Clinical, Endoscopic, and Histopathological Features of HER2 Expression and Two-Year Survival in Gastric Adenocarcinoma

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ABSTRACT

Background: *HER2 is a proto-oncogene and therapeutic target in advanced gastric adenocarcinoma. Reports on its association with clinicopathological features and prognosis remain inconsistent. This study aimed to evaluate the relationship of clinical, endoscopic, and histopathological features with HER2 expression and its impact on two-year survival.*

Methods: *A retrospective cohort study was conducted among patients ≥18 years with newly diagnosed gastric adenocarcinoma at four hospitals in Jakarta (2015–2019). Eligible cases had complete records and paraffin blocks. HER2 was assessed by immunohistochemistry and CISH using ToGA criteria. Chi-square/Fisher's tests evaluated associations, while survival was analysed with Kaplan-Meier and Cox regression.*

Results: *Among 122 patients, 15 (12.3%) were HER2-positive. More frequent expression was observed in liver metastases than in non-liver metastases (17.6% vs. 10.2%), in Borrmann type I/II than in Borrmann type III/IV (16.1% vs. 9.1%), in moderately rather than in poorly differentiated tumors (14.3% vs. 11%), and in intestinal-type rather than in diffuse/mixed-type tumors (13.9% vs. 10%); however, none were statistically significant. Median survival was 5 months in HER2-positive patients and 4 months in HER2-negative patients. HER2 was not significantly associated with two-year survival (HR [95% CI] = 1.12 [0.61, 2.06]). Mortality in patients with palliative therapy was higher than that of those with definitive/therapeutic therapy (76.8% vs 75.8%; HR = 1.547 [1.022, 2.343]). The combination of resection and chemotherapy intervention provided a protective effect on mortality with HR = 0.456 [0.219, 0.95]. There was a significant association between resection-chemotherapy combination therapy and survival in subjects with negative HER2 expression (HR = 0.409 [0.176, 0.947].*

Conclusion: *In this study, HER2 expression in gastric adenocarcinoma was 12.3%. HER2 expression tended to be higher in liver metastases, Borrmann type I/II, moderate differentiation, and intestinal type histopathology results. Combination therapy with resection and chemotherapy had a protective effect on mortality in this study. Median survival in HER2-positive patients was higher than in HER2-negative patients, but HER2 expression status was not a prognostic factor for two-year survival in gastric adenocarcinoma.*

Keywords: *Clinicopathological Features, Gastric Adenocarcinoma, HER2, Survival*

ABSTRAK

Latar Belakang: *HER2 merupakan protoonkogen yang berperan penting sekaligus menjadi sasaran terapi pada adenokarsinoma gaster stadium lanjut. Namun, bukti mengenai keterkaitan HER2 dengan faktor klinis, endoskopi, histopatologi, maupun prognosis masih belum konsisten. Penelitian ini bertujuan mengevaluasi hubungan karakteristik klinis, endoskopi, dan histopatologi dengan ekspresi HER2, serta dampaknya terhadap kesintasan dua tahun.*

Metode: *Studi kohort retrospektif dilakukan pada pasien ≥18 tahun dengan diagnosis baru adenokarsinoma gaster di empat rumah sakit di Jakarta selama periode 2015–2019. Subjek yang memenuhi syarat memiliki rekam medis lengkap dan blok parafin yang tersedia. Ekspresi HER2 dianalisis menggunakan imunohistokimia dan dikonfirmasi dengan CISH berdasarkan kriteria ToGA. Hubungan antara variabel diuji dengan Chi-square/ Fisher, sedangkan kesintasan dinilai menggunakan Kaplan-Meier dan regresi Cox.*

Hasil: *Dari 122 pasien, 15 (12,3%) HER2-positif. Ekspresi cenderung lebih tinggi pada kasus dengan metastasis hati dibandingkan tanpa metastasis hati (17,6% vs. 10,2%), dengan Borrmann tipe I/II dibandingkan Borrmann tipe III/IV (16,1% vs. 9,1%) , dengan diferensiasi moderat dibandingkan diferensiasi buruk (14,3% vs. 11%), dan dengan tipe intestinal dibandingkan tipe difus/campuran (13,9% vs. 10%); namun, hubungan ini tidak bermakna secara statistik. Median kesintasan adalah 5 bulan pada HER2-positif dan 4 bulan pada HER2-negatif. Tidak terdapat hubungan bermakna antara ekspresi HER2 dan kesintasan dua tahun (HR [IK95%] = 1,12 [0,61, 2,06]). Mortalitas pada pasien dengan terapi paliatif lebih tinggi dibandingkan dengan pemberian terapi definitif/terapetik (76,8% vs. 75,8%; HR = 1,547 [1,022, 2,343]). Kombinasi terapi reseksi dan kemoterapi memberikan efek proteksi terhadap terjadinya mortalitas dengan (HR = 0,456 [0,219, 0,95]). Terdapat hubungan bermakna antara terapi kombinasi reseksi-kemoterapi dengan kesintasan pada subjek dengan ekspresi HER2 negatif dengan HR = 0,409 [0,176, 0,947].*

Kesimpulan: *Pada penelitian ini, ekspresi HER2 positif pada adenokarsinoma gaster sebesar 12,3%. Ekspresi HER2 cenderung lebih tinggi pada metastasis liver, tipe Borrmann I/II, diferensiasi moderat dan tipe intestinal pada pemeriksaan hi. Terapi kombinasi reseksi dan kemoterapi memberikan efek protektif terhadap mortalitas pada penelitian ini. Median survival pada HER2 positif lebih besar dibandingkan dengan HER2 negatif, tetapi ekspresi HER2 bukan faktor prognostik kesintasan dua tahun pada adenokarsinoma gaster.*

Kata kunci: *Adenokarsinoma Gaster, HER2, Karakteristik Klinis, Kesintasan*

INTRODUCTION

Globally, gastric cancer ranks fourth for incidence and second for mortality. Around 990,000 new cases and 738,000 deaths occur each year, disproportionately affecting men and populations in developing countries.[1-3] Five-year survival varies widely, about 10–30% in Europe but higher in Japan due to endoscopic screening.[4] In Indonesia, it ranks 19th by incidence; five-year prevalence is 1.4 per 100,000, predominated by adenocarcinoma, and most patients present at advanced stages.[5,6]

Survival variation among patients with the same stage highlights the role of biological factors beyond clinical staging, including molecular markers such as HER2. This proto-oncogene regulates proliferation, apoptosis, and angiogenesis and is overexpressed in 6–30% of gastric cancers.[7,8] HER2 expression varies by tumor site, histology, stage, and geography.[9] Several studies reported higher expression in intestinal-type adenocarcinoma and an association with poor prognosis.[10,11]

Nevertheless, data regarding HER2 prevalence and prognostic value remain inconsistent. The ToGA trial reported 22% HER2 positivity, while a meta-analysis found a median prevalence of 18% with wide variability (4–53%).[12,13] Geographic differences are notable, with prevalence reaching 56% in Northeast India, 20% in Europe and the United States, and 9.7% in multinational Asian cohorts.[9,14,15] In Indonesia, Setiawati et al. reported a prevalence of 14.5%.[16]

Associations between HER2 expression and survival also vary. While some studies linked HER2 positivity to worse outcomes, others found no prognostic significance.[9,13,17,18] Unlike Japan, Europe, and the United States, Indonesia lacks national guidelines for HER2 testing or anti-HER2 therapy. Considering potential variability related to clinicopathological features and ethnicity, but with limited local evidence, further research in Indonesian populations is needed.[10,19–21] Therefore, this study aims to evaluate the association of clinical, endoscopic, and histopathological features with HER2 expression, and

to assess the relationship between HER2 expression and two-year survival in patients with gastric adenocarcinoma.

METHODS

Study Design and Setting

This study employed a retrospective cohort and cross-sectional design. The cross-sectional component was used to evaluate the association between clinical, endoscopic, and histopathological features with HER2 expression at a single point in time, based on existing medical records and pathology specimens. The retrospective cohort component was applied to assess the prognostic value of HER2 expression by following patients' outcomes for two years after the initial diagnosis. Case identification, data abstraction (clinical, endoscopic, radiologic, pathologic), and slide re-evaluation were performed from September 2020 to September 2021 across four AHS-FKUI hospitals (RSCM, RSPAD, Fatmawati, Dharmais). Paraffin blocks from tumor biopsies were reprocessed and examined using immunohistochemistry (IHC) and chromogenic in situ hybridization (CISH), conducted centrally at the Department of Anatomical Pathology, Universitas Indonesia.

Study Population and Sampling

Patients aged ≥18 years with histologically confirmed gastric adenocarcinoma diagnosed between 2015 and 2019 were screened from hospital registries. A total of 204 patients were initially identified across four participating hospitals. After applying inclusion criteria (availability of paraffin blocks and biopsy slides from endoscopic or surgical procedures, and no prior chemotherapy, radiotherapy, or targeted therapy at the time of biopsy) and exclusion criteria (missing or damaged slides and incomplete clinical or endoscopic records), 122 patients were eligible and included in the final analysis.

Sample size was calculated using the hypothesis test for two proportions, with the following formula:

$$n_1 = n_2 = \left(\frac{Z_\alpha \sqrt{2PQ} + Z_\beta \sqrt{P_1 Q_1 + P_2 Q_2}}{P_1 - P_2} \right)^2$$

where Z_α = 1.64 (type I error 5%), Z_β = 0.84 (type II error 20%), P_1 and P_2 represent the proportions in HER2-positive and HER2-negative groups, respectively, Q_1=1 - P_1, Q_2=1 - P_2, P=(P_1+P_2)/2, and Q=1 - P.

Based on previous studies, the minimum sample size required ranged from 34 to 122, depending on the variable assessed: 60 for liver metastasis,[22] 46 for tumor location, 122 for Borrmann classification, 34 for differentiation, and 60 for Lauren classification.[14,23–25] For survival and multivariate analyses, the largest estimate (122 subjects) was adopted. Ultimately, 122 eligible patients were included in this study.

Histopathology and HER2 Assessment

Histopathological slides were reviewed to confirm the diagnosis, classify tumors according to WHO and Lauren criteria, and determine differentiation grade. HER2 expression was evaluated using immunohistochemistry (IHC) with rabbit monoclonal HER2 antibody (Leica) and scored according to ToGA criteria.[12,26] Equivocal cases (IHC 2+) were further analyzed by chromogenic in situ hybridization (CISH) to determine gene amplification.[27,28] Breast carcinoma tissue with known HER2 positivity was used as a positive control, while a negative control was performed by omitting the primary antibody. All assessments were performed by two independent pathologists blinded to clinical data.

Statistical Analysis

Data was analyzed using SPSS version 20. Descriptive statistics were used for baseline characteristics. Associations between HER2 expression and clinicopathological variables (lesion location, morphology, liver metastasis, differentiation, and Lauren classification) were tested with Chi-square or Fisher's exact tests. Variables with $p<0.25$ were entered into multivariate logistic regression.[29] Survival was analyzed using Kaplan-Meier and Cox regression. The proportional hazards assumption was assessed with log-minus-log plots and the global test. Variables with $p<0.25$ and clinically relevant factors were included in multivariate Cox regression. Results were expressed as hazard ratios (HR) with 95% confidence intervals (CI), with $p<0.05$ considered statistically significant.[30]

Ethical Considerations

This research received ethical clearance from the Health Research Ethics Committee, Faculty of Medicine, Universitas Indonesia – Dr. Cipto Mangunkusumo National General Hospital (Approval No. KET-1991/UN2.F1/ETIK/PPM.00.02/2020, dated December 28, 2020). All patient information was coded and de-identified to maintain confidentiality.

Table 1. Clinical characteristics of research subjects

Variable	N=122 (%)
Age at Gastric Cancer Diagnosis	
≤ 60 years	78 (63,9)
>60 years	44 (36,1)
Gender, n (%)	
Female	52 (42,6)
Male	70 (57,4)
Education, n (%)	
Elementary School Graduate	15 (12,3)
Junior High School Graduate	16 (13,1)
High School Graduate	65 (53,3)
Diploma/Bachelor's/Master's/Doctoral Degree Graduate	26 (21,3)
Ethnicity, n (%)	
Jawa	32 (26,2)
Batak	28 (23,0)
Cina	10 (8,3)
Sunda	24 (19,7)
Padang	3 (2,5)
Melayu	7 (5,7)
Makassar	1 (0,8)
Bali	1 (0,8)
Papua	1 (0,8)
Betawi	13 (10,7)
Buton	1 (0,8)
Dayak	1 (0,8)
ECOG at first hospital visit, n (%)	
0	4 (3,3)
1	18 (14,8)
2	34 (27,9)
3	43 (35,2)
4	23 (18,9)
Liver metastasis, n (%)	
Yes	34 (27,9)
No	88 (72,1)
Location of lesion, n (%)	
Gastric cardia	57 (46,7)
Non-gastric cardia	65 (53,3)
Lesion type based on Borrman classification, n (%)	
Type polypoid (type I) or type fungating carcinoma (type II)	56 (45,9)
Type ulcerated (type III) or type diffusely infiltrative (type IV)	66 (54,1)
Cancer therapy	
Target cell therapy	0 (0,0)
Therapeutic resection	40 (32,8)
Palliative resection	7 (5,7)
Chemotherapy	7 (5,7)
Resection and chemotherapy	13 (10,7)
Chemotherapy and radiation	0 (0,0)
Radiation	0 (0,0)
Resection and radiation	1 (0,8)
Chemotherapy and radiation	0 (0,0)
Resection and chemoradiation	0 (0,0)
Palliative/supportive care or not further action taken	56 (45,9)
Cause of Death	
Infection	14 (14,6)
Hemorrhage	3 (3,1)
Thrombosis or embolism	0 (0,0)
Cancer-related	80 (83,3

RESULTS

Patient Characteristics

A total of 122 patients with gastric adenocarcinoma met the inclusion criteria **(Figure 1).** The mean age was 53.9 years (SD 14.4), with 63.9% aged ≤60 years and 57.4% was male. Most patients had poor performance status, with ECOG ≥2 in 82.0% of subjects. Liver metastasis was present in 27.9%, and tumors were evenly distributed between Cardia (46.7%) and non-Cardia regions (53.3%). As shown in **Table 1,** ulcerated and diffusely infiltrative types predominated (54.1%).

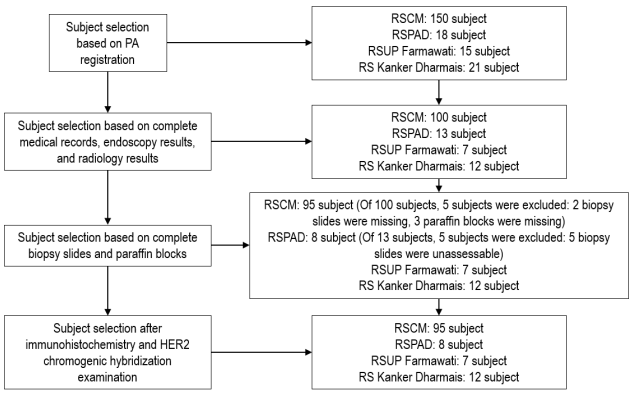

Figure 1. Research subject selection process

Histopathological Features and HER2 Expression

Table 2 outlines tumor histopathological characteristics based on multiple classifications/ criteria. According to the WHO classification, the majority were not otherwise specified (51.6%), followed by poorly cohesive (27.0%) and signet-ring carcinoma (10.7%). Intestinal type was more common than diffuse/mixed (59.0% vs. 41.0%), and 59.8% were poorly differentiated.

Table 2. Histopathological characteristics

Variable	N=122 (%)
WHO Classification, n (%)	
Poorly Cohesive	33 (27,0)
NOS	63 (51,6)
Signet cel ring carcinoma	13 (10,7)
Musinosum	2 (1,6)
Tubuler	9 (7,4)
Mixed type	1 (0,8)
Papillary	1 (0,8)
Lauren Classification, n (%)	
Intestinal type	72 (59,0)
Diffuse or mixed type	50 (41,0)
Poorly Differentiated	73 (59,8)
Tumor differentiation, n (%)	
Well or moderate differentiation	49 (40,2)
Poor differentiation	73 (59,8)

Variable	N=122 (%)
HER2 Expression, n (%)	
Zero HER2 CPI result	57 (46,7)
HER2-positive CPI result 1	31 (25,4)
HER2-positive CPI result 2	21 (17,4)
HER2-positive CPI result 2, CISH negative	19 (15,57)
HER2-positive CPI result 2, CISH positive	2 (1,64)
HER2-positive CPI result 3	13 (10,7)
Conclusion of HER2 expression interpretation, n (%)	
Positive	15 (12,3)
Negative	107 (87,7)

Among subjects with HER2-positive tumors, 13 had IHC 3+, and 2 had IHC 2+ confirmed by CISH. The majority (87.7%) were HER2-negative, including IHC 0 (n=57), IHC 1+ (n=31), and IHC 2+ with negative CISH (n=19).

Association with Clinicopathological Features

No significant associations were found between HER2 expression and liver metastasis, tumor location, Borrmann type, differentiation, or Lauren classification (all p>0.05). A non-significant trend toward higher HER2 positivity was observed in patients with liver metastasis, intestinal type, moderate differentiation, and Borrmann type I/II, summarized in **Table 3.**

HER2 Expression and Survival Analysis

At 24 months, 96 patients (79.5%) had died, 22 (17.2%) were lost to follow-up, and 4 (3.3%) were alive. Most deaths were due to cancer progression (83.3%). Median survival was 5 months in HER2-positive and 4 months in HER2-negative patients, with cumulative survival at 24 months of 0.0% vs. 12.4%, respectively **(Figure 2).**

Table 3. The relationship between clinical features, endoscopic features, and histopathological features with HER2 expression in gastric adenocarcinoma

Variable	HER2 expression in gastric adenocarcinoma		RP (IK 95%)	p
	Yes	No		
Liver Metastasis, n (%)				
Yes	6 (17,6)	28 (82,4)	1,726 (0,655-4,480)	0,355
No	9 (10,2)	79 (89,8)		
Lesion Location, n (%)				
Non-cardiac (gastric)	8 (12,3)	57 (87,7)	1,002 (0,388-2,591)	1,000
Cardia (gastric)	7 (12,3)	50 (87,7)		
Lesion Type based on Borrman Classification, n (%)				
Type polypoid (type I) or type fungating carcinoma (type II)	9 (16,1)	47 (83,9)	1,768 (0,670-4,662)	0,250
Type ulcerated (type III) or type diffusely infiltrative (type IV)	6 (9,1)	60 (90,9)		
Tumor differentiation, n (%)				
Well or Moderate Differentiation	7 (14,3)	42 (85,7)	1,304 (0,505-3,363)	0,789
Poor Differentiation	8 (11,0)	65 (89,0)		
Lauren Classification, n (%)				
Intestinal Type	10 (13,9)	62 (86,1)	1,389 (0,505-3,817)	0,524
Diffuse or Mixed Type	5 (10,0)	45 (90,0)		
Chi square test; Fisher Exact Test				

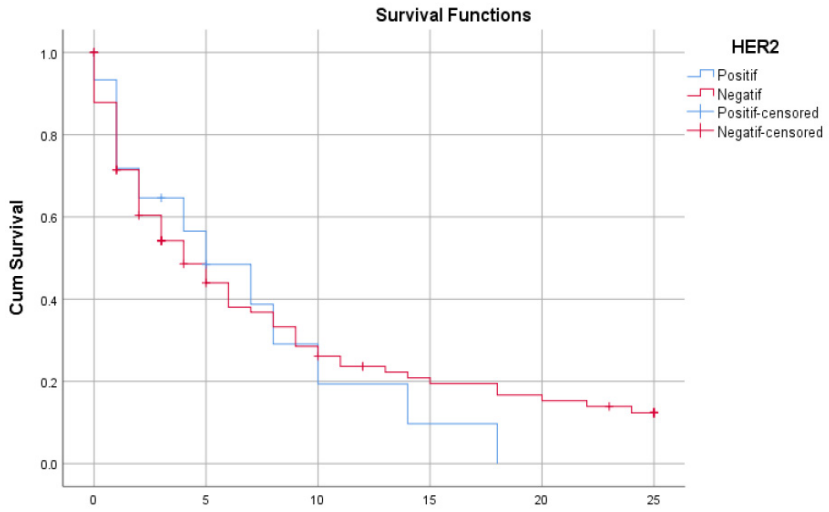

Figure 2. Kaplan Meier curve of two-year survival of HER2 expression in gastric adenocarcinoma

Cox regression confirmed no significant association between HER2 and two-year survival (HR = 1.12 [0.61, 2.06]; p=0.716). Subgroup analysis suggested a trend toward worse outcomes in HER2-positive patients after 10 months, but without statistical significance (HR = 3.34 [0.90, 12.45]; p=0.072).

Therapeutic Modalities and Survival

Overall, 54.1% of subjects received active treatment (surgery, chemotherapy, or combination), while 45.9% received only supportive or palliative care. Multivariate Cox regression identified therapy type as a significant predictor of survival (p=0.039). Palliative care was associated with higher mortality (HR = 1.55 [1.02, 2.34]), whereas combined surgery and chemotherapy was protective (HR = 0.46 [0.22, 0.95]). No significant interaction was observed between HER2 status and treatment effect **(Table 4).**

Table 4. The Type of Therapy Given to Subjects is Associated with Survival

Variable	Death		RP (IK 95%)	p
	Yes	No		
Resection and chemotherapy				
No	24 (22,0)	85 (78,0)		
Yes	5 (38,5)	8 (61,5)	0,456 (0,219-0,950)	0,036
Palliative Therapy				
No	16 (24,2)	50 (75,8)		
Yes	13 (23,2)	43 (76,8)	1,547 (1,022-2,343)	0,039

To determine the role of HER2 expression in the relationship between resection-chemotherapy combination therapy and palliative therapy with survival, a subgroup analysis was performed. The analysis results showed a significant association between resection-chemotherapy combination therapy and survival in subjects with HER2 expression negative (HR = 0.409 [0.176, 0.947]).

DISCUSSION

This study evaluated the relationship between clinicopathological features, HER2 expression, and survival in gastric adenocarcinoma. HER2 positivity was observed in 12.3% of subjects, consistent with reports from Asia (11–16%) and within the global range of 10–30%.[8,16,31] Variability in prevalence across studies may reflect differences in methodology, scoring criteria, and tumor biology.[9,12]

HER2 expression was observed higher in liver metastasis than in non-liver metastasis (17.6% vs. 10.2%), in Borrmann type I/II than Borrmann type III/IV (16.1% vs. 9.1%), in moderately differentiated than in poorly differentiated (14.3% vs. 11%), and in intestinal type rather than diffuse/mixed type (13.9% vs. 10%); however, none were statistically significant. These findings are in line with several studies, although others reported significant correlations, particularly with intestinal-type tumors and proximal gastric location.[9,17,23,32,33] The heterogeneity of gastric cancer, both inter and intratumoral, may account for these discrepancies.[34,35]

Regarding prognosis, median survival was less than six months in both HER2-positive and HER2-negative groups, reflecting the advanced stage and limited treatment options in this cohort. These results are consistent with studies showing HER2 alone may not be an independent prognostic factor, but contrast with others linking HER2 positivity to poorer survival or improved outcomes with trastuzumab.[12,18,21,22,36] Differences in treatment patterns are likely to contribute to these variations, as most of our patients received only palliative care. The combination of resection and chemotherapy provided a protective effect against mortality. There was a significant association between resection-chemotherapy combination therapy and survival in subjects with HER2-negative expression.

Table 5. The relationship between the type of cancer therapy, HER2 expression, and survival

Variable	Death, N(%)		HR [95% CI]	p
	No	Yes		
HER2 (+)				
Resection and chemotherapy				
No	3 (23.1)	10 (76.9)		
Yes	0 (0.0)	2 (100.0)	0.365 [0.044, 3.007]	0.349
Palliative Therapy				
No	1 (16.7)	5 (83.3)		
Yes	2 (22.2)	7 (77.8)	2.073 [0.593, 7.249]	0.254
HER2 (-)				
Resection and chemotherapy				
No	21 (21.9)	75 (78.1)		
Yes	5 (45.5)	6 (54.5)	0.409 [0.176, 0.947]	0.037
Palliative Therapy				
No	15 (25.0)	45 (75.0)		
Yes	11 (23.4)	36(76.6)	1.502 [0.962, 2.345]	0.073

A non-significant trend toward worse outcomes in HER2-positive patients after 10 months was observed, suggesting HER2 may influence tumor progression, particularly in advanced disease with liver metastasis.[33,37] However, the limited sample size and heterogeneous therapies restrict firm conclusions.

Strengths of this study include its multicenter design and use of standardized IHC with confirmatory CISH. Limitations include retrospective design, lack of staging data, and being constrained to four hospitals in Jakarta, which may limit generalizability. Larger prospective studies with standardized treatment regimens are needed to clarify the prognostic role of HER2 in Indonesian gastric cancer patients.

CONCLUSION

In this multicenter study of gastric adenocarcinoma patients in Indonesia, HER2 expression in gastric adenocarcinoma was 12.3%. HER2 expression tended to be higher in liver metastases, Borrmann type I/II, moderate differentiation, and intestinal type in histopathology results. Combination therapy of resection and chemotherapy provided a protective effect on mortality in this study. Median survival in HER2-positive patients was higher than in HER2-negative patients, but HER2 expression status was not a prognostic factor for two-year survival in gastric adenocarcinoma.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest related to this study.

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AUTHOR CONTRIBUTIONS

All authors contributed to data interpretation, critically reviewed the manuscript, and approved the final version for publication.

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DATA AVAILABILITY

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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