Effect of perioperative blood transfusion on prognosis of patients with gastric cancer: a retrospective analysis of a single center database

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Abstract
Background: The association between perioperative blood transfusion and the prognosis of patients with gastric cancer is still unclear.
Methods: A total of 1581 patients with gastric cancer who underwent curative gastrectomy from 2000 to 2008 were evaluated. Perioperative blood transfusion was defined as the transfusion of packed red blood cells within seven days before surgery, during surgery, or within the postoperative hospitalization period. The association between perioperative blood transfusion and prognosis was evaluated using univariate and multivariate Cox regression analyses.
Results: Of 1581 patients, 298 patients (19%) received perioperative blood transfusion. Perioperative blood transfusion correlated with older age ($P < 0.001$); larger tumor size ($P < 0.001$); and more advanced stage ($P < 0.001$). Five-year survival rate was 40% in patients who had perioperative blood transfusion and 55% patients who did not have perioperative blood transfusion, and the difference was statistically significant ($P < 0.001$). Multivariate analysis showed that perioperative blood transfusion was defined as independent prognostic factor. Perioperative blood transfusion was associated with worse outcomes in patients with stage III ($P < 0.001$).
Conclusions: Perioperative blood transfusion independently correlated with poorer prognosis in patients with gastric cancer.
Keywords: Gastric cancer, Perioperative blood transfusion, Prognosis

Background
Although the incidence of gastric cancer has declined, it is still the sixth most frequent cancer and the fourth most common cause of cancer death worldwide [1]. In the United States, most patients with gastric cancer are diagnosed at late stage [2]. Anemia is more likely to exist in patients with advanced gastric cancer. Some studies reported that up to 60% of patients presented with perioperative anemia, and most of them undergoing gastrectomy needed red blood cell transfusion [3, 4]. It is well-known that blood transfusions are associated with some adverse outcomes. In particular, some studies showed that blood transfusions were associated with an increased risk of postoperative morbidity [5, 6]. Additionally, some studies have shown that perioperative blood transfusion correlated with poor prognosis of patients with lung cancer, breast cancer, and colorectal cancer [7–9].

Although there have been some studies about the influence of perioperative blood transfusion on prognosis of patients with gastric cancer after undergoing curative gastrectomy, the results still remains controversial [10–13]. Two studies demonstrated that perioperative blood transfusion was associated with worse clinical outcomes for patients with gastric cancer underwent gastrectomy [10, 11]. In contrast, some other studies have not shown worse outcomes [12, 13].
The purpose of this study is to clarify the effect of perioperative blood transfusion on the prognosis of patients with gastric cancer by analyzing large retrospective sample from our institution.

**Methods**

**Patients**
From 2000 to 2008, 1581 patients with histologically confirmed primary gastric adenocarcinoma underwent curative gastrectomy. Perioperative blood transfusion was defined as the transfusion of packed red blood cells within seven days before surgery, during surgery, or within the postoperative hospitalization period. Postoperative hospitalization is defined as the immediate postoperative period following surgery. Data were retrieved from operative and pathological reports, and follow-up data were obtained by phone, out-patient and clinical database [14].

**Table 1** Patient Cohort

| Variables                  | n = 1581 | 100% |
|----------------------------|----------|------|
| Gender                     |          |      |
| Male                       | 1102     | 70   |
| Female                     | 479      | 30   |
| Age (yr)                   |          |      |
| ≤ 60                       | 891      | 56   |
| >60                        | 690      | 44   |
| Tumor size (cm)            |          |      |
| ≤ 5                        | 1136     | 72   |
| >5                         | 445      | 28   |
| Tumor location             |          |      |
| Upper third                | 563      | 36   |
| Middle third               | 275      | 17   |
| Lower third                | 702      | 44   |
| Two-third or more          | 41       | 3    |
| TNM stage                  |          |      |
| Stage I                    | 403      | 26   |
| Stage II                   | 382      | 24   |
| Stage III                  | 796      | 50   |
| Type of Gastrectomy        |          |      |
| Subtotal                   | 1342     | 85   |
| Total                      | 239      | 15   |
| Operation time (min)       |          |      |
| < 180                      | 1025     | 65   |
| ≥ 180                      | 556      | 35   |
| Albumin level at admission (g/dl) |          |      |
| < 3.5                      | 379      | 24   |
| ≥ 3.5                      | 1202     | 76   |
| Hemoglobin level at admission (g/dl) |         |      |
| < 12                       | 575      | 36   |
| ≥ 12                       | 1006     | 64   |
| Perioperative blood transfusion |      |      |
| Yes                        | 298      | 19   |
| No                         | 1283     | 81   |

**Table 2** Comparison of the clinicopathological characteristics of patients with perioperative blood transfusion and without perioperative blood transfusion

| Variables                  | Group with perioperative blood transfusion n = 298 | Group without perioperative blood transfusion n = 1283 | P value |
|----------------------------|--------------------------------------------------|-----------------------------------------------------|---------|
| Gender                     |                                                  |                                                    | 0.749   |
| Male                       | 210                                              | 892                                                |         |
| Female                     | 88                                               | 391                                                |         |
| Age (yr)                   |                                                  |                                                    | < 0.001 |
| ≤ 60                       | 119                                              | 772                                                |         |
| >60                        | 179                                              | 511                                                |         |
| Tumor size (cm)            |                                                  |                                                    | < 0.001 |
| ≤ 5                        | 148                                              | 988                                                |         |
| >5                         | 150                                              | 295                                                |         |
| Tumor location             |                                                  |                                                    | < 0.001 |
| Upper third                | 116                                              | 447                                                |         |
| Middle third               | 68                                               | 207                                                |         |
| Lower third                | 95                                               | 607                                                |         |
| Two-third or more          | 19                                               | 22                                                 |         |
| TNM stage                  |                                                  |                                                    | < 0.001 |
| Stage I                    | 37                                               | 366                                                |         |
| Stage II                   | 84                                               | 298                                                |         |
| Stage III                  | 177                                              | 619                                                |         |
| Type of Gastrectomy        |                                                  |                                                    | < 0.001 |
| Subtotal                   | 221                                              | 1121                                               |         |
| Total                      | 77                                               | 162                                                |         |
| Operation time (min)       |                                                  |                                                    | 0.001   |
| < 180                      | 168                                              | 857                                                |         |
| ≥ 180                      | 130                                              | 426                                                |         |
| Albumin level at admission (g/dl) |          |                                                    | 0.001   |
| < 3.5                      | 94                                               | 285                                                |         |
| ≥ 3.5                      | 204                                              | 998                                                |         |
| Hemoglobin level at admission (g/dl) |         |                                                    | < 0.001 |
| < 12                       | 211                                              | 364                                                |         |
| ≥ 12                       | 87                                               | 919                                                |         |

TNM Tumor Node Metastasis, n number of patients, min minute.
informed consent had been obtained from all the patients, and this study was approved by the Ethical Committee of Fudan University Shanghai Cancer Center. Staging was carried out according to the American Joint Committee on Cancer TNM (Tumor Node Metastasis) Staging Classification for Carcinoma of the Stomach (Seventh Edition, 2010).

Follow-up
The standard follow-up protocol for patients with gastric cancer was every three months for at least two years, every six months for the next three years, and after five years every 12 months for life [14]. The follow-up items were as follows: physical examination, tumor-marker examination, chest radiography, endoscopic examination, and computed tomographic scan.

Statistical analysis
The Chi-square test was used to analyze patients’ features and clinicopathological characteristics. The Kaplan-Meier method was used to calculate five-year survival rate, and the long-rank test was used to examine the differences between survival curves. The prognostic factors were included into the multivariate survival analysis using Cox proportional hazards model. The level of significance was \( P < 0.05 \). Statistical analyses and graphics were carried out using the SPSS 13.0 statistical package (SPSS, Inc., Chicago, IL).

Results
Clinicopathological characteristics
There were 1102 males and 479 females (2.3:1) with a mean age of 58 years. According to tumor location, 563 (36%) had tumors located in the upper third; 275 (17%) in the middle third; 702 (44%) in the lower third, and 41 (3%) occupied two-thirds or more of stomach. The distribution of pathological stage was as follows: 403 (26%) patients had stage I, 382 (24%) patients had II, and 796 (50%) patients had III. Patients demographics were listed in Table 1.

Clinicopathologic parameters were compared between patients who underwent perioperative blood transfusion and who did not. Results showed that patients with perioperative blood transfusion presented at an older age (\( P < 0.001 \)); larger tumor size (\( P < 0.001 \)); and more advanced stage (\( P < 0.001 \)) (Table 2).

Amount of blood transfusion
Of the 1581 patients, 298 patients (19%) received perioperative blood transfusion. With regard to period and amount of transfusion, 128 (43%) patients received transfusion before operation, 215 (72%) during the operation, and 119 (40%) after the operation. 29 (10%) patients received transfusion only before operation, 105 (35%) only during the operation, and 35 (12%) only after the operation; 134 (45%) patients received less than 4 units, and 164 (55%) patients received more than 4 units.

Univariate analysis
The median follow-up time was 60.2 months. The over-all five-year survival rate was 53% for all 1581 patients. Five-year survival rate was 40 and 55% in group with perioperative blood transfusion and group without perioperative blood transfusion, respectively, and the difference was statistically significant (\( P < 0.001 \)) (Fig. 1). In addition to perioperative blood transfusion, significant prognostic factors included: age, tumor size,
tumor location, TNM stage, type of gastrectomy, operation time, albumin level at admission, and hemoglobin level at admission (Table 3). In patients with perioperative blood transfusion, univariate analysis showed that tumor location and TNM stage significantly affected prognosis, other factors like blood transfusion frequency and blood transfusion amount did not correlate with prognosis (Table 4).

### Multivariate analysis
Multivariate survival analysis was performed to determine the independent prognostic factors for patients with gastric cancer. Multivariate analysis showed that

#### Table 3 Univariate analysis of all patients

|                     | n  | 5-year survival rate (%) | P value |
|---------------------|----|--------------------------|---------|
| **Gender**          |    |                          |         |
| Male                | 1102 | 52                       | 0.759   |
| Female              | 479  | 53                       |         |
| **Age (yr)**        |    |                          | <0.001  |
| ≤ 60                | 891  | 58                       |         |
| > 60                | 600  | 45                       |         |
| **Tumor size (cm)** |    |                          | <0.001  |
| ≤ 5                 | 1136 | 59                       |         |
| > 5                 | 445  | 36                       |         |
| **Tumor location**  |    |                          | <0.001  |
| Upper third         | 563  | 39                       |         |
| Middle third        | 275  | 49                       |         |
| Lower third         | 702  | 65                       |         |
| Two-third or more   | 41   | 32                       |         |
| **TNM stage**       |    |                          | <0.001  |
| Stage I             | 403  | 94                       |         |
| Stage II            | 382  | 61                       |         |
| Stage III           | 796  | 27                       |         |
| **Type of Gastrectomy** | |                          | <0.001  |
| Subtotal            | 1342 | 56                       |         |
| Total               | 239  | 34                       |         |
| **Operation time (min)** | |                          | <0.001  |
| < 180               | 1025 | 58                       |         |
| ≥ 180               | 556  | 43                       |         |
| **Albumin level at admission (g/dl)** | |                          | 0.006   |
| < 3.5               | 379  | 47                       |         |
| ≥ 3.5               | 1202 | 54                       |         |
| **Hemoglobin level at admission (g/dl)** | |                          | <0.001  |
| < 12                | 575  | 46                       |         |
| ≥ 12                | 1006 | 56                       |         |
| **Perioperative blood transfusion** | |                          | <0.001  |
| Yes                 | 298  | 40                       |         |
| No                  | 1283 | 55                       |         |

**Table 4 Univariate analysis of patients with perioperative blood transfusion**

|                     | n  | 5-year survival rate (%) | P value |
|---------------------|----|--------------------------|---------|
| **Gender**          |    |                          |         |
| Male                | 210 | 41                       | 0.838   |
| Female              | 88  | 39                       |         |
| **Age (yr)**        |    |                          |         |
| ≤ 60                | 119 | 43                       | 0.411   |
| > 60                | 179 | 38                       |         |
| **Tumor size (cm)** |    |                          | 0.103   |
| ≤ 5                 | 148 | 44                       |         |
| > 5                 | 150 | 36                       |         |
| **Tumor location**  |    |                          | 0.035   |
| Upper third         | 116 | 35                       |         |
| Middle third        | 68  | 35                       |         |
| Lower third         | 95  | 51                       |         |
| Two-third or more   | 19  | 32                       |         |
| **TNM stage**       |    |                          | <0.001  |
| Stage I             | 37  | 89                       |         |
| Stage II            | 84  | 57                       |         |
| Stage III           | 177 | 22                       |         |
| **Type of Gastrectomy** | |                          | 0.060   |
| Subtotal            | 221 | 42                       |         |
| Total               | 77  | 34                       |         |
| **Operation time (min)** | |                          | 0.057   |
| < 180               | 168 | 45                       |         |
| ≥ 180               | 130 | 34                       |         |
| **Albumin level at admission (g/dl)** | |                          | 0.245   |
| < 3.5               | 94  | 35                       |         |
| ≥ 3.5               | 204 | 42                       |         |
| **Hemoglobin level at admission (g/dl)** | |                          | 0.655   |
| < 12                | 211 | 41                       |         |
| ≥ 12                | 87  | 38                       |         |
| **Frequency of blood transfusion** | |                          | 0.434   |
| < 2                 | 169 | 42                       |         |
| ≥ 2                 | 129 | 37                       |         |
| **Amount of blood transfusion (unit)** | |                          | 0.287   |
| < 4                 | 134 | 43                       |         |
| ≥ 4                 | 164 | 38                       |         |

TNM Tumor Node Metastasis, n number of patients, P value obtained by chi-squares tests or Fisher's exact test, min minute
perioperative blood transfusion did not influence the clinical outcome in patients undergoing gastrectomy, though other studies have associated with worse clinical outcome in patients likely to receive perioperative blood transfusion, multivariate analysis suggested that only TNM stage was independent prognostic factor (Table 5).

**Comparison of survival according to perioperative blood transfusion at same stage**

Patients with gastric cancer were analyzed by stage (I, II, or III) and whether they underwent perioperative blood transfusion. Patients with gastric cancer were divided into three stages: stage I, stage II, and stage III. Based on perioperative blood transfusion, each stage was divided into group with perioperative blood transfusion and group without perioperative blood transfusion. There was a significant difference of over-all 5-year survival between group with perioperative blood transfusion and group without perioperative blood transfusion according to stage III ($P < 0.001$) (Fig. 2).

**Discussion**

The association between overall prognosis and perioperative blood transfusions has been investigated in several solid tumors [15–20]. However, the results have been inconsistent. Two studies have demonstrated that perioperative blood transfusion was associated with worse clinical outcome in patients undergoing gastrectomy, though other studies have not [10, 11]. Stefano Rauseiet al.’s study showed that perioperative blood transfusion did not influence the survival of patients with gastric cancer [12]. Moriguchi et al. reported that there was no relationship between perioperative blood transfusion and survival of patients with gastric cancer [13]. Some reasons should be taken into account of the conflicting results. First, influence of perioperative blood transfusion might be coincidental with other factors, which could result in more blood loss and more transfusions. The present study showed that patients with older age, larger tumor size, and more advanced stage were more likely to receive perioperative blood transfusion, which was consistent with other results [21, 22]. Second, most of the published studies were small-size sample, which had small statistic power to get a positive relationship. Therefore, the present study was carried out in a large-scale sample to avoid the above-mentioned limitations.

In this study, perioperative blood transfusions were associated with a worse prognosis in patients with gastric cancer following gastrectomy. Transfusion was an independent prognostic factor confirmed by Cox regression analysis. In subgroup analysis, the difference in overall 5-year survival was significant for patients with Stage III disease, but not Stage I or II. This finding is consistent with results reported by Xue L et al. [23]. Additionally, we analyzed the relationship between frequency of blood transfusion, amount of blood transfusion, and prognosis. Results showed frequency and amount of blood transfusion did not correlate with the survival, which is consistent with other studies [11, 21, 24]. Therefore, it was possible that blood transfusion itself resulted in poor prognosis rather than frequency and amount of blood transfusion. Despite restrictive usage of blood transfusion is recommended by clinical guidelines, perioperative blood transfusion is still overused in clinical practice.

Although the exact mechanism is not clear, immunosuppression may explain the association between worse overall survival and perioperative blood transfusion. Immunosuppression can be caused by decreased natural killer cell activity and increased suppressor T lymphocytes activity [25]. Other suppressor factors such as anti-idiotypic antibodies can be produced after receiving blood transfusion [26]. In addition, blood transfusion could promote the proliferation of tumor cells through inducing angiogenesis [27]. This theory was confirmed by Patel et al.’ finding that blood transfusion stimulated proliferation and angiogenesis of endothelial cells [28].

| Table 5 Multivariate analysis of patients by Cox model |
|---------------------------------|--------|--------|--------|--------|
| Variable       | Wald   | P value | RR    | 95% CI |
| Gender         | 0.419  | 0.518  | 1.056 | 0.895–1.245 |
| Age            | 7.192  | 0.007  | 1.230 | 1.057–1.431 |
| Tumor location | 9.187  | 0.002  | 0.879 | 0.808–0.955 |
| TNM stage      | 161.018| <0.001 | 3.151 | 2.639–3.762 |
| Type of gastrectomy | 12.311| <0.001 | 1.403 | 1.161–1.696 |
| Perioperative blood transfusion | 5.385  | 0.020  | 0.799 | 0.661–0.966 |

**Table 6 Multivariate analysis of patients with perioperative blood transfusion by Cox model**

| Variable       | Wald   | P value | RR    | 95% CI          |
|----------------|--------|--------|--------|-----------------|
| Gender         | 0.839  | 0.360  | 0.859  | 0.621–1.189     |
| Age            | 0.690  | 0.406  | 1.138  | 0.839–1.545     |
| Tumor location | 0.942  | 0.332  | 0.929  | 0.801–1.078     |
| TNM stage      | 59.565 | <0.001 | 3.268  | 2.419–4.415     |

TNM Tumor Node Metastasis, P value obtained by chi-squares tests or Fisher’s exact test, RR relative risk, CI confidence interval
complications and tumor recurrence. Second, adjuvant radiotherapy and chemotherapy were not included into the analysis. Therefore, it is necessary to carry out prospective, randomized, controlled studies to investigate the prognostic effect of blood transfusion in patients with gastric cancer.

Conclusions
In conclusion, perioperative blood transfusion independently correlated with poorer prognosis in patients with gastric cancer.

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Availability of data and materials
The datasets generated and/or analysed during the current study are not publicly available because they are derived from the patient database of the center and hence subject to confidentiality but are available from the corresponding author on reasonable request.

Authors’ contributions
XWL, MZM and YNW built the conception and designed the study. HH assisted in acquisition of data. YNW provided administrative support for this study. XWL, MZM and HH provided statistical analysis and interpretation. XWL and MZM wrote, reviewed and revised the manuscript. All authors participated in final approval of the version.

Ethics approval and consent to participate
The study was approved by the Ethics Committee of the Fudan University Shanghai Cancer Center. All patients provided written informed consent.

Competing interests
The authors declare that they have no competing interests.

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Fig. 2 Comparison of survival according to perioperative blood transfusion in same stage. a There was no significant difference in patients with stage I. b There was no significant difference in patients with stage II. c There was significant difference in patients with stage III.

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