

## ORIGINAL PAPER

## EXTRAMURAL VENOUS INVASION AS AN INDEPENDENT PREDICTOR OF LYMPH NODE METASTASIS IN COLON ADENOCARCINOMA: A MULTIVARIATE ANALYSIS

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Lymph node metastasis (LNM) is a key determinant of prognosis and treatment decisions in colon adenocarcinoma. Among histopathological features associated with tumor aggressiveness, extramural venous invasion (EMVI) has been increasingly recognized as an adverse factor; however, its independent role in predicting nodal metastasis remains incompletely defined.

In this retrospective study, 180 consecutive patients who underwent primary surgical resection for colon adenocarcinoma, excluding rectal tumors, neoadjuvant-treated cases, and histological subtypes other than adenocarcinoma NOS, were evaluated. Histopathological parameters, including EMVI, intramural venous invasion, lympho-vascular invasion (LVI), perineural invasion (PNI), tumor budding, and tumor deposits, were systematically reviewed, and elastic staining was used in equivocal cases. Associations with LNM were analyzed using univariate and multivariate logistic regression.

Lymph node metastasis was identified in 47.8% of patients, and EMVI was present in 21.7% and was significantly more frequent in patients with nodal metastasis. In multivariate analysis, LVI was the strongest independent predictor of LNM, followed by PNI, EMVI, and high tumor budding. The model demonstrated good calibration and an overall accuracy of 80%. Extramural venous invasion is an independent predictor of LNM and reflects a biologically aggressive tumor phenotype. Its routine assessment, together with other high-risk features, may improve risk stratification and support more informed clinical decision-making.

**Key words:** colon adenocarcinoma, extramural venous invasion, lymph node metastasis, lymphovascular invasion, tumor budding.

## Introduction

Colon adenocarcinoma remains a major cause of cancer-related morbidity and mortality worldwide, and pathological staging continues to be the cornerstone for prognostic stratification and treatment planning [1]. Lymph node metastasis (LNM) is one of the most powerful determinants of outcome and directly influences the indication for adjuvant therapy, making accurate prediction of nodal status clinically meaningful [2].

Beyond pT stage and lymph node status, several histopathological features reflect the biological aggressiveness of colon cancer and are associated with metastatic potential [1]. Among these, vascular invasion – particularly venous invasion – has long been recognized as an adverse prognostic marker, yet its detection and reporting have historically shown substantial interobserver variability and practice heterogeneity [3]. Methodological factors such as tissue

sampling and the use of ancillary stains can significantly affect venous invasion detection rates [4].

Venous invasion is commonly categorized by the anatomical level of the involved vessel as intramural (within the submucosa or *muscularis propria*) or extramural (beyond the *muscularis propria*) [1]. Extramural venous invasion (EMVI) has been highlighted as a particularly important subtype because it reflects tumor access to larger caliber veins and is consistently linked to adverse oncologic outcomes in colorectal cancer [5]. Contemporary reporting standards emphasize structured assessment of lymphatic and vascular invasion and recommend documenting venous invasion with respect to intramural vs. extramural location; however, in routine pathological practice, this distinction may not always be consistently highlighted or uniformly applied [6].

In addition to its prognostic significance, EMVI is clinically relevant because it often coexists with other aggressive pathological features, including lymphovascular invasion (LVI), perineural invasion (PNI), and high tumor budding, which may collectively contribute to the likelihood of nodal dissemination [1]. Prior work has also shown that EMVI is an adverse feature in colon cancer resections and may complement nodal metrics in risk stratification [2]. Furthermore, evidence syntheses have reinforced the clinical importance of EMVI in colorectal cancer, underscoring its association with unfavorable outcomes across studies and assessment methods [7].

Despite its recognized prognostic importance in colorectal cancer, the specific role of EMVI in predicting LNM independent of other aggressive histopathological features remains incompletely defined. While traditional histopathological techniques detect EMVI and other high-risk features, recent evidence suggests that more sensitive detection methods, such as elastin staining, can increase venous invasion detection rates but may not always translate into prognostic significance for survival outcomes [8]. Emerging studies continue to show that EMVI, particularly when identified beyond the *muscularis propria*, is associated with a more advanced pathological stage, increased nodal involvement, and poorer oncological outcomes [9]. Moreover, incorporation of EMVI into multivariable models has demonstrated that it retains independent prognostic value even after adjustment for other risk factors such as LVI, PNI, tumor grade, and tumor budding [10].

Taken together, these findings suggest that although EMVI is widely accepted as an adverse pathological feature, its independent contribution to LNM in colon adenocarcinoma warrants further clarification. Therefore, in the present study, we aimed to evaluate the association between EMVI and LNM and to determine whether EMVI is an independent predictor of nodal

metastasis when evaluated alongside established histopathological markers of aggressive tumor behavior.

## Material and methods

### Study design and case selection

This retrospective observational study was conducted in the Department of Pathology, Manisa Celal Bayar University Faculty of Medicine. The study included consecutive patients who underwent surgical resection for primary colon adenocarcinoma between January 2022 and December 2025.

Cases were identified through the pathology information system. Only resection specimens diagnosed as adenocarcinoma, not otherwise specified, were included. Rectal tumors, cases receiving neoadjuvant therapy, and tumors with special histological subtypes (including mucinous adenocarcinoma, medullary carcinoma, signet-ring cell carcinoma, and other specific variants) were excluded. Cases with incomplete pathological data or insufficient archival material were also excluded. All eligible cases meeting the inclusion criteria during the study period were included in the analysis.

### Histopathological evaluation

Archived hematoxylin and eosin (HE)-stained slides of all eligible cases were retrieved and systematically reviewed. The following histopathological parameters were recorded: tumor location, histological grade, pT stage according to the American Joint Committee on Cancer 8<sup>th</sup> edition [11], total number of examined lymph nodes, number of metastatic lymph nodes, and LNM status. In addition, the presence of intramural venous invasion (IMVI), EMVI, LVI, PNI, tumor budding, tumor deposits, and serosal involvement was assessed.

Venous invasion was classified as intramural when tumor cells were identified within venous structures located in the submucosa or *muscularis propria*, and as extramural when invasion involved venous structures beyond the *muscularis propria*. Lymphovascular invasion was defined as the presence of tumor cells within endothelial-lined lymphatic and/or small vascular spaces. In this study, LVI was recorded separately from venous invasion. Venous invasion was diagnosed only when tumor cells were identified within a vessel showing features of a venous structure, such as a recognizable venous wall, residual smooth muscle, or elastic fibers. Cases showing tumor cells within small endothelial-lined spaces without definite evidence of venous wall involvement were classified as LVI but not as IMVI or EMVI. Conversely, cases with definite venous wall involvement were recorded as venous invasion and were further classified as IMVI or EMVI according to the anatomical location of the involved vessel.

Histological grade was categorized as low-grade or high-grade according to the current World Health Organization classification [12]. Tumor budding was evaluated in accordance with the recommendations of the International Tumor Budding Consensus Conference (ITBCC) and categorized as low or high grade [13].

In cases where EMVI or IMVI was suspected on HE sections but the findings were equivocal, elastic Van Gieson staining was performed to highlight elastic fibers in the venous wall, confirm the presence of venous wall structures, and verify true venous invasion. Only cases with histologically confirmed venous invasion were recorded as positive.

All histopathological evaluations were performed independently by two experienced gastrointestinal pathologists. In instances of discrepancy, the slides were reviewed jointly, and a consensus diagnosis was reached.

Mismatch repair (MMR) status was evaluated by immunohistochemistry performed as part of the routine diagnostic workup. Nuclear expression of MLH1, PMS2, MSH2, and MSH6 was assessed in tumor cells. Complete loss of nuclear staining for one or more MMR proteins in tumor cells, in the presence of retained internal positive control staining in non-neoplastic epithelial, stromal, or inflammatory cells, was interpreted as deficient MMR (dMMR). Preserved nuclear expression of all four proteins was interpreted as proficient MMR.

#### Data collection

Clinicopathological data were extracted from pathology reports and archival materials and recorded in a standardized data form prepared for the study. All patient identifiers were removed, and data were analyzed anonymously.

#### Statistical analysis

Statistical analyses were performed using SPSS software (version 25, IBM Corp., Armonk, NY, USA). Continuous variables were assessed for normality using the Shapiro-Wilk test. Non-normally distributed variables were expressed as median (interquartile range, IQR). Comparisons between two groups were performed using the Mann-Whitney *U* test. Categorical variables were compared using the  $\chi^2$  test or Fisher's exact test when appropriate. To identify factors associated with LNM, univariate logistic regression analyses were performed. Variables found to be statistically significant in univariate analysis were entered into a multivariate logistic regression model to determine independent predictors of LNM. Model calibration was evaluated using the Hosmer-Lemeshow goodness-of-fit test, and explanatory power was assessed using the Nagelkerke

$R^2$  coefficient. Odds ratios (OR) with 95% CI were calculated. A *p*-value < 0.05 was considered statistically significant.

## Results

### Clinicopathological characteristics

A total of 180 patients with colon adenocarcinoma were included, and no missing data were present for categorical variables. The cohort consisted of 105 males (58.3%) and 75 females (41.7%). Lymph node metastasis was identified in 86 patients (47.8%).

Extramural venous invasion and IMVI were observed in 39 (21.7%) and 7 (3.9%) cases, respectively, while any venous invasion was present in 42 patients (23.3%). Representative examples of EMVI confirmed by elastic Van Gieson staining are shown in Figure 1. Lymphovascular invasion and PNI were detected in 91 (50.6%) and 105 (58.3%) cases, respectively. Tumor deposits were identified in 35 patients (19.4%).

Most tumors were advanced stage, with pT3–4 disease present in 165 patients (91.7%). High tumor budding was observed in 68 patients (37.8%). dMMR was identified in 15 cases (8.3%). Detailed clinicopathological characteristics are presented in Table I.

### Distribution of continuous variables

The median age of the cohort was 69 years (IQR 58–76), and the median tumor size was 4.35 cm (IQR 3.5–6.0). The median number of examined lymph nodes was 17 (IQR 13–24), while the median number of metastatic lymph nodes was 0 (IQR 0–2). Tumor budding count had a median of 3 (IQR 2–6). All continuous variables showed non-normal distributions (Table I).

### Association between clinicopathological factors and lymph node metastasis

There were no significant differences between patients with and without LNM in terms of age, tumor diameter, or total number of examined lymph nodes (all *p* > 0.05). However, tumor deposit count and tumor budding count were significantly higher in patients with LNM (both *p* < 0.001) (Table II).

Significant associations with LNM were observed for tumor grade, advanced pT stage, serosal involvement, EMVI, IMVI, any venous invasion, LVI, PNI, tumor deposits, high tumor budding, and MMR status (all *p* < 0.05). Among these, LVI (76.7% vs. 26.6%), PNI (77.9% vs. 40.4%), and EMVI (36.0% vs. 8.5%) were markedly more frequent in patients with LNM. Tumor deposits were also strongly associated with LNM (34.9% vs. 5.3%). Tumor location and adequacy

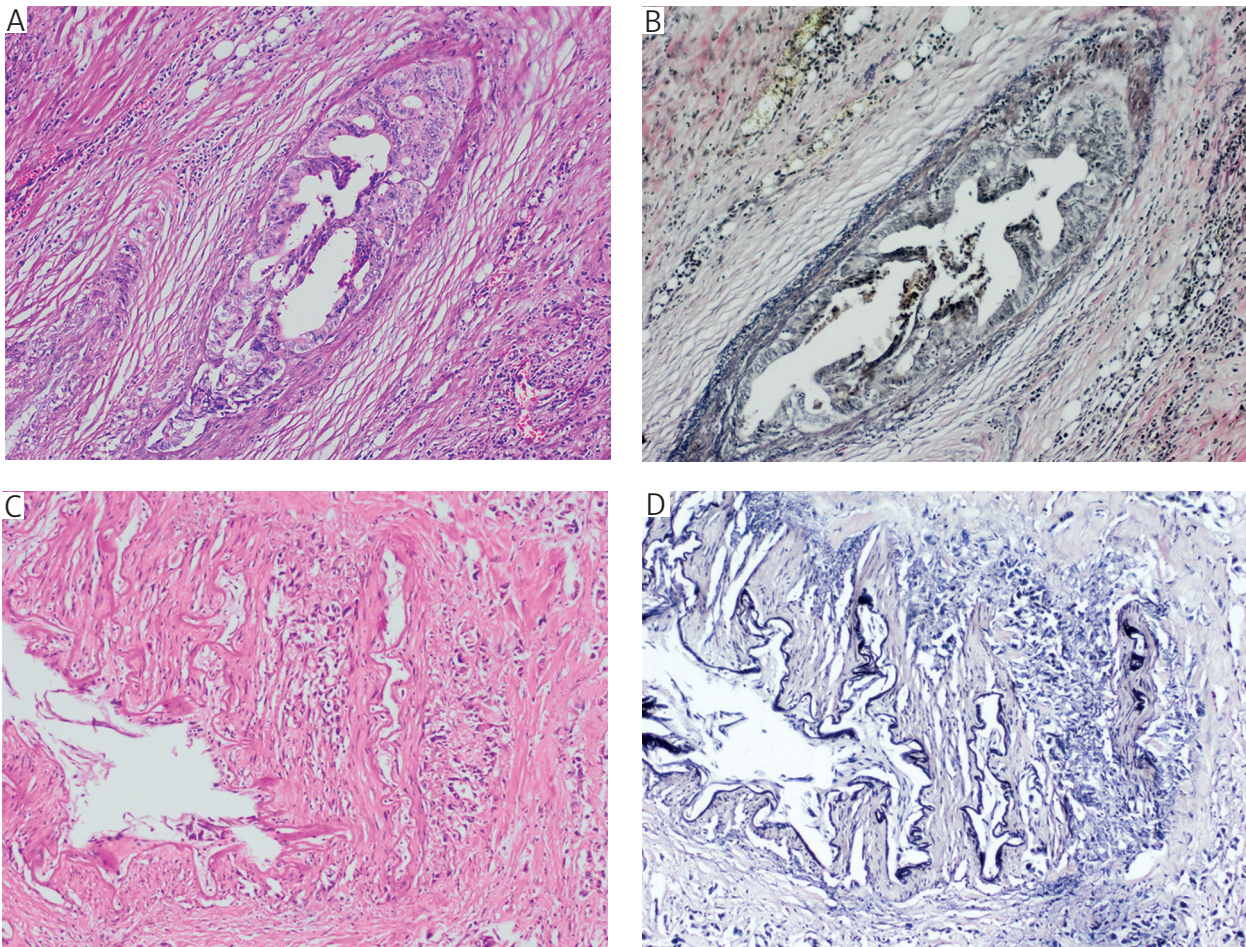


**Figure 1.** Extramural venous invasion in colon adenocarcinoma. Hematoxylin and eosin (HE) sections show tumor cells within vessel-like spaces in the pericolic tissue (A, C), while elastic Van Gieson staining highlights the venous wall and supports true venous invasion (B, D) (HE and elastic Van Gieson stain, 100×)

of lymph node dissection were not significantly associated with LNM (Table III).

#### Univariate and multivariate logistic regression analysis

In univariate analysis, several factors were significantly associated with increased risk of LNM, including LVI (OR = 9.11), tumor deposits (OR = 9.54), PNI (OR = 5.20), EMVI (OR = 6.06), high tumor budding (OR = 3.39), serosal involvement (OR = 6.80), advanced pT stage (OR = 6.74), and tumor grade (OR = 3.53) (all  $p < 0.05$ ). Intramural venous invasion showed a borderline association with LNM ( $p = 0.075$ ). Detailed results are presented in Table IV.

In multivariate analysis, LVI emerged as the strongest independent predictor of LNM (adjusted OR = 6.49,  $p < 0.001$ ). Perineural invasion (adjusted OR = 3.35,  $p = 0.002$ ), EMVI (adjusted OR = 2.72,  $p = 0.046$ ), and high tumor budding (adjusted OR = 2.16,  $p = 0.045$ ) also remained independently associated with LNM. The model demonstrated good calibration (Hosmer-Lemeshow  $p = 0.146$ ), moderate explanatory power (Nagelkerke  $R^2 = 0.442$ ), and an overall classification accuracy of 80.0% (Table V).

#### Discussion

In this retrospective cohort of colon adenocarcinoma resections, EMVI showed a strong association with LNM and remained independently predictive after adjustment for established adverse histopathological variables, including LVI, PNI, and tumor budding. These findings support the concept that EMVI is not merely a bystander feature of advanced disease but reflects a biologically aggressive phenotype that contributes to nodal dissemination [1, 2].

Venous invasion has long been recognized as a clinically meaningful adverse feature in colorectal cancer; however, its detection and reporting have historically been heterogeneous across institutions and even among pathologists [3, 4]. Contemporary datasets and structured reporting recommendations emphasize careful documentation of venous invasion – particularly extramural involvement – because of its prognostic and treatment implications [6]. In this context, our results add practical value by focusing specifically on LNM as an endpoint, because nodal

**Table I.** Baseline clinicopathological characteristics of the study cohort with colon adenocarcinoma ( $N = 180$ )

| PARAMETERS              |            | MEDIAN (IQR) [RANGE]; MEAN $\pm$ SD        |            |
|-------------------------|------------|--------------------------------------------|------------|
| Age [years]             |            | 69 (58–76) [32–92]; 67.4 $\pm$ 11.9        |            |
| Tumor size [cm]         |            | 4.35 (3.5–6.0) [1.0–13.0]; 4.84 $\pm$ 1.94 |            |
| Examined lymph nodes    |            | 17 (13–24) [3–71]; 19.7 $\pm$ 10.1         |            |
| Number of metastatic LN |            | 0 (0–2) [0–45]; 1.93 $\pm$ 4.31            |            |
| Tumor budding count     |            | 3 (2–6) [0–16]; 3.95 $\pm$ 3.21            |            |
| Tumor deposit count     |            | 0 (0–0) [0–7]; 0.33 $\pm$ 0.98             |            |
| PARAMETERS              | N (%)      | PARAMETERS                                 | N (%)      |
| Sex                     |            | Any VI (EMVI and/or IMVI)                  |            |
| Male                    | 105 (58.3) | Absent                                     | 138 (76.7) |
| Female                  | 75 (41.7)  | Present                                    | 42 (23.3)  |
| Tumor location          |            | LVI                                        |            |
| Right colon             | 75 (41.7)  | Absent                                     | 89 (49.4)  |
| Left colon              | 105 (58.3) | Present                                    | 91 (50.6)  |
| Tumor grade             |            | PNI                                        |            |
| Low-grade               | 154 (85.6) | Absent                                     | 75 (41.7)  |
| High-grade              | 26 (14.4)  | Present                                    | 105 (58.3) |
| pT stage                |            | Tumor deposits                             |            |
| pT1                     | 3 (1.7)    | Absent                                     | 145 (80.6) |
| pT2                     | 12 (6.7)   | Present                                    | 35 (19.4)  |
| pT3                     | 75 (41.7)  | Tumor budding                              |            |
| pT4                     | 90 (50.0)  | Low                                        | 112 (62.2) |
| pN stage                |            | High                                       | 68 (37.8)  |
| pN0                     | 89 (49.4)  | MMR status                                 |            |
| pN1                     | 51 (28.3)  | dMMR                                       | 15 (8.3)   |
| pN2                     | 40 (22.2)  | pMMR                                       | 165 (91.7) |
| LNM                     |            | Immune response                            |            |
| Absent                  | 94 (52.2)  | Absent                                     | 20 (11.1)  |
| Present                 | 86 (47.8)  | Peritumoral                                | 117 (65.0) |
| Serosal involvement     |            | Intratumoral                               | 14 (7.8)   |
| Absent                  | 90 (50.0)  | Crohn-like                                 | 29 (16.1)  |
| Present                 | 90 (50.0)  | Adequate LN dissection ( $\geq 12$ LN)     |            |
| EMVI                    |            | No                                         | 17 (9.4)   |
| Absent                  | 141 (78.3) | Yes                                        | 163 (90.6) |
| Present                 | 39 (21.7)  |                                            |            |
| IMVI                    |            |                                            |            |
| Absent                  | 173 (96.1) |                                            |            |
| Present                 | 7 (3.9)    |                                            |            |

dMMR – deficient mismatch repair, EMVI – extramural venous invasion, IMVI – intramural venous invasion, IQR – interquartile range, LN – lymph node, LNM – lymph node metastasis, LVI – lymphovascular invasion, MMR – mismatch repair, pMMR – proficient mismatch repair, PNI – perineural invasion, SD – standard deviation, VI – venous invasion

Continuous variables are presented as median (interquartile range) [range]; mean  $\pm$  standard deviation. Categorical variables are presented as numbers (percentages).

status determines the pN category and informs adjuvant treatment decisions [6].

Our observation that EMVI is independently associated with nodal involvement is in line with prior evidence linking EMVI to aggressive behavior and worse oncologic outcomes. In a landmark study evaluating

intramural vs. extramural vascular invasion, extramural involvement was associated with an adverse prognosis and highlighted quality issues in routine reporting [1]. Subsequent cohorts have also confirmed the prognostic importance of EMVI/EMVI-like extramural vascular invasion in colon cancer resections [2, 14].

**Table II.** Comparison of continuous clinicopathological variables according to lymph node metastasis status

| PARAMETERS           | LNM NEGATIVE (N = 94) | LNM POSITIVE (N = 86) | P-VALUE* |
|----------------------|-----------------------|-----------------------|----------|
| Age, median (IQR)    | 69 (59–75)            | 69 (58–77)            | 0.535    |
| Examined lymph nodes | 17 (13–24)            | 17 (13–25)            | 0.655    |
| Tumor diameter [cm]  | 4.35 (3.5–6.0)        | 4.30 (3.5–6.0)        | 0.847    |
| Tumor deposit count  | 0 (0–0)               | 0 (0–1)               | < 0.001  |
| Tumor budding count  | 2.50 (1.00–4.25)      | 5.00 (2.75–7.00)      | < 0.001  |

IQR – interquartile range, LNM – lymph node metastasis

\* Mann-Whitney U test

Meta-analytic evidence further supports the adverse impact of EMVI across colorectal cancer settings, although effect sizes and detection methods vary among studies [7].

Methodological issues are central when interpreting EMVI. Routine HE examination can underestimate venous invasion, and elastin-based stains can improve detection and interobserver agreement [4, 5]. At the same time, more recent data suggest that venous invasion detected only by elastic stains – without convincing morphology on routine sections – may carry weaker prognostic value, particularly in laboratories with already high baseline detection rates [8]. Therefore, the most balanced approach in routine practice may be to prioritize robust morphology on HE, use elastin stains in equivocal cases, and report EMVI clearly and consistently, rather than reflexively staining all cases [4, 8].

Among all variables in our multivariable model, LVI emerged as the strongest independent predictor of LNM. This is expected, because LVI represents direct access of tumor cells to lymphatic and vascular channels, facilitating regional spread [15, 16]. Large cohort data and stage-focused analyses continue to show that LVI stratifies risk and correlates with worse outcomes, underscoring why it is considered a key adverse feature in colorectal cancer pathology reporting [15, 17]. In addition, PNI remained independently predictive of LNM in our study. Perineural invasion is increasingly recognized as a marker of invasive capacity and poor prognosis in colorectal cancer, and systematic reviews support its association with adverse outcomes [18, 19]. Additional clinicopathological series have likewise demonstrated strong correlations between invasion-related parameters and nodal metastasis in colorectal cancer [20, 21].

Tumor budding also retained independent predictive value for LNM. This is consistent with ITBCC recommendations, which position budding as a reproducible, clinically relevant feature reflecting tumor-stromal interaction and invasive potential [13]. Recent literature continues to support the integration of budding into risk assessment frameworks and routine reporting, particularly in settings where refined risk stratification is needed [13, 22].

Another clinically relevant observation in our dataset is the strong association between tumor depos-

its and nodal positivity. Tumor deposits have been the focus of increasing attention, with modern reviews emphasizing their adverse prognostic implications and ongoing debates about optimal staging integration [23]. Contemporary cohorts likewise show that tumor deposits correlate with worse cancer-specific outcomes and recurrence risk, supporting their value as a high-risk feature that should be carefully documented and considered in multidisciplinary decision-making [24].

From a practical standpoint, our results support a “combined high-risk morphology” view: EMVI, LVI, PNI, and high tumor budding together identify a subgroup with substantially increased probability of nodal involvement. This may be particularly useful when grossly adequate lymph node harvest is achieved, but nodal status remains borderline, or when clinicians request refined risk information beyond pT and pN alone [6, 13].

Although EMVI is widely recognized as an adverse prognostic factor in colorectal cancer, its role in guiding adjuvant treatment decisions remains less clearly defined. Current clinical guidelines primarily rely on tumor stage and nodal status, while the incorporation of histopathological high-risk features such as EMVI into adjuvant therapy decision-making algorithms is still evolving and not uniformly standardized. In particular, while features such as LVI and PNI are often considered in risk stratification – especially in stage II disease – the independent contribution of EMVI to treatment selection remains controversial. In this context, our findings suggest that EMVI, when evaluated together with other aggressive histopathological parameters such as LVI, PNI, and tumor budding, may provide additional value in predicting LNM and refining risk stratification beyond conventional staging systems. This combined approach may help bridge the gap between pathological risk assessment and clinical decision-making, particularly by improving the prediction of nodal involvement when conventional staging parameters are insufficient or borderline [25–27].

The clinical implications of our findings are noteworthy. Identification of EMVI may improve risk stratification in colon cancer, particularly in patients with borderline pathological risk profiles. Integrating EMVI into predictive models alongside LVI, PNI, and tumor budding may enhance the ability to identify patients at

**Table III.** Association between categorical clinicopathological variables and lymph node metastasis status

| PARAMETERS                             | LNM NEGATIVE, <i>N</i> (%) | LNM POSITIVE, <i>N</i> (%) | <i>P</i> -VALUE |
|----------------------------------------|----------------------------|----------------------------|-----------------|
| Sex                                    |                            |                            |                 |
| Male                                   | 60 (63.8)                  | 45 (52.3)                  | 0.118           |
| Female                                 | 34 (36.2)                  | 41 (47.7)                  |                 |
| Tumor location                         |                            |                            |                 |
| Right colon                            | 35 (37.2)                  | 40 (46.5)                  | 0.207           |
| Left colon                             | 59 (62.8)                  | 46 (53.5)                  |                 |
| Tumor grade                            |                            |                            |                 |
| Low-grade                              | 87 (92.6)                  | 67 (77.9)                  | 0.005           |
| High-grade                             | 7 (7.4)                    | 19 (22.1)                  |                 |
| pT stage                               |                            |                            |                 |
| pT1–2                                  | 13 (13.8)                  | 2 (2.3)                    | 0.005           |
| pT3–4                                  | 81 (86.2)                  | 84 (97.7)                  |                 |
| Serosal involvement                    |                            |                            |                 |
| Absent                                 | 67 (71.3)                  | 23 (26.7)                  | < 0.001         |
| Present                                | 27 (28.7)                  | 63 (73.3)                  |                 |
| EMVI                                   |                            |                            |                 |
| Absent                                 | 86 (91.5)                  | 55 (64.0)                  | < 0.001         |
| Present                                | 8 (8.5)                    | 31 (36.0)                  |                 |
| IMVI                                   |                            |                            |                 |
| Absent                                 | 93 (98.9)                  | 80 (93.0)                  | 0.046*          |
| Present                                | 1 (1.1)                    | 6 (7.0)                    |                 |
| Any VI (EMVI and/or IMVI)              |                            |                            |                 |
| Absent                                 | 85 (90.4)                  | 53 (61.6)                  | < 0.001         |
| Present                                | 9 (9.6)                    | 33 (38.4)                  |                 |
| LVI                                    |                            |                            |                 |
| Absent                                 | 69 (73.4)                  | 20 (23.3)                  | < 0.001         |
| Present                                | 25 (26.6)                  | 66 (76.7)                  |                 |
| PNI                                    |                            |                            |                 |
| Absent                                 | 56 (59.6)                  | 19 (22.1)                  | < 0.001         |
| Present                                | 38 (40.4)                  | 67 (77.9)                  |                 |
| Tumor deposits                         |                            |                            |                 |
| Absent                                 | 89 (94.7)                  | 56 (65.1)                  | < 0.001         |
| Present                                | 5 (5.3)                    | 30 (34.9)                  |                 |
| Tumor budding                          |                            |                            |                 |
| Low                                    | 71 (75.5)                  | 41 (47.7)                  | < 0.001         |
| High                                   | 23 (24.5)                  | 45 (52.3)                  |                 |
| MMR status                             |                            |                            |                 |
| dMMR                                   | 13 (13.8)                  | 2 (2.3)                    | 0.005           |
| pMMR                                   | 81 (86.2)                  | 84 (97.7)                  |                 |
| Adequate LN dissection ( $\geq 12$ LN) |                            |                            |                 |
| No                                     | 10 (10.6)                  | 7 (8.1)                    | 0.574           |
| Yes                                    | 84 (89.4)                  | 79 (91.9)                  |                 |

dMMR – deficient mismatch repair, EMVI – extramural venous invasion, IMVI – intramural venous invasion, LN – lymph node, LNM – lymph node metastasis, LVI – lympho-vascular invasion, MMR – mismatch repair, pMMR – proficient mismatch repair, PNI – perineural invasion, VI – venous invasion

\* Fisher's exact test was used due to small expected counts.

**Table IV.** Univariate logistic regression analysis of factors associated with lymph node metastasis

| PARAMETERS                               | OR   | 95% CI     | P-VALUE |
|------------------------------------------|------|------------|---------|
| EMVI (present vs. absent)                | 6.06 | 2.60–14.14 | < 0.001 |
| IMVI (present vs. absent)                | 6.98 | 0.82–59.17 | 0.075   |
| Any VI (present vs. absent)              | 5.88 | 2.61–13.26 | < 0.001 |
| LVI (present vs. absent)                 | 9.11 | 4.62–17.94 | < 0.001 |
| PNI (present vs. absent)                 | 5.20 | 2.70–10.01 | < 0.001 |
| Tumor deposits (present vs. absent)      | 9.54 | 3.49–26.03 | < 0.001 |
| Tumor budding (high vs. low)             | 3.39 | 1.80–6.38  | < 0.001 |
| Serosal involvement (present vs. absent) | 6.80 | 3.54–13.07 | < 0.001 |
| pT stage (pT3–4 vs. pT1–2)               | 6.74 | 1.48–30.81 | 0.014   |
| Tumor location (right vs. left colon)    | 1.47 | 0.81–2.66  | 0.208   |
| Tumor grade (high-grade vs. low-grade)   | 3.53 | 1.40–8.87  | 0.007   |

EMVI – extramural venous invasion, IMVI – intramural venous invasion, LNM – lymph node metastasis, LVI – lymphovascular invasion, OR – odds ratio, PNI – perineural invasion, VI – venous invasion

**Table V.** Independent predictors of lymph node metastasis in multivariate logistic regression analysis

| PARAMETERS         | ADJUSTED OR | 95% CI     | P-VALUE |
|--------------------|-------------|------------|---------|
| LVI                | 6.49        | 3.12–13.53 | < 0.001 |
| PNI                | 3.35        | 1.57–7.14  | 0.002   |
| EMVI               | 2.72        | 1.02–7.29  | 0.046   |
| High tumor budding | 2.16        | 1.02–4.60  | 0.045   |

EMVI – extramural venous invasion, LNM – lymph node metastasis, LVI – lymphovascular invasion, OR – odds ratio, PNI – perineural invasion

Parameters entered into the model were LVI, PNI, EMVI, and high tumor budding. Model performance: Hosmer-Lemeshow test:  $p = 0.146$ , Nagelkerke  $R^2 = 0.442$ , overall classification accuracy: 80.0%.

high risk for nodal metastasis and may contribute to more individualized therapeutic decision-making.

The present study also has several methodological strengths. All cases were systematically reviewed by experienced gastrointestinal pathologists using standardized criteria, and venous invasion was confirmed with elastic staining in equivocal cases, minimizing the risk of misclassification. In addition, the relatively homogeneous cohort of colon adenocarcinoma cases and the use of comprehensive multivariate modeling allowed a more accurate assessment of the independent contribution of EMVI to nodal metastasis.

Several limitations should be acknowledged. First, the retrospective single-institution design may limit generalizability. Second, although all eligible cases during the study period were included, the relatively limited sample size may reduce the statistical power of subgroup analyses. Third, assessment of vascular invasion may be subject to interobserver variability, even when evaluated by experienced gastrointestinal pathologists. Finally, survival outcomes were not analyzed, preventing assessment of the prognostic impact of EMVI on long-term oncologic endpoints.

## Conclusions

Our study demonstrates that EMVI is an independent predictor of LNM in colon adenocarcinoma. Together with LVI, PNI, and tumor budding, EMVI represents a key histopathological marker of tumor aggressiveness that should be carefully evaluated and consistently reported in routine pathological practice. Given its independent predictive value for LNM, EMVI should be routinely reported in pathology practice and considered alongside established high-risk features such as LVI and PNI when making decisions regarding adjuvant therapy and risk stratification.

## Disclosures

1. Institutional review board statement: This study was approved by the Ethics Committee of Manisa Celal Bayar University Faculty of Medicine (approval decision no. 20.478.486/3927, dated 25.02.2026).
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5. Declaration of generative AI and AI-assisted technologies: During the preparation of this manuscript, the authors used ChatGPT (OpenAI) for language editing and stylistic refinement. After using this tool, the authors carefully reviewed and edited the content and take full responsibility for the integrity and accuracy of the work.

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