# Combination of CD47 Expression and SIRI as a Prognostic Factor in Nasopharyngeal Carcinoma Patients

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# Abstract

**Aim:** The present study aimed to investigate the prognostic value of the combination of CD47 expression and SIRI level in nasopharyngeal carcinoma (NPC) patients.

**Materials & Methods:** NPC patients who received radical chemoradiation therapy between January 2012 and December 2016 at the Second Xiangya Hospital were retrospectively reviewed. The clinical and laboratory data was collected from the electro-history system. The expression of CD47 was detected by immunohistochemical (IHC) method. Receiver operating characteristic curve analysis was used to determine the optimal cut-off value. Survival curves were analyzed using Kaplan-Meier method, and Cox proportional hazard model was used to identify prognostic factors.

**Results:** A cohort of 183 NPC patients were enrolled. CD47 was highly expressed in 36.1% (66/183) patients at a cut-off value of 35%. And SIRI was elevated in 35.0% (64/183) patients at a cut-off value of 0.94. CD47 expression had no significant correlation with NPC patients' age, gender, ECOG status, clinical stage, smoking history or chemo-agent. While SIRI level was significantly higher in male patients and patients who has smoking history. Univariate analyzes shown that younger age, better ECOG PS, earlier clinical stage, and low expression of CD47 and SIRI level predicts better PFS, while better ECOG PS, earlier clinical stage, and low expression of CD47 and SIRI level predicts longer OS. Further multivariate Cos regression model showed that aside from ECOG PS and clinical stage, CD47 and SIRI statue was an independent prognostic factor for PFS and OS.

**Conclusion:** Our findings indicate that the combination of CD47 expression and SIRI level might be a promising prognostic predictor for the NPC patients.


# Introduction

Nasopharyngeal carcinoma (NPC) is a common malignancy in Southern China and Southeast Asia with a frequency of 20 cases per 100,000 people [1]. Radiotherapy alone or with chemotherapy is the preferred treatment regimen for early or locally advanced NPC patients, with a 5-year survival rate of about 85%-90%[2]. However, about 14%-20% of these NPC patients develop a relapse disease or distant metastasis disease[3]. Prognostic biomarker for NPC is still lacking and identifying more prognostic biomarkers is an urgent need.

Recent evidence shows that local and systemic immune-inflammation statue could affect the prognosis of patients. PD-1/PD-L1 based immunotherapy, the immune checkpoint inhibitor (ICI), has been succeeded in the treatment of various cancers, including NSCLC[4], melanoma[5], and head and neck squamous cell carcinoma[6], etc. PD-L1 expression has been demonstrated to be the most effective local immune statue biomarker for treatment response and patient prognosis[7]. However, PD-L1 in isolation is not enough for patient stratification. CD47 is another immune check point which plays major role in maintenance of immune system homeostasis. And it is a promising target for the immune therapy and effective prognostic biomarker in various cancers[8]. By interacting with its ligands, CD47 regulates

phagocytosis and activation of immune cells through macrophages[9]. CD47 was reported highly expressed in various cancers, such as breast cancer[10], non-small cell lung cancer[11], colon cancer[12], etc. However, the evidence about its expression and prognostic role in NPC is limited.

Systemic inflammation is hallmark of cancer and is demonstrated to be of prognostic significance in various cancer patients. During the past decade, serials of blood-based markers, including neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ration (PLR), have been demonstrated to be predictive markers for prognosis for cancer patients[13]. Systemic inflammation response index (SIRI) is a new systemic inflammation biomarker which has been demonstrated to be effective in predicting the prognosis of NPC patients[14]. However, no reports have demonstrated the prognostic value of combination of CD47 expression and inflammatory markers, such as SIRI, in NPC patients.

In this study, we aimed to investigate the prognostic value of the combination of CD47 expression and SIRI in NPC patients, which may provide insights into patient stratification and treatment adjustment.

## Materials And Methods

# Patients

NPC patients treated at the Second Xiangya Hospital, Central South University, from January 2012 to December 2016 were retrospectively analyzed. The inclusion criteria were as follows: (1) diagnosis of pathologically proven poorly differentiated nasopharyngeal squamous cell carcinoma, (2) receiving radiotherapy or chemoradiotherapy in the Department of Oncology, the Second Xiangya Hospital, Central South University, with complete follow-up data available. The exclusion criteria were as follows: (1) uncontrolled active infections, (2) history of autoimmune diseases, (3) history of chronic inflammatory diseases, (4) without sufficient laboratory data and tissue sample. Finally, a cohort of 183 patients were included. Clinical information including age, gender, smoking history, Eastern Cooperative Oncology Group performance status (ECOG PS) scores, T stage, N stage, clinical stage, chemotherapy agent and blood test results were collected. SIRI was calculated according to the following formula: SIRI=neutrophil count×monocyte count/lymphocyte count. All paraffin-embedded specimens were collected according to the Helsinki Declaration of 1975, revised in 2008, and the experiment was approved by the ethics committee of the Second Xiangya Hospital, Central South University. And the need for informed consent was waived by the ethics committee of the Second Xiangya Hospital, Central South University.

All patients were followed-up from the day diagnosed to death, or 31st May 2021. Progression free survival (PFS) is defined as the interval between the date of treatment initiation and the date of disease progression or death. Overall survival (OS) was defined as the interval between the date of treatment initiation and the date of death due to any cause or to the date of the last follow-up.

# Immunohistochemistry

CD47 expression in NPC tumor tissues was evaluated by immunohistochemistry (IHC) staining using formalin-fixed paraffin-embedded tumor tissue specimens. According to the antibodies' manuals, we used phosphate buffer instead of primary antibodies as negative control. The tumor tissue specimens were first dewaxed and hydrated. Antigen retrieval was achieved by heat mediation in citrate buffer (pH 6.0), and then 3% hydrogen peroxide was used for 20 minutes at 37℃, blocked with serum for 30 minutes at 37℃. Tissues were incubated at 4℃ overnight with primary antibodies—anti-CD47 rabbit monoclonal antibody (1:40, clone B6H12, sc-12730; Santa Cruz). After washing, tissues were incubated with biotin-conjugated secondary antibody for 20 minutes at 37℃, horseradish peroxidase-linked avidin was then added to incubate for 30 minutes at 37℃. The IHC reaction was evaluated by DAB according to the manufacturer's protocol. Finally, the slides were dehydrated, mounted and visualized using a Leica microscope.

Expression in tumor cells were judged to be positive if membranous staining was present and evaluated by tumor proportion score (TPS), which is the percentage of viable tumor cells showing partial or complete membrane staining[34]. All pathological evaluation was made by two experienced pathologists in a blinded fashion.

# Statistical analysis

We used SPSS software (Version 26.0) for data analysis. $\chi^2$ test and Mann-Whitney test were used to compare the NPC patients clinicopathological features between high and low expression of CD47, and high and low level of SIRI. Receiver operating characteristic (ROC) curves were used to calculate the cut-off values for CD47 TPS and SIRI. Kaplan-Meier method was performed to calculate the progression free survival (PFS) and overall survival (OS). Multivariate analysis was performed using a Cox regression model. A two-sided *p* value of <0.05 was considered statistically significant.

## Results

# Patient characteristics

The clinicopathological features of 183 NPC patients are summarized in Table 1. The median age was 49 (range: 21-83 years). A total of 123 (67.2%) were male and 60 (32.8%) were female. Most patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 (83.6%). A total of 74 (40.4%) patients had smoking history. As for the T stage, 23 (12.6%) patients were T1, 71 (38.8%) patients were T2, 56 (30.6%) patients were T3, and 33 (18.0%) patients were T4. As for N stage, 12 (6.6%) patients were N0, 30 (16.4%) patients were N1, 118 (64.5%) patients were N2, 23 (12.5%) patients were N3. As for clinical stage, 20 (10.9%) patients were stage II, 110 (60.1%) patients were stage III, and 53 (29.0%) patients were stage IV. Among all patients, 115 (62.8%) received cisplatin-based chemotherapy, 59 (32.2%) received nedaplatin-based chemotherapy, while 9 (5.0%) received other platin-based chemotherapy.

Table 1
Clinicopathological characteristics of patients (n=183)

| Characteristics | Number (%) |
|---|---|
| Age (years) | |
| Median | 49 |
| Range | 21-83 |
| Sex | |
| Male | 123(67.2%) |
| Female | 60(32.8%) |
| Smoking history | |
| Yes | 74(40.4%) |
| No | 109(59.6%) |
| ECOG PS | |
| 0 | 153(83.6%) |
| 1 | 30(16.4%) |
| T stage | |
| 1 | 23(12.6%) |
| 2 | 71(38.8%) |
| 3 | 56(30.6%) |
| 4 | 33(18.0%) |
| N stage | |
| 0 | 12(6.6%) |
| 1 | 30(16.4%) |
| 2 | 118(64.5%) |
| 3 | 23(12.5%) |
| Clinical stage | |
| II | 20(10.9%) |
| III | 110(60.1%) |
| Abbreviations: | |
| ECOG PS, Eastern Cooperative Oncology Group performance status. | |

| Characteristics | Number (%) |
|---|---|
| IV | 53(29.0%) |
| Chemotherapy agent type | |
| Cisplatin | 115(62.8%) |
| Nedaplatin | 59(32.2%) |
| others | 9(5.0%) |
| Abbreviations: | |
| ECOG PS, Eastern Cooperative Oncology Group performance status. | |

# Cut-off values of CD47 TPS and SIRI, and Their correlation with clinicopathological features

The typical IHC staining for CD47 was shown in Figure 1. As shown in Figure S1, the optimal cut-off value of CD47 and SIRI were 35% and 0.94 according to the ROC curves. One hundred and seventeen patients (63.9%) presented with low CD47 expression, and 119 patients (65.0%) presented with low SIRI level. The association between CD47 expression, SIRI level, and the clinicopathological features are shown in Table 2. CD47 expression had no correlation with NPC patients' age, gender, ECOG status, clinical stage, smoking history or chemo-agent. And SIRI level was significantly higher in male patients ($p$=0.003) and patients who has smoking history($p$=0.007).

Table 2
Correlation between CD47 expression, SIRI and Clinicopathological characteristics

| Characteristics | CD47 low | CD47 high | p | SIRI low | SIRI high | p |
|---|---|---|---|---|---|---|
| Age (years) | | | | | | |
| ≤60 | 103(88.0%) | 52(78.8%) | 0.133 | 104(87.4) | 51(79.7) | 0.198 |
| 60 | 14(12.0%) | 14(21.2%) | | 15(12.6) | 13(20.3) | |
| Gender | | | | | | |
| Male | 81(69.2%) | 42(63.6%) | 0.512 | 71(59.7) | 52(81.3) | **0.003** |
| Female | 36(30.8%) | 24(36.4%) | | 48(40.3) | 12(18.7) | |
| Smoking history | | | | | | |
| Yes | 70(59.8%) | 39(59.1) | 1.000 | 62(52.1) | 47(73.4) | **0.007** |
| No | 47(40.2%) | 27(40.9) | | 57(47.9) | 17(26.6) | |
| ECOG PS | | | | | | |
| 0 | 99(84.6%) | 54(81.8%) | 0.679 | 101(84.9) | 52(81.3) | 0.536 |
| 1 | 18(15.4%) | 12(18.2%) | | 18(15.1) | 12(18.7) | |
| T stage | | | | | | |
| 1-2 | 59(50.4%) | 35(53.0%) | 0.760 | 61(51.3) | 33(51.6) | 1.000 |
| 3-4 | 58(49.6%) | 31(47.0%) | | 58(48.7) | 31(48.4) | |
| N stage | | | | | | |
| 0-1 | 31(26.5%) | 11(16.7%) | 0.146 | 26(21.8) | 16(25.0) | 0.713 |
| 2-3 | 86(73.5%) | 55(83.3%) | | 93(78.2) | 48(75.0) | |
| Clinical stage | | | | | | |
| II-III | 81(69.2%) | 49(74.2%) | 0.502 | 89(74.8) | 41(64.1) | 0.171 |
| IV | 36(30.8%) | 17(25.8%) | | 30(25.2) | 23(35.9) | |
| Chemo-agent | | | | | | |
| Cisplatin | 73(62.4%) | 42(63.6%) | 0.392 | 76(63.9) | 39(60.9) | 0.414 |
| Nedaplatin | 40(34.2%) | 19(28.8%) | | 39(32.8) | 20(31.3) | |
| others | 4(3.4%) | 5(7.6%) | | 4(3.4) | 5(7.8) | |

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status. SIRI: Systemic Immune Response Index

# Univariate and Multivariate Survival Analyses in NPC patients

Univariate and Multivariate analyses were performed to evaluate the impact of CD47 expression, SIRI level and other clinicopathological factors on survival of patients (Table 3). The results of univariate analyses showed that Age ($p$=0.015), ECOG PS ($p$<0.001), clinical stage($p$=0.006), CD47 expression($p$=0.004), SIRI level ($p$=0.014), and CD47 and SIRI statue($p$=0.001) were significantly associated with PFS, while ECOG PS($p$=0.001), N stage($p$=0.026), clinical stage($p$=0.007), CD47 expression($p$<0.001), and CD47 and SIRI statue($p$=0.001) were significantly associated with OS. The Kaplan-Meier survival curves for PFS and OS regard to CD47 and SIRI statue were shown in Figure 2. Patients with low expression of CD47 and low SIRI level had significantly longer PFS and OS ($p$=0.001).

Table 3
Univariate analysis of potential factors associated with OS and PFS

| Variables | PFS | | | OS | | |
|---|---|---|---|---|---|---|
| | N | MST (95%CI) | *p* | N | MST (95%CI) | *p* |
| Age (years) | | | | | | |
| ≤60 | 155 | 74.62(69.60-79.63) | **0.015** | 155 | 79.42(75.27-83.56) | 0.129 |
| 60 | 28 | 52.70(42.46-62.93) | | 28 | 60.71(51.49-69.93) | |
| Gender | | | | | | |
| Male | 123 | 71.60(65.58-77.62) | 0.815 | 123 | 77.44(72.43-82.43) | 0.750 |
| Female | 60 | 70.89(63.99-77.80) | | 60 | 75.58(69.60-81.56) | |
| Smoking history | | | | | | |
| Yes | 109 | 66.58(60.63-72.54) | 0.502 | 109 | 72.39(67.55-77.22) | 0.406 |
| No | 74 | 75.22(68.48-81.96) | | 74 | 79.95(74.03-85.88) | |
| ECOG PS | | | | | | |
| 0 | 153 | 76.76(71.91-81.61) | **0.001** | 153 | 80.85(76.83-84.86) | **0.001** |
| 1 | 30 | 46.85(36.64-57.07) | | 30 | 57.33(47.57-67.10) | |
| T stage | | | | | | |
| 1-2 | 94 | 71.44(65.93-76.94) | 0.085 | 94 | 75.79(71.21-80.38) | 0.096 |
| 3-4 | 89 | 68.02(60.83-75.20) | | 89 | 74.50(68.46-80.54) | |
| N stage | | | | | | |
| 0-1 | 42 | 70.92(64.34-77.50) | 0.116 | 42 | 76.19(71.38-80.99) | **0.026** |
| 2-3 | 141 | 70.08(64.47-75.68) | | 141 | 75.44(70.66-80.21) | |
| Clinical stage | | | | | | |
| II-III | 130 | 76.80(71.73-81.86) | **0.006** | 130 | 81.24(76.91-85.57) | **0.007** |
| IV | 53 | 58.88(49.45-68.31) | | 53 | 66.88(59.10-74.66) | |
| Chemo-agent | | | | | | |
| Cisplatin | 115 | 70.29(64.74-75.83) | 0.799 | 115 | 74.72(70.14-79.30) | 0.889 |
| Nedaplatin | 59 | 73.56(68.79-78.39) | | 59 | 79.38(72.63-86.12) | |

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status PFS, progression-free survival; OS, overall survival. SIRI: Systemic Immune Response Index.

| Variables | PFS | | | OS | | |
|---|---|---|---|---|---|---|
| CD47 | | | | | | |
| Low | 117 | 77.43(71.97-82.88) | **0.004** | 117 | 83.32(79.01-87.63) | **0.001** |
| High | 66 | 59.57(51.90-67.25) | | 66 | 65.05(58.49-71.60) | |
| SIRI | | | | | | |
| Low | 119 | 76.66(71.18-82.13) | **0.014** | 119 | 79.91(75.14-84.67) | 0.144 |
| High | 64 | 58.80(51.37-66.24) | | 64 | 67.67(61.69-73.64) | |
| CD47 and SIRI | | | | | | |
| CD47 low/SIRI low | 79 | 81.83(75.94-87.71) | **0.001** | 79 | 85.23(80.36-90.10) | **0.001** |
| others | 104 | 61.10(55.01-67.19) | | 104 | 68.03(62.94-73.12) | |

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status PFS, progression-free survival; OS, overall survival. SIRI: Systemic Immune Response Index.

In multivariate analyses, Cox proportional hazards regression model shown that ECOG PS, clinical stage and CD47 and SIRI statue were independent prognostic factors for PFS with hazard ratio (HR) at 2.918(95% CI 1.639-5.197, $p$ 0.001), 2.023 (95% CI 1.191-3.439, $p$=0.009), and 2.660 (95% CI 1.444-4.899, $p$=0.002), respectively. Moreover, ECOG PS, clinical stage and CD47 and SIRI statue were independent prognostic factors for OS with HR at 2.603 (95% CI1.356-4.997, $p$=0.004), 2.118 (95% CI 1.185-3.787, $p$=0.011), and 2.755 (95% CI1.392-5.452, $p$=0.004), respectively (Table 4).

Table 4
Multivariable Cox regression analyses for OS and PFS

| Variables | PFS | | OS | |
|---|---|---|---|---|
| | HR (95% CI) | *p* | HR (95% CI) | *p* |
| Age(years) | | | | |
| ≤60 | 1.320(0.679-2.500) | 0.394 | 1.136(0.545-2.369) | 0.734 |
| >60 | | | | |
| ECOG PS | | | | |
| 0 | 2.918(1.639-5.197) | **<0.001** | 2.603(1.356-4.997) | **0.004** |
| 1 | | | | |
| Clinical stage | | | | |
| II-III | 2.023(1.191-3.439) | **0.009** | 2.118(1.185-3.787) | **0.011** |
| IV | | | | |
| CD47 and SIRI | | | | |
| CD47 low/SIRI low | 2.660(1.444-4.899) | **0.002** | 2.755(1.392-5.452) | **0.004** |
| others | | | | |

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status, PFS, progression-free survival; OS, overall survival.

# Discussion

NPC is a malignancy arising from the epithelium of the nasopharynx. Environmental factors, genetic background, and EBV infection are reported to be involved in the etiology of the disease[15]. Radiotherapy or chemo-radiotherapy are the major treatment regimens for NPC[16]. However, some patients develop relapse or metastasis disease. Therefore, finding new prognostic factors for NPC patients is an urgent need. In the present study, we investigated the prognostic value of CD47 and SIRI in a retrospective cohort of 183 NPC patients. The results showed that patients with low CD47 expression and low SIRI level had longer PFS and OS, and CD47/SIRI statue was an independent prognostic factor for NPC patients' prognosis.

The development and progression of tumors occur in concert with alterations in the surrounding environment. Previous research has shown that local and systemic immune inflammation statue are interconnected and significantly associated with disease progression and patients' prognosis. The secretion of various cytokines, and chemokines can affect the tumor microenvironment (TME)[17]. Several blood-based inflammation biomarkers have been established as effective prognostic biomarker

in NPC, including NLR[18] and PLR[19], etc. SIRI is a newly established biomarker, which reflected the change of neutrophil, monocyte and lymphocyte associated with systemic inflammation statue. It has been studied as a prognostic biomarker in NPC patients[20, 21]. In the present study, we also found that SIRI is a prognostic factor for PFS, which is in accordance with previous reports. It indicated that SIRI could be an effective systemic inflammation biomarker for prognosis prediction.

CD47 is an importance biomarker presenting local immune statue in the TME. It is a transmembrane protein which plays an important role in mediating cell proliferation[8], migration[22], phagocytosis[23], apoptosis[24], immune homeostasis[25] and other immune reactions. CD47 binds to signal regulatory proteins (SIRPs) with high affinity[26]. The binding of CD47 and SIRPs sends a “don’t eat me” signal to the macrophages, and inhibits phagocytosis of tumor cells by macrophages, leading to immune suppression[27]. Inhibition of macrophage-mediated phagocytosis has emerged as an essential mechanism for tumor immune evasion. Therefore, research of CD47-SIRPα immune checkpoint in tumor immunotherapy has become more and more popular in recent years. The prognostic role of CD47 expression has been shown in several cancers. A retrospective study of colorectal cancer showed that high expression of CD47 correlated with distant metastasis and shorter PFS[28]. In advanced non-small cell lung cancer, high expression of CD47 (with a cut-off of TPS≥50%) predicted shorter PFS and OS[29].

The evidence of prognostic role of CD47 expression in NPC patients is limited. In a previous study, 66 NPC patients were retrospectively investigated, results showed that high expression of CD47 (with a cut-off of TPS≥10%) was an independent prognostic factor for PFS (HR=5.452, $p$=0.016)[30]. In the present study, we found in a larger cohort that CD47 expression is an independent prognostic factor for NPC patients’ prognosis, which was in consistent with the previous findings. Moreover, we combined the biomarker of local immune statue, CD47, and the biomarker of systemic immune statue, SIRI, and found that patients with low CD47 expression and low SIRI level had better PFS and OS. It indicated that both a local and systemic immunocompetent statue are needed to avoid tumor immune escape and disease progression. CD47 is a promising new immune checkpoint in tumor immunotherapy, and multiple clinical trials involving CD47-SIRPα blocking agents are ongoing for leukemia, lymphoma, and solid tumors[31]. Further studies are needed to evaluate prognostic and therapeutical significance of CD47 in cancers.

Obviously, our study has several limitations. Firstly, it is a retrospective study with comparatively small sample size, which may bring selection bias. Secondly, the cut-off value of CD47 TPS in our study was different from previous study. Since the data from large sample size research is lacking, the optimal cut-off value still needs further investigation. Thirdly, some other clinicopathological factors which may affect the prognosis of patients were not included, such as EBV-DNA[32], LDH[33]. It may bring bias to the results.

In summary, our study indicated that combination of CD47 expression and SIRI may be a promising prognostic biomarker. It is a convenient and easy-to-get biomarker that may help patient stratification. However, the underlying mechanism of the mutual effecting of local and systemic immune statue in cancer immune escaping and disease progression still needs further investigation.

# Declarations


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### Conflict of interest statement.

The authors declare no conflicts of interest.

### Author contributions

T.H., X.L.L., C.H.H. conceived and designed the study. C.D., H.H.W. and S.Q.F. contributed to data acquisition. Data analysis and manuscript drafting were performed by C.D., Y.H.F. and H.X.Z. Figures and tables were created by Y.H.F. and J.A.M. All authors were involved in the writing or review of the manuscript and approved the final version.

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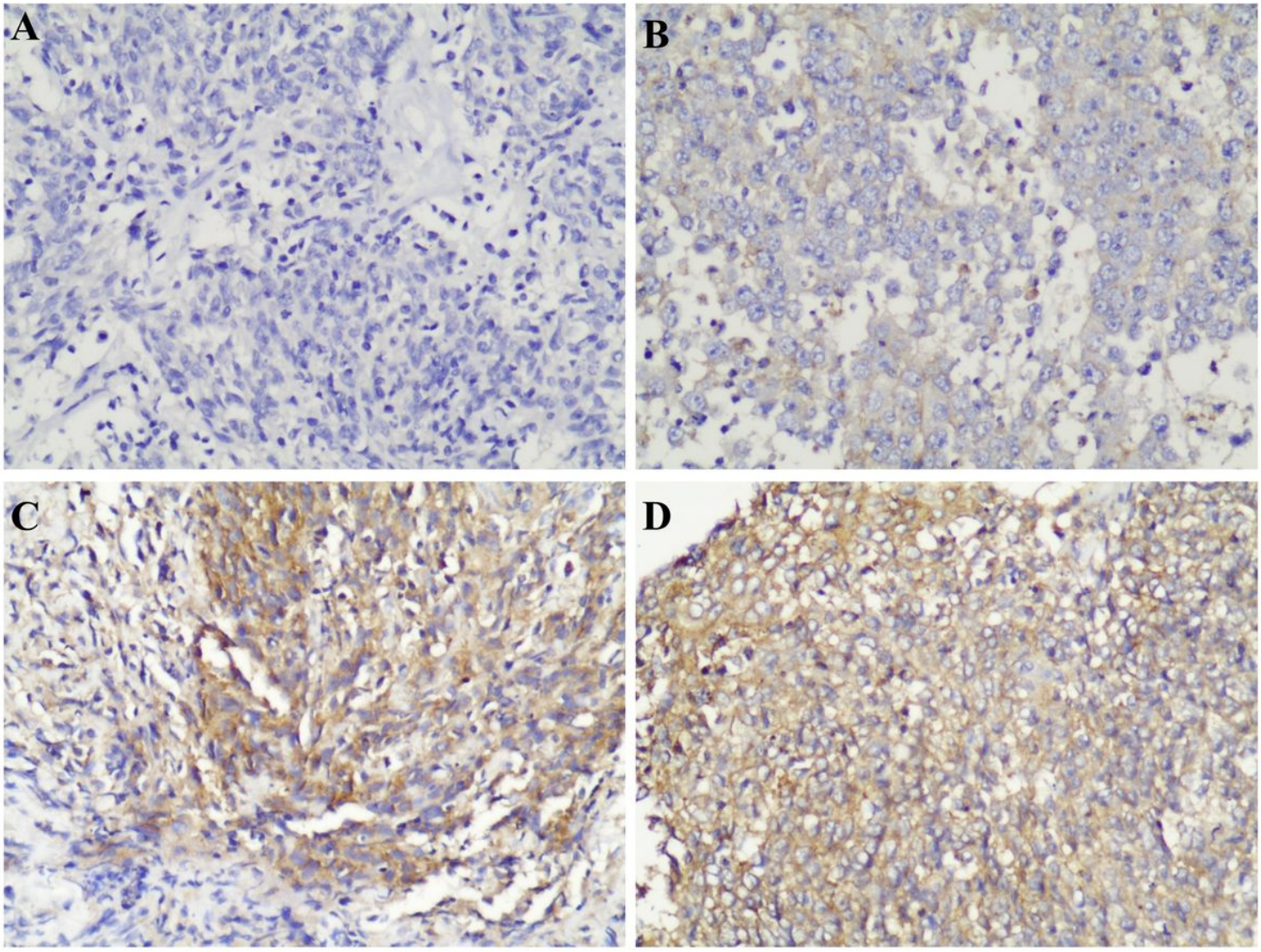
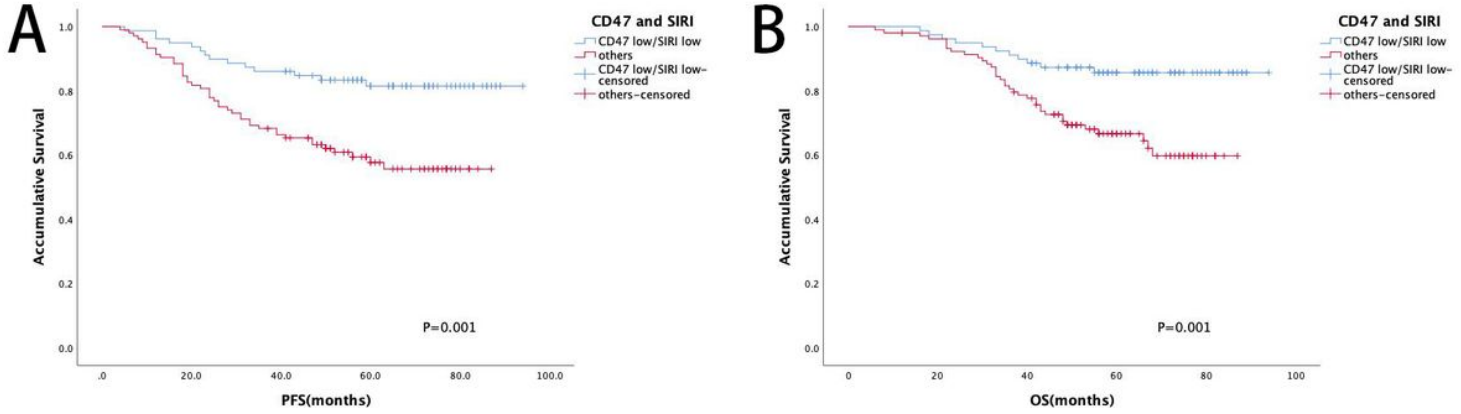
# Figures




## Figure 1

Immunohistochemical study of CD47 expression in NPC tissues. The tumor percentage score (TPS) of membrane staining was graded as 0 (A), 15%(B), 60%(C) and 90% (D) (A–D, ×200).




## Figure 2

Kaplan-Meier survival curves of patients with NPC stratified by CD47 and SIRI. (A) Progression-free survival and (B) overall survival.

## Supplementary Files

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- FigureS1.jpg