Serum cell division cycle 42 reflects the treatment response and survival in patients with advanced cervical cancer who receive immune checkpoint inhibitor treatment

LILI GUO, YUE SU, XIAOYU LIU, WAN XIE, SILU MENG, YUHUAN LIU, WEIJIAO WANG, XIAOFENG LV and CHANGYU WANG

Department of Obstetrics and Gynecology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, P.R. China

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Abstract. Cell division cycle 42 (CDC42) regulates immune escape, which predicts immune checkpoint inhibitor (ICI) treatment response in several types of cancer. The present study aimed to evaluate the potential of serum CDC42 in predicting the ICI treatment outcome in patients with advanced cervical cancer. A total of 46 patients with advanced cervical cancer who received ICI treatment with or without antiangiogenic agents were enrolled. Serum CDC42 was detected in all patients before treatment (baseline) and following two treatment cycles by enzyme-linked immunosorbent assay. CDC42 at baseline was elevated in patients with target lesion size ≥5 cm (P=0.020), pelvis metastasis (P=0.031) and lung metastasis (P=0.043). Following treatment, the objective response rate (ORR) and disease control rate (DCR) were 30.4 and 78.3%, respectively. Meanwhile, the median progression-free survival (PFS) and overall survival (OS) were 5.8 and 13.1 months. CDC42 at baseline was decreased in patients achieving ORR (P=0.042) but not DCR (P=0.055). PFS (P=0.006) and OS (P=0.019) were decreased in patients with baseline CDC42 ≥600 pg/ml. After two treatment cycles, CDC42 was generally reduced (P<0.001). CDC42 following two treatment cycles was more significantly decreased in patients with ORR (P=0.032) and DCR (P=0.019). Multivariate Cox's regression analysis showed that CDC42 ≥600 pg/ml following two treatment cycles was associated with the shorter PFS (P=0.022, hazard ratio=2.469) and OS (P=0.013, hazard ratio=4.166). Serum CDC42 was reduced after treatment; high expression following treatment reflected a lower possibility of achieving treatment response and poorer survival in patients with advanced cervical cancer.

Correspondence to: Dr Changyu Wang, Department of Obstetrics and Gynecology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Avenue, Qiaokou, Wuhan, Hubei 430030, P.R. China
E-mail: wcy1992@tjh.tjmu.edu.cn

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Introduction

Cervical cancer is one of the most common types of gynecological cancer, with an incidence of 7.7 per 100,000 population and mortality of 2.2 per 100,000 population worldwide according to the Cancer Statistics (2023) (1,2). Despite multi-therapy choice (such as surgery and chemoradiation) for early and locally advanced-stage cervical cancer, treatment options for patients with advanced cervical cancer patients are limited and primarily include platinum-based chemotherapy regimens (3-6). There are few therapeutic options beyond first-line chemotherapy.

Immune checkpoint inhibitors (ICIs) provide another therapeutic option for advanced cervical cancer (7-9). ICI regimens have promising treatment outcomes [for example, 13.3-17.0% of patients achieved objective response rate (ORR) in the KEYNOTE-028 and KEYNOTE-158 trials (10,11)], however ~80% of patients exhibit no response (10,11). Hence, to minimize ineffective treatment, avoid the adverse reactions of ICI regimens and reduce the consumption of medical resources, it is urgent to find a potential biomarker to achieve individualized ICI treatment in patients with advanced cervical cancer.

Cell division cycle 42 (CDC42) is a small hydrolase that regulates immune escape by several mechanisms, such as regulating antigen-specific cytotoxic T lymphocyte-mediated cytotoxicity and differentiation of macrophages into M2 phenotype (12-14). For example, CDC42-deficient naïve T cells preferentially differentiate to $CD8^+$ effector cells both *in vitro* and *in vivo* (15). Clinically, CDC42 could predict the response of ICI treatment in several types of cancer, such as hepatocellular carcinoma and colorectal cancer (16,17). However, the effect of CDC42 on response of ICI treatment have not been verified in patients with advanced cervical cancer. Hence, the present study aimed to evaluate the potential of serum CDC42 in predicting ICI treatment outcome in patients with advanced cervical cancer.

Materials and methods

Patients. From July 2020 to December 2022, 46 patients (age, 36.0-70.0 years) with advanced cervical cancer who planned to receive ICI treatment with or without antiangiogenic agents were enrolled at Tongji Hospital (Wuhan, China). The inclusion criteria were as follows: i) Histopathologically diagnosed as cervical cancer; ii) confirmed as recurrent, persistent or metastatic cervical cancer; iii) aged >18 years; iv) progression after at least once standardized systemic chemotherapy; v) Eastern Cooperative Oncology Group Performance Status (ECOG PS) (18) 0-1; vi) at least one measurable lesion by the Response Evaluation Criteria in Solid Tumors (RECIST) V.1.1 (19); vii) scheduled to receive ICI treatment with or without antiangiogenic agents. The exclusion criteria were as follows: i) Presence of other primary malignant disease; ii) inadequate liver, kidney, heart, bone marrow, and blood coagulation function; iii) history of ICI treatment; iv) complicated with autoimmune disease; v) presence of hematological diseases; vi) pregnancy or breastfeeding. The patients provided written informed consent. The study was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China; approval no. ChiECRCT20200180).

Clinical characteristics. Clinical characteristics of patients were collected from medical records, including age, International Federation of Gynecology and Obstetrics (FIGO) (20) stage, ECOG PS, histology type, target lesion size, metastasis, programmed death-ligand 1 combined positive score [PD-L1 CPS; as previously described (21)] and treatment history.

Treatment. Patients received ICI treatment with or without antiangiogenic agents according to their willingness, disease condition and doctor's advice. The treatment was given in 3-week cycles. ICI was given continually until intolerable toxicity occurred or the disease progressed (up to 24 months) and included camrelizumab (200 mg/cycle), sintilimab (200 mg/cycle), pembrolizumab (200 mg/cycle) and atezolizumab (1,200 mg/cycle). For patients who received ICI treatment combined with antiangiogenic agents, antiangiogenic agents were given until the occurrence of intolerable toxicity or disease progression and included bevacizumab (15 mg/kg/cycle) and apatinib (250 mg/day). The dosing adjustments were allowed based on conditions such as intolerance.

Blood samples. Peripheral blood (5 ml) of patients was collected before treatment (at baseline) and following two treatment cycles. The serum was isolated (centrifugation at 1,800 x g for 10 min) and serum CDC42 was detected by ELISA using commercial kits (cat. no. JM-1116H1; Jiangsu Jingmei Biotechnology Co., Ltd.) according to the manufacturer's instructions.

Assessment. Patients were routinely followed up until May 2023 and underwent imaging examinations (computed tomography or nuclear magnetic resonance) after every two cycles of treatment. Based on the imaging results after four cycles of treatment, the tumor response was assessed via RECIST V.1.1 (19). Progression-free survival (PFS) and overall survival (OS) were recorded for prognosis analysis.

Table I. Clinical characteristics.

Characteristic	Patients (n=46)
Age, years	
Median	49.5
IQR	45.8-52.0
Range	36.0-70.0
FIGO stage at initial diagnosis (%)	
I	15 (32.6)
II	11 (23.9)
III	8 (17.4)
IV	12 (26.1)
ECOG PS (%)	
0	19 (41.3)
1	27 (58.7)
Histology type (%)	
Squamous cell carcinoma	28 (60.9)
Adenocarcinoma	15 (32.6)
Adenosquamous	3 (6.5)
Target lesion size, cm	
Median	5.0
IQR	4.0-7.5
Range	2.0-14.0
Pelvis metastasis (%)	22 (47.8)
Lung metastasis (%)	18 (39.1)
Liver metastasis (%)	13 (28.3)
Other distant metastases (%)	13 (28.3)
Previous platinum (%)	46 (100.0)
Previous paclitaxel (%)	46 (100.0)
Previous bevacizumab (%)	16 (34.8)
PD-L1 CPS (%)	
Positive	33 (71.7)
Negative	10 (21.7)
Unknown	3 (6.5)
Treatment line (%)	
1st	0 (0.0)
2nd	19 (41.3)
3rd	19 (41.3)
4th or above	8 (17.4)
Treatment (%)	
ICI + antiangiogenic therapy	26 (56.5)
ICI-alone	20 (43.5)
CDC42 at baseline, pg/ml	
Median	599.0
IQR	422.8-973.3
Range	226.0-2161.0

IQR, interquartile range; FIGO, International Federation of Gynecology and Obstetrics; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PD-L1, programmed death-ligand 1; CPS, combined positive score; ICI, immune checkpoint inhibitor; CDC42, cell division cycle 42.

CDC42 cutoff value. To explore the association of CDC42 with PFS and OS, the CDC42 levels (baseline and following

Table II. CDC42 in patients with different clinical characteristics at baseline.

Characteristic	Median CDC42 (IQR), pg/ml	P-value
Age, years (%)		0.531
<50	616.0 (349.0-917.0)	
≥50	582.0 (439.0-1296.0)	
ECOG PS (%)		0.251
0	554.0 (425.0-735.0)	
1	616.0 (416.0-1296.0)	
Histology type (%)		0.905
Squamous cell carcinoma	658.5 (439.5-853.8)	
Adenocarcinoma	503.0 (301.0-1321.0)	
Adenosquamous	554.0 (462.0-NA)	
Target lesion size (%), cm		0.020
<5	516.0 (373.0-690.5)	
≥5	770.0 (473.5-1388.0)	
Pelvis metastasis (%)		0.031
No	511.0 (329.8-674.3)	
Yes	771.5 (492.8-1127.3)	
Lung metastasis (%)		0.043
No	511.0 (361.0-798.5)	
Yes	727.5 (517.3-1354.5)	
Liver metastasis (%)		0.414
No	582.0 (411.0-893.0)	
Yes	661.0 (459.5-1315.0)	
Other distant metastases (%)		0.134
No	576.0 (352.0-915.5)	
Yes	616.0 (527.0-1183.5)	
Previous bevacizumab (%)		0.106
No	532.0 (353.5-903.5)	
Yes	727.5 (515.8-1212.5)	
PD-L1 CPS (%)		0.095
Positive	516.0 (406.5-838.5)	
Negative or unknown	680.0 (565.0-1308.5)	
Treatment (%)		0.278
ICI + antiangiogenic therapy	532.0 (337.0-945.5)	
ICI-alone	668.0 (472.3-995.8)	

Wilcoxon and the Kruskal-Wallis H rank sum test were applied. CDC42, cell division cycle 42; IQR, interquartile range; FIGO, International Federation of Gynecology and Obstetrics; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PD-L1, programmed death-ligand 1; CPS, combined positive score; ICI, immune checkpoint inhibitor; NA, not available.

Table III. Tumor response.

Tumor response (%)	Patients, n=46
CR	0 (0.0)
PR	14 (30.4)
SD	22 (47.8)
PD	10 (21.7)
ORR	14 (30.4)
DCR	36 (78.3)

ORR was calculated as CR + PR. DCR was calculated as CR + PR + SD. CR, complete response, PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

two treatment cycles) were divided based on the cutoff value of 600 pg/ml (approximate median value of CDC42 at baseline).

Statistical analysis. SPSS V.24.0 (IBM Corp.) was used for data processing. Data are presented as median and interquartile range (IQR). Comparisons were performed by the Wilcoxon or Kruskal-Wallis H rank sum or Wilcoxon signed-rank test. Correlation analysis was performed by Spearman's rank correlation test. PFS and OS were determined by Kaplan-Meier curves and analyzed by log-rank test. Factors associated with PFS and OS were determined by univariate and backward-stepwise multivariate Cox's proportional hazard regression models. A total of three independent experimental repeats was performed. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Clinical characteristics. The median (IQR) age of patients was 49.5 (45.8-52.0) years. A total of 15 (32.6%), 11 (23.9%), 8 (17.4%) and 12 (26.1%) patients had FIGO stage I, II, III and IV, respectively. A total of 28 (60.9%) patients had squamous cell carcinoma; 15 (32.6%) patients had adenocarcinoma, while 3

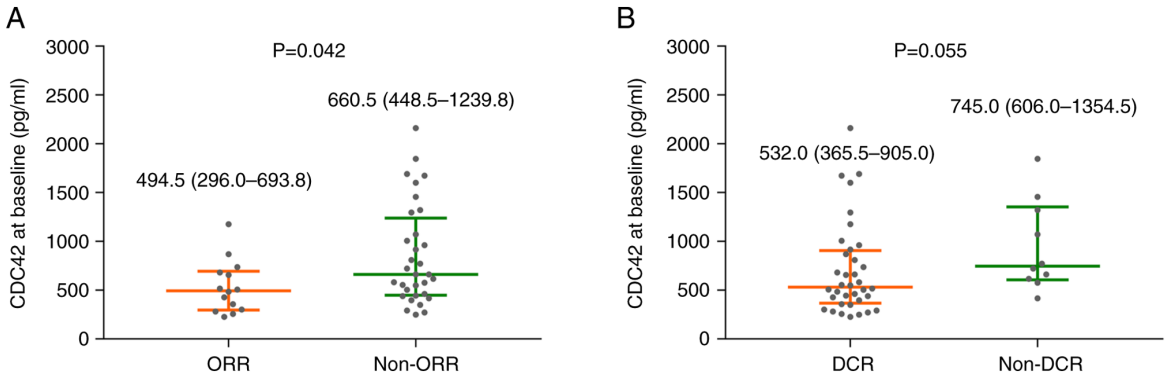

Figure 1. Serum CDC42 at baseline in patients with and without response. Median (interquartile range) level of CDC42 between the patients with and without (A) ORR and (B) DCR. CDC42, cell division cycle 42; ORR, objective response rate; DCR, disease control rate.

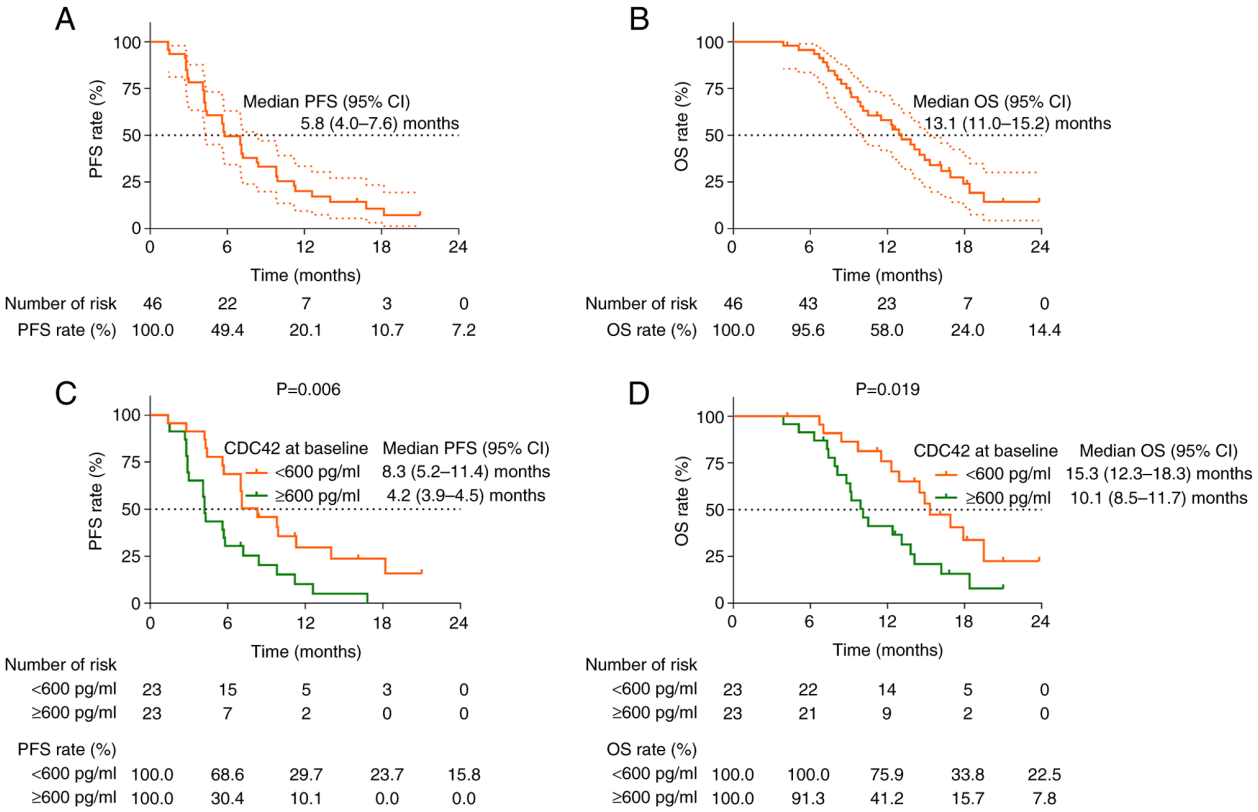

Figure 2. Predictive value of serum CDC42 at baseline for survival. Kaplan-Meier curves of (A) PFS and (B) OS. Association of serum CDC42 at baseline with (C) PFS and (D) OS in patients with advanced cervical cancer who received immune checkpoint inhibitor treatment with or without antiangiogenic agents. CDC42, cell division cycle 42; PFS, progression-free survival; OS, overall survival.

(6.5%) patients had adenosquamous carcinoma. The baseline median (IQR) CDC42 expression was 599.0 (422.8-973.3) pg/ml. Baseline characteristics are shown in Table I.

High CDC42 at baseline is associated with target lesion ≥5 cm and pelvis and lung metastases. CDC42 at baseline was increased in patients with target lesion size ≥5 cm (P=0.020), the presence of pelvis metastasis (P=0.031) and lung metastasis (P=0.043). However, CDC42 at baseline was not significantly different between patients with other clinical characteristics including age (based on median cutoff value of 50 years), ECOG PS and histology type (all P>0.05; Table II). Furthermore, CDC42 was not correlated with FIGO stage at initial diagnosis or treatment line (both P>0.05) (Table SI).

CDC42 at baseline is associated with worse treatment response. No patients with advanced cervical cancer achieved the complete response (CR), 14 (30.4%) patients achieved the partial response (PR), 22 (47.8%) patients exhibited stable disease (SD), while 10 (21.7%) patients exhibited progressive disease (PD). Therefore, ORR was 30.4%, and disease control rate (DCR) was 78.3% (Table III). CDC42 at baseline was decreased in patients who achieved the ORR compared with non-ORR (P=0.042; Fig. 1A) but remained unchanged between patients who achieved DCR and non-DCR (P=0.055; Fig. 1B).

Table IV. Cox's proportional hazard regression model for PFS.

Characteristic	P-value	HR	95% CI	
			Lower	Upper
Univariate model				
CDC42 at baseline, ≥600 vs. <600 pg/ml	0.009	2.402	1.249	4.618
CDC42 following two treatment cycles, ≥600 vs. <600 pg/ml	0.006	2.550	1.301	5.001
Age, ≥50 vs. <50 years	0.176	1.554	0.821	2.940
Higher FIGO stage at initial diagnosis	0.164	1.220	0.922	1.615
ECOG PS (1 vs. 0)	0.091	1.761	0.913	3.397
Histology type				
Squamous cell carcinoma	Reference			
Adenocarcinoma	0.354	1.402	0.686	2.866
Adenosquamous	0.551	1.446	0.430	4.864
Target lesion size, ≥5 vs. <5 cm	0.104	1.711	0.895	3.272
Pelvis metastasis, yes vs. no	0.194	1.546	0.801	2.985
Lung metastasis, yes vs. no	0.011	2.435	1.223	4.851
Liver metastasis, yes vs. no	0.154	1.652	0.829	3.291
Other distant metastases, yes vs. no	0.274	1.503	0.724	3.123
Previous bevacizumab, yes vs. no	0.142	1.618	0.852	3.073
PD-L1 CPS, positive vs. negative or unknown	0.017	0.441	0.224	0.866
Higher treatment line	0.006	1.986	1.219	3.234
Treatment, ICI + antiangiogenic therapy vs. ICI-alone	0.007	0.396	0.202	0.778
Backward-stepwise multivariate model				
CDC42 following two treatment cycles, ≥600 vs. <600 pg/ml	0.022	2.469	1.139	5.352
Age, ≥50 vs. <50 years	0.101	1.918	0.881	4.176
ECOG PS, 1 vs. 0	0.007	2.709	1.310	5.603
Lung metastasis, yes vs. no	0.025	2.517	1.124	5.636
PD-L1 CPS, positive vs. negative or unknown	0.002	0.284	0.130	0.618
Treatment, ICI + antiangiogenic therapy vs. ICI-alone	<0.001	0.259	0.125	0.539

Cox proportional hazard regression was used. PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; CDC42, cell division cycle 42; FIGO, International Federation of Gynecology and Obstetrics; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PD-L1, programmed death-ligand 1; CPS, combined positive score; ICI, immune checkpoint inhibitor.

CDC42 at baseline is associated with worse survival profile. The median [95% confidential interval (CI)] PFS was 5.8 (4.0-7.6) months (Fig. 2A) and the median OS was 13.1 (11.0-15.2) months (Fig. 2B) in all patients. PFS (P=0.006; Fig. 2C) and OS (P=0.019; Fig. 2D) were reduced in patients with baseline CDC42 ≥600 pg/ml compared with those with baseline CDC42 <600 pg/ml.

CDC42 following two treatment cycles is associated with unfavorable treatment response. Following two treatment cycles, CDC42 expression decreased (P<0.001; Fig. 3). CDC42 following two treatment cycles showed a significant difference between patients with ORR and non-ORR (P=0.032; Fig. 4A), as well as patients with DCR and non-DCR (P=0.019; Fig. 4B).

CDC42 following two treatment cycles is associated with unfavorable prognosis. PFS (P=0.004; Fig. 4C) and OS (P=0.005; Fig. 4D) were also worse in patients with CDC42 ≥600 pg/ml compared with CDC42 <600 pg/ml following two treatment cycles.

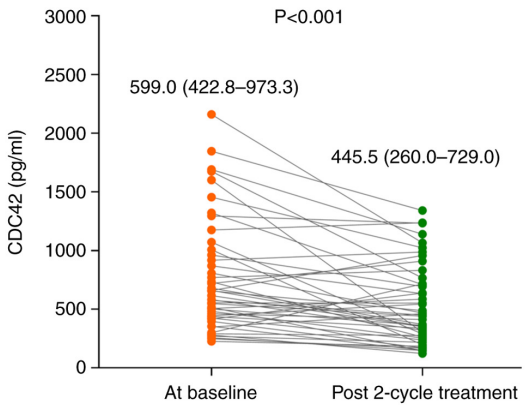

Figure 3. Change of serum CDC42 after treatment. Median (interquartile range) CDC42 at baseline and following two treatment cycles. CDC42, cell division cycle 42.

CDC42 following two treatment cycles was an independent factors for shorter PFS and OS. After adjusting the

Table V. Cox's proportional hazard regression model for OS.

Characteristic	P-value	HR	95% CI	
			Lower	Upper
Univariate model				
CDC42 at baseline, ≥600 vs. <600 pg/ml	0.022	2.306	1.126	4.719
CDC42 following two treatment cycles, ≥600 vs. <600 pg/ml	0.007	2.737	1.321	5.667
Age, ≥50 vs. <50 years	0.066	1.982	0.956	4.109
Higher FIGO stage at initial diagnosis	0.059	1.328	0.989	1.784
ECOG PS, 1 vs. 0	0.031	2.393	1.082	5.292
Histology type				
Squamous cell carcinoma	Reference			
Adenocarcinoma	0.176	1.723	0.784	3.786
Adenosquamous	0.417	1.673	0.483	5.792
Target lesion size, ≥5 vs. <5 cm	0.011	2.645	1.247	5.610
Pelvis metastasis, yes vs. no	0.557	1.233	0.613	2.478
Lung metastasis, yes vs. no	0.011	2.592	1.244	5.400
Liver metastasis, yes vs. no	0.172	1.698	0.795	3.628
Other distant metastases, yes vs. no	0.055	2.116	0.984	4.552
Previous bevacizumab, yes vs. no	0.430	1.332	0.654	2.714
PD-L1 CPS, positive vs. negative or unknown	0.032	0.447	0.214	0.932
Higher treatment line	0.003	2.256	1.329	3.829
Treatment, ICI + antiangiogenic therapy vs. ICI-alone	0.012	0.401	0.197	0.816
Backward-stepwise multivariate model				
CDC42 following two treatment cycles, ≥600 vs. <600 pg/ml	0.013	4.166	1.349	12.860
Age, ≥50 vs. <50 years	0.003	4.175	1.613	10.811
Higher FIGO stage at initial diagnosis	0.008	1.621	1.131	2.322
ECOG PS, 1 vs. 0	0.033	2.619	1.081	6.342
Target lesion size, ≥5 vs. <5 cm	0.001	5.628	1.997	15.856
PD-L1 CPS, positive vs. negative or unknown	0.001	0.197	0.078	0.501
Higher treatment line	<0.001	3.809	2.061	7.040

Cox proportional hazard regression analysis was applied. OS, overall survival; HR, hazard ratio; CI, confidence interval; CDC42, cell division cycle 42; FIGO, International Federation of Gynecology and Obstetrics; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PD-L1, programmed death-ligand 1; CPS, combined positive score; ICI, immune checkpoint inhibitor.

confounders by the multivariate Cox's regression analysis, CDC42 following two treatment cycles (≥600 vs. <600 pg/ml) was independently associated with a shorter PFS [P=0.022, hazard ratio (HR)=2.469]. Furthermore, ECOG PS (1 vs. 0; P=0.007, HR=2.709) and lung metastasis (yes vs. no; P=0.025, HR=2.517) independently predicted shorter PFS, while PD-L1 CPS (positive vs. negative or unknown; P=0.002, HR=0.284) and treatment type (ICI + antiangiogenic therapy vs. ICI-alone; P<0.001, HR=0.259) were associated with prolonged PFS (Table IV).

Multivariate cox's regression analysis for OS showed that CDC42 following two treatment cycles (≥600 vs. <600 pg/ml) was also associated with a shorter OS (P=0.013, HR=4.166). Age (≥50 vs. <50 years; P=0.003, HR=4.175), higher FIGO stage at initial diagnosis (P=0.008, HR=1.621), ECOG PS (1 vs. 0; P=0.033, HR=2.619), target lesion size (≥5 vs. <5 cm; P=0.001, HR=5.628) and higher treatment line (P<0.001, HR=3.809) were linked with a shorter OS, while PD-L1 CPS (positive vs. negative or unknown) was associated with prolonged OS (P=0.001, HR=0.197; Table V).

Discussion

CDC42 is a key protein responsible for progression of cervical cancer (22,23). Knockdown of CDC42 increases C-terminal domain Ser phosphatases RNA polymerase II associated protein 2 and F-cell production 1 (FCP1) in cervical cancer cells, thus controlling cell proliferation (22). Another study reported that activation of CDC42/p21-activated kinases 1 is associated with the tumorigenic and invasive properties of tumorsphere cells enriched from cervical cancer cell line HeLa (23). Nevertheless, the association between CDC42 and the clinicopathological features of patients with cervical cancer needs exploration. Here, serum CDC42 was elevated in patients with advanced cervical cancer with larger tumor size, pelvis metastasis and lung metastasis. These findings might be explained by the

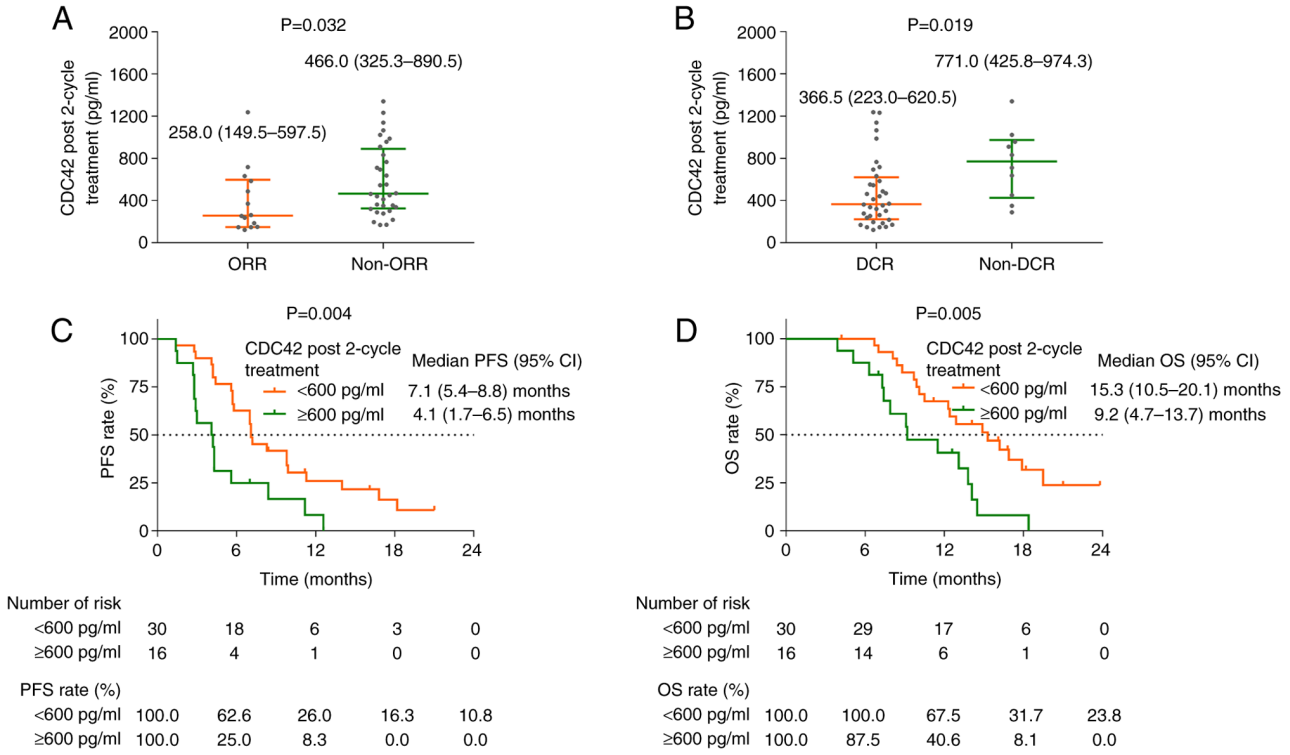

Figure 4. Predictive value of serum CDC42 for treatment response and survival. Association of serum CDC42 at baseline with (A) ORR, (B) DCR, (C) PFS and (D) OS in patients with advanced cervical cancer who received ICI treatment with or without antiangiogenic agents. CDC42, cell division cycle 42; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival.

proliferation- and invasion-enhancing property of CDC42 in cervical cancer cells, (24-26). However, CDC42 was not significantly different between patients with PD-L1 CSP positive and those with PD-L1 CSP negative or known. The potential reason is that the sample size was too small, which resulted in low statistical power. CDC42 might participate in regulation of immune escape via modulating $CD8^+$ T cells, rather than modulating the expression of PD-L1 (27).

In recent years, clinical investigations have revealed that ICI is a potential treatment modality for patients with advanced cervical cancer (28-30). A recent phase II, single-arm study showed that in previously treated patients with PD-L1-positive cervical cancer, serplulimab + nab-paclitaxel achieves ORR of 51.7%, median PFS is 5.7 months and the median OS is 15.5 months (28). Balstilimab achieves ORR of 15% in patients with recurrent/metastatic cervical cancer who receive prior platinum-based treatment (31). Another phase III trial revealed that in patients with cervical cancer and disease progression after first-line platinum-based chemotherapy, ORR (16.4 vs. 6.3%) and median OS (12.0 vs. 8.5 months) are both improved following treatment with cemiplimab compared with chemotherapy (29). In the present study, the ORR and DCR were 30.4 and 78.3%, respectively, after ICI treatment in patients with advanced cervical cancer. Median PFS and OS were 5.8 and 13.1 months, respectively. These findings are in line with previous studies and support application of ICI treatment in these patients (28,29,31).

CDC42 is reported to predict treatment response and survival in patients with cancer who receive ICI treatment (16,17). The present study revealed that serum CDC42 at baseline was not significantly decreased in patients with objective response achievement and disease control achievement; PFS and OS after ICI treatment in patients with advanced cervical cancer were decreased in patients with baseline CDC42 ≥600 pg/ml. These findings might be because CDC42 negatively modulated the differentiation of $CD8^+$ T cells, which killed tumor cells following suppression of immune escape by ICI treatment (15,32). As aforementioned, CDC42 was associated with larger tumor size, pelvis metastasis and lung metastasis, which represent higher tumor burden. Patients with a higher tumor burden might have worse survival. Patients with better treatment responses tended to have better survival. Another key finding of this study was that serum CDC42 was decreased following two cycles of treatment and showed stronger prognostic value for treatment response and survival in patients with advanced cervical cancer compared with serum CDC42 at baseline. Moreover, the association of serum CDC42 with survival was confirmed by multivariate Cox's proportional hazard regression model. These findings provide a potential prognostic tool for patients with advanced cervical cancer, thus improving the management of these patients.

Nevertheless, the present study had limitations. First, the present study only enrolled patients with advanced cervical cancer who received ICI treatment with or without antiangiogenic agents. Therefore, the findings might not be applicable in patients with cervical cancer who receive surgical resection of the tumor. Second, the present study only detected serum CDC42, however, the prognostic value of CDC42 from other sources, such as tumors, should be explored in future. Third, the sample size was not large enough to draw a definitive conclusion. Further studies with larger sample sizes should be conducted to verify the prognostic value of serum CDC42.

In conclusion, serum CDC42 was reduced after treatment and its high expression reflected a lower possibility of achieving treatment response and worse survival in patients with advanced cervical 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

LLG and CYW conceived the study. YS, XYL, WX and SLM collected data and drafted the manuscript. LLG, YHL, WJW, XFL and CYW analyzed data and revised the manuscript. LLG and CYW confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The patients provided written informed consent to participate. Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China) provided ethics approval (approval no. ChiECRCT20 200180).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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