 patients

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Abstract

Background

Prognostic nutritional index (PNI) is a parameter which reflects nutritional and inflammatory status. The prognostic value of PNI in renal cell carcinoma (RCC) remains in debate. The aim of this study is to evaluate the prognostic value and clinicopathological features of PNI in RCC.

Methods

A literature search was performed in the databases of PubMed, Embase, Web of Science, and Cochrane Library. Hazard ratios (HRs), odds ratios (ORs), and 95% confidence intervals (CIs) were extracted for meta-analysis. The association between PNI and overall survival (OS), cancer-specific survival (CSS), disease-free survival (DFS), progression-free survival (PFS), recurrence-free survival (RFS), and clinicopathological factors were evaluated.

Results

Eleven studies involving 7,629 patients were included for meta-analysis. A decreased PNI was shown to be a significant predictor of worse OS (HR = 2.00, 95%CI = 1.64–2.42, p<0.001), CSS (HR = 2.54, 95%CI = 1.61–4.00, p<0.001), and DFS/PFS/RFS (HR = 2.12, 95%CI = 1.82–2.46, p<0.001) in RCC. Furthermore, a low PNI was correlated with Fuhrman grade III-IV (OR = 1.96, 95%CI = 1.27–3.02, p = 0.002), T stage T3-T4 (OR = 2.21, 95%CI = 1.27–3.87, p = 0.005), presence of sarcomatoid differentiation (OR = 5.00, 95%CI = 2.52–9.92, p<0.001), and presence of tumor necrosis (OR = 3.63, 95%CI = 2.54–5.19, p<0.001).
Conclusion
PNI is an independent prognostic indicator of survival and associated with Fuhrman grade, T stage, sarcomatoid differentiation, and tumor necrosis in patients with RCC.

Introduction
Kidney cancer is the 13th most common cancer worldwide [1]. It is estimated that there are 403,262 new cases diagnosed and 175,098 cancer-related deaths of kidney cancer in 2018 globally [2]. The most common type of kidney originating cancer is renal cell carcinoma (RCC) [1]. When initially diagnosed, about 70% of patients with RCC have localized diseases and the remaining 30% are at regional metastatic and distant metastatic status [3]. Although most patients with RCC at localized stages are treated by surgical resection, RCC remains one of the most lethal urological malignancies [4]. Between 20% and 40% of patients with localized RCC experience disease relapse after curative intent surgery [5]. Patients with advanced RCC have a median survival of 2 years [6]. The prognostic factors play a pivotal role in identifying high-risk patients and optimizing of clinical assessment tools for patients with RCC [7].

Accumulating evidence has shown the association between prognostic nutritional index (PNI) and prognosis of various malignancies in recent years [8–12]. PNI is derived from the following formula: serum albumin (g/L) + 5 × peripheral lymphocyte count (10^9/L), which both evaluates the nutrition and immunologic status of patients [9]. PNI was firstly reported by Buzby and colleagues [13] in 1980 and was regarded as a simply obtained nutritional and immunological parameter calculated with serum albumin level and peripheral lymphocyte count of the laboratory test. Then in 1984, Onodera et al. [14] simplified PNI and confirmed that low PNI was associated with poor prognosis after gastrointestinal surgery of malnourished cancer patients [14]. Onodera firstly introduced PNI in the prognostication of patients with cancer [14]. The prognostic significance of pretreatment PNI has been verified in many tumors including non-small cell lung cancer (NSCLC) [15], breast cancer [12], glioblastoma [16], oral squamous cell carcinoma [17], gastric cancer [18], and thyroid carcinoma [19]. The low PNI was shown as a significant prognostic factor. Previous studies have investigated the prognostic impact of PNI on RCC, with conflicting results presented [20–23]. Therefore, to clarify the prognostic role of PNI in RCC, we carried out a meta-analysis of the current published evidence on PNI and survival of RCC. In addition, we explored the association between PNI and clinical factors in PNI in this meta-analysis.

Materials and methods
Study guideline
We performed the current meta-analysis according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline [24]. Approval of an ethics committee or institutional review board is not needed because this is a meta-analysis.

Publication search
The literature databases of PubMed, Embase, Web of Science, and Cochrane Library were retrieved. The databases were searched from inception up to June 2021. We searched the literature using the following strategies: (PNI OR prognostic nutritional index) AND (renal cell carcinoma OR RCC OR kidney cancer OR kidney neoplasms). And studies from the bibliographies of retrieved articles were also scanned for pertinent publications.
Inclusion and exclusion criteria

We recruited eligible studies according to the following inclusion criteria: (1) the publication are English literature; (2) patients were diagnosed with RCC by histopathological or pathological analysis; (3) the PNI was measured and recorded before surgery or treatment in laboratory test; (4) survival endpoints, such as overall survival (OS), disease-free survival (DFS), progression-free survival (PFS), recurrence-free survival (RFS), and cancer-specific survival (CSS) were explored in the studies; (5) studies evaluated the prognostic clinicopathologic and value of PNI for survival endpoints and hazard ratios (HRs) with 95% confidence intervals (CIs) were provided. The exclusion criteria were as follows: (1) meeting abstracts, case reports, reviews, letters, and comments; (2) animal studies; (3) studies with overlapping patients; (4) studies with insufficient data for meta-analysis.

Data extraction and quality evaluation

A standardized data collection form was employed to extract the following information by two authors (Q.P. and L.L.) independently: first author, year of publication, country, number of patients, sex, recruitment period, study design, metastatic status, follow-up period, clinical treatments, PNI cut-off value, and numbers of patients with low/high PNI. In case of any discrepancies during data extraction, two investigators (C.L. and H.W.) will discuss to consensus reached. The quality of included studies was assessed by the Newcastle–Ottawa Scale (NOS) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). It assessed study quality by 3 classifications including selection, comparability and outcome. NOS has a full score of 9 and studies obtained more than 6 are regarded of high-quality studies.

Statistical analysis

All statistical procedures in this meta-analysis were performed using Stata version 14.0 (Stata Corp LP, College Station, TX, USA). The prognostic value of PNI for OS, CSS, and DFS/PFS/RFS were evaluated by combined HRs and 95%CIs. If HRs and 95% CIs were not directly reported by articles, they were calculated from Kaplan–Meier curves according to Parmar’s methods [25]. The association between PNI and clinicopathological factors were assessed by pooling odds ratios (ORs) and 95%CIs. We adopted the $\chi^2$ and Higgins $I^2$ to measure heterogeneity among the included studies. The results of $P < 0.1$ and $I^2 > 50\%$ were considered indicative of significant heterogeneity. If no significant heterogeneity was detected, a fixed effect model was used. Otherwise, a random effect model was selected. We carried subgroup analysis to detect the source of heterogeneity. The Begg’s funnel plot and Egger’s linear regression teats were used to evaluate potential publication bias. The p<0.05 was considered as statistically significant.

Results

Literature search procedures

As shown in Fig 1, a total of 454 articles were retrieved after initial search of the databases. However, among them, 292 studies remained after exclusion of duplicates. Then 276 records were removed by screening title and abstract, and 16 studies were evaluated by full-text examination. After full-text reading, a total of 5 studies were eliminated for the following reasons: 3 studies did not provide sufficient data for analysis and 2 studies recruited overlapped patients. Finally, 11 studies with 7,629 patients [20–23, 26–32] were included in the meta-analysis.
Characteristics of included studies

The included studies all reported association between PNI and survival outcomes, including 9 studies for OS [21–23, 26–29, 31, 32], 5 studies for CSS [20, 23, 26, 29, 30], and 8 studies for DFS/PFS/RFS [20–23, 27, 28, 30, 32]. Regarding geographical regions, 5 studies are from China [22, 23, 28, 29, 32], 3 from Korea [26, 27, 30], and one each from Austria [20], United States [21], and Turkey [31]. All included studies are of retrospective study design. Eight studies use surgery [20, 21, 23, 26, 28–30, 32] and 3 studies adopt targeted therapy [22, 27, 31] as treatment method. The cut-off values of PNI are various among included studies, ranging from 38.5 to 51.62, and the median value is 48. The included are published from 2015 to 2021, indicating the recent interest of prognostic role of PNI for RCC. The NOS scores of included studies are from 6 to 9 and are all of high quality. The detailed characteristics and quality assessment of eligible studies are shown in Table 1.

Prognostic role of PNI for RCC

All included studies investigated the prognostic role of PNI for survival in RCC. For OS, based on pooled data from 9 studies [21–23, 26–29, 31, 32], the HR and 95%CI are: HR = 2.00, 95% CI = 1.64–2.42, p<0.001, with significant heterogeneity (Fig 2). As for CSS, 5 studies [20, 23,
provide relevant data, and the pooled results are: HR = 2.54, 95%CI = 1.61–4.00, 
p < 0.001 (Fig 3). Regarding DFS/PFS/RFS, according to data of 8 studies [20–23, 27, 29, 30, 32], the pooling data suggest that a low PNI indicates a worse DFS/PFS/RFS in RCC (HR = 2.12, 95%CI = 1.82–2.46, p < 0.001), with non-significant heterogeneity (I² = 35.9%, 
P = 0.142) (Fig 4). These results demonstrate that a decreased PNI is significantly associated 
with poorer OS, CSS, and DFS/PFS/RFS in patients with RCC. To further detect the source of 
heterogeneity, we performed subgroup analyses stratified by sample size, metastatic status, 
cut-off value, and treatment. As shown in Table 2, the results indicate that a low PNI still asso-
ciates with inferior OS in all subgroups. For CSS, PNI with cut-off value ≤48 predicted worse 
CSS. And for DFS/PFS/RFS, a low PNI was a significant prognostic factor irrespective of sam-
ple size, cut-off value, and treatment methods.

The correlation between PNI and clinicopathological factors

We explored the association between PNI and clinicopathological features based on data 
derived from 5 studies [21–23, 26, 30]. As shown in Fig 5 and Table 3, the pooled results sug-
gested that a low PNI was associated with Fuhrman grade III-IV (n = 5, OR = 1.96, 95% 
CI = 1.27–3.02, p = 0.002), T stage T3-T4 (n = 4, OR = 2.21, 95%CI = 1.27–3.87, p = 0.005), 
presence of sarcomatoid differentiation (n = 3, OR = 5.00, 95%CI = 2.52–9.92, p < 0.001), and 
presence of tumor necrosis (n = 2, OR = 3.63, 95%CI = 2.54–5.19, p < 0.001). However, there 
was no significant association between PNI and sex (n = 5, OR = 0.85, 95%CI = 0.65–1.12, 
p = 0.225) or histological type (n = 4, OR = 0.99, 95%CI = 0.60–1.61, p = 0.953) in RCC.

Table 1. Basic characteristics of included studies.

| Study | Year | Country | Sample size | Sex (M/F) | Study design | metastatic status | Treatment | Follow-up (month) median (range) | Cut-off value | No. of patients with PNI (low/high) | Survival outcomes | NOS score |
|-------|------|---------|-------------|-----------|-------------|-------------------|-----------|-------------------------------|--------------|-----------------------------------|------------------|-----------|
| Hofbauer, S. L. | 2015 | Austria | 1344 | 892/452 | Retrospective | Mixed | Surgery | 40 | 48 | CSS, DFS | 8 |
| Broggi, M. S. | 2016 | United States | 341 | 204/115 | Retrospective | Mixed | Surgery | NA | 44.7 | 168/172 | OS, RFS | 7 |
| Jeon, H. G. | 2016 | Korea | 1437 | 1011/426 | Retrospective | Mixed | Surgery | 68.6 (1.2–212.6) | 51 | 477/960 | OS, CSS | 8 |
| Cai, W. | 2017 | China | 178 | 135/43 | Retrospective | Metastatic | Targeted therapy | 22 | 51.62 | 80/98 | OS, PFS | 7 |
| Kwon, W. A. | 2017 | Korea | 125 | 99/26 | Retrospective | Metastatic | Targeted therapy | 45.3 | 41 | 57/68 | OS, PFS | 8 |
| Peng, D. | 2017 | China | 1360 | 962/408 | Retrospective | Mixed | Surgery | 67(2–108) | 47.6 | 382/978 | OS, PFS | 9 |
| Zheng, Y. Q. | 2018 | China | 635 | 400/235 | Retrospective | Non-metastatic | Surgery | 48.4 | 48 | NA | OS, CSS | 7 |
| Hu, X. | 2020 | China | 660 | 256/404 | Retrospective | Mixed | Surgery | 83 | 44.3 | 69/391 | OS, CSS, PFS | 7 |
| Kim, S. J. | 2020 | Korea | 459 | 307/152 | Retrospective | Non-metastatic | Surgery | 72(4–272) | 51 | 164/259 | CSS, RFS | 7 |
| Yasar, H. A. | 2020 | Turkey | 396 | 258/138 | Retrospective | Metastatic | Targeted therapy | NA | 38.5 | 157/156 | OS | 6 |
| Tang, Y. | 2021 | China | 694 | 442/252 | Retrospective | Non-metastatic | Surgery | 60.9 | 49.08 | 267/427 | OS, RFS | 7 |

M: male, F: female, NA: not available, NOS: Newcastle-Ottawa Scale, OS: overall survival, DFS: disease-free survival, PFS: progression-free survival, RFS: recurrence-free survival, CSS: cancer-specific survival, PNI: Prognostic Nutritional Index.

https://doi.org/10.1371/journal.pone.0265119.t001
Publication bias

Begg’s test and Egger’s test were carried out to evaluate potential publication bias in this meta-analysis. As shown in Fig 6, there was non-significant publication bias in the present meta-analysis for OS, CSS, and DFS/PFS/RFS (all p > 0.05).
Discussion

The prognostic value of PNI in patients with RCC were controversial according to previous studies [20–23, 26–32]. In the present meta-analysis including 7,629 patients, the results demonstrated that a low PNI was a significant prognostic factor for worse short-term and long-term survival outcomes in patients with RCC. The subgroup analyses confirmed the reliability of the results. In addition, we also investigated the connection between PNI and clinical factors in RCC, and the data showed that a low PNI suggested the progression and aggressively biological behaviors of the disease.

A number of studies have investigated the prognostic significance of PNI in diverse cancer types through meta-analytic methods [33–38]. A meta-analysis including 7 studies indicated that the low PNI was significantly associated with inferior prognosis of patients with biliary tract cancer and aggressive clinical factors [38]. Another recent meta-analysis showed that low PNI could be interpreted as adverse prognosis for patients with diffuse large B-cell lymphoma [39]. A meta-analysis with 6372 patients suggested that a low PNI was significantly associated with reduced survival and increased incidence of total and severe postoperative complications in patients with colorectal cancer [40]. Hu et al. showed that the PNI was a negative predictor for DFS, RFS, and PFS in patients with NSCLC in a meta-analysis [41]. A very recent meta-analysis demonstrated that a low PNI level was correlated with worse OS, PFS, and distant metastasis-free survival in patients suffering from nasopharyngeal carcinoma [42]. In the present meta-analysis, we identified the prognostic impact of PNI on survival outcomes in RCC, which was in accordance with previous findings in other types of cancer [33, 35, 38, 39, 41, 42]. Moreover, we also reported the correlation between a low PNI and various clinical features in RCC, which implied that PNI should be monitored in the management of patients.

Accumulating evidence have shown that the nutritional and immunization status are involved in the development and progress of malignancies, and therefore affect the survival outcomes [43]. On one hand, the low PNI could be caused by hypoalbuminemia and decreased
lymphocyte counts. The serum albumin concentration is a reliable tool to screen nutritional status. And it is reported that a decreased pretreatment serum albumin level implies a poor prognosis for patients with RCC [44]. Malnutrition in patients with cancer is usually caused by

| Subgroup                  | No. of studies | HR (95%CI)     | p       | Effects model | Heterogeneity | F²(%) | P     |
|--------------------------|----------------|----------------|---------|---------------|---------------|-------|-------|
| **OS**                   |                |                |         |               |               |       |       |
| Total                    | 9              | 2.00(1.64–2.42)| <0.001 | Random        |               | 53.8  | 0.027 |
| Sample size              |                |                |         |               |               |       |       |
| <500                     | 4              | 2.08(1.58–2.74)| <0.001 | Random        |               | 51.0  | 0.106 |
| ≥500                     | 5              | 1.95(1.44–2.64)| <0.001 | Random        |               | 62.6  | 0.030 |
| **Metastatic status**    |                |                |         |               |               |       |       |
| Non-metastatic           | 2              | 2.86(1.60–5.11)| <0.001 | Random        |               | 62.9  | 0.101 |
| Metastatic               | 3              | 2.20(1.53–3.15)| <0.001 | Random        |               | 64.5  | 0.060 |
| Mixed                    | 4              | 1.60(1.32–1.94)| <0.001 | Fixed         |               | 0     | 0.960 |
| **Cut-off value**        |                |                |         |               |               |       |       |
| <48                      | 5              | 1.75(1.49–2.06)| <0.001 | Fixed         |               | 0     | 0.980 |
| ≥48                      | 4              | 2.44(1.57–3.79)| <0.001 | Random        |               | 77.3  | 0.004 |
| **Treatment**            |                |                |         |               |               |       |       |
| Surgery                  | 6              | 1.90(1.47–2.45)| <0.001 | Random        |               | 53.5  | 0.056 |
| Targeted therapy         | 3              | 2.20(1.53–3.15)| <0.001 | Random        |               | 64.5  | 0.060 |
| **CSS**                  |                |                |         |               |               |       |       |
| Total                    | 5              | 2.54(1.61–4.00)| <0.001 | Random        |               | 81.4  | <0.001|
| Sample size              |                |                |         |               |               |       |       |
| <500                     | 1              | 4.21(1.67–10.56)| 0.002  | -             |               | -     | -     |
| ≥500                     | 4              | 2.36(1.43–3.90)| 0.001  | Random        |               | 85.3  | <0.001|
| Metastatic status        |                |                |         |               |               |       |       |
| Non-metastatic           | 2              | 4.39(2.63–7.32)| <0.001 | Fixed         |               | 0     | 0.914 |
| Mixed                    | 3              | 1.99(1.12–3.55)| 0.019  | Random        |               | 88.4  | <0.001|
| **Cut-off value**        |                |                |         |               |               |       |       |
| <48                      | 1              | 1.51(0.94–2.43)| 0.086  | -             |               | -     | -     |
| ≥48                      | 4              | 2.91(1.76–4.82)| <0.001 | Random        |               | 80.7  | 0.001 |
| **DFS/PFS/RFS**          |                |                |         |               |               |       |       |
| Total                    | 8              | 2.12(1.82–2.46)| <0.001 | Fixed         |               | 35.9  | 0.142 |
| Sample size              |                |                |         |               |               |       |       |
| <500                     | 4              | 2.79(2.18–3.58)| <0.001 | Fixed         |               | 0     | 0.750 |
| ≥500                     | 4              | 1.82(1.51–2.19)| <0.001 | Fixed         |               | 0     | 0.508 |
| Metastatic status        |                |                |         |               |               |       |       |
| Non-metastatic           | 2              | 2.16(0.99–4.71)| 0.054  | Random        |               | 75.8  | 0.042 |
| Metastatic               | 2              | 2.94(2.12–4.06)| <0.001 | Fixed         |               | 0     | 0.769 |
| Mixed                    | 4              | 1.95(1.61–2.36)| <0.001 | Fixed         |               | 0     | 0.617 |
| **Cut-off value**        |                |                |         |               |               |       |       |
| <48                      | 3              | 1.92(1.51–2.45)| <0.001 | Fixed         |               | 18.7  | 0.292 |
| ≥48                      | 5              | 2.24(1.86–2.70)| <0.001 | Fixed         |               | 46.7  | 0.111 |
| **Treatment**            |                |                |         |               |               |       |       |
| Surgery                  | 6              | 1.94(1.64–2.29)| <0.001 | Fixed         |               | 15.7  | 0.313 |
| Targeted therapy         | 2              | 2.94(2.12–4.06)| <0.001 | Fixed         |               | 0     | 0.769 |

OS: overall survival, DFS: disease-free survival, PFS: progression-free survival, RFS: recurrence-free survival, CSS: cancer-specific survival.

https://doi.org/10.1371/journal.pone.0265119.t002
loss of appetite and exhaustion due to tumor metabolism, which is reflected by hypoalbuminemia. In addition, the development of malignant tumor and metastases in liver could impair liver function and reduce albumin synthesis [44]. On the other hand, lymphocytes play an important in suppressing cancer cells proliferation and migration [45]. The infiltration of CD4+ T cells activates CD8+ T cells, and further induce cancer cell apoptosis. In addition, tumor-

Fig 5. Forest plot of PNI with clinicopathological features in patients with renal cell carcinoma. (A) sex (male vs female); (B) Fuhrman grade (III-IV vs I-II); (C) T stage (T3-T4 vs T1-T2); (D) histology (ccRCC vs non-ccRCC); (E) sarcomatoid differentiation (yes vs no); (F) tumor necrosis (yes vs no).

https://doi.org/10.1371/journal.pone.0265119.g005

| Clinopathological factors                  | No. of studies | OR (95%CI)       | p     | Effects model | Heterogeneity I² (%) | P     |
|-------------------------------------------|----------------|------------------|-------|--------------|---------------------|-------|
| Sex (male vs female)                      | 5              | 0.85 (0.65–1.12) | 0.225 | Random       | 51.1                | 0.085 |
| Fuhrman grade (III-IV vs I-II)            | 5              | 1.96 (1.27–3.02) | 0.002 | Random       | 81.1                | <0.001|
| T stage (T3-T4 vs T1-T2)                  | 4              | 2.21 (1.27–3.87) | 0.005 | Random       | 88.3                | <0.001|
| Histology (ccRCC vs non-ccRCC)            | 4              | 0.99 (0.60–1.61) | 0.953 | Random       | 54.1                | 0.088 |
| Sarcomatoid differentiation (yes vs no)   | 3              | 5.00 (2.52–9.92) | <0.001| Fixed        | 0                   | 0.979 |
| Tumor necrosis (yes vs no)                | 2              | 3.63 (2.54–5.19) | <0.001| Fixed        | 0                   | 0.390 |

cccRCC: clear cell renal cell carcinoma; non-ccRCC: clear cell renal cell carcinoma.

https://doi.org/10.1371/journal.pone.0265119.t003
infiltrating lymphocytes (TILs) can exhibit cytotoxic activity toward cancer cells and can be applied in immunotherapy for patients with RCC [46]. Therefore, the low lymphocyte counts can result in an insufficient immunological activity and lead to worse prognosis in patients with RCC.

The recent studies also revealed the possible mechanisms between low PNI and poor prognosis in RCC. The metabolic reprogramming covers different processes such as aerobic glycolysis, fatty acid metabolism, and the utilization of tryptophan, glutamine, and arginine in RCC could be impaired because RCC is also a metabolic disease [47]. In addition, in RCC the Warburg effect is a grade-dependent feature [48], and fatty acid oxidation can be activated for different grade-dependent metabolic needs [49]. In addition, Lucarelli et al. find that oncogenic signaling pathways may promote ccRCC through rerouting the sugar metabolism. Blocking the flux through this pathway may serve as a novel therapeutic target [50]. An integrated multi-omics characterization reveals a distinctive metabolic signature and the role of NDUF4L2 in promoting angiogenesis, chemoresistance, and mitochondrial dysfunction in ccRCC [51]. Moreover, the subcellular distribution of phospholipid-binding protein annexin A3 in the cellular endocytic compartment suggests its involvement in modulation of vesicular
trafficking, and it might serve as a putative mechanism of lipid storage regulation in ccRCC cells, opening novel translational outcomes [52]. Stearoyl-CoA desaturase (SCD1) inhibition significantly reduced cancer cell proliferation and increased cisplatin sensitivity, suggesting that this pathway can be involved in ccRCC chemotherapy resistance [53]. In addition, renal cell carcinoma is one of the most immune-infiltrated tumors [54, 55]. Emerging evidence suggests that the activation of specific metabolic pathway have a role in regulating angiogenesis and inflammatory signatures [56]. Additionally, activation of the kynurenine pathway predicts poor outcome in patients with ccRCC [57]. Features of the tumor microenvironment heavily affect disease biology and may affect responses to systemic therapy. Recent studies revealed that metabolomics represented a potential strategy for the real-time selection and monitoring of patients treated with immunotherapy in NSCLC [58].

The current meta-analysis suggested that a low PNI was predictive of poor survival outcomes of RCC, including short-term and long-term survival. In clinical practice, patients with low PNI should be managed by supplementary nutrition and be treated with other interventions which have therapeutic effect on malnutrition. Our meta-analysis suggests that PNI is an indicator for assessing survival outcomes and disease progression in RCC. Recent studies also suggested the effective prognostic role of PNI in RCC. Kwon et al. have shown that PNI is an independent prognostic factor in patients with metastatic RCC treated with targeted therapy [27]. Hu and colleagues have found that the patients of RCC with lower preoperative PNI were associated with adverse factors following nephrectomy [23]. Kim et al. have reported that The PNI is an independent prognostic factor for RFS and CSS in patients with nonmetastatic RCC treated with partial or radical nephrectomy [30].

Several limitations to our study need to be acknowledged. First of all, the included studies are all of retrospective, which may introduce selection bias. The inherent nature of retrospective studies can increase clinical heterogeneity. Secondly, the PNI cut-off values of included studies varied from 38.5 to 51.62, as a standard cut-off value of the PNI for RCC has not been determined. Thirdly, significant heterogeneity among the included studies was observed.

**Conclusion**

In summary, our meta-analysis has shown that a decreased PNI is a significant prognostic factor for poorer OS, CSS, and DFS/PFS/RFS in patients with RCC. Moreover, a low PNI indicated highly aggressive biological behaviors of the disease. PNI could be applied as an independent prognostic factor for patients with RCC in clinical practice.

**Supporting information**

S1 Checklist. PRISMA checklist. (DOC)

**Author Contributions**

**Conceptualization:** Qingping Peng.

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**Funding acquisition:** Ting Li, Changjiang Lei.

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Supervision: Ling Liu, Huan Wan.

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References

1. Scelo G, Larose TL. Epidemiology and Risk Factors for Kidney Cancer. Journal of Clinical Oncology. 2018; 36(36):3574–+. https://doi.org/10.1200/JCO.2017.79.1905 PMID: 30372394

2. 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: a cancer journal for clinicians. 2018; 68(6):394–424. Epub 2018/08/13. https://doi.org/10.3322/caac.21492 PMID: 30207593.

3. Hu X, Liao DW, Yang Q, Yang WX, Xiong SC, Li X. Sarcopenia predicts prognosis of patients with renal cell carcinoma: A systematic review and meta-analysis. International braz j urol: official journal of the Brazilian Society of Urology. 2020; 46(5):705–15. Epub 2020/03/28. https://doi.org/10.1590/S1677-5538.IBJU.2019.0636 PMID: 30243799.

4. Capitanio U, Bensalah K, Bex A, Boorjian SA, Bray F, Coleman J, et al. Epidemiology of Renal Cell Carcinoma. European Urology. 2019; 75(1):74–84. https://doi.org/10.1016/j.eururo.2018.03.036 PMID: 30243799.

5. Speed JM, Trinh QD, Choueiri TK, Sun M. Recurrence in Localized Renal Cell Carcinoma: a Systematic Review of Contemporary Data. Current urology reports. 2017; 18(2):15. Epub 2017/02/19. https://doi.org/10.1007/s11934-017-0661-3 PMID: 28213859.

6. Motzer RJ, Hutson TE, Olsen MR, Hudes GR, Burke JM, Edenfield WJ, et al. Randomized phase II trial of sunitinib on an intermittent versus continuous dosing schedule as first-line therapy for advanced renal cell carcinoma. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2012; 30(12):1371–7. Epub 2012/03/21. https://doi.org/10.1200/JCO.2011.36.4133 PMID: 22430274.

7. Graham J, Dudani S, Heng DYC. Prognostication in Kidney Cancer: Recent Advances and Future Directions. Journal of Clinical Oncology. 2018; 36(36):3567–+. https://doi.org/10.1200/JCO.2018.79.0147 PMID: 30372388.

8. Paku M, Uemura M, Kitakaze M, Fujino S, Ogino T, Miyoshi N, et al. Impact of the preoperative prognostic nutritional index as a predictor for postoperative complications after resection of locally recurrent rectal cancer. BMC Cancer. 2021; 21(1):435. Epub 2021/04/22. https://doi.org/10.1186/s12885-021-01860-5 PMID: 33874596; PubMed Central PMCID: PMC8040881.

9. Liu N, Jiang A, Zheng X, Fu X, Zheng H, Gao H, et al. Prognostic Nutritional Index identifies risk of early progression and survival outcomes in Advanced Non-small Cell Lung Cancer patients treated with PD-1 inhibitors. J Cancer. 2021; 12(10):2960–7. Epub 2021/04/16. https://doi.org/10.7150/jca.55936 PMID: 33854596; PubMed Central PMCID: PMC8040881.

10. Ishiyama Y, Kondo T, Nemoto Y, Kobayashi T, Ishihara H, Tachibana H, et al. Predictive Impact of Prognostic Nutritional Index on Pemetrexed for Metastatic Urothelial Carcinoma Resistant to Platinum-based Chemotherapy. Anticancer Res. 2021; 41(3):1607–14. Epub 2021/04/01. https://doi.org/10.2173/anticancerres.14922 PMID: 33788756.

11. Fang KH, Chang SW, Lee YC, Huang EI, Lai CH, Chang GH, et al. Preoperative prognostic nutritional index predicts prognosis of patients with oral cavity cancer. Oral diseases. 2021. Epub 2021/03/11. https://doi.org/10.1111/odi.13840 PMID: 33690959.

12. Chen L, Bai P, Kong X, Huang S, Wang Z, Wang X, et al. Prognostic Nutritional Index (PNI) in Patients With Breast Cancer Treated With Neoadjuvant Chemotherapy as a Useful Prognostic Indicator. Front Cell Dev Biol. 2021; 9:656741. Epub 2021/04/17. https://doi.org/10.3389/fcell.2021.656741 PMID: 33859996; PubMed Central PMCID: PMC8042235.

13. Buzby GP, Mullen JL, Matthews DC, Hobbs CL, Rosato EF. Prognostic nutritional index in gastrointestinal surgery. Am J Surg. 1980; 139(1):160–7. Epub 1980/01/01. https://doi.org/10.1016/0002-9610(80)90246-9 PMID: 7350839
14. Onodera T, Goseki N, Kosaki G. Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. Nihon Geka Gakkai zasshi. 1984; 85(9):1001–5. Epub 1984/09/01. PMID: 6438478.

15. Xu S, Cao S, Geng J, Wang C, Meng Q, Yu Y. High prognostic nutritional index (PNI) as a positive prognostic indicator for non-small cell lung cancer patients with bone metastasis. The clinical respiratory journal. 2021; 15(2):225–31. Epub 2020/10/11. https://doi.org/10.1111/crj.13288 PMID: 33037791.

16. Alan O, Telli TA, Basoğlu T, Arıkan R, Demircan NC, Ercelepl O, et al. Impact of prognostic nutritional index on survival in recurrent glioblastoma. Neurociencia (Asturias, Spain). 2021. Epub 2021/01/18. https://doi.org/10.1016/j.neuci.2020.11.005 PMID: 33454185.

17. Abe A, Hayashi H, Ishihama T, Furuta H. Prognostic impact of the prognostic nutritional index in cases of resected oral squamous cell carcinoma: a retrospective study. BMC Oral Health. 2021; 21(1):40. Epub 2021/01/24. https://doi.org/10.1186/s12903-021-01394-6 PMID: 33482792; PubMed Central PMCID: PMC7821535.

18. Liu JY, Dong HM, Wang WL, Wang G, Pan H, Chen WW, et al. The Effect of the Prognostic Nutritional Index on the Toxic Side Effects of Radiochemotherapy and Prognosis After Radical Surgery for Gastric Cancer. Cancer Manag Res. 2021; 13:3385–92. Epub 2021/04/24. https://doi.org/10.2147/CMAR.S301140 PMID: 33889027; PubMed Central PMCID: PMC8057790.

19. Offi C, Romano RM, Cangiano A, Candela G, Docimo G. Clinical significance of neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, platelet-to-lymphocyte ratio and prognostic nutritional index in low-risk differentiated thyroid carcinoma. Acta otorhinolaryngologica Italiana: organo ufficiale della Societa italiana di otorinolaringologia e chirurgia cervico-facciale. 2021; 41(1):31–8. Epub 2021/03/23. https://doi.org/10.14639/0392-100X-N1099 PMID: 33748220; PubMed Central PMCID: PMC7987251.

20. Hofbauer SL, Pantuck AJ, de Martino M, Lucca I, Haitel A, Shariat SF, et al. The preoperative prognostic nutritional index is an independent predictor of survival in patients with renal cell carcinoma. Urologic oncology. 2015; 33(2):68.e1-7. Epub 2014/09/23. https://doi.org/10.1016/j.uroonc.2014.08.005 PMID: 25240758.

21. Broggi MS, Pati D, Baum Y, Nieh PT, Alemezaffar M, Pattaras JG, et al. Onodera’s Prognostic Nutritional Index as an Independent Prognostic Factor in Clear Cell Renal Cell Carcinoma. Urology. 2016; 96:99–105. Epub 2016/07/20. https://doi.org/10.1016/j.urology.2016.05.064 PMID: 27431662.

22. Cai W, Zhong H, Kong W, Dong B, Chen Y, Zhou L, et al. Significance of preoperative prognostic nutritional index as prognostic predictors in patients with metastatic renal cell carcinoma with tyrosine kinase inhibitors as first-line target therapy. Int Urol Nephrol. 2017; 49(11):1955–63. Epub 2017/09/11. https://doi.org/10.1007/s11255-017-1693-9 PMID: 28889323.

23. Hu X, Wang YH, Lia T, Yang QZ, Shao YX, Yang WX, et al. Prognostic value of preoperative prognostic nutritional index in patients with renal cell carcinoma after nephrectomy. Clinica chimica acta; international journal of clinical chemistry. 2020; 509:210–6. Epub 2020/06/21. https://doi.org/10.1016/j.cca.2020.06.025 PMID: 32562664.

24. Moher D, Liberati A, Tetzlaff J, Altman DG, Grp P. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. Plos Medicine. 2009; 6(7). https://doi.org/10.1371/journal.pmed.1000097 WOS:000268452400005. PMID: 19621072.

25. Parmar MKB, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med. 1998; 17(24):2815–34. https://doi.org/10.1002/(sici)1097-0258(19981230)17:24<2815::aid-sim110>3.0.co;2-8 WOS:000077527600003. PMID: 9921604.

26. Jeon HG, Choi DK, Sung HH, Jeong BC, Seo SI, Jeon SS, et al. Preoperative Prognostic Nutritional Index is a Significant Predictor of Survival in Renal Cell Carcinoma Patients Undergoing Nephrectomy. Ann Surg Oncol. 2016; 23(1):321–7. Epub 2015/06/06. https://doi.org/10.1245/s10434-015-4614-0 PMID: 26045392.

27. Kwon WA, Kim S, Kim SH, Jong YJ, Seo HK, Lee KH, et al. Pretreatment Prognostic Nutritional Index Is an Independent Predictor of Survival in Patients With Metastatic Renal Cell Carcinoma Treated With Targeted Therapy. Clinical genitourinary cancer. 2017; 15(1):100–11. Epub 2016/09/08. https://doi.org/10.1016/j.cjc.2016.07.025 PMID: 27601363.

28. Peng D, He ZS, Li XS, Tang Q, Zhang L, Yang KW, et al. Prognostic Value of Inflammatory and Nutritional Scores in Renal Cell Carcinoma After Nephrectomy. Clinical genitourinary cancer. 2017; 15(5):582–90. Epub 2017/05/22. https://doi.org/10.1016/j.cjc.2017.04.001 PMID: 28528087.

29. Zheng YQ, Bao LM, Wang WH, Wang QQ, Pan Y, Gao XM. Prognostic impact of the Controlling Nutritional Status score following curative nephrectomy for patients with renal cell carcinoma. Medicine. 2018; 97(49). https://doi.org/10.1097/MD.00000000000013409 PMID: 30544418.

30. Kim SJ, Kim SI, Cho DS. Prognostic Significance of Preoperative Prognostic Nutritional Index in Patients Undergoing Nephrectomy for Nonmetastatic Renal Cell Carcinoma. American journal of
31. Bastid J, Bonnefoy N, Eliaou JF, Bensussan A. Lymphocyte-derived interleukin-17A adds another brick in the wall of inflammation-induced breast carcinogenesis. Oncoimmunology. 2014; 3:e28273. Epub 2014/07/23. https://doi.org/10.4161/onci.28273 PMID: 3003914225000074. PMID: 26261892.

32. Tang Y, Liang J, Liu Z, Zhang R, Zou Z, Wu K, et al. Clinical significance of pretreatment prognostic nutritional index in renal cell carcinomas. Medicine (Baltimore). 2021; 100(10):e25127. Epub 2021/03/18. https://doi.org/10.1097/MD.00000000000025127 PMID: 33729513; PubMed Central PMCID: PMC7969234.

33. Sun KY, Chen SL, Xu JB, Li GH, He YL. The prognostic significance of the prognostic nutritional index in cancer: a systematic review and meta-analysis. Journal of Cancer Research and Clinical Oncology. 2014; 140(9):1537–49. https://doi.org/10.1007/s00432-014-1714-3 WOS:PMID: 2487893194000111.

34. Tang Y, Xu P, Kang HF, Lin S, Wang M, Yang PT, et al. Prognostic nutritional index as a prognostic biomarker for survival in digestive system carcinomas. Oncotarget. 2016; 7(52):86573–83. https://doi.org/10.18632/oncotarget.13472 WOS:000391422500074. PMID: 27888808.

35. Zhao Y, Xu P, Kang HF, Lin S, Wang M, Yang PT, et al. Prognostic nutritional index as a prognostic biomarker for survival in digestive system carcinomas. Oncotarget. 2016; 7(52):86573–83. https://doi.org/10.18632/oncotarget.13472 WOS:000391422500074. PMID: 27888808.

36. Qi F, Zhou X, Wang Y, Wang Y, Wang Y, Zhang Q, et al. Pretreatment prognostic nutritional index may serve as a potential biomarker in urinary cancers: a systematic review and meta-analysis. Cancer Cell Int. 2018; 18:207. Epub 2018/12/20. https://doi.org/10.1186/s12935-018-0708-7 PMID: 30564063; PubMed Central PMCID: PMC6296044.

37. Wang Z, Wang J, Wang P. The prognostic significance of the nutritional index in hepatocellular carcinoma patients: A meta-analysis of observational studies. PLoS One. 2018; 13(10):e0202987. Epub 2018/10/13. https://doi.org/10.1371/journal.pone.0202987 PMID: 30312295; PubMed Central PMCID: PMC6185720.

38. Lv X, Zhang Z, Yuan W. Pretreatment Prognostic Nutritional Index (PNI) as a Prognostic Factor in Patients with Biliary Tract Cancer: A Meta-Analysis. Nutr Cancer. 2020;1–10. Epub 2020/09/17. https://doi.org/10.1080/01635581.2020.1817955 PMID: 32933337.

39. Luan C, Wang F, Wei N, Chen B. Prognostic nutritional index and the prognosis of diffuse large b-cell lymphoma: a meta-analysis. Cancer Cell Int. 2020; 20:455. Epub 2020/09/26. https://doi.org/10.1186/s12935-020-01535-x PMID: 32973400; PubMed Central PMCID: PMC7493866.

40. Sun G, Li Y, Peng Y, Lu D, Zhang F, Cui X, et al. Impact of the preoperative prognostic nutritional index on postoperative and survival outcomes in colorectal cancer patients who underwent primary tumor resection: a systematic review and meta-analysis. Int J Colorectal Dis. 2019; 34(4):681–9. Epub 2019/01/27. https://doi.org/10.1007/s00384-019-03241-1 PMID: 30680451.

41. Hu Y, Shen J, Liu R, Feng Z, Zhang C, Ling L, et al. Prognostic value of pretreatment prognostic nutritional index in non-small cell lung cancer: A systematic review and meta-analysis. The International journal of biological markers. 2018; 33(4):372–8. Epub 2018/10/05. https://doi.org/10.1177/1724600818799876 PMID: 30282502.

42. Tang M, Jia Z, Zhang J. The prognostic role of prognostic nutritional index in nasopharyngeal carcinoma: A systematic review and meta-analysis. Int J Clin Oncol. 2021; 26(1):66–77. Epub 2020/10/09. https://doi.org/10.1007/s10147-020-01791-x PMID: 33029749.

43. Mantzorou M, Koutelidakis A, Theocharis S, Giaginis C. Clinical Value of Nutritional Status in Cancer: What is its Impact and how it Affects Disease Progression and Prognosis? Nutr Cancer. 2017; 69(8):1151–76. Epub 2017/10/31. https://doi.org/10.1080/01635581.2017.1367947 PMID: 29083236.

44. Chen Z, Shao Y, Wang K, Cao W, Xiong Y, Wu R, et al. Prognostic role of pretreatment serum albumin in renal cell carcinoma: a systematic review and meta-analysis. Onco Targets Ther. 2016; 9:6701–10. Epub 2016/10/13. https://doi.org/10.2147/OTT.S108469 PMID: 27822073; PubMed Central PMCID: PMC5094571.

45. Bastid J, Bonnefoy N, Eliaou JF, Bensussan A. Lymphocyte-derived interleukin-17A adds another brick in the wall of inflammation-induced breast carcinogenesis. Oncomunology. 2014; 3:e28273. Epub 2014/07/23. https://doi.org/10.4161/onci.28273 PMID: 25050201; PubMed Central PMCID: PMC4063083.

46. Minami T, Minami T, Shimizu N, Yamamoto Y, De Velasco M, Nozawa M, et al. Identification of Programmed Death Ligand 1-derived Peptides Capable of Inducing Cancer-reactive Cytotoxic T Lymphocytes From HLA-A24+ Patients With Renal Cell Carcinoma. Journal of immunotherapy (Hagerstown, Md: 1997). 2015; 38(7):285–91. Epub 2015/08/12. https://doi.org/10.1097/CJI.0000000000000900 PMID: 26261892.
47. Ragone R, Sallustio F, Piccinonna S, Rutigliano M, Vanessa G, Palazzo S, et al. Renal Cell Carcinoma: A Study through NMR-Based Metabonomics Combined with Transcriptomics. Diseases (Basel, Switzerland). 2016; 4(1). Epub 2016/01/22. https://doi.org/10.1016/j.euf.2016.11.008 PMID: 28753823; PubMed Central PMCID: PMC5456302.

48. Bianchi C, Meregalli C, Bombelli S, Di Stefano V, Salerno F, Torsello B, et al. The glucose and lipid metabolism reprogramming is grade-dependent in clear cell renal cell carcinoma primary cultures and is targetable to modulate cell viability and proliferation. Oncotarget. 2017; 8(69):113502–15. Epub 2018/01/27. https://doi.org/10.18632/oncotarget.23056 PMID: 29371925; PubMed Central PMCID: PMC5768342.

49. Lucarelli G, Loizzo D, Franzin R, Battaglia S, Ferro M, Cantiello F, et al. Metabolomic insights into pathophysiological mechanisms and biomarker discovery in clear cell renal cell carcinoma. Expert Rev Mol Diagn. 2019; 19(5):397–407. Epub 2019/04/16. https://doi.org/10.1080/14737159.2019.1607729 PMID: 30983433.

50. Lucarelli G, Galleggiante V, Rutigliano M, Sanguedolce F, Cagiano S, Bufo P, et al. Metabolomic profile of glycolysis and the pentose phosphate pathway identifies the central role of glucose-6-phosphate dehydrogenase in clear cell renal cell carcinoma. Oncotarget. 2015; 6(15):13371–86. Epub 2015/05/07. https://doi.org/10.18632/oncotarget.3823 PMID: 25945836; PubMed Central PMCID: PMC4537021.

51. Lucarelli G, Rutigliano M, Sallustio F, Ribatti D, Giglio A, Lepore Signorile M, et al. Integrated multi-omics characterization reveals a distinctive metabolic signature and the role of NDUFA4L2 in promoting angiogenesis, chemoresistance, and mitochondrial dysfunction in clear cell renal cell carcinoma. Aging. 2018; 10(12):3957–85. Epub 2018/12/13. https://doi.org/10.1086/701016 PMID: 30538212; PubMed Central PMCID: PMC6326659.

52. Bombelli S, Torsello B, De Marco S, Lucarelli G, Cifola I, Grasselli C, et al. 36-kDa Annexin A3 Isoform Negatively Modulates Lipid Storage in Clear Cell Renal Cell Carcinoma Cells. The American journal of pathology. 2020; 190(11):2317–26. Epub 2020/08/31. https://doi.org/10.1016/j.ajpath.2020.08.008 PMID: 32861643.

53. Lucarelli G, Ferro M, Loizzo D, Bianchi C, Terracciano D, Cantiello F, et al. Integration of Lipidomics and Transcriptomics Reveals Reprogramming of the Lipid Metabolism and Composition in Clear Cell Renal Cell Carcinoma. Metabolites. 2020; 10(12). Epub 2020/12/17. https://doi.org/10.3390/metabo10120509 PMID: 33322148; PubMed Central PMCID: PMC7763469.

54. Vuong L, Kotecha RR, Voss MH, Hakimi AA. Tumor Microenvironment Dynamics in Clear-Cell Renal Cell Carcinoma. Cancer Discov. 2019; 9(10):1349–57. Epub 2019/09/19. https://doi.org/10.1158/2159-8290.CD-19-0499 PMID: 31527133; PubMed Central PMCID: PMC6774890.

55. Tamma R, Rutigliano M, Lucarelli G, Annese T, Ruggieri S, Cascardi E, et al. Microvascular density, macrophages, and mast cells in human clear cell renal carcinoma with and without bevacizumab treatment. Urologic oncology. 2019; 37(6):355.e11–.e19. Epub 2019/02/11. https://doi.org/10.1016/j.urolonc.2019.01.025 PMID: 30736745.

56. Netti GS, Lucarelli G, Spadaccino F, Castellano G, Gigante M, Divella C, et al. PTX3 modulates the immunoflogosis in tumor microenvironment and is a prognostic factor for patients with clear cell renal cell carcinoma. Aging. 2020; 12(8):7585–602. Epub 2020/04/30. https://doi.org/10.18632/aging.103169 PMID: 32345771; PubMed Central PMCID: PMC7202504.

57. Lucarelli G, Rutigliano M, Ferro M, Giglio A, Intini A, Triggiano F, et al. Activation of the kynurenine pathway predicts poor outcome in patients with clear cell renal cell carcinoma. Urologic oncology. 2017; 35 (7):461.e15–.e27. Epub 2017/04/01. https://doi.org/10.1016/j.urolonc.2017.02.011 PMID: 28359744.

58. Ghini V, Laera L, Fantechi B, Monte FD, Benelli M, McCartney A, et al. Metabonomics to Assess Response to Immune Checkpoint Inhibitors in Patients with Non-Small-Cell Lung Cancer. Cancers (Basel). 2020; 12(12). Epub 2020/12/04. https://doi.org/10.3390/cancers12123574 PMID: 33265026; PubMed Central PMCID: PMC7760033.