Prognostic Factors in Patients with Advanced HER2-Positive Gastric Cancer Treated with Trastuzumab-Based Chemotherapy: a Cohort Study

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Abstract
Purpose Prognostic factors for the survival of patients with advanced HER2-positive gastric cancer treated with trastuzumab-based chemotherapy remain controversial. The aim of this study was to identify the clinical factors that predict prognosis in patients with advanced HER2-positive gastric cancer.

Methods We retrospectively reviewed the medical records of HER2-positive gastric cancer patients treated with trastuzumab-based chemotherapy at our institution. Clinical features and laboratory test results that considered prognostic factors were re-examined. Overall survival (OS) was estimated using the Kaplan–Meier method. Univariate analysis was performed with the log-rank test and multivariate analysis was performed using Cox’s proportional hazard regression model.

Results A total of 133 patients with advanced HER2-positive gastric cancer were enrolled. The median OS in this cohort was 18.7 months. Four prognostic factors: visceral metastasis (lung or liver), levels of hemoglobin (Hb) (< 11.6 g/dl), lactate dehydrogenase (LDH) (> 222 mg/dl), and C-reactive protein (CRP) (> 0.14 mg/dl), were identified as independent prognostic factors. The patients were placed into three groups according to their number of prognostic factors. These included low (0, 1), moderate (2, 3), and high (4) risk factors. The OS was separated into three categories with a median OS of 32.0, 18.7, and 10.1 months, respectively. Compared to the low-risk group, hazard ratios for the moderate- and high-risk groups were 1.75 and 3.49, respectively.

Conclusion Visceral metastasis and abnormal Hb, LDH, and CRP levels were associated with unfavorable OS. These findings may be beneficial for the management of advanced HER2-positive gastric cancer treated with trastuzumab-based chemotherapy.

Keywords HER2 · Gastric cancer · Trastuzumab · Prognostic factor · Visceral metastasis · Low hemoglobin · High LDH · High CRP

Background
Gastric cancer is currently the third most common cause of cancer-related deaths and the fifth most commonly diagnosed cancer worldwide [1]. The standard of care for advanced gastric cancer includes systemic chemotherapy with fluoropyrimidine plus platinum. However, the prognosis of advanced gastric cancer remains poor. The global median overall survival (OS), excluding Japan and Korea, is less than 1 year. Regional differences between Asian and Western countries are well known in terms of gastric cancer etiology and clinicopathological features. Gastroesophageal junction cancer is more common in Western countries. On the other hand, distal
stomach cancer with intestinal metaplasia due to *Helicobacter pylori* infection is more common in East Asia. These two presentations of the disease are associated with their different molecular profiles [2]. In addition, second- or third-line treatments are more prevalent in East Asia. This suggests a lack of efficacy of the first-line option and may explain the difference in prognoses observed throughout the world.

Prognostic factors assist in the prediction of a patient’s outcome. They are beneficial for developing a treatment strategy and follow-up schedule. They are also helpful for obtaining informed consent prior to initiating chemotherapy. Several gastric cancer prognostic factors have been previously proposed [3–5] and are included in the Royal Marsden Hospital (RMH) Index, Glasgow Prognostic Score (GPS), and Japan Clinical Oncology Group (JCOG) Prognostic Index. However, their true prognostic value has not yet been clearly established. Asian and Western disparities in the prognosis of advanced gastric cancer may be attributed to inconsistencies in the prognostic indexes used in various studies.

Human epidermal growth factor receptor 2 (HER2) is a driver oncogene that promotes cell proliferation and inhibits apoptosis. This results in the progression and metastasis of cancer [6]. It is overexpressed in breast and gastric cancers. HER2 overexpression accounts for up to 21% of advanced gastric cancer cases in Japan [7–9]. It displays specific characteristics including predominant intestinal types and an absence of peritoneal and hepatic metastasis compared to HER2-negative gastric cancer [7]. Therefore, treatment regimens for HER2-positive gastric cancer differ from those used for treating HER2-negative gastric cancer. Furthermore, the addition of the anti-HER2 agent trastuzumab to standard chemotherapy results in an improved outcome [10, 11]. Consequently, trastuzumab in combination with chemotherapy has become the standard therapy.

Despite the abovementioned differences, no data focusing on the evaluation of specific prognostic factors in patients with advanced HER2-positive gastric cancer treated with trastuzumab are currently available. Thus, the application of pre-existing prognostic factors to define proper treatment options for HER2-positive gastric cancer seems contradictory. The aim of this study was to identify the clinical factors that predict the prognosis of patients with advanced HER2-positive gastric cancer who were treated with trastuzumab-based chemotherapy.

**Methods**

**Patients and Study Design**

In this retrospective observational study, we enrolled patients with advanced or metastatic HER2-positive gastric cancer. These patients received trastuzumab-based chemotherapy as the first-line chemotherapy in our institution between March 2011 and June 2016. All patients were histologically confirmed to have HER2-positive gastric or gastroesophageal junction adenocarcinoma. The clinical data evaluated in this study were as follows: sex, age, Eastern Cooperative Oncology Group performance status (ECOG PS), measurability, extent of disease, number of metastatic organs, number of metastatic lesions, presence of visceral metastasis, pathological type of gastric cancer, HER2 status, previous adjuvant chemotherapy, previous gastrectomy, the neutrophil-to-lymphocyte ratio (N/L) [12–14], hemoglobin (Hb), serum albumin (Alb), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), C-reactive protein (CRP) [4, 15–17], carcinoembryonic antigen (CEA), and carbohydrate antigen (CA) 19–9. These parameters have been investigated as prognostic survival factors [18]. The reference range values used for the cutoff points of these laboratory data were previously defined in our institution. The exception was the N/L ratio, which was dichotomized according to the median of the collected data. Clinical data and treatment outcomes were collected from electronic medical records. This study was approved by the Institutional Review Board of the Cancer Institute Hospital of the Japanese Foundation for Cancer Research (IRB number 2017–1044).

**HER2 Evaluation**

Immunohistochemistry scoring (IHS) and fluorescent in situ hybridization (FISH) were used as the criteria for HER2 expression, as reported by Hoffman et al. [19] IHC 3+ was defined as positive, corresponding to strong complete or basolateral membranous staining in ≥ 10% of the neoplastic cells in surgical specimens or strong complete or basolateral membranous staining of at least five cohesive cells in a biopsy. A test for HER2 gene amplification by FISH was performed if IHC was equivocal (2+). This corresponded to moderate/weak complete or basolateral membranous staining in ≥ 10% of the neoplastic cells in surgical specimens or moderate/weak complete or basolateral membranous staining of at least five cohesive cells in a biopsy. When FISH results were positive (HER2/CEP17 ≥ 2), the patient was considered to be eligible for trastuzumab-based chemotherapy.

**Treatments and Treatment Outcomes**

Trastuzumab-based chemotherapy regimens included capecitabine and cisplatin (XP, capecitabine 1000 mg/m² administered orally b.i.d. for 14 days, followed by 7 days of drug rest, and cisplatin 80 mg/m² intravenously infused on day 1), fluorouracil and cisplatin (FP, fluorouracil 800 mg/m² per day administered by continuous intravenous infusion...
on days 1 to 5 of each cycle and intravenous cisplatin 80 mg/m² on day 1), S-1, tegafur/gimeracil/oteracil, and oxaliplatin (SOX, S-1 administered orally b.i.d. for 14 days followed by 7 days of drug rest, at a dose according to the body surface area: 80 mg/day for ≤ 1.25 m², 100 mg/day for 1.25–1.5 m², and 120 mg/day for ≥ 1.5 m², and oxaliplatin 100 mg/m² or 130 mg/m² administered intravenously on day 1). Trastuzumab was administered intravenously at a starting dose of 8 mg/kg on day 1, followed by 6 mg/kg every 3 weeks. Trastuzumab-based chemotherapy was administered on a 3-week cycle. Each type of chemotherapy was continued until disease progression, unacceptable toxicity, or patient’s refusal. The exception was cisplatin, which was discontinued after a maximum of six cycles. Objective responses, according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1), were assessed using computerized tomography (CT) or magnetic resonance imaging every 6 to 8 weeks.

**Statistical Analysis**

The OS was used as the primary endpoint. OS was defined as the date of the initial treatment until death from any cause. If patients did not meet the endpoint prior to May 31, 2017, they were censored at the time of the last contact. All statistical analyses were conducted using R (version 3.3.3; 2017–03–06). OS was assessed using the Kaplan–Meier method. The baseline hazards assumption was upheld in our Cox analysis. Martingale residuals were used for residual analysis. Univariate log-rank analysis was used to assess the potential prognostic factors for OS. Independent significant factors were investigated using Cox’s proportional hazard regression model. This included only those clinical factors with a p-value < 0.05 in the univariate analysis, because the number of variants selected with a p-value < 0.1 was too many regarding the number of events in performing multivariate analysis. For the multivariate analysis, a stepwise Akaike’s information criterion [20] method was chosen as the best fit for the regression model to build a scoring system for different risk groups. A multivariate analysis, using R, identified the variants.

**Results**

**Patient’s Demographics and Treatment Regimen**

A total of 133 patients treated with trastuzumab-based chemotherapy between March 2011 and June 2016 were enrolled in the study. The baseline characteristics of the patients are summarized in Table 1. The median age was 65 years (range 21–86 years); 68% were ECOG PS 0, and more than 70% of the patients had their primary tumor in the stomach. Almost all patients (95%) presented with metastatic disease, and 86% of the patients had 1–2 metastatic organs. We categorized lung and liver metastases as visceral metastases according to the ToGA study [10]. Using this criterion, 58% of the patients were determined to have visceral metastasis. Among the patients with visceral metastasis, 75% had liver metastases. Histopathological types of gastric cancer were classified according to the Japanese Classification of Gastric Carcinoma (The 14th Edition). A total of 68% of the patients had differentiated types such as papillary adenocarcinoma and tubular

| Characteristics                                      | N = 133 (%) |
|------------------------------------------------------|-------------|
| Sex                                                   |             |
| Male                                                  | 92 (69)     |
| Female                                                | 41 (31)     |
| Age                                                   |             |
| Median age (years)                                    |             |
| < 65                                                  | 62 (47)     |
| ≥ 65                                                  | 71 (53)     |
| ECOG performance status                               |             |
| 0                                                     | 90 (68)     |
| 1                                                     | 42 (32)     |
| 2                                                     | 1 (1)       |
| Primary tumor site                                    |             |
| Stomach                                               | 97 (73)     |
| Gastro-esophageal junction                            | 36 (27)     |
| Measurable tumor                                      | 116 (87)    |
| Extent of disease                                     |             |
| Locally advanced                                      | 7 (5)       |
| Metastatic                                            | 126 (95)    |
| Number of metastatic sites                            |             |
| 1–2                                                   | 114 (86)    |
| > 2                                                   | 19 (14)     |
| Number of metastatic lesions                          |             |
| 1–4                                                   | 38 (29)     |
| > 4                                                   | 95 (71)     |
| Visceral metastasis (lung or liver)                   |             |
| Yes                                                   | 77 (58)     |
| No                                                    | 56 (42)     |
| Type of gastric cancer                                |             |
| Differentiated                                        | 90 (68)     |
| Undifferentiated                                      | 43 (32)     |
| HER2 status                                           |             |
| IHC 3+                                                | 114 (86)    |
| IHC 2+ /FISH-positive                                 | 19 (14)     |
| Previous chemotherapy                                 | 26 (20)     |
| Previous gastrectomy                                  | 45 (34)     |

ECOG Eastern Cooperative Oncology Group, IHC immunohistochemistry
adenocarcinoma. The remaining patients had undifferentiated types, such as poorly differentiated adenocarcinoma and signet-ring cell carcinoma. Most (86%) were scored as 3+ on IHC for HER2 status. Forty-five patients (34%) had a previous gastrectomy. Among them, 26 patients received S-1 for 1 year as adjuvant chemotherapy.

Treatment regimens combined with trastuzumab are shown in Table 2. Most patients (71%) received cisplatin-based chemotherapy. Twenty-one patients (16%) received the SOX regimen, and 12 patients (9%) received single oral agents such as capecitabine or S-1.

| Chemotherapy regimen | N=133 (%) |
|-----------------------|-----------|
| FP                    | 5 (4)     |
| XP                    | 95 (71)   |
| SOX                   | 21 (16)   |
| Others                | 12 (9)    |
| No. of trastuzumab cycles | Median 9.5 (range 1–68) |
| Dose reduction        | 103 (77)  |

FP fluourouracil + cisplatin, XP capecitabine + cisplatin, SOX S-1 (tegafur/gimeracil/oteracil) + oxaliplatin

Treatment outcomes

The median number of trastuzumab treatment cycles was 9.5 (range 1–68) (Table 2). The median follow-up period was 18.7 months (95% CI 15.4–23.2) for all patients and 16.6 months (95% CI 14.4–18.2) for censored patients. At the data cutoff date of June 2017, there were 89 (67%) deaths, while 15 (11%) patients continued to undergo trastuzumab-based chemotherapy. Among the 115 patients who discontinued trastuzumab-based chemotherapy, 95 patients (83%) received post-treatment. This included systemic therapy in 85 patients (89%) and surgery as conversion therapy in 13 patients (14%). Three patients were lost to follow-up (Fig. 1). Paclitaxel with or without trastuzumab, ramucirumab, irinotecan, and other agents was administered to 85 patients who received salvage systemic therapy. Paclitaxel with trastuzumab therapy was administered to 15 patients. Paclitaxel with ramucirumab therapy was administered to 19 patients. There were no cases in which nivolumab was administered. Pembrolizumab was administered to three patients as part of a clinical trial.

The median OS in this cohort was 18.8 months (95% CI 15.4–23.1) (Fig. 2). The objective response rates by the investigator are shown in Table 3. Among the enrolled patients, 120 had targeted lesions. Complete responses

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**Fig. 1** Study consort flow chart. Diagram of the number of patients who continued and discontinued trastuzumab (t-mab)-based chemotherapy, including those who received post-treatment.
were observed in 3 patients (2%) and partial responses in 74 patients (56%). The response rate was 58%, and the disease control rate was 81%.

**Prognostic Factors**

In the univariate analysis, metastatic lesions per patient (>4), visceral metastasis, median N/L (>3.2), and abnormal test results for Hb (<11.6 g/dl), serum Alb (<4.1 mg/dl), LDH (>222 mg/dl), ALP (>322 IU/l), and CRP (>0.14 mg/dl) levels were significantly associated with shorter OS. The hazard ratios (HRs) are shown in Table 4. On multivariate analysis, visceral metastasis, Hb, LDH, and CRP levels were independent prognostic factors for OS, with HRs of 1.57 (95% CI 0.98–2.50, \( p = 0.059 \)), 1.51 (95% CI 0.97–2.34, \( p = 0.068 \)), 1.50 (95% CI 0.96–2.34, \( p = 0.072 \)), and 1.74 (95% CI 1.01–2.99, \( p = 0.044 \)), respectively. We categorized patients into three risk groups according to the number of OS-associated prognostic factors. Hence, patients with 0–1, 2–3, and 4 prognostic factors were categorized into low-, moderate-, and high-risk groups, respectively. The number of deaths in the low-, moderate-, and high-risk groups was 21, 50, and 18, respectively. The median OS of each group was 32.0, 18.7, and 10.1 months, respectively (Fig. 3).

Table 3  Objective response rate

| Best overall response | \( N = 133 \) (%) |
|-----------------------|------------------|
| CR                    | 3 (2)            |
| PR                    | 74 (56)          |
| SD                    | 24 (18)          |
| PR                    | 19 (14)          |
| ORR                   | 77 (58)          |
| NE or NA              | 13 (10)          |

CR = complete response, PR = partial response, SD = stable disease, ORR = overall response rate, NE = not evaluable, NA = not assessed

Compared to the low-risk group, the HRs of the moderate- and high-risk groups were 1.75 (95% CI 1.05–2.93) and 3.49 (95% CI 1.81–6.71), respectively (Table 5).

**Discussion**

An enhanced understanding of the prognostic factors associated with OS is useful for preparing a treatment plan. Because HER2-positive gastric cancer has a distinct driver oncogene and a specific treatment regimen, prognostic factors in patients treated with trastuzumab should...
be investigated separately. In this study, visceral metastasis (lung or liver metastasis) and Hb, LDH, and CRP levels were identified as significant prognostic factors for OS. Moreover, after stratification by risk group (low, moderate, or high), survival curves were clearly separated. The median OS of each group was 32.0, 18.7, and 10.1 months. The HRs of the moderate- and high-risk groups, when compared to the low-risk group, were 1.75 (95% CI 1.05–2.93) and 3.49 (95% CI 1.81–6.71), respectively. Our data identified for the first time, prognostic factors associated with the survival of patients with advanced HER2-positive gastric cancer. These patients were treated with trastuzumab-based chemotherapy. Various prognostic scores or indices have been suggested for classifying patients with advanced gastric cancer. The most well-known prognostic score is the GPS, which is based on serum biomarkers such as elevated CRP and hypoalbuminemia [21]. GPS has been validated in several types of cancers, including gastric cancer [4, 21, 22]. For upper gastrointestinal cancers such as locally advanced and metastatic esophagogastric cancer, Chau et al. proposed the use of the RMH index. This index was obtained using data from randomized phase III trials in the UK [4]. It consists of ECOG PS (≥ 2), liver metastases, peritoneal metastases, and serum ALP (≥ 100 U/L). Likewise, the JCOG index is based on randomized phase III trials conducted in Japan [17]. It uses ECOG PS ≥ 1, the number of metastatic sites ≥ 2, no prior gastrectomy, and elevated ALP levels as markers of a poor prognosis.

Takahari et al. showed how survival curves were clearly separated when patients were stratified by the JCOG prognostic index. This was opposed to what was observed when they were stratified by the RMH index [3]. The reasons for these inconsistent results could be explained by several disparities in the backgrounds, including clinicopathological features, molecular biology, and treatment strategies, between the UK and Japan studies. First, more than half of the patients had either lower esophageal (27.3%) or gastroesophageal junction cancer (23.0%) in the RMH index sample. However, these tumor locations were less prevalent (generally less than 10%) in Japan [23]. Second, recent data from The Cancer Genome Atlas (TCGA) demonstrated that gastric cancer consists of four molecular categories:

| Table 4 Univariate and multivariate analysis of prognostic factors for overall survival |
|---------------------|---------------------|---------------------|
| Prognostic factors          | N (% )              | Univariate analysis                          | Multivariate analysis                          |
|                          | HR (95% CI)         | p value | HR (95% CI)         | p value |
| Male                     | 92 (69)             | 1.07 (0.68–1.68) | 0.77 | - |
| ≥ 65                     | 71 (53)             | 1.13 (0.75–1.72) | 0.56 | - |
| PS (1–2)                 | 43 (32)             | 1.53 (0.10–2.34) | 0.052 | - |
| Primary tumor site (stomach) | 97 (73)         | 0.91 (0.57–1.45) | 0.7 | - |
| Measurable tumor         | 116 (87)            | 1.67 (0.83–3.32) | 0.15 | - |
| Extent of disease (metastatic) | 126 (95)         | 2.28 (0.72–7.21) | 0.15 | - |
| Metastatic sites per patient (≥ 2) | 19 (14)            | 1.22 (0.69–2.16) | 0.5 | - |
| Metastatic lesions per patient (≥ 4) | 95 (71)         | 1.74 (1.05–2.89) | 0.03 | - |
| Visceral metastasis (lung or liver) | 77 (58)         | 1.69 (1.09–2.60) | 0.017* | 1.57 (0.98–2.50) | 0.059** |
| Type of gastric cancer (por, sig) | 42 (32)         | 1.50 (0.97–2.33) | 0.068 | - |
| HER2 status (IHC 3 +)     | 114 (86)            | 0.68 (0.37–1.24) | 0.21 | - |
| Previous chemotherapy     | 26 (20)             | 0.95 (0.56–1.61) | 0.85 | - |
| Previous gastrectomy      | 45 (34)             | 0.89 (0.57–1.37) | 0.59 | - |
| N/L (median, > 3.2)       | 75 (56)             | 1.69 (1.10–2.61) | 0.016* | - |
| Hb level (< 11.6 g/dl)    | 67 (50)             | 1.67 (1.10–2.55) | 0.016* | 1.51 (0.97–2.34) | 0.068** |
| Alb level (< 4.1 mg/dl)   | 99 (74)             | 2.0 (1.17–3.40) | 0.0096* | - |
| LDH level (> 222 mg/dl)   | 53 (40)             | 1.84 (1.20–2.81) | 0.0043* | 1.50 (0.96–2.34) | 0.072** |
| ALP level (> 322 IU/l)    | 53 (40)             | 2.06 (1.35–3.15) | < 0.001 | - |
| CRP level (> 0.14 mg/dl)  | 89 (67)             | 2.01 (1.24–3.27) | 0.0041* | 1.74 (1.01–2.99) | 0.044* |
| CEA (> 5.0 ng/ml)         | 83 (62)             | 1.17 (0.76–1.79) | 0.48 | - |
| CA 19–9 (< 37.0 U/ml)     | 72 (55)             | 1.28 (0.84–1.96) | 0.25 | - |

HR hazard ratio, CI confidence interval, PS performance status, por poorly differentiated adenocarcinoma, sig signet-ring cell carcinoma, N/L neutrophil/lymphocytes, Hb hemoglobin, Alb albumin, LDH lactate dehydrogenase, ALP alkaline phosphatase, CRP C-reactive protein, CEA carcinoembryonic antigen, CA 19–9 carbohydrate antigen 19–9

* p < 0.05; ** p < 0.1
Epstein-Barr virus (EBV), microsatellite instability (MSI), chromosomal instability (CIN), and genomic stable (GS) type [24]. According to TCGA data, chromosomal unstable tumors are more prevalent in gastroesophageal junction/cardia cancer (65%) than in the gastric body or fundus. This suggests the existence of molecular disparity between the two studies. Third, the majority of patients were treated with an epirubicin, cisplatin, and 5-fluorouracil (ECF) regimen in the RMH index study, although all patients received fluoropyrimidine plus platinum in the JCOG prognostic index study. Finally, post-disease progression treatment is commonly applied in Japan, whereas the proportion of patients receiving post-disease progression treatment is low in Western countries [25]. Takashima et al. emphasized the importance of subsequent treatment to prolong OS by showing a positive correlation between the duration of post-progression survival and the proportion of patients receiving subsequent chemotherapy [26]. Indeed, in the AVAGAST trial, Japanese patients received subsequent chemotherapy with a higher frequency (77%). They had a longer median OS (14.1 months) than patients in the USA or Western Europe (37%; median OS 9.1 months) [7]. These regional differences in the treatment of gastric cancer may cause inconsistent results between the RMH index and JCOG index. This underscores the importance of considering regional differences when identifying prognostic factors.

Notably, this cohort was relatively homogeneous in terms of molecular status and treatment strategy compared with previous studies [4, 17]. HER2-positive gastric cancer, a specific tumor subtype, is associated with intestinal histology, liver metastasis, and the absence of peritoneal metastasis [27]. Indeed, this cohort demonstrated a high incidence of differentiated histology (68%) and visceral metastasis (58%). In addition, according to TCGA, HER2-positive gastric cancer is classified as a chromosomally unstable tumor [24]. Moreover, all patients in our study were treated with

**Table 5** Hazard ratios of moderate- and high-risk groups

|           | N=133 (%) | Median OS (months) | HR (95% CI) |
|-----------|-----------|--------------------|-------------|
| Low (0–1) | 42 (32)   | 32.0               | -           |
| Moderate  | 70 (53)   | 18.7               | 1.75 (1.05–2.93) |
| High (4)  | 21 (16)   | 10.1               | 3.49 (1.81–6.71) |

OS overall survival
trastuzumab-based chemotherapy. Their median OS was higher (18.8 months) than that obtained in previous studies. Under these circumstances, that is advanced HER2-positive gastric cancer treated with trastuzumab-based chemotherapy, we identified four independent prognostic factors for OS. These include the presence of visceral metastases and levels of Hb, LDH, and CRP. Visceral metastasis, especially liver metastasis, is a well-known negative prognostic factor for gastrointestinal cancer. Conventionally, tumor burden is considered one of the reasons why liver metastasis is associated with shorter survival [28]. However, recent data suggest that liver metastasis is associated with aggressive properties such as vascular invasion, angiogenesis, and systemic immune tolerance. It is also associated with fewer infiltrating CD8+ T cells at the invasive margin in distant metastasis [29, 30]. Likewise, lower Hb levels could reflect not only the presence of a primary tumor, which can cause bleeding, but also exhaustion due to a prolonged illness.

Rapid proliferation and abnormal vasculature induce hypoxia within tumors [31]. Regardless of the available oxygen level, tumors mainly rely on the anaerobic glycolysis pathway. This is known as the Warburg effect [32]. Under this metabolic pathway, glucose changes to pyruvate, which is subsequently converted to lactate through catalysis by LDH. As a result, tumor cells take up more glucose and produce more LDH to obtain the energy needed for proliferation. In 18F-FDG-PET, a high maximum standardized uptake value (SUVmax) is recognized as a negative prognostic factor. SUVmax and LDH levels are positively correlated. Therefore, LDH levels could be an indicator of tumor activity [33]. Hypoxia also induces central necrosis in tumors. This results in cancer-related inflammation and increased CRP levels. Recent data suggest that vascular endothelial growth factor (VEGF) is induced by hypoxia. VEGF stimulates immunosuppressive cells such as regulatory T cells, tumor-associated macrophages, and myeloid-derived suppressive cells in the tumor microenvironment [34]. Because one of the mechanisms of action of trastuzumab is antibody-dependent cellular cytotoxicity (ADCC) [35], trastuzumab might not show sufficient efficacy and anti-tumor effects under this immunosuppressive microenvironment. Therefore, our prognostic factors may reflect not only the tumor burden but also the tumor activity and immune status of the host.

In contrast to previous reports, PS was not significantly associated with OS in univariate analysis in our study as all except one of our patients had a PS of 0–1. In addition, there is a limitation in our study when assigning PS between 0 and 1 as it was a retrospective study. In previous studies, a high ALP level has been proposed as an independent risk factor. However, this was not reproduced in the multivariate analysis in this study. The exact reason why high ALP levels were not significantly associated with OS in this study is unclear. Considering the distinct molecular profile of the tumors and treatment strategy of patients with HER2-positive gastric cancer, the prognostic factors for survival may differ from those of patients with HER2-negative gastric cancer.

There are several limitations to this study that should be considered. First, this was a retrospective study conducted at a single institution. Second, the sample size was relatively small, and no comorbidity data were available. Third, peritoneal metastasis, which has been indicated as a prognostic factor in several reports, was not evaluated. Finally, we do not have molecular data regarding the immune status and ADCC activity of trastuzumab under hypoxia. These limitations require further clinical validation using a larger prospective independent cohort and molecular correlative analysis. Nevertheless, considering the low incidence of HER2-positive gastric cancer, these data are valuable. Our study included and analyzed only the patients with advanced HER2-positive gastric cancer treated with trastuzumab-based chemotherapy. Our prognostic factors (visceral metastasis, Hb, LDH, and CRP levels) might not necessarily be specific to HER2-positive gastric cancer, but may prove useful in clinical practice, because it uses a simple and inexpensive scoring system, using laboratory and imaging tests. These factors provide a concrete prognosis stratified according to each risk group, which prognosis differs significantly between the high- and low-risk groups. These factors can be used to assist in the treatment decision-making process for patients with advanced HER2-positive gastric cancer as they are based on the estimated prognosis. It may be of benefit to those with a very poor prognosis, enabling a greater range of choices such as early involvement of the palliative care team, early termination of treatment, or withholding therapy.

**Conclusion**

We identified four independent prognostic factors for the survival of patients with HER2-positive gastric cancer treated with trastuzumab. They included the presence of visceral metastases, levels of Hb, LDH, and CRP. These factors can be useful prognostic markers for the management of HER2-positive gastric cancer.

**Abbreviations**  
ADCC: Antibody-dependent cell cytotoxicity; ALB: Albumin; ALP: Alkaline phosphatase; CA: Carbohydrate antigen; CEA: Carcinoembriogenic antigen; CIN: Chromosomal instability; CRP: C-reactive protein; EBV: Epstein-Barr virus; ECF: Epirubicin, cisplatin, 5-fluorouracil; ECOG: Eastern Cooperative Oncology Group; FDG-PET: Fluorodeoxyglucose positron-emission tomography; FISH: Fluorescent in situ hybridization; FP: Fluorouracil + cisplatin; GPS: Glasgow Prognostic Score; HB: Hemoglobin; HER2: Human epidermal growth factor receptor 2; HR: Hazard ratio; IHS: Immunohistochemistry scoring; JCOG: Japan Clinical Oncology Group;
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Author Contribution SM and TW wrote the manuscript. SM and TM collected the data from the medical records. NI contributed to the statistical analysis. All authors read and approved the final manuscript.

Availability of Data and Materials The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics Approval and Consent to Participate This study was approved by the Cancer Institute Hospital of the Japanese Foundation for Cancer Research Institutional Review Board (2017-1044). The study followed the Declaration of Helsinki by the World Medical Association. Written informed consent was obtained from all study participants.

Consent for Publication Not applicable

Conflict of Interest Shoko Marshall, Takeru Wakatsuki, Tomohiro Matsushima, Naoki Ishizuka, Izuma Nakayama, Hiroki Osumi, Mariko Ogura, Takashi Ichimura, Keisho Chin declare no competing interests. Daisuke Takahari reports lecture-related fees from Taiho, Eli Lilly, Ogura, Takashi Ichimura, Keisho Chin declare no competing interests.

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