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PREOPERATIVE ANEMIA AS A PREDICTOR OF RECURRENCE IN GASTRIC CANCER

Anemia pré-operatória como preditor de recorrência em câncer gástrico

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ABSTRACT

Introduction: Cancer-related preoperative anemia is one of the most common comorbidities in several malignancies. It has been reported as an independent prognostic factor for disease-free survival. The aim of this study is to investigate preoperative anemia as a predictor of recurrence in patients with gastric carcinoma. **Methods**: This is a retrospective study that included patients submitted to curative resection for gastric adenocarcinoma between January 2015 and December 2019 at our institution. We collected clinicopathological characteristics and chose a hemoglobin cut-off value (12.0 g/dL). Groups (anemia versus no anemia) were compared regarding disease-free survival (DFS) and overall survival (OS) using Kaplan-Meier curves and the log-rank test. Statistical analysis was performed using the SPSS program, with significance defined as $p<0.05$. **Results**: A total of 81 patients were included, with preoperative anemia defined as a hemoglobin level below 12.0 g/dL. The analysis revealed that anemia was significantly associated with decreased disease-free survival (DFS), with patients exhibiting a median DFS of 62.1 months compared to 65.7 months in non-anemic patients (p=0.040). Furthermore, anemia was linked to higher rates of lymphatic invasion (80.4% vs. 51.4%, p=0.008) and higher recurrence rates, especially distant recurrence (23.9% vs. 2.9%, p=0.010). Multivariate analysis confirmed that anemia remained an independent risk factor for recurrence (p=0.027), alongside lymphatic invasion (p=0.023). However, no significant impact on overall survival (OS) was observed. **Discussion**: The findings suggest that preoperative anemia serves as an independent marker of recurrence risk and highlights the importance of incorporating it into clinical decision-making. These results warrant
further prospective, multicenter studies to confirm the role of preoperative anemia as a reliable prognostic factor in gastric cancer.

Keywords: preoperative anemia; gastric cancer, recurrence, disease-free survival, prognostic factor.

RESUMO

Introdução: A anemia pré-operatória relacionada com o cancro é uma das comorbilidades mais frequentes em várias neoplasias. Tem sido descrita como um fator prognóstico independente para a sobrevivência livre de doença. O objetivo deste estudo é avaliar a anemia pré-operatória como fator preditivo de recidiva em doentes com carcinoma gástrico. **Métodos**: Trata-se de um estudo retrospetivo que incluiu doentes submetidos a resseção curativa por adenocarcinoma gástrico entre janeiro de 2015 e dezembro de 2019 na nossa instituição. Foram recolhidas características clinicopatológicas e foi definido um valor de hemoglobina de corte (12,0 g/dL). Os grupos (com anemia versus sem anemia) foram comparados relativamente à sobrevivência livre de doença (DFS) e à sobrevivência global (OS) utilizando curvas de Kaplan-Meier e o teste log-rank. A análise estatística foi realizada com o programa SPSS, considerando significância para p<0,05. **Resultados**: Foram incluídos 81 doentes, sendo considerada anemia um valor de hemoglobina inferior a 12,0 g/dL. A análise revelou que a anemia se associou significativamente a uma diminuição da sobrevivência livre de doença (DFS), com os doentes anémicos a apresentarem uma DFS mediana de 62,1 meses, em comparação com 65,7 meses nos doentes não anémicos (p=0,040). Além disso, a anemia esteve associada a taxas mais elevadas de invasão linfática (80,4% vs. 51,4%, p=0,008) e de recidiva, sobretudo à distância (23,9% vs. 2,9%, p=0,010). A análise multivariada confirmou a anemia como fator independente de risco para recidiva (p=0,027), tal como a invasão linfática (p=0,023). Não foi, no entanto, observada qualquer associação significativa com a sobrevivência global (OS). **Discussão**: Os resultados sugerem que a anemia pré-operatória constitui um marcador independente de risco de recidiva, reforçando a importância da sua consideração na decisão clínica. Estes dados justificam a realização de estudos prospetivos e multicêntricos para confirmar o papel da anemia como fator prognóstico fiável no carcinoma gástrico.

Palavras-chaves: anemia pré-operatória; carcinoma gástrico; recidiva; sobrevivência livre de doença; fator prognóstico.

INTRODUCTION

Gastric carcinoma is the sixth most common cancer worldwide[1]. Oncologic surgical resection associated with adjuvant therapy is the gold standard treatment. However, the prognosis remains poor[2]. Despite improvements in diagnosis and treatment, it remains the fifth leading cause of cancer-related death[3]. Several studies have investigated new biomarkers to stratify the prognosis of gastric cancer[4]. Identifying and characterizing analytical parameters, particularly blood-derived values, is cost-effective in clinical practice and may help define a more reliable prognosis[5]. Cancer-related preoperative anemia is one of the most common comorbidities in several malignancies, including gastrointestinal cancers[6]. It has been reported as an independent prognostic factor for disease-free survival[7]. However, its prognostic value remains controversial and under study (8). The aim of this study is to investigate preoperative anemia as a predictor of recurrence in patients with gastric carcinoma.

METHODS

We conducted a retrospective, unicentric study that included patients selected for curative radical resection of gastric adenocarcinoma between January 2015 and December 2019 at our institution. The inclusion criteria were patients aged over 18 years with a diagnosis of gastric adenocarcinoma. We collected several clinicopathological characteristics, including age, gender, date of surgery, preoperative serum parameters (hemoglobin and albumin), CEA value, pathological classification (pTNM) of the tumor, grade of differentiation, lymphovascular and perineural invasion, and recurrence data (both local and distant). Exclusion criteria included lack of follow-up (3 patients), missing preoperative serum parameters (7 patients), and synchronous distant metastases (5 patients) (Figure 1).

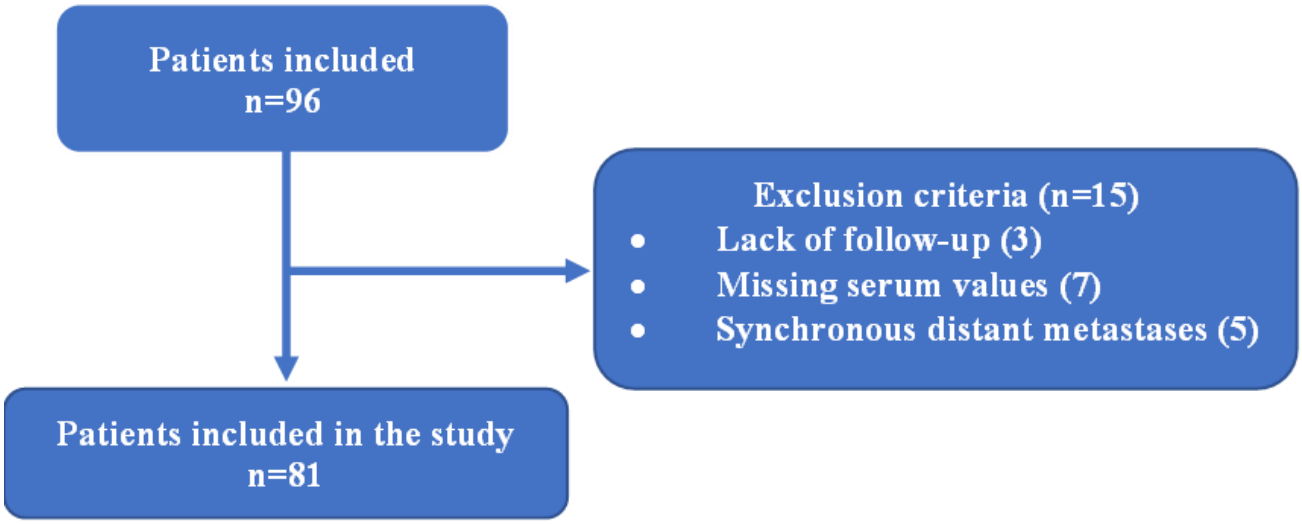

Figure 1 – Flow diagram of included and excluded patients in the study

Our study was carried out according to the Ethics Committee of our hospital, which did not require informed consent, since clinical data were collected anonymously.

Statistical analysis

Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences), version 24. Statistical significance was defined as $p < 0.05$. Categorical variables were expressed as frequencies (n) or percentages (%), while continuous variables were presented as mean ± standard deviation or median with a 95% confidence interval. The chi-square test and independent t-test were used for univariate analysis. Independent prognostic factors were assessed using multivariate analysis (binary regression), with hazard ratios (HR). We selected a hemoglobin cut-off value of 12.0 g/dL to compare two patient groups (anemia vs. no anemia) in terms of demographic and clinical characteristics, as well as overall survival and disease-free survival, using Kaplan-Meier curves and the log-rank test. The risk of poor outcomes associated with preoperative anemia was assessed using a multivariate Cox regression model.

RESULTS

A total of eighty patients were included in the study, with a median age of 68 years. The majority of the patients were male (62.5%). All patients had albumin levels within the normal range and 44 (55%) had a hemoglobin level <12.0 mg/dL. Preoperative anemia was not associated with a higher incidence of postoperative complications, nor with lymphovascular (LNV) or perineural invasion, or the tumor's histological differentiation grade. However, preoperative anemia was identified as an independent prognostic factor for recurrence, as shown by both univariate and multivariate analyses (p=0.032; p=0.006, respectively). Low hemoglobin levels were significantly correlated with a decrease in disease-free survival (65.7 vs. 62.1 months; log-rank p=0.040), though no significant differences were found in overall survival (p=0.385). (Table 1).

Table 1 – Clinicopathological characteristics of groups with or without anemia.

Analysed variables	Demographic characteristics of the sample n = 81 patients (%)
Age, in years (mean ± SD)	66.27 ± 12.45
Gender (male)	50 (61.7)
Anemia	46 (56.8)
ASA (>=3)	45 (55.6)
ECOG (>=2)	12 (14.8)
Post-operative complications	15 (18)
ICU admission	6 (7.4)
Cancer-related mortality	10 (12.3)
INVASION	
Linfatic	54 (66.7)
Perineural	41 (50.6)
Vascular	43 (53.8)
TNM classification	
Stage I	41 (50.6)
Stage II	21 (25.9)
Stage III	19 (23.5)
Recurrence	13 (16.0)

The study on anemia as a prognostic factor in gastric cancer revealed several key findings (table 2). Anemic patients were more likely to have a higher ASA score (>3) compared to non-anemic patients (69.6% vs. 37.1%, p=0.006), indicating worse preoperative health status. There was a trend

towards worse functional status in the anemic group (ECOG >2: 21.7% vs. 5.7%, p=0.060), although it did not reach statistical significance.

In terms of tumor characteristics, anemia was significantly associated with lymphatic invasion (80.4% vs. 51.4%, p=0.008). There was a trend towards a higher rate of vascular invasion in anemic patients (60.9% vs. 40.0%, p=0.075), although this did not reveal statistical significance. On the other hand, perineural invasion showed no difference between the two groups (60.9% vs. 45.7%, p=0.187).

Regarding TNM staging, the distribution across stages I, II, and III did not differ significantly between the two groups. However, anemic patients had a significantly higher recurrence rate (23.9% vs. 5.7%, p=0.034), with a notable difference in distant recurrence (23.9% vs. 2.9%, p=0.010). Local recurrence rates were not significantly different between groups (6.5% vs. 2.9%, p=0.630).

Multivariate analysis confirmed anemia as an independent risk factor for recurrence (p=0.027), along with lymphatic invasion (p=0.023). The ASA score was not significantly associated with recurrence in this analysis (p=0.183).

Disease-free survival was significantly shorter in the anemic group (62.4 ± 5.2 months) compared to non-anemic patients (65.8 ± 2.1 months, p=0.043) (Figure 2). Interestingly, no significant differences were observed in postoperative complications (13.0% vs. 25.7%, p=0.122), ICU admissions (8.7% vs. 5.7%, p=0.476), or cancer-related mortality (17.4% vs. 5.7%, p=0.105), although there was a trend towards higher mortality in the anemic group. These findings suggest that preoperative anemia is associated with poorer outcomes in gastric cancer patients, including increased tumor invasion, higher recurrence rates, and shorter disease-free survival, underlining its importance as a prognostic factor in managing these patients.

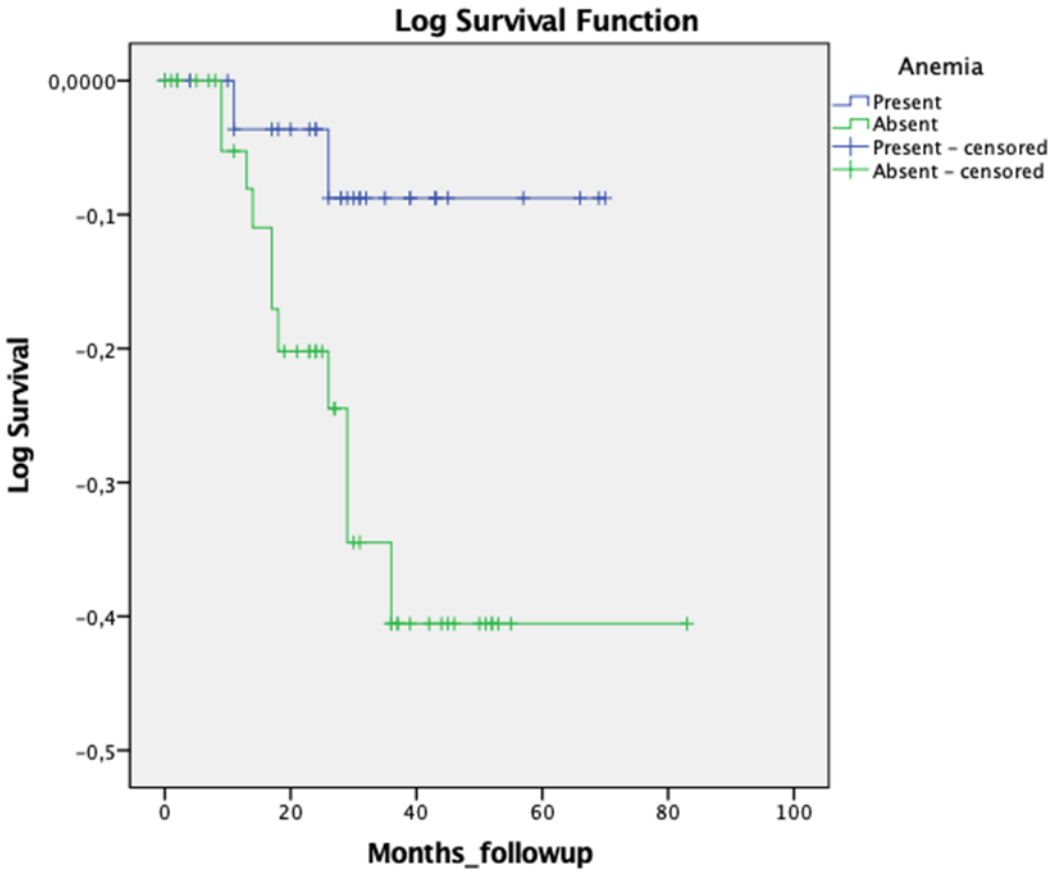

Figure 2 – Kaplan-Meier survival curves comparing disease-free survival (DFS) between patients with and without preoperative anemia. The curve for patients without anemia shows a significantly higher DFS compared to those with anemia

Table 2 – Comparison of clinical and tumor characteristics, recurrence, and disease-free survival between patients with and without preoperative anemia in gastric cancer.

Analysed variables	No Anemia (>12.0 g/dL) n = 35 (%)	With Anemia (<12.0 g/dL) n = 46 (%)	p-value
Gender (Male)	26 (74.3)	24 (52.2)	0.064
ASA (>3)	13 (37.1)	32 (69.6)	0.006
ECOG (>2)	2 (5.7)	10 (21.7)	0.060
Post-operative complications	9 (25.7)	6 (13.0)	0.122
ICU admission	2 (5.7)	4 (8.7)	0.476
Cancer-related mortality	2 (5.7)	8 (17.4)	0.105
Lymphatic invasion	18 (51.4)	37 (80.4)	0.008
Perineural invasion	16 (45.7)	28 (60.9)	0.187
Vascular invasion	14 (40.0)	28 (60.9)	0.075
TNM Classification (Stage I)	18 (51.4)	20 (43.5)	0.141
TNM Classification (Stage II)	9 (25.7)	13 (28.2)	0.563
TNM Classification (Stage III)	8 (22.8)	12 (26.0)	0.537
Recurrence	2 (5.7)	11 (23.9	0.034
Local recurrence	1 (2.9)	3 (6.5)	0.630
Distant recurrence	1 (2.9)	11 (23.9)	0.010
Disease-free survival (months)	65.8 ± 2.1	62.4 ± 5.2	0.043

DISCUSSION

Gastric cancer remains a significant global health challenge, with high recurrence rates and poor long-term survival, despite advances in diagnostic and therapeutic strategies[1]. Preoperative anemia, a common condition in cancer patients, has been linked to worse clinical outcomes across various malignancies, including gastric carcinoma. Our study aimed to assess the prognostic role of preoperative anemia in predicting recurrence in patients undergoing curative resection for gastric adenocarcinoma. We found that preoperative anemia, defined as a hemoglobin level below 12.0 g/dL, was significantly associated with a decreased disease-free survival (DFS), but did not impact overall survival (OS).

These findings align with previous studies, such as those by Huang XZ et al.[8], which suggested that preoperative anemia is an independent risk factor for recurrence in gastric cancer, negatively affecting both DFS and OS. Similarly, anemia has been associated with poor prognosis in other solid

tumors, often linked to more aggressive tumor behavior and increased likelihood of recurrence[9]. In our cohort, patients with anemia had significantly lower DFS compared to those without anemia, with a median DFS of 62.4 ± 5.2 months for anemic patients, compared to 65.8 ± 2.1 months for non-anemic patients (p=0.043). This difference remained significant even after adjusting for other clinicopathological factors, including lymphatic invasion (p=0.008), ASA score (p=0.006), and tumor stage. Notably, anemic patients also had a significantly higher rate of distant recurrence (23.9% vs. 2.9%, p=0.010), reinforcing the notion that anemia is associated with more aggressive tumor behavior.

While preoperative anemia was associated with higher recurrence rates in our study, it did not have a significant impact on OS (p=0.385). This could be attributed to the multifactorial nature of long-term survival, where factors such as tumor stage, perineural invasion, and postoperative treatment may have a more substantial influence on OS. This is consistent with other studies, which have found that the effect of anemia on OS is often less pronounced compared to its impact on recurrence[10]. It suggests that anemia may play a more significant role in the early stages of tumor progression, possibly through mechanisms like hypoxia-induced tumor progression, but its effect on survival could be overshadowed by other variables.

The underlying mechanisms through which anemia impacts recurrence remain incompletely understood, but tissue hypoxia is a key factor. Anemia-induced hypoxia can promote tumor cell proliferation, angiogenesis, and metastasis, all of which are associated with increased tumor aggressiveness and recurrence. Additionally, hypoxia has been linked to resistance to chemotherapy and radiotherapy, further enhancing tumor recurrence[11,12]. Therefore, anemia may act as a surrogate marker for tumor hypoxia, which could help identify patients at higher risk for recurrence and guide clinical decisions regarding postoperative management, including the need for adjuvant therapies.

Our study has several limitations, including its retrospective design, relatively small sample size, and single-center nature, all of which may limit the generalizability of our findings. Furthermore, the lack of detailed data on the type of chemotherapy or other adjuvant treatments received by patients restricts our ability to assess their influence on recurrence and survival outcomes. Future prospective, multicenter studies with larger cohorts are needed to better evaluate the prognostic value of preoperative anemia in gastric cancer and to explore the biological mechanisms driving its association with recurrence.

While anemia did not significantly impact overall survival, its association with decreased disease-free survival underscores its importance as a marker for high recurrence risk. Clinicians should consider preoperative anemia as a key factor in risk stratification, with implications for postoperative monitoring and personalized treatment strategies for these high-risk patients.

Conclusion

Our study suggests that preoperative anemia is an independent prognostic factor for recurrence in patients with gastric adenocarcinoma undergoing curative resection. While preoperative anemia did not significantly affect overall survival, its association with decreased disease-free survival emphasizes its potential role as an early indicator of recurrence risk. The relationship between anemia and tumor biology, potentially mediated through mechanisms such as tumor hypoxia, highlights the need for more intensive monitoring and pre-treatment strategies in these patients, including preoperative habilitation to optimize their physiological condition prior to gastric carcinoma treatment. Further multicentric, prospective studies are necessary to confirm the role of preoperative anemia as a reliable prognostic marker. Incorporating anemia into risk stratification models could aid in identifying high-risk patients, thereby enabling tailored therapies and improving clinical outcomes.

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