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ORIGINAL ARTICLE

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

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Abstract

Purpose We aimed to explore whether the preoperative prognostic nutritional index (PNI) could be an indicator of prognostic outcomes in colorectal cancer (CRC) patients.

Methods A systematic review and meta-analysis was conducted using the PubMed, Embase, and Web of Science databases. All original comparative studies published in English that were related to a high PNI versus a low PNI in CRC patients were included.

Results A total of 10 studies involving 6372 patients were included in our meta-analysis. Our overall analysis indicated that the low-PNI group had a significantly reduced overall survival (OS) (HR = 1.87, 95% CI = 1.45–2.42, $P < 0.01$), cancer-specific survival (HR = 1.53, 95% CI = 1.07–2.19, $P = 0.02$), and disease-free survival (HR = 1.67, 95% CI = 1.23–2.26, $P < 0.01$) compared with the high-PNI group. Furthermore, our subgroup results indicated that a high PNI could be a significant indicator of improved OS in TNM stage II (HR = 1.93, 95% CI = 1.29–2.90, $P < 0.01$) and III (HR = 1.71, 95% CI = 1.25–2.34, $P < 0.01$), and a similar trend in TNM stage I or IV could also be observed though without statistical significance. Regarding postoperative complications, our pooled results indicated that the low-PNI group had a significantly increased incidence of total and severe postoperative complications.

Conclusions Our findings indicated that CRC patients with a preoperative high PNI had a significantly improved OS. However, almost only Asian CRC patients were included based on current issue.

Keywords Prognostic nutritional index · Colorectal cancer · Complications · Overall survival · Meta-analysis

Introduction

Colorectal cancer (CRC) is one of the most common malignancies worldwide and is characterized by high morbidity and mortality [1]. Curative surgical resection remains the main method for resectable localized CRC based on the clinical guidelines [2]. However, the prognosis of patients differs even in patients with the same pathological stage. Moreover, approximately 30% of patients may still suffer from serious postoperative complications [3–6]. Hence, identifying the subgroup population that can benefit more from colorectal resection remains an urgent issue for further exploration. Novel biomarkers, especially preoperative host-related factors, are necessary to predict poor surgical and oncological outcomes of CRC.

The prognostic nutritional index (PNI) is calculated based on the serum albumin concentration and total lymphocyte count. The PNI was calculated according to the following formula from the report of Onodera et al.: 10 × albumin (g/dl) + 0.005 × total lymphocyte count (per mm^3) [7]. Numerous studies have demonstrated that PNI is a significant indicator of postoperative complications and survival in various cancer patients (gastric cancer [8], breast cancer [9], CRC [10], lung cancer [11], esophageal cancer [12], and ovarian

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cancer [13]). Although past investigations have shown important findings related to PNI, its clinical significance has not yet been systematically discussed. In terms of PNI in CRC patients, studies have mainly followed a retrospective design with small sample sizes. In addition, the optimal cutoff value and prognosis in subgroup populations based on TNM stage need to be studied further. There is an urgent need to collect and update the current evidence on this issue for clinical application.

Based on the aforementioned findings, the aim of our study was to comprehensively explore the predictive value of PNI on postoperative and survival outcomes in CRC patients who underwent primary tumor resection through meta-analysis.

Methods

Search strategy

We conducted our systematic review and meta-analysis based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (http://www.prisma-statement.org/). Our search was restricted to the English language based on the following MeSH/main keywords: "prognostic nutritional index," "PNI," "colorectal," "rectal," "colonic," "colon," and "rectum" using datasets from PubMed, Embase, and the Web of Science (up to October 2018). The detailed search strategy for the PubMed dataset was as follows: (colorectal [All Fields] OR rectal [All Fields] OR colonic [All Fields] OR colon [All Fields] OR rectum [All Fields]) AND (cancer [All Fields] OR carcinoma [All Fields] OR neoplasms [All Fields]) AND ("PNI" [All Fields] OR "prognostic nutritional index" [All Fields]). To avoid redundant studies, we checked all authors and organizations and evaluated the recruitment period and population of patients enrolled in each study. In addition, the lists of references in the relevant studies were also screened for additional studies.

Inclusion and exclusion criteria

According to the PICOS criteria (population, intervention, comparison, outcomes, and study design), studies were selected for our present meta-analysis according to the following eligibility criteria: (1) population: patients with CRC; (2) intervention: patients who underwent primary tumor resection (curative-intent resection); (3) comparison: low-PNI versus high-PNI CRC patients; (4) outcomes: primary outcome: overall survival (OS), secondary outcomes: disease-free survival (DFS), cancer-specific survival (CSS), and postoperative complications; OS was defined as death due to any cause, DFS was defined as disease recurrence or death, and CSS was defined as death due to cancer, and serious complications were defined based on the Clavien-Dindo classification [14]: grade II and higher were regarded as having complications, and grade III or IV was regarded as serious; and (5) study design: comparative studies (retrospective and prospective studies).

In addition, the exclusion criteria were (1) population: patients with unresectable metastatic CRC; (2) intervention: patients who did not undergo primary tumor surgical resection; (3) comparison: more than two groups; (4) outcomes: no data on the primary outcome of OS; and (5) study design: single-arm without comparison.

Data extraction and quality assessment of included studies

Two reviewers (Guangwei Sun and Yalun Li) reviewed and assessed each of the included studies independently, and the following information was collected: first author, country, year period, study population, number of patients enrolled, age, male/female percentage, cancer stage, and cutoff value of PNI. In addition, extraction of postoperative and survival outcome data was also performed by the two reviewers independently. Moreover, the Newcastle–Ottawa Scale (NOS) criteria were used to evaluate the quality of the studies included [15]. All disagreements in terms of the aforementioned studies were resolved by discussion between the two reviewers (Guangwei Sun and Yalun Li).

Statistical analysis

In our systematic review and meta-analysis, the most appropriate statistic for evaluating survival outcomes (time-to-event outcomes) was the hazard ratio (HR) derived from multivariate analyses of the included studies. If studies did not provide the HR directly, we obtained an estimated HR by the methods designed by Tierney [16]. In addition, we pooled the odds ratios (ORs) derived from the multivariate analyses of the postoperative complications. All analyses were performed using Stata software, version 12.0 (2011; Stata Corp., College Station, TX, USA). All the analyses in this study used a random-effects model because it provided more conservative estimates and was tailored to multicenter studies in which heterogeneity was usually present [17]. All statistical values were reported with the 95% confidence interval (CI), and a two-tailed P value less than 0.05 was defined as significant. Finally, publication bias was assessed using Begg's and Egger's tests based on the primary outcome of OS [18, 19].

Results

Selected studies

Based on our search strategy, a total of 850 published studies were identified. After removing the duplicates and screening

the title and abstract, 15 studies concerning PNI in CRC patients who underwent primary tumor resection were eligible for our further evaluation. Among these 15 studies, four studies [20–23] enrolled an overlapped population that had been included in their other investigations based on the same center, and one study [24] divided patients into four groups without a single cutoff value for PNI. Hence, 10 studies involving 6372 patients that met our inclusion and exclusion criteria were included in our systematic review and meta-analysis [10, 25–33]. A flow chart of the search strategy, which includes the reasons for exclusion of studies, is illustrated in Fig. 1. Among our included studies, 9 studies [10, 26–33] were conducted in Asian countries (China, Korea, and Japan), and all the included studies followed a retrospective design. The cutoff value for PNIs ranged from 35 to 49.22; three studies [27, 28, 33] set 45 as the cutoff value and two studies used 45.5 [10, 30]. In addition, 9 studies had an NOS score ≥ 5 [10, 26–33]. The detailed information of our included studies is shown in Table 1.

Overall analyses of survival outcomes

All the included studies provided OS data, and our overall analysis indicated that the low-PNI group had a significantly shorter OS than the high-PNI group (HR = 1.87, 95% CI = 1.45–2.42, $P < 0.01$) (Fig. 2). In addition, Yang et al. [33] and Tokunaga et al. [10] provided data on CSS, and Park et al. [30] and Peng et al. [31] provided data on DFS. Our pooled analysis also indicated that patients with high PNI showed significantly improved CSS (HR = 1.53, 95% CI = 1.07–2.19, $P = 0.02$) and DFS (HR = 1.67, 95% CI = 1.23–2.26, $P < 0.01$) (Supplementary Fig. S1). Moreover, we did not observe publication bias in terms of OS by using Begg's and Egger's tests (Begg's test, $P = 0.25$; Egger's test, $P = 0.08$).

Subgroup analyses of OS based on pathological stage

Six included studies [10, 26, 27, 30, 31, 33] provided subgroup data of OS between two groups. Hence, we conducted subgroup analyses based on the pathological TNM stage (I = 602, II = 2244, III = 1474, IV = 259) to provide a comprehensive evaluation of the prognostic value of PNI. Our results indicated that high PNI could be a significant indicator of improved OS in CRC patients with TNM stage II (HR = 1.93, 95%CI = 1.29-2.90, $P < 0.01$) and III (HR = 1.71, 95% CI = 1.25–2.34, $P < 0.01$) cancer who had undergone surgical resection. For TNM stage I (HR = 1.88, 95% CI = 0.95–3.71, $P = 0.07$) and IV (HR = 1.19, 95% CI = 0.66–2.12, $P = 0.57$) patients, the high-PNI group also showed a similar trend of improved OS when compared with low-PNI patients, though this difference was not statistically significant. The detailed results of subgroup analyses are shown in Fig. 3.

Association of PNI and postoperative complications

Two studies [26, 28] provided data on total postoperative complications, and the pooled results showed that the low-PNI group had a significantly increased incidence of postoperative complications compared with the high-PNI group (OR = 1.94, 95% CI = 1.29–2.92, $P < 0.01$). In terms of severe

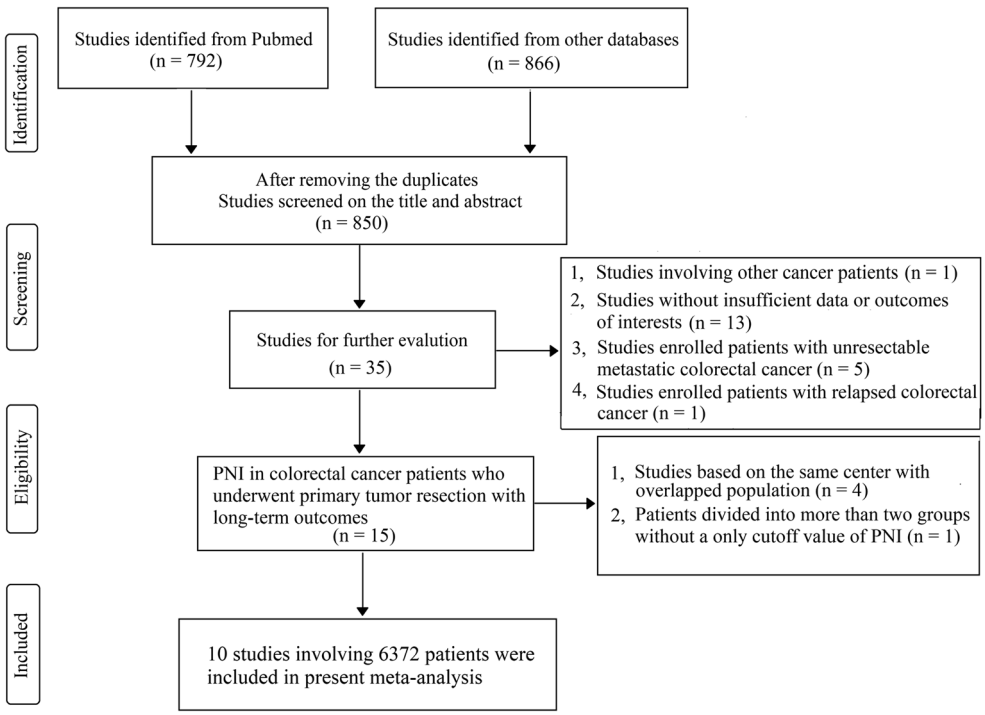

Fig. 1 Flow chart of study selection

Table 1 Baseline information of included studies

Author	Country	Year duration	Population source	Group	Number	Age	Male/female (%)	Stage	Cutoff	NOS
Yang et al. [33]	China	1995–2014	China Medical University	High-PNI	1787	Mean 61	56/44	I–IV	45	6
				Low-PNI	275	Mean 65	62/39	I–IV		
Nozoe et al. [29]	Japan	2002–2010	Fukuoka Higashi Medical Center	High-PNI	196	Mean 70	57/43	0–IV	40	5
				Low-PNI	23	Mean 75	61/39	I–IV		
Tokunaga et al. [10]	Japan	2005–2014	Kumamoto University Hospital	High-PNI	325	Mean 65	61/39	0–IV	45.5	6
				Low-PNI	231	Mean 70	57/43	0–IV		
Mohri et al. [28]	Japan	2001–2006	Mie University Hospital	High-PNI	203	58% ≤ 65	62/38	I–IV	45	5
				Low-PNI	162	47% ≤ 65	60/40	I–IV		
Chen et al. [27]	China	1994–2007	Sun Yat-sen University	High-PNI	772	55% ≤ 60	58/42	I–IV	45	6
				Low-PNI	549	46% ≤ 60	60/40	I–IV		
Akgul et al.[1] [25]	Turkey	2010–2016	Ankara Numune Training and Research Hospital	High-PNI	183	Mean 64	61/39	0–III	35	4
				Low-PNI						
Park et al.[1] [30]	Korea	2002–2010	Seoul National University Hospital	High-PNI	1035	Median 65	63/37	IIA	45.5	5
				Low-PNI				IIA		
Peng et al. [31]	China	2007–2013	Sun Yat-sen University	High-PNI	152	74% ≤ 60	60/40	III	49.22	6
				Low-PNI	122	63% ≤ 60	47/53	III		
Shibutani et al. [32]	Japan	2005–2011	Osaka City University	High-PNI	106	61% ≤ 70	49/51	II/III	43	5
				Low-PNI	23	35% ≤ 70	78/22	II/III		
Cao et al. [26]	China	2009–2012	Beijing Hospital	High-PNI	96	61% < 65	61/39	I–III	44.55	6
				Low-PNI	132	22% < 65	57/43	I–III		

PNI prognostic nutritional index, *NOS* Newcastle–Ottawa Scale

[1] Baseline information of all the included patients

postoperative complications, Mohri et al. [28] indicated that 41 patients (11.2%) had serious postoperative complications in their cohort. Serious complications included anastomotic leakage in 22 patients, severe infection in 19, bowel obstruction requiring further surgery in 7, severe cardiopulmonary failure in one, and pulmonary embolism in one. Furthermore, Cao et al. [26] demonstrated that 24 patients (10.5%) had serious postoperative complications, including bleeding in 2 patients, anastomotic leakage in 6 patients, serious infection in 13 patients, bowel obstruction in 1 patient, and pulmonary embolism in 1 patient. In addition, Tokunaga et al. [10] showed that 85 patients (15.3%) had serious postoperative complications but did not provide detailed information on the individuals. All three studies [10, 26, 28] demonstrated that PNI was an independent factor associated with the incidence of severe postoperative complications in multivariate analysis, and our pooled results also indicated that the low-PNI group had a significantly increased incidence of serious postoperative complications (OR = 2.27, 95% CI = 1.53–3.38, $P < 0.01$) (Fig. 4). Furthermore, in the subgroup analyses, Tokunaga et al. [10] indicated that the rate of serious postoperative complications in patients with stage II cancer was significantly higher in the low-PNI group ($P < 0.01$), but the same association was not seen in other stages of cancer. However, the subgroup analyses in study by Cao et al. [26] did not demonstrate a significant association of the incidence of serious postoperative complications in patients with stage I, II, and III cancers between the low-PNI and high-PNI groups.

Discussion

Surgical resection is still the main treatment method for resectable localized CRC; however, the subgroup population that would benefit most from surgery remains unclear. Hence, exploring preoperative predictive factors of postoperative outcomes is an important and urgent topic that remains to be further studied. The PNI, a simple and useful systemic inflammation-based prognostic score, is calculated based on laboratory assessments of total lymphocyte count and serum albumin level [7] and can reflect the pretreated host's immunological and nutritional status [27]. However, regarding CRC, there is still no uniform consensus or comprehensive evidence concerning whether PNI could be a prognostic indicator in CRC patients. Hence, based on the aforementioned findings, we conducted this meta-analysis to explore whether preoperative PNI could be a predictive factor of postoperative

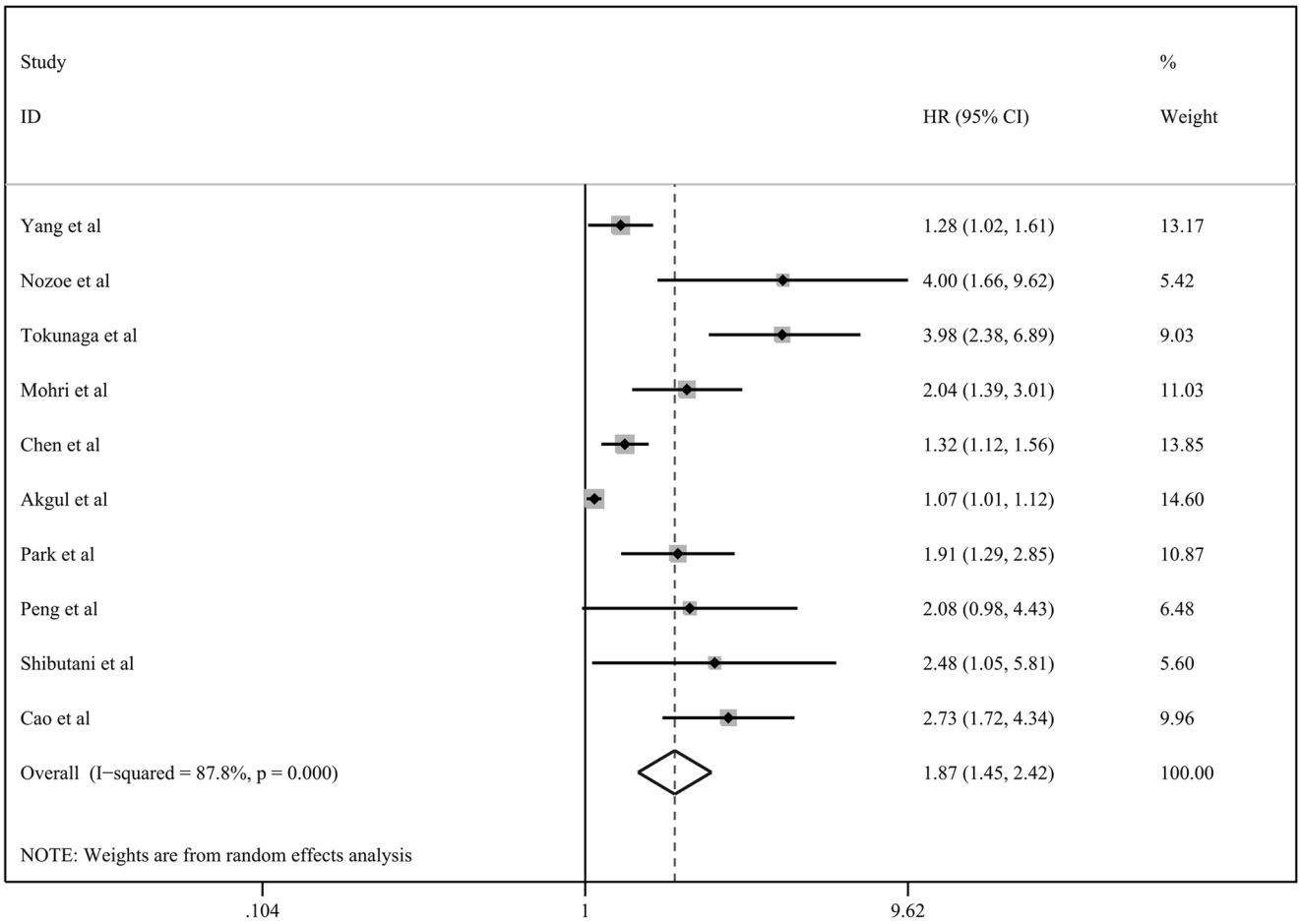

Fig. 2 Overall analyses of overall survival between the low-PNI and high-PNI groups

and survival outcomes in CRC patients who underwent primary tumor resection.

Our study found that CRC patients with high preoperative PNI showed significantly improved OS compared to the low-PNI group. Meanwhile, in terms of subgroup analyses based on pathological TNM stage, CRC patients with TNM stage II and III cancers also showed significant differences in OS between the high- and low-PNI groups. In addition, preoperative low-PNI CRC patients demonstrated an increased incidence of total and serious postoperative complications compared to that of high-PNI patients. Our findings demonstrated that preoperative PNI could be a predictive factor of prognosis in CRC patients who underwent surgical resection, especially for locally advanced (pathological TNM stage II and III) cancers.

Regarding our overall analyses of OS, there are some potential explanations for the association between low PNI and impaired OS in CRC patients who underwent surgical resection. First, lymphocytes and serum albumin are significantly associated with the prognosis of CRC patients based on current evidence [34–37]. Hence, PNI calculated based on the lymphocytes and serum albumin could reflect the prognosis of CRC patients. In addition, our previous investigation also indicated that sarcopenia could be an indicator of prognosis in non-metastatic CRC patients [38]; therefore, PNI that reflects the nutritional and immune condition of patients might also influence the prognosis of patients. Moreover, previous investigations [10, 27, 33] indicated that low-PNI status was correlated with older ages and aggressive clinicopathological features, which led to a worse OS for CRC patients. In terms of the results of the subgroup analyses based on the pathological stage, we noted that the predictive value of PNI was significant in TNM stage II and III patients. Furthermore, a similar tendency was also observed in TNM stage I and IV patients, although without statistical significance. Previous evidence [39–41] also found that preoperative PNI could be a prognostic factor in unresectable metastatic CRC patients. Hence, the effect of PNI in TNM stage IV patients needs to be further studied based on large-scale individual data.

The present results suggested that postoperative complications occurred more frequently in the low-PNI group than in the high-PNI group. In addition, Tokunaga et al. [10] indicated that the rate of serious postoperative complications in patients with stage II cancer, but not other stages, was significantly higher in the low-PNI group ($P < 0.01$). This might be explained by the theory that the inflammatory response and malnutrition are

important factors that contribute to postoperative complications, especially severe complications [26, 42]. Past reports have also shown that low albumin and lymphocyte levels are closely related to the development of an inflammatory response in CRC patients [43, 44]. Hence, PNI could be an indicator of postoperative complications, especially severe complications, for CRC patients who have undergone surgical resection.

To date, there is still no consensus on the uniform cutoff value for PNI for clinical applications. In our included studies, the cutoff value for PNIs ranged from 35 to 49.22; three studies [27, 28, 33] set 45 as the cutoff value, and two studies used 45.5 [10, 30]. In addition, the majority of the studies on this topic were conducted in Asian countries; hence, the reported cutoff values for PNI might be applicable in only Asian populations. Hence, we expect that more clinicians from European and American countries can focus on and further explore the significance of PNI in CRC patients. Based on the results of the current study, we could not determine the optimal cutoff value for PNI based on current evidence. Individual data and pooled analysis are needed to update our findings and determine the cutoff value for PNI for clinical practice.

There were some limitations in our current study. First, all the included studies were retrospective cohort studies. Hence, heterogeneities in patient selection might cause bias in our

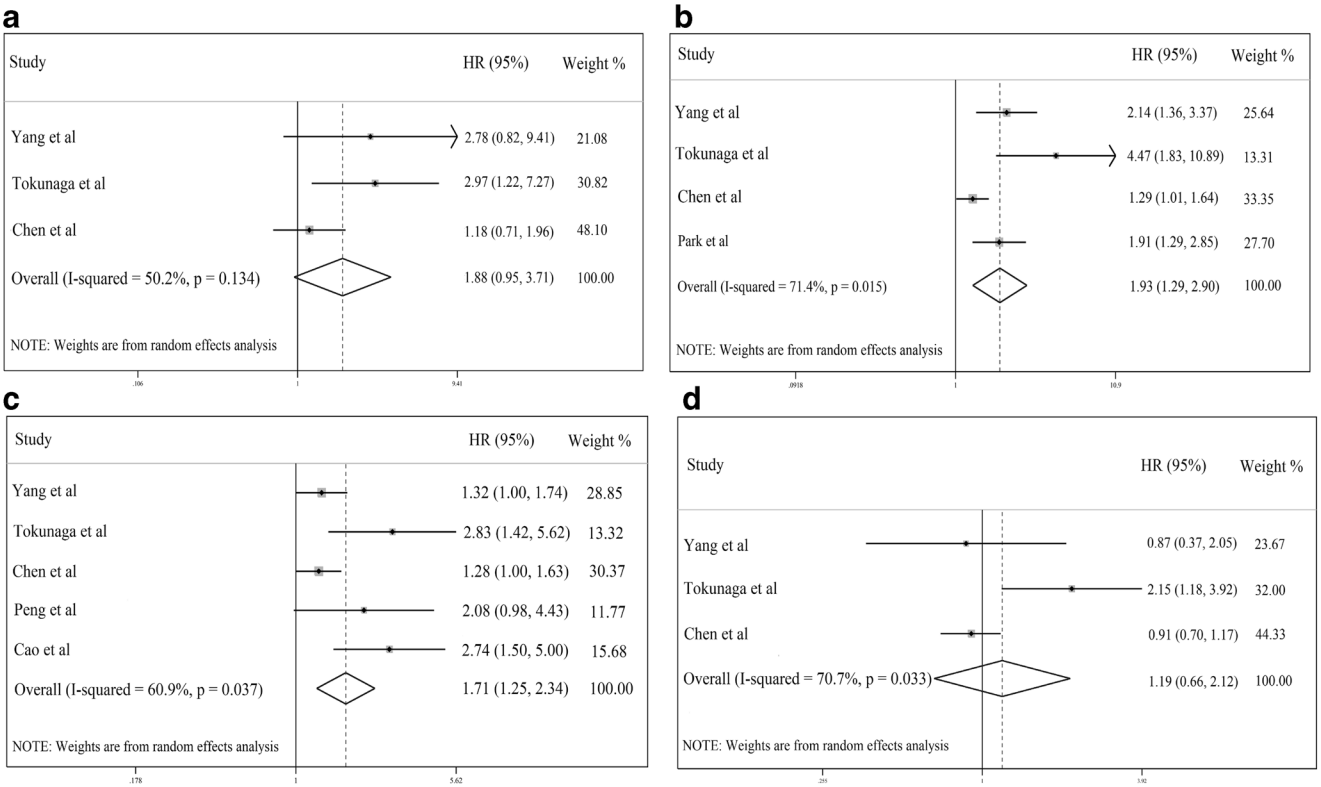

Fig. 3 Subgroup analyses of overall survival based on pathological TNM stage between the two groups. **a** TNM I. **b** TNM II. **c** TNM III. **d** TNM IV

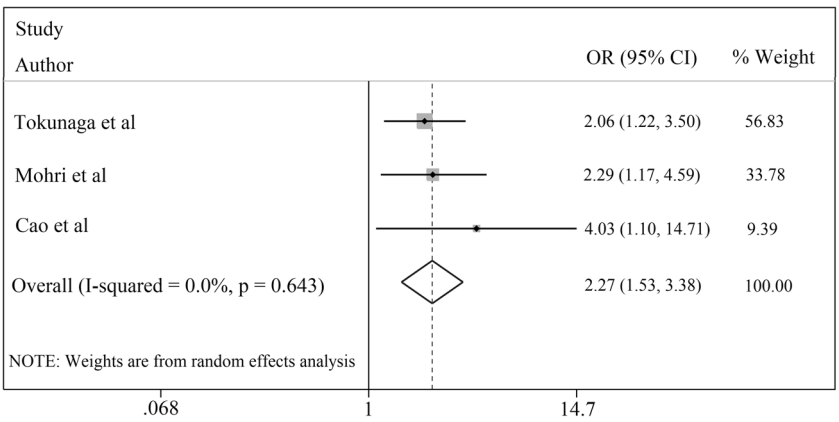

Fig. 4 Serious postoperative complications in the low-PNI and high-PNI groups

overall analyses. For example, Shibutani et al. [32] and Cao et al. [26] enrolled more elderly patients in the low-PNI groups. In addition, 9 of the 10 included studies were conducted in Asian countries; to the best of our knowledge, there is no related study of CRC published from European and American countries. Hence, our findings might be applicable only to Asian CRC patients. Furthermore, except of study by Akgul et al. [25] and Peng et al. [31] did not provide the number of tumor location (colon or rectal), other eight included studies had involved a total of 3234 colonic and 2676 rectal cancer patients. However, no included studies had provided the data of subgroup analyses based on the primary location of tumors (rectum or colon) between high-PNI and low-PNI groups. The prognosis was different based on the primary tumor location in CRC patients [45]; therefore, the mixed baseline information might restrict our further exploration of the significance of PNI in rectal and colon cancer.

Conclusion

Our findings indicated that CRC patients with preoperative high-PNI showed significantly improved OS and decreased postoperative complications when compared to the low-PNI group. Moreover, in terms of subgroup analyses based on pathological TNM stage, CRC patients with TNM stage II and III cancers also showed significant differences in OS between the high- and low-PNI groups. Hence, preoperative PNI could be a predictive factor of prognosis in CRC patients who underwent surgical resection, especially for patients with locally advanced cancers. However, individual data are needed to further explore the optimal cutoff value for PNI for clinical applications in CRC patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent No informed consent.

Disclosure statement The authors have nothing to disclose.

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