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Postoperative PNI Change Relative to the Individual Preoperative Level Is Associated With Overall Survival in Patients With Colorectal Cancer: A Retrospective Cohort Study

Guowei Li

19834230021@163.com

Hebei North University

Ye Zhang

Hebei North University

Ning Zhang

Hebei North University

Jiandong Fei

The First Affiliated Hospital of Hebei North University

Research Article

Keywords: colorectal cancer, prognostic nutritional index, PNI change, overall survival, postoperative PNI, delayed-entry Cox model

Posted Date: November 26th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11488252/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

We investigated the association between postoperative prognostic nutritional index (PNI) change relative to the individual preoperative level and overall survival (OS) after curative colorectal cancer (CRC) resection.

Methods

This single-center retrospective cohort study included patients undergoing CRC surgery between 2018 and 2021. ΔPNI was defined as PNI at 3–8 weeks after surgery minus preoperative PNI. Patients were classified into maintenance/recovery (ΔPNI ≥ 0) and decline (ΔPNI < 0) groups. The primary analysis used delayed-entry Cox regression. Sensitivity analyses included age stratification, adjustment for preoperative PNI, and a 2-month landmark analysis. Additional analyses assessed potential selection bias, adjuvant chemotherapy, model stability, and incremental prognostic performance.

Results

Of 960 screened surgical patients, 271 were included in the survival analysis, with 58 deaths during a median follow-up of 73 months. Median PNI decreased from 47.95 preoperatively to 38.15 on postoperative day 1 and increased to 48.10 at 3–8 weeks. PNI decline was associated with a higher hazard of death in the primary adjusted model (hazard ratio [HR], 1.793; 95% confidence interval [CI], 1.046–3.073; P = 0.0336). This association persisted in age-stratified analysis (HR, 1.726; 95% CI, 1.006–2.963; P = 0.0476) and after adjustment for preoperative PNI (HR, 2.347; 95% CI, 1.304–4.224; P = 0.0044). The 2-month landmark analysis also showed poorer subsequent OS in the decline group (log-rank P = 0.0226). After inclusion of the recorded chemotherapy variable, the association was attenuated (HR, 1.626; 95% CI, 0.938–2.817; P = 0.0833). The bootstrap optimism-corrected calibration slope was 0.825. Adding PNI-change status to a model containing postoperative PNI did not improve optimism-corrected discrimination (C-index, 0.679 versus 0.675).

Conclusions

Postoperative PNI decline relative to the individual preoperative level was associated with poorer long-term OS after curative CRC resection. However, potential selection and treatment-related biases, limited events, and a lack of demonstrated incremental discrimination beyond postoperative PNI warrant cautious interpretation. External validation is needed.

1. Background

Colorectal cancer (CRC) is one of the leading contributors to the global burden of malignant disease. According to GLOBOCAN 2022, approximately 1.926 million new cases of CRC and 904,000 CRC-related deaths occurred worldwide in 2022 [1]. Despite advances in surgical techniques, perioperative management, and multimodal oncological treatment, long-term outcomes remain heterogeneous among patients undergoing curative resection. Although tumor–node–metastasis (TNM) stage and pathological characteristics are fundamental to prognostic assessment, substantial differences in survival can persist among patients with comparable tumor burdens and pathological features. This suggests that host-related factors, including nutritional, inflammatory, and immune status, may also contribute to long-term outcomes [2].

The prognostic nutritional index (PNI), calculated using serum albumin and the peripheral blood absolute lymphocyte count, was originally developed to assess nutritional status and surgical risk in patients undergoing gastrointestinal cancer surgery [3]. Because it is straightforward to calculate from routinely available laboratory measurements, PNI has been widely investigated as a prognostic marker in patients with cancer. In CRC, lower preoperative PNI has been associated with poorer long-term survival and less favorable postoperative outcomes, and systematic reviews and meta-analyses have supported an association between PNI and survival [4–6]. However, conventional studies have generally treated PNI as a static measure obtained before surgery or at a single time point. In clinical practice, nutritional and immune-related status is not static: it may change in response to surgical trauma, inflammation, metabolic stress, and postoperative recovery. Consequently, a single PNI measurement may not fully capture changes in a patient's condition across the perioperative period.

Recent research has increasingly shifted from preoperative PNI alone toward postoperative nutritional status and perioperative changes in PNI. Previous studies have associated postoperative PNI with long-term outcomes in CRC, and combined assessments of preoperative and postoperative PNI may further distinguish prognostic patterns [7, 8]. Postoperative nutritional status has also been associated with overall survival (OS) and recurrence-free survival (RFS) in patients with CRC [9]. More recent studies have directly examined perioperative changes in PNI. Zhang et al. reported associations between changes in PNI (ΔPNI) and OS and progression-free survival in patients undergoing CRC surgery [10]. Tatsuta et al. found that postoperative PNI below the preoperative level was associated with poorer OS and RFS in patients with stage II or III CRC, with the association persisting after adjustment for preoperative nutritional status [11]. A more recent study combined preoperative and postoperative PNI measurements to construct a change-PNI classification and explored the relationship between different preoperative and postoperative PNI states and OS [12]. Collectively, these findings suggest that longitudinal changes in PNI may convey host-related information that cannot be fully captured by a single measurement.

Against this background, an important clinical question is whether postoperative PNI returns to the individual patient's preoperative level after curative CRC resection. Unlike a fixed population-based threshold, the individual's preoperative PNI provides a personal reference against which postoperative status can be assessed. This approach characterizes the direction of change relative to the patient's baseline. Accordingly, the present study was not designed simply to reconfirm the prognostic relevance

of PNI itself. Rather, it focused on whether postoperative PNI change relative to the individual preoperative level was associated with long-term OS. Importantly, this change is a descriptive difference between laboratory measurements and should not be interpreted as a direct measure of nutritional or physiological recovery.

This question also has an important temporal dimension. A patient's postoperative PNI-change status cannot be determined until the postoperative laboratory measurement has been obtained; therefore, this status is not a fixed exposure known on the day of surgery. If the subsequently determined PNI-change category is assigned retrospectively from the date of surgery and analyzed as though it were known at baseline, the timing of exposure ascertainment may be misaligned with the start of the risk period, potentially introducing immortal time bias [13, 14]. To address this concern, the present study used a delayed-entry Cox model, with entry into the risk set determined by the actual date of postoperative PNI measurement, in accordance with principles of delayed entry and left truncation [15, 16]. A complementary 2-month postoperative landmark analysis was also performed to assess the association between PNI change and subsequent OS from a common time point.

Therefore, this study aimed to investigate the association between PNI measured 3–8 weeks after curative CRC resection, relative to each patient's preoperative level, and long-term OS. The robustness of the primary findings was examined using age-stratified analysis, adjustment for preoperative PNI, and a 2-month landmark analysis. Continuous ΔPNI, restricted cubic spline analysis, four dynamic PNI phenotypes, and adjuvant chemotherapy were additionally examined in supportive or exploratory analyses.

Additional analyses evaluated potential selection bias, model stability, and whether PNI-change status provided incremental prognostic performance beyond conventional PNI measurements.

2. Materials and Methods

2.1. Study Design and Study Population

This single-center retrospective cohort study was conducted at the First Affiliated Hospital of Hebei North University using hospital records of patients who underwent surgery for colorectal cancer (CRC) between January 2018 and December 2021.

A total of 960 CRC surgical patients were initially screened. Clinical eligibility assessment excluded 374 patients: 104 who did not undergo curative resection, 125 who underwent emergency or non-elective surgery, 56 who had received neoadjuvant or conversion treatment, 3 with severe infection, autoimmune disease, or hematological disease meeting the exclusion criteria, and 86 with a history of another malignancy. Thus, 586 patients were clinically eligible.

Among these patients, 224 had incomplete PNI measurement data and 64 lacked other essential study variables, leaving 298 patients with complete study data. Survival information could not be obtained for

27 patients, and they were excluded from the survival analysis. The final time-to-event cohort comprised 271 patients (Fig. 1).

Inclusion criteria were: (1) curative resection for primary CRC confirmed by postoperative pathology; (2) eligible preoperative laboratory data for PNI calculation; (3) PNI measurements at 3–8 weeks after surgery; and (4) complete other essential clinicopathological and study information. Exclusion criteria included emergency or non-elective surgery, neoadjuvant or conversion treatment, severe infection or specified autoimmune/hematologic diseases, severe cardiac/hepatic/renal dysfunction, other malignancy, or incomplete essential study information.

Tumor stage was classified according to the eighth edition of the American Joint Committee on Cancer TNM staging system.

2.2. Collection of Clinical and Pathological Data

Clinical data were obtained from the hospital's electronic medical record system. The collected variables included demographic characteristics, perioperative laboratory measurements, tumor pathological characteristics, medical history, comorbidities, and treatment information.

Demographic variables included age and sex. Medical history and lifestyle-related variables included smoking status, alcohol consumption, and previous surgery. Comorbidities included diabetes mellitus, hypertension, and heart disease. Tumor-related variables included tumor location, surgical approach, histological type, TNM stage, vascular invasion, and perineural invasion. Information on adjuvant chemotherapy was recorded according to the treatment received by each patient.

Detailed, consistently recorded patient-level postoperative complication data were unavailable for systematic analysis and therefore could not be included as model covariates.

2.3. PNI Calculation and Measurement Timing

The prognostic nutritional index (PNI) was calculated using serum albumin and the peripheral blood absolute lymphocyte count according to the method described by Onodera et al. [3]:

PNI = serum albumin (g/L) + 5 × absolute lymphocyte count ($\times 10^9$/L)

Preoperative PNI was calculated using the first routine blood test obtained after hospital admission and before surgery. PNI on postoperative day 1 was calculated from the blood sample collected on the first postoperative day and was used to describe early perioperative changes. The PNI measured 3–8 weeks after surgery was the principal postoperative exposure measure in this study.

The postoperative measurement window was prespecified as postoperative days 21–56. In the study cohort, the actual postoperative PNI measurements were obtained between postoperative days 21 and 54, with a median measurement time of 28 days (interquartile range [IQR], 23–34.5 days).

For patients who received adjuvant chemotherapy, the first eligible PNI measurement obtained before the initiation of adjuvant chemotherapy within the prespecified postoperative window was selected. For patients who did not receive chemotherapy, the first eligible PNI measurement within the same window was used.

2.4. Definition of Postoperative PNI Change

The change in PNI (ΔPNI) was calculated as the postoperative PNI measured 3–8 weeks after surgery minus the preoperative PNI:

ΔPNI = Postoperative PNI (3–8 weeks) − Preoperative PNI

Patients were classified into two groups according to the change in PNI relative to their individual preoperative levels.

The PNI maintenance/recovery group comprised patients whose postoperative PNI was equal to or higher than their preoperative PNI (ΔPNI ≥ 0). The PNI decline group comprised patients whose postoperative PNI was lower than their preoperative PNI (ΔPNI < 0).

The PNI decline group was compared with the PNI maintenance/recovery group, which served as the reference group in the primary analysis.

The terms “maintenance/recovery” and “decline” describe PNI measurement categories and do not necessarily indicate overall nutritional, immunological, or functional recovery or deterioration.

2.5. Perioperative Changes in PNI

To characterize perioperative changes in PNI, measurements obtained preoperatively, on postoperative day 1, and 3–8 weeks after surgery were compared. Postoperative day 1 PNI was used only to describe early perioperative changes and was not treated as the primary prognostic exposure.

All three measurements were obtained from the same patients. Paired statistical methods were used to assess differences between the measurement time points.

2.6. Follow-up and Overall Survival

Final vital status was ascertained in June 2026.

Overall survival (OS) was defined as the time from the date of surgery to death from any cause or the last date on which the patient was confirmed to be alive. Patients who were alive at their last confirmed follow-up were censored on that date. Patients without reliable final survival information were excluded from the time-to-event analysis.

Median follow-up duration was estimated using the reverse Kaplan–Meier method.

2.7. Primary Delayed-Entry Cox Proportional Hazards Model

Because postoperative PNI-change status could only be determined after the postoperative laboratory measurement had been obtained, a delayed-entry Cox proportional hazards model was used for the primary survival analysis.

The date of surgery was defined as the time origin. The actual date of postoperative PNI measurement was used as the entry time, and the date of death or the last confirmed date alive was used as the exit time. Death was treated as the event of interest.

Patients entered the corresponding risk set only when their postoperative PNI information became available, while the survival time scale remained anchored to the date of surgery. This approach aligned entry into the risk set with the actual ascertainment of the exposure while retaining a common postoperative time scale.

2.8. Two-Month Postoperative Landmark Analysis

A postoperative landmark analysis using 2 months after surgery as the landmark time was conducted as a sensitivity analysis. All postoperative PNI measurements had been obtained by postoperative day 54; therefore, PNI-change status was available for all patients by the 2-month landmark.

Post-landmark OS was evaluated using the Kaplan–Meier method, and survival curves were compared between the PNI maintenance/recovery and PNI decline groups using the log-rank test.

The earliest observed death occurred 3 months after surgery, and no deaths were observed before the 2-month landmark. Consequently, all 271 patients were eligible for inclusion in the landmark analysis.

2.9. Cox Regression Models and Covariate Strategy

The association between postoperative PNI change and overall survival (OS) was evaluated using delayed-entry Cox proportional hazards regression. The PNI-change group was the primary exposure, with the maintenance/recovery group ($\Delta PNI \geq 0$) serving as the reference category.

Three sequential models were fitted:

Model 1 (unadjusted model)

PNI-change group was included as the only predictor.

Model 2 (demographically adjusted model)

Model 1 was additionally adjusted for age and sex.

Model 3 (primary multivariable model)

Model 2 was further adjusted for TNM stage, vascular invasion, and perineural invasion.

Age was included as a continuous variable in Models 2 and 3. Male sex, TNM stage I, absence of vascular invasion, and absence of perineural invasion were used as the corresponding reference categories.

The date of surgery was used as the time origin, and patients entered the risk set on the actual date of postoperative PNI measurement. Results were reported as hazard ratios (HRs) with 95% confidence intervals (CIs).

2.10. Assessment of the Proportional Hazards Assumption

The proportional hazards assumption was assessed using Schoenfeld residuals. When evidence of a violation was identified for a covariate, an appropriate stratified Cox model was used in a sensitivity analysis to assess the robustness of the estimated association.

2.11. Age-Stratified Sensitivity Analysis

Because age showed evidence of a departure from the proportional hazards assumption in the primary adjusted model, an age-stratified Cox model was fitted as a sensitivity analysis.

Age was categorized into two strata: younger than 65 years and 65 years or older. Age group was incorporated as a stratification variable, while PNI-change group, TNM stage, vascular invasion, and perineural invasion were included as covariates.

2.12. Sensitivity Analysis Adjusted for Preoperative PNI

The definition of PNI-change group incorporated both preoperative and postoperative PNI, and preoperative PNI differed between the two groups. To assess whether the primary association was sensitive to these baseline differences, preoperative PNI was additionally included as a continuous covariate in an age-stratified Cox model.

This model also adjusted for sex, TNM stage, vascular invasion, and perineural invasion. The analysis was intended to evaluate the robustness of the association between postoperative PNI change and OS after accounting for differences in baseline PNI.

Because ΔPNI depends mathematically on both preoperative and postoperative measurements, adjustment for baseline PNI was interpreted as a sensitivity analysis and cannot eliminate mathematical coupling, regression to the mean, or measurement error.

2.13. Continuous ΔPNI and Exploratory Analyses

In addition to the primary binary exposure analysis, ΔPNI was modeled as a continuous variable in a delayed-entry Cox model adjusted for age, sex, TNM stage, vascular invasion, and perineural invasion. A restricted cubic spline (RCS) model with four knots was fitted using the same adjustment covariates to

explore the potential shape of the association between continuous ΔPNI and mortality risk. These analyses were considered exploratory.

Four dynamic PNI phenotypes were also examined using previously reported cutoffs of 48.05 for preoperative PNI and 43.65 for postoperative PNI measured 3–8 weeks after surgery. Patients were classified as Persistent low, Recovery, Deterioration, or Persistent high according to their preoperative and postoperative PNI values.

Differences in overall survival among the four PNI phenotypes were explored using Kaplan–Meier analysis with a 2-month postoperative landmark. Subsequent survival was compared from the common landmark time using the log-rank test. Pairwise comparisons were adjusted for multiple testing using the Holm method.

Because the Deterioration group was small, this phenotype analysis was intended to describe potential prognostic heterogeneity across different patterns of PNI change. The findings were interpreted as exploratory evidence and were not used as the basis for the primary effect estimate.

For the four phenotypes, Persistent low was defined as preoperative PNI < 48.05 and postoperative PNI < 43.65; Recovery as preoperative PNI < 48.05 and postoperative PNI ≥ 43.65; Deterioration as preoperative PNI ≥ 48.05 and postoperative PNI < 43.65; and Persistent high as preoperative PNI ≥ 48.05 and postoperative PNI ≥ 43.65. These phenotypes were operational laboratory-defined categories rather than confirmed clinical states.

2.14. Adjuvant Chemotherapy and Sensitivity Analysis

Adjuvant chemotherapy information was recorded according to each patient's treatment history. Because chemotherapy occurred after postoperative PNI measurement and determination of PNI-change status, whether a patient received chemotherapy was not included as a baseline covariate in the primary Cox models.

Given the difference in adjuvant chemotherapy use between the two PNI-change groups, an exploratory sensitivity model (Model 4) was fitted by adding a binary indicator of ever having received adjuvant chemotherapy to Model 3. In the original treatment records, “none” indicated no adjuvant chemotherapy, whereas “1–8 cycles” indicated that adjuvant chemotherapy had been received; these categories were recoded as “no” and “yes,” respectively.

The database did not contain sufficiently detailed temporal information on chemotherapy initiation, total treatment duration, dose intensity, or treatment completion. Accordingly, chemotherapy was not modeled as a time-dependent variable. The resulting analysis was not intended to establish a causal relationship among PNI change, chemotherapy, and OS.

Because the fixed indicator of ever receiving chemotherapy is defined using subsequent treatment, it may be affected by treatment selection and time-related bias, including potential immortal time bias.

Model 4 was regarded as exploratory, not as proof of independence from adjuvant treatment.

2.15. Statistical Analysis

Continuous variables were summarized as medians and IQRs according to their distributions. Between-group comparisons were performed using the Wilcoxon rank-sum test. Categorical variables were summarized as counts and percentages and compared using the Pearson chi-square test or Fisher's exact test, as appropriate to the contingency table.

Overall differences in PNI across the three perioperative measurement time points were assessed using the Friedman test. Pairwise comparisons were performed using the paired Wilcoxon signed-rank test, with Holm adjustment for multiple comparisons.

OS was described using Kaplan–Meier curves, and between-group differences were assessed using the log-rank test. The primary survival analysis used delayed-entry Cox regression, with the date of surgery as the time origin and entry time determined by the actual date of postoperative PNI measurement. Tied event times were handled using the Efron approximation.

The robustness of the primary findings was further assessed through age-stratified analysis, adjustment for preoperative PNI, the 2-month landmark analysis, and other specified sensitivity analyses. Continuous ΔPNI with RCS and the four-phenotype analysis were treated as exploratory analyses.

No variables included in the primary analysis had missing data; therefore, no imputation was performed. All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant. Statistical analyses were performed using R software, version 4.6.0.

Two additional comparisons of available baseline characteristics evaluated potential selection bias. Clinically eligible patients with complete study data (n = 298) were compared with those with incomplete study data (n = 288), and patients included in survival analysis (n = 271) were compared with those with unavailable survival information (n = 27). Wilcoxon rank-sum, Pearson chi-square, and, for tumor location in the latter comparison, Fisher's exact test with Monte Carlo simulation (20,000 replicates) were used as appropriate; absolute standardized mean differences described the magnitude of baseline differences. These comparisons were restricted to available age, sex, and tumor location information.

Given the limited number of deaths, the primary delayed-entry Cox model was subjected to 1,000 patient-level bootstrap resamples, retaining the original covariate set. The median, empirical 2.5th–97.5th percentiles of the bootstrap HR distribution, percentage of bootstrap HRs > 1, and optimism-corrected calibration slope of the Cox linear predictor were calculated.

Six Cox models were compared in the common two-month postoperative landmark cohort. Each contained age, sex, TNM stage, vascular invasion, and perineural invasion. Model A included clinical variables alone; Model B added continuous preoperative PNI; Model C added continuous postoperative PNI; Model D added binary PNI-change status; Model E added preoperative PNI and binary PNI-change

status; and Model F added postoperative PNI and binary PNI-change status. Harrell's C-index was evaluated, with optimism correction from 1,000 paired patient-level bootstrap resamples. Exploratory nested-model likelihood-ratio tests compared Models E versus B and F versus C. These analyses assessed discrimination and model fit, not established clinical utility.

2.16. Ethics Approval

This study was approved by the Ethics Committee of the First Affiliated Hospital of Hebei North University (approval No. K2025409). The requirement for written informed consent was waived by the ethics committee.

3. Results

3.1. Study Population and Clinicopathological Characteristics

A total of 960 patients who underwent surgery for colorectal cancer between January 2018 and December 2021 were initially screened. Clinical eligibility assessment excluded 374 patients (noncurative surgery, n = 104; emergency or non-elective surgery, n = 125; neoadjuvant or conversion treatment, n = 56; severe infection, autoimmune or hematologic conditions, n = 3; and history of another malignancy, n = 86), leaving 586 clinically eligible patients. Among these, 224 had incomplete PNI data and 64 lacked other essential variables. Of the 298 patients with complete study data, survival information was unavailable for 27, leaving 271 patients in the final survival analysis (Figure 1).

Comparisons of available baseline characteristics showed no statistically significant differences between patients with complete and incomplete study data in age (P = 0.346), sex (P = 0.596), or tumor location (P = 0.357; Additional file 1: Table S1). Likewise, patients included in survival analysis and those with unavailable survival information did not show statistically significant differences in age (P = 0.418), sex (P = 0.542), or tumor location (P = 0.832; Additional file 1: Table S2). These limited comparisons cannot exclude selection bias.

Among the 271 patients in the survival analysis, 136 (50.2%) had PNI maintenance/recovery and 135 (49.8%) had PNI decline. Median age was 65 years (IQR, 58.5–71 years) in the overall cohort, 65 (58–70) in the maintenance/recovery group, and 66 (59.5–71) in the decline group (P = 0.580). No statistically significant between-group differences were observed in sex, tumor location, surgical approach, histological type, TNM stage, vascular invasion, perineural invasion, or recorded comorbidities and history variables (all P > 0.05; Table 1).

Adjuvant chemotherapy was received by 119 of 136 patients (87.5%) in the maintenance/recovery group and 94 of 135 (69.6%) in the decline group (P < 0.001). This post-exposure treatment variable was evaluated in a separate exploratory sensitivity analysis.

Table 1. Baseline clinicopathological characteristics according to postoperative PNI-change group

Characteristic	PNI maintenance/recovery (n = 136)	PNI decline (n = 135)	P value
Age, years, median (IQR)	65 (58–70)	66 (59.5–71)	0.580
Sex, n (%)			0.806
Male	80 (58.8)	77 (57.0)	
Female	56 (41.2)	58 (43.0)	
Tumor location, n (%)			0.347
Right colon	35 (25.7)	24 (17.8)	
Transverse colon	3 (2.2)	2 (1.5)	
Left colon	26 (19.1)	33 (24.4)	
Rectum	72 (52.9)	76 (56.3)	
Surgical approach, n (%)			0.112
Laparoscopic	83 (61.0)	69 (51.1)	
Open	53 (39.0)	66 (48.9)	
Histological type, n (%)			0.748
Moderately differentiated adenocarcinoma	100 (73.5)	93 (68.9)	
Moderately to poorly differentiated adenocarcinoma	29 (21.3)	31 (23.0)	
Moderately to well differentiated adenocarcinoma	2 (1.5)	2 (1.5)	
Poorly differentiated adenocarcinoma	3 (2.2)	7 (5.2)	
Well differentiated adenocarcinoma	2 (1.5)	2 (1.5)	
TNM stage, n (%)			0.987
I	24 (17.6)	25 (18.5)	
II	62 (45.6)	60 (44.4)	
III	50 (36.8)	50 (37.0)	
Vascular invasion, n (%)			1.000
Absent	97 (71.3)	96 (71.1)	
Present	39 (28.7)	39 (28.9)	

Characteristic	PNI maintenance/recovery (n = 136)	PNI decline (n = 135)	P value
Perineural invasion, n (%)			0.383
Absent	109 (80.1)	102 (75.6)	
Present	27 (19.9)	33 (24.4)	
Diabetes mellitus, n (%)			0.724
No	119 (87.5)	116 (85.9)	
Yes	17 (12.5)	19 (14.1)	
Hypertension, n (%)			1.000
No	97 (71.3)	96 (71.1)	
Yes	39 (28.7)	39 (28.9)	
Heart disease, n (%)			0.550
No	124 (91.2)	120 (88.9)	
Yes	12 (8.8)	15 (11.1)	
Smoking, n (%)			0.766
No	109 (80.1)	106 (78.5)	
Yes	27 (19.9)	29 (21.5)	
Alcohol consumption, n (%)			0.874
No	111 (81.6)	112 (83.0)	
Yes	25 (18.4)	23 (17.0)	
Previous surgery, n (%)			0.692
No	93 (68.4)	96 (71.1)	
Yes	43 (31.6)	39 (28.9)	
Adjuvant chemotherapy, n (%)			<0.001
No	17 (12.5)	41 (30.4)	
Yes	119 (87.5)	94 (69.6)	

Abbreviations: IQR, interquartile range; PNI, prognostic nutritional index; TNM, tumor–node–metastasis. P values were calculated using the Wilcoxon rank-sum test and chi-square or Fisher exact test, as appropriate.

3.2. Perioperative Changes in PNI

PNI changed substantially across the perioperative period in the overall cohort (Table 2). The median preoperative PNI was 47.95 (IQR, 43.35–51.53), decreased to 38.15 (IQR, 35.35–40.90) on postoperative day 1, and subsequently increased to 48.10 (IQR, 44.23–51.10) at 3–8 weeks after surgery.

The overall difference across the three measurement time points was statistically significant according to the Friedman test ($\chi^2 = 339.41$, $P < 0.001$). In pairwise comparisons using the Wilcoxon signed-rank test with Holm adjustment, PNI on postoperative day 1 was significantly lower than preoperative PNI ($P < 0.001$), and PNI at 3–8 weeks was significantly higher than PNI on postoperative day 1 ($P < 0.001$). However, the difference between preoperative PNI and PNI at 3–8 weeks was not statistically significant ($P = 0.985$).

According to the prespecified definition of postoperative PNI change, 136 patients (50.2%) had a postoperative PNI equal to or higher than their individual preoperative level and were classified into the maintenance/recovery group. The remaining 135 patients (49.8%) had a postoperative PNI below their preoperative level and were classified into the decline group. The timing of postoperative PNI measurement was comparable between the groups: the median was 27.5 days in the maintenance/recovery group and 28 days in the decline group ($P = 0.441$).

Between-group comparisons showed that the median preoperative PNI was lower in the maintenance/recovery group than in the decline group (44.88 [IQR, 41.19–48.79] vs. 50.25 [IQR, 46.45–53.45]; $P < 0.001$). On postoperative day 1, the corresponding values were 37.50 (IQR, 34.60–40.11) and 38.80 (IQR, 35.98–41.93), respectively ($P = 0.014$). At 3–8 weeks after surgery, the median PNI was 50.38 (IQR, 46.85–53.68) in the maintenance/recovery group and 45.70 (IQR, 40.48–49.35) in the decline group ($P < 0.001$).

The median ΔPNI was 3.95 (IQR, 1.89–7.39) in the maintenance/recovery group and −4.05 (IQR, −7.93 to −1.93) in the decline group ($P < 0.001$). Notably, patients in the PNI decline group had a higher preoperative PNI but a lower postoperative PNI at 3–8 weeks than those in the maintenance/recovery group. This pattern indicates that the between-group distinction reflected postoperative PNI relative to each patient's preoperative level rather than simply differences in the absolute preoperative PNI.

Table 2. Perioperative changes in prognostic nutritional index

PNI measurement	Overall cohort (n = 271)	PNI maintenance/recovery (n = 136)	PNI decline (n = 135)	P value
Preoperative PNI, median (IQR)	47.95 (43.35–51.53)	44.88 (41.19–48.79)	50.25 (46.45–53.45)	<0.001
PNI on postoperative day 1, median (IQR)	38.15 (35.35–40.90)	37.50 (34.60–40.11)	38.80 (35.98–41.93)	0.014
Postoperative PNI at 3–8 weeks, median (IQR)	48.10 (44.23–51.10)	50.38 (46.85–53.68)	45.70 (40.48–49.35)	<0.001
ΔPNI, median (IQR)	—	3.95 (1.89–7.39)	−4.05 (−7.93 to −1.93)	<0.001
Timing of postoperative PNI measurement, days, median	28	27.5	28	0.441

Abbreviations: IQR, interquartile range; PNI, prognostic nutritional index; ΔPNI, postoperative minus preoperative PNI. PNI = albumin (g/L) + 5 × lymphocyte count (×10⁹/L). Between-group comparisons used Wilcoxon rank-sum tests; Friedman $\chi^2 = 339.41$ ($P < 0.001$). Holm-adjusted pairwise P values were <0.001, <0.001, and 0.985.

3.3. Association Between Postoperative PNI Change and Overall Survival

The median follow-up duration estimated using the reverse Kaplan–Meier method was 73 months (95% CI, 71–75 months). During follow-up, 58 deaths occurred among the 271 patients included in the survival analysis. There were 21 deaths (15.4%) in the PNI maintenance/recovery group and 37 deaths (27.4%) in the PNI decline group.

The primary survival analysis used a delayed-entry Cox proportional hazards model, with the date of surgery as the time origin and the actual date of postoperative PNI measurement as the entry time. Using the PNI maintenance/recovery group as the reference, the unadjusted model (Model 1) showed that PNI decline was associated with a higher risk of death (HR, 1.848; 95% CI, 1.081–3.158; P = 0.0248).

This association remained statistically significant after adjustment for age and sex in Model 2 (HR, 1.824; 95% CI, 1.066–3.121; P = 0.0283). In the primary multivariable model (Model 3), which additionally adjusted for TNM stage, vascular invasion, and perineural invasion, PNI decline remained associated with a higher risk of death (HR, 1.793; 95% CI, 1.046–3.073; P = 0.0336).

The estimated association was directionally consistent across the three models, supporting an association between failure to recover PNI to the individual preoperative level and poorer OS after adjustment for the prespecified clinicopathological covariates (Table 3).

Table 3. Cox regression analyses of postoperative PNI change and overall survival

Analysis/model	Covariates or analysis approach	PNI effect HR (95% CI)	P value
Model 1	Unadjusted delayed-entry Cox model	1.848 (1.081–3.158)	0.0248
Model 2	Adjusted for age and sex	1.824 (1.066–3.121)	0.0283
Model 3 (primary model)	Model 2 + TNM stage, vascular invasion, and perineural invasion	1.793 (1.046–3.073)	0.0336
Age-stratified sensitivity analysis	Age strata: <65 vs ≥65 years; adjusted for TNM stage, vascular invasion, and perineural invasion	1.726 (1.006–2.963)	0.0476
Preoperative PNI-adjusted sensitivity analysis	Age-stratified model adjusted for preoperative PNI, sex, TNM stage, vascular invasion, and perineural invasion	2.347 (1.304–4.224)	0.0044
Model 4: exploratory chemotherapy analysis	Model 3 + ever received adjuvant chemotherapy	1.626 (0.938–2.817)	0.0833
Two-month landmark analysis	Unadjusted landmark Cox model	1.848 (1.081–3.158)	0.0248
Continuous ΔPNI analysis	ΔPNI modeled as a continuous variable in the adjusted delayed-entry Cox model	0.963 (0.930–0.997) per unit increase	0.0319

Abbreviations: CI, confidence interval; HR, hazard ratio; PNI, prognostic nutritional index; ΔPNI, postoperative minus preoperative PNI. In the first seven rows HRs compare decline versus maintenance/recovery; in the final row the HR is per one-unit increase in ΔPNI. Model 4 is exploratory because chemotherapy was recorded after PNI assessment.

3.4. Sensitivity Analyses

3.4.1. Two-month landmark analysis

In the prespecified landmark analysis, OS was evaluated from 2 months after surgery. All postoperative PNI measurements had been obtained by postoperative day 54, and the earliest observed death occurred 3 months after surgery; therefore, all 271 patients were included in the landmark analysis.

Post-landmark OS differed significantly between the two PNI-change groups, with poorer subsequent survival in the PNI decline group (log-rank P = 0.0226; Figure 2). The unadjusted landmark Cox analysis also indicated a higher risk of death in the PNI decline group (HR, 1.848; 95% CI, 1.081–3.158; P = 0.0248). The direction of the association was consistent with that observed in the primary delayed-entry Cox analysis.

3.4.2. Assessment of the proportional hazards assumption and age-stratified analysis

In Model 3, the Schoenfeld residual test did not indicate a significant departure from the proportional hazards assumption for PNI-change group (P = 0.657). However, age showed evidence of a proportional hazards violation (P = 0.012), and the global test was also significant (P = 0.031).

To address the age-related violation, an age-stratified Cox model was fitted using age categories of <65 and ≥65 years as strata. After stratification, PNI decline remained associated with a higher risk of death (HR, 1.726; 95% CI, 1.006–2.963; P = 0.0476). The proportional hazards tests did not indicate a clear violation in this stratified model (P = 0.52 for PNI-change group; global P = 0.28).

3.4.3. Sensitivity analysis adjusted for preoperative PNI

Because preoperative PNI differed between the two exposure groups, a further age-stratified Cox model included preoperative PNI as a continuous covariate, together with sex, TNM stage, vascular invasion, and perineural invasion.

In this model, PNI decline remained associated with a higher risk of death (HR, 2.347; 95% CI, 1.304–4.224; P = 0.0044). Higher preoperative PNI was inversely associated with mortality risk (HR, 0.939; 95% CI, 0.893–0.988; P = 0.0161). The global proportional hazards test for this model did not indicate a clear violation (P = 0.27).

3.4.4. Exploratory sensitivity analysis incorporating adjuvant chemotherapy

Given the significant difference in adjuvant chemotherapy use between the PNI-change groups, Model 4 was fitted by adding ever-received adjuvant chemotherapy to Model 3. After inclusion of this variable, the association between PNI decline and mortality remained directionally consistent but was attenuated and no longer reached conventional statistical significance (HR, 1.626; 95% CI, 0.938–2.817; P = 0.0833).

In the same model, ever having received adjuvant chemotherapy was associated with a lower estimated risk of death, although the result did not reach conventional statistical significance (HR, 0.546; 95% CI, 0.293–1.018; P = 0.0571).

Because chemotherapy occurred after postoperative PNI assessment and the available data lacked detailed information on treatment initiation, duration, dose intensity, and completion, this analysis was interpreted as exploratory. It was used to assess how the estimated PNI association changed after accounting for the recorded chemotherapy variable, rather than to infer a causal mechanism (Table 3).

3.5. Exploratory Analyses

3.5.1. Continuous ΔPNI and restricted cubic spline analysis

When ΔPNI was modeled as a continuous variable in the delayed-entry Cox model adjusted for age, sex, TNM stage, vascular invasion, and perineural invasion, a higher ΔPNI was associated with a lower estimated risk of death. For each one-unit increase in ΔPNI, the HR for death was 0.963 (95% CI, 0.930–0.997; P = 0.0319).

An RCS model with four knots was then used to explore the potential shape of the association. The overall association did not reach conventional statistical significance (P for overall association = 0.0703), and there was no statistically significant evidence of nonlinearity (P for nonlinearity = 0.2431; **Additional file 2:** Figure **S1**). Thus, the continuous ΔPNI analysis suggested an inverse association in the fitted linear model, whereas the spline analysis did not establish a statistically significant overall or nonlinear relationship.

3.5.2. Four PNI dynamic phenotypes

Using the preoperative PNI cutoff of 48.05 and the postoperative PNI cutoff of 43.65, patients were classified into four dynamic phenotypes: Persistent low (n = 45), Recovery (n = 91), Deterioration (n = 17), and Persistent high (n = 118).

In the 2-month landmark Kaplan–Meier analysis, subsequent OS differed significantly across the four groups (overall log-rank P = 0.000952; **Additional file 2:** Figure **S2**). In pairwise comparisons with Holm adjustment, survival differed significantly between Persistent low and Persistent high (adjusted P = 0.00628) and between Deterioration and Persistent high (adjusted P = 0.00281). The remaining pairwise comparisons did not reach statistical significance.

Because the Deterioration group included only 17 patients, these phenotype comparisons were considered exploratory and were interpreted as evidence of potential prognostic heterogeneity across different patterns of PNI status rather than as definitive estimates of group-specific effects.

3.6. Bootstrap Internal Validation of the Primary Cox Model

The primary multivariable Cox model contained seven estimated regression coefficients and 58 deaths, corresponding to approximately 8.3 events per parameter.

In 1,000 patient-level bootstrap resamples retaining the original delayed-entry Cox model, all resamples produced valid PNI-change HR estimates. The median bootstrap HR for decline versus maintenance/recovery was 1.805, with empirical 2.5th and 97.5th percentiles of 1.072 and 3.288. An estimated HR greater than 1 was observed in 98.7% of resamples.

The apparent calibration slope was approximately 1.000, whereas the optimism-corrected calibration slope was 0.825, suggesting some overfitting despite the generally consistent estimated direction of association (Additional file 1: Table S3). The bootstrap percentile range represents a distribution of estimates, not the original model's confidence interval.

3.7. Exploratory Comparison of Prognostic Discrimination and Incremental Model Performance

Six Cox models with the same clinical covariates were compared using the common two-month postoperative landmark cohort (n = 271; 58 deaths). The models differed by whether preoperative PNI, postoperative PNI, and binary PNI-change status were included.

The apparent and optimism-corrected Harrell's C-indices were 0.65719 and 0.62511 for Model A, 0.66089 and 0.62355 for Model B, 0.71108 and 0.67906 for Model C, 0.68360 and 0.65005 for Model D, 0.70026 and 0.66410 for Model E, and 0.71259 and 0.67478 for Model F (Additional file 1: Table S4). Of 1,000 paired bootstrap resamples, 999 produced valid results for all six models.

Adding binary PNI-change status to a model including preoperative PNI increased the optimism-corrected C-index from 0.62355 (Model B) to 0.66410 (Model E) and improved exploratory nested-model fit (likelihood-ratio $\chi^2 = 8.189$; P = 0.00421). However, adding PNI-change status to a model already containing postoperative PNI did not improve optimism-corrected discrimination (Model C, 0.67906; Model F, 0.67478) or nested-model fit ($\chi^2 = 0.130$; P = 0.71862).

These analyses did not establish incremental discrimination beyond postoperative PNI, superiority of ΔPNI, or its clinical predictive utility.

4. Discussion

4.1. Principal Findings

In this single-center retrospective cohort of patients undergoing curative resection for colorectal cancer (CRC), we investigated whether postoperative change in the prognostic nutritional index (PNI) relative to each patient's own preoperative level was associated with long-term overall survival (OS). Three principal findings emerged. First, PNI decreased markedly on postoperative day 1 and subsequently returned to a

cohort-level median close to the preoperative value by 3–8 weeks after surgery. Nevertheless, approximately half of the patients had a postoperative PNI below their individual preoperative level. Second, in the primary delayed-entry Cox model, patients whose postoperative PNI remained below their preoperative level had a higher hazard of death than those whose PNI was maintained or recovered (HR, 1.793; 95% CI, 1.046–3.073; P = 0.0336). The direction of this association was consistent in age-stratified, preoperative-PNI-adjusted, and two-month landmark analyses. Third, exploratory analyses of continuous ΔPNI and four dynamic PNI phenotypes suggested potential heterogeneity in the relationship between PNI trajectories and survival, although the restricted cubic spline (RCS) analysis did not establish a statistically significant overall or nonlinear association.

These findings suggest that postoperative PNI interpreted relative to an individual's preoperative level may provide complementary information about long-term prognosis after curative CRC resection. However, the observed association does not establish that postoperative PNI decline causes poorer survival, nor does it demonstrate that ΔPNI provides superior predictive performance compared with conventional preoperative or postoperative PNI measurements.

Additional analyses qualified these findings. The association attenuated after inclusion of the recorded ever-received chemotherapy variable (HR, 1.626; 95% CI, 0.938–2.817; P = 0.0833); bootstrap validation suggested some overfitting (optimism-corrected calibration slope, 0.825). The exploratory six-model comparison did not demonstrate incremental discrimination from PNI-change status beyond postoperative PNI. The findings therefore support an observational association rather than a demonstrated prognostic advantage or independent clinical predictive utility.

4.2. Relationship to Previous Studies and Contribution of the Present Study

Previous studies have consistently investigated the prognostic relevance of nutritional and inflammatory status in CRC. Lower preoperative PNI has been associated with unfavorable postoperative outcomes and poorer survival, as reported in individual cohorts and systematic reviews and meta-analyses [4–6]. These findings support the relevance of preoperative nutritional and immune-related status in patients undergoing CRC surgery. Other studies have examined postoperative PNI and the combined use of preoperative and postoperative measurements, suggesting that postoperative nutritional and inflammatory status may also be associated with subsequent outcomes [7–9].

More recent studies have begun to examine changes in PNI rather than relying exclusively on a single measurement. Zhang et al. reported associations between ΔPNI and OS and progression-free survival [10]. Tatsuta et al. found that patients with stage II or III CRC whose postoperative PNI remained below their preoperative level had poorer OS and recurrence-free survival (RFS) [11]. A study published in 2025 further categorized patients according to combinations of preoperative and postoperative PNI and

investigated their associations with OS [12]. Collectively, these studies support further investigation of postoperative PNI trajectories as potential markers of prognosis.

The present study builds on this literature in two respects. First, the primary exposure was defined according to whether postoperative PNI had returned to or exceeded each patient's own preoperative level. This within-person approach differs conceptually from classifying patients solely according to an absolute postoperative PNI threshold. Second, the primary survival analysis explicitly accounted for the timing of exposure ascertainment by using a delayed-entry Cox model, in which patients entered the risk set when their postoperative PNI status became available.

These design features provide a complementary perspective on the prognostic relevance of postoperative PNI change. An exploratory six-model comparison evaluated apparent and bootstrap optimism-corrected Harrell's C-indices and nested-model fit in a common postoperative landmark cohort. Binary PNI-change status improved fit beyond preoperative PNI (Model E vs. B, P = 0.00421), but did not improve fit beyond postoperative PNI (Model F vs. C, P = 0.71862). Postoperative PNI alone had a higher optimism-corrected C-index than binary PNI change alone (0.67906 vs. 0.65005). Therefore, we cannot conclude that ΔPNI is a superior prognostic marker or that it improves the accuracy of existing risk-prediction models. Its incremental prognostic value requires formal evaluation in independent cohorts.

4.3. Individual Preoperative Baseline and Interpretation of ΔPNI

PNI combines serum albumin concentration and peripheral blood lymphocyte count and is commonly used as a composite indicator related to nutritional and immune-inflammatory status [3]. In the present cohort, the PNI decline group had a higher median preoperative PNI but a lower median postoperative PNI than the maintenance/recovery group. This finding illustrates why postoperative PNI should be interpreted in the context of the patient's baseline value rather than solely by reference to an absolute postoperative measurement.

A within-person change measure may help characterize whether a patient has returned to their preoperative state after surgery. However, ΔPNI also has important statistical properties that require careful interpretation. Because it is calculated from two measurements, its value depends on both the baseline measurement and the subsequent measurement. Differences between the exposure groups may therefore reflect baseline variation, measurement variability, regression to the mean, and postoperative changes, rather than a single underlying biological process.

To address this issue, we performed an additional age-stratified analysis incorporating preoperative PNI as a continuous covariate. The association between PNI decline and mortality persisted after this adjustment (HR, 2.347; 95% CI, 1.304–4.224; P = 0.0044). This finding suggests that the observed association was not fully explained by measured baseline PNI under the specified model. Nevertheless,

statistical adjustment cannot eliminate all potential confounding or fully resolve the mathematical dependence between a change score and its component measurements.

Furthermore, ΔPNI should not be interpreted as a comprehensive measure of postoperative recovery. It does not directly quantify dietary intake, body composition, skeletal muscle mass, physical function, or the severity of systemic inflammation. The group labels describe laboratory-defined categories rather than confirmed recovery or deterioration of nutritional or physiological status. Its potential value lies in providing a simple measure of change relative to an individual reference point, which may complement rather than replace established clinical and pathological prognostic factors.

4.4. Potential Biological Context

The observed perioperative PNI trajectory is broadly compatible with the physiological responses associated with major surgery. Surgical stress can induce systemic inflammation, neuroendocrine responses, metabolic changes, and transient modulation of immune function [17]. Changes in oral intake, protein metabolism, circulating lymphocyte counts, inflammatory activity, and fluid balance may also affect the laboratory components used to calculate PNI. These processes may contribute to the marked early postoperative decrease and subsequent **increase in measured PNI** observed in this cohort.

Previous studies have reported associations between postoperative inflammatory markers and outcomes in CRC [18–20]. In addition, malnutrition and sarcopenia have been associated with adverse outcomes following CRC surgery [21,22]. This literature provides a broader clinical context for investigating postoperative changes in PNI, but these conditions are not interchangeable with a decline in PNI relative to an individual baseline.

Several mechanisms could plausibly contribute to persistently reduced postoperative PNI, including ongoing inflammation, inadequate nutritional intake, postoperative complications, altered immune status, and underlying comorbidities. However, these factors were not comprehensively measured in the present study. Albumin is influenced by inflammatory responses and fluid distribution as well as nutritional status, while lymphocyte counts may vary in response to infection, physiological stress, medications, and other conditions. Consequently, a postoperative PNI decline should not be interpreted as evidence of nutritional deterioration alone.

The present findings are therefore best understood as an observed prognostic association involving a composite laboratory measure. Further studies incorporating inflammatory biomarkers, nutritional assessments, body composition, postoperative complications, and functional recovery measures are needed to clarify the biological processes underlying the association.

4.5. Exposure Timing, Survival Analysis, and Adjuvant Chemotherapy

An important methodological consideration in studies of postoperative biomarkers is that the exposure cannot be classified until the relevant postoperative measurement has been obtained. In the present study, postoperative PNI was measured within a prespecified window of 3–8 weeks after surgery. Patients could therefore be classified according to their postoperative PNI change only after the date of the relevant measurement.

The primary delayed-entry Cox model retained the date of surgery as the survival time origin while allowing each patient to enter the risk set on the actual date when postoperative PNI status became available. This approach aligns risk-set entry with exposure ascertainment and avoids treating the pre-measurement interval as though the postoperative exposure status had already been observed. It is particularly relevant when postoperative measurements occur at different times among patients.

The two-month landmark analysis provided a complementary assessment by comparing subsequent survival from a common postoperative time point after all eligible PNI measurements had been obtained. The persistence of a between-group survival difference in this analysis supports the robustness of the observed association under a different temporal framework. However, delayed entry and landmark analysis address different aspects of the study design and do not eliminate all possible selection mechanisms, residual confounding, or other sources of bias.

Adjuvant chemotherapy also requires careful consideration. Chemotherapy receipt was more frequent in the PNI maintenance/recovery group than in the decline group. When an indicator of ever having received chemotherapy was added to the primary adjusted model, the estimated association between PNI decline and mortality was attenuated and no longer reached conventional statistical significance. This change should not be interpreted as proof that chemotherapy explains or mediates the association between PNI change and OS.

Chemotherapy is a post-exposure treatment variable, and its receipt may be influenced by tumor stage, postoperative recovery, patient fitness, clinical decision-making, and other prognostic factors. Previous studies have investigated the relationship between the timing of adjuvant chemotherapy and outcomes after CRC surgery [23,24], while perioperative immunonutrition studies provide broader context regarding nutritional support in surgical patients [25]. These studies do not establish a causal pathway linking postoperative PNI decline, chemotherapy timing, and survival in the present cohort.

Because detailed information on chemotherapy initiation, duration, dose intensity, and completion was unavailable, the exploratory chemotherapy model could not adequately account for treatment timing or treatment-selection processes. Moreover, the fixed indicator of ever receiving chemotherapy was defined using subsequent treatment information and may therefore be subject to time-related bias, including potential immortal time bias, as well as confounding by treatment selection. Accordingly, the attenuation of the estimated PNI association in Model 4 should not be interpreted as evidence that chemotherapy mediated the association between PNI change and OS or that the association was independent of adjuvant treatment. Model 4 was considered exploratory and did not provide a causal treatment-adjusted estimate.

4.6. Clinical Implications, Strengths, and Limitations

PNI is derived from routinely available laboratory measurements, making it relatively straightforward to calculate in clinical practice. Assessing whether postoperative PNI has returned to an individual's preoperative level at 3–8 weeks may provide an additional perspective on changes in a composite laboratory marker. For patients whose PNI remains below baseline, this finding could prompt a broader clinical assessment of nutritional intake, inflammatory status, postoperative complications, comorbidities, and functional recovery.

However, postoperative PNI decline should not, by itself, determine adjuvant treatment decisions or trigger changes in oncological management. The present study was retrospective and did not evaluate whether interventions guided by PNI change could improve patient outcomes. Moreover, exploratory model comparisons did not demonstrate improved discrimination when binary PNI-change status was added to a model already containing postoperative PNI. Its reproducibility, incremental prognostic value, and clinical utility therefore require further evaluation in independent cohorts.

The study has several strengths. First, the primary exposure was defined relative to each patient's preoperative PNI, allowing postoperative change to be assessed against an individual reference level. Second, the primary delayed-entry Cox analysis explicitly accounted for the timing of postoperative exposure ascertainment. Third, complementary analyses, including age stratification, adjustment for preoperative PNI, and a 2-month landmark analysis, were performed to assess the consistency of the primary association. Additional analyses examined potential selection bias, bootstrap model stability, and incremental prognostic performance relative to preoperative and postoperative PNI. These analyses increased the transparency of the study but did not eliminate its observational limitations.

Several limitations should be acknowledged. First, the retrospective single-center design limits generalizability and may be affected by selection bias, information bias, and residual confounding. Among 586 clinically eligible patients, 288 (49.1%) had incomplete PNI or other essential study data. In addition, survival information was unavailable for 27 of the 298 patients with otherwise complete study data. Although comparisons of available age, sex, and tumor location showed no statistically significant differences between the respective groups, these limited comparisons cannot exclude selection bias related to unmeasured clinical or prognostic factors (Additional file 1: Tables S1 and S2).

Second, the final survival analysis included 271 patients and 58 deaths. The primary adjusted Cox model contained seven estimated regression coefficients, corresponding to approximately 8.3 events per parameter. Although bootstrap resampling showed that the estimated association was directionally consistent across most resamples, the optimism-corrected calibration slope of 0.825 suggested some degree of overfitting. Furthermore, the Deterioration phenotype included only 17 patients, limiting the reliability of exploratory comparisons involving this subgroup.

Third, PNI is a nonspecific composite measure that may be influenced by inflammation, infection, fluid balance, comorbidities, and other perioperative factors. The available data did not comprehensively

capture dietary intake, body composition, skeletal muscle mass, functional status, or postoperative complications. In particular, detailed and consistently recorded patient-level postoperative complication data were unavailable, preventing systematic adjustment for this potentially relevant factor. Furthermore, although postoperative PNI was measured within a prespecified 3–8-week window, differences in actual measurement timing may have influenced the observed values.

Fourth, neither delayed-entry Cox modeling nor the 2-month landmark analysis can eliminate all sources of selection bias or residual confounding. The exploratory chemotherapy analysis was limited by incomplete treatment-timing and intensity data. In addition, treating subsequent chemotherapy receipt as a fixed binary variable may introduce treatment-selection and time-related biases, including potential immortal time bias.

Fifth, ΔPNI is mathematically dependent on its preoperative and postoperative components and may be influenced by measurement variability and regression to the mean. Although the association persisted after adjustment for preoperative PNI, this adjustment cannot fully resolve mathematical coupling or establish a causal effect of PNI change.

Finally, the exploratory six-model comparison did not establish incremental prognostic discrimination beyond postoperative PNI. Although discrimination and model fit were examined, external validation and comprehensive assessments of absolute-risk calibration, reclassification, and clinical decision-making utility were not performed. The continuous ΔPNI analysis suggested an inverse association in the fitted linear Cox model, whereas the restricted cubic spline analysis did not demonstrate a statistically significant overall or nonlinear association. Therefore, no definitive conclusion can be drawn regarding the shape of the dose–response relationship.

Larger multicenter studies with standardized postoperative PNI assessment, more comprehensive clinical and treatment data, and independent external validation are needed to clarify the prognostic and clinical utility of postoperative PNI change.

5. Conclusions

In patients undergoing curative resection for colorectal cancer, postoperative PNI decline relative to the individual's preoperative level was associated with poorer long-term overall survival. The direction of this observational association was broadly consistent across complementary sensitivity analyses.

However, the association attenuated after inclusion of the recorded adjuvant chemotherapy variable, and bootstrap validation indicated some model overfitting. Exploratory model comparisons did not demonstrate incremental discrimination when binary PNI-change status was added to postoperative PNI.

These findings support further investigation of PNI change as a laboratory-based prognostic marker but do not establish superiority over absolute postoperative PNI or independent clinical predictive utility.

Larger multicenter studies with external validation and more comprehensive clinical and treatment data are warranted.

Abbreviations

AJCC
American Joint Committee on Cancer
CI
confidence interval
CRC
colorectal cancer
HR
hazard ratio
IQR
interquartile range
OS
overall survival
PNI
prognostic nutritional index
RCS
restricted cubic spline
RFS
recurrence-free survival
SMD
standardized mean difference
TNM
tumor–node–metastasis
ΔPNI
postoperative PNI minus preoperative PNI.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the First Affiliated Hospital of Hebei North University (approval No. K2025409). The requirement for written informed consent was waived by the **same** ethics committee.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are not publicly available because of patient privacy considerations but may be made available from the corresponding author on reasonable request, subject to institutional approval and applicable regulations.

Competing interests

The authors declare that they have no competing interests.

Funding

This study received no dedicated funding.

Authors' contributions

GL contributed to study conception, methodology, investigation, data curation, analysis, and original drafting; YZ and NZ contributed to data curation and investigation; JF contributed to study conception, supervision, project administration, and critical revision of the manuscript. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

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Figures

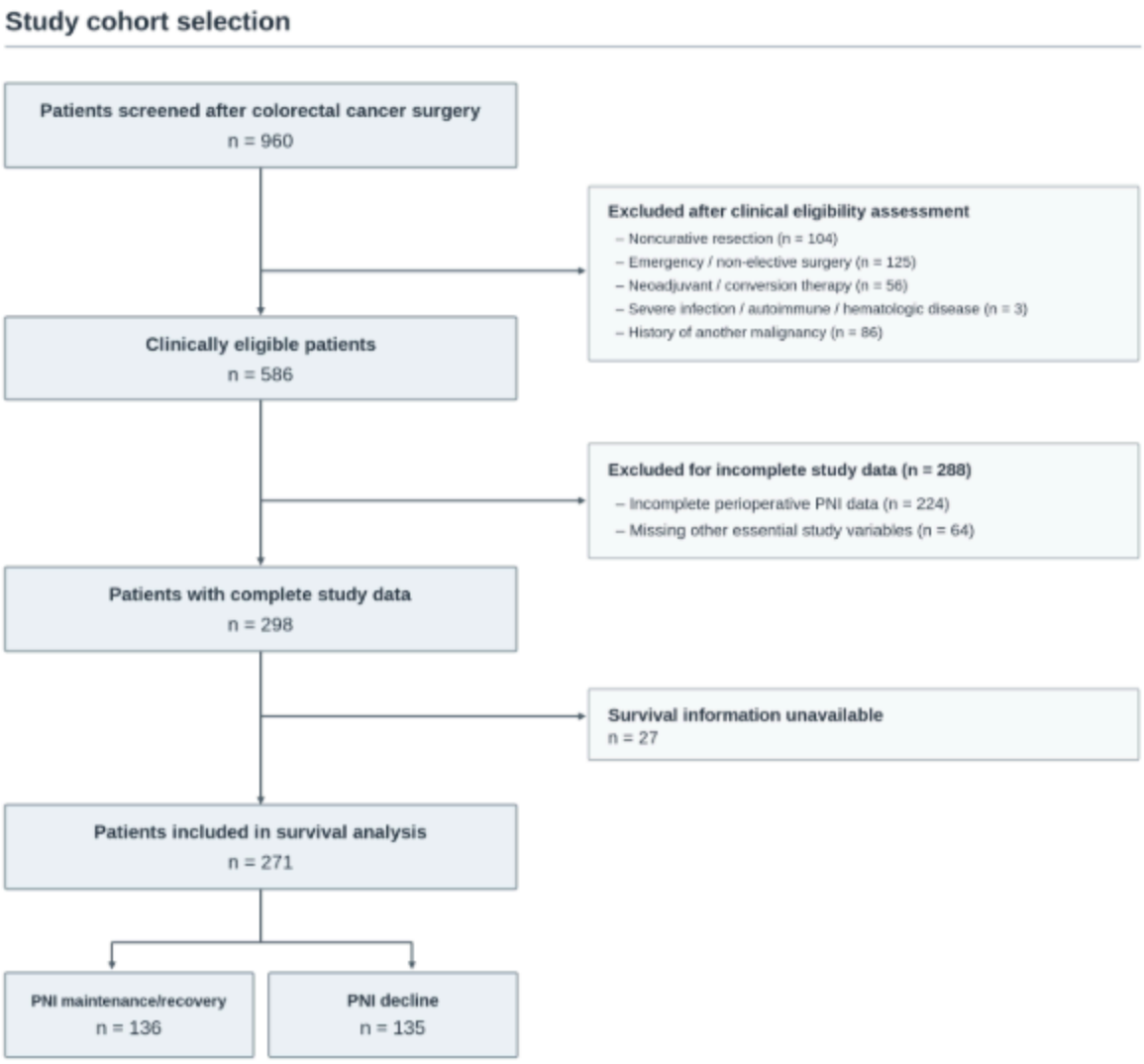

Figure 1

Flow diagram of patient selection.

Among 960 screened patients, 374 were excluded at clinical eligibility assessment; 224 had incomplete PNI data, 64 lacked other essential variables, and survival information was unavailable for 27. The final survival cohort included 271 patients (PNI maintenance/recovery, n = 136; decline, n = 135).

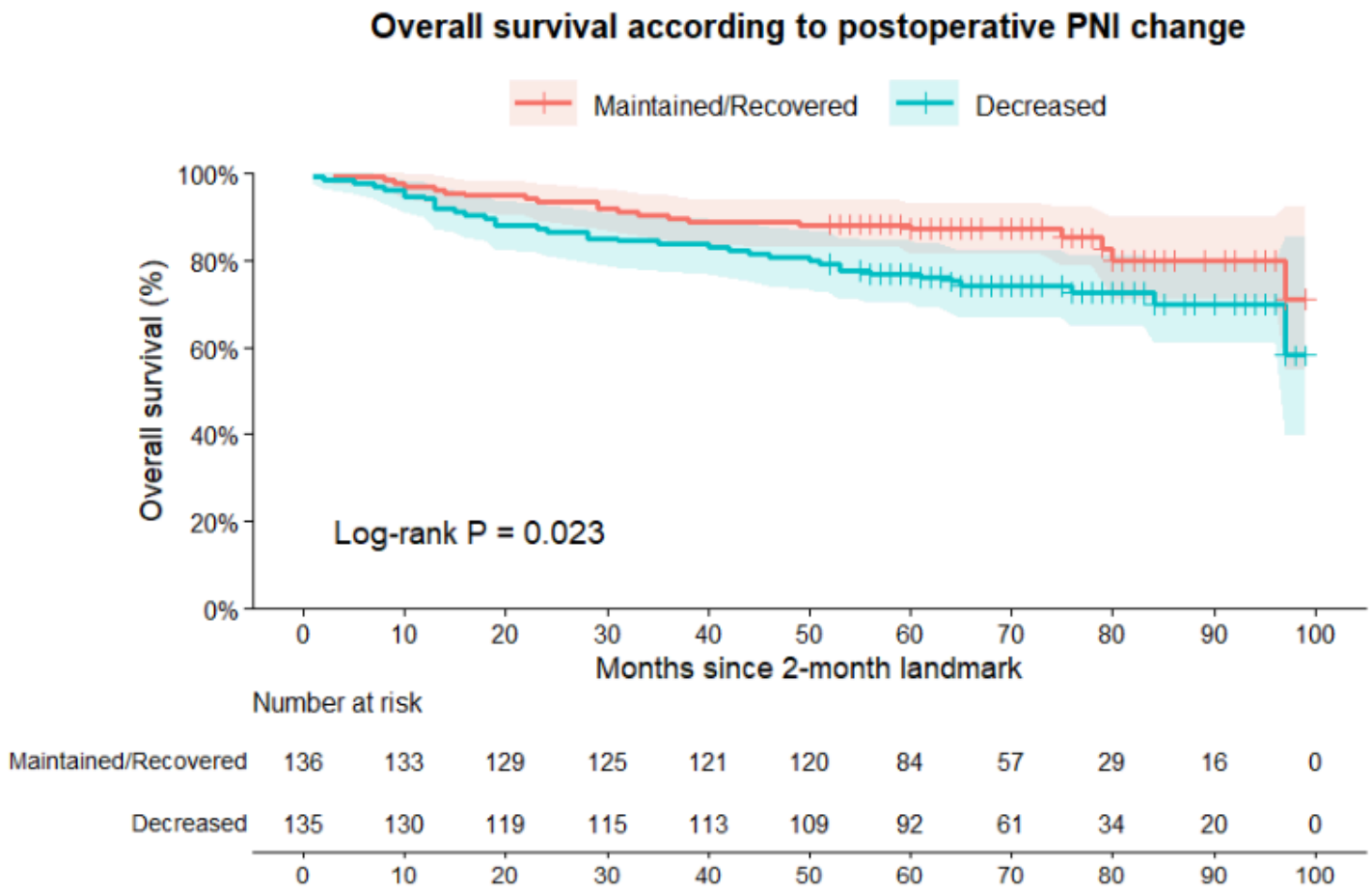

Figure 2

Overall survival according to postoperative PNI-change group in the two-month landmark analysis.

Kaplan–Meier analysis after the two-month landmark for patients with ΔPNI ≥ 0 or ΔPNI < 0; 271 patients; log-rank P = 0.0226.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- WJSOAdditionalFile1TablesS1S4.docx
- WJSOAdditionalFile2FiguresS1S2.docx