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Perioperative transfusion of leukocyte depleted blood products in gastric cancer patients negatively influences oncologic outcome

A retrospective propensity score weighted analysis on 610 curatively resected gastric cancer patients

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Abstract

The influence of perioperative transfusion (PT) on outcome following surgery for gastric cancer (GC) remains controversial, with randomized trials lacking and observational series confounded by patient risk factors. This analysis determines the association between reception of leukocyte-depleted blood products and post-operative survival for GC.

Data from 610 patients who underwent curative surgery for GC in a German tertiary care clinic from 2001 to 2013 were included. Kaplan–Meier survival curves and Cox proportional hazards regression were applied to determine the association of PT and clinical and patient risk factors for overall and relapse-free survival. Propensity score analysis was performed to adjust for observational biases in reception of PT.

Higher Union International Contre le Cancer/American Joint Committee on Cancer (UICC/AJCC)-stages ($P<0.001$), postoperative complications and severity according to the Clavien–Dindo (CD) classification ($P<0.001$), PT ($P=0.02$), higher age ($P<0.001$), and neoadjuvant chemotherapy ($P<0.001$) were related to increased mortality rates. Higher UICC-stages ($P<0.001$), neoadjuvant chemotherapy ($P<0.001$), and type of surgery ($P=0.02$) were independently associated with increased relapse rates. Patients were more likely to receive PT with higher age ($P=0.05$), surgical extension to adjacent organs/structures ($P=0.002$), tumor location ($P=0.003$), and female gender ($P=0.03$). In the adjusted propensity score weighted analysis, PT remained associated with an increased risk of death (hazard ratio (HR): 1.31, 95% CI: 1.01–1.69, $P=0.04$).

Because of the association of PT with negative influence on patient survival following resection for GC, risks from application of blood products should be weighed against the potential benefits.

Abbreviations: AIC = Akaike information criterion, AJCC = American Joint Committee on Cancer, CD = Clavien–Dindo, CT = computed tomography, EGD = esophagogastroduodenoscopy, GC = gastric cancer, GEJ = gastroesophageal junction, HR = hazard ratio, IRB = institutional review board, LVI = lymphatic vessel infiltration, OS = overall survival, PRBC = packed red blood cells, PT = perioperative transfusion, RFS = relapse-free survival, TUM = Technical University Munich, UICC = Union International Contre le Cancer.

Keywords: gastric cancer, perioperative blood transfusion, prognosis

Editor: Jorg Kleeff.

Statement: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study. This manuscript fully consists of original material, which has not been published or submitted to another journal. All authors declare that they participated in the analysis and that they have seen and approved the final version.

Data acquisition and analysis were performed according to local ethic standards and GCP guidelines.

Funding: This work was supported by the German Research Foundation (DFG) and the Technical University of Munich (TUM) in the framework of the Open Access Publishing Program.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

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Medicine (2016) 95:29(e4322)

Received: 9 February 2016 / Received in final form: 27 June 2016 / Accepted: 29 June 2016

http://dx.doi.org/10.1097/MD.0000000000004322

1. Introduction

Gastric cancer (GC) belongs to the most common malignant diseases worldwide with the highest incidence in Eastern Asia.[1] Despite decreasing incidence in the West, it remains a therapeutic challenge. In the Western hemisphere, gastric malignancy is often diagnosed at an advanced stage and in contrast to Eastern Asia, it is preferably located in the proximal third of the stomach or the gastroesophageal junction (GEJ).[2] Hence, multimodal treatment concepts have been introduced after demonstrating outcome benefit in randomized controlled trials.[3–5] These therapies not only influence patients' outcome because of compromised immune functions and anemia after neoadjuvant chemotherapy, but also lead to the notion that oncologic resection as the only option for cure is technically demanding. Extended lymphadenectomy (D2) in advanced GC is considered a standard of care[6] in specialized centers and surgical extension to the distal esophagus to achieve clear margins is sometimes crucial for the patient's survival.[7] These factors in conjunction increase the risk for allogeneic blood transfusion during or after surgery in patients with advanced disease.

To date, several studies have investigated the influence of perioperative blood transfusion (PT) on clinical outcome following curative resection, resulting in conflicting results.[8] A recent meta-analysis by Sun et al[8] demonstrated that PT may be related to worsened prognosis after GC surgery. However, there was considerable heterogeneity and possible confounders that could not be adjusted for in the analysis. Further shortcomings of previous studies were that patients who were treated for GC before the year 2000 received non-leukocyte-depleted blood products and that multimodal therapies were not applied in clinical routine. In addition, most of the data published to date were derived from Eastern Asian patient cohorts, rendering conclusions on Western patients difficult. However, the most critical issue was that previous studies did not rule out the possibility of confounding factors leading to bias in the observed effects of PT on outcome. This bias arises because of the selection of patients with poorer clinical profiles or increased surgical complications to receive PT, thus artificially enhancing the association of PT with diminished clinical outcome. The aim of the present analysis was to compare the oncologic outcomes of Western patients who received leukocyte-depleted blood products versus those that did not in an era of multimodal treatment and modern perioperative patient care, and to adjust for selection-bias through propensity score matching.[9]

2. Patients, materials and methods

2.1. Study subjects

Data from 610 patients who underwent curative surgery for GC at a tertiary referral hospital in southern Germany (Surgical Department of the Technische Universitaet Muenchen (TUM/MRI) from 2001 to 2013 were extracted from a prospectively documented database. Data was obtained from the medical records and transferred to the institutional database as soon as the patients were discharged from inpatient hospital care. Patients staged cT3/cT4cN$_{any}$ or cT2N1 received neoadjuvant chemotherapy after multidisciplinary team review. All other patients underwent primary surgical resection. Exclusion criteria were metastatic disease, gastric stump cancer, hospital mortality within 30 days, loss of follow-up within a 60-month period, and residual cancer after surgery (R1/R2). All surgical procedures were performed according to the Japanese guidelines for GC treatment including standardized D2 lymph node dissection. Perioperative period was defined as 3 days before and after surgery. In case of transfusion, patients received leukocyte-depleted packed red blood cells (PRBC). PRBCs were processed and leukocyte depleted according to the guidelines of the German Medical Association.[10] Adjuvant chemotherapy was not applied in a standardized manner, but rather on a case by case basis after multidisciplinary team review. After oncologic surgery, all patients were followed-up every 6 to 12 months in an outpatient department (Roman Herzog Comprehensive Cancer Center) for the next 5 years according to local guidelines including physical examination, EGD, and annual computed tomography (CT) scans. Institutional Review Board (IRB) approval for this study was obtained according to local guidelines.

2.2. Statistical analysis

Wilcoxon and χ^2 tests were used to compare continuous and categorical clinical characteristics, respectively, between patients who did and did not receive PT. Patients with missing data were omitted from this analysis. Overall survival (OS) and relapse-free survival (RFS, time to onset of recurrent disease) were graphed using empirical Kaplan–Meier curves with differences in 5-year survival rates among patient groups evaluated using the log-rank test. Associations between prognostic factors, including PT, and survival were estimated by univariable and multivariable Cox proportional hazards regression. Risk factors associated with reception of PT were calculated using logistic regression.

Optimal multivariable predictive models for all endpoints were selected using stepwise regression with the Akaike Information Criterion (AIC) as the performance benchmark. To correct for the observational bias in receiving PT, a propensity score analysis adjusting for risk factors selecting for PT use was performed for the association of PT and overall and RFS following recommended statistical practice.[9] Propensity scores were calculated using logistic regression with PT as the outcome variable and all available variables as predictors. Weighted Cox proportional hazards regression using the scores as inverse weights to assess the effect of PT on survival endpoints was then performed.

All statistical tests were performed at the two-sided 0.05 level of significance. Statistical analyses were performed using SAS-software (Version 9, SAS-Institute, Cary, NC) and R (Version 3.1.2, R-foundation, Vienna, Austria) together with the survival package (Version 2.37–7, Rochester, MN).

3. Results

3.1. Patient data

Demographic data are shown in Table 1. Among 610 curatively resected patients (R0, pM0), 275 (45%) received at least 1 perioperative blood transfusion (Table 1). The median of transfused units was 2 [1–11]. The mean hemoglobin level before surgery in those patients receiving blood transfusion was 12.3 g/dL (SD 1.37). In the transfusion group, significantly more patients had lymph node metastasis ($P=0.005$), had more extensive surgeries ($P<0.001$), and a higher frequency of tumor located in the proximal third of the stomach ($P=0.012$). There were no significant differences in the distributions of pT- and UICC-stages, tumor grade, type of surgery, Lauren histotype, gender, age, neoadjuvant chemotherapy, adjuvant chemotherapy, histopathologic response rate, frequency of splenectomy, vessel infiltration, and dissected lymph nodes.

Table 1

Characteristics of patients who did and did not receive PT.

	No transfusion (n = 335)		At least one transfusion (n = 275)		
	n	%	n	%	*P*
Gender					0.28
Female	95	28.4	90	32.7	
Male	240	71.6	185	67.3	
Age					0.07
≤65 years	194	57.9	138	50.2	
>65 years	141	42.1	137	49.8	
Neoadjuvant chemotherapy					0.66
No	180	53.7	142	51.6	
Yes	155	46.3	133	48.4	
Adjuvant chemotherapy					0.52
No	328	97.9	272	98.9	
Yes	7	2.1	3	1.1	
Localization					0.01
Proximal	160	47.8	168	61.1	
Middle	79	23.6	48	17.4	
Distal	89	26.6	54	19.6	
Total	7	2.1	5	1.8	
Type of surgery					0.33
Total gastrectomy	222	66.3	187	68.0	
Subtotal gastrectomy	64	19.1	41	14.9	
Other	49	14.6	47	17.1	
Surgical extension					<0.001
None	184	54.9	122	44.4	
Luminal/transhiatal	104	31.0	81	29.4	
Extraluminal	47	14.0	72	26.2	
Splenectomy					0.19
Not done	322	96.1	257	93.5	
Done	13	3.9	18	6.5	
Dissected LN					0.64
≤21	123	36.7	97	35.3	
22–29	99	29.5	91	33.1	
>29	113	33.7	87	31.6	
Complications					0.18
None	219	65.4	169	61.4	
CD I/II	57	17.0	41	14.9	
CD III–V	59	17.6	65	23.6	
pT stage					0.33
pT0/is	14	4.2	10	3.6	
pT1	105	31.3	67	24.4	
pT2	57	17.0	46	16.7	
pT3	112	33.4	105	38.2	
pT4	47	14.0	47	17.1	
pN stage					
pN0	193	57.6	137	49.8	0.005
pN1	47	14.0	64	23.3	
pN2	47	14.0	25	9.1	
pN3	48	14.3	49	17.8	
UICC stage					
UICC 0	13	3.9	10	3.6	0.28
UICC I	134	40.0	90	32.7	
UICC II	101	30.1	90	32.7	
UICC III	87	26.0	85	30.9	
Grade					
G1	15	4.5	12	4.4	0.42
G2	81	24.2	68	24.7	
G3	233	69.5	184	66.9	
G4	6	1.8	11	4.0	
Lauren histotype					0.11
Intestinal	167	49.8	139	50.5	
Diffuse	85	25.4	52	18.9	
Mixed	41	12.2	34	12.4	
Others	42	12.5	50	18.2	
LVI					1.0
Absent	325	97.0	267	97.1	
Present	10	3.0	8	2.9	
Histopathologic response					0.95
Untreated	180	53.7	142	51.6	
Becker Ia/Ib	47	14.0	41	14.9	
Becker II	37	11.0	33	12.0	
Becker III	71	21.2	59	21.4	

Complications according to CD; pT/pN/UICC stages according to the 7th edition.

Becker Ia = no residual tumor detectable, Becker Ib = <10% viable tumor cells in relation to tumor bed, Becker II = 10%–50% viable tumor cells in relation to tumor bed, Becker III = >50% viable tumor cells in relation to tumor bed, CD = Clavien–Dindo, LN = lymph nodes; LVI = lymphatic vessel infiltration, UICC = Union International Contre le Cancer.

Median follow-up was 41 months [range: 0.1–153 months], comprising 61 months [range: 0.4–153 months] for survivors and 22.5 months [range: 0.1–124 months] for deceased patients. During the follow-up period, 258 patients (42.3%) died; the 5-year survival rate for patients not having been transfused was 62% compared with 53% in the transfused group ($P=0.025$); the 10-year survival rates are 54% versus 38%, respectively ($P=0.003$).

3.2. Predictors of overall and relapse-free survival

Univariate regression analysis revealed UICC stage, type of surgery, incidence of postoperative complications, PT, neo-adjuvant chemotherapy, splenectomy, surgical extension, and tumor localization in the proximal third of the stomach to be significantly related to postoperative survival (Table 2). Multivariable analysis demonstrated UICC stage, severe postoperative complications (CD III–V), age, application of neoadjuvant chemotherapy, and PT to be significantly and independently related to worsened postoperative survival (Table 2, Supplementary Table 1, http://links.lww.com/MD/B137). The number of transfused blood units did not influence overall survival significantly among patients who received at least 1 transfusion ($P=0.20$).

Regarding RFS, in univariable analysis UICC stage, type of surgery, incidence of postoperative complications, gender, neoadjuvant chemotherapy, histopathologic response, splenectomy, surgical extension, and tumor localization in the proximal third of the stomach were significant predictors (Supplementary Table 2, http://links.lww.com/MD/B137). In the multivariable analysis, UICC stage, type of surgery, and neoadjuvant chemotherapy remained independent predictors. PT was not associated with RFS, neither in univariable nor the multivariable analysis (Supplementary Table 3, http://links.lww.com/MD/B137, Supplementary Table 2, http://links.lww.com/MD/B137).

3.3. Predictors of PT

Factors predicting whether patients were more likely to receive PT (Supplementary Table 4, http://links.lww.com/MD/B137) were higher age ($P=0.05$), surgical extension to adjacent organs/structures ($P=0.02$), tumor localization at the proximal third of the stomach ($P=0.003$), and female gender ($P=0.03$).

3.4. Results of propensity score weighting analysis

In order to balance for potential confounders, the adjusted propensity score was calculated using the following variables: UICC stage, grading, type of surgery, Lauren histotype, CD grades, gender, age, neoadjuvant treatment, adjuvant chemotherapy, lymphatic vessel infiltration, splenectomy, surgical extension, number of dissected lymph nodes, and tumor localization (Table 3). The propensity score weighting for those variables demonstrated that PT was associated with an increased risk of death (hazard ratio (HR): 1.31, 95%CI: 1.01–1.69, $P=0.04$). As for the unadjusted analysis, adjusted propensity score analysis on RFS revealed an increased risk of recurrence without statistical significance (HR: 1.19, 95%CI: 0.88–1.61, $P=0.27$). Kaplan–Meier analysis for overall survival after propensity score weighting revealed that patients who received PT demonstrated a 9.4% lower 5-year ($P=0.07$) and a 19.7% lower 10-year survival rate ($P=0.01$). The weighted log-rank test[11] indicated a significant difference in the Kaplan–Meier estimates ($P=0.04$, Fig. 1). The results of a propensity score analysis may be sensitive to the choice of variables used in the calculation of the propensity scores. Use of all baseline characteristics is most often recommended, but to assess the robustness of conclusions the choice of predictors to use in the propensity score calculation varied. Results showed that PT remained statistically significant in the majority of alternative analyses for overall and RFS (Supplementary Fig. 1, http://links.lww.com/MD/B137 and Supplementary Tables 5 and 6, http://links.lww.com/MD/B137).

4. Discussion

This propensity score weighted retrospective analysis of 610 patients undergoing curative GC surgery demonstrates an important influence of perioperative blood transfusion on OS but not on RFS. Several studies investigating the effect of perioperative transfusion (PT) were published over the recent years with conflicting results making it difficult to draw definite conclusions. A recent meta-analysis concluded that the negative effects of PT prevail; however, the authors also stated that confounders could not be ruled out and that heterogeneity jeopardizes clear conclusions from their results.[8]

There are several reasons that should be considered in the context of previous analyses. Most of the so far published analyses date back to a period from 1980 to 2000 during which transfusions guidelines were almost nonexistent.[12–20] Clear transfusion triggers were not defined at that time and transfusion was left to the surgeon's discretion. Previous publications reported on patient data from that specific period. Another issue to be considered is that many of those papers reported on long-time periods between 1980 and 2000. During those periods, perioperative care may have improved considerably and therefore influenced the outcome. Furthermore, whole blood transfusions (buffy coat depleted) were applied before the year 2000. Leukocyte-depleted PRBCs are known to possess less immunogenic properties.[12] Most of the published studies did not report on how the respective transfusions were prepared, which may have led to the contradictory results. Lastly, most of the analyses originated in Eastern Asia, where GC incidence is known to be the highest worldwide. Recently, new insights in different molecular properties between Asian and Caucasian patients were reported, identifying various genes that may be responsible for the considerably better oncologic outcome in Eastern Asian patients.[21]

Previous analyses of Western patients could not conclusively determine a negative influence of perioperative blood transfusions.[16,17,22–24] The present analysis therefore aimed to eradicate the above-mentioned limitations. In this respect the unicentric nature of the present analysis may be advantageous. Only patients having been surgically treated in a curative manner (R0 resection, M0 stage) after the year 2000 were included in this analysis. All transfused patients received leukocyte-depleted blood products only. The frequency of transfusion in this analysis was comparable to previously published data and can be considered quite high. However, a decrease in transfusion frequency was noticed over the investigated period, which is related to introduction of specific transfusion triggers in the institution in 2007.[25,26] The transfusion rate was reduced from 62% (period 2001–2006) to 27% (period 2007–2013). This was achieved by introducing stricter transfusion triggers allowing for lower hemoglobin values.

Table 2

Univariate and multivariate analyses for overall survival.

	Univariate			Multivariate			5-year survival	
	HR	95%CI	*P* value	HR	95%CI	*P* value	%	*P* value
Gender								0.12
Female	Ref			Ref			65.1	
Male	1.25	0.95–1.64	0.12	1.07	0.80–1.44	0.653	54.7	
Age	1.02	1.01–1.03	0.003	1.03	1.02–1.04	<0.001		0.06
Neoadjuvant chemotherapy								0.001
No	Ref			Ref			65.0	
Yes	1.49	1.17–1.91	0.001	1.46	1.08–1.98	0.013	49.6	
Adjuvant chemotherapy								0.64
No	Ref			Ref			58.0	
Yes	1.26	0.47–3.40	0.64	1.34	0.48–3.74	0.588	43.8	
Localization								0.001
Proximal	Ref			Ref			52.8	
Middle	0.70	0.50–0.98	0.04	0.78	0.50–1.22	0.270	64.1	
Distal	0.63	0.46–0.87	0.006	0.81	0.49–1.32	0.394	67.7	
Total	1.94	0.95–3.96	0.07	1.34	0.61–2.94	0.466	16.7	
Type of surgery								0.02
Total gastrectomy	Ref			Ref			53.9	
Subtotal gastrectomy	0.58	0.40–0.86	0.006	1.04	0.63–1.72	0.881	70.4	
Others	0.89	0.63–1.26	0.52	0.91	0.63–1.33	0.629	62.9	
Surgical extension								<0.001
None	Ref			Ref			66.6	
Luminal/transhiatal	1.69	1.27–2.26	<0.001	1.18	0.79–1.76	0.418	50.6	
Extraluminal	1.93	1.42–2.62	<0.001	1.15	0.77–1.72	0.490	46.8	
Splenectomy								0.01
Not done	Ref			Ref			58.6	
Done	1.77	1.13–2.77	0.01	1.02	0.59–1.76	0.957	45.2	
Dissected LN	1.01	1.00–1.02	0.05	0.99	0.98–1.01	0.354		
Complications								<0.001
None	Ref			Ref			61.7	
CD I/II	1.03	0.72–1.47	0.87	0.98	0.68–1.42	0.927	58.6	
CD III–V	1.96	1.47–2.60	<0.001	2.11	1.57–2.85	<0.001	45.9	
Peri-op transfusion								<0.001
Absent	Ref			Ref			62.5	
Present	1.53	1.20–1.96	<0.001	1.32	1.02–1.71	0.033	52.6	
UICC stage								<0.001
UICC 0	Ref			Ref			93.3	
UICC I	2.73	0.67–11.21	0.16	3.00	0.72–12.57	0.133	80.1	
UICC II	6.30	1.55–25.61	0.01	6.42	1.56–26.39	0.010	55.4	
UICC III	14.55	3.59–58.88	<0.001	17.61	4.29–72.28	<0.001	27.4	
Grade								0.28
G1	Ref			Ref			80.2	
G2	1.86	0.85–4.06	0.12	1.07	0.48–2.39	0.872	60.2	
G3	1.95	0.92–4.16	0.08	0.87	0.39–1.95	0.730	55.7	
G4	2.48	0.94–6.51	0.07	0.80	0.28–2.27	0.674	57.8	
Lauren histotype								0.98
Intestinal	Ref			Ref			57.5	
Diffuse	0.94	0.69–1.29	0.70	1.33	0.90–1.97	0.155	59.0	
Mixed	0.93	0.62–1.40	0.74	1.16	0.74–1.80	0.522	58.8	
Others	0.99	0.69–1.40	0.94	0.79	0.53–1.17	0.234	57.7	
LVI								0.08
Absent	Ref			Ref			58.2	
Present	1.74	0.92–3.27	0.09	1.27	0.65–2.47	0.488	50.0	

Complications according to CD; UICC stages according to the 7th edition.

CD = Clavien–Dindo, CI = confidence interval, HR = hazard ratio, LN = lymph nodes, LVI = lymphatic vessel infiltration, peri-op = perioperative, UICC = Union International Contre le Cancer.

Similar to previous publications the present analysis reveals considerable differences in the baseline characteristics between transfused and nontransfused patients, which are related to tumor localization, surgical extent, and postoperative complications. The distribution of tumor stages was not significantly different between the groups. However, multivariable analysis demonstrated UICC stage, postoperative complications, PTs, application of neoadjuvant chemotherapy, and age to be significantly related to overall survival, which is comparable to previous data.[27]

Previous studies primarily made inference from the results of multivariable cox regression analysis. This analysis in addition

Table 3

Propensity score balanced characteristics.

	No transfusion (n = 335)			At least one transfusion (n = 275)			
	PS	%	SD	PS	%	SD	*P* value
Gender							1.0
Female	100.39	30.0	8.40	81.99	29.8	7.60	
Male	234.61	70.0	8.40	193.01	70.2	7.60	
Age	62.9		11.5	62.8		11.9	0.92
Neoadjuvant chemotherapy							0.96
No	178.74	53.4	9.14	145.25	52.8	8.29	
Yes	156.26	46.6	9.14	129.75	47.2	8.29	
Adjuvant chemotherapy							
No	329.02	98.2	2.43	270.06	98.2	2.21	1.0
Yes	5.98	1.8	2.43	4.94	1.8	2.21	
Localization							1.0
Proximal	179.18	53.5	9.14	147.41	53.6	8.29	
Middle	70.23	21.0	7.46	57.85	21.0	6.77	
Distal	78.94	23.6	7.78	63.76	23.2	7.01	
Total	6.65	2.0	2.56	5.99	2.2	2.42	
Type of surgery							1.0
Total gastrectomy	225.47	67.3	8.60	185.59	67.5	7.78	
Subtotal gastrectomy	59.48	17.8	7.00	48.14	17.5	6.31	
Others	50.05	14.9	6.53	41.28	15.0	5.93	
Surgical extension							0.99
None	168.07	50.2	9.17	137.01	49.8	8.31	
Luminal/transhiatal	100.55	30.0	8.40	83.95	30.5	7.65	
Extraluminal	66.38	19.8	7.31	54.04	19.7	6.60	
Splenectomy							0.99
Not done	316.89	94.6	4.15	260.56	94.8	3.71	
Done	18.11	5.4	4.15	14.55	5.2	3.71	
Dissected LN	26.40		11.1	26.30		10.1	0.93
Complications							1.0
None	213.99	63.9	8.81	175.92	64.0	7.98	
CD I/II	54.38	16.2	6.76	44.07	16.0	6.09	
CD III–V	66.63	19.9	7.32	55.01	20.0	6.65	
UICC							1.0
UICC 0	11.72	3.5	3.37	9.30	3.4	3.00	
UICC I	121.49	36.3	8.81	100.33	36.5	8.00	
UICC II	105.07	31.4	8.50	87.49	31.8	7.74	
UICC III	96.72	28.9	8.31	77.89	28.3	7.49	
Grading							1.0
G1	15.22	4.5	3.82	12.85	4.7	3.51	
G2	80.06	23.9	7.82	64.84	23.6	7.05	
G3	229.51	68.5	8.51	189.49	68.9	7.69	
G4	10.21	3.0	3.15	7.81	2.8	2.76	
Lauren histotype							1.0
Intestinal	168.63	50.3	9.16	137.37	50.0	8.31	
Diffuse	75.28	22.5	7.65	63.47	23.1	7.00	
Mixed	40.41	12.1	5.97	33.21	12.1	5.41	
Others	50.68	15.1	6.57	40.95	14.9	5.91	
LVI							1.0
Absent	326.09	97.3	2.95	267.78	97.4	2.66	
Present	8.91	2.7	2.95	7.22	2.6	2.66	

Each single observation was weighted by the inverse probability of receiving the actual treatment (i.e., blood transfusion). Those probabilities were estimated by logistic regression on transfusion status. The weights were normalized in order to produce the same sample sizes as the original data. For each stratum, patient count, proportion of patients in the stratum, and standard deviation are listed. Complications according to CD; UICC stages according to the 7th edition.

CD = Clavien–Dindo, LN = lymph nodes; , LVI = lymphatic vessel infiltration, PS = propensity score, SD = standard deviation, UICC = Union International Contre le Cancer.

implemented propensity score weighting to rule out possible confounders. Propensity score weighting is a statistical method applied to reduce possible selection-bias in observational/nonrandomized studies, which was initially proposed by Rosenbaum and Rubin in 1983.[28] It remains the state-of-the art for adjusting for confounding in nonrandomized studies.[29,30] In this analysis, inversion of the propensity score was used to calculate weights because the patient cohorts were almost comparable in size.[30] After propensity score adjusting of both groups, perioperative blood transfusion was still predictive for overall survival and revealed a pronounced difference in overall postoperative survival.

There are multiple recommendations for determining which variables should be included in a propensity score analysis, ranging from all available to only those predictive of outcome.[9] In this study all available patient factors were used. However,

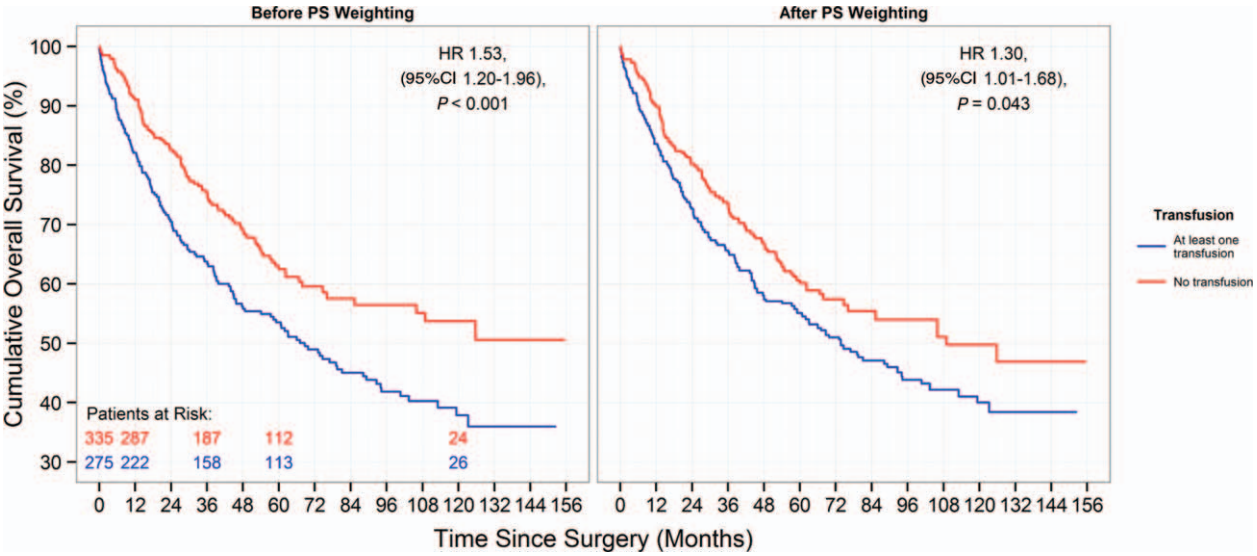

Figure 1. Kaplan–Meier curves for overall survival before and after propensity score weighting.

additional sensitivity analyses demonstrated that the choice of factors to use in the propensity scores had negligible influence on results. Exploratory statistical analyses following adjustment by propensity scores demonstrated that patient characteristics were balanced between those who received and did not receive transfusions. After adjustment, the statistically significance and magnitude of the influence of PTs on overall survival remained, but were dampened.

RFS was not significantly affected by PT, suggesting that the influence of PT on survival did not operate via this intermediary pathway. Factors affecting overall and RFS showed considerable differences. Whereas UICC stage, application of neoadjuvant chemotherapy, and extended surgery were associated with relapse risk, UICC stage, severe postoperative complications (CD III–V), age, application of neoadjuvant chemotherapy, and PT were associated with overall survival. These prognosticators suggest that relapse risk is primarily associated with advanced tumors, whereas overall survival is also influenced by perioperative factors, such as blood transfusions and severe complications. Under this scenario, factors related to postoperative complications and blood transfusion could have an impact on immune functions, allowing for dissemination of tumor cells. Patients having undergone transfusion and subsequent relapse were more prone to experience earlier mortality in the further course of disease. Nonetheless, a benefit for RFS could be detected (HR: 1.19, 95%CI: 0.88–1.61, Fig. 2), which was just not statistically significant. In prior investigations, the influence of splenectomy was argued as significantly influencing the detrimental effects of allogeneic blood transfusions.[22] The splenectomy rate was considerably low in this patient cohort, prohibiting conclusions as to its effect.

Regarding the present data, in concordance with the previously published results, definitive conclusions on perioperative blood

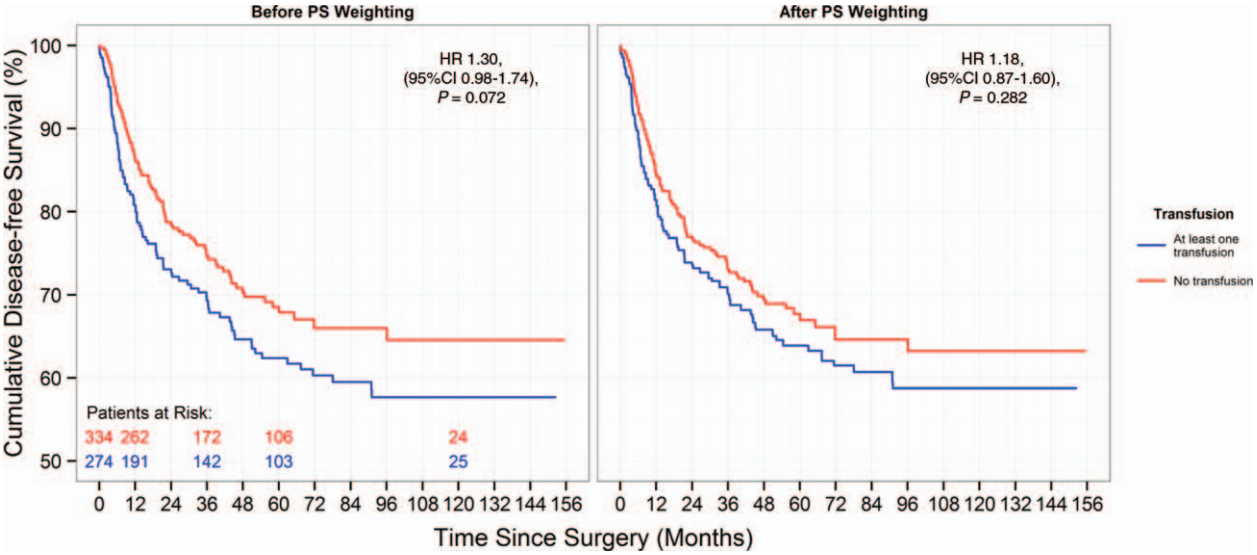

Figure 2. Kaplan–Meier curves for relapse-free survival before and after propensity score weighting.

transfusion cannot be drawn. Although there are several strengths in this analysis, such as propensity weighting of confounders,[31] inclusion of only curatively treated patients in an experienced center, and application of leukocyte-depleted blood products only, the following limitations have to be taken into account: propensity score weighting is not able to balance for unmeasured factors such as surgical quality and interindividual biologic or genetic differences. Further unmeasured factors such as surgical quality, influence of surgical trauma, the influence of improved postoperative intensive care, and general improvements in a time period over 12 years could not be assessed in this analysis. A randomized controlled trial is crucial in order to shed light on the influence of perioperative blood transfusion in GC patients. To the authors knowledge no such trial has been conducted to date. Therefore, patient blood management programs[32] are encouraged to be applied until further data is available on the possibly negative influence of allogeneic blood transfusion in GC patients.

Acknowledgments

The authors thank Dr Frick from the Department of Clinical Chemistry, Klinikum Rechts der Isar Muenchen for supporting this study by providing database access and his ambitious efforts for patient data retrieval.

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