Cyclin D1 and Clinicopathological Characteristics of Gastric Cancer

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Abstract

Gastric cancer is found at a rate of 2.4 to 3.5 percent in Indonesia, with the majority of cases discovered at an advanced stage. Cyclin D1 is a protein that promotes cancer cell growth. It has been shown to be expressed in a variety of cancers, including stomach cancer. A recent study of cyclin D1 in gastric cancer has been associated with lymph node involvement, metastasis, poor prognosis, and lack of response to platinum chemotherapy. This study aims to determine the relationship between cyclin D1 expression and clinicopathological features in gastric cancer. This cross-sectional study used medical records and paraffin blocks of gastric cancer patients at Cipto Mangunkusumo General Hospital, Jakarta, in 2015–2020. Demographic data, clinical characteristics, radiological findings, histopathological features, and cyclin D1 expression were collected and examined. Data was collected from 39 subjects. Most of the subjects experienced eating disorders (69.23%), weight loss (76.92%), melena (53.85%), and anemia (51.28%). Tumor locations were mostly found in the cardia and corpus of the gaster. Overexpression of cyclin D1 was found in 30.77% of cases. Cyclin D1 expression was greater in subjects with liver metastases (50% vs. 14.8%, p 0.04). Cyclin D1 expression was not associated with tumor location, TNM stage, and histopathological findings.

1. Introduction

Gastric cancer is estimated to occur at a rate of 2,4–5,6 percent in Indonesia. This data is derived from a variety of referral hospitals in Indonesia. [1, 2] Infection with *Helicobacter pylori* is a risk factor that is highly related to the incidence of stomach cancer. [3, 4] In Indonesia, the majority of instances of stomach cancer are discovered at an advanced stage. Early-stage gastric cancer accounts for between 1.7% and 9.1% of all cases of gastric cancer. [2]

Cyclin D1 is a protein that is involved in the cell cycle from G1 to S phase. The CCND1 gene on chromosome 11q13 encodes Cyclin D1. [5] Cyclin D1 shorten the duration of the G1 phase of the cell cycle, promoting cancer cell growth. [5] Increased expression of cyclin D1 has been observed in a variety of cancers, including those of the esophagus, breast, uterine, colon, lung, prostate, lymphoma, and stomach, as well as neck and head cancer. [6] Cyclin D1 expression has been linked to tumor development, stage, lymph node involvement, distant metastases, and poor prognosis. [6, 7]

It is stated that elevated cyclin D1 expression occurs in between 50% and 55% of cases of gastric cancer. [8, 9] Previous research on cyclin D1 expression in gastric cancer has shown that it is related to lymph node involvement, metastasis, poor prognosis, and resistance to platinum treatment. [10]

Cyclin D1 expression has been associated with lymph node involvement, metastasis, a poor prognosis, and a lack of response to platinum treatment in gastric cancer. [11-13] cyclin D1 was not regularly examined in stomach cancer cases in Indonesia. The purpose of this study is to establish a correlation between cyclin D1 expression and clinicopathological characteristics of gastric cancer.

2. Patients And Methods

The paraffin blocks of gastric cancer patients at the Department of Anatomical Pathology and the medical records of gastric cancer patients at Cipto Mangunkusumo General Hospital in Jakarta were used in this cross-sectional study between 2015 and 2020. Demographic and clinical information, endoscopic findings, and histological characteristics were all included in the research data. The following scores were used to assess cyclin D1 expression: negative, weak 1+ (10% cell nucleus), moderate 2+ (11–50% cell nucleus), and strong (> 50% cell nucleus). Brown nuclear staining is considered positive. [10] The American Joint Committee on Cancer (AJCC)’s current seventh edition is used for cancer clinical staging. The Medical Research Ethics Commission approved this study under protocol number KET-563/UN2.F1/ETIK/PPM.00.00/2020.

The data collected is subsequently analyzed using the SPSS 20 software. Statistical tests such as the Chi-square or Fisher test were employed.

3. Results

Thirtynine patients were included in this study. Table 1 below describes the characteristics of the study subjects. The majority of participants lost weight, developed eating disorders, or experienced gastrointestinal hemorrhage. An endoscopic examination revealed a tumor in the corpus and cardia of the gastric corpus.

Table 1 Clinical and pathological characteristics

Characteristic	No. (N = 39)	Percentage (%)
Age, mean (standard deviation)	51,77 (14,23)	
Gender, n (%)		
Male	19	48,72
Female	20	51,28
Performance Status (ECOG)		
0–2	21	67,74
3–4	10	32,26
Sign and symptoms		
Intake problem	27	69,23
Abdominal pain	19	48,72
Weight loss	30	76,92
Abdominal distention	6	15,38
Hematemesis	8	20,51
Melena	21	53,85
Comorbidities		
Hypertension	8	20,51
Diabetes mellitus	3	7,69
Cardiac disease	3	7,69
Smoking	6	15,38
Alcohol	3	7,69
Laboratory abnormality		
Anemia (<10 mg/dL)	20	51,28
Hypoalbuminemia (<3,5 g/dL)	12	30,77
Tumor Location		
Cardia	17	43,59
Fundus	10	25,64
Corpus	23	58,97
Antrum	14	35,90
Pylorus	10	25,64

T Stage		
T2	3	7,69
T3	14	35,90
T4	22	56,41
N Stage		
Nx	6	15,38
N0	2	5,13
N1	16	41,03
N2	10	25,64
N3	5	12,82
Metastasis		
M0	18	46,15
M1	21	53,85
Metastatic Site (M1)		
Liver	10	25,64
Lung	8	20,51
Bone	1	2,56
Histopathological Finding		
Lymphovascular Invasion	9	23,08
Perineural Invasion	5	12,82
Tumor Differentiation		
Well differentiated	12	30,77
Poor differentiated	27	69,23
WHO Classification		
NOS	19	48,72
Poorly cohesive	12	30,77
Signet ring cell	7	17,95
Musinosum	1	2,56
Cyclin D1 Expression		
Negative	27	69,23

Positive	12	30,77
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n, number of patient; ECOG, Eastern Cooperative Oncology Group; WHO, World Health Organization; NOS, not otherwise specified.

In this investigation, Cyclin D1 overexpression was detected in 30.77 percent of patients. In Figure 1, the comparison between a negative and a positive Cyclin D1 expression was shown.

Table 2 demonstrates the distribution of clinical features based on the presence or absence of cyclin D1 expression. The expression of Cyclin D1 was higher in those who had liver metastases (50 percent vs. 14.8 percent, *p* 0.04).

Table 2 Clinical characteristics and cyclin D1 expression

Clinical Characteristic	Positive Cyclin D1 (N = 12)	Negative Cyclin D1 (N = 27)	p value	OR (95%CI)
Age, mean (standard deviation)	56,1 (12,26)	49,85 (14,83)	1,27	
Gender, n (%)				
Male	7 (58,33)	12 (44,44)	0,65	1,75 (0,44–6,93)
Performance Status (ECOG)			1,00	0,92 (0,20–4,31)
0–2				
3–4	8 (66,67)	13 (68,42)		
	4 (33,33)	6 (31,58)		
Smoking	3 (25,00)	3 (11,11)	0,35	0,38 (0,07–2,21)
Alcohol	1 (8,33)	2 (7,41)	1,00	0,89 (0,07–10,75)
Laboratory				
Anemia	9 (75,00)	11 (40,74)	0,10	0,23 (0,05–1,04)
Hypoalbumin	7 (58,33)	12 (44,44)	1,00	1,36 (0,25–7,32)
Tumor location				
Cardia	6 (50,00)	11 (40,74)	0,85	0,69 (0,18–2,70)
Fundus	2 (16,67)	8 (29,63)	0,69	2,11 (0,37–11,86)
Corpus	8 (66,67)	15 (55,56)	0,73	0,62 (0,15–2,59)
Antrum	3 (25,00)	11 (40,74)	0,48	2,06 (0,45–9,39)
Pylorus	2 (16,67)	8 (29,63)	0,69	2,11 (0,37–11,86)
T Stage, n (%)				
T2	2 (5,13)	1 (2,56)	0,65	
T3	2 (5,13)	12 (30,77)		
T4	8 (20,51)	14 (35,90)		

N Stage, n (%)			0,16	
Nx	3 (25,00)	3 (11,11)		
N0	0 (0,00)	2 (7,41)		
N1	4 (33,33)	12 (44,44)		
N2	3 (25,00)	7 (25,93)		
N3	2 (16,67)	3 (11,11)		
Metastasis, n (%)			0,47	0,46 (0,11–1,92)
M1	8 (66,67)	13 (48,15)		
Metastatic Site (M1)				
Liver	6 (50,00)	4 (14,81)	0,04*	0,17 (0,37–0,82)*
Lung	3 (25,00)	5 (18,52)	0,68	
Bone	0 (0,00)	1 (3,70)	1,00	0,68 (0,13–3,47)

The statistical significance is marked with “*”. *Indicates $p < 0.05$.

Using histopathological features as a basis, Table 3 demonstrates the distribution of cyclin D1 expression. There was no statistically significant difference in the proportion of cyclin expression according to histological findings, such as degree of differentiation, lymphovascular invasion, perineural involvement, or WHO (World Health Organization) classification.

Table 3 Pathological characteristics and cyclin D1 expression

Pathology Characteristics	Positive Cylin D1 (N =12)	Negative Cyclin D1 (N = 27)	<i>p</i> value	OR (95%CI)
Lymphovascular invasion	5 (41,67)	4 (14,81)	0,11	0,24 (0,05-1,16)
Perineural invasion	2 (16,67)	3 (11,11)	0,63	0,63 (0,10-4,33)
Tumor differentiation			0,72	0,67 (0,14-3,09)
Well differentiated	3 (25,00)	9 (33,33)		
Poor differentiated	9 (75,00)	18 (66,67)		
WHO Classification			1,00	
NOS	6 (50,00)	13 (48,15)		
Poorly cohesive	4 (33,33)	8 (29,63)		
Signet ring cell	2 (16,67)	5 (18,52)		
Musinosum	0 (0,00)	1 (3,70)		

The statistical significance is marked with “*”. *Indicates $p < 0.05$.

4. Discussion

This study found that 30.7% of patients had positive cyclin D1 expression. This percentage was lower than that reported by Feakins et al.[8], who claimed that cyclin D1 was overexpressed in 55% of gastric cancer cases. Another study conducted by Ibrahim et al.[10], indicated that cyclin D1 expression was high in 50% of the individuals studied. The findings of this study are comparable with those of Casasola et al. [14], who found that overexpression of cyclin D1 was observed in 29 percent of the gastric cancer cases examined.

There are a variety of growth stimuli that can cause increased production of cyclin D1 in cancer cells. In a study on prostate cancer, it was discovered that overexpression of the Epidermal Growth Factor Receptor (EGFR) causes an increase in the levels of the cyclin D1 messenger Ribonucleic Acid (mRNA) and protein. Breast tumors that express Her2 will also have higher amounts of cyclin D1 than other types of breast cancer. [12] According to additional research, the average incidence of gastric cancer has increased by 17.9 percent. [15]

According to this study, the expression of Cyclin D1 was not associated with tumor location, TNM stage, or histological characteristics of the tumor. In line with the findings of Gao et al. [16], who found that cyclin D1 expression was not associated with age, lymphatic involvement, or histological grade.

The proportion of cyclin D1 expression was shown to be linked with liver metastases in this investigation (50 percent vs. 14,8 percent, $p = 0,04$). This is consistent with the literature, which indicates that cyclin D1

expression is connected with cancer metastasis occurrence. [17] The liver is a frequently involved organ in gastric cancer. [18]

5. Conclusion

The proportion of cyclin D1 overexpression in this study was 30.7%. The overexpression of cyclin D1 was associated with an increased risk of liver metastases in gastric cancer in this study.

Abbreviations

AJCC	American Joint Committee on Cancer
ECOG	Eastern Cooperative Oncology Group
WHO	World Health Organization
NOS	not otherwise specified
mRNA	messenger Ribonucleic Acid
EGFR	Epidermal Growth Factor Receptor
TNM	Tumor, Nodes, Metastases

Declarations

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Conflicts of Interest

The authors declare they have no conflicts of interest. The funders had no role in the conceptualization of the study; data collection, analysis, or interpretation; writing of the manuscript, or in the decision to publish the results.

Data Availability

Raw data could not be share publicly due to on going research, but could be requested through author once paper published.

Code Availability

Not applicable

Authors' Contributions

All authors contributed in study conceptualization; material preparation; data collection, analysis, and interpretation; and writing the manuscript. All authors also reviewed and approved the final draft.

Ethical Approval

This research has obtained permission from the Medical Research Ethics Commission of Faculty of Medicine, Universitas Indonesia (KET-563/UN2.F1/ETIK/PPM.00.00/2020).

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Not applicable

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Figures

Figure 1

(a) Negative cyclin D1 expression (b) Strong positive cyclin D1 expression