

ORIGINAL ARTICLE

Malnutrition is associated with adverse postoperative outcome in patients undergoing elective colorectal cancer resections

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Summary

Purpose: Malnutrition results in a significant increase in postoperative morbidity and mortality after abdominal surgery. Apart from the anthropometric assessments, malnutrition can be also assessed using laboratory scores, with the most widely used being Onodera's Prognostic Nutritional Index (PNI). The purpose of our study was to assess if the presence of malnutrition as calculated by the Onodera's PNI was associated with higher postoperative morbidity after elective colorectal cancer resection.

Methods: We performed a retrospective analysis of our institutional database including the patients who underwent elective colorectal cancer resection over a 24-month period. PNI scores were calculated and correlated amongst other parameters, such as cancer stage, severity of postoperative complications, unplanned transfusion of blood products, need for unplanned level 2/3 care after surgery and overall length of hospitalization.

Results: A total of 213 patients were included in this analysis, with 22.5% being classified as malnourished based on the preoperative PNI. Of note, PNI values were inversely associated with advanced-stage disease, severity of postoperative complications and unplanned intensive care unit (ICU) admission postoperatively. Also, malnourished patients had a statistically significant prolonged length of in-hospital stay. No difference in PNI scores was identified between groups requiring unplanned blood products' transfusions.

Conclusions: Preoperative malnutrition status as defined by PNI is associated with greater postoperative morbidity after elective surgery for colorectal cancer. Routine nutritional assessment and ad hoc nutritional support prior to surgery could contribute to an improvement of postoperative outcome after colorectal cancer resections.

Key words: cancer, colorectal, nutrition, PNI, surgery

Introduction

Although there are national and international initiatives to tackle the problem of malnutrition in hospitalized patients, there is solid data supporting that the prevalence of patients with malnutrition is still considerably high [1]. In addition, malnutrition is considered to be a major factor affecting postoperative morbidity and mortality rates in various types of surgery [2-4]. Furthermore, in the field of colorectal cancer surgery, it has been demonstrated that the occurrence of postoperative complications, apart from their ob-

vious adverse impact on the morbidity and mortality rates, is associated with worse survival outcomes [5].

It seems to follow, therefore, that early recognition and prompt intervention to optimize the preoperative nutritional status of patients scheduled to undergo a resection for colorectal cancer, should be an integral part of the preoperative assessment. Under this notion, there is a clinical need for implementation of malnutrition screening tools before planning a colorectal cancer re-

section operation, which are easy to use, can be widely available and do not increase the overall health cost. However, the anthropometric tests and questionnaires which are currently used as malnutrition screening tools, require the dedication of time and previous relevant training of the medical and allied health professional staff in order to be completed accurately [6]. For this reason, numerous previous studies have described laboratory indices-based scores as markers of patients' nutritional status, with the most widely used being the Onodera's PNI [7].

Onodera's PNI is calculated by the serum albumin concentration and peripheral blood lymphocyte count as follows: $10 \times \text{serum albumin (g/dl)} + 0.005 \times \text{total lymphocyte count (per mm}^3\text{)}$ [7]. Previous studies in cancer patients, including those with colorectal cancer, have demonstrated that PNI is a reliable prognostic factor of survival [8]. However, to the best of our knowledge, its potential role as a marker of postoperative complications after colorectal cancer resection has been scarcely investigated. Thus, the purpose of this study was to assess if the presence of malnutrition as calculated by the Onodera's PNI was associated with higher postoperative morbidity after elective colorectal cancer resection.

Methods

We performed a retrospective study across a single NHS Foundation Trust, including patients who underwent elective colorectal cancer resection over a 2-year period. Preoperative PNI values were calculated after data extraction from the institutional electronic records platform. Additional data regarding the patients' demographics, Dukes stage and location of cancer, performance of laparoscopic or open procedure, formation of stoma during initial operation, overall length of stay, unplanned admission to High Dependency (HI)/ICU, occurrence of postoperative complication(s) and emergency reoperation within 30 days post discharge, perioperative blood transfusion(s) were also extracted from the same electronic system. In terms of defining the presence or absence of malnutrition, based on the original description by Onodera et al. [7], we classified as "malnourished" those patients who had a PNI value less than 40. Postoperative complications were graded according to the Clavien-Dindo classification [9], as follows: grade I: deviation from the normal postoperative course without need for therapy; grade II: complications requiring pharmacological treatment; grade III: complications requiring surgical, endoscopic, or radiological intervention; grade IV: life-threatening complications requiring intensive care; and grade V: death.

Patients were grouped with respect to the severity of the postoperative complications as follows: no complications group, minor complications group (Clavien-Dindo grades I & II) and major complications group

(Clavien-Dindo grades III & IV). Occurrence of postoperative complications was recorded until 30 days post discharge from the primary operation. Patients who underwent emergency colorectal cancer resection or those whose electronic records had missing relevant data were excluded from our study.

Statistics

Statistical analyses were performed using SPSS 16.0 software. Continuous variables were assessed for normal value distribution. The one-sample Kolmogorov-Smirnov test was used to test if a variable was normally distributed. Correlations between PNI and Dukes stage and location of cancer, performance of laparoscopic or open procedure, formation of stoma during initial operation, overall length of stay, unplanned admission to ICU, occurrence & grade of postoperative complication(s), emergency reoperation within 30 days post discharge and administration of perioperative blood transfusion(s) were performed using t-test and ANOVA analyses. Probability (P) values less than 0.05 were considered statistically significant.

Results

A total of 213 patients (118 males/55.4% and 95 females/44.6%), with a mean age of 69.46 years were included in the final analysis. In terms of tumor location, 153/213 (71%) of the patients had colonic primary malignancy and the remaining 60/13 (29%) had a rectal primary. With respect to Dukes stage classification of the cancerous lesion, Dukes stage A accounted for the 19.2% of the cases, while 43.7% were classified as Dukes B stage and 25.8% and 11.3% as Dukes stage C and D, respectively.

Laparoscopic resection was performed in 47.4% of the cases. In addition, formation of stoma was performed in 31.9% of the cases. The mean overall length of stay (LOS) on initial admission was 10.4 ± 1.02 days. With regards to postoperative complications occurring during the 30-period post initial discharge, there were no postoperative complications in 56.3% of patients. Grade I-IV complications occurred in 10.3, 29.1, 0.5 and 3.8% of the patients, respectively; there was no 30-day mortality in this study population. Overall, 15/213 (7%) of the patients required unplanned admission to ITU during either the initial admission or during unplanned re-admission 30 days postoperatively. Unplanned postoperative transfusion of blood products was required in 4.2% of the patients. The overall occurrence of wound infections requiring admission in hospital was 12.7%. Finally, radiologically suggested anastomotic leak was recorded in 14/213 (6.6%) of the cases during either their initial hospital stay or unplanned re-admission within a month following surgery.

Lymphocyte count, albumin and PNI did not differ significantly between males and females. No statistically significant difference was observed between males and females regarding the overall length of hospitalization after surgery. Overall, 48/213 (22.5%) of the patients were classified as malnourished on admission prior to surgery, defined as PNI score less than 40, using the cut-off value as in Onodera's original study [7]. Of note, as shown in Figure 1, patients with advanced Dukes stage appeared to have significantly lower PNI scores, reaching almost the malnutrition cut-off value of 40. Specifically, mean PNI values were 46.67, 43.91, 45.64 and 42.28 for patients with Dukes stages A to D, respectively ($p=0.043$ between Dukes A & D). There was no statistically significant difference in PNI values between patients with primary colonic or rectal tumors. Moreover, patients with $PNI < 40$ had a statistically significant prolonged LOS after the initial operation, with a mean LOS 9.2 vs. 16.4 days when PNI was above 40 ($p=0.034$; Figure 2). In terms of preferred surgical approach, patients that underwent a laparoscopic procedure had a significantly higher preoperative PNI, compared to those who were subjected to laparotomy (mean PNI 45.7 ± 6.35 vs. 43.8 ± 7.58 between laparoscopy vs. open surgery groups, respectively ($p=0.048$; Figure 3). With respect to stoma formation during the operation, there was no significant difference between the patients' groups (formation of stoma or not), however PNI values were lower in patients with a stoma vs. no stoma (mean PNI 44.1 ± 7.6 vs. 44.97 ± 6.83 , respectively, $p > 0.05$).

As mentioned, when comparing the PNI scores depending on the occurrence of postoperative complications, we grouped the patients in 3 categories: patients with no complications ($n=119$, 55.9%) or patients with Grade I&II complications ("minor complication group": $n=85$, 39.9%) and patients with Grade III&IV complications ("major complications group": $n=9$, 4.2%). Our analysis demonstrated that there was a statistically significant inverse association between the preoperative PNI score and the magnitude of complications as categorized ($p=0.001$). This can be seen in Figure 4. In addition, patients who had a radiologically proven anastomotic leak ($n=14$), as well as those who required unplanned admission to ITU ($n=15$) had significantly lower PNI values (mean PNI 39.53 ± 11.01 vs. 45.07 ± 6.06 , $p=0.04$ for patients with occurrence or not of anastomotic leak; mean PNI 38.02 ± 11.35 vs. 45.21 ± 6.4 , $p=0.03$ for patients with vs. without unplanned ITU admission) (Figures 5 & 6). Of note, 4 patients who underwent an emergency laparotomy for postoperative

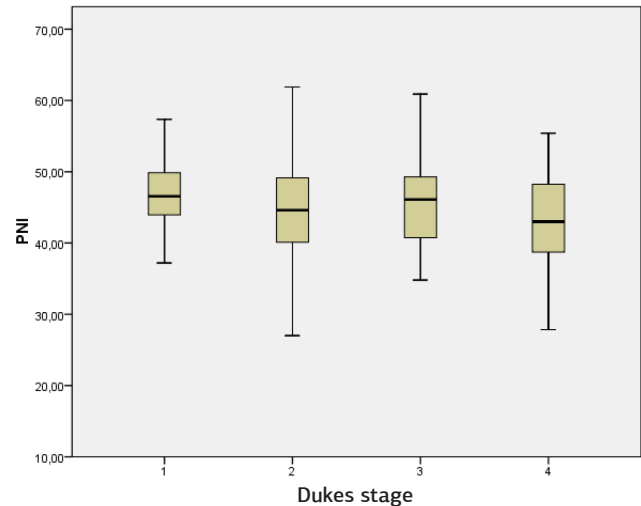


Figure 1. PNI scores depending on Dukes stage of the colorectal tumor. PNI values were significantly lower in patients with Dukes D stage, when compared to those with Dukes A ($p=0.043$).

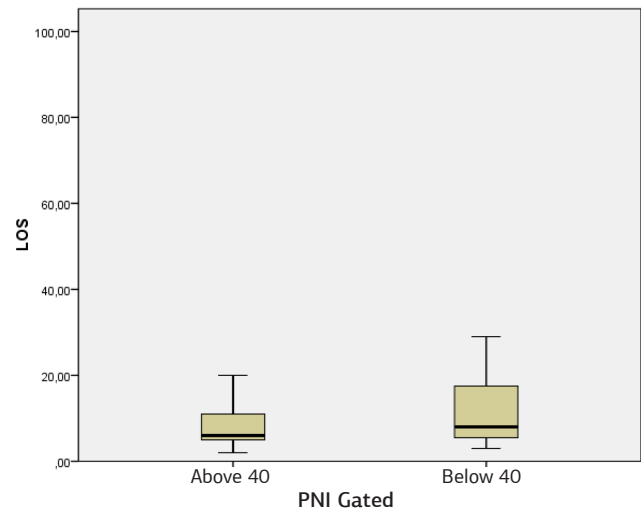


Figure 2. Mean LOS post surgery was significantly higher in patients with $PNI < 40$ compared to those with $PNI > 40$ ($p=0.034$).

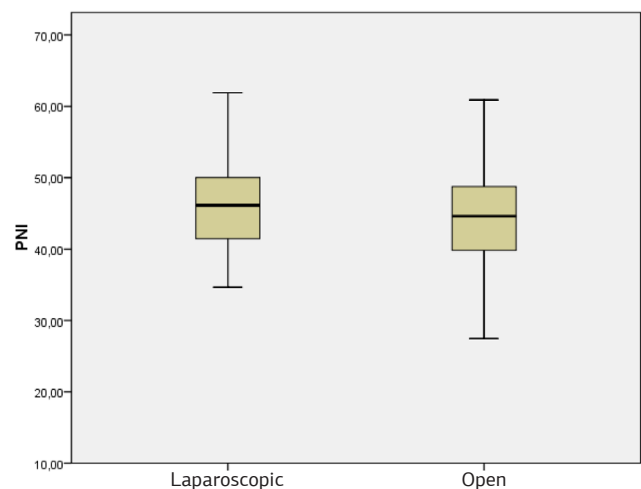


Figure 3. Mean PNI values between patients who underwent laparoscopic vs open colorectal cancer resection; PNI scores were significantly higher in the laparoscopic surgery group ($p=0.034$).

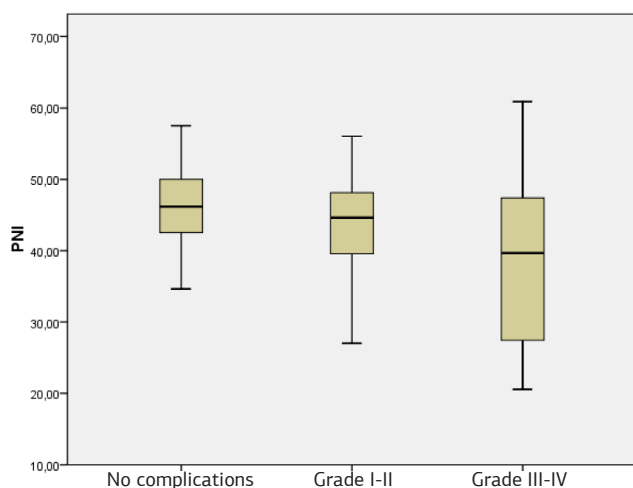


Figure 4. Mean PNI values depending on the complications' severity. Significant inverse association was noted between PNI values and the severity of postoperative complications ($p=0.001$).

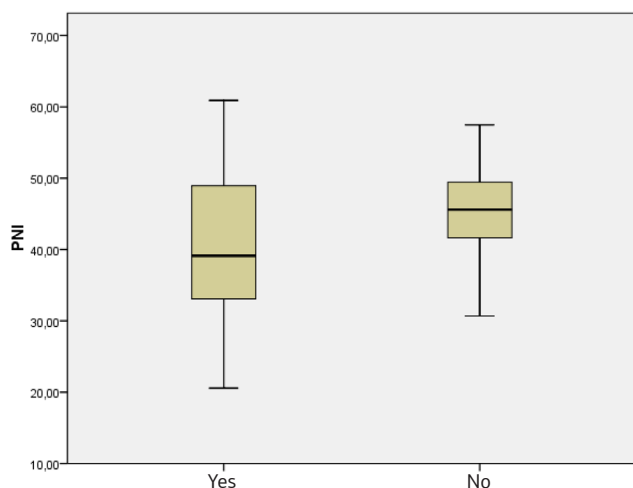


Figure 5. Mean PNI values were significantly lower in the patients with anastomotic leak ($p=0.04$).

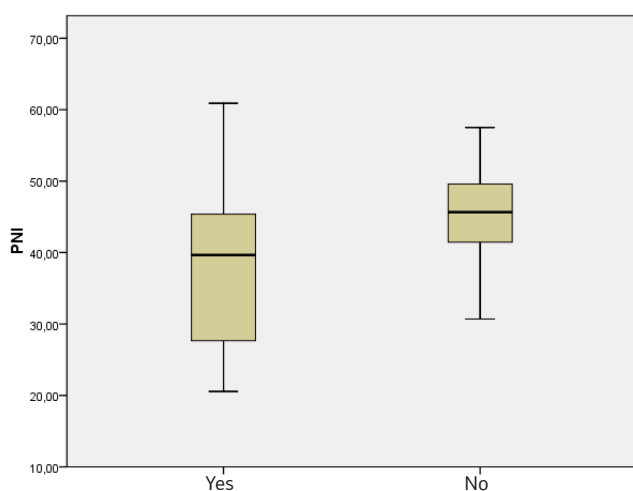


Figure 6. Mean PNI values were significantly lower in the patients who required unplanned admission to HD/ICU postoperatively ($p=0.03$).

complications had a PNI of 40.36 vs 44.8 of the non-emergency laparotomy group, however due to the small number of this group statistical analysis was not performed. Finally, our results did not demonstrate any significant differences between PNI scores and the occurrence of wound infections or requirement for emergency blood product transfusions.

Discussion

Previous studies have demonstrated that low albumin values, as well as low absolute lymphocyte counts are predictive of a more dismal prognosis in patients with colorectal malignancies, with albumin being indicative of patients' general nutritional status, while lymphocyte counts correspond to the host's anticancer immunity capabilities [10-13]. With respect to decreased albumin levels in cancer patients, one of the main proposed mechanisms for hypoalbuminemia is the increased production of pro-inflammatory cytokines, such as IL-6 and TNF- α by hepatocytes [14-16].

Further studies have demonstrated an inverse association between the circulating levels of these cytokines and the aggressive biological behavior of gastrointestinal tumors, including colorectal cancer [17,18]. In addition, lymphocytes comprise a mixed cellular population which is regarded as the cornerstone of cellular immunity against malignant cells [19]. Under this notion, the presence of lymphocytopenia is considered as a negative prognostic factor in patients with colorectal cancer [20].

Combining these two laboratory parameters in a unifying scoring system, Onodera and co-workers proposed and validated PNI, a cost-effective and globally accessible score for assessing malnutrition [7].

To-date, there is mounting evidence correlating poor nutritional status, as assessed by the calculation of PNI, with dismal prognosis in patients with colorectal cancer. Through a retrospective study including 100 patients with end-stage colorectal cancer, Maeda and colleagues in 2014 [21] demonstrated that a low PNI score was an independent negative prognostic factor of overall survival, using a cut-off value of 44.5. However, they did not demonstrate the presence of any differences in terms of progression-free survival between their study groups. Using the same cut-off value for PNI, Ikeya and colleagues [22] suggested that a PNI score greater than 44.5 was associated with longer overall survival in a study of 80 patients with unresectable colorectal metastases. In keeping with these findings, Nozoe et al. [23] found that along with an advanced tumor stage and the

presence vascular invasion, a PNI score below 40 was an independent negative prognostic factor of survival in 219 patients undergoing colorectal cancer surgery with curative intent. In agreement with our findings, they also demonstrated an inverse association between PNI and tumor stage.

However, in their study population, only 10.5% of the patients had a PNI <40, in contrast to the 22.5% that was found in the current study. Finally, Yang et al. [24], demonstrated through their relevant retrospective study and meta-analysis of the previously published studies regarding the prognostic significance of preoperative PNI in colorectal cancer patients that low PNI was predictive of a poor prognosis and was associated with clinicopathological features in patients with colorectal cancer.

To the best of our knowledge, few large-series studies have previously investigated the value of PNI as a predictive factor of postoperative outcome after curative colorectal cancer resection. Mohri et al. [25] and Tokunaga et al. [26], in their retrospective studies of 365 and 556 patients respectively, demonstrated that low PNI scores (below 45 and 45.5 respectively), were correlated with significant postoperative morbidity in alignment with our results and additionally correlated them with poorer survival rates. In addition, a more recent study by Miyaktia and coworkers [27] demonstrated that preoperatively low PNI (<40) was significantly associated with overall morbidity and ileus after surgery for rectal cancer, but was not associated with the occurrence of anastomotic leak.

Our results demonstrated for the first time that patients with better preoperative nutritional status were more likely to have a laparoscopic resection rather than open surgery. However, this needs to be addressed in conjunction with the presence of advanced disease in our patients' group with lower PNI scores. Therefore, in cases of colorectal tumors with more advanced stage, associated in our cohort with lower PNI values, the laparoscopic approach might not have been feasible due to increased technical complexity.

Interestingly, we demonstrated that patients with a lower PNI score were more likely to require an unplanned admission to HDU, as well as to develop an anastomotic leak and required reoperation due to intraoperative complications. Furthermore, as demonstrated by previously published studies [25-27] we found a statistically significant inverse association between the PNI values and the severity of postoperative complications, based on the Clavien-Dindo classification system.

We acknowledge the presence of certain limitations of our study. Its retrospective design can result in selection bias. In addition, our data extraction was dependent on the accuracy of patients' discharge summaries, which are sometimes performed by the most junior members of the surgical teams or occasionally by the on-call surgical team. Therefore, important information about the postoperative course of patients could have been missed or inadequately recorded. Moreover, our study sample was limited due to the data collection from a single Trust over an only 2-year period. Finally, it is possible that we have underestimated the occurrence of postoperative complications, as patients could have been admitted to other hospitals within the one month postoperative period.

In summary, we recommend that nutritional assessment prior to elective colorectal cancer resection should be a part of the standard preoperative assessment. We believe that the early recognition and treatment of malnutrition in patients scheduled to undergo an elective resection for colorectal cancer seems to be a promising field towards optimizing patients' care and improving postoperative outcomes. Aiming towards this direction, PNI could be a useful screening tool of malnutrition in colorectal cancer patients, as it is a validated tool, which is widely available in every hospital setting and does not add any extra cost to the preoperative work-up.

Conflict of interests

The authors declare no conflict of interests.

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