Role of the initial degree of anaemia and treatment model in the prognosis of gastric cancer patients treated by chemotherapy: a retrospective analysis

CURRENT STATUS: UNDER REVISION

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DOI: 10.21203/rs.2.10440/v2

SUBJECT AREAS
- Cancer Biology
- Oncology

KEYWORDS
- Anaemia, Gastric cancer, Chemotherapy, Prognosis, Decrease in haemoglobin
Abstract
Background: Anaemia is highly prevalent in gastric cancer (GC) patients. The role of initial haemoglobin levels in predicting the prognosis of GC patients treated by chemotherapy has not been well determined. Our present study aims to evaluate the relationship between the degree of anaemia and the overall survival (OS) and progression-free survival (PFS) of patients with GC. Methods: Our retrospective study enrolled 598 patients who were treated with chemotherapy when the recurrent GCs and metastatic GCs were unsuitable for surgical resection. Univariate and multivariate analyses were performed to identify risk factors that had the potential to affect patient prognosis. Additionally, the relationship between clinicopathological characteristics, including treatment method, and degree of chemotherapy-related reduction in haemoglobin was further analysed. Results: Our results revealed that patients with HBini level ≤ 80 g/L had a trend toward a shortened median OS and PFS (p=0.009 and p=0.049, respectively). Interestingly, we also found that HBdec ≥30 g/L was associated with a significantly shortened median OS and PFS (p=0.039 and p=0.001, respectively). Multivariate analysis showed that HBini levels ≤80 g/L could be used as an independent prognostic factor for recurrent and metastatic GC. More importantly, HBdec ≥30 g/L and treatment response were also significantly associated with OS and PFS. Furthermore, the degree of haemoglobin decrease was associated with chemotherapy including platinum and the number of chemotherapy cycles. Conclusion: Our study concludes that the initial degree of anaemia and a decrease in haemoglobin of ≥ 30 g/L can serve as biomarkers to predict prognosis in recurrent or metastatic GC patients, while chemotherapy treatment rather than red blood cell (RBC) transfusion can improve their prognosis. Additionally, paclitaxel should not be recommended for treating severely anaemic GC patients.

Background
Gastric cancer (GC) is the fifth most common malignant tumour and the third leading cause of death worldwide (1). Recurrence and metastasis are the most important characteristics of cancers including GC (2, 3). The incidence of anaemia in advanced gastric cancer patients is high, with a large variability ranging from 10% to 30% (4, 5). Anaemia can weaken the fragile patient and has been reported to be associated with a poor clinical outcome. However, the role of the degree of anaemia
and treatment model in recurrent or metastatic GC patient prognosis is unclear. Therefore, managing and improving the condition of GC-related anaemia through medical approaches are urgently needed to improve the prognosis of patients with recurrent or metastatic GC.

Cancer-related anaemia (CRA) is considered to be associated with multiple pathological and clinical factors, such as bleeding, nutritional deficiency, and bone marrow suppression (6). Bone marrow suppression can be caused by both malignant cell infiltration and chemotherapy treatment (7, 8). Functional iron deficiency is usually associated with insufficient iron intake because of cancer-related appetite loss and bleeding (9, 10). At present, the treatments of anaemia and cancer are complementary. Under these circumstances, it is critical to identify the association of relevant elements, including clinicopathological characteristics and GC treatment model, with anaemia in recurrent or metastatic GC.

Our study aimed to determine the role of initial degree of anaemia and chemotherapy-related haemoglobin reduction in the prognosis of recurrent or metastatic GC patients. The relationships between clinicopathological characteristics, including treatment regimens, and chemotherapy-related haemoglobin reduction degree were further analysed. Our study will contribute to the determination of treatment approaches for recurrent or metastatic GC-related anaemia patients.

Patients And Methods

Patients

All procedures followed were in accordance with the ethical standards of the ethical committee of Shandong Provincial Hospital regarding human experimentation and with the 1964 Helsinki Declaration and later versions. Informed consent for inclusion in the study was obtained from all patients.

Our retrospective study analysed the data collected from patients diagnosed with metastatic GC or recurrent GC at Shandong Provincial Hospital in China from January 1, 2010, to December 31, 2014. The entry criteria included the following: 1) metastatic GC or recurrent GC after radical surgical treatment was histologically confirmed as gastric adenocarcinoma — radical gastric resection was defined as negative margins, en bloc resection of the greater and lesser omentum, and D2 lymph
node dissection, and standard lymphadenectomy was defined as when the number of retrieved lymph
nodes was ≥15; 2) The Eastern Cooperative Oncology Group performance score (ECOG PS) was used
to estimate a life expectancy of more than 3 months (11); and 3) patients had received at least one
cycle of chemotherapy. The exclusion criteria included the following: 1) accompaniment by other
types of malignancies, 2) use of neoadjuvant chemotherapy, and 3) loss to follow-up. All the
pathologic specimens were reviewed by at least 2 pathologists to confirm the diagnosis of GC.

**Haemoglobin level measurement**

The initial haemoglobin level ($H_{B_{ini}}$) was collected at the initial diagnosis of recurrent or metastatic
GC. The lowest haemoglobin level was determined as the lowest level obtained from the day of
diagnosis to the date of death or the final follow-up visit. The decrease in haemoglobin ($H_{B_{dec}}$) was
defined by subtracting the lowest haemoglobin level from the initial haemoglobin level. Evaluation
and grading of anaemia were performed according to National Comprehensive Cancer Network
(NCCN) guidelines for cancer- and chemotherapy-induced anaemia (12).

When the $H_{B_{ini}}$ was less than 70 g/L, RBC transfusions were used to improve the anaemia until the
initial Hb was more than 70 g/L, and the dose of chemotherapeutic drugs was not regulated.

**Chemotherapy regimens**

The regimens used to treat the patients included the combination chemotherapy of docetaxel,
cisplatin, and 5-fluorouracil (DCF) and related modifications (docetaxel 75 mg/m$^2$ on day 1, cisplatin
60 mg/m$^2$ or oxaliplatin 130 mg/m$^2$ on day 1, fluorouracil 2500 mg/m$^2$ continuous infusion 120 hours,
cycled every 21 days); XP or modifications (capecitabine 1000 mg/m$^2$ twice daily (BID) on days 1-14,
cisplatin 75 mg/m$^2$ or oxaliplatin 130 mg/m$^2$ on day 1); FOLFIRI (irinotecan 180 mg/m$^2$ on day 1,
leucovorin 400 mg/m$^2$ on day 1, fluorouracil 400 mg/m$^2$ IV push on day 1, fluorouracil 2400 mg/m$^2$
continuous infusion 46 hours, cycled every 14 days); paclitaxel liposome 100 mg/m$^2$ (q2w) or 135-150
mg/m$^2$ (q3w) on day 1, combine with capecitabine or S-1; and single agents such as docetaxel 75-100
mg/m$^2$ on day 1, capecitabine 1000-1250 mg/m$^2$ BID on days 1-14, or S-1 80-120 mg on days 1-14,
cycled every 21 days.

**Follow-up**

Tumour responses to the chemotherapy regimens were evaluated after every 2-3 cycles of chemotherapy and categorized based on the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines (13). The number of malignant ascites and peritoneal cytology were also considered when assessing the antitumour effects.

Overall survival (OS) was calculated as the time from the date of initial diagnosis of metastatic GC or the date of recurrence after GC resection to the date of either death or the final follow-up.

Progression-free survival (PFS) was calculated as the date of either disease progression, confirmed by magnetic resonance imaging or computed tomography using a contrast medium if possible, or death from any cause.

Clinical variables for risk assessment consisted of patient demographics, surgical and pathological factors, chemotherapy regimens, and packed red cell transfusion. Data regarding recurrence, defined as disease recurrence at any site, and survival outcomes were also collected.

Peritoneal metastasis is a frequent type of metastasis of gastric cancer and is a definitive determinant for prognosis. Peritoneal metastasis was diagnosed by histological diagnosis of peritoneal metastasis and/or by peritoneal lavage cytology positive for cancer cells.

**Statistical analysis**

Survival analyses were performed by Kaplan-Meier curves with log-rank tests for significance.

Univariable Cox regression analyses were performed using PFS, OS and HB$_{dec}$ as the outcomes, with a significance level of $p<0.05$. Multivariate analysis was carried out with a Cox proportional hazards model to evaluate prognostic factors with respect to PFS, OS and HB$_{dec}$. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. A value of $p<0.05$ was considered statistically significant.

All statistical analyses were conducted using SPSS statistical software (Version 24.0; IBM Corporation, Armonk, NY, USA).

**Results**

**Patients**
Based on the inclusion and exclusion criteria, 598 patients were included in our study. Our study included 170 recurrent GC patients and 428 metastatic GC patients. The general characteristics including the kinds of chemotherapy regimen of all enrolled patients are listed in Table 1. The age and gender proportions and surgical and pathological factors of the patient population were similar to those observed in other studies [14].

There were 312 patients treated with the first line chemotherapy regimens, yet the GC in 188 patients remained in a development condition, and then those patients were treated with the second or/and third line chemotherapy regimens including FOLFIRI and docetaxel single agent.

**Follow-up and survival**

Of the 598 GC patients, the median follow-up time was 11.60 months (range 0-76), and the median OS after chemotherapy was 12 months (95 % CI 11.221-12.779), with 1-, 3-, and 5-year OS rates of 45.40%, 3.80%, and 0.90 %, respectively.

The 598 patients were divided into the HB\(_{\text{ini}}\) ≤ 80 g/L cohort and the HB\(_{\text{ini}}\) level > 80 g/L cohort. Our study included 40 patients in the HB\(_{\text{ini}}\) ≤ 80 g/L cohort and 558 patients in the HB\(_{\text{ini}}\) level > 80 g/L cohort. The clinical features which have potential effects on GC patient OS and PFS were well matched between our two groups (Table 2).

For the HB\(_{\text{ini}}\) ≤ 80 g/L cohort, the median OS was 10 months with 1-, 3-, and 5-year survival rates of 35.40%, 0%, and 0%, respectively, while in the HB\(_{\text{ini}}\) level > 80 g/L cohort, the median OS was 12 months with 1-, 3-, and 5-year survival rates of 46.10%, 4.10%, and 3.00%, respectively. The OS of the HB\(_{\text{ini}}\) ≤ 80 g/L cohort was significantly worse than that of the HB\(_{\text{ini}}\) level > 80 g/L cohort (p=0.009, Figure 1A, Table 3).

Then, we compared the OS and PFS between the HB\(_{\text{ini}}\) ≤ 80 g/L cohort and the cohort with HB\(_{\text{ini}}\) between 80 g/L and 110 g/L. Our results revealed that the HB\(_{\text{ini}}\) ≤ 80 g/L cohort did not have a trend of worse OS and PFS than the mild anaemia cohort (Supplementary Table 1).

Kaplan-Meier analysis was also used to analyse the correlation between HB\(_{\text{ini}}\) level and PFS. Our results revealed that patients with HB\(_{\text{ini}}\) levels ≤ 80 g/L also had a trend toward a shortened median
PFS ($p=0.049$, Figure 1B, Table 3). Interestingly, we also found that $\text{HB}_{\text{dec}} \geq 30 \text{ g/L}$ was associated with a significantly shortened median OS ($p=0.039$, Figure 1C, Table 3), and a similar relationship was found with decreased median PFS ($p=0.001$, Figure 1D, Table 3).

Red blood cell (RBC) transfusion is an important treatment modality, while chemotherapy is beneficial for improving the prognosis of recurrent and metastatic GC patients. We analysed the different treatment modalities and clinicopathological parameters for the OS and PFS in our patients. Using univariate analysis, we found that RBC transfusion was associated with neither median OS nor median PFS. The factors that significantly influenced OS were $\text{HB}_{\text{ini}}$ level, $\text{HB}_{\text{ini}} \leq 80 \text{ g/L}$, metastatic sites $\geq 3$, liver metastases, paclitaxel-based combination of three regimens, the number of chemotherapy cycles, treatment response, and $\text{HB}_{\text{dec}} \geq 30 \text{ g/L}$ ($p<0.05$). Additionally, $\text{HB}_{\text{ini}}$ level, the lowest haemoglobin level, metastatic sites $\geq 3$, liver metastases, bone metastases, number of chemotherapy cycles, chemotherapy including paclitaxel, treatment response and $\text{HB}_{\text{dec}} \geq 30 \text{ g/L}$ were significantly associated with PFS ($p<0.05$) (Table 4).

Multivariate analysis showed that $\text{HB}_{\text{ini}}$ level $\leq 80 \text{ g/L}$ ($\text{HR}=1.879$, 95% CI=1.301-2.767, $p=0.001$), liver metastases ($\text{HR}=1.234$, 95% CI=1.022-1.490, $p=0.029$), chemotherapy including paclitaxel ($\text{HR}=1.225$, 95% CI=1.013-1.481, $p=0.036$), treatment response ($\text{HR}=1.457$, 95% CI=1.173-1.808, $p=0.001$), and $\text{HB}_{\text{dec}} \geq 30 \text{ g/L}$ ($\text{HR}=1.536$, 95% CI=1.206-1.957, $p=0.001$) were significant adverse prognosis factors of OS. More importantly, the number of chemotherapy cycles was also significantly correlated with improved OS ($\text{HR}=0.879$, 95% CI=0.855-0.904, $p<0.001$) (Table 5).

For PFS, $\text{HB}_{\text{ini}}$ level $\leq 80 \text{ g/L}$ ($\text{HR}=1.516$, 95% CI=1.082-2.126, $p=0.016$), chemotherapy including paclitaxel ($\text{HR}=1.273$, 95% CI=1.068-1.517, $p=0.007$), treatment response ($\text{HR}=2.235$, 95% CI=1.818-2.747, $p<0.001$), the number of chemotherapy cycles ($\text{HR}=0.922$, 95% CI=0.899-0.945, $p<0.001$), and $\text{HB}_{\text{dec}} \geq 30 \text{ g/L}$ ($\text{HR}=1.543$, 95% CI=1.233-1.932, $p<0.001$) were independent prognostic factors (Table 5).

**Relationship between the degree of decrease in haemoglobin levels and the clinicopathological parameters of our patients**
We then investigated whether we could identify correlations between the degree of decrease in haemoglobin levels and the clinicopathological parameters of our GC patients. Our results suggested that bone metastases, chemotherapy including platinum, the number of chemotherapy cycles, and treatment response were associated with the degree of haemoglobin decrease ($p<0.05$) (Table 6). Multivariate analyses revealed that the number of chemotherapy cycles and chemotherapy including platinum were significantly correlated with improved $\text{HB}_{\text{dec}}$ ($p<0.001$ and $p=0.019$, respectively) (Table 7).

Chemotherapy drugs can not only kill cancer cells, but also damage healthy cells, which causes side effects. Our results revealed that the most common side effects of chemotherapy were myelosuppression, diarrhea and vomiting, yet which could not influence the OS and PFS in our cohort (Table 8).

**Discussion**

CRA occurs as a result of multiple aetiologies, including blood loss, functional iron deficiency, erythropoietin deficiency due to renal disease, chemotherapy-induced myelosuppression, marrow involvement with tumours and other factors. The relationship between anaemia and the prognosis of GC patients is rarely reported. Zhang et al. reported that patients with less than $\leq 65$ g/L haemoglobin had a significantly shorter median OS than patients with $65$ g/L to normal haemoglobin or patients with normal haemoglobin and demonstrated that a lower haemoglobin level might predict poorer OS in advanced GC patients (15). There is little information to evaluate the effect of anaemia status and RBC transfusion treatment on the OS and PFS of recurrent or metastatic GC patients.

According to the NCCN guidelines for cancer- and chemotherapy-induced anaemia, a haemoglobin level $\leq 80$ g/L is used to define severe-grade anaemia. Our present study also chose a haemoglobin level of $80$ g/L as the cut-off value for severe anaemia. Our results revealed that pretreatment of severe anaemia could serve as a prognostic factor in metastatic GC or recurrent GC patients who underwent radical resection and were then treated with chemotherapy. Multivariate analysis also showed that an initial haemoglobin level $\leq 80$ g/L was an independent adverse prognostic factor for our patients. In addition, the degree of haemoglobin decrease (haemoglobin level $\geq 30$ g/L) during
chemotherapy or the follow-up period was also an important risk factor for the prognosis of recurrent or metastatic GC.

The cause of anaemia in patients with cancer is often multifactorial. The malignancy itself can lead to or exacerbate anaemia, and underlying comorbidities may also contribute to anaemia. Cancer cells can directly suppress haematopoiesis through bone marrow infiltration and produce cytokines, leading to iron sequestration. Chronic blood loss, nutritional deficiencies, myelosuppressive effects of chemotherapy, and radiation therapy to the skeleton can further exacerbate anaemia in patients with cancer (6-10). Due to the potentially multifactorial complexity of anaemia, defining the causes of anaemia in cancer patients is essential; this knowledge will contribute to determining the appropriate treatment method to apply. Groopman et al. reported that platinum-based regimens are well known to induce anaemia due to the combined bone marrow and kidney toxicity, and the use of chemotherapy regimens including paclitaxel is an adverse prognostic factor for decreased haemoglobin, although this effect is not significant (16). Another article also showed a similar result, in that treatment with docetaxel as a single agent can cause a progression in anaemia from grade III to IV in 9% of patients (17). Those results are similar to the findings of the present study. Our study revealed that chemotherapy including paclitaxel and \( \text{HB}_{\text{dec}} \geq 30 \text{ g/L} \) were independent adverse prognostic factors. Chemotherapy including platinum was associated with a decrease in haemoglobin in recurrent or metastatic GC patients. Therefore, we consider that the improvement in anaemia may be one of the most important reasons for the improved prognosis of GC patients observed after chemotherapy treatment, and paclitaxel should not be recommended to treat severely anaemic recurrent or metastatic GC patients until the anaemia has been improved through treatment. Besides, the other regimens such as oxaliplatin and capecitabine can be chose to treated the severely anaemic GC patients.

The most common treatment options for CRA include erythropoietic-stimulating agents, RBC transfusion and nutritional therapy, such as iron intake. Previous studies have reported that the lowest postoperative haemoglobin level and postoperative transfusion were the most significant risk factors for postoperative complications in GC surgery (18). Squires et al. reported that perioperative
allogeneic blood transfusion was associated with decreased PFS and OS after resection of GC, independent of adverse clinicopathologic factors (19). In addition, RBC transfusion could not improve the chemotherapy outcomes by increasing the haemoglobin level (20). However, the role of RBC transfusion in improving the prognosis of recurrent or metastatic GC patients remains unclear. Our present data support the notion that transfusion neither significantly improved the OS and PFS nor served as a risk factor for PFS and OS in recurrent or metastatic GC. These results may be attributed to the fact that transfusion was used only when haemoglobin was not more than 70 g/L in our hospital. Insufficient blood transfusion may be another possible reason for this result.

Despite its several limitations, including being retrospective and having a small specific patient population size, our study has some advantages. First, a large range of clinical and pathological factors was comprehensively collected and compared. Second, this study is the first to analyse the effect of initial severe anaemia on the prognosis of recurrent or metastatic GC patients.

In conclusion, our study demonstrated that the initial degree of anaemia can serve as a biomarker for predicting the prognosis of recurrent or metastatic GC patients, while chemotherapy treatment rather than RBC transfusion can improve OS and PFS. In addition, paclitaxel should not be recommended to treat severely anaemic GC patients.

**Abbreviations**

GC, Gastric cancer; CRA, Cancer-related anaemia; ECOG PS, the Eastern Cooperative Oncology Group performance score; $\text{Hb}_{\text{ini}}$, the initial haemoglobin level; $\text{Hb}_{\text{dec}}$, the decrease of haemoglobin; NCCN, National Comprehensive Cancer Network; DCF, docetaxel, cisplatin, and 5-fluorouracil; BID, twice daily; RECIST, Response Evaluation Criteria in Solid Tumors; OS, Overall survival; PFS, Progression-free survival; HRs, Hazard ratios; Cis?, confidence intervals; RBC, Red blood cell.

**Declarations**

**Ethics approval and consent to participate**

All procedures followed were in accordance with the ethical standards of the ethical committee of Shandong Provincial Hospital regarding human experimentation and with the 1964 Helsinki Declaration and later versions. Informed consent for inclusion in the study was obtained from all
patients.

Consent for Publication

Not applicable.

Availability of data and material

Yes.

Competing interests

The authors declare no conflict of interest. There are no financial and non-financial competing interests (political, personal, religious, ideological, academic, intellectual, commercial or any other) to declare in relation to this manuscript.

Funding

This study was supported by Shandong Key Research and Development Plan (2016GSF201145).

Authors’ contributions

WH L conceived the study. WH L and XX C made substantial contributions to data acquisition, WH L, JY Z, WH L and XX C performed measurements, analyzed the data and drafted the manuscript. All authors have read and approved the final manuscript.

Acknowledgements

Not applicable.

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### Table 1 Patients characteristics

| Table 1 Patients characteristics |
|---------------------------------|
| **Total N=598**                  |
| **Age**                         |
| <65 years, N (%)                | 230(38.5) |
| ≥65 years, N (%)                | 368(61.5) |
| **Gender**                      |
| Male, N (%)                     | 469(78.4) |
| Female, N (%)                   | 129(21.6) |
| **Palliative setting**          |
| Initially metastatic            | 428(71.6) |
| Recurrent                       | 170(28.4) |
| **Operation method**            |
| Proximal gastrectomy            | 60(35.3)  |
| Distal gastrectomy              | 83(48.8)  |
| Total gastrectomy               | 27(15.9)  |
| **Pathological type**           |
| Well differentiated             | 4(0.7)    |
| Moderately differentiated       | 59(9.8)   |
| Poorly differentiated           | 250(41.8) |
| Signet ring cell                | 61(10.2)  |
| Unassorted                      | 224(37.5) |
| **Fecal occult blood**          |
| Positive                        | 129(33.9) |
| Negative                        | 381(74.7) |
| **Combination of three regimens**|
| 217(36.3)                       |
| **Treatment response**          |
| Partial response                | 14(2.3)   |
| Stable disease                  | 246(41.1) |
| Progressive disease             | 188(31.4) |
| Not evaluable                   | 150(25.1) |
| **Tumor location**              |
| Upper part (U)                  | 253(42.3) |
| Middle part (M)                 | 91(15.2)  |
| Lower part (L)                  | 206(34.4) |
| ML                              | 29(4.8)   |
| MU                              | 19(3.2)   |
| **T/N stage**                   |
| Ia+lb                           | 4+7(6.5)  |
| Iia+llb                         | 8+15(13.5)|
| IIIa+llb+llc                    | 34+46+56(80.0)|
| **Hemoglobin level (g/L)**      |
| >110                            | 398       |
| 100-110                         | 78        |
| 80-100                          | 82        |
| 65-80                           | 26        |
| <65                             | 14        |
| **Etiology of anemia**          |
| Fecal occult blood +            | 33        |
| Erosion and bleeding by endoscopy| 92       |
| Hematemesis                     | 21        |
| Iron deficiency anemia          | 3         |
| chemotherapy-induced anemia     | 0         |
| Unknown                         | 50        |
| DIC                             | 0         |
| Bone marrow infiltration        | 0         |
| **Chemo regimens**              |
| DCF                             | 217       |
| FOLFIRI                         | 152       |
| Paclitaxel liposome+Capecitabine/S-1 | 207     |
| XP                              | 264       |
| Sigle agent                     | 215       |

#Fecal occult blood: 88 patients not testing at the date of diagnosis

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### Table 2 Clinical features which have potential effects on GC patient’s OS and PFS
Table 3 Median OS and PFS

| Variable                  | HB_{ini} ≤80 g/L | HB_{ini} >80 g/L | p value |
|---------------------------|------------------|------------------|---------|
| Liver metastasis          | 17               | 229              | 0.856   |
| Bone metastasis           | 1                | 24               | 0.888   |
| Peritoneal metastasis     | 1                | 66               | 0.122   |
| Lung metastasis           | 5                | 94               | 0.475   |
| Metastatic sites ≥3       | 11               | 116              | 0.316   |

Table 4 Univariate analyses of risk factors for OS and PFS,
|                | OS               |         | PFS               |         |
|----------------|------------------|---------|-------------------|---------|
|                | \(p\) value     | HR      | 95\% CI           | \(p\) value | HR      | 95\% CI |
| HB\(_{ini}\)   | 0.010            | 0.995   | 0.991-0.999       | 0.013    | 0.995   | 0.992-0.999 |
| HB\(_{lowest}\)| 0.575            | 0.999   | 0.995-1.003       | 0.010    | 0.995   | 0.991-1.003 |
| HB\(_{ini}\) \(\leq\) 80 g/L | 40(6.7)         | 0.012   | 1.608 1.109-2.332 | 0.065    | 1.371   | 0.992-1.371 |
| HB\(_{ini}\) >80 g/L | 558(93.3)       |         |                   |         |         |         |
| Metastases     |                  |         |                   |         |         |         |
| Metastatic sites \(\geq\) 3 | 127(21.2)       | 0.033   | 1.268 1.020-1.577 | 0.015    | 1.289   | 1.01-1.577 |
| Metastatic sites <3 | 471(78.8)     | 0.849   | 0.980 0.794-1.209 | 0.276    | 0.896   | 0.79-1.05 |
| Lymph node     | 457(76.4)       | 0.010   | 1.271 1.059-1.525 | 0.001    | 1.354   | 1.10-1.65 |
| Liver          | 246(41.1)       | 0.399   | 0.899 0.703-1.151 | 0.221    | 1.150   | 0.92-1.41 |
| Lung           | 99(16.6)        | 0.072   | 1.495 0.964-2.318 | 0.017    | 1.651   | 1.02-2.41 |
| Bone           | 25(4.2)         |         |                   |         |         |         |
| Chemotherapy regimen |            |         |                   |         |         |         |
| Included paclitaxel | 239(40.0)    | 0.116   | 1.160 0.964-1.397 | 0.018    | 1.232   | 1.00-1.49 |
| Included platinum | 61(10.2)      | 0.290   | 0.849 0.626-1.150 | 0.734    | 0.985   | 0.73-1.28 |
| Number of cycles | \(<0.001\)   | 0.916   | 0.894-0.940       | 0.006    | 0.97    | 0.92-1.06 |
| Number of PTX3* | 0.023          | 0.937   | 0.885-0.991       | 0.940    | 1.002   | 1.00-1.01 |
| Treatment response |                  |         |                   |         |         |         |
| Progressive disease | 188(31.4)   | 0.041   | 1.223 1.008-1.484 | \(<0.001\) | 1.959   | 1.66-2.31 |
| Non-progressive disease |            |         |                   |         |         |         |
| HB\(_{dec}\) \(\geq\) 30 | 410(68.6)    |         |                   |         |         |         |
| \(<30\) Transfusion |            |         |                   |         |         |         |
| No transfusion | 467(78.1)      | 0.778   | 1.038 0.802-1.342 | 0.492    | 1.085   | 0.84-1.36 |
| Adjuvant chemotherapy |        |         |                   |         |         |         |
| Peritoneal metastasis | 511(85.5)   | 0.735   | 1.010 0.954-1.070 | 0.470    | 0.981   | 0.91-1.05 |

*PTX3 paclitaxel-based combination of three regimens

Table 5 Multivariate analyses of risk factors for OS and PFS
Table 6 Univariate analyses of risk factors for HB\textsubscript{dec}

| Variable                    | p value | HR   | 95% CI       |
|-----------------------------|---------|------|--------------|
| Metastases                  |         |      |              |
| metastatic sites ≥3         | 0.141   | 0.838| 0.663-1.060  |
| metastatic sites <3         |         |      |              |
| Metastatic site             |         |      |              |
| Lymph node                  | 0.325   | 1.131| 0.885-1.444  |
| Liver                       | 0.328   | 1.107| 0.903-1.358  |
| Lung                        | 0.936   | 0.989| 0.763-1.283  |
| Bone                        | 0.017   | 0.574| 0.365-0.905  |
| Chemotherapy regimen        |         |      |              |
| Included paclitaxel         | 0.876   | 0.984| 0.802-1.207  |
| Included platinum           | 0.010   | 0.645| 0.463-0.899  |
| Number of cycles            | <0.001  | 0.933| 0.907-0.961  |
| Number of PTX3*             | 0.161   | 0.96 | 0.908-1.016  |
| Treatment response          |         |      |              |
| Non-progressive disease     | 0.037   | 0.798| 0.646-0.986  |

Table 7 Multivariate analyses of risk factors for HB\textsubscript{dec}

| Variable                              | p value | HR   | 95% CI       |
|---------------------------------------|---------|------|--------------|
| Chemotherapy included platinum        | 0.019   | 0.661| 0.468-0.934  |
| Metastatic sites ≥3                   | 0.371   | 0.895| 0.702-1.141  |
| Bone metastases                       | 0.055   | 0.633| 0.396-1.010  |
| Chemotherapy included paclitaxel      | 0.061   | 1.226| 0.991-1.517  |
| Number of chemotherapy cycles         | <0.001  | 0.938| 0.911-0.966  |
| Liver metastases                      | 0.060   | 1.227| 0.991-1.520  |
| Treatment response                    | 0.111   | 0.833| 0.665-1.043  |

Table 8 Univariate analyses of chemotherapy side effects for OS and PFS,
|                      | N=598 | OS          | PFS         |
|----------------------|-------|-------------|-------------|
|                      | p value | HR  | 95%CI      | p value | HR  | 95% |
| **Myelosupression**  |        |     |            |         |     |     |
| Degree I             | 103   | 0.001 | 3.117     | 1.809-4.371 | 0.148 | 1.47 | 0.8 |
| Degree II            | 137   | 0.075 | 1.371     | 0.911-2.943 | 0.598 | 1.157 | 0.3 |
| Degree III           | 63    | 0.102 | 1.591     | 0.911-2.776 | 0.680 | 1.119 | 0.6 |
| Degree IV            | 15    | 0.998 | 1.001     | 0.552-1.814 | 0.600 | 0.860 | 0.4 |
| **Diarrhea**         | 519   |      |            |         |     |     |
| Grade 2              | 52    | 0.196 | 0.757     | 0.496-1.155 | 0.227 | 0.787 | 0.5 |
| Grade 3              | 27    | 0.045 | 0.580     | 0.40-0.989  | 0.313 | 0.785 | 0.4 |
| **Vomiting**         | 136   |      |            |         |     |     |
| Grade 1              | 136   |      |            |         |     |     |
| Grade 2              | 443   | 0.189 | 0.702     | 0.414-1.190 | 0.738 | 0.917 | 0.5 |
| Grade 3              | 19    | 0.213 | 0.727     | 0.440-1.201 | 0.252 | 0.752 | 0.4 |

**Figures**
Figure 1
the OS and PFS curves for 598 patients according to the degree of anaemia
A. OS curve according to HBini level (≤80 g/L and >80 g/L); B. PFS curve according to HBini level (≤80 g/L and >80 g/L); C. OS curve according to HBdec (≥ 30 g/L and <30 g/L); D. PFS curve according to HBdec (≥ 30 g/L and <30 g/L).

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.
Table S1 Median OS and PFS.docx
STROBE Checklist.doc