RESEARCH ARTICLE

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EMMPRIN Correlated with β-CATENIN in Various t Stages of Colorectal Adenocarcinoma

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Abstract

Objective: Colorectal cancer is the third malignant tumor and the second cause of death in the world. There are several prognostic factors in colorectal adenocarcinoma, one of which is the TNM stage. The T stage is determined based on the depth of tumor invasion. Various proteins can be involved in the invasion process. EMMPRIN is expressed and functions on the surface of cancerous cells. as a mediator of tumor cell invasion. Increased β-Catenin accelerates the process of tumor cell proliferation, migration, and invasion. We aimed to analyze the correlation between EMMPRIN and β-Catenin expression in the T stages of colorectal adenocarcinoma. **Methods:** An observational analytic study was conducted using a cross-sectional approach on 47 paraffin blocks of colorectal adenocarcinoma at the Anatomic Pathology Laboratory of Dr. Soetomo Hospital Surabaya from January 2018 to December 2022. An immunohistochemical examination was performed using EMMPRIN and β-Catenin antibodies, and then the expression of both antibodies will be analyzed using statistical tests. **Result:** There was a significant correlation between the expression of β-Catenin with various T stages of colorectal adenocarcinoma (p-value 0.0201). There was a significant correlation between the expression of EMMPRIN and β-Catenin in various T-stages of colorectal adenocarcinoma (p-value: 0.0209). **Conclusion:** There is a positive correlation between EMMPRIN and β-Catenin expression and various T-stages of colorectal adenocarcinoma with weak strength. The existence of EMMPRIN and β-Catenin stimulates colorectal cancer cells to continue invasion.

Keywords: Colon cancer- colorectal adenocarcinoma- EMMPRIN- β-Catenin

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Introduction

Colorectal cancer is one of the most common malignancies worldwide. Colorectal cancer is the third malignant tumor and the second leading cause of death in the world. Globocan data in 2022 states that the incidence of colorectal cancer in Indonesia is around 8,7%, with 35,676 new cases per year, with the most common histopathologic being adenocarcinoma [1]. Colorectal cancer patients in Indonesia have previously been shown to be younger than colorectal cancer patients in developed countries. More than 30% of cases occur in individuals aged 40 years or younger, while only 2-8% of patients aged 50 years or younger occur in developed countries [2]. One of the prognostic factors of colorectal cancer is the T stage, which is determined by the depth of invasion of the cancer. Based on the T stage, colorectal adenocarcinoma is divided into T1, where the tumor invades the submucosa, T2 the tumor cell invades the muscularis propria, T3 invades the subserosa and T4 the tumor cell invades other organs or visceral peritoneum [3]. The eighth edition of the American Joint Committee on Cancer (AJCC) (2017) states that the depth of invasion determines the prognosis of the patient, and the deeper the invasion, the worse the prognosis [3]. The depth of invasion involves several proteins, one of which is extracellular matrix metalloproteinase protein (EMMPRIN) and β-Catenin.

EMMPRIN in colorectal cancer stimulates hyaluronan production by increasing hyaluronan synthase, thereby promoting colorectal tumor growth by disrupting the balance between apoptosis and proliferation [4]. CD147 activates MMP-2 and MMP-9 in colorectal adenocarcinoma to promote invasion and EMT [5] and β-Catenin phosphorylation through the destruction complex, which is made up of the kinases GSK-3β and casein kinase (CK1α), as well as the scaffolding proteins Axin and APC. β-Catenin phosphorylated by GSK-3β is targeted for proteasomal degradation [6], which plays a role by degrading the basement membrane. EMMPRIN expression causes loss of polarity in tumor cells, leading to susceptibility to apoptosis, and can degrade the β-Catenin complex on the membrane. In addition, EMMPRIN activates the Wnt pathway by inhibiting GSK-3β kinase, thus increasing the levels of phosphorylated β-Catenin in

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the cell nucleus [7].

This study aimed to analyze the correlation of EMMPRIN and β-Catenin expression with the T stage of colorectal adenocarcinoma. EMMPRIN and β-Catenin play a role in the invasion process.

Materials and Methods

Sample collection

The sample was taken by random sampling technique from a population that met the inclusion and exclusion criteria, which were obtained from the Lameshow formula:

$$n = \frac{Z\alpha^2 pq}{d^2}$$

The formula above obtained the minimum total number of samples needed in this study of 40, adding a correction factor of 15% to reduce the possibility of errors occurring in this study, so the number of samples needed in this study was 47 paraffin blocks, consisting of 1 paraffin block of T1 stage colorectal adenocarcinoma, 13 paraffin blocks of T2 stage colorectal adenocarcinoma. The number of samples needed in this study was 47 paraffin blocks, consisting of 1 paraffin block of colorectal adenocarcinoma stage T1, 13 paraffin blocks of colorectal adenocarcinoma stage T2, 24 paraffin blocks of colorectal adenocarcinoma stage T3, and 9 paraffin blocks of colorectal adenocarcinoma T4.

Immunohistochemistry

EMMPRIN and β-catenin expression was evaluated using the immunohistochemical method with a monoclonal antibody against EMMPRIN ((1.BB.218): sc-71038 dilute 1:250, Santa Cruz Biotechnology) and β-catenin ((E-5): sc-7963 (dilution 1:200, Santa Cruz Biotechnology, USA)). It was done according to the protocol specified by the manufacturer. β-catenin was positively expressed in the nucleus and cytoplasm. EMMPRIN was positively expressed in the cytoplasm of tumor cells. Scoring was done by two anatomical pathologists using Olympus CX31 binocular light microscope (Olympus Optical Co. Ltd, Japan) at 400X objective magnifications. H-scores from these two pathologists will be averaged into the final H-scores.

Scoring

EMMPRIN and β-catenin expression was quantified using the histochemical score (H-score). The H-score formula is stated below:

H-score=(0 x P0)+(1 x P1)+(2 x P2)+(3 x P3)

The H-score system was calculated based on the proportion and intensity of stained cells (H-Score = (% of cells weakly stained×1) + (% of cells moderately stained×2) + (% of cells strongly stained×3)). The H-score results were classified into four levels as follows: (1) 0: negative (0-50); (2) 1: weak (51-100) (3) 2: medium (101-200); (4) 3: strong (201-300) [8, 9].

Statistical analysis

All data obtained were statistically analyzed with the EZR program, where the correlation between EMMPRIN and β-Catenin in various T stages of colorectal adenocarcinoma was assessed using the Spearman correlation test. Statistical results are significant if the p-value is <0.05.

Results

Patient and tumor characteristics

This study used 47 surgical samples from adenocarcinoma colorectal patients and analyzed the correlation of EMMPRIN and β-Catenin expression with clinicopathologic data, including age, sex, and pathologic T stage. The characteristics of the samples' clinicopathology are shown in Table 1. Most all patients were female (55%). The patient's average age was 53.8 years, with the youngest being 25 and the oldest being 75. Most samples were in the T3 stage (51.06%), followed by the T2 stage (13.65%) (Figure 1, 2).

EMMPRIN Expression

The distribution of EMMPRIN expression in the T1 stage group was moderate positive expression. Seven (53.85%) samples of T2 stage group had a moderate positive expression, followed by strong and weak expression, each in 3 (23.07%) samples. T3 stage group had the highest frequency (58.33%) in moderate positive expression, followed by strong and weak positive expression, in 9 (37.50%) and 1 (4.16%) samples, respectively. EMMPRIN expression at stage T4 was highest in moderate positive expression of 5 (55.56%) samples (Table 2).

β-Catenin Expression

β-Catenin expression in the T1 stage group was moderate positive expression. The majority (76.92%) of

Table 1. Characteristic of Colorectal Adenocarcinoma Patients

Characteristic	Total N (%)
Sex	
Male	21 (45)
Female	26 (55)
Age	
20-30	3 (6.38)
31-40	5 (10.64)
41-50	8 (17.02)
51-60	16 (34.04)
61-70	11 (23.40)
>70	4 (8.51)
T Stage	
pT1	1 (2.12)
pT2	13 (27.65)
pT3	24 (51.06)
pT4	9 (19.14)

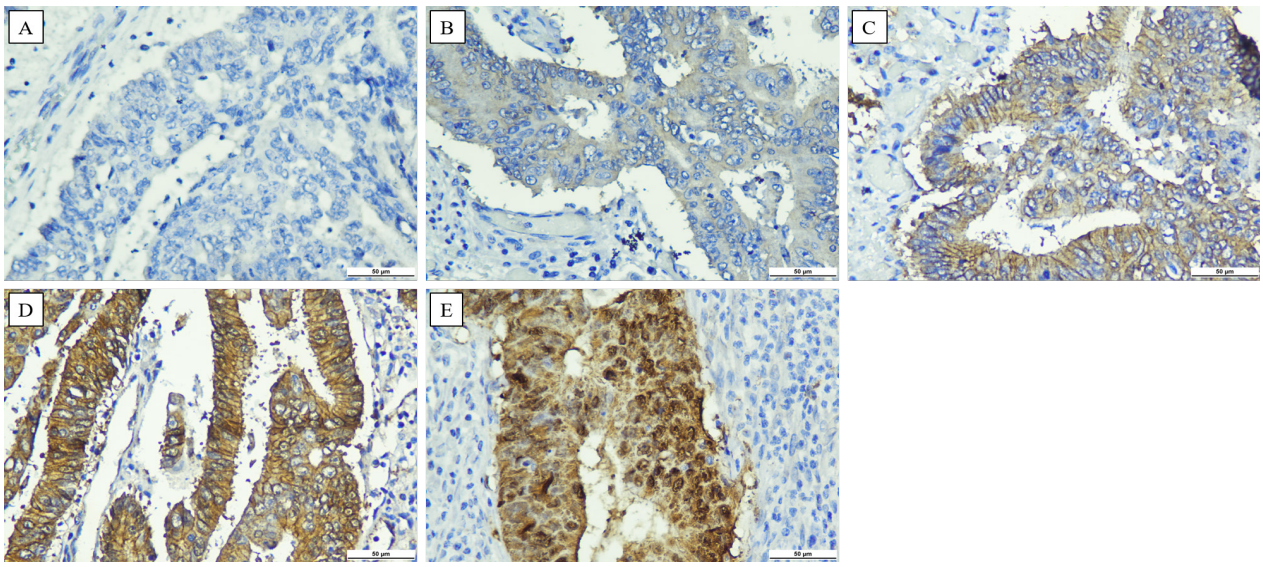

Figure 1. β-catenin Staining was Observed in Invasive Breast Carcinoma of no Special Type (IBC-NST) Tumor Cell's Nuclei (black arrow). (A) Negative staining. (B) Weakly positive staining. (C) Moderately positive staining. (D) Strongly positive staining. All figures were captured at 400x magnification. Scale bar: 50 µm.

Table 2. The EMMPRIN Expression in Various Stage of Colorectal Aenocarcinoma

T Stage of colorectal adenocarcinoma	Score 1	Percentage (%)	Score 2	Percentage	Score 3	Percentage (%)
T1	0	0	1	100	0	0
T2	3	23,07	7	53,85	3	23,07
T3	1	4,16	14	58,33	9	37,50
T4	1	11,11	5	55,56	3	33,33

the T2 stage group had a moderate β-Catenin expression, followed by a strong expression in 3 (23.07%) samples. β-Catenin expression at stage T3 group mainly was in moderate and strong positive expression, each accounting for 12 (50%) samples. Most (55.56%) of the T4 stage group had strong positive β-Catenin expression (Table 3).

Correlation between EMMPRIN and β-Catenin Expression

A Spearman correlation test was used to statistically examine the relationship between EMMPRIN and β-Catenin expression in different stages of colorectal adenocarcinoma. The analysis's findings revealed a strong association, with a Spearman correlation coefficient value of 0.317 and a p-value of 0.0209 ($p < 0.05$). This indicates

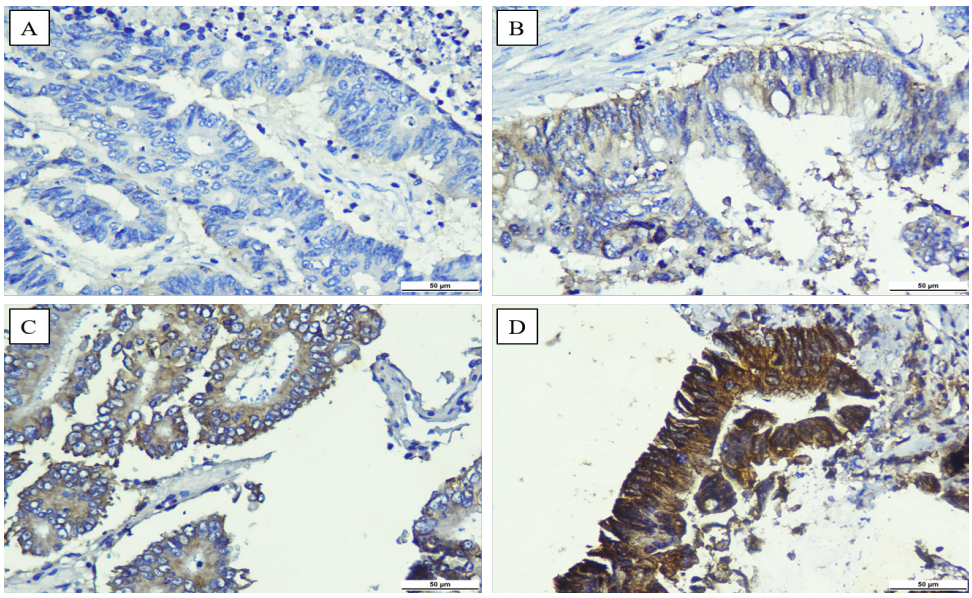

Figure 2. EMMPRIN Staining was Observed in Invasive Breast Carcinoma of no Special Type (IBC-NST) Tumor Cell's Nuclei (black arrow). (A) Negative staining. (B) Weakly positive staining. (C) Moderately positive staining. (D) Strongly positive staining. All figures were captured at 400x magnification. Scale bar: 50 µm.

Table 3. The β-Catenin Expression in Various Stage of Colorectal Adenocarcinoma

T stage of colorectal adenocarcinoma	Score 1	Percentage (%)	Score 2	Percentage (%)	Score 3	Percentage (%)
T1	0	0	1	100	0	0
T2	0	0	10	76,92	3	23,07
T3	0	0	12	50	12	50
T4	0	0	4	44,44	5	55,56

Table 4. Parameter and Value

Parameter	P value
Correlation EMMPRIN with T stage colorectal adenocarcinoma	0,297
Correlation β-Catenin with T stage colorectal adenocarcinoma	0.02
Correlation EMMPRIN and β-Catenin with T stage colorectal adenocarcinoma	0.02

that in colorectal adenocarcinomas of different T stages, the higher the expression of β-Catenin, the higher the expression of EMMPRIN (Table 4).

Discussion

The age group between 51 and 60 years old was the most common, occurring in 16 cases (34.04%), while the age group between 21 and 30 years old was the least common (6.38%), this is following another study which states that the incidence of colorectal adenocarcinoma occurs mostly at the age of over 50 years and the least age under 40 years. One of the factors causing the increase in incidence can be due to the sedentary lifestyle [10]. Increased visceral fat levels and dietary intake may be linked to this increased risk of colorectal adenocarcinoma. This is because visceral fat activates the hormonal component of total body fat that promotes the development of the disease by secreting proinflammatory cytokines that can cause inflammation in the colon and rectum, insulin resistance, and modulation of metabolic enzymes like lectin or adiponectin [11]. Higher levels of obesity, elevated plasma glucose, insulin resistance, and irregular intestinal peristalsis in sedentary adults can help to explain some of the lifestyle cardiovascular disease (CRC) risks [12]. Risk factors that can occur at the age of >50 years are one of the factors that cause colorectal carcinoma. The development of colorectal carcinogenesis is influenced by several factors, including elevated insulin concentration and insulin-like growth factor (IGF)-1 levels, hyperglycemia, and extended exposure of the colon mucosa to fecal bile acids due to constipation [13]. There is a slight female predominance in this study, about 55% of patients, which following previous studies by Jung Y and White et al. [14] that biological factors, such as elevated estradiol, which is positively correlated with the incidence of colorectal adenocarcinoma, as well as the presence of BRAF and KRAS mutations, can also raise the risk of colorectal adenocarcinoma, may be the cause of the high incidence of the disease in women [15]. Proto-oncogene KRAS is capable of causing carcinogenesis in a variety of cancer forms. KRAS gene mutations are present in around 35–40% of instances of colorectal cancer. This single nucleotide point mutation impacts codons 12, 13, and 61. This mutation manifests throughout the process of colon cancer carcinogenesis [16]. The incidence rate in women is higher due to gene-related BRAF mutations, N-ras, and high microsatellites instability (MSI) status, with women 8.8 times more likely to have methylation-positive cancer [17], and more on the right side of the colon [18]. Variations in the research sample characteristics could account for our study's findings and those of certain other studies. The distribution of patients based on pathologic T stages shows the most frequent T stage was pT3 (51.06%). A study by Deo et al. [8] had a similar result, in which the most frequent pathologic stages were at stages T2 and T3. This can be due to self-awareness of early detection and access to health.

EMMPRIN, which is upregulated by Tumor Associated Macrophage (TAM), which occurs at all stages of the tumor regardless of tumor invasion [9]. This study, consistent with Rahniayu et al. [19] stated that there were no differences in EMMPRIN expression in ovarian tumor types, which could be caused by different carcinogenesis processes.

EMMPRIN stimulates the secretion of MMP-1, MMP-3, and MMP-9 in cancer cells leading to basement membrane degradation, increasing tumor proliferation, invasion, and metastasis [20]. EMMPRIN overexpression correlates with decreased survival. Survival rates in colorectal adenocarcinoma are highly dependent on the level of metastasis and invasion, with less than 10% for metastases and higher than 80% for minimal invasion. The capacity of tumor cells to pass through the basement membrane and subepithelial connective tissue is closely associated with the risk of invasion and metastasis. However, it does not correlate with TNM stage [21]. EMMPRIN can be an independent prognostic factor of survival in colorectal adenocarcinoma where the mechanism of EMMPRIN stimulates MMPs to reduce extracellular matrix that can facilitate tumor cell invasion and metastasis [22]. Based on meta-analysis studies on various types of cancer, EMMPRIN is associated with tumor growth, invasion and angiogenesis in many malignant cancers such as breast cancer, liver cancer, colorectal cancer through regulation of MMP (Matrix metalloproteinase) and VEGF (vascular endothelial growth factor) expression [23].

The analysis showed no difference in β catenin at various T stage of colorectal adenocarcinoma, and the expression of β catenin expression correlated with various T stages of colorectal adenocarcinoma. Where this is following previous research conducted by Lee et al. [24] there is no difference in β catenin expression due to differences in molecular and biological factors. This study is in line with the research of Gao et al. [25] who reported that β-Catenin expression in the nucleus of tumor cells significantly correlates with TNM stage, metastasis in lymph nodes, and histological differentiation. The canonical pathway can cause this is activated after the binding of the Wnt ligand secreted to Frizzle receptor and LRP coreceptor, which CK1α and GSK-3β then phosphorylate by recruiting Disheveled protein (Dvl) to inactivate the destruction complex, resulting in accumulated β-Catenin that moves into the nucleus [26]. β-Catenin creates an active complex in the nucleus with the proteins TCF (T cell factor) and lymphoid enhancer-binding factor (LEF). Causing changes in several cellular processes, β-Catenin is phosphorylated by GSK-3β targeted for proteasomal degradation. β-Catenin is induced and transferred to the nucleus by extracellular Wnt ligands binding to membrane receptors, which activates the canonical pathway and promotes the activation of genes involved in cell proliferation [7, 10, 12, 13, 16-18, 21, 24-38].

Increased expression of β-Catenin in the nucleus and E cadherin is associated with tumor progression, tumor cell invasion, and worse prognosis [28]. In particular, the Wnt pathway also activates epithelial-mesenchymal transition (EMT), increasing invasion and metastasis of cell malignancies20. β-Catenin expression in the nucleus of tumor cells significantly correlates with TNM stage, metastasis in lymph nodes, and histological features of differentiation [25]. There is a correlation between increased β-Catenin expression tumor size, and tumor metastasis, proving that activation of the β-Catenin pathway promotes tumor cell proliferation, invasion and migration through different mechanisms such as Long noncoding RNAs regulation and interaction with histone demethylase [30].

The analysis showed a significant correlation between the expression of EMMPRIN and β-Catenin in the T stage of colorectal adenocarcinoma. This study is in line with Sidhu et al research on lung organs getting significant results between EMMPRIN and β catenin expression [39]. Research conducted by Hasaneen et al. [40] also said overexpression of EMMPRIN can increase proliferation, migration, and differentiation associated with activation of Wnt / β catenin signaling pathway. EMMPRIN regulates adhesion with ECM through the adhesion pathway. Overexpression of EMMPRIN causes loss of polarity of tumor cells that interact with proteins that function as apoptosis, thus inhibiting the protein complex formed with E cadherin. Inhibition of this complex cleaves E cadherin and β catenin at the cell membrane, activating the β catenin pathway and increasing β catenin levels in tumor cell nuclei [7]

Overexpression of EMMPRIN can increase proliferation, migration, and differentiation associated with signaling via the Wnt/β catenin pathway being activated. In epithelial-mesenchymal transition (EMT), signaling induced by EMMPRIN and the Wnt/β catenin pathway are undoubtedly intricately linked [31]. EMMPRIN will activate the Wnt pathway through the downregulation of E-cadherin to encourage invasion and metastasis, affecting the T stage [32]. Wu et al stated that EMMPRIN plays an EMT role by activating MMPs activated by β catenin in the cell nucleus [33]. Fang et al. [41] mentioned that the role of EMMPRIN depends on the Wnt / β catenin signaling pathway by inhibiting the phosphorylation of GSK-3β so that it will result in the upregulation of β catenin in the cell nucleus, which activates snail associated with EMT [41].

Author Contribution Statement

All authors contributed to the conception and design of the study. Rista Widhi Nugrahani was responsible for data collection, analysis, interpretation, and manuscript writing. Alphania Rahniayu and Gondo mastutik developed the concept and critically revised the manuscript for important intellectual content, reviewed the text and manuscript writing, and approved the final version. All authors read and approved the final manuscript.

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Ethical Declaration

Protocol used in this study has been ethically approved by the Health Research Ethics Committee in this institutions (NO.1047/KEPK/VII/2024).

Conflict of Interest

All of the authors declare no conflict of interest.

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