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Integrating E-cadherin expression levels with TNM staging for enhanced prognostic prediction in colorectal cancer patients

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Abstract

Purpose This study aimed to investigate the clinical significance of E-cadherin expression levels in colorectal cancer tissues and explore the relationship between E-cadherin expression and tumor node metastasis (TNM) stage. The goal was to establish a more accurate prognostic prediction for colorectal cancer patients by analyzing E-cadherin expression levels alongside TNM staging.

Methods The study examined colorectal cancer patients by dividing them into groups based on E-cadherin expression levels. It then assessed their 5-year event-free survival (EFS) and disease-specific survival (DSS) hazard ratios (HRs). Additionally, the prognosis of patients was analyzed by combining E-cadherin expression levels with TNM staging, particularly focusing on patients in stages III and IV.

Results The E-cadherin^{Low} group had significantly worse outcomes, with HRs of 2.30 for EFS and 2.76 for DSS compared to the E-cadherin^{High} group. When combined with TNM stage III/IV, patients with E-cadherin^{Low} expression showed a poor prognosis, with HRs of 1.93 for EFS and 2.35 for DSS compared to those with E-cadherin^{High} expression at the same TNM stage.

Conclusions Low levels of E-cadherin expression are associated with a poor prognosis and decreased survival in colorectal cancer patients. Combining E-cadherin expression levels with TNM staging provides a more precise prediction of patient prognosis and survival, potentially guiding personalized treatment strategies.

Keywords Colorectal cancer, E-cadherin, Prognosis, TNM staging

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Introduction

Colorectal cancer (CRC) is one of the most common malignant tumors in humans, causing significant mortality and burden [1]. Despite advances in treatment, the 5-year survival rate for CRC remains at approximately 60–70%, and for metastatic CRC, it drops drastically to around 14% [2]. These statistics highlight the urgent need to understand the mechanisms driving CRC progression and metastasis. One of the critical processes involved in cancer metastasis is the epithelial-mesenchymal transition (EMT), which allows epithelial cells to acquire mesenchymal properties, increasing their motility and invasiveness [3]. EMT is not only a key driver of metastasis but is also associated with resistance to conventional therapies, which further contributes to the poor prognosis of metastatic CRC [4]. Therefore, elucidating the molecular mechanisms underlying EMT in CRC could provide valuable insights into improving diagnosis, treatment strategies, and prognosis prediction.

E-cadherin (E-cad) is a cell–cell adhesion molecule that regulates tissue production, epithelial stabilization, and differentiation. In normal cells, E-cad expression plays an important role in tissue structure and maintenance. In contrast, in tumor cells, E-cad expression is reduced, causing epithelial conversion to a mesenchymal-like form [5, 6]. Downregulation of E-cad expression occurs in the first step of the invasion–metastasis cascade, allowing CRC cells to detach from one another and nearby normal or cancer cells. This eventually leads to the release of vascular endothelial growth factor (VEGF) and other proangiogenic factors, promoting the migration of CRC cells into the bloodstream [2].

Several *in vitro* and *in vivo* studies have verified that downregulation of E-cad expression is the first step in cancer metastasis and EMT, and accordingly, many mechanisms related to E-cad have been identified [7, 8]. However, only few studies have investigated the clinical significance of E-cad expression levels. Several studies have confirmed that reduced E-cad is correlated with various types of carcinomas, including CRC, breast cancer, sarcoma, and ovarian cancer [9–12]. Most studies that aimed to identify the underlying mechanisms and clinical significance of E-cad, especially in patient prognosis, simply confirmed the association of prognosis with E-cad expression [13, 14].

Previous studies have shown that decreased E-cad expression in CRC is associated with poor patient prognosis. However, it remains unclear whether combining E-cadherin expression levels with TNM (Tumor, Node, Metastasis) staging can effectively predict prognosis in clinical practice. TNM staging is widely used in oncology to stratify patients into prognostic groups, guiding treatment decisions and predicting outcomes [15, 16]. Clinically, it helps determine the severity of cancer and tailor

appropriate therapies. However, TNM has limitations in accounting for the biological diversity of tumors and the influence of emerging molecular factors. Despite these drawbacks, it remains a critical tool in cancer diagnosis and management. In light of these challenges, and considering the growing importance of clinically meaningful biomarkers in reverse translational research, we aimed to confirm the clinical significance of E-cad levels by evaluating it alongside TNM staging and survival rates, which are crucial in real-world clinical settings.

Methods

Patient population and clinical specimens

This study included 597 patients diagnosed with CRC at Gachon University Gil Medical Center between January 2009 and January 2013. Clinical specimens consisted of primary CRC tissues preserved in paraffin blocks after surgery. Patients with recurrent CRC, those with previous surgeries that altered the normal intestinal structure of the colon, those who had undergone chemotherapy or abdominal radiotherapy before CRC surgery, and those treated for other cancers were excluded. The study was approved by the Gachon University Gil Medical Center IRB (GBIRB2023-224).

Clinicopathologic factors

Clinicopathological analysis included variables such as age, sex, diabetes mellitus, smoking history, family history, anemia, white blood cell (WBC) count, carcinoembryonic antigen (CEA) level, tumor location, differentiation, and TNM stage. Smoking history was defined as either past or current smoking. Family history referred to the occurrence of CRC cases in first-degree relatives. Anemia was defined as a hemoglobin level of less than 13 g/dL for men and less than 12 g/dL for women. Abnormal WBC counts were characterized by either leukocytosis (more than 10,000 cells/L) or leukopenia (less than 4,000 cells/L). Abnormal CEA levels were identified as those exceeding 5 ng/mL.

CRC was classified into left-sided CRC (LCC) and right-sided CRC (RCC) based on the location of the primary tumor. LCC included tumors located at the splenic flexure and distal regions, including the rectum, while RCC encompassed tumors from the cecum to the ascending and transverse colons [17]. CRC tumors were further classified as either differentiated or undifferentiated. Differentiated tumors included well-differentiated (WD) and moderately differentiated (MD) tumors, while undifferentiated tumors comprised poorly differentiated (PD) tumors, tumors with signet ring cells, and mucinous carcinomas.

Tissue microarray and immunohistochemistry

We used tissue microarray (TMA) for clinical validation of patients with CRC using the method we have previously reported [18, 19]. Paraffin-embedded tumor blocks were sliced into 4- μ m-thick sections, stained using hematoxylin and eosin, and histopathologically observed. We selected tumor cores to capture the intrinsic characteristics of the tumor epithelium while ensuring stable and reproducible results across patients. Two tumor cores were marked in each corresponding tissue block. Cylindrical tissue samples with a diameter of 2 mm were extracted and transferred to a new pathology block using a TMA machine. Cylindrical tissue samples from 69 patients were inserted into a single pathology block to create a new TMA block. TMA slides were baked, deparaffinized, rehydrated, and recovered. To prevent non-specific staining, TMA slides were preincubated with 10% normal goat serum (#31872, Invitrogen, Danvers, MA, USA) for 30 min and then placed in a humidified container containing E-cad antibody (1:40

dilution, ab40772, Abcam, Cambridge, UK) and incubated overnight at 4 °C. A non-biotin horseradish peroxidase detection system (Leica Bond-III system, GmbH, Germany) was used to treat the tissue slides according to the manufacturer's instructions. E-cad protein expression scores ranged from 0 to 3; with 0 indicating faint and rare immunostaining, 1 indicating focal and weak staining, 2 indicating moderate and diffuse staining, and 3 indicating strong and diffuse staining (Fig. 1). In this study, two pathologists with over eight years of experience in tertiary hospitals conducted the expression scoring in a blinded manner. Each pathologist independently evaluated the staining results without prior knowledge of patient data. In cases where their scoring differed, a consensus was reached through mutual discussion, ensuring accuracy and consistency in the assessments. To simplify prognosis interpretation, patients with grade 0 (E-cad^{low}) were distinguished from those with grades 1–3 (E-cad^{high}). This classification reflects the biological significance of E-cadherin loss (grade 0), associated with EMT and

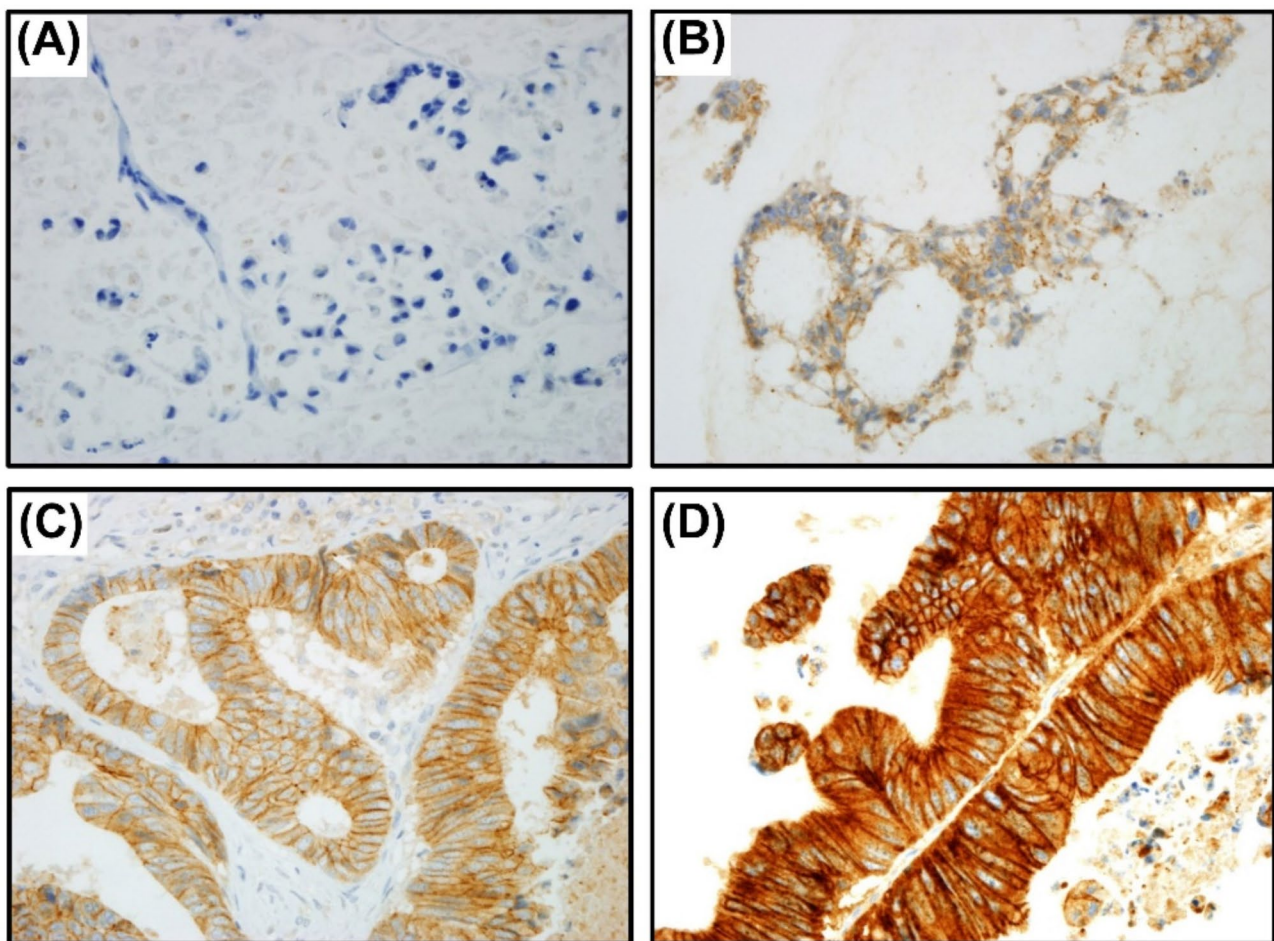


Fig. 1 Classification of E-cadherin expression scores according to intensity of immunohistochemical staining. (A) Score 0, faint and rare staining; (B) Score 1+, focal and weak staining; (C) Score 2+, moderate and diffuse staining; (D) Score 3+, strong and diffuse staining. Original magnification, 400 $\times$

aggressive tumor behavior, while partial retention (grades 1–3) suggests less invasiveness, enabling meaningful stratification of colorectal cancer prognosis.

Survival rate analysis

To confirm the clinical significance of E-cad, event-free survival (EFS) and disease-specific survival (DSS) were analyzed according to E-cad expression levels. EFS was defined as the time from surgery to the first event, which included cancer progression, recurrence, and CRC-related mortality. DSS was defined as the time from surgery to death due to CRC, excluding death from diseases other than CRC. Patients with CRC were classified into four groups for survival prediction based on TNM stage and E-cad expression; (1) Group 1: E-cad^{High} and TNM stages I/II, (2) Group 2: E-cad^{Low} and TNM stages I/II, (3) Group 3: E-cad^{High} and TNM stages III/IV, (4) Group 4: E-cad^{Low} and TNM stages III/IV. EFS and DSS were then analyzed according to E-cad expression levels and reflecting the TNM stage.

Table 1 Baseline characteristics

	Total (n = 597)
Age	64.4 ± 11.5
Sex	
Male	366 (61.3%)
Female	231 (38.7%)
Histology	
Size (mm)	52.5 ± 23.1
Laboratory findings	
Hemoglobin (g/dL)	12.2 ± 2.4
WBC (10 ³ /μL)	7.7 ± 3.0
CEA (ng/mL)	65.7 ± 356.2
Location	
Cecum	14 (2.3%)
Ascending colon	100 (16.8%)
Hepatic flexure	9 (1.5%)
Transverse colon	38 (6.4%)
Splenic flexure	5 (0.8%)
Descending colon	18 (3.0%)
Sigmoid descending	5 (0.8%)
Sigmoid colon	149 (25.0%)
Rectosigmoid colon	108 (18.1%)
Rectum	151 (25.3%)
Pathology	
WD	40 (6.7%)
MD	506 (84.8%)
PD	24 (4.0%)
Mucinous	25 (4.2%)
SRC	2 (0.3%)
TNM stage	
I	102 (17.1%)
II	217 (36.3%)
III	205 (34.3%)
IV	73 (12.2%)

Statistical analysis

Continuous variables are expressed as means ± standard deviation, whereas categorical variables are represented as absolute numbers and percentages. The chi-square test was used to determine the relationship between E-cad expression and clinical data. Survival curves were plotted using the Kaplan–Meier method with the log-rank test. Cox proportional hazards (CPH) regression was used for survival analysis. All survival analyses were performed using R version 4.0 and the survival and forest model packages. Statistical significance was set at $P < 0.05$ (two-tailed).

Results

Baseline characteristics

Table 1 shows the baseline characteristics of the study population. The mean age of the 597 patients was 64.4 ± 11.5 years; 366 patients (61.3%) were male; and the mean tumor size was 52.5 ± 23.1 mm. The mean hemoglobin, WBC, and CEA levels were 12.2 ± 2.4 g/dL, 7,661.1 ± 2,955.5/μL, and 65.7 ± 356.2 ng/mL, respectively. Common tumor locations included the rectum ($n = 151$, 25.3%), sigmoid colon ($n = 149$, 25.0%), and ascending colon ($n = 100$, 16.8%). The degree of differentiation of most tumors was MD, with 506 (84.8%) cases. When the patients were classified according to TNM stage, 102 (17.1%) were stage I, 217 (36.3%) were stage II, 205 (34.3%) were stage III, and 73 (12.2%) were stage IV.

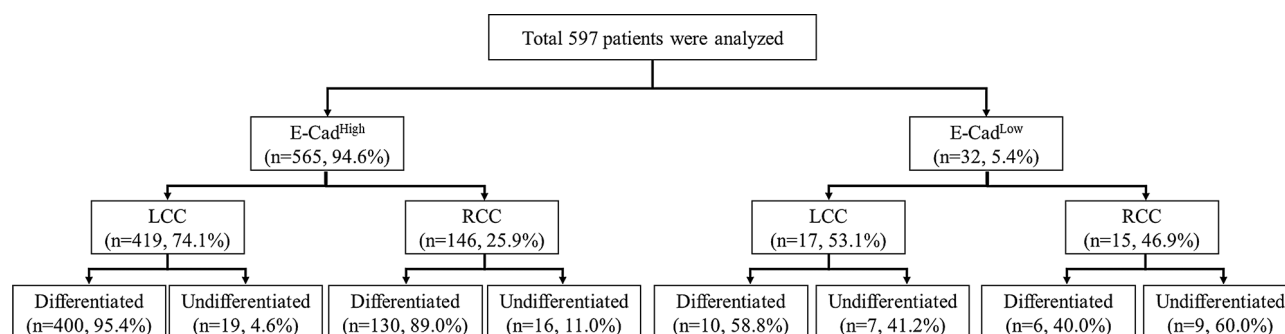
Differences in clinicopathological characteristics according to E-cad expression

Table 2 shows the clinicopathological differences according to E-cad expression levels. E-cad protein expression scores ranged from 0 to 3. We classified E-cad^{Low} and E-cad^{High} groups according to E-cad expression scores of 0–1 and 2–3, respectively. E-cad^{High} was identified in 565/597 (94.6%) patients. Univariate analysis revealed statistically significant differences in tumor location ($P = 0.009$) and differentiation status ($P = 0.001$) with respect to E-cad expression, but no statistically significant difference was found for age, gender, diabetes mellitus, smoking, family history of CRC, anemia, WBC count, CEA level, and TNM stage. According to the multivariate analysis, tumor location (OR: 0.396; 95% CI: 0.183–0.856; $P = 0.019$) and differentiation status (OR: 0.066; 95% CI: 0.032–0.143; $P = 0.019$) were identified as significant independent prognostic factors.

These significant variables, namely differentiation status and tumor location, were cross-analyzed to confirm the differences according to E-cad expression level. Among patients with high E-cad expression, 74.1% had LCC and 25.9% had RCC, while in patients with decreased E-cad expression, 53.1% had LCC and 46.9% had RCC. The ratios of differentiated and undifferentiated

Table 2 Correlation of clinicopathological characteristics with E-cadherin status

Variables	Univariate			Multivariate	
	Total (n = 597)	E-cadherin (n = 32), Low	E-cadherin (n = 565), High	P	OR (CI)
Age (y)				0.971	
<65	278 (46.6%)	15 (46.9%)	263 (46.9%)		1 (Reference)
≥65	319 (53.4%)	17 (53.1%)	302 (53.5%)		1.158 (0.539–2.488)
Sex				0.374	
Male	366 (61.3%)	22 (68.8%)	344 (60.9%)		1 (Reference)
Female	231 (38.7%)	10 (31.3%)	221 (39.1%)		1.789 (0.783–4.084)
Diabetes mellitus				0.146	
No	487 (81.6%)	23 (71.9%)	464 (82.1%)		1 (Reference)
Yes	110 (18.4%)	9 (28.1%)	101 (17.9%)		0.559 (0.245–1.296)
Smoking				0.788	
No	458 (76.6%)	26 (81.2%)	467 (82.7%)		1 (Reference)
Yes	104 (17.4%)	6 (18.8%)	98 (17.3%)		0.909 (0.365–2.268)
Family history				0.153	
No	571 (95.6%)	29 (90.6%)	542 (95.9%)		1 (Reference)
Yes	26 (4.4%)	3 (9.4%)	23 (4.1%)		0.416 (0.103–1.677)
Anemia				0.415	
No	303 (50.8%)	14 (43.8%)	289 (51.2%)		1 (Reference)
Yes	294 (49.2%)	18 (56.3%)	276 (48.8%)		0.987 (0.443–2.199)
WBC counts				0.328	
Normal	503 (84.3%)	25 (78.1%)	478 (84.6%)		1 (Reference)
Abnormal	94 (15.7%)	7 (21.9%)	87 (15.4%)		0.741 (0.301–1.828)
Serum CEA				0.244	
Normal	444 (74.4%)	21 (65.6%)	423 (74.9%)		1 (Reference)
Abnormal	153 (25.6%)	11 (34.4%)	142 (25.1%)		0.673 (0.305–1.489)
Tumor location				0.009	
LCC	436 (73.0%)	17 (53.1%)	419 (73.0%)		1 (Reference)
RCC	161 (27.0%)	15 (46.9%)	146 (25.8%)		0.396 (0.183–0.856)
Tumor differentiation status				0.001	
Differentiated	545 (91.3%)	16 (50.0%)	530 (93.8%)		1 (Reference)
Undifferentiated	52 (8.7%)	16 (50.0%)	35 (6.2%)		0.066 (0.032–0.143)
TNM stage				0.063	
I/II	319 (54.3%)	12 (37.5%)	307 (54.3%)		1 (Reference)
III/IV	278 (46.6%)	20 (62.5%)	278 (46.6%)		0.996 (0.684–1.451)

**Fig. 2** Flow chart of patient groups according to E-cadherin expression, tumor differentiation, and location

tumors in LCC with high E-cad expression were 95.4% and 4.6%, respectively. In contrast, these ratios were 58.8% and 41.2% in LCC tumors with low E-cad expression ($P < 0.001$). Similarly, the ratios of differentiated

and undifferentiated tumors in RCC with high E-cad expression was 89.0% and 11.0%, respectively, and 40.0% and 60.0%, respectively, in RCC tumors with low E-cad expression ($P < 0.001$) (Fig. 2).

Low E-cad expression is associated with poor prognosis

We performed a survival analysis using the Kaplan–Meier method to evaluate the association between E-cad expression and the 5-year EFS rate. The 5-year EFS rate was 51.6% for the E-cad^{Low} group and 72.9% for the E-cad^{High} group ($P=0.002$). The median 5-year EFS for the E-cad^{Low} group was 1,195.4 days, compared to 1,501.2 days for the E-cad^{High} group. Additionally, the hazard ratio (HR) for the E-cad^{Low} group was 2.3 (Cox proportional hazards (CPH) model adjusted for age and sex, 95% confidence interval [CI]: 1.35–3.92, $P=0.002$) when compared to the E-cad^{High} group (Fig. 3A and C).

In addition, the same analysis was performed to evaluate the association between E-cad expression levels and the 5-year DSS rate. The 5-year DSS rate was 51.6% for the E-cad^{Low} group and 76.6% for the E-cad^{High} group ($P=0.0001$). The median 5-year DSS for the E-cad^{Low} group was 1,214.9 days, compared to 1,565.7 days for the E-cad^{High} group. The HR for the 5-year DSS in the E-cad^{Low} group was 2.76 (CPH model adjusted for age and sex, 95% CI: 1.62–4.72, $P<0.001$) when compared to the E-cad^{High} group (Fig. 3B and D). Thus, analysis of the correlation between the E-Cad expression level and the

5-year EFS rate or DSS rate confirmed that patients with CRC had a poor prognosis when the E-Cad expression level was low.

Clinical significance of combined TNM staging and E-cad expression analysis in patients with CRC

To more accurately determine the clinical impact of E-cad expression on the prognosis of patients with CRC, we performed survival analysis by combining E-cad expression and TNM stage. We classified the patients into four subgroups based on E-cad expression and TNM stage: Group 1 (E-cad^{High} and TNM stages I/II, $n=307$), Group 2 (E-cad^{Low} and TNM stages I/II, $n=12$), Group 3 (E-cad^{High} and TNM stages III/IV, $n=258$), and Group 4 (E-cad^{Low} and TNM stages III/IV, $n=20$).

The HR of 5-year EFS was 2.30 (CPH model adjusted for age and sex, 95% CI: 0.71–7.44, $P=0.16$) in Group 2, compared with Group 1. The HRs for Groups 3 and 4, compared to Group 1, were 4.27 (95% CI: 2.98–6.12, $P<0.001$) and 8.13 (95% CI: 4.35–15.19, $P<0.001$), respectively, according to a CPH model adjusted for age and sex (Fig. 4A and C). In the DSS analysis, the HR of 5-year DSS was 2.85 (CPH model adjusted for age and

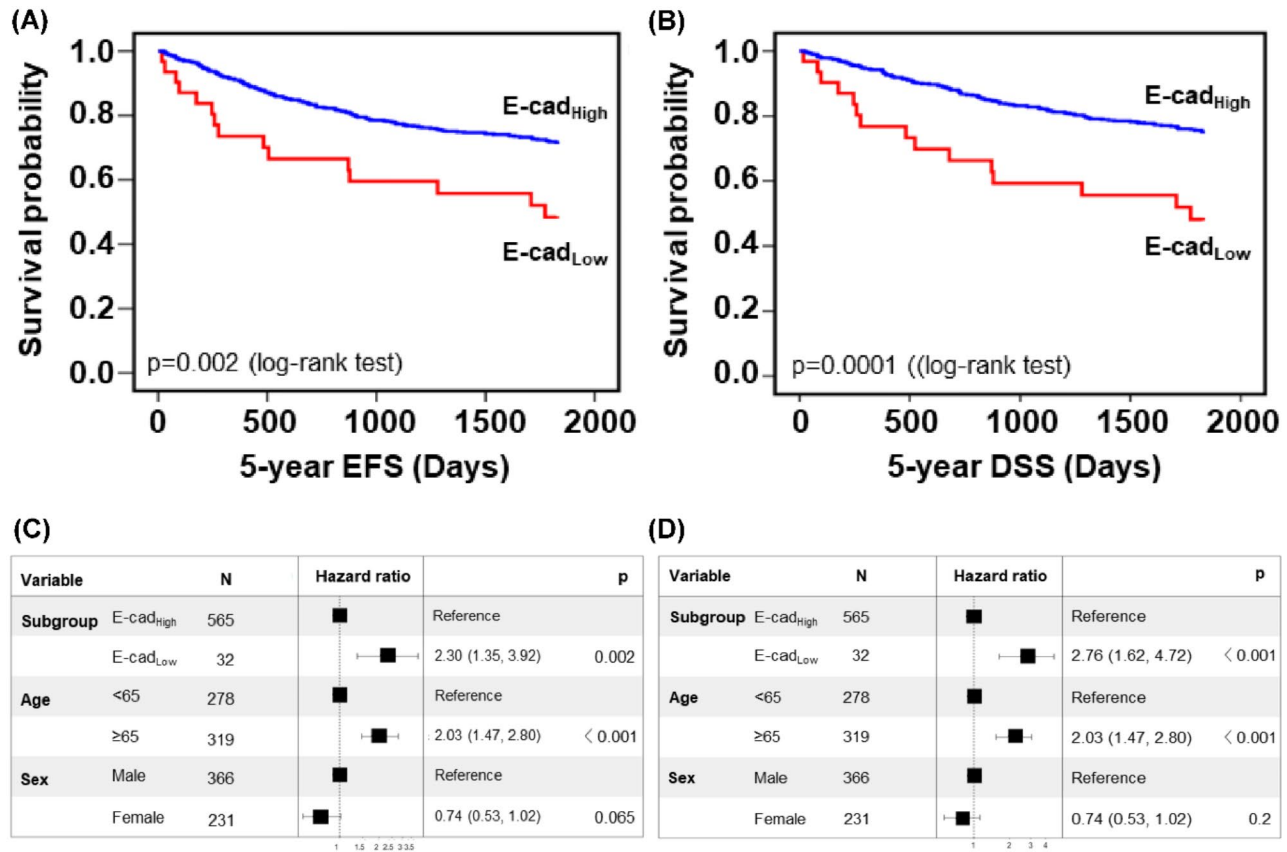
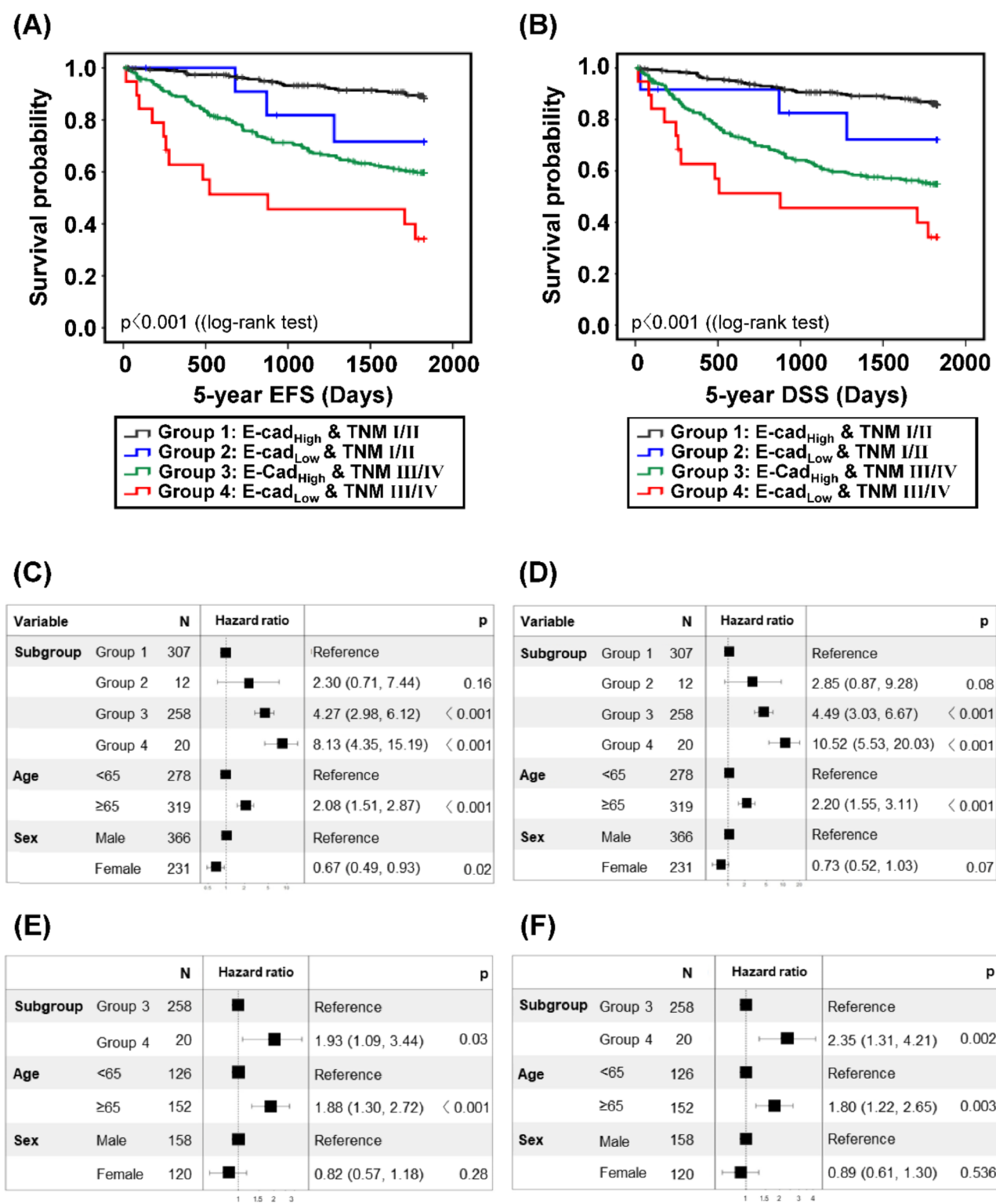


Fig. 3 Lower E-cadherin expression in colorectal cancer (CRC) is associated with poorer prognosis. Kaplan–Meier curves showing the 5-year event-free survival (EFS) (A and C) and disease-specific survival (DSS) (B and D) in patients with CRC according to E-cadherin expression



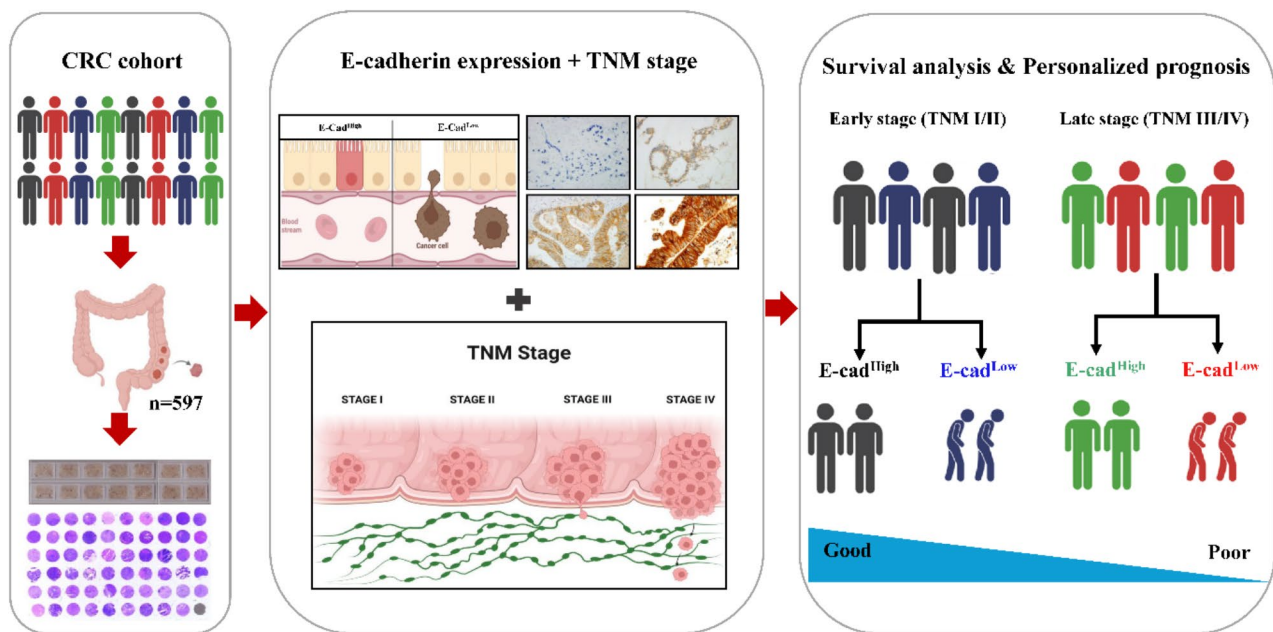


Fig. 5 Schematic representation of the development of personalized medicine by integrating E-cadherin expression and TNM staging

sex, 95% CI: 0.87–9.28, $P=0.08$) in Group 2, 4.49 (CPH model adjusted for age and sex, 95% CI: 3.03–6.67, $P<0.001$) in Group 3, and 10.52 (CPH model adjusted for age and sex, 95% CI: 5.53–20.03, $P<0.001$) in Group 4; all groups were compared to Group 1 (Fig. 4B and D).

To evaluate the HR based on E-cad expression in patients with the same TNM stage, we performed additional survival analyses on patients in Groups 3 and 4. The HRs for 5-year EFS and DSS in Group 4 compared to Group 3 were 1.93 (adjusted CPH model for age and sex, 95% CI: 1.09–3.44, $P=0.03$) and 2.35 (adjusted CPH model for age and sex, 95% CI: 1.31–4.21, $P=0.002$), respectively (Fig. 4E and F). These data indicate that low E-cad expression in patients with the same TNM stage is associated with poor prognosis.

The HRs for the 5-year EFS and DSS in Group 4 were 1.93 (CPH model adjusted for age and sex, 95% CI: 1.09–3.44, $P=0.03$) and 2.35 (CPH model adjusted for age and sex, 95% CI: 1.31–4.21, $P=0.002$), respectively, compared to Group 3. Among patients with advanced tumor stages, those with low E-cad expression exhibited significantly worse survival rates compared to those with high E-cad expression. This highlights the prognostic importance of E-cad even within the same TNM stages, as differences in its expression levels can further stratify survival outcomes. These findings reveal distinct prognostic subgroups that are not captured by TNM staging alone, underscoring the added value of incorporating E-cad expression into prognostic evaluations.

Discussion

We demonstrated that the E-cad protein expression level combined with TNM stage can improve prognosis prediction in patients with CRC, showing its clinical application. The data confirmed that patients in the E-cad^{Low} group had significantly lower rates of 5-year EFS and DSS compared to those in the E-cad^{High} group. Our results also showed a significant difference in patient prognosis depending on E-cad expression within the same TNM stage. Additionally, integrated analysis of E-cad expression in advanced TNM stages (III and IV) revealed that patients with low E-cad expression had significantly worse survival rates compared to those with high E-cad expression. These data indicate that E-cad expression plays a crucial role in survival outcomes in patients with advanced TNM stages of colorectal cancer, which indicates that E-cad expression may be used as a predictive tool for personalized prognosis (Fig. 5).

Our results showed that the proportion of LCC in the E-cad^{High} group was 74.1%, and the proportion of RCC was 25.9%. However, in the E-cad^{Low} group, the proportion of LCC was 53.1%, and that of RCC was 46.9%. According to previous reports, LCC tumors have a good prognosis, while RCC tumors have poor prognosis, which aligns with the increased proportion of RCC in the E-cad^{Low} group observed in this study [20]. In addition, the proportion of undifferentiated cancers increased in the E-cad^{Low} group compared to the E-cad^{High} group. This finding is also consistent with previous studies that reported a correlation between undifferentiated tumors and poor prognosis [21, 22]. We performed a

cross-analysis of the above two variables. In patients with decreased E-cad expression, the proportion of undifferentiated cancers increased compared to those in patients with high E-cad expression.

The poor prognosis of CRC associated with downregulation of E-cad expression may be linked to the Wnt/ β -catenin signaling pathway, a key regulator of cell pluripotency and differentiation [23]. Activation of Wnt signaling leads to accumulation of β -catenin, which translocates to the nucleus and inhibits E-cad expression, driving EMT and tumor progression [24]. Additionally, the Ras/Raf/MAPK and PI3K/AKT pathways, triggered by growth factors, increase the expression of transcriptional repressors such as Snail and ZEB1, further reducing E-cad levels [25, 26]. Therefore, the decrease in Wnt/ β -catenin signaling pathway due to decreased expression of E-cad aligns with the increased ratio of undifferentiated tumors in the E-cad^{Low} group.

Interestingly, the impact of E-cad downregulation appears to differ between LCC and RCC, as RCCs are often more aggressive and have a higher proportion of undifferentiated tumors, potentially influenced by these signaling pathways [27]. Furthermore, microsatellite instability high (MSI-H) tumors, particularly those that are undifferentiated, occur more frequently in RCC [28]. It has been reported that HOXB13 protein expression is elevated in RCC, which is negatively correlated with E-cad expression [29]. Thus, decreased E-cad expression may lead to upregulation of HOXB13 expression, and accordingly, the proportion of RCC in patients with CRC may increase. Therefore, the decrease in E-cad expression is in line with the increased ratio of undifferentiated tumors in CRC and increased ratio of RCC in the E-cad^{Low} group as it correlates with disrupted cell differentiation and preferential location of tumors to RCC.

We considered E-cad expression and TNM stage together to enable a more precise prognostic prediction. The TNM stage is a widely used diagnostic, treatment, and prognostic evaluation method in clinical use. However, it does not take into account important characteristics that affect prognosis [30]. Moreover, markers that can be used together have not yet been identified. Integrating E-cad expression in the prediction analysis showed a clear difference in EFS and DSS within the same TNM stage, highlighting its impact on survival outcomes. Notably, E-cad expression is closely related to the prognosis patients with advanced stage (TNM III/IV) CRC. This suggests the need for prognostic predictions based on both E-cad expression and TNM stage, especially in advanced TNM stages (TNM III/IV), emphasizing its importance in personalized patient management.

The results of this study were derived using tissue from patients with CRC. Although various studies are undertaken to discover biomarkers in CRC, their findings are

rarely translated into clinical use. Translating scientific discoveries from basic research to clinical trials is challenging due to genetic, molecular, and physiological differences [31]. However, in this study, we introduced a diagnostic method using tissue from patients with CRC and discovered biomarkers that can be applied to patients.

Tissue microarray (TMA) analysis, widely used in large-scale clinical studies for its efficiency and scalability, does have limitations due to its reliance on small, localized tissue samples. This approach may not fully capture the intratumoral heterogeneity often observed in advanced tumors, potentially leading to sampling bias and affecting the generalizability of findings. Nonetheless, our study demonstrates that E-cadherin expression, assessed through immunohistochemistry (IHC) on TMA samples, combined with TNM staging, provides a simple, cost-effective, and clinically practical method to predict the prognosis of patients with colorectal cancer (CRC). While this study is limited to samples from a single institution, the analysis of nearly 600 patients provides robust clinical validation. The combined analysis of E-cadherin expression and TNM staging shows great potential for diverse applications in precision and personalized medicine, offering a practical and scalable solution for prognosis prediction in clinical settings.

Conclusions

This study provides strong evidence that E-cad expression is a critical prognostic indicator for patients with CRC. Patients with low E-cad expression exhibited significantly lower 5-year EFS and 5-year DSS rates, particularly among those with advanced TNM stages. These findings suggest that evaluating E-cad expression could play a vital role in guiding personalized treatment strategies for patients with CRC. Incorporating E-cad expression levels into clinical practice may enhance the accuracy of prognosis prediction and improve treatment outcomes by allowing for more tailored therapeutic approaches.

Author contributions

J-G Lee and I Park contributed to the design of hypotheses, analysis of all experiments, and the writing of manuscript. H Lee and W-S Lee contributed to the production of TMA for tissue collection and tissue analysis. M Kang and J Kim presented pathological findings after tissue staining and contributed to the writing of the paper. H Lee and S Nam collected and analyzed patient data for survival rate analysis. M Kang and JHK contributed to the design of hypotheses, analysis of all experiments, the writing of manuscript and supervision of the study. All authors read and approved the final manuscript.

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Data availability

Data is provided within the manuscript or supplementary information files.

Declarations**Ethical approval**

All methods were carried out in accordance with relevant guidelines and regulations. Ethical approval for study was obtained from Institutional Review Board of Gachon University Gil Medical Center (GBIRB2023-224). Informed consent was obtained from all the participants.

Consent for publication

All participants involved in the study have provided written informed consent for the publication of anonymized data and findings derived from the research. The authors affirm that no identifiable personal information or sensitive data has been included in this publication.

Competing interests

The authors declare no competing interests.

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