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Prognostic value of diffusion-weighted imaging to cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy for patients with gastric cancer and peritoneal metastases

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Abstract

Background To investigate the prognostic value of the apparent diffusion coefficient (ADC) calculated from diffusion-weighted imaging (DWI) to cytoreductive surgery (CRS), with or without hyperthermic intraperitoneal chemotherapy (HIPEC), for gastric cancer (GC) patients with peritoneal metastasis (PM).

Methods Between May 2016 and December 2020, 95 newly diagnosed GC patients with PM who underwent CRS combined with HIPEC (CRS + HIPEC group, $n = 61$) and CRS alone (CRS group, $n = 34$) were retrospectively included. All patients underwent abdominal 3.0 T MRI scan, including DWI, and the mean ADC (ADC_{mean}), minimum ADC (ADC_{min}), and maximum ADC (ADC_{max}) values of the whole-volume tumor were measured. The prognostic value of the ADC parameters and clinical and histopathological characteristics were investigated by univariate and multivariate Cox analyses.

Results The median overall survival (OS) periods of the CRS + HIPEC and CRS groups were 18 and 9 months, respectively ([hazard ratio (HR) = 0.44 [95% CI: 0.27–0.71], $P<0.001$). The ADC_{mean} and ADC_{min} values were positively correlated with OS in all patients (Spearman's rho [R] = 0.361 and 0.470), as well as in the CRS + HIPEC ($R = 0.369$ and 0.417) and CRS ($R = 0.192$ and 0.409) groups. The multivariate Cox analysis demonstrated that the $ADC_{mean} \leq 1.39 \times 10^{-3}$ mm^2/s and $ADC_{min} \leq 0.77 \times 10^{-3}$ mm^2/s were significantly associated with a negative prognosis in the total population (HR = 1.68 [95% CI: 1.02–2.75] and 2.48 [95% CI: 1.51–4.08], P all < 0.05) and the CRS + HIPEC group

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(HR = 2.22 [95% CI: 1.19–4.14] and 2.37 [95% CI: 1.26–4.37], *P* all < 0.05), along with pathologic T and N stages. Only the $ADC_{min} \leq 0.77 \times 10^{-3}$ mm^2/s was identified as an independent prognostic factor in the CRS group (HR = 3.49 [95% CI: 1.19–10.20], *P* = 0.022).

Conclusions The minimum ADC was identified as a strong independent prognostic factor for GC patients with PM who underwent CRS, with or without HIPEC.

Keywords Diffusion-weighted imaging, Apparent diffusion coefficient, Gastric cancer, Cytoreductive surgery, Hyperthermic intraperitoneal chemotherapy

Background

Gastric cancer (GC) is the fifth most common malignancy and the fourth leading cause of cancer-related deaths worldwide [1]. The peritoneum is the most common site of metastasis in GC; peritoneal metastasis (PM) has been reported in 20–30% of newly diagnosed patients. Although super-extended (D2plus) D2plus lymphadenectomy after chemotherapy for locally advanced or oligometastatic gastric cancer is feasible and associated with low morbidity/mortality rates [2]. Most of the advanced cases of GC will develop PM within two years of radical surgery for the cancer [3]. The prognosis for GC with PM remains highly poor, even though a standard systemic chemotherapy protocol for the condition has been developed. GC patients with PM have a median overall survival (OS) period of only 8–13 months [4–6].

Complete cytoreductive surgery (CRS), with or without hyperthermic intraperitoneal chemotherapy (HIPEC), is currently the only therapeutic strategy available for improving prognosis in most cases of PM [7–9]. CRS combined with HIPEC (CRS + HIPEC) confers major benefits compared with those achieved with CRS alone in colon and ovarian cancers [7, 9]. However, for GC, the use of CRS + HIPEC remains controversial. Previous multi-center clinical studies have demonstrated that CRS + HIPEC could improve the OS and recurrence-free survival (RFS) compared to that achieved with CRS alone [6, 10]. However, another clinical trial demonstrated that CRS + HIPEC could not improve prognosis [11]. Because of the high tumor heterogeneity and individual differences among patients with GC and PM, the prognostic value of the routine TNM staging system for CRS, with or without HIPEC, is limited and debatable [6, 11, 12]. Therefore, it becomes imperative to explore noninvasive and effective prognostic markers to predict treatment outcomes.

Computed tomography (CT) is the most common noninvasive method for the detection and characterization of GC. Some recent technological developments related to magnetic resonance imaging (MRI), including fast imaging techniques, respiratory motion compensation techniques, use of anti-peristaltic agents, and the introduction of functional MRI, have made MRI a more desirable imaging technique for GC [13]. Diffusion-weighted imaging (DWI)—an advanced MRI technique—allows noninvasive assessment of the biologic features of tumors and is now incorporated into routine clinical practice. Additional DWI could improve the diagnostic sensitivity and detection accuracy for the PM compared to that achieved with conventional MRI alone [14]. In particular, apparent diffusion coefficient (ADC) parameters measured using DWI can be employed for noninvasive and quantitative assessment of tumor cellularity and the biologic structure. These parameters can be used for the diagnosis and prognostic prediction in GC, as well as for evaluating the effects of adjuvant chemotherapy [13, 15]. The mean ADC (ADC_{mean}) is significantly correlated with TNM stages and invasiveness in GC [16–18]. In addition, ADC_{mean} can be used to identify the response to neoadjuvant chemotherapy for locally advanced GC [19–21] and predict the RFS and OS for resectable GC after radical surger [22–24]. As reported in a recent study, apart from the ADC_{mean}, the minimum ADC (ADC_{min}) is also significantly correlated with GC histological types and differentiation [25]. In addition, the ADC_{min} and the maximum ADC (ADC_{max}) are valuable parameters for assessing tumor aggressiveness and prognosis in breast cancer, hepatocellular carcinoma, and nasopharyngeal carcinoma [26–28].

On the basis of these findings, we hypothesized that apart from the ADC_{mean}, the ADC_{min} and ADC_{max} values can also be employed for predicting the treatment outcomes for patients with GC and PM. This study explores the prognostic value of multiparameter ADC values for patients with GC and PM treated with CRS alone or with CRS + HIPEC.

Materials and methods

Patient selection

This retrospective study was approved by the Institutional Review Board of Affiliated Cancer Hospital & Institute of Guangzhou Medical University. The requirement for informed consent was waived off as it is a retrospective study. Between May 2016 and December 2020, a total of 132 newly diagnosed GC patients with PM, as confirmed by surgical pathology, were identified based on the following inclusion criteria: (a) GC patients with PM who underwent CRS, with or without HIPEC; (b)

patients who underwent abdomen 3.0 T MRI, including DWI, before CRS; and (c) patients without distant metastasis at other sites, except for the peritoneum. The exclusion criteria were as follows: (a) patients who had undergone systemic chemotherapy before CRS ($n = 28$); (b) poor quality of DWI ($n = 4$); and (c) a follow-up period of < 1 month ($n = 5$). All cases were evaluated by a multidisciplinary oncology team (MDT), consisting of oncologists, surgeons, radiologists, and nutritionists, to ensure comprehensive treatment planning [29]. The final patient population comprised 95 patients—34 in the CRS group and 61 in the CRS + HIPEC group (Fig. 1).

Acquisition of MR images

All patients underwent epigastric MRI examinations using a 3.0T (Discovery 750, GE Healthcare, Milwaukee, Wisconsin, USA) scanner with a phased-array 16-channel sensitivity encoding abdominal coil prior to HIPEC. Before performing the MR examination, the patients fasted for at least 8 h and drank 500–700 mL of warm water immediately before scanning to distend the gastric lumen. This step was coordinated with respiratory training to ensure normal scan implementation and reduce image motion artifacts. Next, 20 mg of scopolamine–butylbromide was administered through intramuscular injection to control gastric motility after patient positioning. The scanning field of view covered the entire stomach region from the diaphragmatic dome to the level of the renal hilum. Following the method described in previous studies [17, 22], the axial DWI ($b = 0$ and 600 s/mm^2) was carried out by using a respiratory-triggered single-shot spin-echo echo-planar sequence. The ADC map was automatically generated on a voxel-by-voxel basis from the two b-values. Aside from DWI, an axial T2-weighted imaging, with and without fat suppression, and a dynamic enhanced T1-weighted imaging with fat suppression were also performed. For dynamic enhanced T1-weighted imaging, 0.1 mmol/kg of body weight of Gd-DTPA (Magnevist; Schering, Berlin, Germany) was intravenously administered with an automatic injector at a rate of 2.0 mL/s. The detailed MRI parameters are listed in Table 1.

Multiparameter ADC measurements

The ADC measurements were independently performed on a dedicated post-processing workstation (AW VolumeShare 4.7; GE Healthcare, Milwaukee, Wisconsin, USA) by two radiologists (Observer 1: JS, with 8 years

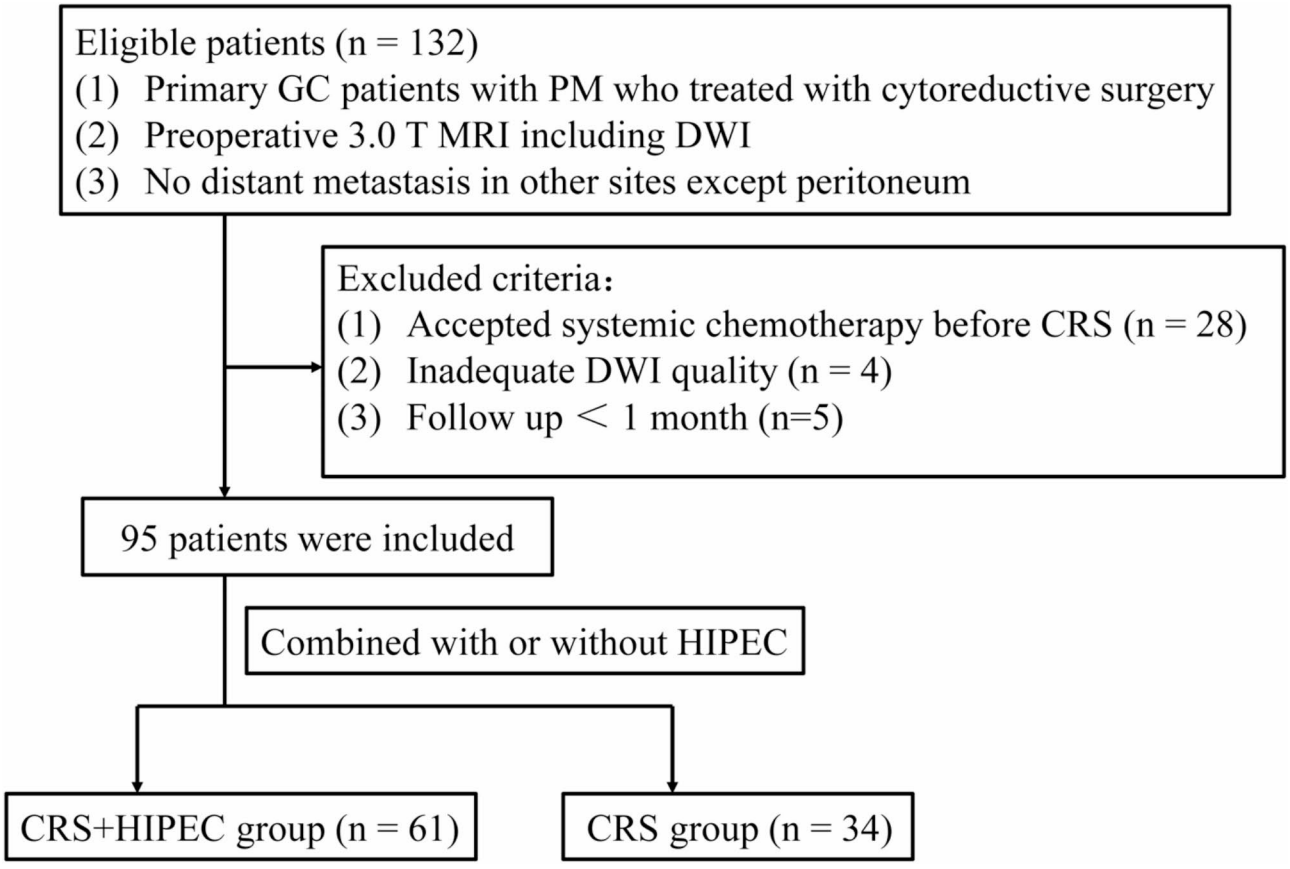

Fig. 1 Flow chart of the patient recruitment pathway

Table 1 MR imaging parameters

Parameter	Pulse Sequence			
	Respiratory fat-suppressed T2-weighted	Respiratory T2-weighted	SS EP Diffusion-weighted*	Dynamic Gadolinium CE
Plane	Axial	Axial	Axial	Axial
TR (msec)	12,857	8571	10,909	4.6
TE (msec)	96.6	96.6	Shortest	Shortest
Section thickness (mm)	6	6	6	2.5
Section gap (mm)	1	1	1	Over contiguous section
Matrix size	320×320	320×320	128×128	320×280
Field of view (mm)	400×400	400×400	360×288	380×304
Flip angle (degrees)	110°	110°	90°	15°
No. of sections	24	24	24	76
No. of signals#	2	2	4	1

Notes:

CE = contrast-enhanced, EP = echo planar, TR = repetition time, TE = echo time, SS = single shot

*b = 0.600 s/mm. #Averaged for each pulse sequence

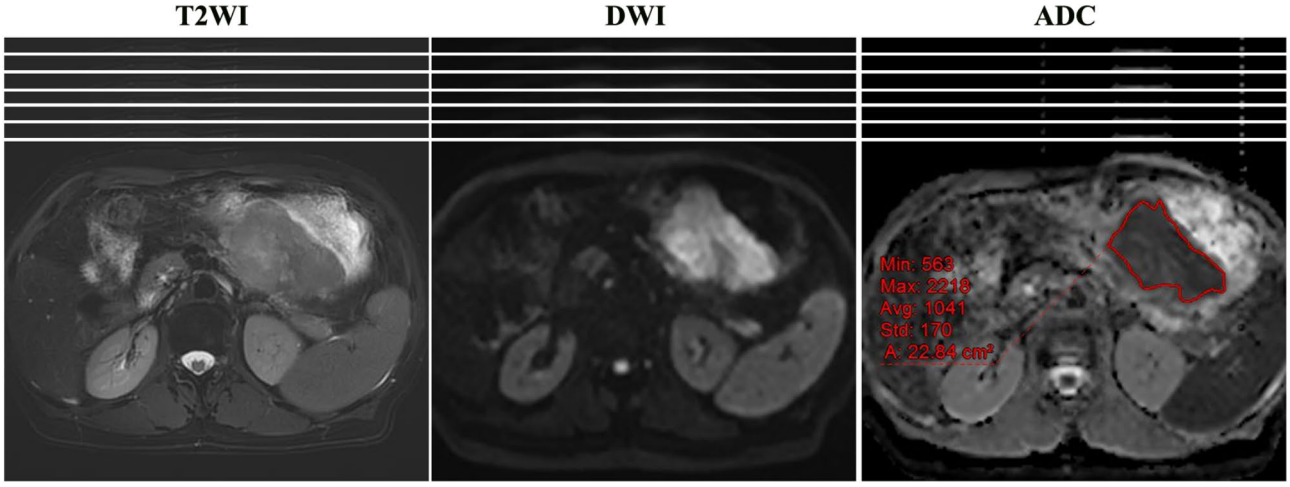

Fig. 2 Measurement of apparent diffusion coefficients (ADCs). The whole-volume ADC values of the tumor were measured by placing regions of interest (ROIs) slice by slice on ADC maps (the illustration only displayed three consistent slices). ROIs covered the edge of the lesion and were drawn along the inner margin of the gastric walls to avoid the inclusion of water in the ROIs. The necrotic components of the tumor were carefully eliminated. Multiparameter ADC values for each section were recorded, including the mean ADC (ADC_{mean}), minimum ADC (ADC_{min}), and maximum ADC (ADC_{max}). Whole-volume ADC values were calculated by averaging the measured ADC values for all sections

of experience in MRI diagnosis; Observer 2: JXY, with 10 years of experience in MRI diagnosis). Before ADC measurements, the tumor location was evaluated by consensus between the two observers to make sure that the regions of interest (ROIs) were positioned on the same lesion. The observers were blinded to pathological findings as well as to the treatment and prognostic results of the patients. Using the method detailed elsewhere [22, 30], the whole-volume ADC values of the tumor were measured by placing ROIs slice by slice on ADC maps. ROIs covered the edge of the lesion and were drawn along the inner margin of the gastric walls to avoid the inclusion of water in the ROIs. The necrotic components (identified by the remarkable hyperintensity on T2W images and hypointensity on DW images) of the tumor were carefully eliminated. The ADC measurement diagram is shown in Fig. 2. The mean values of the ROI area (sum of all sections), as determined by the two observers, were 36.71 ± 19.78 and 36.12 ± 20.11cm^2. Multiparameter ADC values for each section were recorded, including the mean ADC (ADC_{mean}), minimum ADC (ADC_{min}), and maximum ADC (ADC_{max}). Next, the whole-volume ADC values were calculated by averaging the measured ADC values for all sections. The ADC values measured by the two observers were averaged, and the mean values were used for statistical analysis.

CRS and HIPEC procedures

All the 95 patients received complete CRS, which is the surgical removal of visible tumors in the abdominal cavity as completely as possible to reduce tumor burden, including the primary tumor with lymphadenectomy, greater omentectomy, and resection of all peritoneal deposits by combining peritonectomy procedures and resections

of any involved organ. The CRS completeness was evaluated using the completeness of cytoreduction (CC) score [31], as follows: (1) CC-0: no residual peritoneal disease after CRS; (2) CC-1: <0.25 cm of residual disease; (3) CC-2: between 0.25 and 2.5 cm of residual disease; and (4) CC-3: >2.5 cm of residual tumor or the presence of a sheet of unresectable tumor nodules. Only the CC scores of 0 and 1 were identified as CRS completeness.

In the 61 patients who underwent the CRS + HIPEC treatment protocol by using the closed treatment mode, four perfusion tubes (two for inflow and two for outflow) were placed under laparoscopic or direct open visual guidance, allowing continuous peritoneal lavage perfusion in a closed abdominal state. As described in previous study [32], the heated perfusate was circulated at a flow rate of 400 – 600 mL/min and a perfusion volume of 2 L/m^2 for 60–90 min was delivered using the BRTRG-I hyperthermic perfusion intraperitoneal treatment system (Bright Medical Tech., Guangzhou, China). The perfusion temperature was 43 ± 0.1 °C. The following chemotherapy drug dosages were employed: paclitaxel (75–100 mg/m^2) or platinum (oxaliplatin: 100–130 mg/m^2 or cisplatin: 50–75 mg/m^2). HIPEC was implemented on days 1, 3, and 5, 3–5 times as needed, with a median frequency of 3 (range: 2–5).

Follow-up

The endpoint of this study was the OS period from CRS to death from any cause or the last follow-up of the surviving patient. The OS status was determined from the visit to the outpatient department or via telephone calls to patients who could not go for regular hospital visits. The last patient was included in December 2020. The cut-off time for the final follow-up was November 2023, ensuring a potential minimal follow-up period of 36 months. The 3-year OS rate was determined for both the CRS alone and CRS + HIPEC groups.

Statistical analyses

All statistical analyses of the data were implemented by using R software (version 4.0.2; https://www.r-project.org). $P < 0.05$ was identified as statistically significant. Continuous quantitative data were presented as the mean ± standard deviation (SD) or median (range). The independent *t*-test or Mann–Whitney *U*-test was applied to compare differences among the data that obeyed or did not obey normal distribution, respectively. Categorical variables and the 3-year OS rates were expressed as numbers (%). Pearson's χ^2 was performed to analyze the differences. The interobserver reproducibility of ADC measurements between the two observers was assessed based on intraclass correlation coefficients (ICC). An ICC of >0.75 indicated good reproducibility [33]. Univariate Cox regression analysis was used to evaluate the potential association of clinicopathological features and multiparameter ADC values with death. A multivariate Cox regression analysis was performed to determine the independent relative risk for death. Spearman's correlation coefficient (*R*) was applied to assess the correlation of multiparameter ADC values with the OS period. The Kaplan–Meier survival curve was employed to determine the relationship between multiparameter ADC values and OS by using the log-rank test.

Results

Patient characteristics

Among the 95 GC patients with PM, 61 patients (64.21%) were grouped into the CRS + HIPEC group and 34 patients (35.79%) were assigned to the CRS group, based on the therapeutic methods used. The following frequencies of the baseline characteristics were employed: age, gender, tumor site, pathological TN stage, histologic type, and systemic chemotherapy (Table 2). No statistical significance was observed among the baseline characteristics of the CRS + HIPEC and CRS groups. The median follow-up period was 22 months (range: 2–65 months) for the CRS + HIPEC group (47 of 61 events [77.05%]) and 12 months (range: 2–44 months) for the CRS group (30 of 34 events [88.24%]), while it was 16 months (range: 2–65 months) for all patients. As shown in Fig. 3, the OS of patients treated with CRS + HIPEC was significantly longer than that of those treated with CRS alone (median OS: 18 vs. 9 months, hazard ratio [HR] = 0.44 [95% CI: 0.27–0.71], $P < 0.001$). The 3-year OS rate of patients treated with CRS + HIPEC was also significantly higher than that of those treated with CRS alone (32.79% vs. 11.76%, $P = 0.024$). The detailed characteristics are listed in Table 2.

Interobserver agreement for ADC measurements

The ADC_{mean} and ADC_{min} measurements demonstrated excellent interobserver reproducibility, with the ICC values of 0.881 (95% confidence interval [CI]: 0.823, 0.921) and 0.846 (95% CI: 0.773, 0.897), respectively. The interobserver reproducibility of ADC_{max} was also good (ICC = 0.704, 95% CI: 0.578, 0.797). As shown in Fig. 4a-c, Spearman's correlation analysis plot presented good agreement for ADC measurements determined by the two observers, with the correlation coefficient rho (*R*) values of 0.827, 0.84, and 0.674 for ADC_{mean}, ADC_{min}, and ADC_{max}, respectively. The average of these ADC values, as displayed in Table 3; Fig. 4d, showed no significant difference between the CRS + HIPEC and CRS groups.

The median ADC values for all patients were used as the cutoff for risk grouping. As shown in Table 4, univariate Cox analysis indicated that $ADC_{mean} \le 1.39 \times 10^{-3}$ mm^2/s and $ADC_{min} \le 0.77 \times 10^{-3}$ mm^2/s were associated with a negative prognosis in all patients, as well as

Table 2 Patient characteristics

Characteristic	All patients (*n* = 95)	CRS + HIPEC group (*n* = 61)	CRS group (*n* = 34)	*P*
Age (years)*	60.32 ± 11.93	61.56 ± 12.04	58.34 ± 11.57	0.452
Gender, (No. %)				
Male	59 (62.1%)	34 (55.7%)	25 (73.5%)	0.23
Female	36 (37.9%)	27 (44.3%)	9 (26.5%)	
Tumor site, No. (%)				
Gastric antrum	10 (10.5%)	7 (11.5%)	3 (8.8%)	0.784
Gastric body	26 (27.4%)	2 (32.8%)	6 (17.6%)	
Esophagogastric junction	34 (35.8%)	19 (31.1%)	15 (44.1%)	
Asystematic	25 (26.3%)	15 (24.6%)	10 (29.4%)	
Pathological T stage, No. (%)				
T2 or T3	42 (44.2%)	27 (44.3%)	15 (44.1%)	0.99
T4	53 (55.8%)	34 (55.7%)	19 (55.9%)	
Pathological N stage, No. (%)				
N0 or N1	40 (42.1%)	27 (44.3%)	13 (38.2%)	0.85
N2 or N3	55 (57.9%)	34 (55.7%)	21 (61.8%)	
Histologic type, No. (%)				
Adenocarcinoma	79 (83.2%)	52 (85.2%)	27 (79.4%)	0.767
Signet ring and mucinous cell carcinoma	16 (16.8%)	9 (14.8%)	7 (20.6%)	
Pathological differentiation, No. (%)				
Poorly differentiated	21 (22.1%)	17 (27.9%)	4 (11.8%)	0.193
Moderately and well differentiated	74 (77.9%)	44 (72.1%)	30 (88.2%)	
Systemic chemotherapy after CRS, No. (%)				
Yes	20 (21.1%)	12 (19.7%)	8 (23.5%)	0.907
No	75 (78.9%)	49 (80.3%)	26 (76.5%)	
OS (months, median [range])#	16 (2, 65)	18 (2, 65)	9 (2, 44)	0.003
3-year OS rate, No. (%)	24 (25.26%)	20 (32.79%)	4 (11.76%)	0.024

Note:

Categorical data are presented as numbers, with percentages in parentheses. *P* values were calculated using the χ2 test or Fisher exact test for categorical variables. *Continuous data are presented as mean ± SD, and *P* value was calculated using the independent *t*-test. #Continuous data are presented as median (range), and *P* value was calculated using the Mann-Whitney *U*-test. OS = overall survival, CRS = cytoreductive surgery. HIPEC = hyperthermic intraperitoneal chemotherapy

in the CRS + HIPEC and CRS groups; however, no such prognostic value was observed for ADC_{max}. Pathologic TN stages and differentiation were identified as strong prognostic factors for all patients, while pathologic TN and T stages and differentiation were found to be strong prognostic factors in the CRS + HIPEC and CRS groups, respectively. The multivariate analysis demonstrated that $ADC_{mean} \leq 1.39 \times 10^{-3}$ mm^2/s and $ADC_{min} \leq 0.77 \times 10^{-3}$ mm^2/s, along with pathologic T and N stages, were independently associated with death risk among all patients (HR = 1.68 [95% CI: 1.02–2.75] and 2.48 [95% CI: 1.51–4.08], *P* all < 0.05) as well as in the CRS + HIPEC group (HR = 2.22 [95% CI: 1.19–4.14]) and 2.37 [95% CI: 1.26–4.37], *P* all < 0.05) (Table 5). Only $ADC_{min} \leq 0.77 \times 10^{-3}$ mm^2/s was identified as an independent death risk factor in the CRS group (HR = 3.49 [95% CI: 1.19–10.20], *P* = 0.022)

Association of ADC_{mean} and ADC_{min} with OS

The ADC_{mean} was found to be positively related to the OS period among all patients (*R* = 0.361, *P* < 0.01) (Fig. 5a), as well as with the CRS + HIPEC group (*R* = 0.369, *P* = 0.003) (Fig. 5b). However, no significant relation was observed between the ADC_{mean} and the OS period for the CRS group (*R* = 0.192, *P* = 0.276) (Fig. 5c). Kaplan–Meier analysis indicated that patients with $ADC_{mean} \leq 1.39 \times 10^{-3}$ mm^2/s had a significantly shorter OS period than that in patients with $ADC_{mean} > 1.39 \times 10^{-3}$ mm^2/s in all patients (median OS: 11 vs. 22 months, HR = 2.11 [95% CI: 1.34–3.35], *P* = 0.001) (Fig. 5d), as well as in the CRS + HIPEC group (median OS: 14 vs. 40 months, HR = 2.18 [95% CI: 1.20–3.93], *P* = 0.010) (Fig. 5e) and the CRS group (median OS: 8 vs. 15 months, HR = 2.48 [95% CI: 1.16–5.32], *P* = 0.019) (Fig. 5f). The ADC_{min} was positively correlated to the OS period in all patients (*R* = 0.470, *P* < 0.01) (Fig. 6a) and in the CRS + HIPEC (*R* = 0.417, *P* < 0.01) (Fig. 6b) and CRS groups (*R* = 0.409, *P* = 0.016) (Fig. 6c). Kaplan–Meier analysis indicated that $ADC_{min} \leq 0.77 \times 10^{-3}$ mm^2/s was associated with a significantly shorter OS period than that achieved when $ADC_{min} > 0.77 \times 10^{-3}$ mm^2/s in all patients (median OS: 10 vs. 31 months, HR = 2.40 [95% CI: 1.51–3.81], *P* < 0.01) (Fig. 6d),

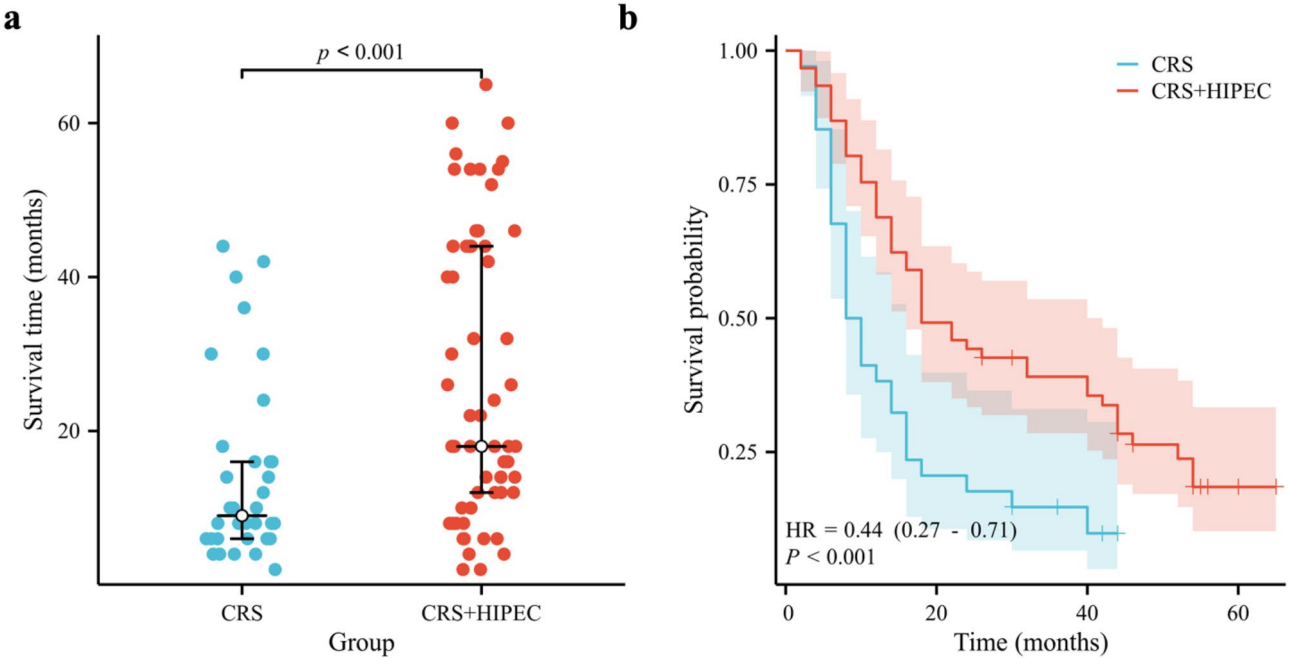

Fig. 3 Comparison of the overall survival (OS) values of the CRS + HIPEC and CRS groups. The OS period of the CRS + HIPEC group was significantly longer than that of the CRS group **(a)**. Kaplan–Meier analysis indicated that the CRS + HIPEC group had a significantly longer OS than that of the CRS group (HR = 0.44, $P < 0.001$) (**b**). CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy

the CRS + HIPEC group (median OS: 14 vs. 40 months, HR = 1.83 [95% CI: 1.03–3.33], $P = 0.039$) (Fig. 6e), and the CRS group (median OS: 8 vs. 15 months, HR = 4.72 [95% CI: 1.82–12.15], $P = 0.001$) (Fig. 6f).

Discussion

This study demonstrated that the OS in patients treated with CRS + HIPEC was significantly longer than in those treated with CRS alone (HR = 0.44, $P < 0.001$). Additionally, the ADC_{mean} value was markedly positively correlated with the OS period in all patients ($R = 0.361$, $P < 0.01$), as well as in the CRS + HIPEC group ($R = 0.369$, $P = 0.003$). The ADC_{min} was significantly positively correlated with the OS period in all patients ($R = 0.470$, $P < 0.01$) and in the CRS + HIPEC ($R = 0.417$, $P < 0.01$) and CRS groups ($R = 0.409$, $P = 0.016$). In particular, the ADC_{min} was identified as a strong independent prognostic factor. The patients with $ADC_{min} \leq 0.77 \times 10^{-3}$ mm^2/s had a significantly shorter OS period than those with $ADC_{min} > 0.77 \times 10^{-3}$ mm^2/s (all patients: HR = 2.40, $P < 0.01$; CRS + HIPEC group: HR = 1.83, $P = 0.039$; CRS group: HR = 4.72, $P = 0.001$). Therefore, our results suggested that ADC measurements can be employed as a noninvasive and dependable method for predicting prognosis in GC patients with PM who underwent CRS, regardless of whether they underwent HIPEC too.

The survival benefits of the CRS + HIPEC protocol for GC remain controversial because of the incomplete nature of the CRS protocol [12]. A previous retrospective study [11] on 159 patients reported a median OS of only 9.2 months for patients undergoing CRS + HIPEC. Notably, the CRS could be completed in only 56% of patients. The largest multicenter prospective study (CYTO-CHIP) conducted so far [6] identified 277 GC patients with PM who were treated with complete CRS, with or without HIPEC, and illustrated that the CRS + HIPEC protocol significantly improved both the median OS (18.8 months) and the 3-year OS rate (26.21%) compared with those (12.1 months and 10.82%, respectively) achieved with CRS alone. Similarly, the median OS (18 months) and the 3-year OS rate (32.79%) of the CRS + HIPEC group were significantly higher than those of the CRS group (9 months and 11.76%, respectively). Thus, the CRS + HIPEC protocol can be considered a more promising and valuable therapeutic strategy for GC patients with PM than the CRS protocol, even when the latter was complete.

GC demonstrates high tumor heterogeneity. In addition, the OS is extremely variable even in patients with the same TNM staging and undergoing the same therapeutic strategies. Therefore, it is crucial to identify feasible prognostic markers for predicting OS in patients with GC. The ADC_{mean} is considered a reliable indicator for predicting the response to neoadjuvant chemotherapy. It is well known that responses to neoadjuvant therapies are associated with prognosis. Li et al. [21] analyzed the baseline ADC_{mean} by considering tumor regression grade (TRG) as the reference standard and

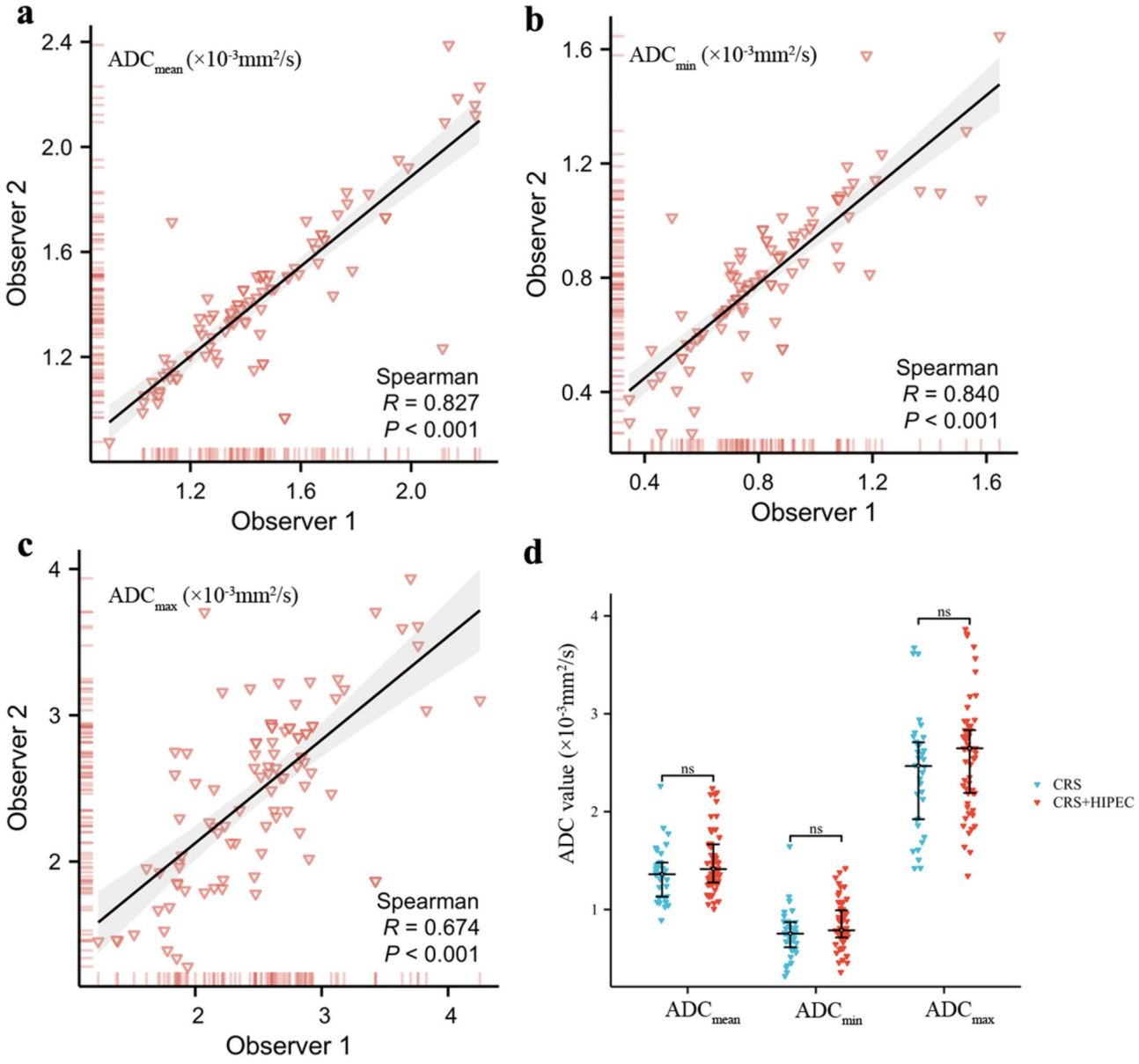

Fig. 4 Spearman's correlation plots presented good measurements agreement for the ADC_{mean}**(a)**, ADC_{min}**(b)**, and ADC_{max}**(c)** between two observers, with the correlation coefficient rho (*R*) values of 0.827, 0.84, and 0.674, respectively. The ADC_{mean}, ADC_{min}, and ADC_{max} values of the CRS + HIPEC and CRS groups showed no significant difference **(d)**. ADC, apparent diffusion coefficient; ADC_{mean}, mean ADC; ADC_{min}, minimum ADC; ADC_{max}, maximum ADC; CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy

demonstrated that the ADC_{mean} has a negative association with the TRG (r = -0.292) and reported an AUC of 0.673 for predicting the treatment response. Some recent studies have shown that the ADC_{mean} is associated with survival prognosis in several malignancies; low ADC_{mean} values are frequently associated with aggressive tumor behavior and worse prognosis, such as in breast cancer [22], cervical cancer [34], and colorectal cancer [26]. Previous studies [17, 22] showed that ADC can be considered a prognostic biomarker for OS and risk stratification in GC. Giganti et al. [22] demonstrated that an $ADC_{mean} \leq 1.5 \times 10^{-3}$ mm^2/s is associated with a poorer OS in patients who underwent a radical surgery, both in the surgery-only and surgery combined with postoperative chemotherapy groups. Another study [17] focused on the association of the ADC_{mean} with OS in GC patients after radical operation. Patients with an $ADC_{mean} \leq 1.36 \times 10^{-3}$ mm^2/s demonstrated markedly lower OS than patients with ADC > 1.36×10^{-3} mm^2/s. In line with these findings, we observed a significant prognostic value of the ADC_{mean} in GC patients with PM. Patients with $ADC_{mean} \leq 1.39 \times 10^{-3}$ mm^2/s showed significantly shorter OS than those with $ADC_{mean} > 1.39 \times 10^{-3}$ mm^2/s, both in the total population as well as in the CRS + HIPEC and

Table 3 Difference comparison of ADC parameters between all patients, CRS + HIPEC group, and CRS group

ADC parameters	All patients (*n* = 95)	CRS + HIPEC group (*n* = 61)	CRS group (*n* = 34)	*P*
Observer 1				
ADC_{mean} (10^{-3} mm^2/s)	1.41 (0.91, 2.25)	1.45 (1.03, 2.25)	1.35 (0.91, 2.14)	0.075
ADC_{min} (10^{-3} mm^2/s)	0.77 (0.35, 1.65)	0.82 (0.35, 1.58)	0.73 (0.35, 1.65)	0.237
ADC_{max} (10^{-3} mm^2/s)	2.58 (1.23, 4.25)	2.60 (1.23, 3.83)	2.52 (1.38, 4.25)	0.823
Observer 2				
ADC_{mean} (10^{-3} mm^2/s)	1.38 (0.88, 2.39)	1.40 (0.97, 2.23)	1.37 (0.88, 2.39)	0.429
ADC_{min} (10^{-3} mm^2/s)	0.78 (0.26, 1.65)	0.79 (0.38, 1.58)	0.77 (0.26, 1.65)	0.323
ADC_{max} (10^{-3} mm^2/s)	2.58 (1.28, 4.89)	2.65 (1.39, 4.89)	2.33 (1.28, 3.71)	0.111
Averaged observer 1 and 2				
ADC_{mean} (10^{-3} mm^2/)	1.39 (0.89, 2.26)	1.41 (1.01, 2.24)	1.36 (0.89, 2.26)	0.179
ADC_{min} (10^{-3} mm^2/s)	0.77 (0.32, 1.65)	0.79 (0.36, 1.42)	0.75 (0.32, 1.65)	0.249
ADC_{max} (10^{-3} mm^2/s)	2.59 (1.34, 3.87)	2.65 (1.34, 3.87)	2.47 (1.42, 3.68)	0.312

Notes:

Data are presented as median (range). *P* value was calculated using the Mann-Whitney *U*-test. CRS = cytoreductive surgery, HIPEC = hyperthermic intraperitoneal chemotherapy, ADC = apparent diffusion coefficient

Table 4 Univariate Cox analysis and relative risk for death

Characteristics	All patients (*n* = 95)			CRS + HIPEC group (*n* = 61)			CRS group (*n* = 34)		
	β	HR (95%CI)	*P* value	β	HR (95%CI)	*P* value	β	HR (95%CI)	*P* value
Tumor site									
Asystematic	0.38	1.47 (0.88, 2.44)	0.139	0.64	1.90 (0.98,3.67)	0.068	0.08	1.08 (0.41, 2.13)	0.859
Local		Reference			Reference			Reference	
Pathological T stage									
T4	0.52	1.69 (1.07, 2.66)	0.025	0.46	2.54 (1.02, 6.29)	0.045	0.80	2.23 (1.05, 4.76)	0.038
T2 or T3		Reference			Reference			Reference	
Pathological N stage									
N2 or N3	0.41	1.50 (1.04, 2.36)	0.046	0.53	1.69 (1.05, 3.01)	0.032	0.35	1.42 (0.68, 2.98)	0.355
N0 or N1		Reference			Reference			Reference	
Histologic type									
Signet ring or mucinous cell carcinoma	0.21	1.23 (0.68, 2.24)	0.497	0.17	1.18 (0.53, 2.64)	0.42	0.15	0.86 (0.35, 2.12)	0.741
Adenocarcinoma		Reference			Reference			Reference	
Pathological differentiation									
Poorly differentiated	0.66	1.92 (1.06, 3.50)	0.032	0.47	1.60 (0.79, 3.23)	0.188	0.88	2.81(1.23, 6.43)	0.014
Moderately or well differentiated		Reference			Reference			Reference	
Combined systemic chemotherapy									
No	0.40	1.50 (0.84, 2.66)	0.155	0.44	1.56 (0.73, 3.34)	0.254	0.45	1.56 (0.63, 3.85)	0.333
Yes		Reference			Reference			Reference	
ADC_{mean}									
$\leq 1.39\times10^{-3}$ mm^2/s	0.75	2.11 (1.34, 3.35)	0.001	0.78	2.18 (1.20, 3.93)	0.01	0.91	2.48 (1.16, 5.32)	0.019
$>1.39\times10^{-3}$ mm^2/s		Reference			Reference			Reference	
ADC_{min}									
$\leq 0.77\times10^{-3}$ mm^2/s	0.88	2.40 (1.51, 3.81)	<0.001	0.61	1.83 (1.03, 3.33)	0.039	1.55	4.72 (1.82, 12.15)	0.001
$>0.77\times10^{-3}$ mm^2/s		Reference			Reference			Reference	
ADC_{max}									
$\leq 2.59\times10^{-3}$ mm^2/s	0.38	1.46 (0.93, 2.30)	0.103	0.37	1.44 (0.81, 2.57)	0.217	0.01	1.01 (0.48, 2.12)	0.98
$>2.59\times10^{-3}$ mm^2/s		Reference			Reference			Reference	

Notes:

CRS = cytoreductive surgery, HR = hazard ratio, HIPEC = hyperthermic intraperitoneal chemotherapy, ADC = apparent diffusion coefficient

Table 5 Multivariate Cox analysis and relative risk for death

Characteristic	All patients ($n=95$)			CRS + HIPEC group ($n=61$)			CRS group ($n=34$)		
	β	HR (95% CI)	*P*	β	HR (95% CI)	*P*	β	HR (95% CI)	*P*
Pathological T stage									
T4	0.81	2.25 (1.36, 3.72)	0.002	0.80	2.22 (1.16, 4.27)	0.016	0.36	1.43 (0.63, 3.33)	0.387
T2 or T3		Reference			Reference			Reference	
Pathological N stage							-	-	-
N2 or N3	0.388	1.47 (0.92, 2.21)	0.107	0.70	2.01 (1.11, 3.62)	0.021	-	-	-
N0 or N1		Reference			Reference		-	-	-
Pathological differentiation				-	-	-			
Poorly differentiated	0.53	1.69 (0.89, 3.20)	0.106	-	-	-	0.13	1.14 (0.30, 4.36)	0.847
Moderately or well differentiated		Reference		-	-	-		Reference	
ADC_{mean}									
$\leq 1.39\times10^{-3}$ mm^2/s	0.52	1.68 (1.02, 2.75)	0.04	0.79	2.22 (1.19, 4.14)	0.012	0.27	1.31 (0.55, 3.10)	0.543
$>1.39\times10-3$ mm^2/s		Reference			Reference			Reference	
ADC_{min}									
$\leq 0.77\times10^{-3}$ mm^2/s	0.91	2.48(1.51, 4.08)	<0.001	0.86	2.37 (1.26, 4.46)	0.008	1.25	3.49 (1.19, 10.20)	0.022
$>0.77\times10^{-3}$ mm^2/s		Reference			Reference			Reference	

Notes:

CRS = cytoreductive surgery, HR = hazard ratio, HIPEC = hyperthermic intraperitoneal chemotherapy, ADC = apparent diffusion coefficient

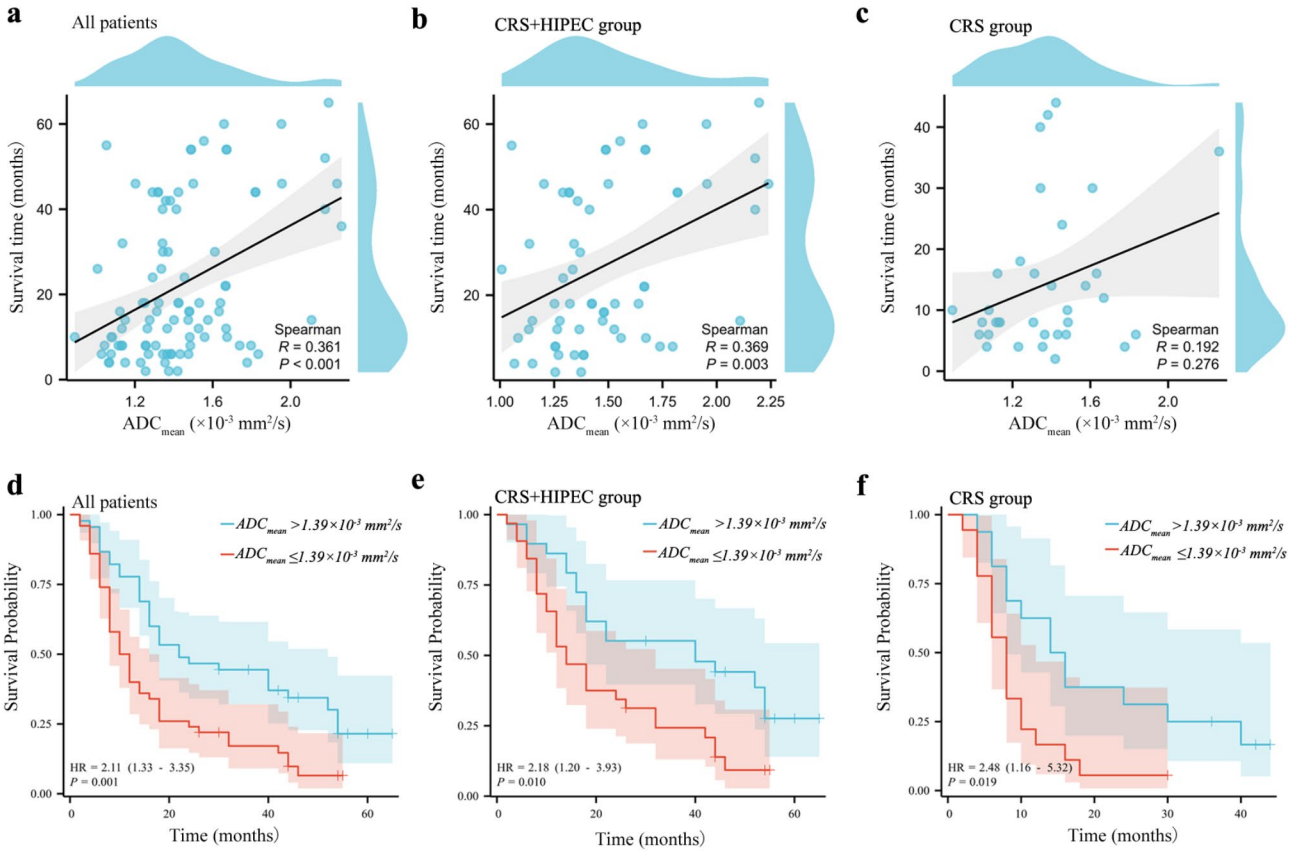

Fig. 5 Relationship between the ADC_{mean} and OS for patients who underwent CRS, with or without HIPEC. Spearman's correlation plots showed that the ADC_{mean} was trended to positively associate with the OS period in all patients **(a)** and in the CRS + HIPEC **(b)** and CRS groups **(c)**, with the correlation coefficient rho (*R*) values of 0.361, 0.369, and 0.192, respectively. Kaplan–Meier analysis indicated that patients with $ADC_{mean} \leq 1.39\times10^{-3}$ mm^2/s had significantly shorter OS periods than those with $ADC_{mean} > 1.39\times10^{-3}$ mm^2/s in all patients (HR = 2.11, *P* = 0.001) **(d)** and in CRS + HIPEC (HR = 2.18, *P* = 0.010) **(e)** and CRS groups (HR = 2.48, *P* = 0.019) **(f)**. ADC, apparent diffusion coefficient; ADC_{mean}, mean ADC; CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy

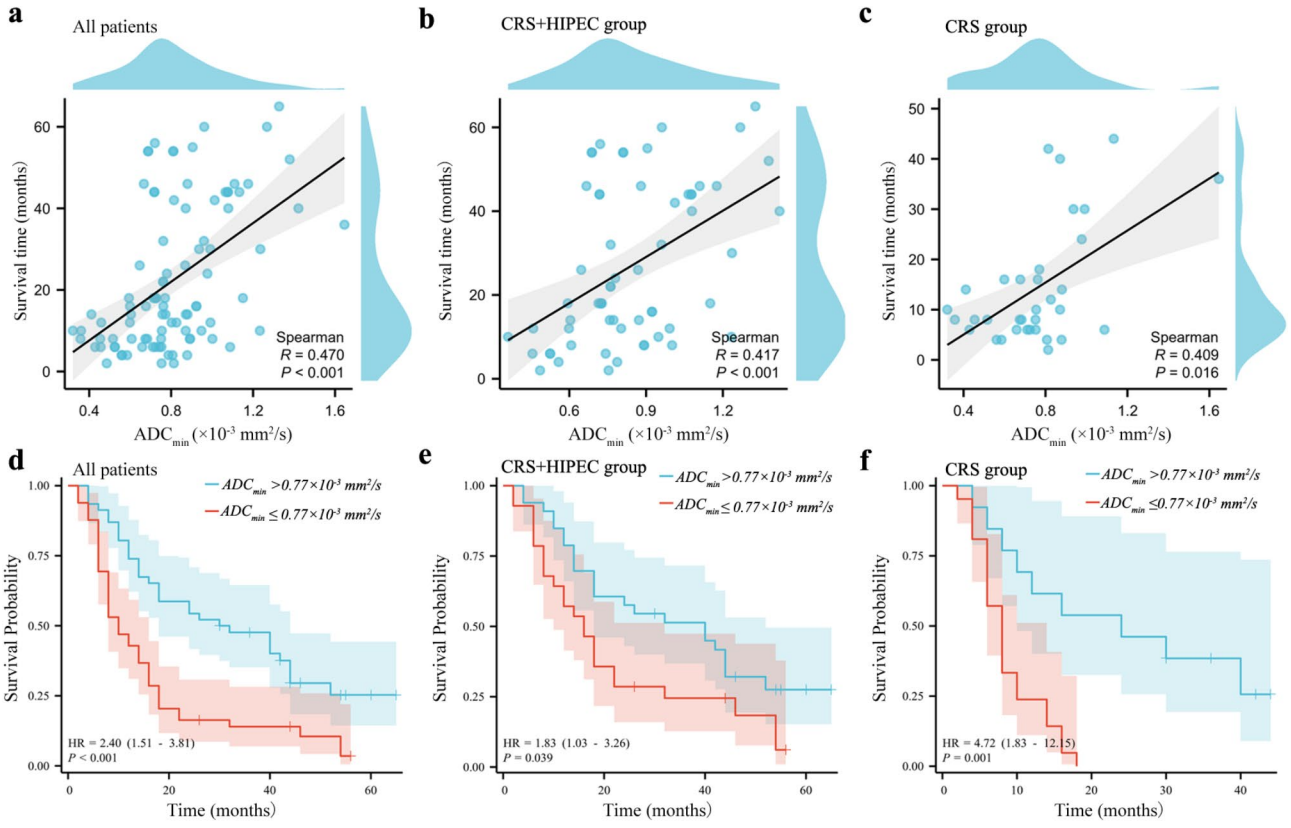

Fig. 6 Relationship between the ADC_{min} and OS in patients who received CRS, with or without HIPEC. Spearman's correlation plots showed that the ADC_{min} was positively related to the OS period in all patients **(a)** and in CRS + HIPEC **(b)** and CRS groups **(c)**, with the correlation coefficient rho (*R*) values of 0.470, 0.417, and 0.409, respectively. Kaplan–Meier analysis indicated that patients with $ADC_{min} \leq 0.77 \times 10^{-3}$ mm^2/s had a significantly shorter OS period than that in those with $ADC_{mean} > 0.77 \times 10^{-3}$ mm^2/s in all patients (HR = 2.40, $P < 0.001$) **(d)** and in CRS + HIPEC (HR = 1.83, $P = 0.039$) **(e)** and CRS groups (HR = 4.72, $P = 0.001$) **(f)**. ADC, apparent diffusion coefficient; ADC_{mean}, mean ADC; ADC_{min}, minimum ADC; CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; OS, overall survival

CRS groups. Thus, regardless of the treatment combination protocol of HIPEC, ADC_{mean} can be employed as a noninvasive and useful marker to predict the OS of GC patients with PM after they have undergone CRS.

ADC is inversely correlated with tissue cellularity [35]. Theoretically, the region showing the ADC_{min} may reflect the area with the highest cellularity within the tumor, and the region with the ADC_{max} may be considered the area with the lowest cellularity composed of stroma. Thus, compared with the ADC_{mean} alone, multi-parameter ADCs may provide additional information that may allow a comprehensive evaluation of tumor heterogeneity and strengthen the clinical application value of ADC measurements. In our previous studies [27, 28], we demonstrated that the ADC_{min} exhibits a superior diagnostic efficiency than ADC_{mean} in the discrimination of malignant and benign cirrhosis nodules [27]. Both the ADC_{min} and ADC_{max} are significantly correlated with the programmed death-ligand 1 expression score [28]. Moreover, a previous study [36] demonstrated that the ADC_{min} and ADC_{max} values can be used to identify invasive components in ductal breast cancer in situ diagnosed with biopsy. According to Liu et al. [25], the ADC_{min} value is significantly correlated with histological differentiation and Lauren classification in GC. Owing to the potential values of ADC_{min} and ADC_{max} in assessing the tumor aggressiveness and heterogeneity, we assumed that these two values may provide valuable information for predicting the OS of patients with GC in clinical practice.

We investigated the values of ADC_{min} and ADC_{max} for predicting OS in GC patients with PM. Although the ADC_{max} did not show any prognostic value, the ADC_{min} was found to be markedly associated with the OS period in the total patient population, as well as in the CRS + HIPEC and CRS groups. Patients with $ADC_{min} \leq 0.77 \times 10^{-3}$ mm^2/s had a significantly shorter OS than those with $ADC_{min} > 0.77 \times 10^{-3}$ mm^2/s in the total population, as well as in the CRS + HIPEC and CRS groups. This uncertain prognostic value of ADC_{max} can partially be explained by the fact that cystic necrosis in the tumor may not be completely excluded when placement ROIs, especially the cystic necrosis, is too small to recognize. Furthermore, the water in the gastral cavity shows marked hyperintensity on ADC maps, which may influence the ADC_{max} measurements. Our findings

were similar to those reported by Kim et al. [37], who demonstrated that the distant metastasis-free survival (DMFS) risk of patients with breast cancer could be accurately classified with the optimal cutoff value of $ADC_{min} \leq 0.71 \times 10^{-3}$ mm^2/s; however, no significant relation was observed between ADC_{max} and DMFS.

Our study has some limitations too, such as the relatively small sample size ($n = 95$) and the distribution of the patients into two distinct and unequal treatment subgroups ($n = 61$ vs. $n = 34$). In addition, as it was a single-center, retrospective study, it became difficult to completely avoid the selection bias because we included only GC patients who had undergone MRI and DWI before CRS. A future multicentered prospective study is needed to verify the results generated. Moreover, the HIPEC frequency was not consistent and ranged from 2 to 5 times, because of the retrospective nature of the study, which may affect the prognosis of patients. Further multicenter and prospective studies are needed for probing the association of HIPEC frequency with survival outcomes. Finally, only three ADC values were calculated and used. A histogram or radiomic analysis should be performed, as it can better reflect tumor heterogeneity.

Conclusion

This study showed that the ADC_{min} and ADC_{max} parameters could be used to predict the treatment outcomes for GC patients with PM. Lower ADC_{mean} and ADC_{min} values before the patients were subjected to CRS were associated with poorer OS in GC patients with PM, regardless of whether HIPEC was used or not. The ADC_{min}, in particular, was identified as a strong independent prognostic factor for GC patients undergoing not only CRS alone, but also CRS + HIPEC. The study results suggested that the quantitative analysis of the ADC_{min} can be employed as a prognostic marker for GC with PM and develop personalized treatment and surveillance plans for such patients.

Abbreviations

GC	Gastric cancer
PM	Peritoneal metastasis
CRS	Cytoreductive surgery
HIPEC	Hyperthermic intraperitoneal chemotherapy
OS	Overall survival
HR	Hazard ratio
DWI	Diffusion-weighted imaging
ADC	Apparent diffusion coefficients
ADC_{mean}	Mean ADC
ADC_{min}	Minimum ADC
ADC_{max}	Maximum ADC
ICC	Interclass correlation coefficients
ROI	Region of interest
DMFS	Distant metastasis-free survival
TRG	Tumor regression grade

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Author contributions

X.Z, Q.B.L, and H.S.T contributed to the conception and design of the work and funding acquisition. X.X and Y.F.T carried out the investigation and drafted the manuscript. M.L, J.H, and L.D.Y collected the MRI and clinical data. J.S and J.X.Y performed ADC value measurements. L.H.D and J.S.L verified the data and conducted the statistical analyses. All authors read and approved the final manuscript.

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Data availability

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

Declarations

Ethical approval and consent to participate

This study was approved by the Institutional Review Board of Affiliated Cancer Hospital & Institute of Guangzhou Medical University. Experiments on humans and/or the use of human tissue samples must confirm that all experiments were performed in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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