# Pretreatment Serum Ferritin as a Prognostic Indicator in Advanced Cancer Patients Treated With Apatinib: A Retrospective Cohort Study

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**Research**

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# Abstract

**Background:** The present study has evaluated the prognostic value of pretherapy serum ferritin (SF) levels in advanced cancer patients receiving apatinib therapy after multiline treatment for drug resistance.

**Methods:** This retrospective cohort reviewed the clinicopathological characteristics and pretreatment levels of SF of 124 patients with advanced cancer treated with apatinib. The Kaplan-Meier method was used to calculate the overall survival rate (OS) and progression-free survival (PFS), and the log-rank test was used to assess the statistical significance. Univariate and multivariate analyses of Cox proportional hazard regression were used to assess the prognostic impact of advanced cancer.

**Results:** Participants in this study were previously treated with at least two treatment regimens. 52.4% of the patients had the Eastern Cooperative Oncology Group Performance Status (ECOG-PS)≥2. Median PFS was 8.57 weeks, and the median overall survival was 9.43 weeks. The OS and PFS of patients with elevated SF were significantly shorter than those with low SF ($p < 0.001$ and $p < 0.001$, respectively).

**Conclusions:** SF can be used as an important prognostic indicator for advanced cancer patients with the treatment of apatinib after multiline treatment for drug resistance.


# 1. Background

In recent years with the rapid development of molecular target therapy, target therapy was considered to be an effective treatment method for cancer(1, 2). Angiogenesis plays a crucial role in tumor growth and metastasis, especially vascular endothelial growth factor (VEGF) and its receptor (VEGFRs) on tumor growth and metastasis(3, 4). Apatinib is a novel small molecule anti-angiogenesis agent that highly selectively competes with the ATP binding site of intracellular VEGFR-2, blocks the downstream signal transduction, inhibits the activity of VEGFR-2 tyrosine kinase, prevents the signal transduction of VEGF binding to its' receptor, thus inhibiting tumor angiogenesis and playing an anti-tumor role. And it has been reported the clinical application of targeted-therapy apatinib for cancer was approved as a second-line treatment for advanced gastric cancer in China in 2014(5, 6). It was showed that advanced gastric cancer patients accepted apatinib treatment and had a clear objective curative effect and the significant survival benefit after the failure of the standard chemotherapy. Besides, different types of cancer patients could also obtain certain effects, such as non-small cell lung cancer (NSCLC), breast cancer and hepatocellular carcinoma (HCC)(7-12). These indicated that apatinib had potential anti-tumor activity in a wide range of advanced solid tumors. According to the different basic characteristics of different patients, the clinician needs to choose suitable treatment methods for individual treatment. Individualized therapy requires the continued discovery and development of markers, such as predictors, to help physicians select appropriate patients for targeted treatment.

Serum ferritin, a major iron-binding protein, was also used in the laboratory as a diagnostic indicator for iron-deficiency anemia. At present, some experts believed that serum ferritin played a role in many physiological and pathological processes, including immunosuppression(13), proliferation (14),

angiogenesis(15) and carcinogenesis(16), and maybe as an indicator of malignant diseases(17). Elevated SF indicated iron overload in the body, indicating serious illnesses, such as inflammation, infection, liver disease, tumors, liver dysfunction, even deterioration and progression(18-22). In recent years, some studies have shown that serum ferritin (SF) was closely related to tumors. The prognostic value of serum ferritin was confirmed in lung cancer, pancreatic cancer, colorectal cancer and other malignant tumors (23-29), and the increase of serum ferritin was also associated with cancer risk(30-32). Some scholars also proposed the concept of tumor-associated macrophages (TAM), thinking that the high expression of ferritin in TAM may protect them from iron-induced damage, and may stimulate their survival or proliferation secretion, or even stimulate the occurrence of tumors. It directly increased the proliferation of cancer cells, increased angiogenesis, and inhibited lymphocyte response. In general, TAM contributed to tumorigenesis. It suggested that ferritin secretion may directly promote and maintain tumorigenesis. Besides, regarding oxidative stress, high levels of serum ferritin accelerated the production of reactive oxygen species or oxidative DNA damage in cells, so some scholars believed that it was a marker of oxidative stress in cancer(33). Besides, increasing evidences showed that ferritin was associated with cancer through a variety of mechanisms, including nuclear factor-κB signaling in tumor cells and mitochondrial ferritin (34-38).

These studies suggest that SF may be a significant biomarker for the diagnosis and prognosis of various cancer types and that they are readily available as a routine test and inexpensive biochemical parameter. However, there have been no studies on the prognostic value of SF in patients receiving apatinib treatment. Therefore, the purpose of this study was to explore the role of SF in the survival outcome of patients receiving apatinib targeted therapy after multiline treatment for drug resistance and whether SF can be as an independent prognostic biomarker for such patients.

# 2. Methods

### 2.1. Patient

Patients, who were hospitalized at Affiliated Nanhai Hospital of Southern Medical University from May 2016 to May 2018, were recruited for this retrospective study. The exclusion criteria for patients were as follows: no laboratory tests at the beginning of the treatment; underwent chemotherapy, radiation therapy, chemoradiotherapy or targeted therapy three weeks prior to laboratory examination; the history of cancer in other organs; inaccurate or incomplete clinical data; related diseases that can cause SF elevation; Liver and kidney insufficiency, other serious primary disease or tumor emergency; or lost to follow-up. Patients eligible for the study: patients were hospitalized after primary histopathological analysis and imaging examination confirmed tumor progression; patients with secondary treatment failure were diagnosed with inoperable stage III or IV, including locally advanced tumors that are difficult to remove, invade adjacent structures or other distant organs; all patients had never received apatinib treatment, and had detailed clinical data available. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study

was approved by Research Ethics Committee of People's Hospital of Nanhai District, Foshan *(NO.:(2018) 1)* and individual consent for this retrospective analysis was waived.

### 2.2. Data Collection

Baseline characteristics, including height, weight, age, gender, ECOG PS, smoking status, drinking status, pathological type, clinical stage and blood index, were collected using an electronic medical records system. Patients routinely underwent blood tests within 10 days (mean: 4 days; range: 2–9) before treatment. Blood samples were obtained for the measurement of SF levels before apatinib treatment. In this study, progression-free survival (PFS) and overall survival (OS) were measured as survival results. PFS was defined as the period from the date of treatment to the first recurrence or last follow-up. OS was defined as the interval between the date of diagnosis and the date of death or last follow-up.

### 2.3. Statistical analysis

Descriptive analysis was used to analyze the characteristics of selected patients. Kaplan-Meier survival curve was used to estimate the survival time, and the log-rank test was utilized to compare the differences in survival distributions between groups. Cox proportional hazards regression analysis was used to determine the prognostic effect of survival. After controlling for confounders that may affect statistics, it was evaluated the prognostic effects of SF on apatinib-targeted therapy and demonstrated the relationship between SF and cancer prognosis. Subgroup analysis was performed based on serum ferritin and patients were identified by the chi-square test. Correlation analysis was applied to analyze the relationship between SF and other biomarkers. A p-value < 0.05 was considered statistically significant. Data were analyzed with the use of the statistical packages R (The R Foundation; http://www.r-project.org; version 3.1.2 2014-10-31)and Empower(R)(www.empowerstats.com; X&Y Solutions Inc.).

## 3. Results

### 3.1. Patient characteristics

The clinicopathological characteristics of the patients were described in Table 1. A total of 131 patients with advanced cancers, excluded for the following reasons: incomplete data and loss to follow-up (n = 7), were analyzed. At a median follow-up of 9.43 weeks (range: 0.29–100 weeks), 115 patients had died as a result of disease progression. Figures 1a and 1b showed the OS and PFS of the patient with the treatment of apatinib.

### 3.2. Prognostic cut-off value for SF

According to the iron overload standard proposed by the world health organization (WHO), the serum ferritin was divided into two groups, in which the male low serum ferritin ≤200 ng/mL and the female low serum ferritin ≤150 ng/ mL. high levels of serum ferritin were defined as >200 ng/mL in men and >150 ng/mL in women(39).

### 3.3. Results of multivariate analysis

On univariate analysis, high SF level was associated with poorer OS and PFS, with a hazard ratio (HR) of 3.4 (95% CI: 2.2–5.1, p<0.001) and 3.3 (95% CI: 2.2–5.0, p<0.001), respectively (Table 2 and 3). On multivariate analysis, it showed that SF level were independent prognostic indicators for OS and PFS, with a hazard ratio (HR) of 3.6 (95% CI: 2.2–5.9, p<0.001) and 3.5 (95% CI: 2.1–5.7, p<0.001), respectively.

### 3.4. Survival analyses and Subgroup analysis

In the cohort, Figure 1a and 1b showed that the OS and PFS of the high SF group was significantly worse than that of the low one.

In the previous section, we found that the SF level was correlated with the prognosis of advanced patients treated with apatinib. However, the study included patients with lung cancer, stomach carcinoma, hepatocellular carcinoma and colorectal cancer, which may have a large heterogeneity. Therefore, as shown in Figure 2,3,4 and 5, we performed subgroup analysis to assess the prognostic value of SF in lung cancer, liver cancer, stomach cancer, and colorectal cancer subgroup, respectively. The results of the subgroup analyzed that SF could also be a useful independent prognostic factor in lung cancer, liver cancer, stomach cancer, and colorectal cancer subgroups before treatment, which also increased the intensity of our study.

## 4. Discussion

In some clinical studies, it was found that serum ferritin levels were closely related to the prognosis in patients with lung cancer, breast cancer, stomach carcinoma, hepatocellular carcinoma and other malignant solid tumors. Based on those, we focused on the prognostic significance of pretreatment serum ferritin for survival in advanced cancer patients who were treated with apatinib.

Notably, our cohort study population had inferior performance status (52.4% ECOS-PS≥2) and was more heavily pretreated (all patients had ≥2 prior systemic treatment regimens) compared to clinical trials that led to the approval of apatinib for solid tumors. Given these key differences, it is not surprising that the PFS and OS in our study group are inferior to the published trials. Therefore, this study only represented patients with advanced cancer after multi-line drug resistance. In the univariate analysis and multivariate analysis, only high SF was associated with shorter OS and PFS, while poor ECOS-PS(≥2), age of previous treatment and line number did not affect.

From this retrospective analysis, we found that SF was correlated with significant improvements in clinical outcomes in advanced cancer patients who were treated with apatinib. It was supported that SF may be a predictive biomarker for the effectiveness of apatinib treatment in this advanced cancer patient. Besides, the median OS and PFS of people with low SF were significantly higher than those with high SF.

Finally, the SF level was considered to be an independent prognostic factor in univariate analysis and multivariate analyses.

Ferritin, an iron storage protein consisting of ferritin H-subunit and ferritin L-subunit, plays a critical role. However, there were many controversies about the cellular origin and subunit composition of serum ferritin. Some have reported that SF was mainly derived from macrophages through nonclassical secretion pathways, particularly originated from macrophages in the tumor microenvironment(14). TAM plays a critical role in the development of tumors. The direct mechanism is the secretion of proto-oncogenic molecules, while the indirect mechanism is iron-binding and ferritin release. TAM's Elevated serum ferritin may be associated with local release in the breast cancer microenvironment, which can promote tumor cell proliferation and growth(14, 27, 40-42). Moreover, elevated serum ferritin may represent increased macrophage infiltration, which is strongly correlated with tumor invasion in the surrounding stroma.

In terms of its regulatory role in angiogenesis, ferritin in the tumor microenvironment directly stimulates tumorigenesis, proliferation and angiogenesis. Ferritin contains a large number of L-subunits, which can bind to high molecular weight kininogen and prevent its antiangiogenic effect on endothelial cells, thereby accelerating migration and tube formation (14, 15). In this retrospective study, we found that OS and PFS were significantly worse in cancer patients receiving apatinib in the high serum ferritin group than in the low serum ferritin group. And apatinib is an anti-angiogenic agent, which selectively inhibits the activity of VEGFR-2 tyrosine kinase and blocks the binding of VEGF to its signal transduction receptor, thus inhibiting tumor angiogenesis and exerting an anti-tumor effect. We can boldly assume that TAM secretes high concentrations of ferritin bound to the high molecular weight kininogen, which affects the binding of apatinib to the ATP junction of VEGFR-2 and inhibits or attenuates the antiangiogenic effect of apatinib.

The results showed that serum ferritin can predict the survival prognosis of advanced cancer patients. As mentioned earlier, the primary source of ferritin was TAM, which suggested that SF was secreted by the host rather than the tumor. Therefore, ferritin can be used as a unique biomarker to predict prognosis, representing the tumor burden, reflecting the overall degree of disease progression of patients and providing information about tumor progression. To verify the clinical significance of serum ferritin in tumor angiogenesis, it is necessary to further study the pathophysiology related to tumor and host.

In clinical practice, serum ferritin predicts survival and provides useful information for the treatment of patients with advanced cancer. Besides, low-cost testing has economic advantages. Therefore, serum ferritin can be used in a variety of clinical settings.

The current study has several limitations. First, the small sample and retrospective design of this study may bias the results. No basic medical studies have been conducted to investigate the biological mechanisms underlying the prognostic significance of SF. However, our study is the first to demonstrate the prognostic value of SF in apatinib therapy and provides evidence and inspiration for future studies. Multicenter randomized controlled trials are needed in the future to confirm our findings, and basic

medical research is urgently needed to elucidate the specific mechanisms of the subject. Secondly, due to the retrospective nature of the study, the time of the CT scan isn't determined in advance. In each hospital, a CT scan is performed every six to eight weeks in routine care(43). Finally, even with careful use of the RECIST 1.1 standard, misclassification can occur. We believe that the assessment of two independent observers can reduce the information bias in this study. Our results were obtained in a homogeneous population of advanced cancer patients with apatinib therapy after multiline drug resistance treatment and cannot be extrapolated to other populations. Besides, further prospective multicenter studies and a sufficient number of samples are needed to determine the validity of our results.

# 5. Conclusion

Despite considerable efforts, no predictive biomarkers for effective antiangiogenic drugs have been identified to date. Serum ferritin is easily monitored, and once treatment is initiated, and it can reflect the expected target inhibition. The results of the retrospective analysis suggest that serum ferritin before treatment may be a cheap, effective and easily measured biomarker for evaluating the antitumor efficacy of apatinib in advanced cancer patients after multiline treatment for drug resistance. Therefore, larger randomized studies should be conducted to evaluate the role of serum ferritin as a potential prognostic biomarker for advanced cancer patients receiving the angiogenic drug apatinib before treatment.

# Abbreviations

SF: serum ferritin; OS: overall survival rate; PFS: progression-free survival; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; VEGF: vascular endothelial growth factor; VEGFRs: vascular endothelial growth factor receptor; NSCLC: non-small cell lung cancer; HCC: breast cancer and hepatocellular carcinoma; TAM: tumor-associated macrophages; WHO: world health organization; HR: hazard ratio.

# Declarations

**Ethics approval and consent to participate:** This study was approved by the ethics committee of Nanhai People's Hospital. The patient gave written informed consent in accordance with the Declaration of Helsinki. Written informed consents were obtained from the patients for publication of the findings.

**Consent for publication:** All authors agree to the publication of this manuscript.

**Availability of data and materials:** Data and materials were open. Please contact the corresponding author for more information.**Competing interests**: The authors report that there is no conflict of interest in this work.

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**Authors' contributions**: (I) Conception and design: Haiming Chen, Yiyu Lu, Weiguang Gu; (II) Administrative support: Yiyu Lu, Weiguang Gu; (III) Provision of study materials or patients: Haiming Chen, Yichao Huang, Xinfu Liu; (IV) Collection and assembly of data: Haiming Chen, Yichao Huang, Xinfu Liu; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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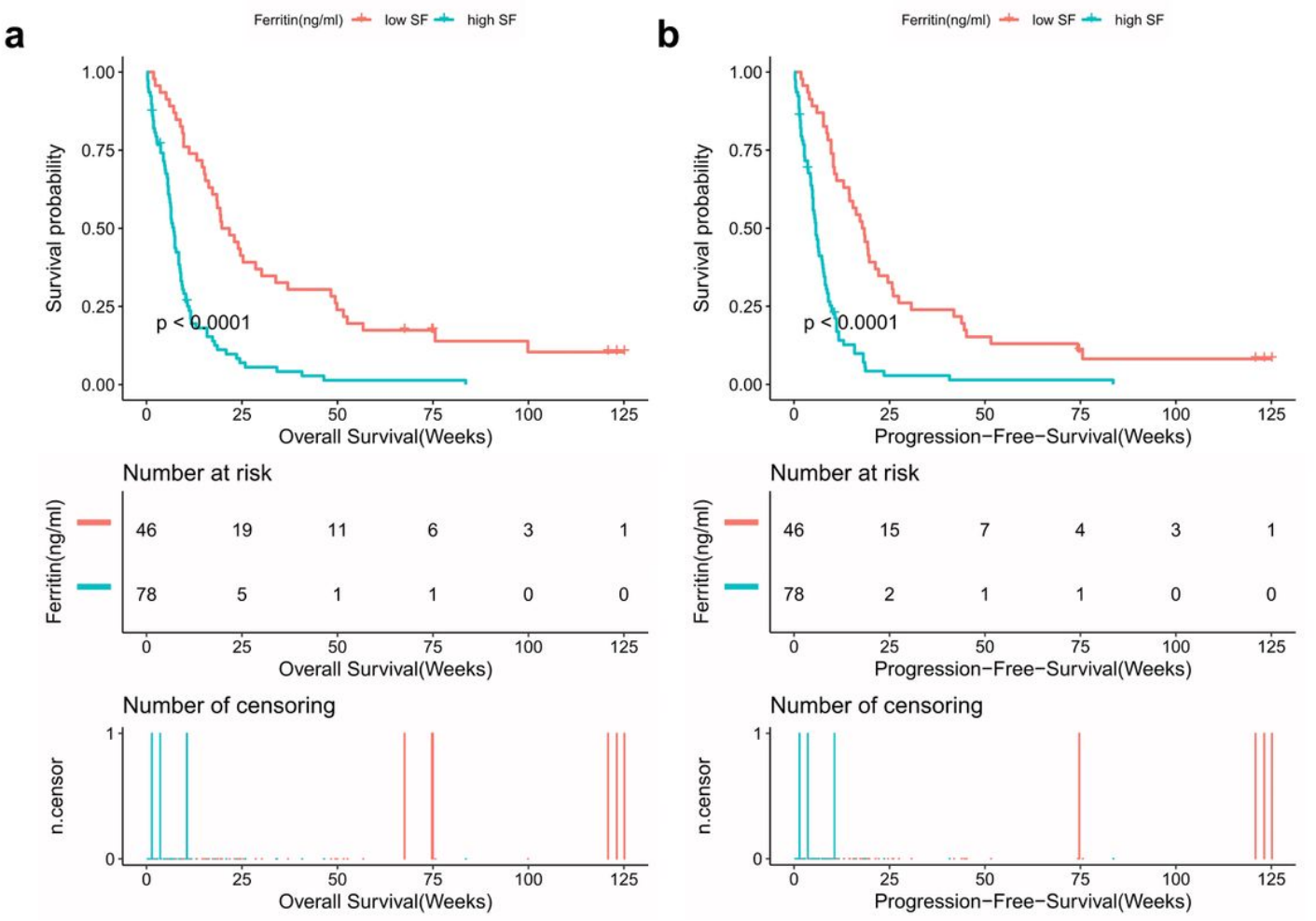
## Tables

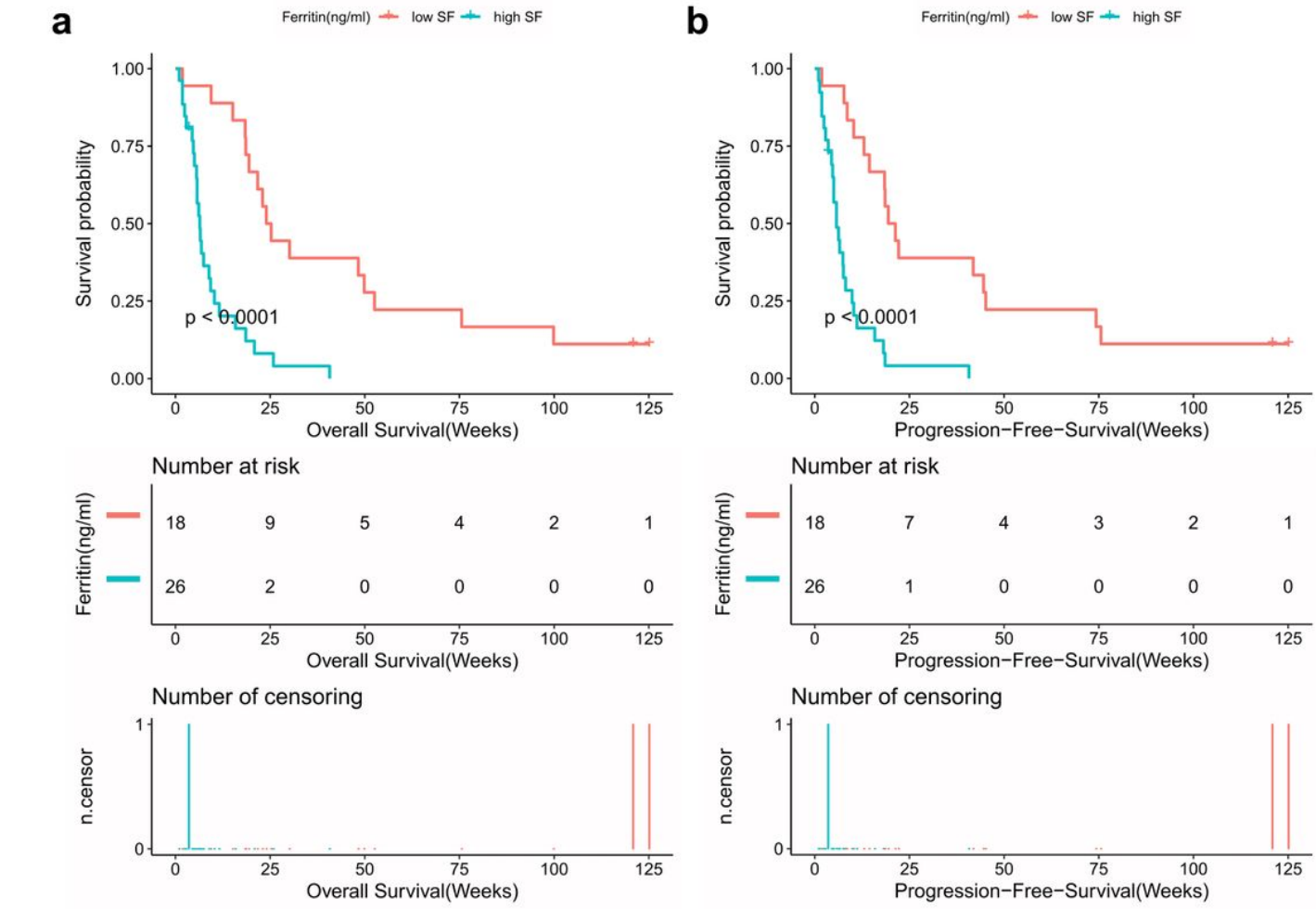
Due to technical limitations, table 1-3 is only available as a download in the Supplemental Files section.

## Figures



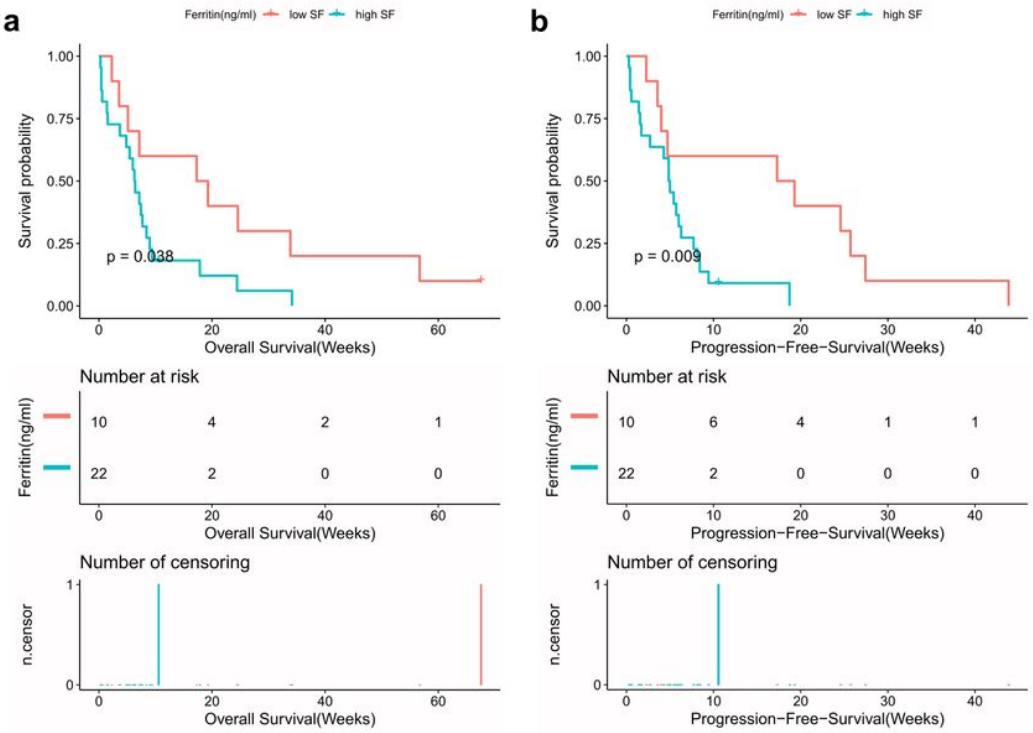
## Figure 1

Survival time of the low SF group and the high SF group. (a) OS of the low SF group and the high SF group. (b) PFS of the low SF group and the high SF group.



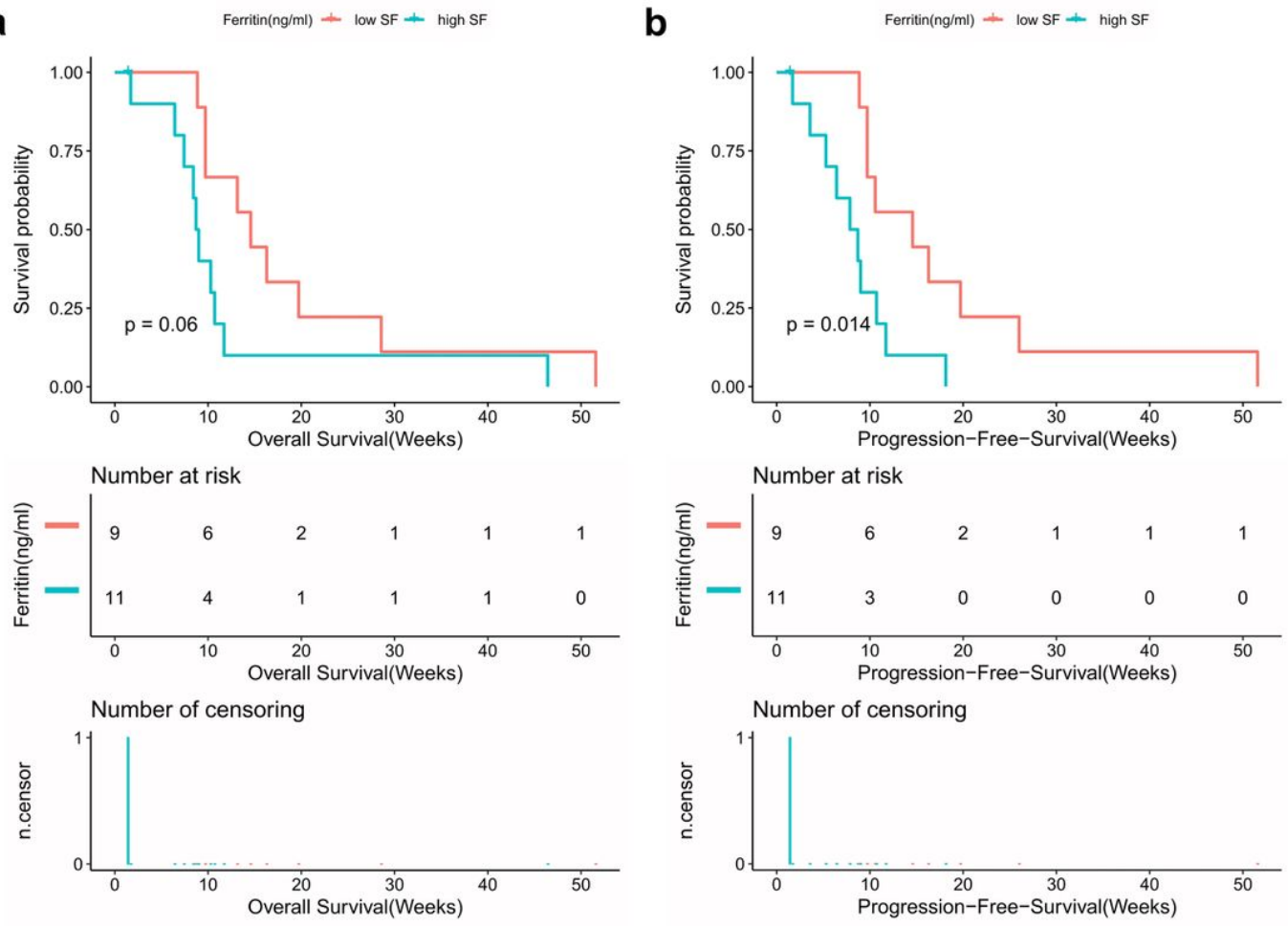

## Figure 2

Comparison of OS (a) and PFS (b) between low SF group and high SF group by Kaplan-Meier survival curves in lung cancer subgroups.




## Figure 3

Comparison of OS (a) and PFS (b) between low SF group and high SF group by Kaplan-Meier survival curves in liver cancer subgroups.




## Figure 4

Comparison of OS (a) and PFS (b) between low SF group and high SF group by Kaplan-Meier survival curves in gastric cancer subgroups.

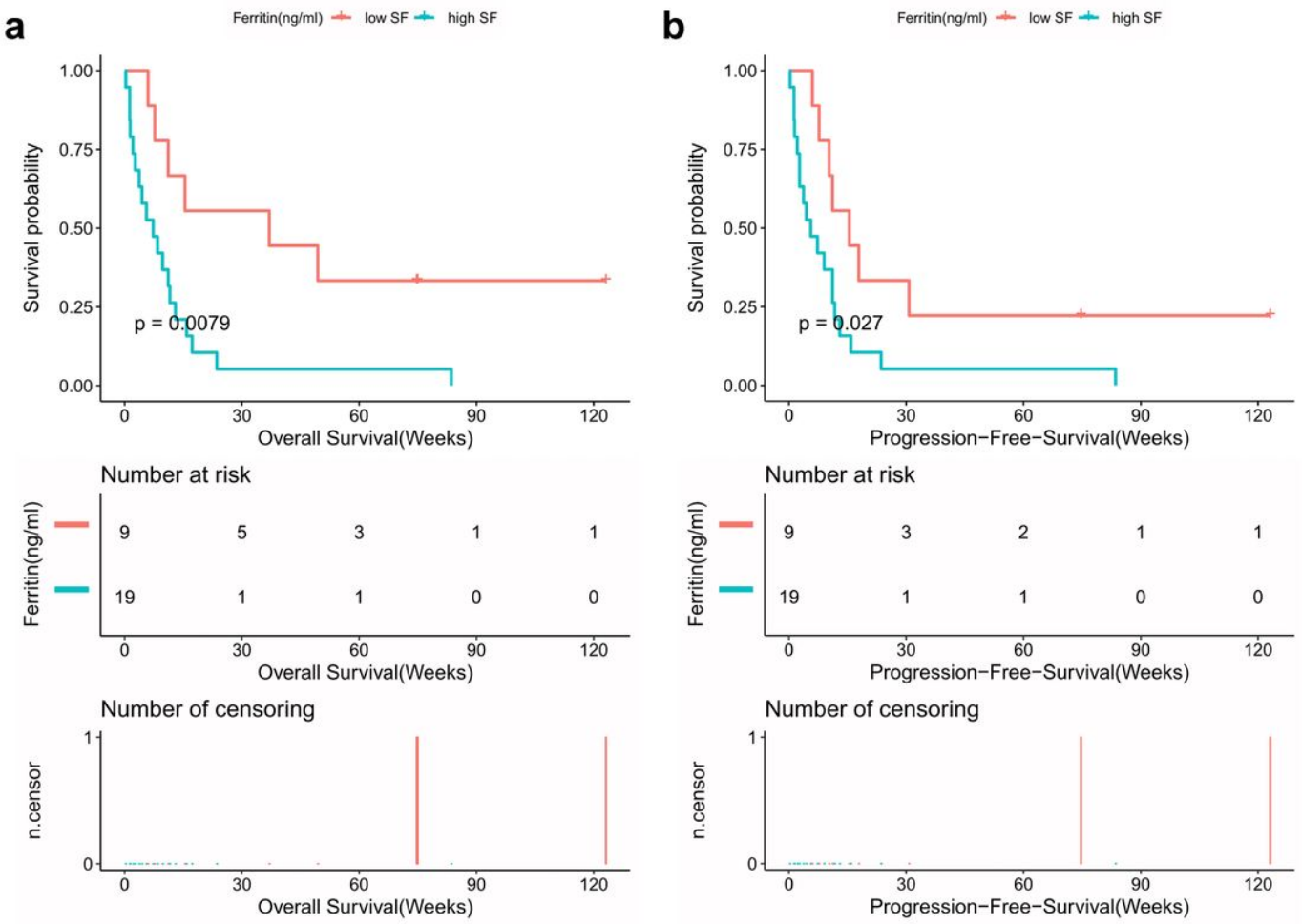



**Figure 5**

Comparison of OS (a) and PFS (b) between low SF group and high SF group by Kaplan-Meier survival curves in colon cancer subgroups.

# Supplementary Files

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