RESEARCH ARTICLE

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The Role of Fibroblast Growth Factor Receptor 2 as A Prognostic Biomarker in Colorectal Adenocarcinoma

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Abstract

Objective: This study aimed to analyze the correlation between fibroblast growth factor receptor 2 (FGFR2) expression with the histopathological grade, tumor budding grade, lymphovascular invasion, and lymph node metastasis in colorectal adenocarcinoma. **Methods:** This study used a cross-sectional design. Immunohistochemistry was performed on one hundred slides from paraffin-embedded blocks of colorectal adenocarcinoma using *FGFR2* rabbit polyclonal antibody (E-AB-60590, Elabscience). *FGFR2* expression was then assessed using an Olympus CX43 light microscope. Correlations between *FGFR2* expression and histopathological grade, tumor budding grade, lymphovascular invasion, and lymph node metastasis of colorectal adenocarcinoma were statistically analyzed using Chi-square, Mann Whitney, and Kruskal Wallis tests with SPSS 27. **Result:** Of the 100 samples analyzed, high-grade tumor budding was the most common (n=56), of which 25% showed weak expression and 75% showed strong expression. In the positive lymphovascular invasion group (n=28), 89.3% showed strong expression, and 10.7% showed weak expression. In the positive lymph node metastasis group (n=32), 87.5% showed strong expression, and 12.5% showed weak expression. Based on the Chi-square test, *FGFR2* expression was significantly correlated with the tumor budding grade ($p = 0.017$), lymphovascular invasion ($p=0.003$), and lymph node metastasis ($p = 0.003$). Still, there was no significant correlation with histopathological grade ($p = 0.127$) of colorectal adenocarcinoma. **Conclusion:** *FGFR2* expression may be an important prognostic biomarker in colorectal adenocarcinoma.

Keywords: Colorectal adenocarcinoma- *FGFR2*- histopathological grade- tumor budding

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Introduction

Colorectal cancer is a serious health problem because, according to GLOBOCAN data in 2022, colorectal cancer ranks third for new cases of cancer (9.6% of the total 19,964,811 instances), while based on cancer mortality, colorectal cancer ranks second (9.3% of the total 9,736,779 cases) [1, 2]. In developed countries, the incidence rate is decreasing, mainly due to the widespread use of colonoscopy screening [3]. However, the prevalence of colorectal cancer is increasing in younger people [3, 4]. It can be attributed to several factors, including genetic predisposition, dietary habits, lifestyle factors (such as a lack of exercise and insufficient intake of fiber), being overweight or obese, the presence of chronic gut infections, and others. Another factor believed to contribute to this phenomenon is the disruption of the gut microbiota [4]. In Indonesia, GLOBOCAN reported 35,676 new cases of colorectal cancer in 2022, or about 8.7 % of the total 408,661 cases. This increased from the number of new cases in 2020, 33,427 new cases or about 8.4% of the total 396,914 cases [1].

The majority of colorectal malignancies are adenocarcinomas, which are malignant tumours of the colonic epithelium with glandular and mucinous differentiation [5, 6]. Histopathologically, there are several essential features to be considered in reporting colorectal adenocarcinoma, including histopathological grade, which assesses the degree of tumor cell differentiation, tumor budding, which is associated with tumor aggressiveness, tumor-infiltrating lymphocytes (TILs), which indicate the host immune response against cancer, lymphovascular invasion, perineural invasion, and lymph node metastasis, all of which affect patient prognosis [6 ,7]. Despite well-developed therapeutic options, colorectal cancer remains one of the leading causes of cancer mortality due to high recurrence rates, resistance to chemotherapy, invasion, and metastasis. This requires continued research and innovation [8, 9]. Predicting the outcome of colorectal cancer involves consideration of several prognostic

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factors, including histopathological grade, tumor budding grade, resection margin status, depth of invasion, lymphovascular invasion, and lymph node metastasis [10, 11].

Fibroblast growth factor receptors (*FGFRs*) are receptor tyrosine kinases that can be activated by signals from outside of the cell. These receptors are found on the cell membrane [12]. There are five types of *FGFR,* namely *FGFR1, FGFR2, FGFR3, FGFR4,* and *FGFR5/FGFRL1*, which has the unique feature of not having a kinase domain like other receptors [13–15]. Fibroblast growth factors (FGFs) are natural ligands for FGFRs [12, 13]. Members of the FGFR family have different ligand affinities and tissue expression patterns [13, 15]. The FGFR/FGF signaling pathway is essential for various physiological processes [13]. The pathway plays a role in embryonic development, wound healing, angiogenesis, tissue regeneration, proliferation, and cell differentiation. Numerous studies have shown that this mechanism also plays a vital role in oncogenesis [15, 16]. Several conditions can lead to the deregulation of the FGFR/FGF signaling pathway, including FGF overproduction, FGFR gene amplification, chromosomal translocation, FGFR mutation, FGFR rearrangement/fusion, and Germline Single-Nucleotide Polymorphisms [13, 14].

The binding between *FGFR2* and FGF activates *FGFR2*. Subsequent receptor activation initiates a cascade of signaling pathways, including the RAS/MAPK, the ERK/AKT, the PLCγ, and the JAK-STAT signaling pathway [13, 14]. These pathways regulate several cellular processes, including proliferation, differentiation, survival, migration, and angiogenesis [13, 14]. *FGFR2* overexpression is associated with a worse prognosis in colorectal adenocarcinoma patients [17].

This study aimed to ascertain whether *FGFR2* can be a prognostic biomarker for colorectal adenocarcinoma. Research on *FGFR2* associated with colorectal adenocarcinoma has not been widely conducted. The results of this study are expected to contribute to the development of oncology science, especially regarding colorectal cancer.

Materials and Methods

This cross-sectional study was performed from January to July 2024 at the Anatomical Pathology Laboratory, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia. From January 2021 to May 2024, it analyzed one hundred paraffin block samples from patients diagnosed with colorectal adenocarcinoma at the Anatomical Pathology Laboratory of Wahidin Sudirohusodo General Hospital, Hasanuddin University Hospital, and Makassar Pathology Diagnostic Centre.

FGFR2 expression was assessed by immunohistochemistry (IHC) examination using *FGFR2* rabbit polyclonal antibody at a dilution of 1:200 (E-AB-60590, Elabscience). Slides for immunohistochemistry examination were prepared from paraffin blocks, which were cut to a thickness of 3 µm and then deparaffinized. After deparaffinisation, slides were stained with *FGFR2* rabbit polyclonal antibody. Reactivity to *FGFR2* antibody can be observed in the membrane and cytoplasm of tumor cells and investigated using a light microscope at 400x magnification. The evaluation was performed by two pathologists who were not privy to the information and clinical outcomes of the patient.

FGFR2 expression was measured semiquantitatively and was obtained by multiplying the intensity and proportion scores, resulting in a total immunostaining score (TIS) on a scale of 1 to 12. The intensity score is divided into the following categories: 0/negative (not stained), +1 (weakly and faintly stained), +2 (moderately stained), and +3 (strongly stained). The proportion score is divided into the following categories: 0 (stained 0-5%), 1 (stained 6-25%), 2 (stained 26-50%), 3 (stained 51-75%), and 4 (stained 76-100%) [18]. *FGFR2* expression was classified as weak if TIS <6 and strong if TIS ≥6.

The statistical analysis was conducted using SPSS 27 software. The data were presented univariately, in the form of frequencies and distribution tables of clinicopathological characteristics of samples, and bivariate to analyze the association of *FGFR2* expression with clinicopathological parameters. The Chi-square, Mann-Whitney, and Kruskal Wallis tests were used to analyze the data, with a p-value < 0.05, indicating a statistically significant result.

Results

Characteristics of The Colorectal Adenocarcinoma Samples

Table 1 presents the characteristics of the colorectal adenocarcinoma samples in our study based on clinicopathological data, including age, sex, tumor location, histopathological grade, tumor budding grade, lymphovascular invasion, lymph node metastasis, and *FGFR2* expression.

A total of one hundred (100) samples were examined, and the highest prevalence of colorectal adenocarcinoma was observed in the ≥ 50 years age group (72%), with a higher incidence among males (55%) compared to females. About the location of the tumor, colorectal adenocarcinoma was most frequently identified in the distal colon (37%), followed by the rectum (31%) and the proximal colon (25%). Low-grade colorectal adenocarcinoma was more prevalent (82%) than high-grade colorectal adenocarcinoma (18%). In the context of tumor budding, high-grade tumor budding was the most predominant (56%), followed by intermediate (32%) and low-grade tumor budding (12%). The group with positive lymphovascular invasion constituted 28% of the total, while samples with negative lymphovascular invasion accounted for 72%. The group with positive lymph node metastasis was 32%, while samples without were 68%. Based on the depth of invasion, pT2 (55%) was found to be the most prevalent, indicating that tumor cells have reached the muscularis propria layer of the colon, followed by pT3 (41%) and pT1 (4%). For *FGFR2* expression, 35% of samples exhibited weak expression, while 65% demonstrated strong expression.

The intensity of *FGFR2* immunohistochemistry staining can be observed in the membrane and cytoplasm

Table 1. Clinicopathology Characteristics of The Colorectal Adenocarcinoma Samples

Characteristics	n (%)
Age (years)	
<50	28 (28)
≥ 50	72 (72)
Mean ± SD= 54,89 ± 10,71	
Sex	
Male	55 (55)
Female	45 (45)
Tumor Location	
Proximal	25 (25)
Distal	37 (37)
Rectum	31 (31)
Rectosigmoid	7 (7)
Histopathological Grade	
Low	82 (82)
High	18 (18)
Tumor Budding Grade	
Low	12 (12)
Intermediate	32 (32)
High	56 (56)
Lymphovascular Invasion	
Positive	28 (28)
Negative	72 (72)
Lymph Nodes Metastasis	
Positive	32 (32)
Negative	68 (68)
Depth of Invasion (pT)	
pTis	0 (0)
pT1	4 (4)
pT2	55 (55)
pT3	41 (41)
pT4	0 (0)
FGFR2 Expression	
Weak	35 (35)
Strong	65 (65)
Total	100

of tumor cells to varying degrees. Figure 1 below shows the expression of *FGFR2* for each intensity score.

The Relationship between FGFR2 Expression and Histopathological Grade, Tumor Budding Grade, Lymphovascular Invasion, Lymph Node Metastasis and Others Clinicopathological Characteristics

Table 2 illustrates that based on histopathological grade, within the low-grade group (n=82), 32 samples (39.1%) exhibited weak expression, while 50 samples (60.9%) showed strong expression. In the high-grade group (n=18 samples), three samples (16.7%) exhibited weak expression, while 15 samples (83.3%) demonstrated strong expression. In the low-grade tumor budding category (n=12), eight samples (66.7%) exhibited weak expression, while four samples (33.3%) demonstrated strong expression. In the case of intermediate-grade tumor budding (n=32), 13 samples (40.7%) exhibited weak expression, while 19 samples (59.3%) displayed strong expression. In high-grade tumor budding (n=56), 14 samples (25.0%) demonstrated weak expression, while 42 samples (75.0%) exhibited strong expression. Regarding lymphovascular invasion, in the positive lymphovascular invasion group (n=28), three samples (10.7%) exhibited weak expression, while 25 samples (89.3%) exhibited strong expression. In the negative lymphovascular invasion group (n=72), 32 samples (44.4 %) showed weak expression, and 40 samples (55.6%) exhibited strong expression. In the group of positive lymph node metastasis (n=32), four samples (12.5%) exhibited weak expression, while 28 samples (87.5%) demonstrated strong expression. In the group of negative lymph node metastasis (n=68), 31 samples (45.6%) showed weak expression, while 37 samples (54.4%) showed strong expression.

A Chi-square test revealed a statistically significant relationship between *FGFR2* expression and several variables in colorectal adenocarcinoma. These variables included tumor budding grade (p=0.017), lymphovascular invasion (p=0.003), and lymph node metastasis (p=0.003). However, there was no significant association between *FGFR2* expression and histopathological grade of colorectal adenocarcinoma (p=0.127).

Discussion

The fibroblast growth factor receptor (FGFR) family plays a pivotal role in many essential physiological processes, including embryonic development, regeneration, adult response to trauma, and tissue repair [19]. Additionally, this family is a key driver in the formation and progression of various cancers, particularly colorectal cancer [19]. The oncogenic mechanisms associated with FGFR can be attributed to several factors, including cell growth and survival triggered by mutation or activation of drivers, formation of new blood vessels (neo-angiogenesis), and acquired resistance that develops from other cancer therapies [13].

This study examined the relationship between *FGFR2* and histopathological grade, tumor budding grade, lymphovascular invasion, and lymph node metastasis in colorectal adenocarcinoma. Based on histopathological grade, our study statistically showed no significant correlation between *FGFR2* expression and histopathological grade (Table 2). This result is consistent with Li P et al. [20] research, where there was no significant association between *FGFR2* expression with histopathological grade and with other clinicopathological factors, including age, gender, and depth of invasion in colorectal cancer. Research conducted by Hu M et al. [18] also showed the same results, where there was no significant relationship between *FGFR2* expression and histopathological grading/degree of differentiation in laryngeal squamous cell carcinoma.

We also examined the correlation between *FGFR2* expression and tumor budding grade, lymphovascular

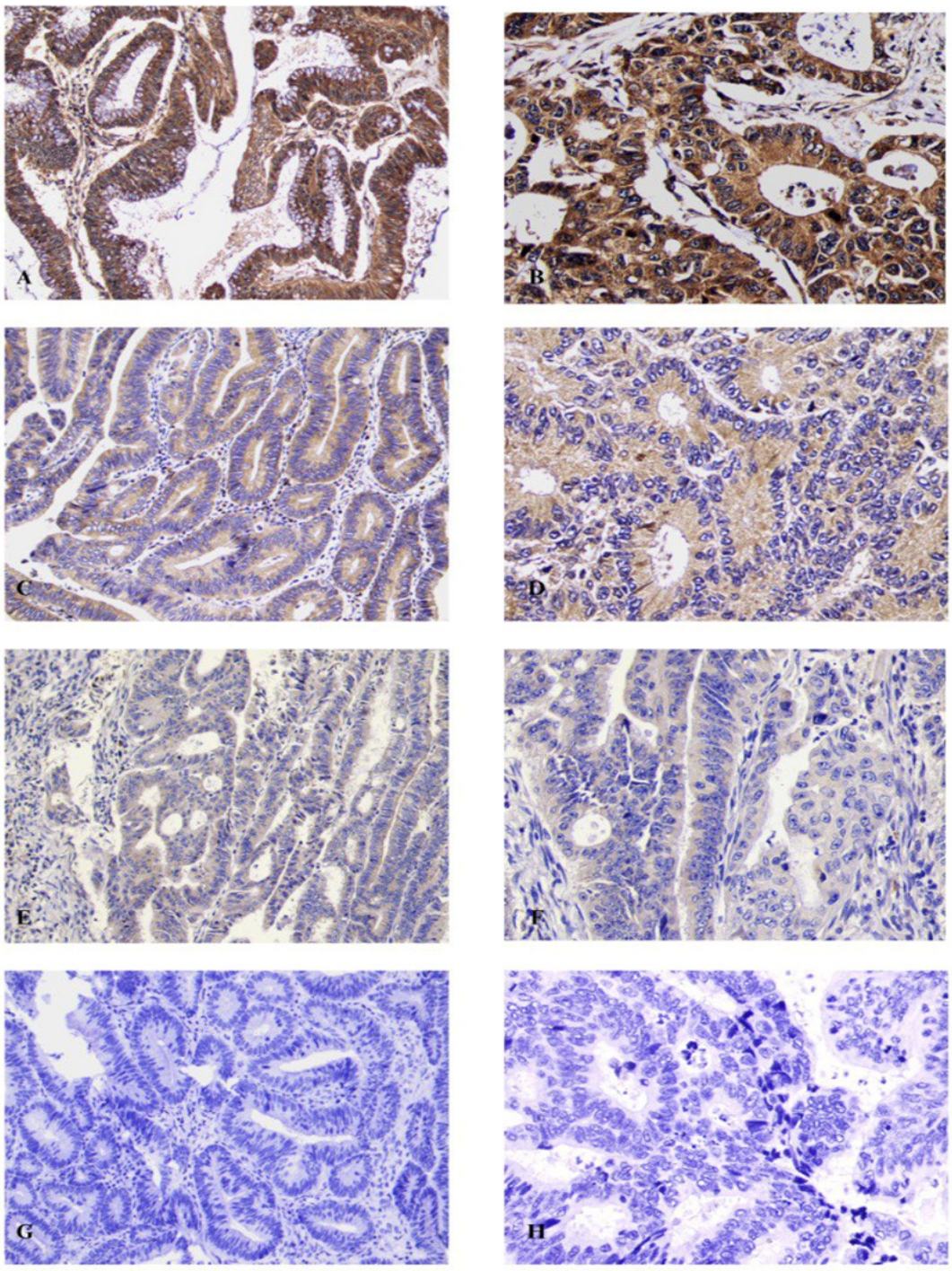

Figure 1. *FGFR2* Intensity in Colorectal Adenocarcinoma. A-B: Strong (+3); C-D: Moderate (+2); E-F: Weak (+1); G-H: Negative (0). (IHC, 200x and 400x Magnification)

invasion, and lymph node metastasis (Table 2). These data show that *FGFR2* expression is higher in colorectal adenocarcinoma with high-grade tumor budding than low and intermediate-grade tumor budding. Statistically, there is a significant correlation between *FGFR2* expression and tumor budding grade. The binding between FGFR and FGF will activate the RAS-MAPK and *PI3K-Akt* signaling pathways [13, 15]. Activation of this signaling pathway will cause the induction of epithelial-to-mesenchymal transition (EMT) transcription factors, namely Snail, Twist, and Zeb, which will subsequently trigger the epithelial-to-mesenchymal transition process [21]. EMT is characterized by decreased expression of *E-cadherin*, claudin, and occludin and increased expression of vimentin and N-cadherin [22].

Epithelial cells bind to each other through cell junctions. These include adherens junctions, gap junctions, desmosomes, and tight junctions. Epithelial cells also bind to the basement membrane through hemidesmosome junctions. The presence of these junctions allows for apicobasal polarity in epithelial cells. EMT makes epithelial cells lose their apicobasal polarity, causing the intercellular junction to weaken and eventually detach. EMT also facilitates remodeling of the cytoskeleton,

Table 2. Relationship of *FGFR2* Expression with Histopathological Grade, Tumor Budding Grade, Lymphovascular Invasion, Lymph Node Metastasis and Others Clinicopathological Characteristic of Colorectal Adenocarcinoma Samples

Characteristics	(n)	*FGFR2* Expression		p Value[a]	*FGFR2* Total Immunostaining (TIS)	p Value
		Weak n (%)	Strong n (%)		(Mean ± SD)	
Age (yrs)						
<50	28	10 (35.7)	18 (64.3)	1.000	5.89 ± 2.23	0.753[b]
≥ 50	72	25 (34.7)	47 (65.3)		5.78±2.16	
Sex						
Male	55	21 (38.2)	34 (61.8)	0.598	5.6±2.07	0.332[b]
Female	45	14 (31.1)	31 (68.9)		6.06±2.28	
Tumor Location						
Proximal	25	8 (32.0)	17 (68.0)	0.804	6.12±2.17	0.638[c]
Distal	37	12 (32.4)	25 (67.6)		5.97±2.36	
Rectum	31	13 (41.9)	18 (58.1)		5.42±1.96	
Rectosigmoid	7	2 (28.6)	5 (71.4)		5.57±2.15	
Histopathological Grade						
Low	82	32 (39.1)	50 (60.9)	0.127	5.68±2.23	0.158[b]
High	18	3 (16.7)	15 (83.3)		6.39±1.79	
Tumor Budding Grade						
Low	12	8 (66.7)	4 (33.3)	0.017*	5.00±2.66	0.069[c]
Intermediate	32	13 (40.7)	19 (59.3)		5.50±2.09	
High	56	14 (25.0)	42 (75.0)		6.16±2.06	
Lymphovascular Invasion						
Positive	28	3 (10.7)	25 (89.3)	0.003*	6.29±1.67	0.070[b]
Negative	72	32 (44.4)	40 (55.6)		5.63±2.32	
Lymph Node Metastasis						
Positive	32	4 (12.5)	28 (87.5)	0.003*	6.28±1.59	0.050[b]
Negative	68	31 (45.6)	37 (54.4)		5.59±2.37	
Depth of Invasion (pT)						
pT1	4	3 (75.0)	1 (25.0)	0.178	4.5±1.00	0.176[c]
pT2	55	20 (36.4)	35 (63.6)		5.62±2.00	
pT3	41	12 (29.3)	29 (70.7)		6.20±2.40	

[a], Chi-square test; [b], Mann Whitney test; [c], Kruskal Wallis test; *Significant p value

which allows tumor cells to change their shape and take on the properties of mesenchymal cells, including a back-front polarity in their actin stress fibers, allowing cell movement using focal adhesions that contain integrin to adhere to the extracellular matrix [23, 24].

This entire process results in a loss of intercellular polarity, which in turn leads to enhanced cell motility and the capacity of cells to break away from the primary tumor mass and infiltrate surrounding tissues [23]. This process is referred to as tumor budding. Tumor budding is defined as the presence of single or small clusters of cancer cells at the invasive margin of the tumor. It represents a histological manifestation of an epithelial-to-mesenchymal transition [25, 26]. Furthermore, EMT transcription factors can also induce the upregulation of matrix metalloproteinase (MMP 2), which functions for extracellular matrix degradation, thus further supporting the expansion of tumor cells [22]. EMT is regulated by a core regulatory circuit of two microRNAs (miR-34 and miR-200) [26].

Furthermore, this study demonstrated that *FGFR2* expression was significantly correlated with lymphovascular invasion in colorectal adenocarcinoma. Lymphovascular invasion, defined as the infiltration of tumor cells into blood vessels and lymph vessels, is a significant prognostic indicator of this disease. It increases the risk of metastasis and is associated with poorer patient outcomes [27].

Besides *FGFR2* contributing to cancer cell invasion through the EMT pathway, *FGFR2* also promotes angiogenesis [13 ,27, 28]. Angiogenesis is the formation of new blood vessels to provide the necessary blood supply for tumor growth and distant invasion [13, 27]. *FGFR2* activation can also stimulate the production of Matrix Metalloproteinases 2 and 9 (MMP2 and MMP 9). These enzymes facilitate the degradation of the extracellular matrix, thereby creating a pathway for tumor cells to migrate and invade [29, 30]. Collectively,

these mechanisms facilitate tumor cell invasion of lymphovascular vessels and circulation within the bloodstream, ultimately enabling tumor cell metastasis [23].

Our study also revealed a significant correlation between *FGFR2* overexpression and lymph node metastasis in colorectal adenocarcinoma. This result is consistent with a study by Li P et al. [20], which indicated that high *FGFR2* expression significantly correlated with metastasis to lymph nodes in colorectal adenocarcinoma. Metastasis to lymph nodes and metastasis to distant organs are consequences of lymphovascular invasion [31]. High *FGFR2* expression is associated with an increased risk of lymphovascular invasion and an increased risk of tumor cell metastasis to regional lymph nodes and metastasis to distant organs [32].

This indicates that the overexpression of *FGFR2* contributes to tumor progression and a poor prognosis in colorectal adenocarcinoma [17]. The significance of *FGFR2* as a prognostic biomarker makes it a promising candidate for developing a therapeutic target.

This study was limited by using a single marker and immunohistochemistry modalities to detect the abnormalities of *FGFR2*. Future studies should add another molecule involved in the *FGFR2* signaling mechanism (such as Snail, ZEB, Twist, β-Catenin, E-Cadherin, and others) using a combination of modalities other than immunohistochemistry. Therefore, they can provide a more comprehensive understanding of the pathomechanism of the FGF/FGFR signaling pathway and its role in influencing patient prognosis.

In conclusion, fibroblast growth factor receptor 2 (*FGFR2*) expression is significantly correlated with tumor budding grade, lymphovascular invasion, and lymph node metastasis, but there is no significant correlation with histopathological grade of colorectal adenocarcinoma. The significant correlation between *FGFR2* expression and tumor budding grade, lymphovascular invasion, and lymph node metastasis suggests that *FGFR2* may serve as an important prognostic biomarker in colorectal adenocarcinoma.

Author Contribution Statement

All authors contributed equally in this study.

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Study Approval

This work has been approved by the Research Committee of the Faculty of Medicine, Hasanuddin University.

Ethical approval

The Ethics Committee of the Faculty of Medicine has given approval for this study (Protocol #UH24060469 – Registry No. 607/UN4.6.4.5.31/PP36/2024).

Availability of Data

On reasonable request, the associated author will release the datasets used in this work

Conflict of Interest

All of the authors declare that they have no conflicts of interest

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