The prognosis of hepatoid adenocarcinoma of the stomach: a propensity score-based analysis

CURRENT STATUS: UNDER REVIEW

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Abstract

Background To investigate whether there is a distinct difference in prognosis between hepatoid adenocarcinoma of the stomach (HAS) and non-hepatoid adenocarcinoma of the stomach (non-HAS) and whether HAS can benefit from radical surgery.

Methods We retrospectively reviewed 722 patients with non-HAS and 75 patients with HAS who underwent radical gastrectomy between 3 November 2009 and 17 December 2018. Propensity score matching (PSM) analysis was used to eliminate the bias among the patients in our study. First, univariate analysis, including the chi-square and Mann-Whitney U tests, was used to investigate the relationship between all included clinical indicators and dependent variables, and some clinical indicators that might be meaningless were excluded. Then, clinical indicators with statistical and clinical significance were included in the logistic regression analysis to obtain more reliable results. The relationships between gastric cancer types and overall survival (OS) were evaluated by the Kaplan-Meier method and Cox regression models.

Results Our data demonstrate that there is no statistically significant difference in the OS between HAS and non-HAS {K-M, P=log rank (Mantel-Cox), (before PSM P=0.490); (1:1 PSM P=0.345); (1:2 PSM P=0.195)}. Moreover, there were no significant differences in the 1-, 2-, or 3-year survival rates between patients with non-HAS and patients with HAS (before propensity matching, after 1:1 propensity matching, and after 1:2 propensity matching).

Conclusion HAS is generally considered to be an aggressive gastric neoplasm, but its prognosis may not be as unsatisfactory as previously believed.

Background

Gastric carcinoma (GC) is not only the fifth most common cancer but also the third leading cause of death in the world [1, 2], which poses a great threat to people’s health in China [3]. Although the incidence rate of GC has been declining steadily with the improvement of heath standards, nutrition levels and radical treatment of Helicobacter pylori, the long-term survival is far from satisfactory [4–6]. Rare types of cancer without standard treatment modalities partly contribute to the adverse outcomes of GC. As a rare type of GC [7, 8], HAS is a special type of extrahepatic carcinoma.
characterized by histological resemblance to hepatocellular carcinoma [9, 10]. In 1970, Bourreille first reported one case of α-fetoprotein-producing gastric carcinoma with liver metastasis [11]. Later, Ishikura et al. named it “hepatoid adenocarcinoma of the stomach” for primary GC [12, 13]. It was reported that this rare type of GC accounts for 0.38–1% of GC. In addition to similar clinical features, such as occurrence mainly in elderly and male patients [7] [14], HAS was found to be accompanied by a higher rate of lymph node and liver metastasis in comparison with GC [15, 16]. Additionally, more than 80% of HAS patients have elevated serum AFP levels [15, 17]. Considering the higher rate of metastasis, the prognosis of HAS has been widely reported to be inferior to that of non-HAS [18–20]. To the best of our knowledge, however, most studies have been limited to case reports or case series [21]. Therefore, a more systematic study with more cases is especially meaningful for the prognostic exploration of HAS.

In our study, to explore the prognosis of HAS and whether HAS can benefit from radical surgery, we conducted propensity score-based analyses on a larger number of patients with HAS.

Methods
Patients
All patients who underwent radical surgical resection for gastric carcinoma at the Peking University Cancer Hospital between 3 November 2009 and 17 December 2018 were considered for inclusion in the study. Patients with GC were diagnosed by gastroscopy, biopsy and computed tomography. Once lesions were found with both adenocarcinoma and hepatocellular carcinoma or with the sole hepatocyte-like regions in morphology, patients were diagnosed with HAS. In addition to the serum AFP level, the tumour cells were immunohistochemically positive for AFP in HAS.

GC patients with sufficient clinicopathological information were included in our research. For HAS, we included patients with positive AFP expression in postoperative pathological immunohistochemistry. However, patients without radical surgery who were diagnosed with non-adenocarcinoma were excluded. For advanced gastric cancer (including non-HAS and HAS), if there was no distant metastasis or invasion of surrounding organs, D2 lymphadenectomy is recommended, which is performed by experienced doctors.
We collected clinical information, including sex, age, tumour location, surgery type, and levels of carcinoembryonic antigen (CEA), carbohydrate antigen 19 – 9 (CA199) and AFP. Pathological features such as vascular invasion, TNM classification (International Union Against Cancer/AJCC (American Joint Committee on Cancer)), immunohistochemistry results and neoadjuvant chemotherapy were also gathered. OS was recorded as the time from the date of surgery to the date of death from cancer or the date of the last follow-up. The basic clinical characteristics are listed in (Table 1).

**Table 1**
Clinicopathological characteristics of patients with HAS and Non-HAS treated with radical gastrectomy

| Factors                      | Before propensity matching | After 1:1 propensity matching | After 1:2 propensity matching |
|------------------------------|----------------------------|--------------------------------|--------------------------------|
| Sex (M/F)                    | Non-HAS: 517/205 | HAS: 61/14 | P value*   | Non-HAS: 60/12 | HAS: 59/13 | P value   | Non-HAS: 87/23 | HAS: 44/11 | P value   |
| Age (yr)                     | Non-HAS: 81/282 | HAS: 359 | 0.785 | Non-HAS: 3/26 | HAS: 43 | 0.213 | Non-HAS: 12/50 | HAS: 50/48 | 0.674 |
| Location                     | Non-HAS: 217/10 | HAS: 365/10 | 0.762 | Non-HAS: 19/11 | HAS: 11 | 0.640 | Non-HAS: 39/11 | HAS: 59/1 | 0.785 |
| Surgery type                 | Non-HAS: 9/354 | HAS: 356/3 | 0.170 | Non-HAS: 0/42 | HAS: 30 | 1.000 | Non-HAS: 1/55 | HAS: 53/1 | 0.445 |
| Vascular invasion no/yes     | Non-HAS: 327/395 | HAS: 29/46 | 0.272 | Non-HAS: 18/54 | HAS: 28/44 | 0.074 | Non-HAS: 49/61 | HAS: 20/35 | 0.315 |
| T                           | Non-HAS: 171/263 | HAS: 288/21 | 0.001 | Non-HAS: 18/26 | HAS: 28 | 0.051 | Non-HAS: 34/51 | HAS: 25/17 | 0.990 |
| N                           | Non-HAS: 15/155 | HAS: 146/11 | 0.229 | Non-HAS: 12/18 | HAS: 14 | 0.182 | Non-HAS: 29/24 | HAS: 20/17 | 0.566 |
| M                           | Non-HAS: 711/11 | HAS: 73/2 | 0.791 | Non-HAS: 69/3 | HAS: 70 | 1.000 | Non-HAS: 109/1 | HAS: 54/1 | 1.000 |
| EGFR +/++/+++                | Non-HAS: 64/169 | HAS: 212/6 | <0.001 | Non-HAS: 1/16 | HAS: 32 | 0.940 | Non-HAS: 6/10 | HAS: 46/48 | 0.695 |
| Ki-67 0–25% 26–50% 51–75% 76–100% | Non-HAS: 67/274 | HAS: 25/39 | 0.003 | Non-HAS: 3/10 | HAS: 18 | 0.648 | Non-HAS: 10/12 | HAS: 41/47 | 0.741 |
|               | CEA(ng/ml) |     |     |     |     |     |     |     |
|---------------|------------|-----|-----|-----|-----|-----|-----|-----|
|               | ≤ 5        | 582 | 45  | 49  | 23  | 0.384 | 77  | 33  |
|               | > 5        | 140 | 30  | 44  | 28  |       | 43  | 12  |
|               |            |     |     |     |     |     |     |     |
|               | CA199(u/ml)| ≤ 37| 614 | 71  | 65  | 0.022 | 105 | 5   |
|               | > 37       | 108 | 4   | 68  | 4   |       | 51  | 4   |
|               |            |     |     |     |     |     |     |     |
|               | Her-2     | -/+ | 541 | 44  | 43  | 0.010 | 74  | 10  |
|               |           | ++  | 126 | 21  | 10  |       | 26  | 35  |
|               |           | +++ | 55  | 18  | 20  |       | 17  | 9   |
|               | neoadjuvant chemotherapy | no | 637 | 57  | 52  | 0.003 | 93  | 17  |
|               |            | yes| 85  | 18  | 20  |       | 46  | 9   |
|               |            |     |     |     |     |     |     |     |
| M = male, F = female |

| Divided the major and minor curvature of the stomach into 3 equal parts, connect their corresponding points, can be divided into upper 1/3(U), middle 1/3 (M), lower 1/3 (L) and the total stomach (T). |

TG = total gastrectomy
DG = distal gastrectomy
PG = proximal gastrectomy
TGC = gastrectomy combined with visceral resection

* Categorical data were using the chi-square test (X² test), and continuous data were using the Mann-Whitney U test.

Follow-up Visits
The status of all patients was assessed every 3 to 6 months during follow-up. We used chest and abdominal computed tomography, liver imaging and tumour markers. Magnetic resonance imaging (MRI) and positron emission tomography-computed tomography (PET-CT) were also adopted according to the special situations of the patients. The follow-up period lasted three years.

Propensity Score Analysis
To accurately analyse the prognosis of HAS, we used propensity score matching to balance out the bias between HAS and non-HAS patients. The propensity score of all patients was determined by using the chi-square and Mann-Whitney U tests (Table 1). According to a 0.02 calliper width, one-to-one nearest neighbour matching was carried out. One-to-two nearest neighbour matching was performed with a 0.05 calliper width. For the analysis of this article, the results were obtained by propensity score matching.

Statistical analysis
Statistical analysis was performed by using SPSS software version 23.0 (IBM, United States).

Significant bias in categorical data were evaluated using the chi-square test (X² test), and bias in continuous data were evaluated using the Mann-Whitney U test. For the univariate analysis of OS, the Kaplan-Meier approach was used, and for multivariate analysis, the Cox proportional hazards model was used. P < 0.05 was regarded as the threshold of significance.
Results
Study population
From November 2009 to December 2018, 797 patients were enrolled in our research. A total of 722 (90.6%) gastric adenocarcinoma cases (non-HAS) and 75 (9.4%) HAS cases were detected by histological morphology and immunohistochemistry. Through one-to-one nearest-neighbour matching with a 0.02 calliper width, 144 patients were included for analysis, with 72 HAS and non-HAS patients each. Through one-to-two nearest-neighbour matching with a 0.05 calliper width, 165 patients were included in our study, with 110 non-HAS patients and 55 HAS patients.

Clinicopathological Characteristics
For the 797 patients, the two groups (HAS and non-HAS) were consistent in terms of sex, age, tumour location, surgery type, vascular invasion, and N and M classification. Nevertheless, the two groups were differentially distributed in terms of T classification, EGFR, Ki-67, CEA, CA199, HER-2 and neoadjuvant chemotherapy. One-to-one and one-to-two nearest-neighbour matching were used to generate 144 and 165 patients from the two groups, respectively. They showed no significant bias in clinicopathological characteristics (Table 1). Before matching, 11.8% (85/722) of patients with non-HAS received neoadjuvant chemotherapy, and 24% (18/75) with HAS received neoadjuvant chemotherapy. In the 1:1 propensity score matching group, the proportion of patients with non-HAS and HAS was 27.8% (20/72) and 22.2% (16/72), respectively. In the 1:2 propensity score matching group, the proportion of patients who underwent neoadjuvant chemotherapy was 15.5% (17/110) and 16.4% (9/55), respectively.

Survival Among All Patients And Propensity-matched Pairs
In our analysis, we found that OS was not significantly different between the HAS group and the non-HAS group (Fig. 1). Among the 797 patients in our study, the 1-, 2-, and 3-year survival rates of non-HAS patients were 92.2%, 80.7%, and 74.2%, and those of HAS patients were 93.1%, 86.8%, and 85.0%, respectively. Among the one-to-one nearest-neighbour matched pairs of patients, the 1-, 2-, and 3-year survival rates of non-HAS patients were 94.4%, 86.5%, and 82.3%, and those of HAS patients were 92.9%, 86.3% and 84.5%, respectively. Among one-to-two nearest-neighbour matched pairs of patients, the 1-, 2-, and 3-year survival rates of non-HAS patients were 98.1%, 98.1%, and
96.9%, and those of HAS patients were 90.3%, 83.9% and 79.9%, respectively.

**Risk Factors For Prognosis**

Among the 797 patients, univariate analysis showed that the tumour location, surgery type, TNM stage, levels of CEA and CA19-9, EGFR expression, and neoadjuvant chemotherapy were significantly associated with OS. Among the one-to-one nearest-neighbour matched pairs of patients, T and M stage, EGFR expression and neoadjuvant chemotherapy were found to be significantly related to OS. Among the one-to-two propensity-matched pairs of patients, T and M stage, level of CEA and EGFR expression were significantly associated with OS (Table 2).

| Factors(k-m)       | Before propensity matching p value* | After 1:1 propensity matching p value | After 1:2 propensity matching p value |
|-------------------|------------------------------------|--------------------------------------|--------------------------------------|
| GC types          | OS 0.490                           | OS 0.345                             | OS 0.195                             |
| Age               | 0.158                              | 0.277                                | 0.446                                |
| Sex               | 0.964                              | 0.584                                | 0.322                                |
| Location          | 0.003                              | 0.903                                | 0.555                                |
| Surgery type      | < 0.001                            | 0.530                                | 0.471                                |
| Vascular invasion | < 0.001                            | 0.120                                | 0.101                                |
| T                 | < 0.001                            | 0.001                                | 0.013                                |
| N                 | < 0.001                            | 0.201                                | 0.431                                |
| M                 | < 0.001                            | < 0.001                              | < 0.001                              |
| CEA               | 0.002                              | 0.066                                | < 0.002                              |
| CA199             | < 0.001                            | 0.552                                | 0.312                                |
| EGFR              | < 0.001                            | < 0.001                              | 0.007                                |
| HER2              | 0.520                              | 0.397                                | 0.644                                |
| Ki-67             | 0.291                              | 0.067                                | 0.258                                |
| Neoadjuvant chemotherapy | 0.008 | 0.043                               | 0.08                                 |

*GC types: hepatoid adenocarcinoma of the stomach and non-hepatoid adenocarcinoma of the stomach

**Multivariable survival analysis to identify factors predicting OS by using Cox proportional hazards model**

| Factor     | Before propensity matching |
|------------|----------------------------|
| GC type    | HR 95%CI P value           |
| a          |                            |
| Factor                        | HR (95% CI) | P    |
|-------------------------------|-------------|------|
| GC type                       |             |      |
| non-HAS                      | 1.377       | 0.706–2.687 | 0.348 |
| HAS                          |             |      |
| Age (yr)                      |             |      |
| <45                           | -0.706–2.687 | 0.185 |
| 60 > age ≥ 45                | -0.706–2.687 | 0.369 |
| ≥ 60                          | -0.706–2.687 | 0.096 |
| Location                      |             |      |
| U                             | 0.912       | 0.569–1.461 | 0.914 |
| M                             | 1.056       | 0.592–1.885 | 0.703 |
| L                             | 1.242       | 0.431–3.577 | 0.688 |
| T                             |             |      |
| Surgery type                  |             |      |
| PG                            | 1.133       | 0.142–9.039 | 0.155 |
| DG                            | 1.810       | 0.243–13.473 | 0.906 |
| TG                            | 5.152       | 0.431–61.637 | 0.562 |
| TGC                           |             |      |
| Vascular invasion             |             |      |
| no                            | -1.152      | 0.778–1.705 | 0.480 |
| yes                           |             |      |
| T                             | 1.940       | 0.946–3.980 | <0.001 |
| T1 T2 T3                      | 3.645       | 1.817–7.314 | 0.071 |
| T4                            |             |      |
| N                             |             |      |
| N0                            | 1.827       | 0.924–3.613 | <0.001 |
| N1                            | 2.058       | 1.034–4.095 | 0.083 |
| N2                            | 3.649       | 1.885–7.066 | 0.040 |
| N3                            |             |      |
| M                             | 2.253       | 1.061–4.781 | 0.034 |
| M0                            |             |      |
| M1                            |             |      |
| CEA (ng/ml)                   |             |      |
| ≤5                            | 1.403       | 0.969–2.031 | 0.073 |
| >5                            |             |      |
| CA199 (u/ml)                  |             |      |
| ≤37                           | 1.537       | 1.022–2.309 | 0.039 |
| >37                           |             |      |
| EGFR                          |             |      |
| -                             | -           |      |
| +                             | 1.315       | 0.774–2.234 | 0.026 |
| ++                            | 0.727       | 0.381–1.387 | 0.312 |
| +++                           | 0.736       | 0.386–1.404 | 0.334 |
| Neoadjuvant chemotherapy      |             |      |
| no                            | -           |      |
| yes                           | 1.504       | 0.982–2.304 | 0.061 |
| Factor                        |             |      |
| HR                            |             |      |
| non-HAS                       | -           |      |
| HAS                           | 1.230       | 0.461–3.278 | 0.679 |
| Age (yr)                      |             |      |
| <45                           | -           |      |
| 60 > age ≥ 45                |             |      |
| ≥ 60                          | -           |      |
| Vascular invasion             | -           |      |
| no                            | -           |      |
| yes                           | 3.224       | 0.623–16.685 | 0.163 |
| T                             | -           |      |
| T1 T2 T3                      | -           |      |
| T4                            | 3.450       | 0.631–18.861 | 0.033 |
| N                             |             |      |
| N0                            | -           |      |
| N1                            | -           |      |
| N2                            | -           |      |
| N3                            | -           |      |
| M                             | -           |      |
| M0                            | -           |      |
| M1                            | -           |      |
| EGFR                          |             |      |
| -                             | -           |      |
| +                             | 0.212       | 0.018–2.466 | 0.082 |
| ++                            | 0.069       | 0.006–0.798 | 0.215 |
| +++                           | 0.208       | 0.018–2.458 | 0.032 |
| +++++                         |             |      |
### Table

| Factor                  | HR      | 95% CI          | P    |
|------------------------|---------|-----------------|------|
| Neoadjuvant chemotherapy no yes | 3.031   | 1.165–7.882     | 0.023|

#### c After 1:2 propensity matching

| Factor                  | HR      | 95% CI          | P    |
|------------------------|---------|-----------------|------|
| GC type                |         |                 |      |
| non-HAS                | 3.348   | 1.124–9.977     | 0.030|
| HAS                    |         |                 |      |
| Age (yr) (<45; 60| 5.775   | 0.167–200.111   | 0.466|
| ≥60)                   | 7.356   | 0.248–217.980   | 0.332|
| Vascular invasion      |         |                 |      |
| no                     | 2.909   | 0.521–16.247    | 0.224|
| yes                    |         |                 |      |
| T                      |         |                 |      |
| Tis, T0, T1, T2        | 5.353   | 0.749–38.243    | 0.171|
| T3                     | 7.229   | 0.898–58.202    | 0.066|
| T4                     |         |                 |      |
| N                      |         |                 |      |
| N0                     | 0.583   | 0.069–4.959     | 0.730|
| N1                     | 0.337   | 0.034–3.335     | 0.621|
| N2                     | 0.724   | 0.088–5.931     | 0.352|
| N3                     |         |                 | 0.764|
| M                      |         |                 |      |
| M0                     | 69.379  | 3.009–1599.499  | 0.008|
| M1                     |         |                 |      |
| CEA (ng/ml) ≤5         | 7.077   | 2.018–24.815    | 0.002|
| >5                     |         |                 |      |
| EGFR                   |         |                 |      |
| -                      | 0.077   | 0.008–0.755     | 0.122|
| +                      | 0.077   | 0.008–0.779     | 0.028|
| ++                     | 0.107   | 0.014–0.800     | 0.030|
| +++                    |         |                 | 0.029|
| Neoadjuvant chemotherapy no yes | 2.169   | 0.641–7.338     | 0.213|

#### Discussion

HAS comprises polygonal cells arranged in solid or trabecular form, similar to that in hepatocellular carcinoma [12, 22]. Many researchers have supported that the common embryos of the stomach and liver originate from the foregut and may have evolved through genetic progression and/or genetic differences [23, 24]. At present, there are two views on the prognosis of HAS and non-HAS. The majority of studies showed that HAS has a distinctly poorer prognosis than non-HAS [9, 10, 25]. However, few reports have suggested that HAS does not have a poorer prognosis. Our study aimed to further elucidate whether HAS has a worse prognosis than non-HAS using a larger number of patients and whether HAS can benefit from radical surgery.

We used the propensity score matching method to eliminate the bias between HAS and non-HAS patients and then compared their prognoses. Our study showed that there was no significant difference in postoperative survival between HAS and non-HAS patients within 3 years after radical
surgical resection, which is contrary to the majority of findings. The research from Liu et al showed a significantly different prognosis between HAS and non-HAS [26]. The 1-, 3-, and 5-year survival rates of HAS and non-HAS (without AFP production) were 30%, 13%, and 9% and 95%, 57%, and 38%, respectively [26]. In their research, the incidence of liver metastasis was 75.6% (34/45), including 8.9% synchronous and 73.2% (30/41) metachronous liver metastasis [26]. However, our research only included nine HAS patients with postoperative liver metastasis (9/75). Therefore, we boldly speculated that the occurrence of liver metastasis contributes to the poorer prognosis of HAS, which was consistent with the findings of some reports [12, 27, 28]. Additionally, their patients with HAS had a markedly higher elevated serum level of AFP, while ours did not. It is worth mentioning that the prognosis of patients with higher serum levels of AFP was poorer than that of patients with lower serum levels of AFP (< 500 ng/ml) [29]. Essentially, there remained no clear reasons for the poorer OS of HAS. Some researchers believe that HAS produces alpha-1 antitrypsin (AAT) and/or alpha-1 antichymotrypsin (ACT) and AFP, which enhance invasiveness and affect immunosuppressive properties [12, 30, 31]. However, few studies are consistent with ours. Wang et al demonstrated that patients with HAS who underwent radical surgery had a 5-year survival rate of 41.1% [7]. Augustin G reported that a 72-year-old man diagnosed with HAS underwent gastrectomy and splenectomy. He was still alive 24 months after surgery without distant metastasis[32]. Giustozzi G et al reported that a HAS patient with radical surgery who underwent chemotherapy was still alive and disease-free (with a 52-month follow-up) [33]. Therefore, radical surgery and chemotherapy may have a positive impact on the therapeutic effect [34, 35].

In our research, univariate analysis suggested that both infiltration depth (T) and distant metastasis (M) were related to the OS of gastric adenocarcinoma in the group of data before and after PSM, but lymph node metastasis (N) had no significant relationship with prognosis in the data after propensity score matching. This finding may be attributed to the limited number of samples after PSM. Multivariate analysis indicated that distant metastasis (M) and the level of CEA were independent risk factors affecting the OS of HAS and non-HAS patients. In addition, HAS and non-HAS were independent risk factors that affected the OS of patients after radical surgery in 1:2 propensity
matching ($P = 0.030$). This result may be due to the small amount of HAS data included in the analysis, which is similar to the cases and results of most of the current studies.

Our study has several limitations. First, it is retrospective and enrolled patients in a single institutional cohort. Second, we did not include information about the patient’s postoperative chemotherapy in our study. However, we usually decide whether to give chemotherapy to patients according to their postoperative pathological results. Last, the follow-up time is not long enough to assess long-term prognosis. Despite these limitations, a relatively large number of patients and rigorous statistical methods made our results convincing.

In conclusion, there was no statistically significant difference in the overall survival time between patients with HAS and non-HAS after radical surgery and chemotherapy. Under the condition that patients with HAS can tolerate the surgery, the choice of surgery indications and methods were the same as that of non-HAS and radical surgery was the best choice.

**Abbreviations**

HAS
hepatoid adenocarcinoma of the stomach;

non-HAS
non-hepatoid adenocarcinoma of the stomach;

OS
the overall survival time;

PSM
Propensity score matching;

GC
Gastric carcinoma;

CEA
carcinoembryonic antigen;

CA199
carbohydrate antigen 19 – 9;

MRI
Magnetic resonance imaging;

AAT
alpha-1 antitrypsin;
alpha-1 antichymotrypsin.

Declarations

Ethics approval and consent to participate

This research was approved by the Ethics Committee of the Peking University Cancer Hospital. Written informed consent was obtained from participating patients.

Availability of data and material

The datasets used and/or analyzed during the current study are available by contacting kai zhou by email on a reasonable request.

Consent for publication: Every participant agreed to publish the results.

Competing interest: This study is no potential conflicts of interest.

Funding: This study was supported by National Science Foundation for Young Scientists of China81802735, Beijing Youth Talent Plan QML20191101 and Science Foundation of Peking University Cancer Hospital 2020-11. These institutions did not play a role in study design, data collection, data analysis, data interpretation, or writing of the manuscript.

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Data analysis and interpretation: KZ, AQW.

Writing original draft: KZ.

Reviewed, methodology and edited this manuscript: AQW

Collected all samples: AS, JHC, KJQFH, XJ, XJW, Z.

Provide pathological information ZWL

Conceptualization, review and financial support of the study: ZDB, JFJ

Final approval of the manuscript: all authors.

Acknowledgements: not applicable

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Figures
Figure 1

Kaplan-Meier survival plots were made by using GraphPad Prism 5