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*Retrospective Study***Risk factors for blood transfusion and its prognostic implication in curative gastrectomy for gastric cancer**

Kawakami LE *et al.* Effects of blood transfusion in GC survival

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Abstract**BACKGROUND**

Gastric cancer (GC) is still a prevalent neoplasm around the world and its main treatment modality is surgical resection. The need for perioperative blood transfusions is frequent, and there is a long-lasting debate regarding its impact on survival.

AIM

To evaluate the factors related to the risk of receiving red blood cell (RBC) transfusion and its influence on surgical and survival outcomes of patients with GC.

1**METHODS**

Patients who underwent curative resection for primary gastric adenocarcinoma at our Institute between 2009 and 2021 were retrospectively evaluated. Clinicopathological and surgical characteristics data were collected. Patients were divided into transfusion and non-transfusion groups in the analysis.

RESULTS

A total of 718 patients were included, and 189 (26.3%) patients received perioperative RBC transfusion (23 were intraoperative, 133 were postoperative, and 33 were in both periods). Patients in the RBC transfusions group were older ($P < 0.001$), and had more comorbidities ($P = 0.014$), American Society of Anesthesiologists classification III/IV ($P < 0.001$), lower preoperative hemoglobin ($P < 0.001$), and albumin levels ($P < 0.001$). Larger tumors ($P < 0.001$) and advanced tumor node metastasis stage ($P < 0.001$) were also associated with the RBC transfusion group. Postoperative complications (POC) and 30-d and 90-d mortality rates were significantly higher in the RBC transfusion group than in the non-transfusion group. Lower hemoglobin and albumin levels, total gastrectomy, open surgery, and the occurrence of POC were factors associated with the RBC transfusion. Survival analysis demonstrated that the RBC transfusions group had worse disease-free survival (DFS) and overall survival (OS) compared with patients who did not receive transfusion ($P < 0.001$ for both). In multivariate analysis, RBC transfusion, major POC, pT3/T4 category, pN+, D1 lymphadenectomy, and total gastrectomy were independent risk factors related to worse DFS and OS.

CONCLUSION

Perioperative RBC transfusion was associated with patients who had worse clinical conditions and more advanced tumors. Further, it was an independent factor related to worse survival in the curative intent gastrectomy setting.

Key Words: Stomach neoplasms; Blood transfusion; Red blood cell; Postoperative complications; Survival; Prognosis

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Core Tip: This is a retrospective study to investigate the association between
⁴perioperative red blood cell (RBC) transfusion, with surgical and survival outcomes in
patients with gastric cancer. Our findings demonstrated that patients who received RBC
transfusion had poorer preoperative clinical conditions, more aggressive tumors, and
were submitted to more invasive procedures. The rate of postoperative complications
and ⁸30-d and 90-d mortality is also significantly higher in patients who receive RBC
transfusions compared to those who do not receive transfusions. Further, receiving an
RBC transfusion was an independent factor associated with worse survival

INTRODUCTION

In 2020, gastric cancer (GC) was ²⁵ the fifth most diagnosed neoplasm and the fourth cause of death by neoplasms^[1]. Although its incidence and mortality rate has decreased in the last two decades, in 2025, GC will be accountable for more than one million cases and eight hundred thousand deaths^[2]. GC is frequently associated with perioperative blood loss, whether by its biological behavior or its most important treatment, radical gastrectomy. Therefore, anemia and blood transfusion in the perioperative setting is a common concern^[3,4].

The Transfusion Requirements in Critical Care trial (1999) was the first study to show worse outcomes related to excessive use of blood components in critical care patients, and since then, more restrictive use of transfusions has been recommended^[5]. In the last ten years, surgeons and oncologists have studied the continuous pro-inflammatory status triggered by surgical tissue damage, postoperative complications (POC), and blood transfusions^[6]. This effort confirmed the association between transfusion and higher recurrence rates in colorectal, pancreatic, and biliary tract cancer^[6-8]. However, current literature seems to struggle to find an answer for the impact of blood components on the outcomes of curative intent treatment in GC. The debate on how blood transfusion impacts survival and POC in GC is a complex topic, given the heterogeneity of results found in recent years. One side supported blood transfusion as an independently associated risk factor for inferior results; the other concluded that using blood components is a confounding factor for the worse prognosis since patients needing transfusions presented unfavorable clinical conditions previous to the surgical procedure and more advanced tumors at pathological staging ⁹ compared to patients who did not receive transfusions^[9-11].

⁵ Thus, this study aimed to evaluate the influence of perioperative red blood cell (RBC) transfusion on surgical and survival outcomes of patients with GC. We also examined the factors related to the risk of receiving a blood transfusion.

MATERIALS AND METHODS

Patient selection and study design

This is a retrospective cohort of patients with GC who underwent gastrectomy with curative intent in an oncological reference center, from February 2009 to December 2021. Non-adenocarcinoma tumors (lymphoma, gastrointestinal stromal tumor, neuroendocrine tumors) were excluded, as well as palliative surgery, diagnosis laparoscopy, previous hematological disorders, and patients with synchronous neoplasms.

Data collection and definitions

The following clinical variables were evaluated: age, sex, preoperative body mass index (BMI), neutrophil-Lymphocyte ratio (NLR), hemoglobin, albumin level, and performance status based on the American Society of Anesthesiologists (ASA) classification. Charlson-Deyo comorbidity index (CCI) was used to measure comorbidities without including age and GC as comorbidity^[12]. Tumor node metastasis (TNM) staging was determined according to the 8th edition of the American Joint Committee on Cancer^[13].

Experienced surgeons performed surgical procedures. The surgical approach (open or laparoscopic) was carried out based on the surgeon's decision after a multidisciplinary meeting composed of the oncology, surgery, radiology, and pathology departments. The extension of the gastric and lymph node (LN) dissection followed the recommendations of the Japanese Gastric Cancer Association (JGCA)^[14]. The classification proposed by Baiocchi *et al*^[15] was employed to define intraoperative complications. Intraoperative blood loss was measured in milliliters, and the length of the surgical procedure was assessed in minutes.

For analysis, patients were divided into two groups: patients who received an RBC transfusion and those who did not receive a transfusion. In addition to the RBC transfusion, we also describe the transfusion of platelet concentrate (PC), and fresh frozen plasma (FFP). Regarding the moment in which the administration occurred, the following periods were considered: the intraoperative; and postoperative periods, until the 30th day.

POC were graded according to Clavien-Dindo's classification. Clavien III to V was considered major complications^[16]. Mortality at 30 and 90 d after the surgical procedure

was also assessed. Adjuvant or perioperative platin-based chemotherapy was administered according to clinical indication (T3, T4, and regional LN metastasis)^[17].

Surgical and oncological teams performed postoperative follow-up medical appointments every 3 mo in the first year and every 6 mo in the following years. The attending clinician assigned to each case determined recurrence based on laboratory tests, CT, or endoscopy reports. Lost to follow-up was defined as an absence for more than 12 mo in follow-up visits.

We obtained all data by reviewing the patient's medical chart and blood center system. The hospital ethics committee approved the study (CAAE: 59337222.7.0000.0068) and it was registered online in the national research projects database (www.plataformabrasil.org.br).

Statistical analysis

The Chi-square test was used to compare categorical variables between the two groups, and the *t*-test or Mann-Whitney test for continuous variables. Univariate and multivariate binary regression analyses were used to identify risk factors for received perioperative RBC transfusion. Odds ratios (ORs) with a 95% CI were calculated.

Survival was estimated using the method of Kaplan-Meier, and the log-rank test was used to identify differences between the survival curves. The Cox proportional hazards model was used to identify risk factors independently associated with survival outcomes. The results were reported as hazard ratios (HRs) with 95% CIs. Disease-free survival (DFS) was calculated from the date of surgery to recurrence or death from any cause. Overall survival (OS) was the duration between the dates of surgery to death. All patients alive were censored at the date of the last follow-up. All tests were two-sided, and $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS software, version 20.0 (SPSS Inc, Chicago, IL).

RESULTS

Population description

During the selected period, 718 patients underwent radical gastrectomy with curative intent. Among them, 189 (26.3%) patients received perioperative RBC transfusion (RBC transfusion group). The remaining 529 (73.6%) patients who did not receive any perioperative RBC formed the non-transfusion group.

Among 189 patients who received RBC transfusion, 23 were intraoperative, 133 were postoperative, and 33 were in both periods (intra and postoperative). Besides RBC transfusion, FFP transfusions occurred in 12 patients (6.4%) and 2 patients (1.1%) also received PC transfusion.

Patients in the RBC transfusions group had older age ($P < 0.001$), higher CCI ($P = 0.014$), ASA III/IV score ($P < 0.001$), and lower BMI ($P = 0.016$) compared with patients who did not receive a transfusion. Higher NLR ($P = 0.010$), lower preoperative hemoglobin ($P < 0.001$), and albumin levels ($P < 0.001$) were also associated with the RBC transfusions group. There was no difference regarding preoperative chemotherapy between the groups ($P = 0.095$). Complete clinical characteristics are demonstrated in Table 1.

Regarding surgical procedures and postoperative features demonstrated in Table 2, total gastrectomy and open surgery were more frequent in the RBC group. There was no difference regarding the duration of surgery, intraoperative complications, and intraoperative blood loss between both groups. Length of hospital stay was higher in the transfusion group (10.4 d vs 21.6 d, $P < 0.001$). Considering the postoperative outcomes, POC and mortality rates at 30 and 90 d were significantly higher in the transfusion group ($P < 0.001$).

The pathological characteristics of the two groups are shown in Table 3. Larger tumor size, intestinal Lauren type, pT3/T4, and advanced pathological TNM (pTNM) stages were more frequent in the RBC transfusion group. The presence of lymphatic, vascular, and perineural invasions was also associated with the transfusion group.

In multivariate analysis, low preoperative hemoglobin ($P < 0.001$), low albumin ($P = 0.017$), total gastrectomy ($P = 0.011$), open surgical access ($P = 0.034$), and occurrence of major POC ($P < 0.001$) were independent factors associated to a higher risk of receiving perioperative RBC transfusions (Table 4).

Survival analysis

The median follow-up time for the entire cohort of cases was 35.6 mo. During the follow-up period, 174 patients had disease recurrence and 261 died.

Patients who received perioperative RBC transfusions had worse DFS and OS than the non-transfusion group ($P < 0.001$) (Figure 1). The median DFS and OS for the RBC transfusion group were 19.5 and 35.8 mo, respectively.

In multivariate analysis, total gastrectomy, more advanced pT stage, LN metastasis, D1 Lymphadenectomy, the occurrence of POC, and perioperative RBC transfusion were independent factors associated with worse DFS (Table 5).

ASA, type of gastrectomy, lymphadenectomy, pT, pN, POC, and perioperative RBC transfusion were factors significantly associated with OS in the multivariate model (Table 5).

Perioperative RBC transfusion remained an independently associated risk factor for both DFS (HR = 1.49, 95%CI: 1.14-1.94, $P = 0.003$) and OS (HR = 1.34, 95%CI: 1.02-1.77, $P = 0.038$).

DISCUSSION

During the progression of GC, cachexia, and uncontrolled tumor bleeding may induce severe anemia leading to life-threatening conditions and worse clinical in this scenario, perioperative RBC transfusion is indicated to improve performance and decrease morbidity in the postoperative period^[4,18,19]. On the other hand, recent advances in immunology have questioned the role of immunosuppression triggered by transfusion and its impact on tumor recurrence in gastrointestinal tract neoplasms performance^[20-22].

In our retrospective cohort composed of 718 patients, perioperative RBC transfusions were related to worse DFS and OS. It is crucial to recognize expressive baseline differences between patients who received RBC transfusions and those who did not. Patients in the transfusion group were older and presented more unfavorable clinical conditions. Further, a higher frequency of total gastrectomy, open surgery, and advanced tumors was observed in the transfusion group. Other studies also reported the same heterogeneity noted in the analyzed population^[9-11,23]. Even though, after multivariate analysis, we found that perioperative RBC transfusion was an independent factor related to recurrence and survival.

Although there is a vast literature investigating the impact of blood components in the oncologic prognosis of GC patients, the current data still present discordant results^[11,24,25]. This situation will probably be extended since it is difficult to perform a randomized controlled trial (RCT) in this scenario since in many situations the need for transfusion is a life-threatening condition. Further, most meta-analysis stress that current studies lack high-quality data^[26]. In the recent retrospective studies that found no impact in long-term survival related to RBC transfusions, some of them applied propensity-score matched analysis; however, preoperative hemoglobin and intraoperative blood loss remain as factors that could not be matched between groups^[11,27]. Despite the knowledge of the relevance of anemia in the perioperative setting, conflicting data persist around the impact of intraoperative blood loss on OS and DFS of GC^[28-30]. Grasso *et al*^[31] carried out prospective studies comparing different hemoglobin threshold values for the indication of transfusion may be an alternative to define this issue.

The current hypothesis that explains the biological association between blood components and poorer oncological outcomes is that transfusion-related immunomodulation (TRIM) acts as a propagating factor for the TH2 immune response, favoring a pro-tumoral environment through inhibition of interleukin (IL)-2 and stimulation of suppressor T cells, allowing tumor spread and recurrence^[20-22]. The recent application of immunotherapy in gastrointestinal tract cancers provided additional data by demonstrating that TRIM could be acting as an opponent and negatively impacting

its effectiveness and survival^[32]. Another important topic related to the immune response is the data provided by Lange *et al*^[33] that showed no difference in using leukocyte depletion in long-term survival, underlining that specific constituents of allogeneic blood may mediate the TRIM effect. This same result was detected when RBC transfusions were applied to other neoplasms^[34].

Preoperative hemoglobin and albumin were independent factors associated with RBC transfusions. Since GC causes feeding and bleeding disturbances, aggressive protocols for improving hematologic and nutritional preoperative status must be paramount in clinical compensation ahead of surgical treatment. Current data support those policies in clinical and financial terms since Jericó *et al*^[35] demonstrated reduced direct and indirect spent resources, lower hospital length of stay, and readmissions succeeding radical gastrectomy^[36].

Interestingly, D1 lymphadenectomy was associated with worse DFS and OS. D2 lymphadenectomy is considered a more aggressive procedure and the standard in GC treatment. However, even though 42% of our population was composed of patients with more advanced stages III/IV, some of them did not have the clinical conditions to perform D2 lymphadenectomy. So, the employment of D1 lymphadenectomy rarely was an oncological indication as proposed in the 2018 JGCA guideline for GC treatment^[14]. It was mainly indicated for patients with unfavorable medical conditions to reduce POC and mortality, as previously reported by our service^[37].

Open surgical access was associated with the transfusion group. Minimally invasive surgery causes less tissue damage to the abdominal wall with reports of less intraoperative blood loss on several RCTs^[38-40]. However, intraoperative blood loss, although higher in the transfusion group, did not show a significant difference between our groups. Intraoperative blood loss is a variable that is difficult to measure in clinical practice. The retrospective nature of the study also makes accurate measurement difficult. Despite this possible bias, we also found that ²there was no difference between the groups in the occurrence of intraoperative complications, a variable that is very well documented. Baiocchi *et al*^[15] reported a low 2% incidence of intraoperative

complications in GC surgery. In our study, 4.45% of intraoperative complications were reported, represented mainly by intraoperative bleeding. Those numbers indicate adequate documentation of the intraoperative complications in our medical reports and eventually, intraoperative blood loss did not differ between the groups. Therefore, our best efforts should focus on better patient perioperative management to avoid RBC transfusion^[41].

Regarding POC, the multivariate analysis indicated that major POC presented the highest OR related to RBC transfusion among the 8 selected variables. It must also be emphasized that the transfusion in the postoperative period was more frequent than in the pre and intraoperative periods. The importance of POC was already stressed in 2020 through a meta-analysis evaluating their repercussions on GC survival^[42]. A plausible reason for cancer recurrence is the pro-inflammatory state caused by surgical trauma, where IL-6 suppresses the specific and non-specific immune responses. This mechanism could be synergically associated with IL-2 suppression caused by TRIM since a retrospective analysis found a signature of cytokines (including IL-2, IL-6) and angiogenic factors associated with poor DFS and OS^[43]. Further, POCs may prevent patients to return to the intended oncological treatment a known prognostic factor^[44].

The performance of retrospective studies has some ³²limitations inherent to its design. Despite the relevant number of patients included for a Western center, the numerous variables evaluated are confounding factors for the adequate definition of ⁴the association between RBC transfusion and prognosis. We choose multivariate ⁴logistic regression to adjust the potential bias of covariates. Ultimately, perioperative transfusion of RBC was an independent prognostic factor together with known prognostic factors such as pTNM staging, demonstrating a good accuracy of the performed analyses. As another limitation, we must point out that our data were collected over 13 years, so variations and advances in oncological treatments and surgical techniques may cause additional heterogeneity.

CONCLUSION

In GC patients who underwent curative surgeries, poor clinical status, more extensive surgical procedures, and advanced tumor stages are common features in patients receiving RBC transfusions. In addition to being associated with a higher POC and mortality rate, receiving an RBC transfusion proved to be an independent factor associated with worse survival.

ARTICLE HIGHLIGHTS

Research background

Anemia and intraoperative blood loss are frequent issues in gastric cancer (GC) surgical treatment. Current literature still debates the impact of perioperative blood transfusion on GC survival.

Research motivation

Red blood cell (RBC) transfusions are sometimes required for patients undergoing surgery for GC. However, the prognostic impact of perioperative RBC transfusion in GC is controversial.

Research objectives

We analyzed the influence of RBC transfusions on the prognosis of patients with gastric adenocarcinoma undergoing gastrectomy with a curative intention.

Research methods

We retrospectively evaluated all GC patients who underwent gastrectomy between 2009 and 2021. Patients were divided into transfusion group and non-transfusion group in the analysis. RBC Transfusions that occurred intraoperatively and postoperatively within 30 d were considered.

Research results

A total of 718 patients were included, and 189 (26.3%) patients received RBC transfusions. Patients who receive transfusions had unfavorable clinical, and pathological characteristics, and underwent more extensive surgical procedures. Patients who receive RBC transfusions have worse survival compared to those who do not receive transfusions. In multivariate analysis, receiving an RCB transfusion was an independent factor ⁵ associated with poor disease-free survival (DFS) and overall survival (OS).

Research conclusions

Even though the patients who receive RCB transfusion have worse clinical conditions, we found that perioperative transfusion represents an independent factor associated with poor prognosis, with worse DFS and OS.

Research perspectives

The application of blood component transfusion in randomized clinical trials presents ethical limitations; however, the current design of retrospective studies still interferes with controlling confounding factors. With this study, we endorse a favorable position for increasing preoperative and postoperative care to avoid RBC transfusion. Further, our findings provide additional data for future meta-analysis.

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