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The correlation of the expression of PD-L1 and Cyclin D1 with histopathological grading in colorectal adenocarcinoma

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***Abstract*---**One of the prognosis factors of colorectal adenocarcinoma is histopathological grading. The expression of programmed death-ligand (PD-L1) and cyclin D1 has the potential to become one of the predictive and prognostic factors for tumor cells in colorectal cancer. This study aimed to identify the relationship between the expression of PD-L1 and cyclin D1 and histopathological grading in colorectal adenocarcinoma. It is an analytic observational study with a cross-sectional approach using a sample of 34 paraffin blocks of colorectal adenocarcinoma preparations at the Anatomical Pathology Laboratory of Dr. Soetomo General Academic Hospital Surabaya for the period January 2016 to December 2020. The parameter of the assessment was the percentage of PD-L1 and cyclin D1 antibodies that were positively stained on the membrane and nucleus of tumor cells which was subjected to histopathological grading assessment based on hematoxylin-eosin (HE) staining. The data were analyzed using Spearman's correlation. PD-L1 expression was positively correlated with histopathological grading in colorectal adenocarcinoma (p=0.006). Cyclin D1 expression did not correlate with histopathological grading in colorectal adenocarcinoma (p=0.891). Statistical analysis showed no significant correlation

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between PD-L1 and cyclin D1 expressions (r = 0.188; p = 0.286). The results of this study showed that higher PD-L1 expression translates to increased histopathological grading in colorectal adenocarcinoma, thus, PD-L1 can be used as a prognostic factor in colorectal adenocarcinoma.

***Keywords*---**PD-L1, Cyclin D1, histopathological grading, cancer, colorectal, adenocarcinoma.

Introduction

The global incidence rate for colorectal cancer is 10% with adult cases of 1,931,590 and a mortality rate of 9.4% of all cancer cases after breast and lung cancer. The incidence of colorectal cancer in Indonesia is ranked fourth at 8.6% with 34,189 new cases, the second highest in males with 12.1% after lung cancer and the fourth highest in females with 5.9% after breast, cervical and ovarian cancer (Globocan, 2020). One of the causes of colorectal cancer is mutations in the KRAS gene, especially in codons 12 and 13. Research conducted at Dr. Soetomo Hospital Surabaya on the status of the KRAS gene mutation in colorectal adenocarcinoma showed that there was no KRAS gene mutation in codon 13 and there were 33% KRAS gene mutations in codon 12 (Mastutik et al., 2016).

Histopathological grading of colorectal adenocarcinoma is evaluated based on the presentation area of gland formation divided into 4 criteria, namely grade 1 (well differentiated), grade 2 (moderately differentiated), grade 2 (poorly differentiated), and grade 4 (undifferentiated). The prognosis of colorectal cancer can be determined through histopathological examination to see the histopathological type and grading of the cancer (Galon et al., 2006). Another prognostic factor is the state of tumour invasion which is the uncontrolled proliferation of tumour cells causing the transformation of paracellular permeability which increases the expression of claudin-4. Research results showed that the expressions of claudin-4 and matrix metalloproteinase-2 (MMP-2) play a role in colorectal adenocarcinoma tumour invasion which can be used as another prognostic marker (Fatimah et al., 2021).

Programmed death-ligand 1 (PD-L1) is a transmembrane protein expressed on cancer cell membranes (Passardi et al., 2017). Studies have shown that PD-L1 expression is linked to poor clinical and pathological features in colorectal cancer patients, and in addition, it also shows a certain degree of PD-L1 as a predictive factor for disease progression and death. Research results showed that patients with positive PD-L1 expression had a significantly higher risk of cancer development and lower overall survival. This increased risk was independent of age, tumor size, tumor location, differentiation status, and TNM stage. Research results showed the expression of PD-L1 as a predictor of poor prognosis in colorectal cancer (Shi et al., 2013). The role PD-L1 expression plays in colorectal carcinoma is still unclear. Several published studies report conflicting results as to whether PD-L1 expression gives an indication of better or worse prognosis (Rosenbaum et al., 2016).

The protein that plays a role in the development of normal colonic epithelium into an adenoma lesion and eventually into a carcinoma is cyclin D1. Cyclin D1 has many functions, one of which is as an oncogene that regulates several processes of cell transformation into malignant, including abnormal growth, angiogenesis and resistance to apoptosis (Wang et al., 2016). Cyclin D1 that is linked to the increase in the rate of cell proliferation is one of the cell-cycle proteins which is responsible for the transition to the S phase of the cell cycle (DNA synthesis phase). Overexpression of cyclin D1 is related to transformation toward malignancy. Studies have shown that around 26% of sporadic cancers showed abnormally excessive cyclin D1 expression (Tashiro et al., 2007).

More than one third of colorectal cancers show overexpression of cyclin D1. Although the role of cyclin D1 in the cell cycle is well-known, there is still controversy surrounding the relationship between its expression and the prognosis of cancer. The literature shows that cyclin D1 expression is associated with a poor prognosis, whereas other literature shows that the expression of this protein is associated with a good prognosis in colorectal cancer (Jang et al., 2012). Another study on bladder urothelial cell carcinoma regarding cyclin D1 expression found no correlation between cyclin D1 both with grading or T stage (Rahaju et al., 2021). Based on the various theory above, the authors were intrigued to conduct a study on the correlation between PD-L1 and cyclin D1 expressions and histopathological grading in colorectal adenocarcinoma, so that their expression can be used to differentiate the two. This study was motivated by the lack of research at the Anatomical Pathology laboratory center at Dr. Soetomo General Academic Hospital Surabaya.

Materials and Methods

After obtaining the approval from the Ethics Committee, Research No. 0426/KEPK/VI/2022 at Dr. Soetomo General Academic Hospital Surabaya using a sample of 34 paraffin blocks of colorectal adenocarcinoma preparations at the Anatomical Pathology Laboratory of Dr. Soetomo General Academic Hospital Surabaya for the period January 2016 to December 2020 was conducted. Sample collection was performed with consecutive sampling that met the inclusion and exclusion criteria. The minimum sample size in this study was 30 samples. Data collection began with coordination with related departments, namely the Anatomical Pathology Laboratory of Dr. Soetomo General Academic Hospital Surabaya. Then, we looked up for medical record numbers, histopathological examination numbers and history from the archive of anatomic pathology examination forms. Preparations were collected according to the histopathological examination number of patients with colorectal adenocarcinoma from the archive of anatomic pathology examination forms. Slides of HE staining were collected and then selected according to the inclusion criteria. A re-examination was performed on the HE slides selected as a sample. Paraffin blocks were collected from the selected preparations, then cut to a thickness of 4 microns for immunohistochemical staining. Immunohistochemical staining was performed with rabbit monoclonal PD-L1 antibody and rabbit monoclonal cyclin D1 antibody. PD-L1 and cyclin D1 were then assessed.

Data were analyzed using statistical test in SPSS program. The first step was a descriptive analysis that described the characteristics of the basic data in the form of frequency distribution, average value, standard deviation and range of values. Data were presented descriptive in the form of tables and narration. The second step was inferential analysis to measure the correlation between the expression of PD-L1 and cyclin D1 with histopathological grading of colorectal adenocarcinoma using the Spearman's Correlation test. The correlation results were considered significant if a value of p,0.05 was obtained.

Results and Discussion

Respondent Characteristics

Table 1
Characteristic Distribution of Colorectal Adenocarcinoma Patients at Dr. Soetomo General Academic Hospital Surabaya

Respondent Characteristics	n=34	%=100
Age		
31-40 years old	3	9
41-50 years old	10	29
51-60 years old	13	38
61-70 years old	4	12
>70 years old	4	12
Sex		
Female	20	59
Male	14	41
Histopathological grading		
Grade 1 (*well differentiated)*	14	41
Grade 2 (*moderately differentiated)*	15	44
Grade 3 (*poorly differentiated)*	5	15
PD-L1 Expression		
Score 0 = stained tumor cell 0-4%	5	15
Score 1 = stained tumor cell 5-49%	29	85
Score 2 = stained tumor cell ≥50 %	0	0
Cyclin D1 Expression		
Score 0 : stained tumor cell < 5%	3	10
Score 1 : if stained tumor cell 5% - 20%	12	35
Score 2 : if stained tumor cell 20%- 50%	19	55

Table 1 shows that the largest proportion of age was the 51-60-year age group with 38%, while the smallest proportion was the 31-40-year age group with 9%. The highest sex proportion was female with 59%. The largest proportion of

histopathological grading was grade 2 with 44% and the smallest proportion was grade 3 with 15%. The largest proportion of PD-L1 expression score 1 with 85%, followed by score 0 with 15%. The highest proportion of cyclin D1 expression was in score 2 with 55%, followed by score 1 and score 0 with 35% and 10%, respectfully.

Correlation between PD-L1 Expression and Histopathological Grading in Colorectal Adenocarcinoma

The observation on PD-L1 in this study used immunohistochemical staining. PD-L1 was positively stained on the tumor cell membranes. Positively stained PD-L1 expression is shown with brown stains on the tumor cell membranes presented with various scores in Figure 1.

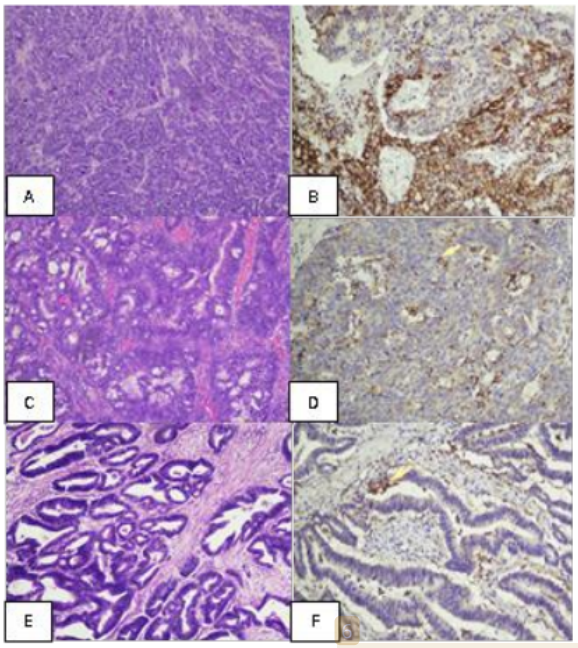

Figure 1. Hematoxylin-eosin stain and PD-L1 expression on colorectal adenocarcinoma tumor cells in the tumor cell membranes. A: HE stain of poorly differentiated adenocarcinoma. B: PD-L1 expression is 40% stained in poorly differentiated adenocarcinoma (200× magnification). C: HE stain of moderately differentiated adenocarcinoma. D: PD-L1 expression is 30% stained in moderately differentiated adenocarcinoma (200× magnification). E: HE stain of well differentiated adenocarcinoma. F: PD-L1 expression is 10% stained in well differentiated adenocarcinoma (200× magnification)

Table 24
Spearman's correlation test results between PD-L1 expression and histopathological grading in colorectal adenocarcinoma

		Histopathological Grading
PD-L1 expression	r	0.461
	p	0.006
	n	34

The correlation between PD-L1 expression and histopathological grading in colorectal adenocarcinoma was tested using the Spearman's correlation. The results showed a significant correlation, where a coefficient value of Spearman's correlation (r) of 0.461 with a p=0.006 (p<0.05) was obtained.

Correlation between Cyclin D1 Expression and Histopathological Grading in Colorectal Adenocarcinoma

The observation on cyclin D1 in this study used immunohistochemical staining. Cyclin D1 was positively stained on the tumor cell nuclei. Positively stained PD-L1 expression is shown with brown stains on the tumor cell membranes presented with various scores in Figure 2.

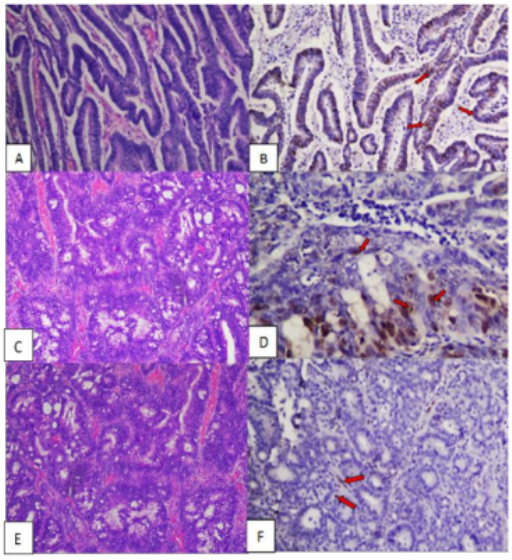

Figure 2. Hematoxylin-eosin stain and cyclin D1 expression on colorectal adenocarcinoma tumor cells in the tumor cell nuclei. A: HE stain of well differentiated adenocarcinoma. B: Cyclin D1 expression is 50% stained in well differentiated adenocarcinoma (200× magnification). C: HE stain of moderately differentiated adenocarcinoma. D: Cyclin expression is 30% stained in moderately differentiated adenocarcinoma (200× magnification). E: HE stain of poorly differentiated adenocarcinoma. F: PD-L1 expression is 2% stained in poorly differentiated adenocarcinoma (200× magnification)

Table 3
Spearman's correlation test results between cyclin D1 expression and histopathological grading in colorectal adenocarcinoma

		Histopathological Grading
Cyclin D1 expression	r	0.024
	p	0.891
	n	34

The correlation between cyclin D1 expression and histopathological grading in colorectal adenocarcinoma was tested using the Spearman's correlation. The results showed a coefficient value of Spearman's correlation (r) of 0.024 with a p=0.891 (p<0.05) was obtained. The result indicates that there is no significant correlation between cyclin D1 expression and histopathological grading in colorectal adenocarcinoma.

Correlation between the Expression of PD-L1 and Cyclin D1 in Histopathological Grading of Colorectal Adenocarcinoma

The correlation between the expression of PD-L1 and cyclin D1 in histopathological grading of colorectal adenocarcinoma was tested using the Spearman's correlation. The results showed a coefficient value of Spearman's correlation (r) of 0.188 with a p=0.286 (p<0.05) was obtained. The result indicates that there is no significant correlation between PD-L1 and cyclin D1 expressions in histopathological grading of colorectal adenocarcinoma.

Table 4
Spearman's correlation test results between PD-L1 and cyclin D1 expressions in histopathological grading of colorectal adenocarcinoma

		Cyclin D1
PD-L1 Expression	r	0.188
	p	0.286
	n	34

Discussion

Research Sample Characteristics

This is a cross-sectional study using 34 paraffin block samples of colorectal adenocarcinoma patients at the Anatomical Pathology Laboratorium of Dr. Soetomo General Academic Hospital Surabaya between 2017 and 2020. Consecutive sampling technique were used to take samples that met the inclusion and exclusion criteria. The minimum sample size in this study was 30 samples. Colorectal adenocarcinoma in this study, based on age grouping, was mostly observed in the age range of 51-60 years with 13 cases (38%), followed by the age range 41-50 with 10 cases (29%), age range 61-70 years with 4 cases (12%), age range >70 years with 4 cases (12%), and age range 31-40 years with 3 cases (9%). This is in line with several previous studies stating that colorectal adenocarcinoma occurs mostly in people over 50 years of age with a peak at 51-60 years of age. The increasing

incidence in old age occurs as a result of the accumulation of several genetic and epigenetic changes that lead to the transformation from normal epithelium to adenocarcinoma. Some of the causes include mutations in tumor suppressor genes such as APC, TP53, and DCC as well as activating mutations in the K-RAS oncogene (Sakai et al., 2014). These results are also consistent with data from WHO which stated that the incidence of colorectal carcinoma increases with age and rarely occurs under the age of 40 years, except in individuals with a genetic predisposition or predisposing conditions such as chronic inflammatory bowel disease (Hamilton et al., 2010).

Colorectal adenocarcinoma is dominated by women in this study with 59%, different from the results of several previous studies which stated that the incidence of colorectal adenocarcinoma was higher in men than women. This can be explained by the protective effect of estrogen and progesterone. This explanation is supported by several epidemiological studies showing that increased levels of estrogen and progesterone are associated with a lower risk of developing colorectal adenocarcinoma. The study of Grodstein et al. did not find a decreased risk of colorectal adenocarcinoma in women with higher levels of estradiol and estrone, suggesting that progesterone is a key factor for reduced risk of colorectal adenocarcinoma in women (Grodstein et al., 1999). The difference between the results of our study and some previous studies may be due to the differences in the characteristics of the samples involved in the study.

The histological grading of colorectal adenocarcinoma in this study was evaluated based on the gland structure according to the World Health Organization (WHO) namely grade 1 (well differentiated with 14 cases (41%), grade 2 (moderately differentiated) with 15 cases (44%), and grade 3 (poorly differentiated) with 5 cases (15%). Grade 2 had the most cases with 15 (44%). These results are in line with studies from United States in 1998-2001 where the majority of colorectal adenocarcinoma samples observed were moderately differentiated (Stewart et al., 2006). These are not in line with previous studies where the majority of them had well differentiated samples (Li et al., 2019). Grading is associated with overall survival, where grade 1 indicates the best prognosis, grade 2 indicates moderate prognosis, while grade 3 indicates the worst prognosis (Steven et al., 2009).

PD-L1 Expression and Histopathological Grading in Colorectal Adenocarcinoma

The role of PD-L1 expression in colorectal carcinoma is rather unclear. Several published studies report conflicting results as to whether PD-L1 expression gives an indication of better or worse prognosis (Rosenbaum et al., 2016). This study observed PD-L1 expression of brown colorectal tumor cells on the cell membrane, which were obtained through histopathological examination results using immunohistochemical staining. PD-L1 expression with histopathological grading in colorectal adenocarcinoma in this study was tested using Spearman's correlation. The results of the Spearman's correlation analysis showed a significant correlation, where a Spearman's correlation coefficient value of 0.461 with a p=0.006 (p<0.05) was obtained. The results of show that higher PD-L1 expression translates to increased histopathological grading in colorectal adenocarcinoma. The results of this study are in line with the previous study, demonstrating a significant

relationship between PD-L1 expression and the survival rate of colorectal carcinoma patients, where high expression of PD-L1 significantly correlates with poor prognosis of colorectal cancer (Shen et al., 2019).

The study by Li et al. (2019) showed that colorectal carcinoma and PD-L1 positive expression have a significant effect on poor prognosis, though studies discussing the significance between PD-L1 expression and poor prognosis in colorectal carcinoma are currently controversial. One of the effects of PD-L1 expression is the weakened host immune response, which in turn can worsen the prognosis. Although there have been quite a number of studies discussing the status of PD-1 and PD-L1, but until now the role of PD-1 and PD-L1 in colorectal carcinoma is still not known with certainty (Li et al., 2019). The results of several studies above are in line with our study, describing that PD-L1 expression significantly correlates with overall colorectal cancer survival. The more PD-L1 was expressed, the more histopathological grading improved, and the worse the prognosis will be for colorectal cancer patients.

Cyclin D1 Expression and Histopathological Grading in Colorectal Adenocarcinoma

More than one third of colorectal cancers show overexpression of cyclin D1. Although the role of cyclin D1 in the cell cycle is well-known, there is still controversy surrounding the relationship between its expression and the prognosis of cancer. The literature shows that cyclin D1 expression is associated with a poor prognosis, whereas other literature shows that the expression of this protein is associated with a good prognosis in colorectal cancer (Jang et al., 2012). This study observed cyclin D1 expression by examining the quantity of brown-stained colorectal tumor cells in the cell nucleus obtained by histopathological examination using immunohistochemical staining. The calculation was carried out based on the percentage of positive staining during immunohistochemical staining.

The results of statistical analysis of this study showed no significant correlation between cyclin D1 expression and histopathological grading in colorectal adenocarcinoma. The results of the analysis were tested using Spearman's correlation and showed a Spearman's correlation coefficient (r) value of 0.024 with $p=0.891$ ($p < 0.05$). This result is not in line with previous studies on cyclin D1 in colorectal adenocarcinoma showing that cyclin D1, cyclin A and Ki-67 were overly expressed in colorectal cancer, but only the overexpression of cyclin D1 and cyclin A that were correlated with poor differentiation. This suggests the advantage of cyclin D1 and cyclin A as a poor prognosis indicator compared to Ki-67 (Bahnassy et al., 2004).

In this study, there was no significant relationship between cyclin D1 and histopathological grading in colorectal adenocarcinoma. The results of this study differ from previous studies that have demonstrated a relationship between cyclin D1 expression and overall survival in colorectal adenocarcinoma, explaining that the ability of cells to initiate the cell cycle depends on the presence of CDK. An active CDK will stimulate the cell cycle continuously to transition to the next stage and with disruption to the CDK, the cyclin-CDK complex will not be formed which

will result in the cessation of the cell cycle which will inhibit the proliferation of cancer cells, thereby affecting overall survival (Gartner and Hiatt, 2007).

Correlation between PD-L1 and Cyclin D1 Expressions in Histopathological Grading of Colorectal Adenocarcinoma

The correlation between the expression of PD-L1 and cyclin D1 in histopathological grading of colorectal adenocarcinoma was tested using the Spearman's correlation. The results showed a coefficient value of Spearman's correlation (r) of 0.188 with a p=0.286 ($p<0.05$) was obtained. The result indicates that there is no significant correlation between PD-L1 and cyclin D1 expressions in histopathological grading of colorectal adenocarcinoma. PD-L1 expression is usually not accompanied by high cyclin D1 expression, suggesting that the ability of cells to initiate the cell cycle depends on the presence of CDK. An active CDK will stimulate the cell cycle continuously to transition to the next stage and with disruption to the CDK, the cyclin-CDK complex will not be formed which will result in the cessation of the cell cycle which will inhibit the proliferation of cancer cells, thereby affecting overall survival (Gartner and Hiatt, 2007).

Other studies have explained the relationship of PD-L1 and cyclin D1 expressions. They stated that cyclin D1-CDK4 directly phosphorylates SPOP at Ser6, which functions as an adapter protein to the cullin3 ubiquitin ligase, thereby reducing PD-L1 expression (Tufano et al., 2021). The results of this study showed that PD-L1 and cyclin D1 are not significantly correlated because cell proliferation is highly dependent on CDK. The inhibition of CDK will stop the cell cycle, affecting the proliferation of cancer cells which in turn can affect the histopathological grading.

Conclusions

There is a correlation between the expression of PD-L1 and histopathological grading in colorectal adenocarcinoma, showing that higher PD-L1 expression translates to increased histopathological grading in colorectal adenocarcinoma. There is no correlation between cyclin D1 expression and histopathological grading in colorectal adenocarcinoma. Furthermore, there is no correlation between PD-L1 and cyclin D1 expressions and histopathological grading in colorectal adenocarcinoma.

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PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7

PAGE 8

PAGE 9

PAGE 10

PAGE 11

PAGE 12