The Prognostic Value of Lymph Node Ratio in Stage III Colorectal Cancer

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Abstract: *Background*: Stage III colorectal cancer (CRC) is prognostically heterogeneous. The lymph node ratio (LNR), defined as metastatic lymph nodes divided by examined lymph nodes, may provide risk information complementary to conventional nodal assessment. We evaluated the association of LNR with overall survival (OS) and disease-free survival (DFS), and explored its relationship with recorded pathological N (pN) category.

Methods: This retrospective cohort included 103 patients with stage III CRC treated by upfront resection with lymphadenectomy at Rizgary Teaching Hospital/Rizgary Oncology Center between September 2013 and January 2025. The primary LNR categorisation was <0.20 versus >=0.20. Time-to-event analyses included 101 patients with usable follow-up. OS was time to all-cause death; DFS was redefined as time to first documented recurrence or death. Kaplan-Meier, log-rank, and parsimonious Cox models were used. Sensitivity analyses assessed LNR cut-offs of 0.10 and 0.25 and continuous LNR. An exploratory complete-case model included both LNR and recorded pN category.

Results: Baseline LNR was <0.20 in 50 patients and >=0.20 in 53. Among 101 patients with outcome follow-up, 27 deaths occurred. OS differed by LNR group (log-rank p=0.006); 3-year Kaplan-Meier OS was 90.3% versus 59.8% and 5-year OS was 80.1% versus 48.4% for low versus high LNR. In a parsimonious model adjusted for adjuvant treatment, high LNR was associated with mortality (HR 3.24, 95% CI 1.37-7.70; p=0.008). Composite DFS also differed (log-rank p=0.007; adjusted HR 2.54, 95% CI 1.24-5.19; p=0.011). Results were similar at the 0.25 cut-off but weaker at 0.10. In 70 patients with recorded pN1/pN2 category, the LNR estimate was imprecise after inclusion of pN (HR 1.39, 95% CI 0.31-6.20; p=0.667).

Conclusions: Higher LNR was associated with poorer OS and DFS in this cohort. However, the small event count, incomplete pN data, and attenuation in the exploratory pN-adjusted analysis do not establish that LNR provides independent incremental prognostic value beyond conventional N staging. Larger prospective, multicentre studies are required.

Keywords: Colorectal cancer, lymph node ratio, stage III, overall survival, disease-free survival, prognosis.

BACKGROUND

Colorectal cancer (CRC) remains a major cause of cancer morbidity and mortality worldwide. Stage III disease is heterogeneous, and nodal assessment is central to pathological staging, prognosis, and decisions about adjuvant therapy. Conventional pN classification is based primarily on the number of involved regional lymph nodes, whereas the total number examined varies with surgical technique and pathological processing. Inadequate nodal harvest may therefore affect staging precision and risk stratification [1-7].

The lymph node ratio (LNR), calculated as the number of metastatic lymph nodes divided by the total number examined, incorporates both nodal tumour burden and nodal yield. Multiple retrospective cohorts and meta-analyses have associated higher LNR with poorer survival in node-positive CRC, and some studies have suggested that LNR-based models may refine prognostic stratification [7-15]. However, cut-offs vary, and LNR is mathematically related to the same nodal burden that determines pN category. Direct within-cohort comparison with pN is therefore important before incremental value is claimed.

Data from Iraq and the Kurdistan Region remain limited in the international CRC outcomes literature. This study therefore evaluated the association between LNR and OS and DFS in patients treated surgically for stage III CRC. The primary hypothesis was that LNR >=0.20 would be associated with worse outcomes than LNR <0.20. We additionally examined alternative LNR cut-offs and performed an exploratory direct comparison with recorded pN category.

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ISSN: 1929-2260 / E-ISSN: 1929-2279/26 © 2026 Neoplasia Research

METHODS

Study Design and Setting

This was a retrospective cohort study based on routinely maintained surgical, pathology, and oncology records from Rizgary Teaching Hospital and Rizgary Oncology Center, Erbil, Kurdistan Region, Iraq. The source dataset contained patients operated between September 2013 and January 2025. The date of definitive colorectal resection was the index date. Reporting was aligned with STROBE recommendations for cohort studies [18].

Participants and Study Size

Consecutive patients were included when the clinical record identified stage III colorectal adenocarcinoma treated with upfront surgical resection and lymphadenectomy and the pathology record contained both total and metastatic lymph-node counts required to calculate LNR. Patients receiving neoadjuvant treatment were excluded because preoperative therapy can alter tumour and nodal response and may affect lymph-node yield; the analysis was intentionally restricted to an upfront-surgery cohort. This restriction is particularly important for interpreting the rectal-cancer subgroup and limits generalisability to patients managed with contemporary neoadjuvant strategies.

The source dataset contained 103 eligible records with calculable LNR. Two patients had no usable vital or recurrence status and were retained for baseline description but excluded from time-to-event analyses, leaving 101 patients for OS and composite DFS. One additional patient had a recorded recurrence without a recurrence date and was excluded only from the descriptive time-to-recurrence analysis. Because this was a retrospective census of available eligible records, no prospective sample-size calculation was performed. The study flow and analysis populations are shown in Figure **1**.

Data Sources and Variables

Data were abstracted from surgical records, oncology follow-up records, and final histopathology reports. Variables included age, sex, body weight, primary tumour site, histological differentiation, total and positive lymph-node counts, recorded pathological T and N categories when available, adjuvant treatment, recurrence status and site, vital status, and dates required for follow-up. LNR was recalculated directly from the supplied node counts for this revision.

Exposure Definition and LNR Cut-Off

LNR was defined as positive lymph nodes divided by total examined lymph nodes. The primary literature-based threshold was 0.20. Re-analysis of the raw data

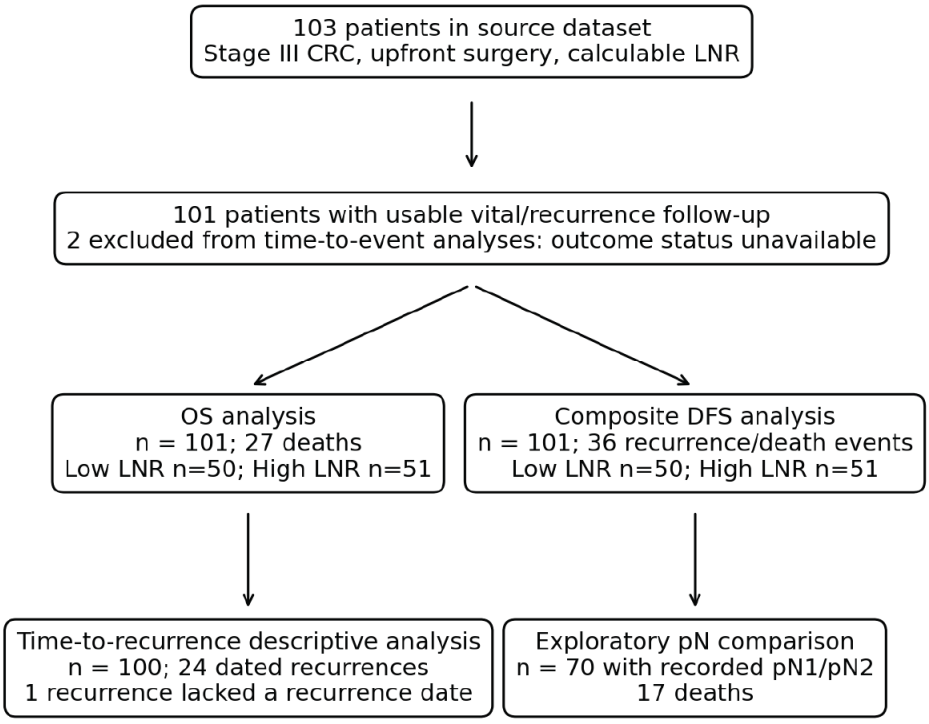


Figure 1: Study flow and analysis populations.

identified that the group counts reported in the original analysis corresponded to LNR <0.20 versus LNR >=0.20; the inequality labels have therefore been corrected throughout the revised manuscript. Three patients had an LNR exactly equal to 0.20 and are included in the high-LNR group. Sensitivity analyses used thresholds of 0.10 and 0.25, and LNR was also modelled continuously per 0.10 increase [8, 16, 17].

Outcome Definitions and Follow-Up

OS was defined as time from surgery to death from any cause. Patients recorded as lost to follow-up were censored on their recorded last-contact date. Patients recorded alive without a separate censoring date were administratively censored at dataset closure for the reproducible re-analysis. Two patients with no usable outcome status were not included in time-to-event analyses.

In response to peer review, DFS was redefined as a composite endpoint: time from surgery to the first documented recurrence or death from any cause, whichever occurred first. This definition avoids treating death before recurrence as ordinary censoring and is more consistent with established colon-cancer endpoint conventions [19]. Time to documented recurrence (TTR), with death before recurrence treated as a competing/censoring event, was retained only as a secondary descriptive analysis and was not used to support the principal prognostic conclusion.

Missing Data and Bias

No missing values were imputed. Baseline summaries used all 103 records. OS and DFS used 101 patients with usable outcome status. TTR used 100 patients because two had unknown recurrence status and one recorded recurrence lacked a recurrence date. Recorded pN category was incomplete: 42 patients were coded pN1, 28 pN2, 6 pN0, and 27 had no pN value. Because tumour-deposit/N1c information was unavailable, the direct pN comparison was conservatively restricted to the 70 patients with unambiguous recorded pN1 or pN2. Characteristics of the two patients excluded from time-to-event analysis are reported descriptively in Supplementary Table **S1**; no formal comparison was performed because n=2. Overall variable-level missingness relevant to these analyses is summarised in Supplementary Table **S3**.

Statistical Analysis

Continuous variables are summarised as median (interquartile range [IQR]) and categorical variables as n (%). Mann-Whitney U tests were used for continuous between-group comparisons. Pearson chi-square tests were used for categorical variables with adequate expected counts, and Fisher exact tests for sparse 2x2 tables. Time-to-event distributions were estimated by Kaplan-Meier methods and compared with two-sided log-rank tests. Numbers at risk are displayed with the survival curves and in Table **3**.

Because only 27 deaths occurred, Cox modelling was deliberately parsimonious. The main OS model included LNR group and receipt of adjuvant treatment, the treatment-related covariate specifically highlighted during peer review. A corresponding DFS model used the same covariates. Hazard ratios (HRs) and 95% confidence intervals (CIs) are reported. Proportional-hazards assumptions for the main OS model were assessed using Schoenfeld residuals against log event time. Additional sensitivity analyses modelled continuous LNR, used LNR cut-offs of 0.10 and 0.25, and fitted an expanded clinicopathological model to demonstrate the sensitivity of the LNR estimate to further adjustment.

To address the requested direct comparison with conventional nodal staging, an exploratory complete-case Cox model included both LNR group and recorded pN2 versus pN1 among 70 patients with unambiguous pN1/pN2 records (17 deaths). The likelihood of a pN-only model was compared with a pN+LNR model using a 1-degree-of-freedom likelihood-ratio test. Given the small event count and missing pN values, this comparison is explicitly exploratory rather than confirmatory. Two-sided $p<0.05$ was considered statistically significant; no multiplicity adjustment was applied to secondary analyses.

Ethical Approval

The research protocol was approved by the Medical Research Scientific & Ethics Committee, Kurdistan Higher Council of Medical Specialties, Kurdistan Regional Government-Iraq (Meeting Code 1630; 18 May 2025). The study used retrospective clinical records, and data used for analysis were de-identified.

RESULTS

Study Population and Baseline Characteristics

The source cohort comprised 103 patients: 50 (48.5%) with LNR <0.20 and 53 (51.5%) with LNR >=0.20. Median age was 53 years (IQR 44-67). As expected, high-LNR patients had substantially more

Table 1: Baseline Characteristics by Primary LNR Group

Characteristic	Overall (n=103)	Low LNR <0.20 (n=50)	High LNR >=0.20 (n=53)	p-value
Age, years	53 (44-67)	51 (45.25-65)	54 (41-70)	0.561
Weight, kg	70 (65-78.50)	71 (65-78)	68 (65-79)	0.646
Total lymph nodes examined	15 (12-24)	17 (13-25.75)	14 (10-22)	0.043
Positive lymph nodes	2 (1-6)	1 (1-2)	6 (4-11)	<0.001
LNR	0.20 (0.08-0.45)	0.08 (0.04-0.11)	0.43 (0.27-0.78)	<0.001
Male sex	55 (53.4%)	26 (52.0%)	29 (54.7%)	0.782
Rectal primary	19 (18.4%)	10 (20.0%)	9 (17.0%)	0.693
Adjuvant treatment	84 (81.6%)	42 (84.0%)	42 (79.2%)	0.534
Well differentiated	72 (69.9%)	41 (82.0%)	31 (58.5%)	0.017
Poorly differentiated	30 (29.1%)	9 (18.0%)	21 (39.6%)	
Other histology (NET)	1 (1.0%)	0 (0.0%)	1 (1.9%)	

Continuous data are median (IQR); categorical data are n (%). The histological differentiation p-value compares well versus poorly differentiated tumours by Fisher exact test; the single NET was not included in that binary test.

positive nodes and higher LNR. Total lymph-node yield was modestly lower in the high-LNR group (median 14 vs 17; p=0.043). Adjuvant treatment was recorded in 84/103 (81.6%) patients. Baseline characteristics by LNR group are presented in Table **1**.

Outcome Completeness and Follow-Up

Usable vital and recurrence follow-up was available for 101/103 patients (98.1%). The two excluded patients were both women in the high-LNR group; both had received adjuvant treatment. Among analysed patients, reverse Kaplan-Meier median follow-up was 3.61 years. Twenty-seven deaths and 36 composite DFS events (recurrence or death) occurred. Event counts for the time-to-event analysis cohort are summarised in Table **2**.

Overall Survival

During follow-up, 27/101 patients died: 7/50 (14.0%) in the low-LNR group and 20/51 (39.2%) in the high-LNR group. Kaplan-Meier OS differed between groups (log-rank chi-square 7.65; p=0.006). Median OS was not reached in the low-LNR group and was 4.60 years in the high-LNR group. At 3 years, estimated OS was 90.3% versus 59.8%; at 5 years it was 80.1% versus 48.4%. Numbers at risk are shown in Figure **2** and Table **3**.

Disease-Free Survival

Using the revised composite definition of DFS (first recurrence or death), 36 events occurred: 11/50 (22.0%) in the low-LNR group and 25/51 (49.0%) in the high-LNR group. DFS differed between LNR groups (log-rank chi-square 7.17; p=0.007). Median DFS was 9.49 years in the low-LNR group and 3.39 years in the high-LNR group. The 3-year DFS estimates were 78.9% and 50.9%, respectively. The corresponding Kaplan-Meier curve is shown in Figure **3**, and time-specific DFS estimates are reported in Table **3**.

Cox Regression and Proportional-Hazards Assessment

In the parsimonious OS model, high LNR was associated with higher all-cause mortality after adjustment for adjuvant treatment (HR 3.24, 95% CI 1.37-7.70; p=0.008). The estimate remained wide

Table 2: Outcome Summary in the Time-to-Event Analysis Cohort (n=101)

Outcome	Low LNR <0.20 (n=50)	High LNR >=0.20 (n=51)	Total
Deaths	7 (14.0%)	20 (39.2%)	27 (26.7%)
Composite DFS events	11 (22.0%)	25 (49.0%)	36 (35.6%)
No death recorded by censoring	43 (86.0%)	31 (60.8%)	74 (73.3%)
No DFS event recorded by censoring	39 (78.0%)	26 (51.0%)	65 (64.4%)

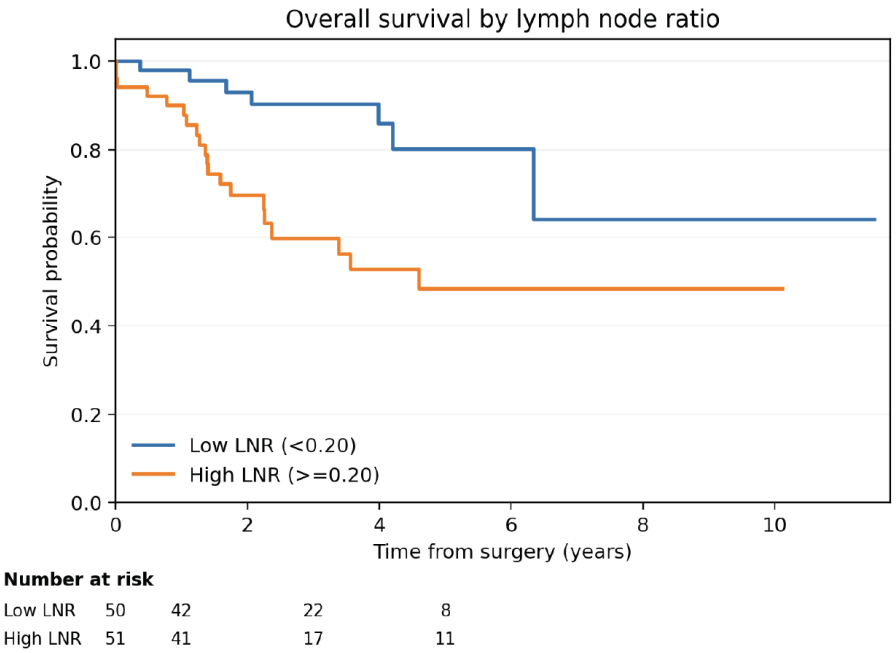


Figure 2: Kaplan-Meier overall survival by LNR group, with numbers at risk.

Table 3: Kaplan-Meier Survival Estimates and Numbers at Risk

Endpoint	Time	Low LNR <0.20	High LNR >=0.20
OS	1 year	97.9% (85.8-99.7); n risk=42	90.0% (77.6-95.7); n risk=41
OS	3 year	90.3% (76.1-96.3); n risk=22	59.8% (42.8-73.2); n risk=17
OS	5 year	80.1% (58.4-91.2); n risk=8	48.4% (30.6-64.0); n risk=11
DFS	1 year	90.9% (77.6-96.5); n risk=39	77.4% (62.9-86.8); n risk=35
DFS	3 year	78.9% (61.4-89.1); n risk=19	50.9% (35.1-64.7); n risk=16
DFS	5 year	74.3% (54.9-86.3); n risk=6	41.4% (25.8-56.3); n risk=11

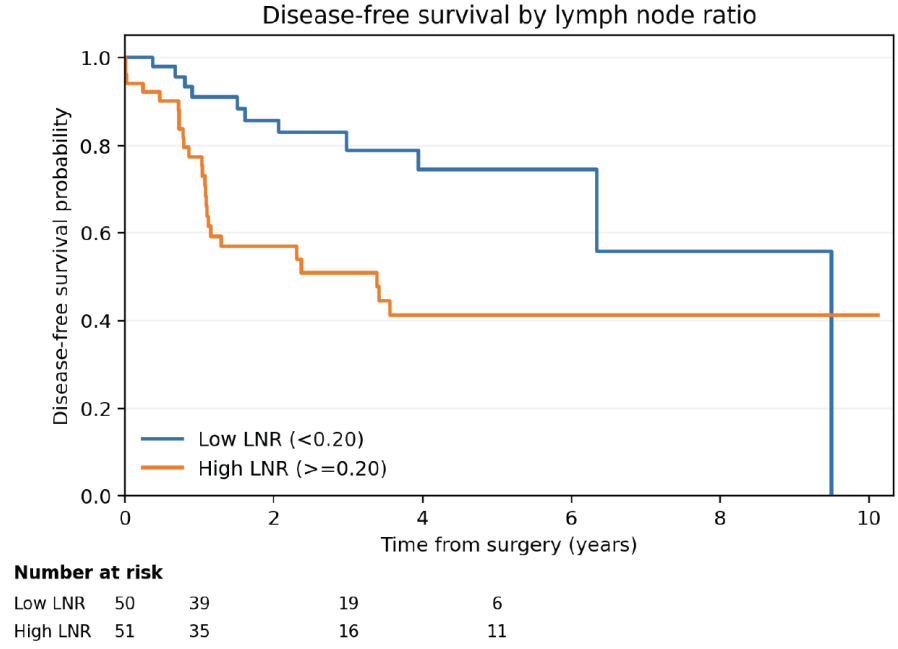


Figure 3: Kaplan-Meier disease-free survival (recurrence or death) by LNR group, with numbers at risk.

Table 4: Parsimonious Cox Models for OS and Composite DFS

Endpoint	Variable	HR	95% CI	p-value
OS	High LNR (>=0.20)	3.24	1.37-7.70	0.008
OS	Adjuvant treatment	0.33	0.14-0.80	0.014
DFS	High LNR (>=0.20)	2.54	1.24-5.19	0.011
DFS	Adjuvant treatment	0.59	0.26-1.37	0.220

Because of the limited number of events, these estimates are association estimates and should not be interpreted as definitive proof of independent prognostic effect.

because only 27 deaths occurred. Schoenfeld residual tests did not identify evidence of non-proportional hazards for the LNR term (p=0.369) or adjuvant treatment (p=0.676); the combined residual test was also non-significant (p=0.596). For composite DFS, high LNR was associated with a higher event rate in the corresponding parsimonious model (HR 2.54, 95% CI 1.24-5.19; p=0.011). The parsimonious OS and DFS Cox models are presented in Table **4**.

Direct Exploratory Comparison with pN Stage

Recorded pN category was suitable for an unambiguous pN1-versus-pN2 comparison in 70 patients, among whom 17 deaths occurred. In a model containing both variables, high LNR had HR 1.39 (95% CI 0.31-6.20; p=0.667) and pN2 versus pN1 had HR 2.87 (95% CI 0.76-10.85; p=0.121). Adding LNR to the pN-only model did not improve fit by likelihood-ratio testing (chi-square 0.18; p=0.667). These estimates are highly imprecise and do not demonstrate incremental prognostic value of LNR beyond pN stage. Results of the combined LNR and recorded pN model are presented in Table **5**.

LNR Sensitivity Analyses

When LNR was modelled continuously, each 0.10 increase was associated with HR 1.21 (95% CI 1.08-1.36; p=0.001) after adjustment for adjuvant treatment. The 0.25 cut-off produced an association in the same direction, whereas the 0.10 cut-off was weaker and its 95% CI included 1.0. Thus, the overall direction was consistent, but statistical strength varied with the selected threshold. Results across the categorical LNR cut-offs are summarised in Table **6**.

An expanded sensitivity model including age, sex, adjuvant treatment, and poor differentiation attenuated the LNR estimate (Table **S2**), highlighting residual confounding and model instability in a dataset with only 27 deaths. This result is the reason the revised manuscript no longer describes LNR as definitively independent.

Recurrence Pattern

Twenty-five patients had a recorded recurrence. Recurrence site is presented descriptively because several cells contain very small counts. One recurrence

Table 5: Exploratory Direct Comparison of LNR and Recorded pN Category (n=70; 17 Deaths)

Variable	HR	95% CI	p-value
High LNR (>=0.20)	1.39	0.31-6.20	0.667
pN2 vs pN1	2.87	0.76-10.85	0.121

Model AIC values in the same 70-patient subset were 122.77 for pN alone, 125.39 for LNR alone, and 124.59 for the combined model. Given the event count, these values are descriptive model-fit indicators rather than a basis for model selection.

Table 6: Sensitivity of the OS Association to Alternative LNR Cut-Offs

Cut-off	Low/high n	Deaths low/high	Adjusted HR*	95% CI	Cox p	Log-rank p
0.10	31 / 70	5 / 22	2.40	0.90-6.38	0.078	0.069
0.20	50 / 51	7 / 20	3.24	1.37-7.70	0.008	0.006
0.25	57 / 44	10 / 17	2.69	1.22-5.92	0.014	0.015

*Adjusted for receipt of adjuvant treatment.

had no site recorded, and one recurrence lacked a date. No site-specific hypothesis test is presented. Recurrence sites by LNR group are summarised in Table **7**.

Table 7: Recurrence Sites by LNR Group (Descriptive Only)

Recurrence site	Low LNR	High LNR	Total
Multiple sites	4	7	11
Pelvic	1	3	4
Liver	1	2	3
Lung/bone	0	3	3
Local	2	1	3
Site not recorded	0	1	1

DISCUSSION

In this retrospective cohort, LNR >=0.20 was associated with poorer OS and composite DFS in the primary Kaplan-Meier analyses. The association persisted in a deliberately parsimonious Cox model adjusted for adjuvant treatment, and a continuous-LNR analysis showed a similar direction. These findings are consistent with prior reports linking greater LNR to adverse outcomes in CRC [7-15]. However, the revised analyses also show why the interpretation must remain cautious.

First, only 27 deaths occurred. The main Cox estimate therefore has a wide confidence interval, and more extensively adjusted models are unstable. When additional clinicopathological covariates were entered in sensitivity analysis, the LNR estimate attenuated. Accordingly, we have removed language describing LNR as definitively or independently prognostic and now describe the result as an adjusted association within this cohort.

Second, the requested direct comparison with conventional pN staging was informative. Among the 70 patients with unambiguous recorded pN1/pN2 category, adding LNR to a model already containing pN did not improve model fit, and the LNR coefficient became small and highly imprecise. This does not establish that LNR adds prognostic information beyond pN stage in this dataset. The analysis is limited by missing pN data and only 17 deaths in the comparison subset, so it also cannot exclude a clinically relevant incremental effect. Larger datasets with complete TNM variables are required.

Third, the revised DFS definition materially improves outcome interpretation. The original analysis treated DFS as time to documented recurrence and did not incorporate death before recurrence. In the revision, DFS is the composite of recurrence or death, avoiding ordinary censoring of deaths and aligning more closely with commonly used colon-cancer trial endpoint conventions [19]. The recurrence-only analysis has been demoted to a descriptive secondary analysis.

The 0.20 cut-off was selected a priori from prior literature rather than optimised on this dataset. Sensitivity analysis showed a similar adverse direction at 0.25 and for continuous LNR, but the 0.10 threshold was weaker. This indicates that the association is not confined to a single threshold, while also underscoring that the numerical strength of evidence is cut-off dependent. A universally accepted LNR threshold has not been established, which remains a barrier to routine staging use.

Histological differentiation was unevenly distributed across LNR groups, with poorly differentiated tumours more common in the high-LNR group. This should not be interpreted as evidence that LNR itself captures tumour biology, because grade and nodal burden are related clinicopathological features and residual confounding is plausible. The expanded model, in which the LNR estimate attenuated after additional adjustment, reinforces this caution.

The restriction to patients managed with upfront surgery was intended to reduce heterogeneity in nodal yield arising from preoperative treatment. However, it limits applicability, particularly for rectal cancer, for which contemporary management frequently includes neoadjuvant approaches. The current results should therefore not be extrapolated to neoadjuvant-treated rectal cancer without validation.

The study contributes outcome data from the Kurdistan Region of Iraq, a setting underrepresented in international CRC prognostic literature. LNR is simple to calculate from routine pathology data, but the present results support its use only as a candidate adjunctive risk marker. They do not justify replacing pN staging, changing chemotherapy regimen or duration, or intensifying surveillance beyond established guidelines solely on the basis of LNR.

LIMITATIONS

The retrospective single-institution design is vulnerable to selection bias, incomplete documentation, and residual confounding. Only 27 deaths occurred,

limiting the complexity and precision of multivariable models. Two patients lacked usable outcome status, one recorded recurrence lacked a recurrence date, and recorded pN category was incomplete, restricting direct comparison with conventional nodal staging to 70 patients with only 17 deaths. The long inclusion period may encompass changes in surgical technique, pathology practice, systemic treatment, and follow-up. The analysis also lacks routinely complete molecular prognostic data such as mismatch-repair/microsatellite-instability status and KRAS, NRAS, and BRAF alterations. Restriction to upfront surgery limits generalisability to neoadjuvant-treated disease, especially rectal cancer. Finally, sensitivity analyses showed that the statistical strength of the LNR association varied across thresholds. These limitations mean that the findings should be regarded as hypothesis-generating rather than proof of incremental prognostic performance beyond TNM staging.

CONCLUSION

In this cohort, LNR >=0.20 was associated with poorer OS and composite DFS, and similar adverse associations were observed when LNR was analysed continuously and at a 0.25 threshold. Nevertheless, the small number of events, incomplete pathological staging data, and lack of demonstrable incremental model fit when LNR was added to pN staging preclude a claim that LNR is independently superior to or adds proven prognostic value beyond conventional N staging. LNR remains a readily available candidate adjunctive marker that warrants prospective multicentre validation in models containing complete TNM, treatment, pathological, and molecular covariates.

DATA AVAILABILITY

The de-identified dataset used for the analyses is available from the corresponding author on reasonable request, subject to institutional and ethical requirements.

FUNDING

The authors received no specific funding for this work.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

MNK conceived the study, collected the data, contributed to the statistical analysis, interpreted the results, and drafted the manuscript. SHM contributed to study design, supervision, and critical review. SSO contributed to supervision, interpretation, methodological guidance, and critical revision. All authors read and approved the final manuscript.

ACKNOWLEDGEMENTS

The authors thank the staff of Rizgary Teaching Hospital and Rizgary Oncology Center, Erbil, Iraq, for facilitating access to the records required for this study.

SUPPLEMENTARY TABLES

The supplementary tables can be downloaded from the journal website along with the article.

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Received on 15-09-2026 Accepted on 17-10-2026 Published on 06-11-2026

https://doi.org/10.30683/1929-2279.2026.15.34

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