Original Article

Screening and validation of a novel T stage-lymph node ratio classification for operable colon cancer

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Background: Lymph node ratio (LNR) has advantages in predicting prognosis compared with American Joint Committee on Cancer (AJCC) pathological N stage. However, the prognostic value of a novel T stage-lymph node ratio (TLNR) classification for colon cancer combining LNR and pathological primary tumor stage (T stage) is currently unknown.

Methods: We included 62,294 patients with stage I–III colon cancer from the Surveillance, Epidemiology, and End Results Program as a training cohort. External validation was performed in 3,327 additional patients. A novel LNR stage was established and combined with T stage in a novel TLNR classification. Patients with similar survival were grouped according to T and LNR stages, with T1LNR1 as a reference.

Results: We developed a novel TLNR classification as follows: stages I (T1LNR1-2, T1LNR4), IIA (T1LNR3, T2LNR1-2, T3LNR1), IIB (T1LNR5, T2LNR3-4, T3LNR2, T4aLNR1), IIC (T2LNR5, T3LNR3-4, T4aLNR2, T4bLNR1), IIIA (T3LNR5, T4aLNR3-4, T4bLNR2), IIIB (T4aLNR5, T4bLNR3-4), and IIIC (T4bLNR5). In the training cohort, the novel TLNR classification had better prognostic discrimination (area under receiver operating characteristic curve, 0.621 *vs.* 0.608, two-sided P<0.001), superior model-fitting ability for predicting overall survival (Akaike information criteria, 561,129 *vs.* 562,052), and better net benefits compared with the AJCC 8th tumor/node/metastasis classification. Similar results were found in the validation cohort for predicting both overall and disease-free survival.

Conclusions: This novel TLNR classification may provide better prognostic discrimination, model-fitting ability, and net benefits than the AJCC 8th TNM classification, for potentially better stratification of patients with operable stage I–III colon cancer; however, further studies are required to validate the novel TLNR classification.

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Keywords: Colon cancer; lymph node ratio (LNR); tumor/node/metastasis (TNM); survival outcome

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Introduction

Colon cancer is one of the most frequently diagnosed cancers and leading causes of cancer-related mortality worldwide (1). The American Joint Committee on Cancer (AJCC) tumor/node/metastasis (TNM) classification of colon cancer has been the most import prognostic assessment tool for colon cancer to date (2). However, the current AJCC 8th TNM classification of colon cancer has limited ability to predict survival, with some stage III patients having a better prognosis than stage II patients (2-4). Regarding the possible reasons for this paradox, previous studies suggested that pT stage had a much lower weight than pN stage in the TNM staging system (5,6). However, pT stage has demonstrated comparable importance to pN stage, given that T4N0 colon cancer patients had significantly poorer survival than T1-2N1-2a patients, regardless of the number of retrieved lymph nodes (7,8).

Patient survival is also affected by the total number of retrieved lymph nodes. This may be because of the therapeutic benefits of optimal lymphadenectomy, or because of the more accurate staging allowed by harvesting more lymph nodes, though the reason remains controversial. It is recommended that at least 12 lymph nodes should be retrieved to ensure optimal staging and reduce staging migration (2); however, the average number of retrieved lymph nodes is often <12 (9,10). This may be because many factors can affect the total number of retrieved lymph nodes, including surgical skills and technique, the way in which the pathologist collects the lymph nodes, the actual number of regional lymph nodes surrounding the tumor, and the patient's immune response (11). Lymph node ratio (LNR) was therefore proposed as a measure to reduce stage migration (12-14). LNR is defined as the ratio between the number of metastatic lymph nodes and the total number of retrieved lymph nodes, and has been reported to have a higher predictive accuracy rate than pN stage, especially when an insufficient number of lymph nodes was retrieved (15).

The prognostic advantages of LNR in colorectal cancer have been widely confirmed (12-14), especially for patients with an inadequate number of retrieved lymph nodes (16). However, the prognostic value of establishing a novel TLNR classification for colon cancer by combining LNR and pT stage is currently unknown. We therefore aimed to establish a novel TLNR classification with improved prognostic value based on the updated 1973–2015 Surveillance, Epidemiology, and End Results Program (SEER) of colon cancer (17). We compared its discriminatory performance, model-fitting ability, and net benefits with those of the AJCC 8th TNM classifications in a training cohort (SEER), and further validated its prognostic capacity in an external validation cohort. We present the following article in accordance with the TRIPOD reporting checklist (available at https://dx.doi.org/10.21037/atm-21-3170).

Methods

Patients and eligibility criteria

Patients with operable stage I–III colon cancer from the SEER database were included as a training cohort (18) to develop a novel TLNR classification. The eligibility criteria were: (I) primary and single colon cancer; (II) necessary information available; (III) no distant metastasis (M0); (IV) met criteria for pathologic staging; (V) underwent surgical treatment; (VI) follow-up at least 5 years or until death; (VII) postoperative survival time >1 month; and (VIII) age ≥18 years (Figure S1). The last date of follow-up for the SEER cohort was December 2015. The data-use agreement of the SEER 1973–2015 research data file was approved.

Patient information from the China Medical University Cancer Hospital database was used for external validation of the predictive performance of the novel TLNR classification. The eligibility criteria for the external validation cohort were the same as that for the training cohort. The last date of follow-up for the external validation cohort was January 2020. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The ethical review was approved by the Institute

Ethics Committees of China Medical University Cancer Hospital (20210206K). Written informed consent was obtained from all patients.

Colon cancer with distant metastasis (M1) has been widely considered as the most advanced stage with the poorest prognosis and is generally considered incurable. We therefore only included colon cancer patients who underwent curative surgical treatments in this study. In the current study, T1-4b and N0-2b were applied to simply present pT1-4b and pN0-2b in both the TNM and novel TLNR classifications.

Statistical analysis

Overall survival (OS) was calculated from the date of surgery until death from any cause, and disease-free survival (DFS) was calculated from the date of surgery to the identification of cancer recurrence and/or metastasis or until death (if no recurrence or metastasis occurred before death). Log-rank tests with Kaplan-Meier survival curves were conducted to analyze differences in OS and DFS rates. Cox proportional hazards models were applied to estimate hazard ratios (HRs) with 95% confidence intervals (CIs).

Establishment of a novel LNR stage

We first classified all patients in the training cohort into 21 groups (LNR from 0 to 1) in units of 0.05. We estimated HRs for all 21 groups using a Cox proportional hazards model, with LNR =0 as a reference, and sorted the groups according to HR values, from lowest (LNR =0) to highest (LNR >0.95). We then compared OS between two sequential LNR stages using log-rank tests, and generated 21 χ^2 values. The four largest χ^2 values were identified as the cutoff values. Finally, using these four χ^2 cutoff values, we created five categories and developed a novel LNR stage that paralleled the AJCC 8th pN stage.

Establishment of a novel TLNR classification

In the training cohort, we further combined the novel LNR and pT stages into 25 groups, with the HR value of T1LNR1 as the reference. The HR values of the 25 T and LNR stage combinations were ordered from lowest (T1LNR1) to highest (T4bLNR5) (*Table 1*). OS was then compared between two sequential stages using log-rank tests and 24 χ^2 values were generated. The six largest values were identified as cutoff values (*Table 1*) and used to create seven categories of the novel TLNR classification that paralleled the AJCC 8th classification.

The model discrimination performances and model-fitting abilities of the novel LNR and previously reported LNR stages, and the novel TLNR and AJCC 8th TNM classifications, were compared by area under the receiver operating characteristic (ROC) curve (AUC) and Akaike information criteria (AICs), respectively. A higher AUC value suggested better discriminatory performance and a lower AIC value indicated superior model-fitting ability (19). Statistically significant differences in AUCs were confirmed using Hanley and McNeil tests (19). The clinical benefits were evaluated by decision curve analyses (DCAs) (20). The prognostic-discrimination performances of the novel LNR stage and novel TLNR classification based on 5-year OS and DFS rates, log-rank tests, and HRs of Cox proportional hazards models were also further assessed.

Data were extracted from the SEER using SEER*Stat version 8.3.5. Statistical analyses were conducted using SPSS version 22.0 and R version 3.5.3. Hanley and McNeil tests were conducted using MedCalc version 18.11.3. All tests were two-sided and P values <0.05 were defined as statistically significant.

Results

Patient characteristics

A total of 62,294 patients with operable stage I–III colon cancer in the SEER database were finally included as the training cohort (Figure S1). A further 3,327 patients with operable stage I–III colon cancer from China Medical University Cancer Hospital were included as the external validation cohort. The baseline characteristics of the training and validation cohorts are presented in Table S1. The mean ages (± standard deviation) were 68.1±13.8 and 59.9±11.6 years in the training and validation cohorts, respectively. The mean numbers of retrieved lymph nodes were 17.2±9.6 and 16.7±10.0 in the training and validation cohorts, respectively. A total of 26.8% patients in the training cohort and 31.6% patients in the validation cohort had <12 retrieved lymph nodes.

The baseline characteristics of the training and validation cohorts in relation to the number of retrieved lymph nodes are presented in Table S2. In the training cohort, there were significant baseline differences between patients with <12 and ≥12 retrieved lymph nodes in terms of age, sex, race, tumor size, histological grade, AJCC 8th pT stage, and

Table 1 The proposed TLNR classification in the training cohort

Stage	5-Y OS, % (95% CI)	HR (95% CI)[†]	Log-rank (Mantel-Cox)[‡]	
			χ^2 value	P value
Stage I	83.1 (82.1–84.1)	–	–	–
T1LNR1 (n=5,260)	83.4 (82.4–84.4)	1.00 (reference)	–	–
T1LNR4 (n=23)	73.9 (50.9–87.3)	1.00 (0.45–2.24)	0	0.999
T1LNR2 (n=511)	80.7 (77.0–83.9)	1.06 (0.89–1.26)	0.024	0.877
Stage IIA	75.0 (74.5–75.4)	–	–	–
T2LNR1 (n=8,941)	78.8 (77.9–79.6)	1.31 (1.23–1.40)	5.79[§]	0.016
T2LNR2 (n=1,465)	76.8 (74.5–78.9)	1.37 (1.24–1.52)	0.925	0.336
T1LNR3 (n=65)	72.3 (59.7–81.6)	1.50 (1.00–2.24)	0.192	0.662
T3LNR1 (n=22,931)	73.3 (72.8–73.9)	1.57 (1.49–1.66)	0.067	0.796
Stage IIB	63.2 (62.3–64.0)	–	–	–
T2LNR3 (n=221)	68.6 (62.0–74.3)	1.75 (1.42–2.16)	1.08[§]	0.298
T2LNR4 (n=56)	69.4 (55.5–79.8)	1.83 (1.24–2.70)	0.048	0.826
T3LNR2 (n=10,504)	63.6 (62.7–64.5)	2.10 (1.98–2.23)	0.434	0.510
T1LNR5 (n=20)	63.5 (38.3–80.7)	2.35 (1.30–4.25)	0.131	0.717
T4aLNR1 (n=1,945)	60.1 (57.8–62.2)	2.40 (2.21–2.61)	0.003	0.959
Stage IIC	49.7 (48.5–50.9)	–	–	–
T4bLNR1 (n=1,499)	55.1 (52.5–57.6)	2.72 (2.49–2.96)	6.36[§]	0.012
T3LNR3 (n=2,845)	50.9 (49.0–52.7)	2.99 (2.79–3.21)	5.11	0.024
T4aLNR2 (n=1,422)	47.4 (44.7–49.9)	3.25 (2.98–3.53)	3.05	0.081
T2LNR5 (n=46)	43.5 (29.0–57.1)	3.49 (2.43–5.00)	0.168	0.682
T3LNR4 (n=1,082)	42.5 (39.6–45.5)	3.73 (3.40–4.08)	0.131	0.718
Stage IIIA	33.6 (31.7–35.4)	–	–	–
T4aLNR3 (n=490)	38.6 (34.2–42.9)	4.23 (3.76–4.76)	2.92[§]	0.088
T4bLNR2 (n=823)	35.3 (32.0–38.6)	4.68 (4.25–5.15)	1.85	0.174
T4aLNR4 (n=207)	31.8 (25.6–38.2)	4.99 (4.23–5.09)	0.808	0.369
T3LNR5 (n=997)	30.0 (27.2–32.9)	5.43 (4.97–5.93)	1.06	0.304
Stage IIIB	22.2 (19.3–25.3)	–	–	–
T4bLNR3 (n=318)	24.4 (19.8–29.3)	6.52 (5.71–7.44)	4.05[§]	0.044
T4bLNR4 (n=148)	22.3 (16.0–29.3)	6.76 (5.63–8.11)	0.098	0.754
T4aLNR5 (n=288)	19.8 (15.4–24.6)	7.70 (6.72–8.81)	1.59	0.207
Stage IIIC	13.4 (8.9–18.8)	–	–	–
T4bLNR5 (n=187)	13.4 (8.9–18.8)	9.76 (8.28–11.50)	4.45[§]	0.035

[†], log-rank tests were conducted between two sequential stages and twenty-one χ^2 values were generated. All stages were compared with T1LNR1 as reference by values of HRs of Cox proportional hazards. [‡], log-rank tests were conducted between two sequential stages. [§], HRs with 95% CIs were estimated using a Cox proportional hazards model, with T1LNR1 =0 as the reference in the training cohort. Twenty-five HR values were ordered from the lowest (T1LNR1) to the highest (T4bLNR5). Then, log-rank tests for 5-year overall survival were conducted between two sequential stages and 24 χ^2 values were generated. Among the 24 χ^2 values, six largest χ^2 values were identified as the optimal cutoff values (5.79, 1.08, 6.36, 2.92, 4.05, 4.45), and we created seven categories of the TLNR classification that paralleled to those of the AJCC 7th and 8th TNM classifications. TLNR, T stage-lymph node ratio classification; 5-Y OS, 5-year overall survival; CI, confidence interval; HR, hazard ratio; LNR, lymph node ratio; No., number.

AJCC 8th pN stage, whereas the validation cohort showed significant baseline differences among these two groups in age, tumor size, histological grade, AJCC 8th pT stage, and AJCC 8th pN stage (Table S2).

A total of 1,582 (47.6%) patients in the validation cohort received adjuvant chemotherapy (Table S1). Adjuvant chemotherapy was generally based on 5-fluorourcil (5-FU)/capecitabine alone or 5-FU/capecitabine combined with oxaliplatin (FOLFOX/CapeOX), and was administered to patients with stage III or high-risk stage II colon cancer, according to the wishes of the patients and their families. Univariate and multivariable analyses confirmed that adjuvant chemotherapy was an independent prognostic factor in patients with <12 retrieved lymph nodes, and also in patients with ≥12 lymph nodes in the validation cohort (Table S3).

LNR stages

A novel LNR stage was established using four identified cutoff values (LNR, 0.05, 0.3, 0.5, and 0.7). Using these four cutoff values, we classified patients in the training cohort as follows: LNR1, 0 to 0.05; LNR2, >0.05 to ≤0.3; LNR3, >0.3 to ≤0.5; LNR4, >0.5 to ≤0.7; and LNR5, >0.7 to ≤1 (Table S4). There were two previous LNR stages named LNR-Berger (12) and LNR-Rosenberg (13), with LNR cutoff values of 0.05, 0.19, and 0.39 for LNR-Berger, and 0, 0.17, 0.41, and 0.69 for LNR-Rosenberg. Kaplan-Meier curves were presented to estimate the survivals associated with AJCC 8th pN stage and these three LNR stages (Figure S2).

TLNR classification

A novel TLNR classification was generated by combining the novel LNR and pT stages into 25 groups. Using these six identified cutoff values, we clustered patients from the 25 groups into seven clusters as follows: stage I (T1LNR1-2, T1LNR4), stage IIA (T1LNR3, T2LNR1-2, T3LNR1), stage IIB (T1LNR5, T2LNR3-4, T3LNR2, T4aLNR1), stage IIC (T2LNR5, T3LNR3-4, T4aLNR2, T4bLNR1), stage IIIA (T3LNR5, T4aLNR3-4, T4bLNR2), stage IIIB (T4aLNR5, T4bLNR3-4) and stage IIIC (T4bLNR5) (*Table 1*, *Figure 1*).

LNR stages versus AJCC 8th pN stage

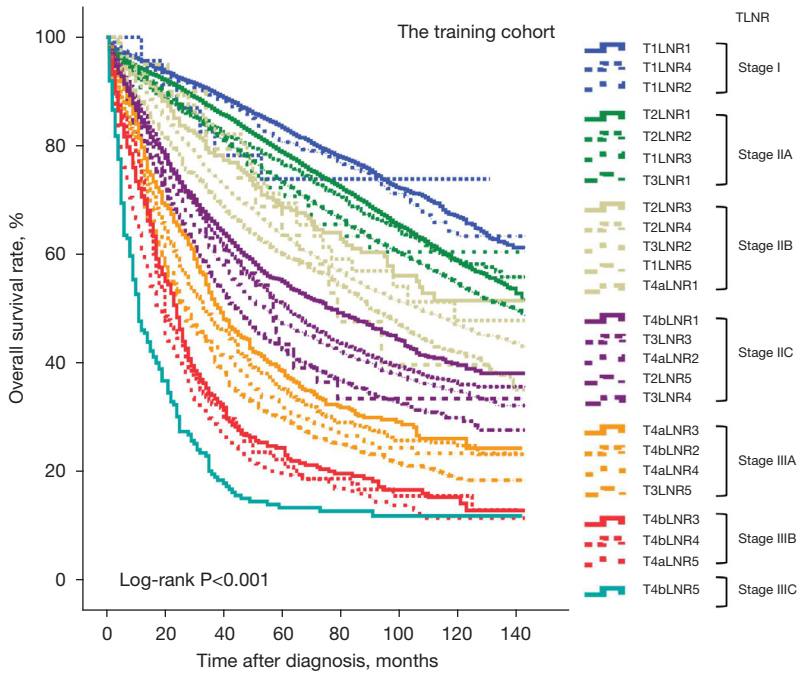
We compared the model-discrimination performances and model-fitting abilities of different LNR stages with AJCC 8th pN stage in the training cohort. All three LNR stages showed significantly better prognostic discrimination (Hanley and McNeil test, all P<0.001) and superior model-fitting ability (Table S5) compared with AJCC 8th pN stage. Similar findings were observed in patients with <12 and ≥12 retrieved lymph nodes (Table S5).

TLNR classification versus AJCC 8th TNM classification

We compared the model discrimination and model-fitting between the novel TLNR and AJCC 8th TNM classifications in the training cohort. Kaplan-Meier curves with log-rank tests confirmed that the novel TLNR classification showed superior model-discrimination performance than the AJCC 8th TNM classification. Using the TLNR classification, the 5-year OS rates steadily decreased and HRs increased as stage increased (HRs, TLNR stages I to IIIC, 1.00, 1.48, 2.13, 3.07, 4.87, 6.94, and 9.70) (*Table 2*, *Figure 2A*,*2B*). The novel TLNR showed better prognostic discrimination (AUC, 0.621 *vs.* 0.608; Hanley and McNeil test, P<0.001) and superior model-fitting ability (AIC, 561,129 *vs.* 562,052) than the AJCC 8th TNM classification for OS (*Table 3*). Similar findings were observed in patients with adequate (≥12) or inadequate (<12) numbers of retrieved lymph nodes (*Table 3*). We further performed DCAs to assess clinical utility, and the novel TLNR classification had superior net benefits over the AJCC 8th TNM classification between the threshold probabilities of 30–45% in the training cohort (Figure S3A).

External validation

We confirmed the findings in the external validation cohort. Similar to the training cohort, the 5-year OS rates steadily decreased and HRs increased as TLNR stages increased in terms of both OS (HRs, TLNR stages I to IIIC, 1.00, 1.76, 2.54, 3.40, 6.35, 10.4, and 16.0) and DFS (HRs, TLNR stages I to IIIC, 1.00, 2.46, 3.71, 4.94, 8.84, 13.8, and 18.1) (*Table 2*, *Figure 2C-2F*). The novel TLNR classification also showed superior prognostic discrimination (AUC of OS, 0.646 *vs.* 0.604; AUC of DFS 0.646 *vs.* 0.622, Hanley and McNeil test, all P<0.001) than the AJCC 8th TNM classification (*Table 3*). Similar findings were observed in patients with inadequate retrieved lymph nodes (<12) but not in patients with an adequate number of retrieved lymph nodes (≥12), suggesting that the novel TLNR classification had particular advantages in patients with inadequate



Number at risk

5794	5425	5124	4718	3111	1769	823	107	Stage I
33402	30126	27292	24383	16296	9461	4365	639	Stage IIA
12746	10807	9171	7841	5132	2918	1390	197	Stage IIB
6894	5294	4131	3341	2173	1284	628	86	Stage IIC
2517	1580	1076	822	526	322	168	21	Stage IIIA
754	395	226	162	105	61	32	5	Stage IIIB
187	71	33	25	17	13	7	2	Stage IIIC

Figure 1 Kaplan-Meier estimates of the proposal novel TLNR in the training cohort. TLNR, T stage-lymph node ratio classification.

retrieved lymph nodes (*Table 3*). Moreover, DCAs revealed that the TLNR had superior net benefits over the AJCC 8th TNM classification between threshold probabilities of around 20–30% in terms of OS and round 22–35% in terms of DFS (Figure S3B,S3C).

A web tool based on the novel TLNR classification was developed to predict individual overall survival (*Figure 3*). The details of the novel TLNR classification are presented in *Figure 4*.

Discussion

The AJCC TNM classification of colon cancer has long been considered to have limited ability to predict survival, with some stage III patients having a better prognosis than some stage II patients (2-4). This has been suggested to be because of stage migration based on an inadequate number of retrieved lymph nodes (21,22). Some studies considered that patient survival was affected by the total number of retrieved lymph nodes, with therapeutic benefits obtained by optimal lymphadenectomy, while others considered that the survival benefits might be due to more accurate staging of the tumors based on the larger number of harvested lymph nodes. However, even among patients with adequate lymph nodes, many patients in stage III still have better survival than patients in stage II, suggesting that these explanations are inadequate to explain this paradox.

However, even with maximum effort, the total number of retrieved lymph nodes is frequently inadequate, with 26.8% of patients in the training cohort and 31.6% in the validation cohort having inadequate numbers of retrieved lymph nodes, in line with previous reports (9,10). This

Table 2 Survival comparisons of the AJCC 8th pN versus LNR stages and the AJCC 8th TNM versus TLNR classifications in the training and validation cohorts

Outcomes	HR (95% CI)	5-Y OS or DFS, % (95% CI)
Training cohort (overall survival) (N=62,294)		
AJCC 8th pN stage		
pN0 (n=37,998)	1.00 (reference)	74.6 (74.2–75.0)
pN1a (n=7,694)	1.27 (1.22–1.32)	66.8 (65.7–67.8)
pN1b/1c (n=7,705)	1.48 (1.43–1.54)	61.0 (59.9–62.1)
pN2a (n=4,988)	1.88 (1.81–1.96)	52.7 (51.3–54.1)
pN2b (n=3,909)	2.72 (2.61–2.84)	39.8 (38.3–41.3)
LNR stage		
LNR1 (n=40,576)	1.00 (reference)	74.5 (74.1–75.0)
LNR2 (n=14,725)	1.45 (1.40–1.49)	62.4 (61.6–63.1)
LNR3 (n=3,939)	2.13 (2.04–2.22)	48.6 (47.0–50.1)
LNR4 (n=1,516)	2.61 (2.45–2.78)	40.6 (38.1–43.0)
LNR5 (n=1,538)	3.96 (3.74–4.20)	26.9 (24.7–29.2)
AJCC 8th TNM classification		
I (n=13,828)	1.00 (reference)	80.5 (79.8–81.1)
IIA (n=21,102)	1.33 (1.28–1.38)	73.1 (72.5–73.7)
IIB (n=1,708)	2.02 (1.88–2.17)	60.3 (57.9–62.5)
IIC (n=1,360)	2.28 (2.11–2.46)	55.3 (52.6–57.9)
IIIA (n=2,384)	1.04 (0.97–1.13)	78.0 (76.2–79.6)
IIIB (n=16,270)	1.86 (1.79–1.93)	61.5 (60.7–62.2)
IIIC (n=5,642)	3.56 (3.41–3.72)	38.3 (37.0–39.5)
TLNR classification		
I (n=5,794)	1.00 (reference)	83.1 (82.1–84.1)
IIA (n=33,402)	1.48 (1.41–1.56)	75.0 (74.5–75.4)
IIB (n=12,746)	2.13 (2.01–2.25)	63.2 (62.3–64.0)
IIC (n=6,894)	3.07 (2.90–3.26)	49.7 (48.5–50.9)
IIIA (n=2,517)	4.87 (4.55–5.21)	33.6 (31.7–35.4)
IIIB (n=754)	6.96 (6.34–7.63)	22.2 (19.3–25.3)
IIIC (n=187)	9.70 (8.24–11.4)	13.4 (8.90–18.8)
Validation cohort (overall survival) (N=3,327)		
AJCC 8th pN stage		
pN0 (n=1,298)	1.00 (reference)	81.0 (78.4–83.2)
pN1a (n=723)	1.38 (1.13–1.70)	79.6 (75.8–82.8)
pN1b/1c (n=709)	1.78 (1.47–2.16)	73.6 (69.3–77.4)
pN2a (n=345)	2.09 (1.65–2.65)	71.5 (65.1–77.0)
pN2b (n=252)	3.76 (3.01–4.71)	52.1 (44.0–59.5)
LNR stage		
LNR1 (n=1,513)	1.00 (reference)	80.9 (78.6–83.1)
LNR2 (n=1,308)	1.48 (1.26–1.74)	76.8 (73.8–79.5)
LNR3 (n=285)	2.20 (1.74–2.80)	66.4 (58.8–72.9)
LNR4 (n=93)	3.21 (2.31–4.47)	54.9 (41.6–66.3)
LNR5 (n=128)	4.95 (3.84–6.38)	44.0 (34.2–53.4)
AJCC 8th TNM classification		
I (n=26)	1.00 (reference)	90.9 (50.8–98.7)
IIA (n=520)	1.78 (0.25–12.8)	84.4 (80.3–87.8)
IIB (n=520)	2.34 (0.33–16.8)	80.0 (76.0–83.5)
IIC (n=232)	2.76 (0.38–19.9)	76.7 (70.5–81.7)
IIIA (n=56)	0.24 (0.02–3.81)	97.7 (84.6–99.7)
IIIB (n=1,460)	3.29 (0.46–23.4)	78.0 (75.3–80.5)
IIIC (n=513)	7.36 (1.03–52.5)	56.3 (51.0–61.3)
TLNR classification		
I (n=21)	1.00 (reference)	90.0 (47.3–98.5)
IIA (n=731)	1.76 (0.25–12.6)	84.8 (81.4–87.7)
IIB (n=1,413)	2.54 (0.36–18.1)	79.8 (77.1–82.1)
IIC (n=737)	3.40 (0.48–24.3)	73.2 (69.4–76.6)
IIIA (n=328)	6.35 (0.89–45.4)	58.2 (51.7–64.1)
IIIB (n=84)	10.4 (1.44–75.6)	47.0 (34.7–58.4)
IIIC (n=13)	16.0 (2.05–125)	36.9 (12.5–62.0)
Validation cohort (disease-free survival) (N=3,327)		
AJCC 8th pN stage		
pN0 (n=1,298)	1.00 (reference)	77.9 (75.2–80.2)
pN1a (n=723)	1.47 (1.22–1.77)	73.8 (69.9–77.3)
pN1b/1c (n=709)	1.91 (1.60–2.28)	66.9 (62.7–70.8)
pN2a (n=345)	2.30 (1.86–2.85)	65.5 (59.3–70.9)
pN2b (n=252)	3.83 (3.11–4.72)	45.9 (38.4–53.1)
LNR stage		
LNR1 (n=1,513)	1.00 (reference)	77.7 (75.3–80.0)

Table 2 (*continued*)

Outcomes	HR (95% CI)	5-Y OS or DFS, % (95% CI)
LNR2 (n=1,308)	1.63 (1.40–1.89)	70.7 (67.7–73.4)
LNR3 (n=285)	2.48 (2.00–3.07)	57.9 (50.7–64.5)
LNR4 (n=93)	3.29 (2.41–4.48)	48.3 (35.8–59.8)
LNR5 (n=128)	4.93 (3.87–6.28)	38.2 (29.0–47.4)
AJCC 8th TNM classification		
I (n=26)	1.00 (reference)	90.9 (50.8–98.7)
IIA (n=520)	2.60 (0.36–18.7)	81.3 (77.0–84.8)
IIB (n=520)	3.18 (0.45–22.8)	77.0 (72.8–80.6)
IIC (n=232)	4.03 (0.56–29.1)	73.1 (66.8–78.5)
IIIA (n=56)	1.14 (0.13–10.2)	90.1 (75.3–96.2)
IIIB (n=1,460)	5.08 (0.71–36.2)	71.9 (69.1–74.5)
IIIC (n=513)	10.5 (1.48–75.1)	49.7 (44.6–54.6)
TLNR classification		
I (n=21)	1.00 (reference)	90.0 (47.3–98.5)
IIA (n=731)	2.46 (0.34–17.6)	81.5 (78.0–84.6)
IIB (n=1,413)	3.71 (0.52–26.4)	74.6 (71.9–77.1)
IIC (n=737)	4.94 (0.69–35.2)	67.6 (63.7–71.2)
IIIA (n=328)	8.84 (1.24–63.1)	51.3 (45.0–57.2)
IIIB (n=84)	13.8 (1.91–99.8)	39.8 (28.3–51.0)
IIIC (n=13)	18.1 (2.32–141)	36.9 (12.5–62.0)

AJCC, American Joint Committee on Cancer; TLNR, T stage-lymph node ratio classification; TNM, tumor/node/metastasis; 5-Y OS, 5-year overall survival; DFS, disease-free survival; HR, hazard ratio; No., number; LNR, lymph node ratio.

could be due to multiple factors, including surgical skills and technique, the way the pathologist collects the lymph nodes, the actual number of regional lymph nodes surrounding the tumor, and even the patient's immune response (23-25). In addition, although some studies suggested that pT stage had a much lower weight than the pN stage in the AJCC TNM classification (5,6,26), pT stage was shown to have comparable importance to pN stage, regardless of the number of retrieved lymph nodes (7,8). Overall, the current AJCC TNM 8th TNM classification could not predict survival adequately, indicating the need for a modification or revision of the current classification.

Importantly, the LNR takes into account both the influence of the number of positive lymph nodes and the number of examined lymph nodes in relation to the stage, and has demonstrated advantages in prognosis prediction over AJCC pN stage for colon cancer (12-14). However, the prognostic value of a novel TLNR classification for colon cancer combining LNR and pT stages is still unknown. We therefore established a novel LNR stage, with better prognostic discrimination than AJCC 8th pN stage, which showed comparable prognostic discrimination to previous studies (12-14). We confirmed the better performance of the LNR compared with pN stage, and demonstrated that this novel classification showed superior prognostic discrimination, model-fitting ability, and clinical usefulness compared with the AJCC 8th TNM classification, especially in patients with inadequate numbers of retrieved lymph nodes.

The performance of a classification can be evaluated by the homogeneity within the subgroups, its ability to distinguish between different groups, and the monotonicity of the gradient of the correlation between stage and survival (27). The novel TLNR classification had several advantages over the AJCC 8th TNM classification. First, HRs and 5-year OS rates differed significantly between each pair of stages in the novel TLNR classification, suggesting enhanced stratification ability. Second, the AUCs of the novel TLNR classification were significantly increased compared with the AJCC 8th TNM classification, indicating better prognostic discrimination. Third, the TLNR classification showed superior net benefits to the AJCC 8th TNM classification according to DCA. Stratified analyses further confirmed that the novel TLNR classification had good model applicability, especially in patients with inadequate lymph node retrieval. We further validated these findings for DFS, and showed that the novel TLNR classification still had superior predictive performance to the AJCC 8th TNM classification. The current findings suggesting that the TLNR provides a more reasonable classification than the AJCC 8th TNM classification should thus be considered reliable, given that they were based on a large-sample SEER training set and validated in an external validation set. The TLNR classification may be considered as a better alternative to the AJCC 8th TNM classification for stratifying patients with colon cancer, especially those with inadequate numbers of retrieved lymph nodes.

This study had several advantages. To the best of our knowledge, it was the first investigation of the use of a novel TLNR classification combining pT and LNR stages

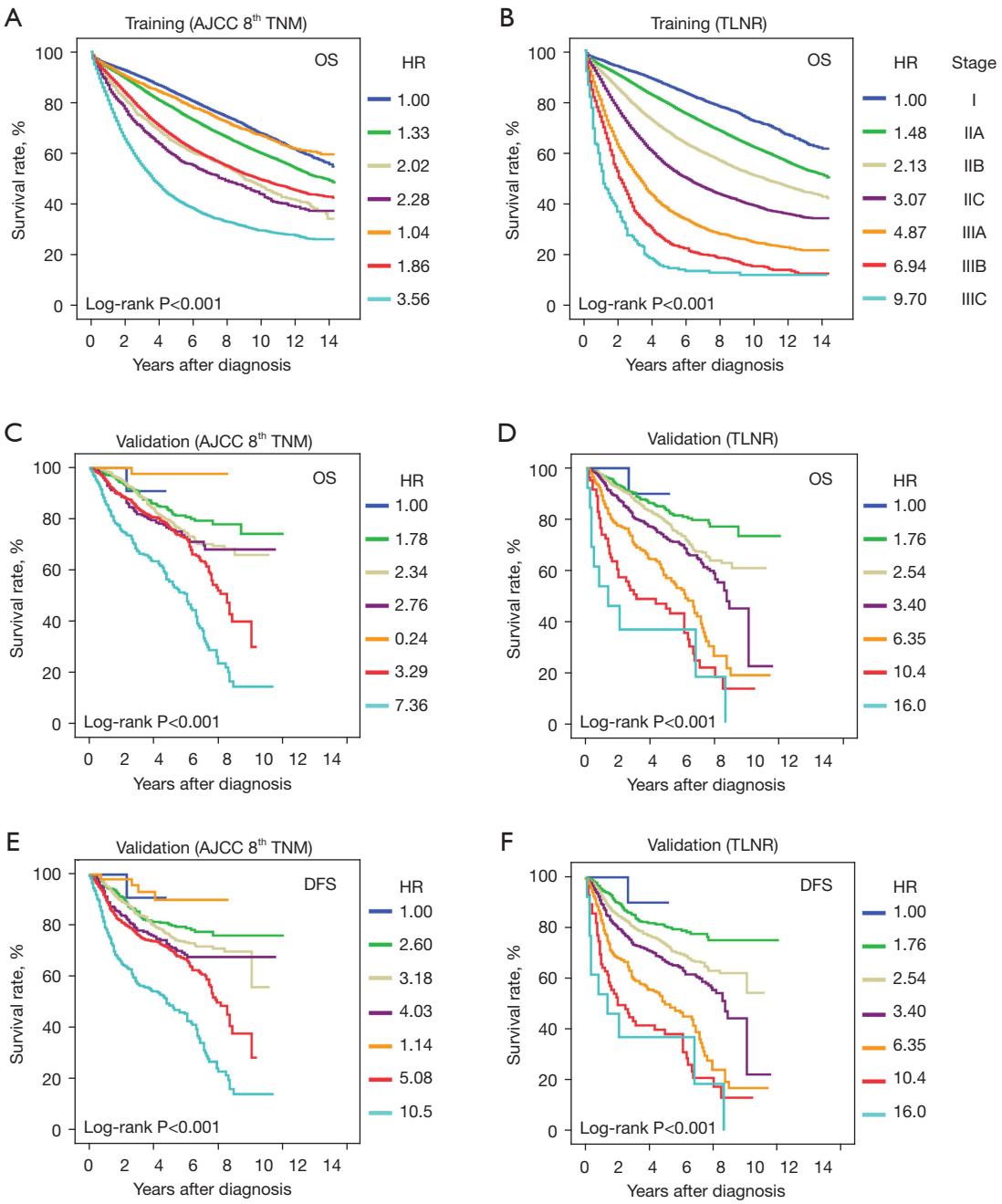


Figure 2 Kaplan-Meier estimates of the AJCC 8th TNM classification and TLNR classification in the training and validation cohorts. (A) AJCC 8th TNM classification in the training cohort predicting OS. (B) TLNR classification in the training cohort predicting OS. (C) AJCC 8th TNM classification in the validation cohort predicting OS. (D) TLNR classification in the validation cohort predicting OS. (E) AJCC 8th TNM classification in the validation cohort predicting DFS. (F) TLNR classification in the validation cohort predicting DFS. AJCC, American Joint Committee on Cancer; TLNR, T stage-lymph node ratio classification; TNM, tumor/node/metastasis; OS, overall survival; DFS, disease-free survival.

Table 3 Comparisons of the TLNR and the AJCC 8th TNM classifications in the training and validation cohorts

Comparisons	AIC†	AUC (95% CI)‡	P value*
Training cohort (overall survival)			
Overall patients (N=62,294)			<0.001
AJCC 8th classification	562,052	0.608 (0.604–0.612)	
TLNR classification	561,129	0.621 (0.617–0.624)	
Patients with lymph nodes <12 (n=16,674)			<0.001
AJCC 8th classification	132,571	0.605 (0.597–0.612)	
TLNR classification	132,337	0.617 (0.609–0.624)	
Patients with lymph nodes ≥12 (n=45,620)			<0.001
AJCC 8th classification	398,469	0.610 (0.605–0.614)	
TLNR classification	397,780	0.622 (0.618–0.627)	
Validation cohort (overall survival)			
Overall patients (N=3,327)			<0.001
AJCC 8th classification	11,500	0.604 (0.587–0.620)	
TLNR classification	11,505	0.646 (0.629–0.662)	
Patients with lymph nodes <12 (n=1,052)			<0.001
AJCC 8th classification	3,736	0.587 (0.556–0.617)	
TLNR classification	3,732	0.641 (0.611–0.670)	
Patients with lymph nodes ≥12 (n=2,275)			0.071
AJCC 8th classification	6,719	0.621 (0.601–0.641)	
TLNR classification	6,716	0.643 (0.623–0.663)	
Validation cohort (disease-free survival)			
Overall patients (N=3,327)			0.008
AJCC 8th TNM classification	13,954	0.622 (0.606–0.639)	
TLNR classification	13,968	0.646 (0.629–0.662)	
Patients with lymph nodes <12 (n=1,052)			<0.001
AJCC 8th classification	4,313	0.598 (0.568–0.628)	
TLNR classification	4,305	0.640 (0.611–0.670)	
Patients with lymph nodes ≥12 (n=2,275)			0.774
AJCC 8th classification	8,418	0.641 (0.621–0.661)	
TLNR classification	8,433	0.645 (0.625–0.664)	

†, a lower AIC indicates superior model-fitting; ‡, a higher AUC indicates better discrimination; *, P value of Hanley & McNeil test of AUCs. AJCC, American Joint Committee on Cancer; TLNR, T stage-lymph node ratio classification; TNM, tumor/node/metastasis; AIC, Akaike's information criterion; AUC, areas under the receiver-operating characteristic curve; CI, confidence interval.

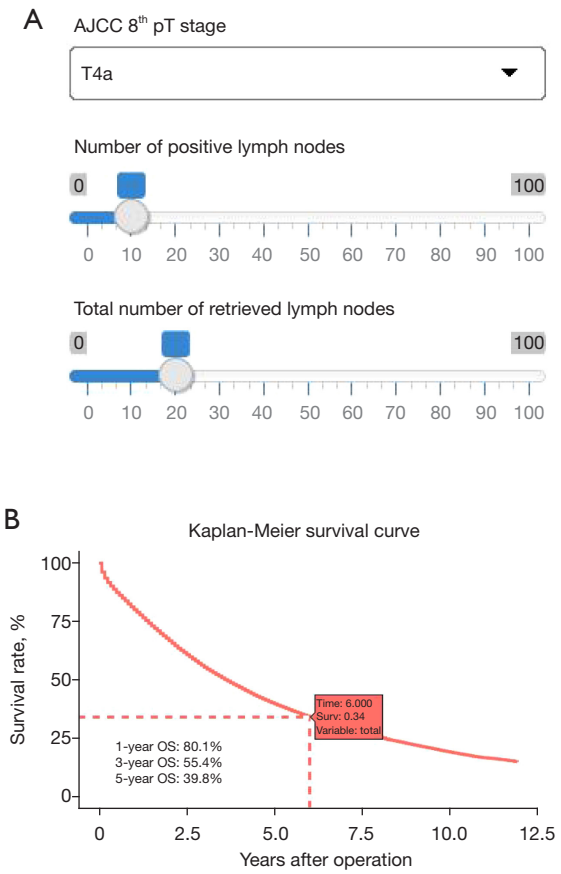


Figure 3 A web tool based on the novel TLNR classification individually predicting overall survival (http://123.206.185.159:6070/). (A) Valuables include AJCC 8th pT stage, number of positive lymph nodes, and total number of retrieved lymph nodes. (B) Kaplan-Meier estimates of individual survival curves based on a web tool. LNR = number of positive lymph nodes/total number of retrieved lymph nodes. Number of positive lymph nodes should be no more than the total number of retrieved lymph nodes. AJCC, American Joint Committee on Cancer; TLNR, T stage-lymph node ratio classification; LNR, lymph node ratio.

for colon cancer. This study was also based on a large training cohort and was successfully validated in an external validation cohort. However, the study also had some limitations. The current novel TLNR classification was only based on LNR and pT stages, and surgical strategy, adjuvant chemotherapy regimens (28,29), and molecular markers, such as microsatellite instability, KRAS and BRAF, may also affect the prognosis. Besides, the Kaplan-Meier

LNR value	0–0.05	0.05–0.30	0.30–0.50	0.50–0.70	0.70–1.00
TLNR	LNR1	LNR2	LNR3	LNR4	LNR5
11	I	I	IIA	I	IIB
T2	IIA	IIA	IIB	IIB	IIC
T3	IIA	IIB	IIC	IIC	IIIA
T4a	IIB	IIC	IIIA	IIIA	IIIB
T4b	IIC	IIIA	IIIB	IIIB	IIIC

Figure 4 Details of the TLNR classification. TLNR, T stage-lymph node ratio classification.

curves of TLNR classification for several substages were overlapping, and thus failed to represent groups with a significant survival outcome. Furthermore, T1LNR3 was catabolized into stage IIA but T1LNR4 was catabolized into stage I in the novel TLNM classification, possibly due to the relatively small number of patients in this subgroup. Further studies are therefore required to validate this novel TLNR classification.

Conclusions

In summary, the current TLNR classification may provide a better prognostic assessment in patients with operable stage I–III colon cancer compared with the AJCC 8th TNM classification. This prognosis-based classification may provide better patient stratification and may be considered as a good alternative to the current AJCC 8th TNM classification for patients with operable colon cancer. However, further studies are required to validate the clinical application of the novel TLNR classification.

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Ethics Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The ethical review was approved by the Institute Ethics Committees of China Medical University Cancer Hospital (20210206K). Written informed consent was obtained from all patients. SEER is a publicly available database with anonymized data, no ethical review was required.

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