Prognostic value of moderate or massive ascites in patients with advanced gastric cancer

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Abstract. Advanced gastric cancer is a highly aggressive malignancy. The available literature does not provide the prognostic value of ascites based on their degree, because most clinical trials exclude patients who present with massive ascites. Therefore, this study examined whether the presence or degree of ascites has a prognostic value in 124 patients with advanced gastric cancer. The degree of ascites was assessed using computed tomography and classified as none, small, moderate or massive. The overall survival (OS) was compared based on the presence or degree of ascites. Furthermore, a Cox proportional hazards analysis was performed to ascertain the predictors of OS. The cumulative 1-year and 2-year OS rates in patients without ascites were 43.5 and 20.2%, respectively, whereas those in patients with ascites were 29.1 and 13.6%, respectively (P=0.116). The cumulative 1-year and 2-year OS rates in patients without moderate or massive ascites were 39.5 and 20.9%, respectively; however, those in patients with moderate or massive ascites were 28.0 and 4.0%, respectively (P=0.027). Multivariate analysis showed that diffuse-type [hazard ratio (HR), 1.532; 95% confidence interval (CI), 1.002-2.343; P=0.049], moderate or massive ascites (HR, 2.153; 95% CI, 1.301-3.564; P=0.003) and chemotherapy (HR, 0.189; 95% CI, 0.101-0.352; P<0.001) were significant predictive factors of OS. In conclusion, the present study indicated that moderate or massive ascites may influence the OS of patients with advanced gastric cancer.

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Key words: ascites, peritoneal metastasis, advanced gastric cancer, prognosis, overall survival

Introduction

Stomach cancer accounts for over 1,000,000 cases annually worldwide. It is the fourth leading cause of cancer and the fifth leading cause of mortality (1). Recent studies show that the five-year overall survival (OS) of patients undergoing endoscopic resection or laparoscopy-assisted distal gastrectomy for gastric cancer is 89.0-98.2% (2,3). However, the long-term outcomes of patients with advanced or unresectable gastric cancer remain poor. Despite recent advances in chemotherapeutics, the median OS was reported to be 13.1-17.45 months when patients with unresectable advanced gastric cancer received immunotherapy plus chemotherapy (4,5).

A study from the Netherlands reported a median OS of four months in gastric cancer patients with peritoneal metastasis (6). Intraperitoneal paclitaxel, in addition to systemic chemotherapy, was developed to improve their outcomes; however, the median OS in patients undergoing intraperitoneal paclitaxel with systemic chemotherapy was not found superior to that of patients undergoing systemic chemotherapy alone (17.7 months vs. 15.2 months, P=0.08) in the PHOENIX-GC trial (7). In clinical settings, the presence of massive ascites can impair activities of daily living, resulting in poor prognosis. Additionally, many clinical trials exclude gastric cancer patients with massive ascites caused by peritoneal metastasis, suggesting that data from clinical studies may not reflect the clinical course of patients with peritoneal metastasis.

Therefore, this study aimed to examine whether the presence or degree of ascites in advanced gastric cancer influenced prognostic value using real-world data.

Patients and methods

Patients. We retrospectively included 124 advanced gastric cancer patients who were diagnosed or treated at Fukuchiyama City Hospital from April 2009 to March 2020. We assessed patient characteristics, including blood chemical analysis at diagnosis, age, sex, and Eastern Cooperative Oncology Group Performance Status (ECOG-PS). We also assessed clinicopathological characteristics such as macroscopic type, location, histological

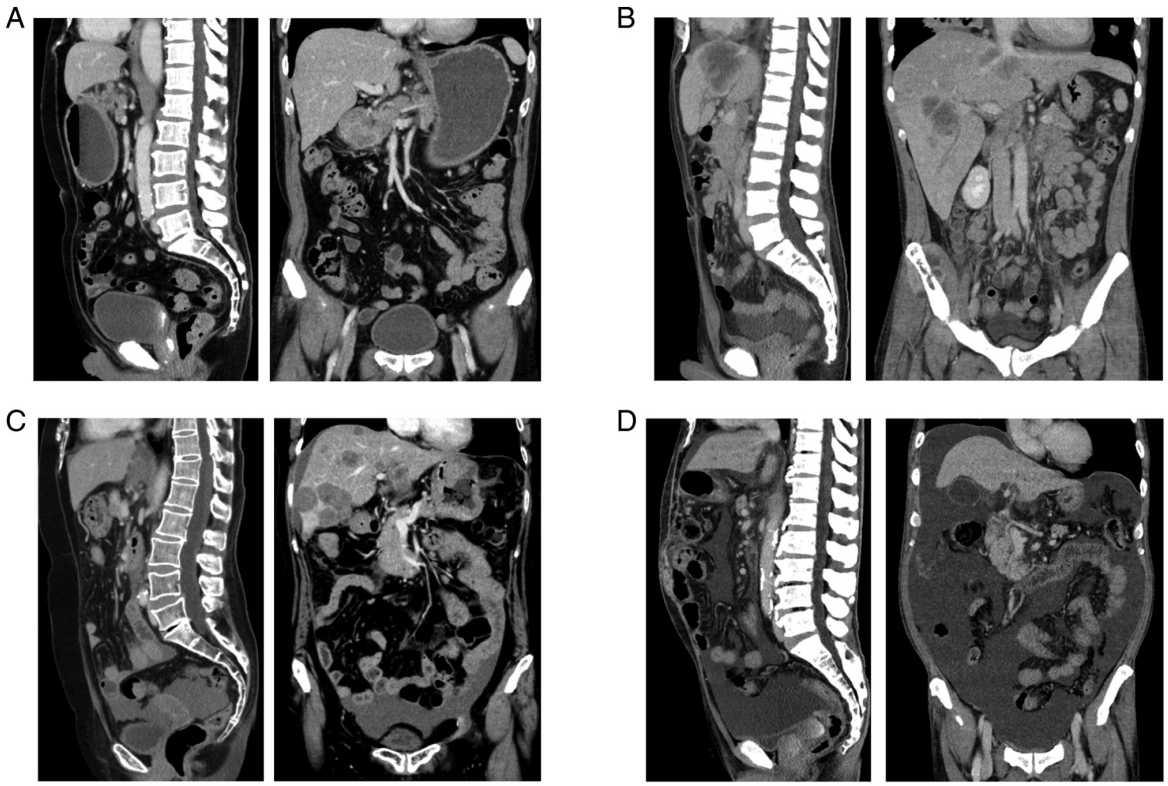

Figure 1. The staging of ascites. (A) The representative images of CT show no ascites. (B) The representative images of CT show small ascites (within the pelvic cavity). (C) The representative images of CT show moderate ascites (beyond the pelvic cavity). (D) The representative images of CT show massive ascites (extending throughout the abdominal cavity). CT, computed tomography.

type, human epidermal growth factor receptor 2 (HER2) status, liver metastasis, bone metastasis, and the presence and degree of ascites. The histological type was classified as intestinal or diffuse type according to the Lauren classification (8). Blood chemical analysis included the following items: white blood cell count, hemoglobin, platelet count, total protein, albumin, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), C-reactive protein (CRP), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9) and neutrophil-to-lymphocyte ratio (NLR). We also assessed psoas muscle mass index (PMI) as a sarcopenia index (9). The calculation of PMI was performed as described previously (10). We also collected the data on the treatment and chemotherapy regimens. This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Fukuchiyama City Hospital (approval no. 2-64). An opt-out method was conducted to obtain informed consent because this was a retrospective study.

Assessment of ascites and overall survival. The degree of ascites was assessed using computed tomography at diagnosis and classified as none, small (within the pelvic cavity), moderate (beyond the pelvic cavity), or massive (extending throughout the abdominal cavity), based on the classification used in previous studies (Fig. 1) (7,11,12). The overall survival (OS) rate was evaluated from the date of computed tomography examination to the last follow-up date or date of death. We compared the OS to the presence or amount of ascites.

Uni- and multivariate Cox proportional hazards analyses were conducted to identify predictors of OS in patients with advanced gastric cancer. The variables included age, sex, ECOG-PS, macroscopic type, histological type, HER2 status, liver metastasis, bone metastasis, ascites, moderate or massive ascites, ALP, LDH, CEA, CA19-9, NLR, PMI, and chemotherapy. The cut-off values for ALP, LDH, CEA, and CA19-9 were defined using the upper limit of the normal ranges. The cut-off values for PMI were defined using medians in the male and female (10). We compared the clinical features of patients with moderate or massive ascites and those without moderate or massive ascites.

Statistical analysis. Statistical analysis was performed using the IBM SPSS Statistics 27 (IBM Japan, Tokyo, Japan) or R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $P<0.05$. Continuous variables are presented as medians and ranges, and comparisons were conducted using the Mann-Whitney U test. Categorical variables are expressed as numbers and percentages, and comparisons were performed using the χ^2 test or Fisher's exact test. The OS rate was evaluated using Kaplan-Meier survival curves and the log-rank tests. Cox proportional hazards model analysis was used to estimate hazard ratio (HR) and 95% confidence interval (CI). Significant variables in the univariate analysis were included in the multivariate analysis.

Results

Clinicopathological characteristics of advanced gastric cancer. Table I presents the clinicopathological characteristics. The median age was 73, and the proportion of males was 66.9%. The median follow-up period was 232.5 days,

Table I. Clinicopathological characteristics of patients with advanced gastric cancer.

Characteristic	Value
Median age, years (range)	73 (31-97)
Sex, n (%)	
Female	41 (33.1)
Male	83 (66.9)
ECOG-PS, n (%)	
0 or 1	96 (77.4)
2 or above	27 (21.8)
Unknown	1 (0.8)
Median follow-up period, days (range)	232.5 (5-2,656)
Deaths during follow-up period, n (%)	112 (90.3)
Macroscopic type, n (%)	
Borrmann type III or IV	64 (51.6)
Others	60 (48.4)
Location, n (%)	
Upper	40 (32.3)
Middle	43 (34.7)
Lower	41 (33.1)
Histological type, n (%)	
Intestinal	56 (45.2)
Diffuse	66 (53.2)
Others	2 (1.6)
HER2 status, n (%)	
Negative	71 (57.3)
Positive	10 (8.1)
Unknown	43 (34.7)
Liver metastasis, n (%)	
Absent	74 (59.7)
Present	50 (40.3)
Bone metastasis, n (%)	
Absent	119 (96.0)
Present	5 (4.0)
Ascites, n (%)	
Absent	70 (56.5)
Present	54 (43.5)
Moderate or massive ascites, n (%)	
Absent	99 (79.8)
Present	25 (20.2)
PMI, cm^2/m^2 (range)	
Male	4.69 (1.98-8.40)
Female	3.39 (1.22-5.41)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; HER2, human epidermal growth factor receptor 2; PMI, psoas muscle mass index.

and 112 patients (90.3%) died. The ratio of Borrmann type III or IV in the macroscopic type was 51.6%. Regarding the histological type, the percentage of the intestinal type was 45.2%, while that of the diffuse type was 53.2%. In this study, 43.5% of the patients had ascites of whom 20.2% had moderate or massive ascites. The median PMI was 4.69 in males, and 3.39 in females.

Table II. Laboratory findings and treatment in advanced gastric cancer patients.

Laboratory findings and treatment pattern	Value
Laboratory findings, median (range)	
White blood cell, /μl	7,025 (3,560-47,500)
Hemoglobin, g/dl	10.75 (3.5-17.8)
Platelet, $10^4/\mu$l	26.6 (11.8-69.6)
Total protein, g/dl	6.4 (4.6-8.5)
Albumin, g/dl	3.4 (1.9-4.5)
ALP, IU/l	267 (116-3,186)
LDH, IU/l	202.5 (122-1,266)
CRP, mg/dl	1.15 (0.01-36.9)
CEA, ng/ml	5.4 (0.7-7,827.1)
CA19-9, U/ml	34.6 (2.0-120,000)
NLR	3.91 (1.20-36.69)
Treatment, n (%)	
Best supportive care	40 (32.3)
First-line chemotherapy	84 (67.7)
Cisplatin-based chemotherapy	38 (30.6)
Oxaliplatin-based chemotherapy	30 (24.2)
Fluoropyrimidine monotherapy	9 (7.3)
Taxane-based chemotherapy	5 (4.0)
Unknown	2 (1.6)

ALP, alkaline phosphatase; LDH, lactate dehydrogenase; CRP, C-reactive protein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; NLR, neutrophil to lymphocyte ratio.

Table II presents the laboratory findings and treatment pattern of patients with advanced gastric cancer. Regarding tumor markers, the median CEA level was 5.4 ng/ml, whereas the median CA19-9 level was 34.6 ng/ml. For the inflammatory markers, the median NLR was 3.91. Regarding treatment, 40 patients (32.3%) received best supportive care, 84 (67.7%) underwent chemotherapy. As for the first-line chemotherapy regimen, 38 (30.6%) patients received cisplatin-based chemotherapy, 30 (24.2%) received oxaliplatin-based chemotherapy, 9 (7.3%) received fluoropyrimidine monotherapy, 5 (4.0%) received taxane-based chemotherapy, while 2 (1.6%) did in other institutions.

Clinical outcomes with respect to ascites. Fig. 2 shows the OS according to the staging of ascites. The median OS was 294.0 days (95% CI, 182.0-406.0 days) in patients without ascites, 216.0 days (95% CI, 0.0-454.3 days) in patients with small ascites, 345.0 days (95% CI, 0.0-808.8 days) in patients with moderate ascites, and 51.0 days (95% CI, 31.3-70.7 days) in patients with massive ascites (P=0.132).

Fig. 3A shows the OS based on the presence of ascites. The median OS was 294.0 days (95% CI, 182.0-406.0 days) in patients without ascites, and 136.0 days (95% CI,

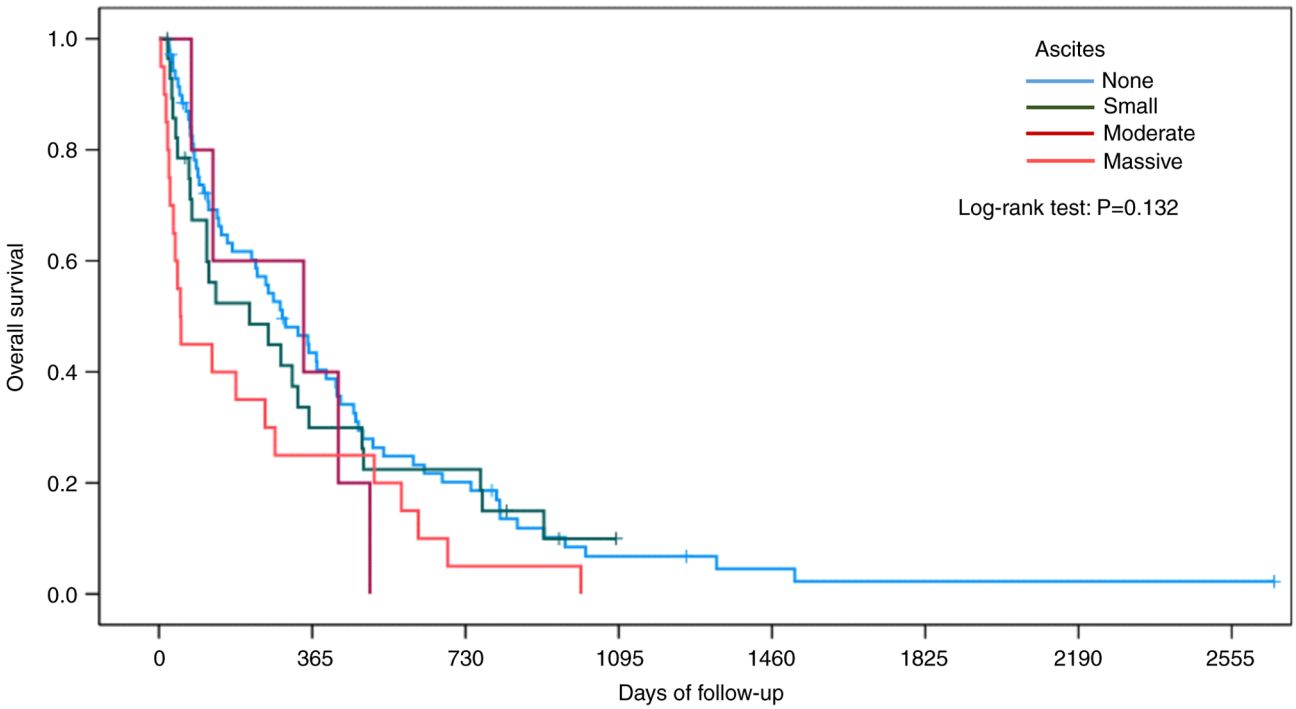

Figure 2. OS according to the staging of ascites, which was classified into none, small, moderate or massive ascites. OS, overall survival.

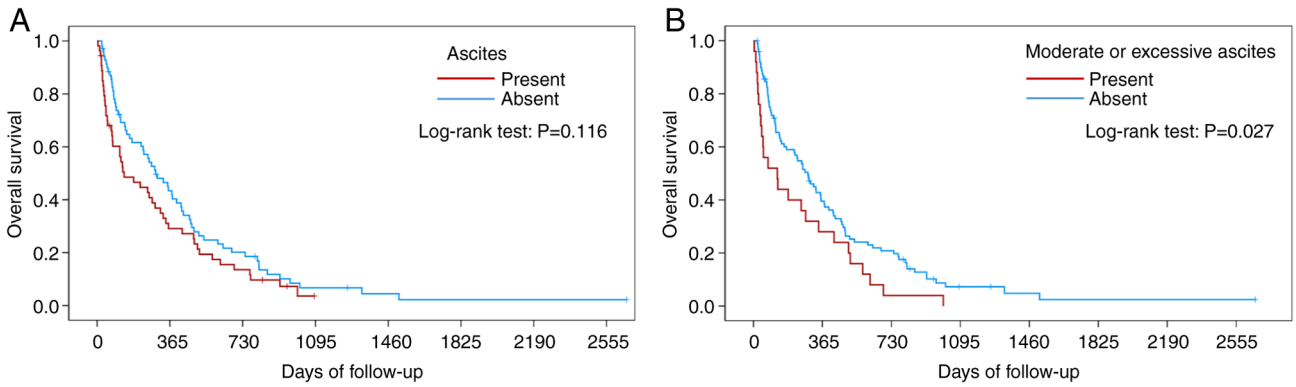

Figure 3. OS according to the presence or degree of ascites. (A) The OS rates in patients with ascites and those without ascites. (B) The OS rates in patients with moderate or massive ascites and those without moderate or massive ascites. OS, overall survival.

17.3-254.7 days) in patients with ascites (P=0.116). The cumulative one-year, and two-year OS rates in patients without ascites were 43.5 and 20.2%, respectively, whereas those in patients with ascites were 29.1 and 13.6%, respectively. Fig. 3B shows the OS according to moderate or massive ascites. The median OS was 289.0 days (95% CI, 204.0-374.0 days) in patients without moderate or massive ascites, and 127.0 days (95% CI, 3.0-251.0 days) in patients with moderate or massive ascites (P=0.027). The cumulative one-year, and two-year OS rates in patients without moderate or massive ascites were 39.5 and 20.9%, respectively, whereas those in patients with moderate or massive ascites were 28.0 and 4.0%, respectively.

Predictors of overall survival in patients with advanced gastric cancer. Table III shows the predictors of OS in patients with advanced gastric cancer. In univariate analysis, age ≥80 (HR, 2.243; 95% CI, 1.503-3.347; P<0.001), ECOG-PS ≥2 (HR, 3.277; 95% CI, 2.049-5.238; P<0.001), diffuse type (HR, 1.551; 95% CI, 1.051-2.289; P=0.027), moderate or massive ascites (HR, 1.650; 95% CI, 1.053-2.586; P=0.029), ALP >321 (HR, 1.569; 95% CI, 1.053-2.336; P=0.027), LDH >245 (HR, 1.535; 95% CI, 1.039-2.267; P=0.031), NLR >5 (HR, 2.187; 95% CI, 1.479-3.232; P<0.001), and chemotherapy (HR, 0.145; 95% CI, 0.091-0.231; P<0.001) were determined to be predictive factors. In multivariate analysis, diffuse type (HR, 1.532; 95% CI, 1.002-2.343; P=0.049), moderate or massive ascites (HR, 2.153; 95% CI, 1.301-3.564; P=0.003), and chemotherapy (HR, 0.189; 95% CI, 0.101-0.352; P<0.001) were significant predictive factors for OS.

Clinical features of patients with moderate or massive ascites and those without moderate or massive ascites. Table IV shows comparative clinical features between patients with

Table III. Predictors of overall survival in patients with advanced gastric cancer.

	Univariate analysis			Multivariate analysis		
Characteristic	HR	95% CI	P-value	HR	95% CI	P-value
Age, years						
80 or above	2.243	1.503-3.347	<0.001	1.387	0.817-2.353	0.226
Sex						
Male	0.775	0.524-1.145	0.200			
ECOG-PS						
2 or above	3.277	2.049-5.238	<0.001	1.661	0.987-2.797	0.056
Macroscopic type						
Borrmann type III or IV	1.387	0.952-2.022	0.089			
Histological type						
Diffuse	1.551	1.051-2.289	0.027	1.532	1.002-2.343	0.049
HER2 status						
Positive	0.961	0.490-1.885	0.909			
Liver metastasis						
Present	0.951	0.647-1.396	0.796			
Bone metastasis						
Present	2.250	0.894-5.663	0.085			
Ascites						
Present	1.351	0.926-1.969	0.118			
Moderate or massive ascites						
Present	1.650	1.053-2.586	0.029	2.153	1.301-3.564	0.003
ALP, IU/l						
>321	1.569	1.053-2.336	0.027	1.722	0.984-3.015	0.057
LDH, IU/l						
>245	1.535	1.039-2.267	0.031	1.184	0.716-1.957	0.511
CEA, ng/ml						
>5	1.001	0.676-1.483	0.996			
CA19-9, U/ml						
>37	1.072	0.722-1.593	0.729			
NLR						
>5	2.187	1.479-3.232	<0.001	1.338	0.863-2.074	0.194
PMI						
Low	1.234	0.849-1.793	0.271			
Chemotherapy						
Present	0.145	0.091-0.231	<0.001	0.189	0.101-0.352	<0.001

ECOG-PS, Eastern Cooperative Oncology Group Performance Status; HER2, human epidermal growth factor receptor 2; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; NLR, neutrophil to lymphocyte ratio; PMI, psoas muscle mass index.

moderate or massive ascites and those without it. Gastric cancer showing Borrmann type III or IV was significantly higher in those with moderate or massive ascites compared with those without moderate or massive ascites (76.0% vs. 45.5%, P=0.012). In contrast, no significant differences were observed regarding age, sex, ECOG-PS, tumor location, histological type, and HER2 status. Regarding laboratory findings, hemoglobin concentration was significantly higher in the patients with moderate or massive ascites than those without moderate or massive ascites (12.3 g/dl vs. 10.4 g/dl, P=0.020). Furthermore, the serum CEA level was significantly lower in patients with moderate or massive ascites than those without moderate or massive ascites (3.4 ng/dl vs. 7.3 ng/dl, P=0.020). As for chemotherapy, the presence or absence of treatment with first- and second-line chemotherapy was not significantly different.

Table IV. Clinical features of patients with moderate or massive ascites and those without moderate or massive ascites.

Characteristic	Patients without moderate or massive ascites	Patients with moderate or massive ascites	P-value
Median age, years (range)	73 (31-97)	72 (31-90)	0.527
Sex, n (%)			0.911
Female	32 (32.3)	9 (36.0)	
Male	67 (67.7)	16 (64.0)	
ECOG-PS, n (%)[a]			0.584
0 or 1	78 (79.6)	18 (72.0)	
2 or above	20 (20.4)	7 (28.0)	
Macroscopic type, n (%)			0.012
Borrmann type III or IV	45 (45.5)	19 (76.0)	
Others	54 (54.5)	6 (24.0)	
Location, n (%)			0.336
Upper	29 (29.3)	11 (44.0)	
Middle	35 (35.4)	8 (32.0)	
Lower	35 (35.4)	6 (24.0)	
Histological type, n (%)[b]			0.108
Intestinal	49 (50.0)	7 (29.2)	
Diffuse	49 (50.0)	17 (70.8)	
HER2 status, n (%)[c]			1.000
Negative	58 (87.9)	13 (86.7)	
Positive	8 (12.1)	2 (13.3)	
Laboratory findings, median (range)			
White blood cell, /μl	6,840 (3,560-47,500)	7,770 (4,140-14,750)	0.130
Hemoglobin, g/dl	10.4 (3.5-17.8)	12.3 (5.4-17.2)	0.020
Platelet, $10^4/\mu$l	26.0 (11.8-69.6)	27.3 (12.4-67.0)	0.711
Total protein, g/dl	6.4 (4.6-8.5)	6.5 (5.2-7.9)	0.165
Albumin, g/dl	3.4 (1.9-4.5)	3.2 (1.9-4.5)	0.456
ALP, IU/l	280 (118-3,186)	253 (116-3,124)	0.581
LDH, IU/l	202 (122-1,266)	203 (156-831)	0.560
CRP, mg/dl	0.69 (0.01-18.51)	2.63 (0.01-36.90)	0.073
CEA, ng/ml	7.3 (0.7-7,827.1)	3.4 (0.7-6,816.0)	0.019
CA19-9, U/ml	36.85 (2.0-120,000)	24.5 (2.1-5,1486.7)	0.908
NLR	3.6 (1.2-36.7)	6.0 (1.2-29.4)	0.054
First-line chemotherapy, n (%)			0.835
Absent	31 (31.3)	9 (36.0)	
Present	68 (68.7)	16 (64.0)	
Second-line chemotherapy, n (%)[d]			1.000
Absent	18 (28.6)	5 (31.3)	
Present	45 (71.4)	11 (68.8)	
PMI, n (%)[e]			0.178
High	52 (53.6)	9 (36.0)	
Low	45 (46.4)	16 (64.0)	

ECOG-PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; CRP, C-reactive protein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; NLR, neutrophil to lymphocyte ratio; PMI, psoas muscle mass index. [a]ECOG-PS data were unknown for 1 patient without moderate or massive ascites. [b]Histological type data were unknown for 1 patient without moderate or massive ascites and 1 patient with moderate or massive ascites. [c]HER2 status data were unknown for 33 patients without moderate or massive ascites and 10 patients with moderate or massive ascites. [d]The patients undergoing the first-line chemotherapy were eligible for this analysis. Second-line chemotherapy data were unknown for 5 patients without moderate or massive ascites. [e]PMI data were unknown for 2 patients without moderate or massive ascites.

Discussion

In this study, we assessed clinicopathological factors, including the degree of ascites, to determine predictive factors in patients with advanced gastric cancer. The OS of patients with moderate or massive ascites was significantly lower than that of patients without moderate or massive ascites. Furthermore, multivariate analysis revealed that diffuse type, moderate or massive ascites, and chemotherapy were pivotal prognostic factors for OS. Collectively, we observed that moderate or massive ascites could influence OS in patients with advanced gastric cancer in a clinical setting.

Previous studies have shown that the presence of ascites or peritoneal metastases is a pivotal prognostic factor in patients with advanced gastric cancer who are undergoing chemotherapy (13-15). A prognostic index consisting of the ECOG-PS, number of metastatic sites, prior gastrectomy, and serum ALP level has been established and validated in advanced gastric cancer using phase III study data (16,17). In clinical settings, patients with advanced gastric cancer who occasionally present with massive ascites cannot receive systemic chemotherapy because of impaired activities of daily living or inadequate oral intake. Absence of chemotherapy, in addition to malignant ascites itself, may worsen the outcomes of such patients. Accordingly, we aimed to evaluate the prognostic factors of advanced gastric cancer, including patients who did not receive chemotherapy.

We determined that age ≥80, ECOG-PS ≥2, diffuse type, moderate or massive ascites, elevated ALP, elevated LDH, elevated NLR, and no chemotherapy were poor prognostic factors in the univariate analysis. Prognostic scoring models in advanced gastric cancer have revealed that malignant ascites and peritoneal metastasis are critical parameters for predicting OS (13-15,18). In contrast, another study showed that peritoneal metastasis is not associated with OS (16). The study used the clinical trial data, in which patients with ascites beyond the pelvic cavity were excluded (19). This may explain why peritoneal metastasis could not influence OS in the study. However, we encountered patients with abdominal distention due to ascites in the clinical setting. Indeed, 20.2% of patients in this study presented with moderate or massive ascites. Our results imply that that moderate or massive ascites could be a more effective prognostic factor than ascites alone. For serum indicators, serum ALP level has been reported to be a predictive factor of OS in previous studies (13-17,20), and serum LDH level was also a prognostic factor in some studies (18,20). The NLR, an inflammatory biomarker, has been recognized as a prognostic factor for solid tumors, including gastric cancer (20-23). Collectively, our data suggest that ALP, LDH, and NLR may influence OS in patients with advanced gastric cancer, as previously reported.

Diffuse type, moderate or excessive ascites, and chemotherapy were the pivotal prognostic factors in multivariate analysis. These findings imply that moderate or massive ascites at diagnosis could influence the OS in patients with advanced gastric cancer.

In this study, the ECOG-PS, or the ratio of patients undergoing first- and second-line chemotherapy did not differ between patients with moderate or massive ascites and those without moderate or massive ascites. In contrast, the NLR and CRP levels tended to be higher in patients with moderate or massive ascites, suggesting carcinomatous peritonitis. Collectively, the poor OS in patients with moderate or massive ascites may be due to systemic inflammation caused by carcinomatous peritonitis. In addition, we determined that the proportion of the macroscopic type showing Borrmann type III or IV was higher in patients with moderate or massive ascites**.** A previous study revealed that macroscopic type III or IV was pivotal in detecting peritoneal metastases in gastric cancer (24). These findings imply that the macroscopic type was associated with peritoneal metastases. Hemoglobin concentration was significantly higher in the patients with moderate or massive ascites. This finding suggests that intravascular dehydration might occur in patients with moderate or massive ascites. Furthermore, the serum CEA level was significantly lower in patients with moderate or massive ascites. The reason for the difference remains unknown. However, the sensitivity of CEA for peritoneal metastasis was 19% (25). Thus, the serum CEA level may not reflect malignant ascites or peritoneal metastasis.

This study had some limitations. First, this was conducted at a single center with a retrospective design; thus, a multicenter prospective study is needed to ascertain our findings. Second, our study included 124 advanced gastric cancer patients. It is difficult to generalize our findings due to the small number of patients. Third, all cases with ascites were not proven to have peritoneal metastases on histological examination. Indeed, peritoneal metastases were not confirmed by histological examinations in five of 25 cases showing moderate or excessive ascites, although peritoneal metastases were clinically diagnosed. Fourth, only Japanese patients with advanced gastric cancer were registered. Therefore, these results should be validated in other populations.

Using real-world data, our study determined that moderate or massive ascites at diagnosis could influence OS in advanced gastric cancer.

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Availability of data and materials

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

Authors' contributions

NI, TOh, TOk, KO, HS, MKK, TTs, JS, KK, TD, KI, OD, NY, KU, TI, TTa, HK and YI contributed to the study's conception and design. Data collection and analysis were performed by NI, TOh, TOk, KO, HS, MKK, TTs and JS. NI, TOh, and TOk confirm the authenticity of all the raw data. All analyses were supervised by KK, TD, KI, OD, NY, KU, TI, TTa, HK and YI. The first draft of the manuscript was written by NI and all authors commented on previous

versions. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Fukuchiyama City Hospital (approval no. 2-64). An opt-out method was conducted to obtain informed consent because this was a retrospective study.

Patient consent for publication

An opt-out method was conducted to obtain informed consent.

Competing interests

All authors declare that they have no competing interests.

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