



## ORIGINAL ARTICLE

## Prediction of Post-operative Survival of Colorectal Cancer Patient by Using the Prognostic Nutritional Index: An Evidence-based Case Report

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### Abstract

**Introduction** Colorectal cancer patients may be treated with several modalities and one of them is surgical treatment. Surgery in cancer patients is a risky procedure and may not always result in prolonged survival. Therefore, before receiving any recommended treatment, the patient's prognosis has to be assessed and defined properly. Several methods are available to assess the prognosis of cancer patients; one of them is the prognostic nutritional index (PNI).

**Objective** This study aimed to predict the survival of a colorectal cancer patient postoperatively by calculating the preoperative PNI score.

**Method** Literature searching was done using inclusion and exclusion criteria on two databases, i.e. the PubMed and the Cochrane Library. The outcome was survival (disease-free survival, relapse-free survival, or overall survival).

**Results** Five articles that address the clinical question were retrieved. All indicated that a patient with low PNI score (<44.5) had a shorter overall survival (HR between 1.92 and 3.98 with all *p* values were <0.05).

**Conclusion** Pre-operative PNI score can be used to assess the overall survival of a colorectal cancer patient who underwent surgical resection. Patients with a PNI score  $\geq 44.5$  had better survival than lower PNI score.

**Keywords** prognostic nutritional index, post-operative colorectal cancer, survival

### Clinical Scenario

Mr. MR, aged 67 years old, was complaining to have bloating and incomplete bowel emptying in the last 8 months. He might have 1-2 defecations per day but the consistency was soft or liquid for about ½ glass each stool; the color is pale yellow and might be accompanied by dark red blood. He denied having

nausea or vomitus and no black stool. During this time, his food intake was unchanged but he felt that his clothing was getting looser. His family also told him that he was getting thinner. Mr. MR visited a doctor in Hospital K and underwent a complete laboratory check-up. The results at 2 weeks before coming to our clinic was as follows: Hb 9.6 g/dL, leukocyte count 8000/mm<sup>3</sup>, platelet count: 200.000/uL, lymphocyte count 2000/m<sup>3</sup>, and albumin 2.8 g/dL. A tumor was found and a biopsy confirmed that it was ascending colon cancer T3N0M0. The doctor recommended complete surgical resection of the tumor, followed by chemotherapy if needed. The patient asked more time to think and to discuss with his family. His

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family suggested him to find another doctor for another opinion. Therefore, Mr. MR came to this clinic to find a second opinion for the recommended surgical treatment. He asked how long his chance to live if he takes the procedure.

## Introduction

Colorectal cancer is the third most common malignancies worldwide with mortality rate rank the second after lung cancer.<sup>1</sup> According to GLOBOCAN 2018 database, over 1.8 million new colorectal cancer cases are estimated to occur in 2018, with 1 mortality in 10 cases. The incidence of colorectal cancer in south-eastern Asia is 5-9% of all cancers,<sup>2</sup> otherwise the incidence rate of colorectal cancer per 100.000 population in Indonesia is 19.1 (men) and 15.6 (female).<sup>3</sup> Colorectal cancer in Indonesia has increased sharply due to the changing pattern of eating habit towards a high fat-low fiber diet or a diet high in processed meat consumption. Surgical management is offered to the patient whenever feasible and may be followed by chemotherapy.<sup>4</sup> Colorectal cancer has a high recurrence rate after surgery; this is an important consideration for clinicians when choosing the best treatment for the patient. Assessment of prognostic factor is needed to assist clinicians in selecting the right treatment and education for the patient.<sup>5</sup> One of the prognostic factors that can be used is the prognostic nutritional index (PNI). It is calculated pre-operatively as follows:  $PNI = 10 \times \text{serum albumin (g/dL)} + 0.005 \times \text{total lymphocyte count (per mm}^3\text{)}$ . Assessment of PNI was first done by Onodera *et al* to predict patients who underwent gastrointestinal surgery (colorectal, gastric, hepatocellular, pancreatic cancer).<sup>6</sup> The PNI is a method to objectively assess the patient's prognosis, which is relatively cheap and easy to use by the clinicians.

## Clinical Question

P: Post-operative adult patient with colorectal cancer

I: The Prognostic Nutritional Index (PNI) score

C: -

O: Post-operative survival

Clinical question: How does the prognostic nutritional index predict the postoperative survival of colorectal cancer patients?

## Methods

### Strategy of Article Searching

Literature searching was done on PubMed and Cochrane Library on October 9, 2018 (Table 1).

### Strategy of Article Selection

#### Eligibility Criteria

Article selection was based on the inclusion and exclusion criteria, which addressed the clinical question. The inclusion criteria were: 1) the study subjects were adult patients (aged  $\geq 18$  years); 2) subjects were diagnosed as colorectal cancer of various stages and underwent surgical treatment; 3) the PNI calculation was done pre-operatively; 4) the study population was originated from Asia and 5) the cutoff PNI score was set between 44 and 46. The exclusion criteria were 1) non-English journal and 2) no available full text.

### Method of Critical Appraisal

Critical appraisal was done by all authors and by using the method of critical appraisal according to the Center of Evidence Based Medicine ([www.cebm.net](http://www.cebm.net)) for prognostic studies that has been modified in Indonesian language.

## Results

Based on the results from the two databases and by assessing the inclusion and exclusion criteria, we obtained 5 eligible articles to be included as references for a critical appraisal (Figure 1).

Selected articles were studies with cohort design, either prospective or retrospective. The number of study subjects should be more than 200 patients in the adult group. Patients should be followed-up at least for 60 months. Study characteristics is shown in Table 2. All studies had a level of evidence of 2 that were individual cohort studies. All their results showed that low PNI score indicated a shorter overall survival. The validity criteria are given in Table 3. There was a report that did not meet the criteria of applicability and importance, i.e. the study by Park *et al*.

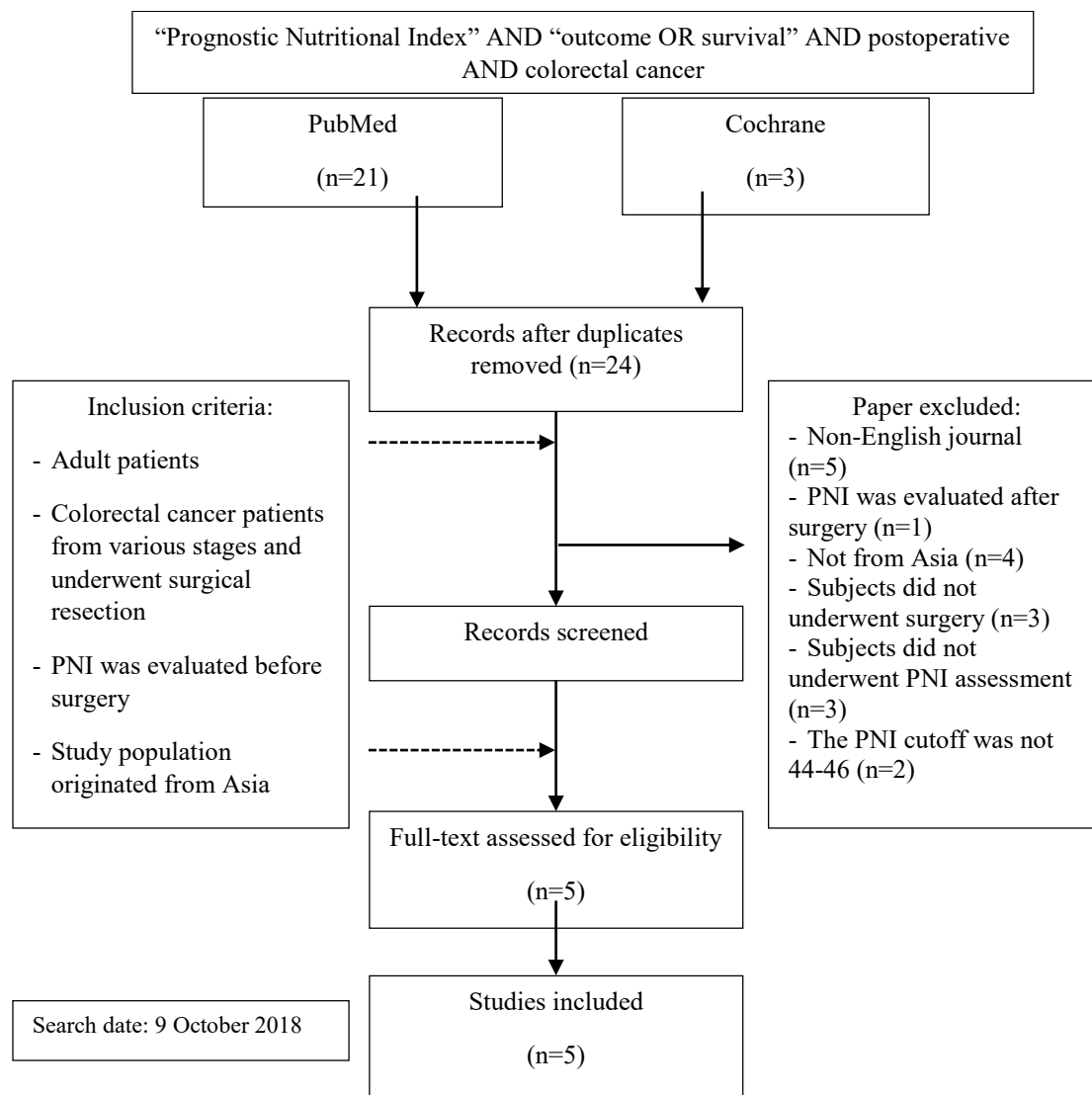


Figure 1. PRISMA Flowchart

## Discussion

Mohri *et al* did a retrospective study by assessing patients who underwent colorectal cancer resection between January 2001 and December 2016 in the Department of Gastrointestinal Surgery at Mie University Hospital, Japan. The study involved 365 subjects with colorectal cancer from stage I to IV. Blood test was done before surgery and was used to count PNI; the score was low if PNI <45. The study results showed that PNI score can be a good predictor of postoperative complication (OR = 1.58 [95% CI 1.03 to 2.42];  $p = 0.04$ ) and overall survival (OR = 2.25 [95% CI 1.42 to 3.59];  $p < 0.0001$ ) of patients with colorectal cancer.<sup>5</sup>

Cao *et al* did a retrospective study in an institution in China under the National Health and Family Planning Commission. The study was held between January 2009 and January 2012 involving 228 study subjects who underwent laparoscopic surgery in Beijing Hospital. Patients' age ranged from 27 to 92 years old and was followed-up every 3 months up to 2 years, then every 6 months up to 5 years and annually afterwards until they died. The median follow-up was 47 months (ranging from 3 to 82 months); the last follow-up was in December 2015. Blood specimen for laboratory test was withdrawn just before surgery was performed. The median overall survival of patients with high PNI score ( $\geq 44.55$ ) was 70.2 months (95% CI: 66.1 to 74.2 months), whereas the median OS of patients with low PNI score ( $<44.55$ ) was 47.1 months (95%

CI: 42.9 to 51.2 months). Multivariate analysis on postoperative severe complications resulted in an OR of 4.03 (95% CI 1.10 to 14.71];  $p = 0.035$ .<sup>7</sup>

Jian Hui *et al*<sup>6</sup> and most of studies set the optimal cut off value of PNI at 45, according to receiver operating characteristic (ROC) analysis for 5-year overall analysis. Patients in the low PNI consider to have a greater aggressive histological features of cancer.

Tokunaga *et al* did a retrospective study in 2017. The study enrolled 468 patients aged more than 18 years with primary colorectal cancer and underwent colectomy in Kumamoto University Hospital, Japan between March 2005 and August 2014. Patients were then followed-up till July 31, 2016, or death with a mean follow-up of 48.5 months (ranged from 2 to 124 months). Blood test was done two weeks before surgery. The study results showed that PNI and modified Glasgow prognostic score (mGPS) were associated with overall survival and relapse-free survival (RFS). PNI score was low if  $<45$ . Multivariate analyses showed that PNI score on overall survival was HR = 2.89 [95% CI 1.81 to 4.64];  $p < 0.001$ ; while PNI analysis on RFS was HR = 2.31 [95% CI 1.53 to 3.48];  $p < 0.001$ .<sup>8</sup>

Park *et al* did a retrospective study on 1035 patients with a median age of 65 years old (ranging from 56 to 71 years old) in National University Hospital Seoul. Subjects were patients who underwent surgery for primary colorectal cancer between January 2002 and December 2010. Blood test was done 4 weeks before surgery. Follow-up was done every three months in the first two years, every 6 months for the next three years and then annually afterward. The median time of follow-up was 66 years (2 to 140 months). The study results show that the American Society of Anesthesiologists (ASA) score, age, tumor location, the number of lymph node involvement, vein invasion, perineural invasion, adjuvant therapy, and PNI were significant prognostic factors. The PNI score of  $<45.5$  was predictive for disease-free survival (DFS) (HR = 1.534; 95% CI 1.065 to 2.211;  $p = 0.022$ ) and overall survival (HR = 1.915; 95% CI 1.286 to 2.852];  $p = 0.001$ .<sup>9</sup>

Tokunaga *et al* in 2015 did a retrospective study on 556 patients with primary colorectal cancer underwent a colectomy at Kumamoto University Hospital, Japan, between March 2005 and August 2014. Patients' age ranged from 63 to 83 years.

Laboratory test was done two weeks before surgery. Patients were followed-up till death or till November 20, 2014, with a mean follow-up of 31.8 months (1 to 104 months). The study results indicated that PNI score of  $<45.5$  was an independent risk factor of postoperative complication (OR = 2.06; 95% CI 1.22 to 3.50;  $p = 0.007$ ) and overall survival (HR = 3.98; 95% CI 2.38 to 6.89];  $p < 0.001$ ).<sup>10</sup>

Predictor of survival is also determined by systemic inflammatory responses, reflected by lymphocyte-to-monocyte ratio (LMR), neutrophil-to-monocyte ratio (NMR), platelet-to-lymphocyte ratio (PLR), and C-reactive protein (CRP). PNI had positive correlation with LMR ( $r = 0.483$ ,  $p < 0.001$ ), but negative correlation with NLR ( $r = -0.441$ ,  $p < 0.001$ ), PLR ( $r = -0.607$ ,  $p < 0.001$ ), and CRP level ( $r = -0.333$ ,  $p < 0.001$ ). A low PNI was associated with short overall survival and disease free survival in patients with stage III C colon cancer but not in patients with stage III A or III B. Patients with stage III C may have a higher tumor burden with more complex systemic pro inflammatory cytokines than those are with lower stage. Therefore, preoperative PNI has significantly correlated with immunological status.<sup>11</sup>

In conclusion, based on the publications appraised in this evidence-based case reports, pre-operative PNI score can assess the overall survival of postoperative patients with colorectal cancer of various stages, either laparoscopically or conventionally. The overall survival of colorectal cancer patients with PNI  $\geq 44.5$  showed an HR between 1.92 and 3.98. The PNI score can also be used to assess DFS and postoperative complication. Thus, PNI should be evaluated before surgical treatment to predict the patient's postoperative prognosis. If the PNI score is low ( $P < 44.5$ ), the nutritional status should be improved (in terms of serum albumin level and lymphocyte count) before surgical treatment to prolong the patient's survival.

Table 1. Terminology

Database	Terminology	Hits	Eligible
PubMed	(((((prognostic nutritional index[MeSH Terms]) OR prognostic nutritional index[Title/Abstract])) AND ((colorectal cancer[MeSH Terms]) OR colorectal cancer[Title/Abstract])) AND ((postoperative[MeSH Terms]) OR postoperative[Title/Abstract])) AND (((survival[Title/Abstract]) OR survival[MeSH Terms]) OR outcome[MeSH Terms]) OR outcome[Title/Abstract]))	21	5
Cochrane	#1 (pni):ti,ab,kw OR (prognostic nutritional index):ti,ab,kw (Word variations have been searched) #2 MeSH descriptor: [Nutrition Assessment] explode all trees #3 #1 or #2 #4 (outcome):ti,ab,kw OR (survival):ti,ab,kw (Word variations have been searched) # MeSH descriptor: [Colorectal Neoplasms] explode all trees #6 (colorectal cancer):ti,ab,kw #7 #5 or #6 #8 (postoperative):ti,ab,kw OR (surgery):ti,ab,kw (Word variations have been searched) #9 #3 and #4 and #7 and #8	3	0

Table 2. Study characteristics

Article by	Study design	Characteristics of the population	Number of subjects	Age group (years)	Prognostic Factor	Control	Outcome	Follow up Period (months)
Mohri Y, <i>et al</i> (2013) <sup>3</sup>	Retrospective Cohort	Postoperative colorectal cancer patients	365	n/a	PNI Score	-	Overall survival	>16
Cao X, <i>et al</i> (2017) <sup>5</sup>	Retrospective Cohort	Post-laparoscopic surgical colorectal cancer patients	228	>18	PNI Score	-	Overall survival and complications	47 (3-82)
Tokunaga R, <i>et al</i> (2017) <sup>6</sup>	Retrospective Cohort	Colorectal cancer patients who underwent surgical treatment	468	>18	Systemic inflammation scores and nutrition (NLR, prognostic index (PI), PLR, PNI)	modified Glasgow prognostic score (mGPS) and TNM	Overall survival	48.5 (2-124)
Park BK, <i>et al</i> (2016) <sup>7</sup>	Retrospective Cohort	Stage II A Colorectal cancer patients	1035	56-71	Systemic inflammation score (NLR, dNL PLR, PNI, and serum fibrinogen)	-	Overall survival	66 (2 - 140)
Tokunaga R, <i>et al</i> (2015) <sup>8</sup>	Retrospective Cohort	Postoperative colorectal cancer patients	556	63-83	PNI Score	-	Severe complications, recurrence, and overall survival	31.8 (1-104)

Table 3. Validity criteria

Validity	Relevance								Result	Level of Evidence
	Authors	Common point	Follow up	Blind fashion	Sub-group analysis	Outcome	Precise	Apply		
Mohri Y, <i>et al</i> (2013) <sup>3</sup>	+	+	-	+	+	+	+	+	A	2
Cao X, <i>et al</i> (2017) <sup>5</sup>	+	+	-	+	+	+	+	+	B	2
Tokunaga R, <i>et al</i> (2017) <sup>6</sup>	+/-	+	-	+	+	+	+	+	C	2
Park BK, <i>et al</i> (2016) <sup>7</sup>	+	+	-	+	+	+	-	-	D	2
Tokunaga R, <i>et al</i> (2015) <sup>8</sup>	+	+	-	+	+	+	+	+	E	2

- A. Subjects with low PNI was associated with low **postoperative** survival ( $p < 0,0001$ );
- B. Low PNI score is an independent factor associated with **postoperative** complication and overall survival of colorectal cancer patient ( $p < 0.001$ ).
- C. PNI score and mGPS are independent prognostic factors for overall survival and relapse-free survival of postoperative colorectal cancer patients ( $p < 0.001$ ). The PNI score can predict the patient's survival more clearly than the mGPS combined with TNM staging.
- D. PNI score can be used for overall survival of stage II colorectal cancer patients **postoperatively** ( $p = 0.001$ ).
- E. Subjects with PNI score  $\leq 45.5$  had shorter overall survival ( $p < 0.001$ ).

Table 4. Relevance criteria

Article	Similarity Population	Similarity determinant/ intervention/ indicators	Similarity Outcome
Mohri Y, <i>et al</i> (2013) <sup>3</sup>	+	+	+
Cao X, <i>et al</i> (2017) <sup>5</sup>	+	+	+
Tokunaga R, <i>et al</i> (2017) <sup>6</sup>	+	+	+
Park BK, <i>et al</i> (2016) <sup>7</sup>	-	+	+
Tokunaga R, <i>et al</i> (2015) <sup>8</sup>	+	+	+

Table 5. Results from critical appraisal

Study	Outcome	n	HR	95% CI
Mohri Y, <i>et al</i> (2013) <sup>3</sup>	Overall survival	365	2.29*	1.42 to 3.59
Cao X, <i>et al</i> (2017) <sup>5</sup>	Overall survival and complications	228	70.2**	66.1 to 74.2
Tokunaga R, <i>et al</i> (2017) <sup>6</sup>	Overall survival	468	2.89	1.81 to 4.64
Park BK, <i>et al</i> (2016) <sup>7</sup>	Overall survival	1035	1.92	1.29 to 2.85
Tokunaga R, <i>et al</i> (2015) <sup>8</sup>	Severe complications, recurrence and overall survival	556	3.98	2.38 to 6.89

\* Odds ratio; \*\* months; HR = hazard ratio; CI = confidence interval

### Conflict of Interest

Authors declared no conflict of interest regarding this study.

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