Prognostic significance of CKS2 and CD47 expression in patients with gastric cancer who underwent radical gastrectomy

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Abstract

To investigate the protein expression levels of cyclin-dependent kinase subunit 2 (CKS2) and the cluster of differentiation (CD) 47 in gastric cancer (GC) and their clinical significance. A total of 126 GC patients who underwent radical resection were selected as study subjects. Additionally, 32 patients with benign gastric tumour, 42 patients with low-grade intraepithelial neoplasia (LGIEN), and 49 patients with high-grade intraepithelial neoplasia (HGIEN) who underwent surgery were selected as the control groups. Immunohistochemistry was used to detect the expression of CKS2 and CD47 in surgical specimens. We statistically analysed the clinical significance of the expression of the two factors. (1) The positivity rates for CKS2 in benign gastric tumour tissue, LGIEN tissue, HGIEN tissue, and GC tissue gradually increased, that is, 6.3% (2/32), 30.9% (13/42), 38.8% (19/49), and 60.3% (76/126), respectively, and the positivity rates for CD47 were 18.8% (6/32), 38.1% (16/42), 46.9% (23/49), and 65.9% (83/126), respectively. (2) High expression of CKS2 and CD47 were associated with tumour diameter, Lauren classification, number of lymph node metastases, and TNM stage. In addition, the immunohistochemical scores for CKS2 and CD47 were positively correlated ($r = .625, P = .000$). (3) The median follow-up time of 126 patients was 46.5 months, and the overall survival (OS) rate was 40.5% (51/126). Survival analysis showed that compared with that in the CKS2 (−) group, the OS rate for patients in the CKS2 (+) group was significantly worse and that compared with the CD47 (−) group, the CD47 (+) group had significantly worse OS (30.1% vs 60.5%, $\chi^2 = 15.67, P = .000$). (4) The OS rates of CKS2 (+) CD47 (+) group, CKS2 (+) CD47 (−) group, CKS2 (−) CD47 (+) group, and CKS2 (−) CD47 (−) group were 20.0% (13/65), 58.3% (7/12), 57.1% (8/14), 65.7% (23/35), respectively, the prognosis of patients in CKS2 (+) CD47 (+) group was significantly poor. High expression levels of CKS2 and CD47 were closely related to the occurrence of GC and can be used as independent risk factors to assess the prognosis of patients.
Gastric cancer (GC) is one of the most common malignant tumours in the world. In 2012, there were a total of 951,000 new GC patients and 723,000 GC-related deaths worldwide, with morbidity and mortality rates ranking fifth and third, respectively, among all malignant tumours.1 In China, GC is the second most common malignant tumour and seriously threatens the health and life of people.2 Despite continuous improvements in the diagnosis and treatment of GC, the overall prognosis is still not satisfactory, with a 5-year survival rate of approximately 30%–60%.3 Surgical resection combined with chemotherapy is one of the conventional treatments for GC, and the application of a series of chemotherapeutic drugs and molecular targeted drugs, such as oxaliplatin, 5-fluorouracil, and herceptin, improves the clinical outcomes of GC patients. However, the prognosis of patients with GC is still not optimistic due to the toxicity/side effects of the drugs.4 Therefore, it is necessary to seek new molecular therapeutic targets and investigate their correlations with the prognosis of patients with GC to further optimize precise treatment for GC patients. Cyclin-dependent kinase subunit 2 (CKS2) is a member of the cyclin-dependent kinase (CDK)1-cyclin B complex and thus participates in multiple processes, such as cell cycle regulation, tumour invasion, metastasis, and apoptosis.5 However, the relationship between CKS2 protein and the prognosis of GC patients remains to be established. A cluster of differentiation (CD) 47, also known as integrin-associated protein (IAP), is a transmembrane glycoprotein with a molecular weight of 50 kD.6 CD47 is expressed not only in tumour cells but also in normal cells to some extent. Studies have shown high CD47 expression in leukaemia cells and a variety of solid tumours.7 However, in GC patients, whether CD47 expression is a risk factor affecting prognosis requires more experimental studies. This study assessed the protein expression levels of CKS2 and CD47 in GC tissues by immunohistochemistry and clarified their potential as independent prognostic factors and molecular therapeutic targets for the treatment of GC.

2 | MATERIALS AND METHODS

2.1 | Patients

Gastric cancer tissue samples were retrospectively collected from 126 patients (stages IB–III) who underwent R0 gastrectomy with extensive node dissection (D2) and adjuvant chemoradiation therapy from 2013 to 2018. The inclusion criteria were as follows: (1) Patients who were initially diagnosed and treated; (2) patients who were diagnosed with primary GC and underwent radical surgical resection; (3) no radiochemotherapy before surgery; (4) histopathological type, adenocarcinoma; (5) age <80 years; and (6) complete clinical and pathological data. The exclusion criteria were as follows: (1) history of other malignancies; (2) GC patients with emergency operation due to sudden obstruction, severe bleeding, and perforation; and (3) perioperative death, for example, pulmonary embolism caused by deep vein thrombosis, septic shock caused by anastomotic fistula, and multiple organ failure. In total, 126 GC patients were included in the study: 78 males, with an average age of (64.8 ± 12.7) years, and 48 females, with an average age of (59.7 ± 10.3) years. The clinicopathological data of the patients, including age, gender, tumour size, depth of invasion, degree of differentiation, histological type, Lauren classification, lymph node metastasis, and tumour-node-metastasis (TNM) stage (according to the 8th Edition of American Joint Committee on Cancer [AJCC] Cancer Staging Manual), were obtained through the electronic medical record system. Additionally, 32 patients with benign gastric tumour, 42 patients with low-grade intraepithelial neoplasia (LG1EN), and 49 patients with high-grade intraepithelial neoplasia (HGIEN) who underwent surgical treatment during the same period were selected as the control group. In the benign gastric tumour group, there were 22 males, with an average age of (50.1 ± 5.3) years, and 10 females, with an average age of (43.6 ± 9.8) years; in the LGIEN group, there were 26 males, with an average age of (55.6 ± 11.8) years, and 16 females, with an average age of (54.6 ± 8.8) years; and in the HGIEN group, there were 23 males, with an average age of (61.6 ± 9.2) years, and 26 females, with an average age of (57.6 ± 9.6) years. This study was approved by the Ethics Review Board at Yangzhou university, and was conducted in accordance with the Helsinki declaration, and informed consent was obtained from all patients.

2.2 | Immunohistochemistry and evaluation

Issues were fixed in formalin, paraffin-embedded, and cut into 4-μm sections. After dewaxing with xylene, dehydration with gradient ethanol, and washing with phosphate-buffered saline 3 times, citrate-mediated high-pressure antigen retrieval was performed. Endogenous peroxide was inactivated with 3% hydrogen peroxide solution, and 5% bovine serum albumin was used to block
nonspecific staining sites. Primary antibody, anti-CKS2 (diluted at 1:200; Rabbit polyclonal antibody; Santa Cruz Biotechnology) or anti-CD47 (diluted at 1:600; Rabbit polyclonal antibody; Santa Cruz Biotechnology), were added, and the tissue sections were incubated at 4°C overnight. A secondary antibody was added, and the tissue sections were incubated at 37°C for 1 hour. The tissue sections were mounted and observed under an optical microscope. The results were evaluated by two pathologists without knowing any clinicopathological data. The evaluation criteria were as follows: the appearance of brownish-yellow particles in the cell membrane or cytoplasm was regarded as positive staining. The staining results were scored based on the percentage of positive cells and staining intensity. The staining intensity score ranged from 0 to 3, and the staining degree score ranged from 0% to 100%. The final quantification of each stain was obtained by multiplying the two scores. The final immune response score of each sample was multiplied by the staining percentage and staining intensity. To calculate. Final score ≤2 points were the negative expression, while >2 points were the positive expression. If the evaluation results obtained by the two experts were consistent, the result was recorded as a final result; if the results were inconsistent, a third chief physician was invited to review the results, and the majority opinion was used as the final result.

2.3 | Follow-up

The patients were followed up through outpatient visits and telephone interviews. Patients were followed up starting from the day of surgery and ending on the day of death or the last follow-up. Overall survival (OS) was defined as the time from the day of surgery to the day of death due to any reason. The follow-up ended on 30 June 2020, and the median follow-up time for the 126 patients was 46.5 months. Patients were followed up once every 1–3 months in the first 3 years, once every 6 months in the following 2 years, and once per year for the rest follow-up time. For the follow-up, tumour markers, that is, carcinoembryonic antigen, alfa-fetoprotein, carbohydrate antigen (CA) 199, CA125, and CA724, were assessed; additionally, B-scan ultrasonography was performed every 3 months after gastrectomy and computed tomograph or magnetic resonance imaging was performed every 6 months after gastrectomy. There was no loss to follow-up in this study.

2.4 | Statistical analysis

All statistical analyses were carried out using SPSS software. The chi-square test was used to analyse the correlation of CKS2 and CD47 expression with clinical data. The Student’s t test was used for comparisons. The correlation of CKS2 with CD47 staining scores was calculated by the Pearson χ² test. Survival curves were generated using the Kaplan–Meier method, and differences between curves were estimated by the log-rank test. The Cox multivariate proportional hazards regression model was used to determine the independent factors that influence prognosis based on the investigated variables. All reported P values were two-sided and P <.05 was considered statistically significant.

3 | RESULTS

3.1 | Expression of CKS2 and CD47 in different gastric tissues

The positivity rates for CKS2 in benign gastric tumour tissues, LGIEN tissues, HGIEN tissues, and GC tissues gradually increased, that is, 6.3% (2/32), 30.9% (13/42), 38.8% (19/49), and 60.3% (76/126), respectively, as did the positivity rates for CD47, that is, 18.8% (6/32), 38.1% (16/42), 46.9% (23/49), and 65.9% (83/126), respectively. Our results suggested that CKS2 and CD47 were a high expression in gastric cancer tissues. The differences were statistically significant (χ² = 27.588, P =.000; χ² = 27.588, P =.000), suggesting that CKS2 and CD47 may be associated with the development of GC (Figure 1).

3.2 | Correlation of CKS2 and CD47 expression with clinicopathological features

To verify the functions of CKS2 and CD47 in GC, we correlated their expression with other widely recognized clinicopathologic features. Univariate analysis showed that high expression of CKS2 and CD47 were associated with tumour diameter, Lauren classification, number of lymph node metastases, and TNM stage of GC patients but were unrelated to patient gender, age, family history of GC, and histological type (Table 1).

3.3 | Correlation analysis of CKS2 and CD47 expression levels in GC tissues

Spearman rank correlation analysis indicated that there was a moderate positive correlation between the expression levels of CKS2 and CD47 (r = .633, P = .019). The correlation analysis of the immunohistochemical
score also showed that there was a significant positive correlation between the immunohistochemical scores for CKS2 and CD47 ($r = 0.625$, $P = .000$) (Table 2 and Figure 2).

### 3.4 High expression of CKS2 and CD47 predicts poor prognosis

The median follow-up time for the 126 patients was 46.5 months, and the OS rate was 40.5% (51/126). The OS rates for the patients in the CKS2 (+) and CKS2 (−) groups were 25.0% (19/76) and 64.0% (32/50), respectively, and the OS rate for the patients in the CKS2 (+) group was significantly poor ($\chi^2 = 15.67$, $P = .000$). The OS rates for the patients in CD47 (+) and CD47 (−) groups were 30.1% (25/83) and 60.5% (26/43), respectively, and the OS rate for the patients in the CD47 (−) group was significantly poor ($\chi^2 = 14.14$, $P = .000$). Based on CKS2 and CD47 expression, the patients were divided into 4 groups: CKS2 (+) CD47 (+) group ($n = 65$), CKS2 (+) CD47 (−) group ($n = 12$), CKS2 (−) CD47 (+) group ($n = 14$), and CKS2 (−) CD47 (−) group ($n = 35$); the OS rates were 20.0% (13/65), 58.3% (7/12), 57.1% (8/14), 65.7% (23/35), respectively, and the differences were statistically significant ($\chi^2 = 18.14$, $P = .000$). The prognosis of patients in CKS2 (+) CD47 (+) group was significantly poor (Figure 3).

### 3.5 Cox multivariate prognosis analysis of GC patients

Cox multivariate survival analysis showed that TNM stage, lymph node metastasis, CKS2 expression, and CD47 expression were independent risk factors affecting the OS of patients ($P < .05$). Table 3.

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4 | DISCUSSION

In mammals, CKS1 and CKS2, are composed of 79 amino acids, and the homology between their protein sequences is 81%. The protein expression levels of CKS1 and CKS2 in various cancer tissues, including breast cancer, cervical cancer, ovarian cancer, prostate cancer, and hepatocellular carcinoma, are increased and closely related to the poor prognosis of patients. To confirm the correlation between CKS2 expression and the occurrence of GC, this study examined CKS2 protein expression in GC tissues. The results indicated that CKS2 expression in cancer tissues was significantly higher than that in noncancerous tissues, a result that was consistent with those reported in the literature. CD47 is a widely expressed antigen and is usually highly expressed in tumour cells. Studies have shown that CD47 is highly expressed on the surface of tumour cells of various cancers, including ovarian cancer, breast cancer, osteosarcoma, small cell lung cancer, and liver cancer. Yoshida et al. found that among 115 GC patients, the positive expression rate of CD47 was 49.5% (57/115). Gan et al showed that the positive expression rate of CD47 in 80 GC tissues was 51.85%, while that in normal paracancerous tissues was 36.84%. In this study, the positivity rate for CD47 in GC tissues was 65.9% (83/126), a result that was consistent with the reported rate for CD47.

The high CD47 expression in tumour cells can protect tumour cells from being phagocytosed by macrophages, thus contributing to the further development of tumours. Therefore, CD47 expression is closely related to the clinicopathological factors of cancer patients, but the correlations are different. Liu et al. showed that in ovarian cancer, CD47 expression was closely related to the degree of ovarian tissue differentiation and the pathological stage: the higher the CD47 expression, the worse
| Index                                | n  | CKS2 express |                     | CD47 express |       |       |
|--------------------------------------|----|--------------|---------------------|--------------|-------|-------|
|                                      |    | Negative     | Positive            |   | Negative       | Positive         | |
|                                      |    | (n = 50)     | (n = 76)            |   | (n = 43)       | (n = 83)           | |
| Gender                               |    |              |                     |   |              |                   | |
| Male                                 | 78 | 33           | 45                  | 0.590        | .443            | 30                | 48             | 1.711          | .191            |
| Female                               | 48 | 17           | 31                  |   |              |                   | |
| Age                                  |    |              |                     |   |              |                   | |
| <60                                  | 62 | 23           | 39                  | 0.341        | .559            | 19                | 43             | 0.658          | .417            |
| ≥60                                  | 64 | 27           | 37                  |   |              |                   | |
| Family history of GC                 |    |              |                     |   |              |                   | |
| Yes                                  | 29 | 12           | 17                  | 0.045        | .831            | 9                 | 20             | 0.160          | .689            |
| No                                   | 97 | 38           | 59                  |   |              |                   | |
| Tumour diameter (cm)                 |    |              |                     |   |              |                   | |
| <5                                   | 73 | 35           | 38                  | 4.950        | .026            | 38                | 35             | 24.812         | .000            |
| ≥5                                   | 53 | 15           | 38                  |   |              |                   | |
| Histological types                   |    |              |                     |   |              |                   | |
| Tubular adenocarcinoma               | 64 | 25           | 39                  | 0.091        | .993            | 21                | 43             | 5.435          | .143            |
| Papillary adenocarcinoma             | 29 | 12           | 17                  |   |              |                   | |
| Low adhesion adenocarcinoma          | 26 | 10           | 16                  |   |              |                   | |
| Mucinous adenocarcinoma              | 7  | 3            | 4                   |   |              |                   | |
| Lauren type                          |    |              |                     |   |              |                   | |
| Intestinal type                      | 36 | 9            | 27                  | 9.432        | .009            | 6                 | 30             | 14.567         | .001            |
| Diffuse type                         | 67 | 35           | 32                  |   |              |                   | |
| Mixed type                           | 23 | 6            | 17                  |   |              |                   | |
| Number of lymph node metastases      |    |              |                     |   |              |                   | |
| ≤5                                   | 69 | 35           | 34                  | 7.770        | .005            | 32                | 37             | 10.181         | .000            |
| >5                                   | 57 | 15           | 42                  |   |              |                   | |
| TNM stage                            |    |              |                     |   |              |                   | |
| I                                    | 37 | 20           | 17                  | 8.910        | .031            | 19                | 18             | 12.056         | .002            |
| II                                   | 48 | 21           | 27                  |   |              |                   | |
| III                                  | 41 | 9            | 32                  |   |              |                   | |

Bold values means $P<.05$. 


differentiation degree of ovarian cancer tissues, and the more advanced the pathological stage. In addition, a report on the correlation between CD47 and bladder cancer

**Table 2** Correlation analysis of CKS2·CD47 expression intensity

| CKS2 express | CD47 express | r  | P    |
|--------------|--------------|----|------|
| Negative     | 34           | 15 | .633 | .019 |
| Positive     | 13           | 64 |      |      |

It has been reported that CKS2 expression is related to the clinicopathologic features of tumours and can be used as a prognostic factor to determine the survival time of patients. CKS2 expression in colorectal cancer has a significantly negative correlation with the degree of tumour differentiation, and CKS2 is also highly expressed in GC and correlated with the degree of tumour differentiation. Liu et al. showed that CKS2 gene expression in GC tissues (0.97 ± 0.16) was higher than that in paracancerous tissues (0.38 ± 0.11) and that the expression of CKS2 protein in GC tissues was closely related to Lauren classification, depth of tumour invasion, lymph node metastasis, and TNM stage. Bioinformatics analysis results further confirmed that the high expression of CKS2 protein in GC tissues was closely related to the occurrence and development of GC and can be used as an independent factor to evaluate the prognosis of patients with GC. This study found that CKS2 protein expression had significant adverse effects on tumour diameter, the number of lymph node metastases,

**Figure 2** Correlation analysis of CKS2 and CD47 immunohistochemical scores. The correlation analysis of the immunohistochemical score also showed that there was a significant positive correlation between the immunohistochemical scores for CKS2 and CD47 (r = .625, P = .000)

**Figure 3** Effect of CKS2 and CD47 expression on overall survival rate of GC patients. A, Comparison with CKS2 (-) group, the overall survival rate for the patients in the CKS2 (+) group was significantly poor ($\chi^2 = 15.67, P = .000$). B, Comparison with CD47 (-) group, the overall survival rate for the patients in the CD47 (+) group was significantly poor ($\chi^2 = 14.14, P = .000$). C, Comparison with CKS2 (+) CD47 (-) group, CKS2 (-) CD47 (+) group, and CKS2 (+) CD47 (+) group, the overall survival rate of CKS2 (+) CD47 (+) group was significantly poor ($\chi^2 = 18.14, P = .000$)
and TNM stage, a result that is consistent with those reported in the literature.

Shi et al.\textsuperscript{20} showed that high CD47 expression was positively correlated with TNM stage, the incidence of distant metastasis, and the mortality rate of melanoma patients and that high CD47 expression was an independent prognostic indicator of OS and progression-free survival in GC patients. However, the relationship between CD47 expression and the prognosis of patients with GC is under debate. Yoshida et al.\textsuperscript{17} showed that the OS rate for CD47 (+) patients was significantly lower than that for CD47 (−) patients and that CD47 expression was considered a risk factor for a poor prognosis of patients with GC. However, Sudo et al.\textsuperscript{19} showed that CD47 expression in primary tumours was unrelated to any clinicopathological factor or prognosis; these results indicated that there might be post-transcriptional differences, such as protein degradation or transport damage, that lead to high CD47 protein expression. Yu et al.\textsuperscript{21} showed that CKS2 expression levels in colorectal cancer tissues were significantly higher than those in paracancerous tissues and that CKS2 protein was highly expressed in colorectal cancer and correlated with the clinicopathological characteristics of tumours; they concluded that CKS2 expression can be utilized as a new molecular marker and therapeutic target for colorectal cancer. Our study showed that the 5-year survival rate of patients in the CD47 (−) CKS2 (−) group was significantly better than that of patients in the CD47 (+) CKS2 (+) group; these results indicated that the higher the expression levels of CD47 and CKS2, the worse the prognosis of patients with GC. Further multivariate analysis using a Cox proportional hazard model showed that CD47 and CKS2 expression levels were independent risk factors affecting the prognosis of patients with GC. Pathological tumour-node-metastasis (pTNM) staging is critical for determining the prognosis of GC and selecting clinical treatments.

In summary, this study found that CKS2 and CD47 expression levels were related to the clinicopathological features of GC and may play an important role in the occurrence and development of GC through a synergistic effect. These results indicated that the CKS2 and CD47 could play important regulatory roles in the biological behaviour of GC. This study provides a theoretical basis for the use of CKS2 and CD47 protein as novel molecular markers and therapeutic targets for GC.

**CONFLICT OF INTEREST**

We have no financial relationships to disclose.

**DATA AVAILABILITY STATEMENT**

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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**REFERENCES**

1. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65(2):87-108.
2. Du Y, Zhu H, Liu J, et al. Consensus on eradication of *Helicobacter pylori* and prevention and control of gastric cancer in China (2019, Shanghai). *J Gastroenterol Hepatol*. 2020;35(4):624-629.
3. Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. *CA Cancer J Clin*. 2014;64(1):9-29.
4. Seo S, Ryu M-H, Park YS, et al. Consensus on eradication of *Helicobacter pylori* and prevention and control of gastric cancer in China (2019, Shanghai). *J Gastroenterol Hepatol*. 2020;35(4):624-629.
5. Huang N, Wu Z, Hong H, et al. Overexpression of CKS2 is associated with a poor prognosis and promotes cell proliferation and invasion in breast cancer. *Mol Med Rep*. 2019;19(6):4761-4769.
6. Martinsson-Ahlzén H-S, Liberal V, Grünfelder B, et al. Cyclin-dependent kinase-associated proteins Cks1 and Cks2 are essential during early embryogenesis and for cell cycle progression in somatic cells. *Mol Cell Biol*. 2008;28(18):5698-5709.
7. Candás-Green D, Xie B, Huang J, et al. Dual blockade of CD47 and HER2 eliminates radioresistant breast cancer cells. Nat Commun. 2020;11(1):1-15.
8. Yang K, Xu J, Liu Q, et al. Expression and significance of CD47, PD1 and PDL1 in T-cell acute lymphoblastic lymphoma/leukemia. Pathol Res Pract. 2019;215(2):265-271.
9. Jonsson M, Fjeldbo CS, Holm R, et al. Mitochondrial function of CKS2 oncoprotein links oxidative phosphorylation with cell division in chemoradioresistant cervical cancer. Neoplasia. 2019;21(4):353-362.
10. Xu JH, Wang Y, Xu D. CKS2 promotes tumor progression and metastasis and is an independent predictor of poor prognosis in epithelial ovarian cancer. Eur Rev Med Pharmacol Sci. 2019;23(8):3225-3234.
11. Li Z, Xue TQ, Yang C, et al. EGFL7 promotes hepatocellular carcinoma cell proliferation and inhibits cell apoptosis through increasing CKS2 expression by activating Wnt/β-catenin signaling. J Cell Biochem. 2018;119(12):10327-10337.
12. Wang H, Tan M, Zhang S, et al. Expression and significance of CD44, CD47 and c-met in ovarian clear cell carcinoma. Int J Mol Sci. 2015;16(2):3391-3404.
13. Zhang H, Lu H, Xiang L, et al. HIF-1 regulates CD47 expression in breast cancer cells to promote evasion of phagocytosis and maintenance of cancer stem cells. Proc Natl Acad Sci. 2015;112(45):E6215-E6223.
14. Mohanty S, Yerneni K, Theruvath JL, et al. Nanoparticle enhanced MRI can monitor macrophage response to CD47 mAb immunotherapy in osteosarcoma. Cell Death Dis. 2019;10(2):1-14.
15. Zhang X, Wang Y, Fan J, et al. Blocking CD47 efficiently potentiated therapeutic effects of anti-angiogenic therapy in non-small cell lung cancer. J Immunother Cancer. 2019;7(1):1-11.
16. Rodríguez MM, Fiore E, Bayo J, et al. 4Mu decreases CD47 expression on hepatic cancer stem cells and primes a potent antitumor T cell response induced by interleukin-12. Mol Ther. 2018;26(12):2738-2750.
17. Yoshida K, Tsujimoto H, Matsumura K, et al. CD 47 is an adverse prognostic factor and a therapeutic target in gastric cancer. Cancer Med. 2015;4(9):1322-1333.
18. Liu R, Wei H, Gao P, et al. CD47 promotes ovarian cancer progression by inhibiting macrophage phagocytosis. Oncotarget. 2017;8(24):39021.
19. Sudo T, Takahashi Y, Sawada G, et al. Significance of CD47 expression in gastric cancer. Oncol Lett. 2017;14(1):801-809.
20. Shi M, Gu Y, Jin K, et al. CD47 expression in gastric cancer clinical correlates and association with macrophage infiltration. Cancer Immunol Immunother. 2021;70(7):1831-1840.
21. Yu MH, Luo Y, Qin SL, et al. Up-regulated CKS2 promotes tumor progression and predicts a poor prognosis in human colorectal cancer. Am J Cancer Res. 2015;5(9):2708-2718.

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