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

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Abstract

Background: 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 reveal the clinical factors that predict prognosis in this patient population.

Methods: We retrospectively reviewed the medical records of HER2-positive gastric cancer patients treated with trastuzumab-based chemotherapy in our institution. Clinical features and laboratory test results 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 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), and levels of haemoglobin (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. After classifying the patients in three groups according to their number of prognostic factors, namely low (0,1), moderate (2,3), and high (4) risk, OS curves were separated into three categories with median OS of 32.0, 18.7, and 10.1 months, respectively (p=0.00025). Compared to the low-risk group, hazard ratios for 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.

Conclusion: Visceral metastasis and abnormal Hb, LDH, and CRP test results were associated with unfavourable OS. These findings are helpful for the management of advanced HER2-positive gastric cancer treated with trastuzumab-based chemotherapy.

Background

Gastric cancer is currently the third-most common cause of cancer-related deaths and the fifth-most commonly diagnosed cancer worldwide [1]. In advanced gastric cancer, systemic chemotherapy with fluoropyrimidine plus platinum is regarded as the standard of care. However, the prognosis of advanced gastric cancer is still poor: the global median overall survival (OS), excluding Japan and Korea, is less than 1 year. In terms of gastric cancer's aetiology and clinicopathologic features, regional differences between Asian and Western countries are well known. Gastroesophageal junction cancer is more common in Western countries, whereas 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 different molecular profiles [2]. In addition, second- or third-line treatments are more prevalent in East Asia, suggesting a lack of efficacy of the first-line option that may explain the prognosis differences observed throughout the world.

Prognostic factors assist the prediction of a patient' s outcome and are useful for building a treatment strategy and follow-up schedule, and obtaining informed consent before starting chemotherapy. Several gastric cancer prognostic factors have been previously proposed [3, 4, 5] and 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 been clearly established. Regional disparities in the prognosis of advanced gastric cancer between Asian and Western populations may be attributed to inconsistencies in the prognostic indexes used in different studies.

Human epidermal growth factor receptor 2 (HER2) is a driver oncogene that promotes cell proliferation and inhibits apoptosis, resulting in the progression and extension of cancer [6]. It is overexpressed in breast and gastric cancers. HER2 overexpression accounts for up to 21% of the advanced gastric cancer cases in Japan [7, 8, 9] and shows specific characteristics including predominant intestinal types and absence of peritoneal and hepatic metastasis compared to HER2-negative gastric cancer [7]. Therefore, treatment regimes for HER2-positive gastric cancer differs from those used for treating HER2-negative gastric cancer. Furthermore, the addition of the anti-HER2 agent trastuzumab to standard chemotherapy predicts a better outcome [10, 11]; consequently, trastuzumab in combination with chemotherapy has now 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. Consequently, to apply pre-existing prognostic factors to define proper treatment options for HER2-positive gastric cancer seems contradictory. The aim of this study was to reveal the clinical factors that predict prognosis in patients with advanced HER2-positive gastric cancer who are 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 who received trastuzumab-based chemotherapy as first-line chemotherapy in our institution between March 2011 and June 2016. All patients were histologically confirmed as HER2-positive gastric or gastroesophageal junction adenocarcinoma. Clinical data evaluated in this study were as follows: sex, age, the Eastern Cooperative Oncology Group performance status (ECOG PS), measurability, the extent of disease, the number of metastatic organs, the number of metastatic lesions, the presence of visceral metastasis, the pathological type of gastric cancer, HER2 status, previous adjuvant chemotherapy, previous gastrectomy, the neutrophil-to-lymphocyte ratio (N/L) [12, 13, 14], and levels of haemoglobin (Hb), serum albumin (Alb), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), C-reactive protein (CRP) [4, 15, 16, 17], carcinoembriogenic antigen (CEA), and carbohydrate antigen (CA) 19 – 9. These parameters were investigated as prognostic survival factors [18]. The reference range values used for the cut-off points of these laboratory data were previously defined in our institution, except for the N/L ratio, which was dichotomised 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 hybridisation (FISH) were used as criteria of 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 specimen or strong complete or basolateral membranous staining of at least 5 cohesive cells in biopsy. If IHC was equivocal (2+), which corresponded to moderate/weak complete or basolateral membranous staining in ≥ 10% of the neoplastic cells in surgical specimen or moderate/weak complete or basolateral membranous staining of at least 5 cohesive cells in biopsy, a test for HER2 gene amplification by FISH was performed. When FISH results were positive (HER2/CEP17 ≥ 2), the patient was considered eligible for trastuzumab-based chemotherapy.

Treatments and treatment outcomes

Trastuzumab-based chemotherapy regimens included: capecitabine and cisplatin (XP, capecitabine 1000 mg/m^2 administered orally b.i.d. for 14 days, followed by 7 days of drug rest, and cisplatin 80 mg/m^2 intravenously infused on day 1), fluorouracil and cisplatin (FP, fluorouracil 800 mg/m^2 per day administered by continuous intravenous infusion on days 1 to 5 of each cycle, and intravenous cisplatin 80 mg/m^2 on day 1), and 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 m^2, 100 mg/day for 1.25–1.5 m^2, and 120 mg/day for ≥ 1.5 m^2, and oxaliplatin 100 mg/m^2 or 130 mg/m^2 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, and 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 by computerised tomography (CT) or magnetic resonance imaging every 6 to 8 weeks.

Statistical analysis

OS was used as the primary endpoint. OS was defined from the date of initial treatment until death from any cause. If patients did not meet the endpoint before 31 May 2017, they were censored at the time of last contact. OS was assessed using the Kaplan-Meier method. Univariate log-rank analysis was used to assess potential prognostic factors for OS. The independent significant factors were investigated using Cox's proportional hazard regression model, only including those clinical factors with p-value < 0.05 in the univariate analysis. For the multivariate analysis, Akaike's Information Criterion [20] was chosen as the best fit for the regression model. Variables with a p-value < 0.1 were considered significant. All statistical analyses were conducted using R, version 3.3.3 (2017-03-06).

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 summarised 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 tumour in the stomach. Almost all patients (95%) presented with metastatic disease, and 86% of the patients had 1 to 2 metastatic organs. We categorised lung and liver metastases as visceral metastases, according to the ToGA study [10], and using this criterion, 58% of the patients were determined as having visceral metastasis. Among the patients with visceral metastasis, 75% had liver metastasis. Histopathological types of gastric cancer were classified according to the Japanese Classification of Gastric Carcinoma (The 14th Edition). Sixty-eight percent of the patients had differentiated types such as papillary adenocarcinoma and tubular adenocarcinoma, and the remaining had undifferentiated types, such as poorly differentiated adenocarcinoma and signet-ring cell carcinoma. Most of the patients (86%) were scored as 3 + on IHC for HER2 status. Forty-five patients (34%) had a previous gastrectomy, and among them, 26 patients had received S-1 for one year as adjuvant chemotherapy.

Table 1
Baseline characteristics of patients (n = 133)

Characteristics	N = 133 (%)
Sex	
Male	92 (69)
Female	41 (31)
Age	
Median age (yr)	65 (range: 21–86)
< 65	62 (47)
≥ 65	71 (53)
ECOG performance status	
0	90 (68)
1	42 (32)
2	1 (1)
Primary tumour site	
Stomach	97 (73)
Gastro-oesophageal junction	36 (27)
Measurable tumour	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)

ECOG Eastern Cooperative Oncology Group, *IHC* immunohistochemistry

Characteristics	N = 133 (%)
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	

Treatment regimens combined with trastuzumab are shown in Table 2. The majority of 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.

Table 2
Chemotherapy regimens

Chemotherapy regimen	N = 133 (%)
FP	5 (4)
XP	95 (71)
SOX	21 (16)
Other	12 (9)
No. Trastuzumab cycles	Median 9.5 (range: 1–68)
Dose reduction	103 (77)
FP fluorouracil + 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 cut-off date of June 2017, there were 89 (67%) deaths, while 15 (11%) patients were still undergoing trastuzumab-based chemotherapy. Among the 115 patients who

discontinued trastuzumab-based chemotherapy, 95 patients (83%) received post treatment, including systemic therapy in 85 patients (89%) and surgery as conversion therapy in 13 patients (14%). Three patients were missing because of lost follow-up (Fig. 1). Paclitaxel with or without trastuzumab or ramucirumab, irinotecan, and other agents were administered to the 85 patients who received salvage systemic therapy. Paclitaxel with trastuzumab therapy was administered to 15 patients, and paclitaxel with ramucirumab therapy was administered to 19 patients. There were no cases where nivolumab was administered. Pembrolizumab was administered to 3 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). Objective response rates by investigator are shown in Table 3. Among the enrolled patients, 120 had targeted lesions. Complete responses were observed in 3 patients (2%) and partial responses, in 74 (56%). The response rate was 58% and the disease control rate was 81%.

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

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. Hazard ratios (HR) 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 categorised patients into three risk groups according to their number of OS-associated prognostic factors. Hence, patients with 0–1, 2–3, and 4 prognostic factors were categorised into low-, moderate-, and high-risk groups, respectively. The median OS of each group was 32.0, 18.7, and 10.1 months, respectively (Fig. 3). Compared to the low-risk group, 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).

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 tumour site (stomach)	97 (73)	0.91 (0.57–1.45)	0.7	-	-
Measurable tumour	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*	-	-

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

*$p < 0.05$

**$p < 0.1$

Prognostic factors	N= (%)	Univariate analysis		Multivariate analysis	
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* haemoglobin, *Alb* albumin, *LDH* lactate dehydrogenase, *ALP* alkaline phosphatase, *CRP* C-reactive protein, *CEA* carcinoembryonic antigen, *CA 19 − 9* carbohydrate antigen 19 − 9					
*$p < 0.05$					
**$p < 0.1$					

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 (2–3)	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			

Discussion

A better understanding of the prognostic factors associated with OS is useful for making treatment decisions. 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 being stratified 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, and 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 identify, for the first time, prognostic factors associated with the survival of patients with advanced HER2-positive gastric cancer who were treated with trastuzumab-based chemotherapy.

Various prognostic scores or indexes have been suggested for classifying patients with advanced gastric cancer. The most famous 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 cancer, including gastric cancer [21, 4, 22]. For upper gastrointestinal cancer such as locally advanced and metastatic esophagogastric cancer, Chau et al. proposed the use of the RMH index, which was obtained using data from randomised phase III trials in the UK [4] and consists of ECOG PS (≥ 2), liver metastases, peritoneal metastases, and serum ALP (≥ 100 U/L). Likewise, the JCOG index is based on randomised phase III trials conducted in Japan [17] and uses ECOG PS ≥ 1, the number of metastatic sites ≥ 2, no prior gastrectomy, and elevated ALP level as markers of poor prognosis.

Takahari et al. showed how survival curves were clearly separated when patients were stratified by the JCOG prognostic index, as opposed to what was observed when they were stratified by the RMH index [3]. The reasons why these results were inconsistent could be explained by several disparities in the backgrounds, including clinicopathological features, molecular biology, and treatment strategy, between the UK and Japan studies. First, more than half of the patients had either lower oesophageal (27.3%) or gastroesophageal junction cancer (23.0%) in the RMH index sample, whereas these tumour 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, namely Epstein-Barr virus (EBV), microsatellite instability (MSI), chromosomal instability (CIN), and genomic stable (GS) type [24]. According to TCGA data, chromosomal unstable tumours are more prevalent in gastroesophageal junction/cardia cancer (65%) than in the gastric body or fundus, suggesting the existence of molecular disparity between the two studies. Third, the majority of patients were treated with an epirubicin, cispaltin, 5-fluorouracil (ECF) regimen in the RMH index study, whereas 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. emphasised 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%) and had a longer median OS (14.1 months) than patients in the USA/Western Europe (37%; median OS: 9.1 months) [7]. These regional differences in gastric cancer may cause inconsistent results between the RMH index and JCOG index, and underscore 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 to those of previous studies [4, 17]. HER2-positive gastric cancer, a specific tumour subtype, is

associated with intestinal histology, liver metastasis, and the absence of peritoneal metastasis [27]. Indeed, this cohort demonstrated high incidences of differentiated histology (68%) and visceral metastasis (58%). In addition, according to TCGA, HER2-positive gastric cancer is classified as a chromosomally unstable tumour [24]. Moreover, all patients in our study were treated with trastuzumab-based chemotherapy and their median OS resulted higher (18.8 months) than that obtained in previous studies. Under these circumstances, i.e. advanced HER2-positive gastric cancer treated with trastuzumab-based chemotherapy, we identified four independent prognostic factors for OS: presence of visceral metastases, and levels of Hb, LDH, and CRP. Visceral metastasis, especially liver metastasis, is a well-known negative prognostic factor in gastrointestinal cancer. Conventionally, tumour burden has been considered one of the reasons why liver metastasis is associated with shorter survival [28]. However, recent data suggest that liver metastasis is associated, not only with aggressive properties such as vascular invasion and angiogenesis, but also with systemic immune tolerance 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 tumour, which can cause bleeding, but also exhaustion due to prolonged illness.

Rapid proliferation and abnormal vasculature induce hypoxia within the tumour [31]. Regardless of the available oxygen level, tumours mainly rely on the anaerobic glycolysis pathway, which is known as the Warburg effect [32]. Under this metabolic pathway, glucose changes to pyruvate and pyruvate is subsequently converted to lactate through catalysis by LDH. As a result, tumour cells take up more glucose and produce more LDH to obtain the energy needed for proliferation. In 18F-FDG-PET, a high maximum standardised uptake value (SUVmax) is known as a negative prognostic factor, and SUVmax and LDH levels are positively correlated; therefore, LDH level could be an indicator of tumour activity [33]. Hypoxia also induces central necrosis in tumours, resulting in cancer-related inflammation and increased CRP levels. Recent data suggest that vascular endothelial growth factor (VEGF) is induced by hypoxia and that VEGF stimulates immunosuppressive cells such as regulatory T cells, tumour-associated macrophages, and myeloid-derived suppressive cells in the tumour 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-tumour effect under this immunosuppressive microenvironment. Therefore, our prognostic factors may reflect not only the tumour burden but also the tumour 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 because 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 because it was a retrospective study. In previous studies, high ALP level was proposed as an independent risk factor. However, this was not reproduced in the multivariate analysis of this study. The exact reason why high ALP level was not significantly associated with OS in this study is unclear. Considering the distinct molecular profile of the tumours and treatment strategy of patients with HER2-positive gastric cancer, their prognostic factors for survival may differ from those with HER2-negative gastric cancer.

There are several limitations that should be considered in this study. 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 was indicated as a prognostic factor in several reports, was not evaluated. Finally, we do not have any molecular data in terms of 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, this data is valuable and our simple and inexpensive scoring system, using laboratory and imaging tests, will be useful in clinical practice. These factors can be used to help in the decision-making process that involves patients with advanced HER2-positive gastric cancer, based on the estimated prognosis.

Conclusion

We have identified four independent prognostic factors for the survival of patients with HER2-positive gastric cancer treated with trastuzumab, namely presence of visceral metastases, and 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, cispaltin, 5-fluorouracil
ECOG
Eastern Cooperative Oncology Group

FDG-PET
fluorodeoxyglucose positron-emission tomography
FISH
fluorescent in situ hybridisation
FP
fluorouracil + cisplatin
GPS
Glasgow Prognostic score
HB
haemoglobin
HER2
Human epidermal growth factor receptor 2
HR
Hazard ratio
IHS
Immunohistochemistry scoring
JCOG
Japan Clinical Oncology Group
LDH
lactate dehydrogenase
MSI
microsatellite instability
OS
Overall survival
PS
performance status
RMH
Royal Marsden Hospital
SOX
S-1 (tegafur/gimeracil/oteracil) + oxaliplatin
TCGA
The Cancer Genome Atlas
VEGF
Vascular endothelial growth factor
XP
capecitabine + cisplatin

Declarations

Ethics approval and consent to participate

This study obtained ethics approval from the Cancer Institute Hospital of the Japanese Foundation for Cancer Research Institutional Review Board (2017-1044). It follows the World Medical Association's Declaration of Helsinki. Written informed consent was obtained from the study participants.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding

Author on reasonable request.

Competing interests

Shoko Marshall, Takeru Wakatsuki, Tomohiro Matsushima, Naoki Ishizuka, Izuma Nakayama, Hiroki Osumi, Mariko Ogura, Takashi Ichimura, Keisho Chin have no conflicts of interest to declare; Daisuke Takahari reports lectures related fees from Taiho, Eli Lilly, Bristol-Myers Squibb, Ono, Chugai outside the submitted work; Eiji Shinozaki reports lectures related fees from Chugai outside the submitted work; and Kensei Yamaguchi reports legal fees from Chugai outside the submitted work.

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Authors' contributions

Shoko Marshall and Takeru Wakatsuki wrote the manuscript; Shoko Marshall and Tomohiro Matsushima collected data from medical records; Naoki Ishizuka contributed to statistical analysis; and all authors read and approved the final manuscript.

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References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136:E359-86.

2. Crew KD, Neugut AI. Epidemiology of upper gastrointestinal malignancies. Semin in Oncol. 2004;31:450–64.
3. Chau I, Norman AR, Cunningham D, Waters JS, Oates J, Ross PJ. Multivariate prognostic factor analysis in locally advanced and metastatic esophago-gastric cancer—pooled analysis from three multicenter, randomized, controlled trials using individual patient data. J Clin Oncol. 2004;22:2395–403.
4. Crumley AB, McMillan DC, McKernan M, McDonald AC, Stuart RC. Evaluation of an inflammation-based prognostic score in patients with inoperable gastro-oesophageal cancer. Br J Cancer. 2006;94:637–41.
5. Takahari D, Mizusawa J, Koizumi W, Hyodo I, Boku N. Validation of the JCOG prognostic index in advanced gastric cancer using individual patient data from the SPIRITS and G-SOX trials. Gastric Cancer. 2017;20:757–63.
6. Boku N. HER2-positive gastric cancer. Gastric Cancer. 2014;17:1–12.
7. Matsusaka S, Nashimoto A, Nishikawa K, Miki A, Miwa H, Yamaguchi K, et al. Clinicopathological factors associated with HER2 status in gastric cancer: results from a prospective multicenter observational cohort study in a Japanese population (JFMC44-1101). Gastric Cancer. 2016;19:839–51.
8. Kurokawa Y, Matsuura N, Kimura Y, Adachi S, Fujita J, Imamura H, et al. Multicenter large-scale study of prognostic impact of HER2 expression in patients with resectable gastric cancer. Gastric Cancer. 2015;18:691–7.
9. Terashima M, Kitada K, Ochiai A, Ichikawa W, Kurahashi I, Sakuramoto S, et al. Impact of expression of human epidermal growth factor receptors EGFR and ERBB2 on survival in stage II/III gastric cancer. Clin Cancer Res. 2012;18:5992–6000.
10. Bang YJ, Cutsem EV, Feyereislova A, Chun HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomized controlled trial. Lancet. 2010;376:687–97.
11. Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, et al. S-2 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol. 2008;9:215–21.
12. Templeton AJ, McNamara MG, Seruga B, Vera-Badillo FE, Aneja P, Ocana A, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst. 2014;106:dju 124.
13. Yamanaka T, Matsumoto S, Teramukai S, Ishiwata R, Nagai Y, Fukushima M. The baseline ratio of neutrophils to lymphocytes is associated with patient prognosis in advanced gastric cancer. Oncology. 2007;73:215–20.
14. Chen L, Zuo Y, Zhu L, Zhang Y, Li S, Ma F, et al. Peripheral venous blood neutrophil-to-lymphocyte ratio predicts survival in patients with advanced gastric cancer treated with neoadjuvant

chemotherapy. Onco Targets Ther. 2017;10:2569–80.

15. Lee J, Lim T, Uhm JE, Park KW, Park SH, Lee SC, et al. Prognostic model to predict survival following first-line chemotherapy in patients with metastatic gastric adenocarcinoma. Ann Oncol. 2007;18:886–91.
16. Koo DH, Ryoo B-Y, Kim HJ, Ryu M-H, Lee S-S, Moon J-H, et al. A prognostic model in patients who receive chemotherapy for metastatic or recurrent gastric cancer: Validation and comparison with previous models. Cancer Chemother Pharmacol. 2011;68:913–21.
17. Takahari D, Boku N, Mizusawa J, Takashima A, Yamada Y, Yoshino T, et al. Determination of prognostic factors in Japanese patients with advanced gastric cancer using the data from a randomized controlled trial, Japan clinical oncology group 9912. Oncologist. 2014;19:358–66.
18. Wang Q, Yang Y, Zhang Y-P, Zou Z, Qian X, Liu B, et al. Prognostic value of carbohydrate tumor markers and inflammation-based markers in metastatic or recurrent gastric cancer. Med Oncol. 2014;31:289.
19. Hofmann M, Stoss O, Shi D, Buttner R, Vijver M, Kim W, et al. Assessment of a HER2 scoring system for gastric cancer: results from a validation study. Histopathology. 2008;52:797–805.
20. Akaike H. Information theory and the maximum likelihood principle. In: Petrov BN, Csaki F, editors. 2nd International Symposium on Information Theory. Budapest: Akademiai Ki à do, Budapest; 1973. p. 267 – 81.
21. Forrest LM, McMillan DC, McArdle CS, Angerson WJ, Dunlop DJ. Evaluation of cumulative prognostic scores based on the systemic inflammatory response in patients with inoperable non-small-cell lung cancer. Br J Cancer. 2003;89:1028–30.
22. Al-Shaiba R, McMillan DC, Angerson WJ, Leen E, McArdle CS, Horgan P. The relationship between hypoalbuminaemia, tumour volume and the systemic inflammatory response in patients with colorectal liver metastases. Br J Cancer. 2004;91:205–7.
23. Hasegawa S, Yoshikawa T, Cho H, Tsuburaya A, Kobayashi O. Is Adenocarcinoma of the Esophagogastric Junction Different between Japan and Western Countries? The Incidence and Clinicopathological Features at a Japanese High-Volume Cancer Center. World J Surg. 2009;33:95–103.
24. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014;513:202–9.
25. Hironaka S, Ueda S, Yasui H, Nishina T, Tsuda M, Tsumura T, et al. Randomized, Open-Label, Phase III Study Comparing Irinotecan With Paclitaxel in Patients With Advanced Gastric Cancer Without Severe Peritoneal Metastasis After Failure of Prior Combination Chemotherapy Using Fluoropyrimidine Plus Platinum: WJOG 4007 Trial. J Clin Oncol. 2013;31:4438–44.
26. Takashima A, Iizumi S, Boku N. Survival after failure of first-line chemotherapy in advanced gastric cancer patients: differences between Japan and the rest of the world. Jpn J Clin Oncol. 2017;47:583–9.

27. Sawaki A, Yamada Y, Yamaguchi K, Nishina T, Doi T, Satoh T, et al. Regional Differences in Advanced Gastric Cancer: Exploratory Analyses of the AVAGAST Placebo Arm. Gastric Cancer. 2018;21:429–38.
28. Sasaki K, Morioka D, Conci S, Margonis GA, Sawada Y, Ruzzenente A, et al. The Tumor Burden Score: A New “Metro-ticket” Prognostic Tool For Colorectal Liver Metastases Based on Tumor Size and Number of Tumors. Ann Surg. 2018;267:132–41.
29. Folkman J. What is the evidence that tumors are angiogenesis dependent? J Natl Cancer Inst. 1990;82:4–6.
30. Tumeh PC, Hellmann MD, Hamid O, Tsai KK, Loo KL, Gubens MA, et al. Liver Metastasis and Treatment Outcome with Anti-PD-1 Monoclonal Antibody in Patients with Melanoma and NSCLC. Cancer Immunol Res. 2017;5:417–24.
31. Jain RK. Normalizing tumor microenvironment to treat cancer: bench to bedside to biomarkers. J Clin Oncol. 2013;31:2205–18.
32. Warburg O. On respiratory impairment in cancer cells. Science. 1956;124:269–70.
33. Novelli S, Briones J, Flotats A, Sierra J. PET/CT Assessment of Follicular Lymphoma and High Grade B Cell Lymphoma-Good Correlation with Clinical and Histological Features at Diagnosis. Adv Clin Exp Med. 2015;24:325–30.
34. Lindau D, Gielen P, Kroesen M, Wesseling P, Adema GJ. The immunosuppressive tumour network: myeloid-derived suppressor cells, regulatory T cells and natural killer T cells. Immunology. 2013;138:105–15.
35. Clynes RA, Towers TL, Presta LG, Ravetch JV. Inhibitory Fc receptors modulate in vivo cytotoxicity against tumor targets. Nat Med. 2000;6:443–6.

Figures

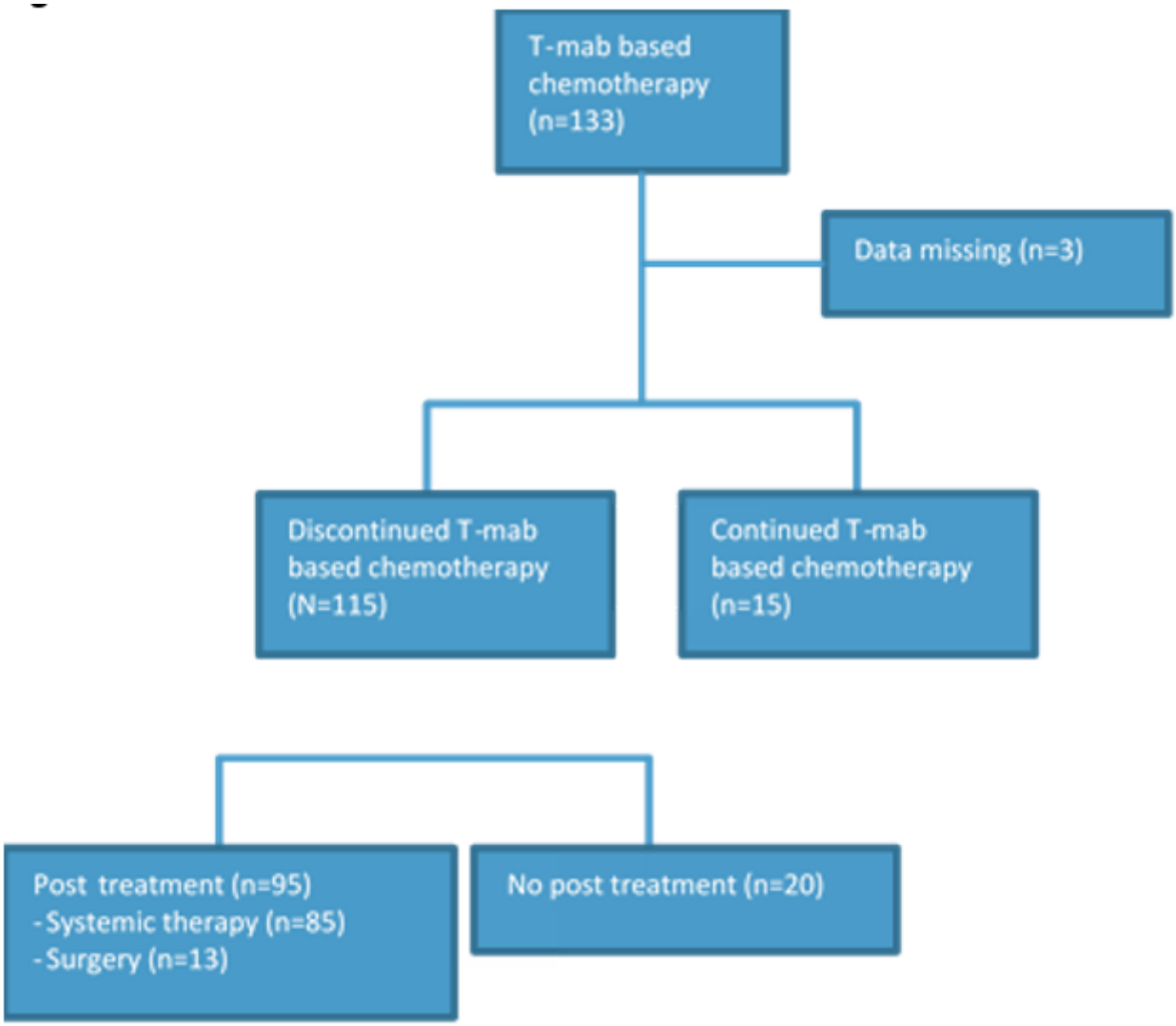
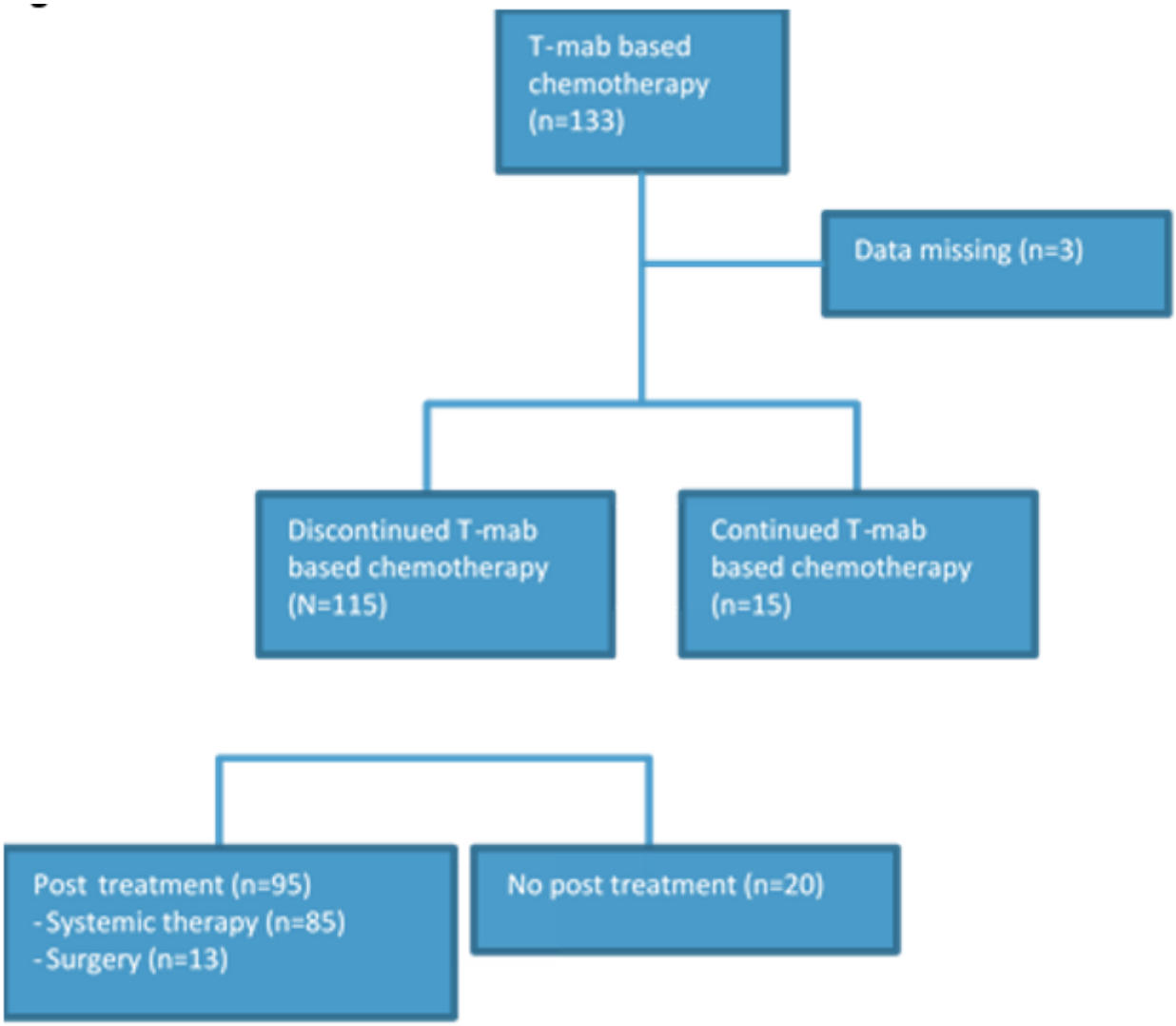


Figure 1

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.



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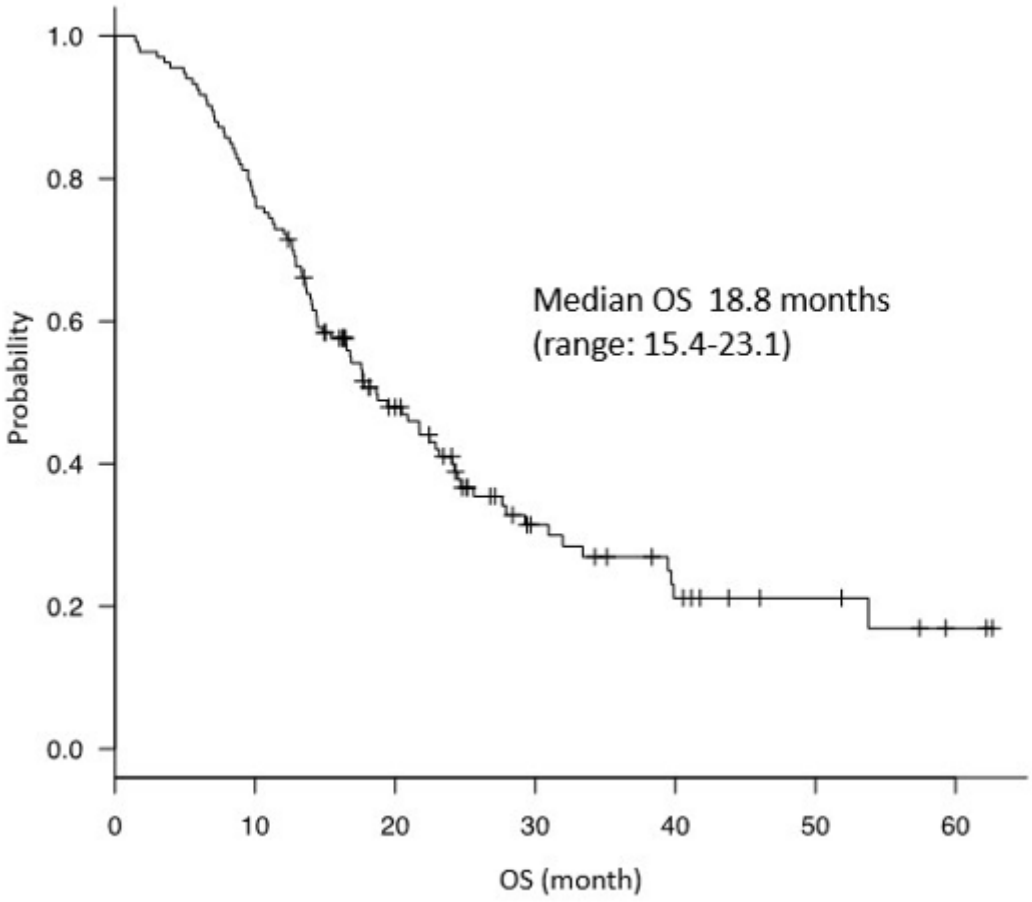
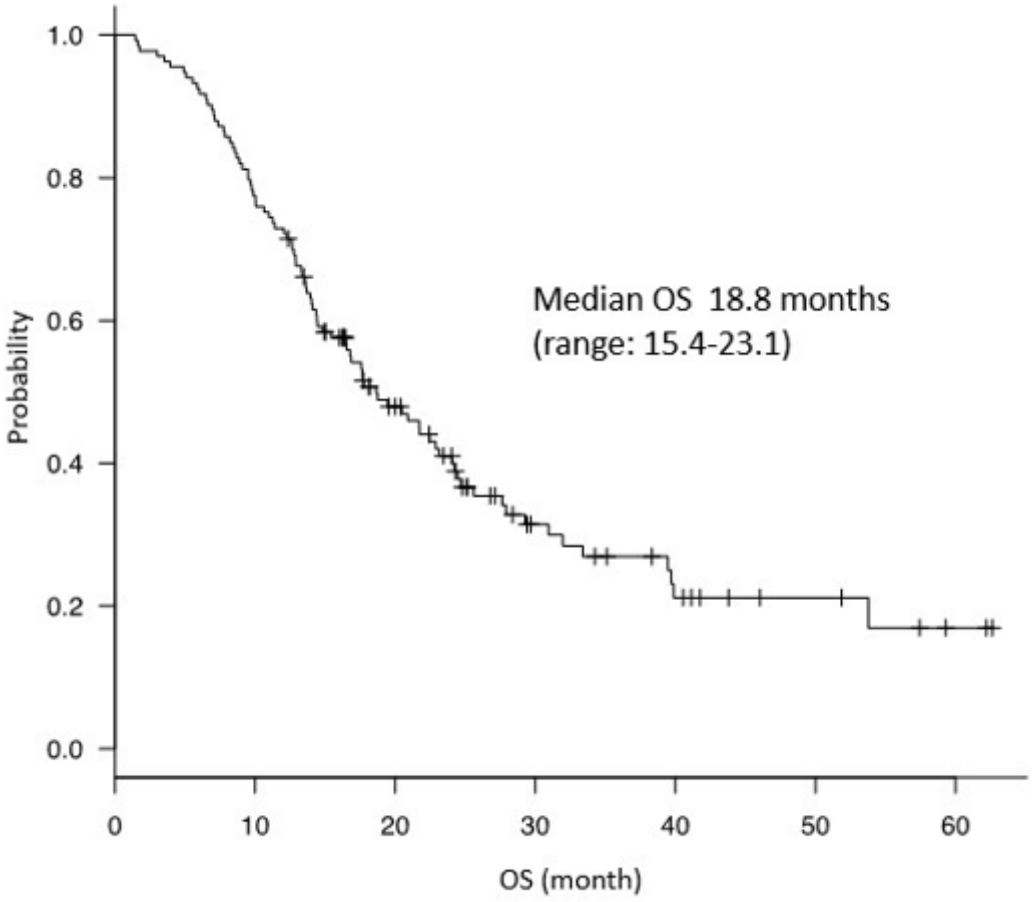


Figure 2

Overall survival (OS) curve. The median OS of the 133 patients enrolled in this study was 18.8 months (95% CI 15.4–23.1).



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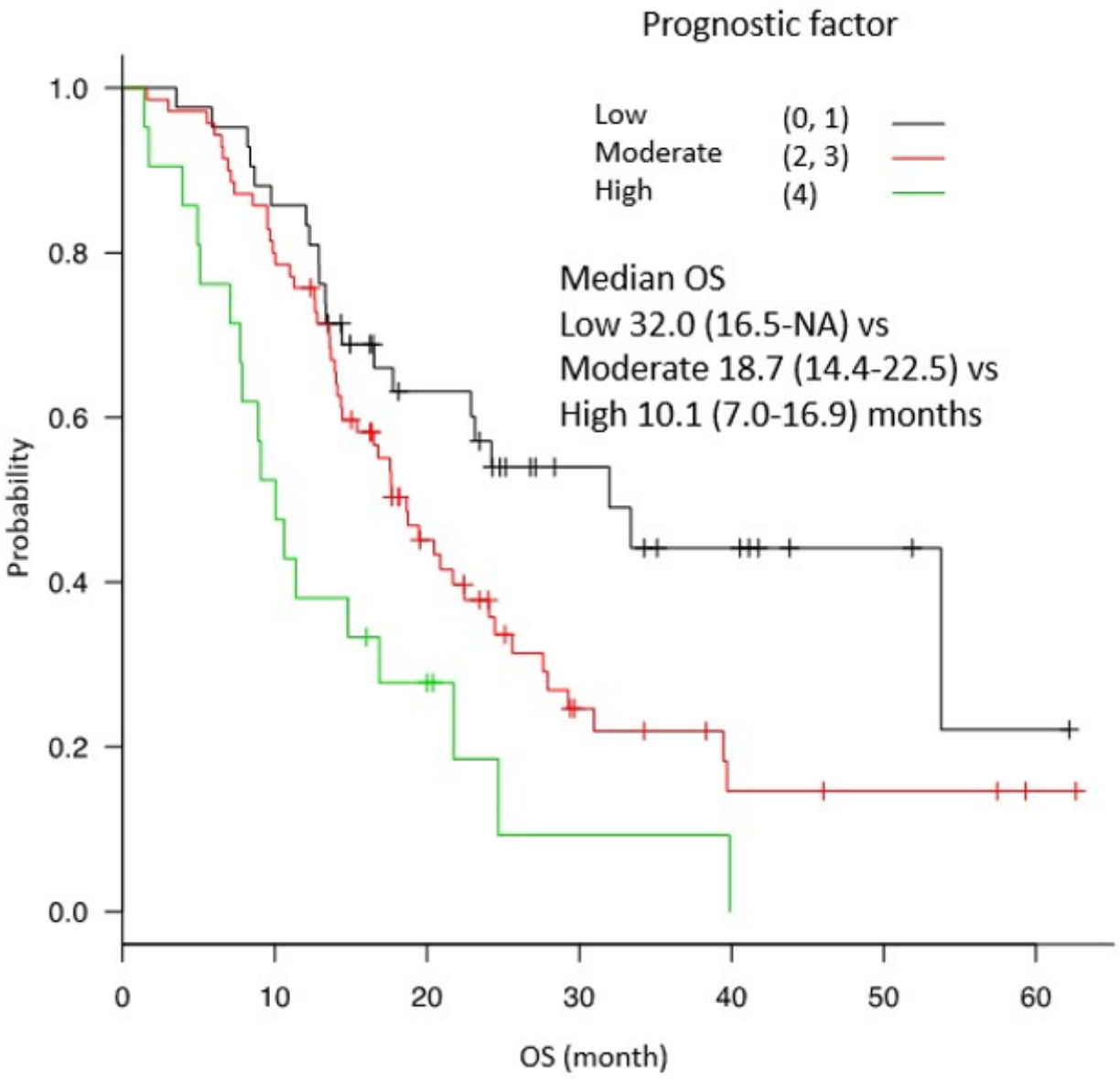
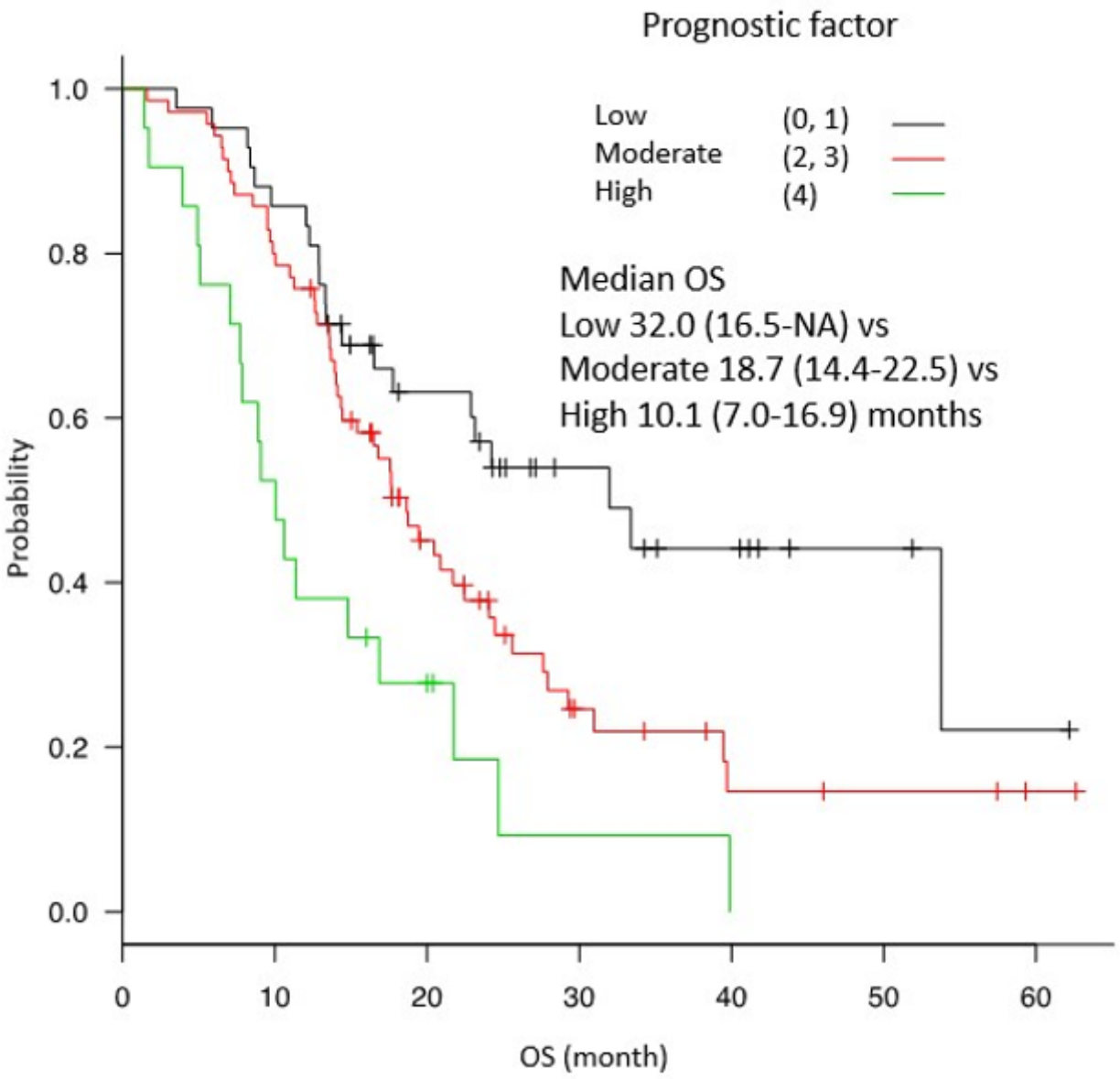


Figure 3

Overall survival (OS) according to risk group. Patients with 0–1, 2–3, and 4 prognostic factors were categorised in low- (black), moderate- (red), and high-risk (green) groups, respectively. Mean overall survival values for each group are indicated in the figure.



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