original article

Eur Surg (2019) 51:246–253
https://doi.org/10.1007/s10353-019-0588-7

european surgery
ACA Acta Chirurgica Austriaca

Prognostic impact of allogenic blood transfusion following surgical treatment of esophageal cancer

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Received: 19 March 2019 / Accepted: 25 March 2019 / Published online: 10 April 2019

Summary
Background Esophageal cancer (EC) surgery is associated with relatively high morbidity and mortality rates and poor overall survival (OS). The impact of allogeneic blood transfusion (aBT) on OS is still a matter of debate. We aimed to investigate the impact of aBT on OS in a homogeneous population of patients undergoing surgical treatment for EC in a single center during a 15-year period.
Methods In total, 409 patients who had undergone surgical resection for EC were studied. The clinicopathological parameters and OS were compared between 170 patients (41.6%) who received perioperative aBT and 239 patients (58.4%) who did not.
Results Compared with the non-transfused patients, patients who received aBT had lower preoperative hemoglobin levels, more comorbidities, and a more advanced stage of disease as reflected by tumor diameter, nodal metastases, perineural invasion, and the need for multiorgan resection. Transfused patients suffered more frequently from major postoperative complications (26/170 [21.5%] vs. 13/239 [5.7%], $p<0.001$) and had a significantly longer hospital stay (17 vs. 15 days, $p<0.001$). Multivariate analysis identified tumor grade ($p=0.02$), perineural invasion ($p=0.001$), N stage ($p < 0.001$), major postoperative complications ($p=0.01$), and comorbidity ($p=0.04$) as independent predictors of OS in patients with EC. Perioperative aBT was not found to be an independent predictor of OS in the entire cohort, neither in the stratified subanalysis.
Conclusion In our study, an advanced stage of disease and comorbidities resulted in the need for blood transfusion and the occurrence of major postoperative complications, which appeared to decrease the OS in patients with EC.

Keywords Outcome · Esophagectomy · Overall survival · Squamous cell carcinoma · Adenocarcinoma

Abbreviations

aBT	Allogeneic blood transfusion
AEG	Adenocarcinoma of the esophagogastric junction
CI	Confidence interval
DFS	Disease-free survival
EC	Esophageal cancer
HR	Hazard ratio
OS	Overall survival
PRBC	Packed red blood cells

Introduction

Esophageal cancer (EC) represents a significant global health burden with 746,000 new cases and 459,300 deaths reported in 2015 [1, 2]. The incidence of EC is rising worldwide, mainly due to the increased incidence rates of adenocarcinoma of the esophagus and esophagogastric junction (AEG) in Western countries [3–5].

Despite the introduction of different neoadjuvant and adjuvant treatment regimens, surgery remains the cornerstone of treatment for patients with localized, curable EC. Regardless of the surgical approach, peri-

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operative morbidity and mortality remain high, even in high-volume centers [6]. Morbidity and mortality rates after esophagectomy reach 50 and 20%, respectively [7, 8]. For patients who are eligible for curative surgery, reported 5-year survival rates can be as low as 15–25% and very rarely exceed 50% [9]. Such poor survival rates are principally a reflection of the advanced stage of the disease at presentation [9].

Factors that affect morbidity, mortality, and overall survival (OS) have been systematically investigated. Based on the observations made in other malignancies, the effect of blood transfusion on outcomes after esophagectomy has also been studied. Esophagectomy, as a representative complex major digestive surgery, is potentially associated with high perioperative blood loss. Therefore, allogeneic blood transfusion (aBT) is frequently administered in the perioperative period. Approximately 60% of patients who undergo esophagectomy receive aBT [10]. Perioperative transfusion has been linked to higher recurrence rates and reduced survival in patients undergoing resection for different types of cancers [6, 11, 12]. The underlying mechanisms of these associations are incompletely understood. Suppression of the innate and acquired immune systems following aBT is thought to play an important role [13–15]. The effect of aBT on the clinical outcome in EC patients was addressed in a few previous studies, with conflicting results [6, 10, 12, 16]. The aim of our study was to investigate the impact of aBT on long-term outcomes in a large homogeneous patient population undergoing curative resection of EC.

Patients and methods

From January 2004 to January 2016, 516 consecutive patients with EC underwent surgical resection with radical intent at our department. Inclusion criteria were histologically proven squamous cell or adenocarcinoma of the esophagus with tumor-free resection margins (R0 resection) and without distant metastases. Patients were excluded from the study if they had synchronous tumors (small bowel, colon, stomach, kidney, and thyroid gland), incomplete perioperative transfusion or follow-up data, and in-hospital or 30-day mortality. Finally, 409 patients met our criteria and were included in the analysis.

All surgical procedures were performed by a single surgical team with extensive experience in esophagogastric surgery. Perioperative mortality was defined as 30-day post-hospital discharge mortality. Perioperative morbidity was classified according to the Clavien–Dindo classification, taking into account only major complications for which further medical or surgical intervention was necessary (grade III–V). The aBT in this study was defined as any aBT in the perioperative in-hospital course. In general, in asymptomatic patients without heart disease, the threshold for aBT was hemoglobin level <80 g/l, or intraoperative blood loss of more than 1000 ml. Patients with significant cardiac or respiratory comorbidity received aBT if their hemoglobin level was <100 g/l. In the case of acute severe hemorrhage, aBT was administered according to the judgment of the clinician in charge and was based on parameters such as estimated blood loss, heart rate, blood pressure, hemoglobin level, and other laboratory test results.

Clinical and follow-up data were obtained from patients' charts, referring physicians, or via a phone interview with the patients. Disease recurrence was defined as radiologically or pathologically confirmed locoregional or distant metastases. Overall survival was calculated from the day of surgery to the date of death from any cause or to the date of the last follow-up. Disease-free survival (DFS) was calculated from the day of surgery to the time of the first relapse (local recurrence or distant metastasis). The last scheduled study follow-up was September 2018. Operative deaths and deaths that were not related to cancer were not included in the analysis.

Statistical analysis

Continuous data are presented as means (standard deviation) or medians (interquartile range) and categorical data are presented as frequencies (percentages). Statistical comparisons between transfused and nontransfused patients were performed using the Student t test, the chi-square test, or Mann–Whitney U test, as appropriate. The DFS and OS curves were determined using the Kaplan–Meier method. The difference in survival between transfused and nontransfused patients was analyzed with the log-rank test.

To determine the impact of aBT on OS, univariate Cox proportional hazards regression analysis was conducted. Variables with p values <0.1 in the univariate analysis (tumor grade, lymphovascular invasion, venous invasion, perineural invasion, aBT, TNM stage, N stage, tumor size, major complications, and comorbidity) were entered in the multivariate analysis to determine factors associated with survival. Adjusted hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were calculated.

A stratified analysis of OS for patients with different tumor types (squamous cell vs. adenocarcinoma) and the surgical approach (thoracoabdominal vs. transhiatal) by transfusion status was performed subsequently. Univariate and multivariate Cox regression analysis was applied to identify the independent predictors of survival in 191 patients with squamous cell carcinoma and 263 patients treated via a thoracoabdominal approach. The level of significance was set at p <0.05. Statistical analysis was performed with IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA).

Table 1 Clinicopathological characteristics of patients stratified by perioperative transfusion status

Variable	All patients, *n* (%) *N* = 409	Nontransfused *N* = 239	Transfused *N* = 170	*p*
Gender				
Male	333 (81.4)	199 (83.3)	134 (78.8)	0.30
Age	59.9 (10.3)	59.1 (10.0)	61.0 (10.8)	0.07
Tumor location				
EC	197 (48.2)	122 (51.0)	75 (44.1)	0.19
AEG	212 (51.8)	117 (49.0)	95 (55.9)	
Histology				
Squamous cell	191 (46.8)	116 (48.7)	75 (44.1)	0.36
Adenocarcinoma	217 (53.2)	122 (51.3)	95 (55.9)	
Surgical approach				
Thoracoabdominal	263 (64.5)	158 (66.4)	105 (61.8)	0.35
Transhiatal	145 (35.5)	80 (33.6)	65 (38.2)	
Multiorgan resection	25 (6.2)	7 (2.9)	18 (10.7)	0.003
Neoadjuvant therapy	34 (8.3)	23 (9.6)	11 (6.5)	0.28
Grade				
G1	131 (33.1)	78 (33.6)	53 (32.3)	0.36
G2	235 (59.3)	133 (57.3)	102 (62.2)	
G3	30 (7.6)	21 (9.1)	9 (5.5)	
Lymphovascular invasion	321 (80.5)	181 (77.4)	140 (84.8)	0.073
Venous invasion	197 (50.1)	105 (46.1)	92 (55.8)	0.07
Perineural invasion	135 (34.4)	68 (29.7)	67 (40.9)	0.03
Maximal tumor diameter in mm	55.0 [40.0–74.0]	52.0 [40.0–70.0]	60.0 [45.0–82.5]	0.004
Tumor size				
≤3.5 cm	71 (17.5)	44 (18.6)	27 (16.0)	0.51
>3.5 cm	335 (82.5)	193 (81.4)	142 (84.0)	
N stage				
N0	80 (19.8)	56 (23.7)	24 (14.2)	0.04
N1	93 (23.0)	54 (22.9)	39 (23.1)	
N2	108 (26.7)	64 (27.1)	44 (26.0)	
N3	124 (30.6)	62 (26.3)	62 (36.7)	
T stage				
T0	6 (1.5)	1 (0.4)	5 (2.9)	0.31
T1	35 (8.6)	22 (9.2)	13 (7.6)	
T2	51 (12.5)	31 (13.0)	20 (11.8)	
T3	269 (65.9)	156 (65.5)	113 (66.5)	
T4	47 (11.5)	28 (11.8)	19 (11.2)	
TNM stage				
0, I, II	40 (10.5)	31 (13.9)	9 (5.7)	0.01
III, IV	342 (89.5)	192 (86.1)	150 (94.3)	
Major complications	39 (11.2)	13 (5.7)	26 (21.5)	<0.001
Hospital stay	15.0 [14.0–19.0]	15.0 [14.0–17.0]	17.0 [14.0–21.0]	<0.001
ASA				
1	34 (8.5)	25 (10.7)	9 (5.4)	0.01
2	300 (75.0)	180 (76.9)	120 (72.3)	
3	65 (16.3)	28 (12.0)	37 (22.3)	
4	1 (0.3)	1 (0.4)	0 (0.0)	
Preoperative hemoglobin (g/l)	132.0 [121.0–141.0]	138.0 [128.0–145.0]	121.0 [105.0–133.0]	<0.001
Comorbidity	191 (47.8)	101 (43.2)	90 (54.2)	0.03
Duration of surgery	390.0 [330.0–450.0]	390.0 [320.0–450.0]	392.5 [340.0–450.0]	0.09

AEG adenocarcinoma of the esophagogastric junction cancer, *ASA* American Society of Anesthesiologists, *EC* esophageal cancer
Data are presented as number (percentage), mean (SD) or median [IQR]; *p* value indicates significance according to chi-square test, *t* test. or Mann–Whitney *U* test as appropriate

Results

Characteristics of study population

During the study period, 516 consecutive patients underwent surgery with radical intent for EC. For 77 (14.9%) of these patients there were incomplete data regarding transfusion or the patients were lost to follow-up and were therefore excluded from the analysis. Out of 439 remaining patients, 11 patients (2.1%) were excluded from the analysis owing to in-hospital or 30-day mortality, and 19 (3.7%) patients because of the positive resection margin. Complete data and follow-up were available for 409 patients.

At the time of study completion, 124 (30.3%) patients were still alive. In the group of 285 (69.7%) non-survivors, 230 (80.8%) had died of recurrent disease, 5 (1.7%) during the course of adjuvant therapy, whereas 50 (17.5%) succumbed to causes unrelated to EC.

In total, 170 patients (41.6%) received perioperative aBT, of whom 106 (62.4%) were given less than three units of packed red blood cells (PRBC) and 64 (37.6%) patients were given three or more units of blood. The maximal number of transfused units of PRBCs was nine (in one patient).

Compared with the nontransfused patients, patients who received aBT had lower preoperative hemoglobin level, more comorbidities, and a more advanced stage of disease as reflected by tumor diameter, nodal metastases, perineural invasion, and the need for multiorgan resection. Transfused patients suffered more frequently from major postoperative complications (26/170 [21.5%] vs. 13/239 [5.7%], $p<0.001$) and had a significantly longer hospital stay (17 vs. 15 days, $p<0.001$; Table 1).

Transfusion and clinical outcome

The OS for the entire cohort of patients was 26.0 months (95% CI 20.7–31.3). The TNM stage-specific OS for stages I–IV was 96.0 (79.0–112.9), 91.8 (60.3–123.3), 52.0 (34.1–69.9), and 16.0 (14.0–18.0) months respectively. There was no difference in the OS between patients with EC and those with AEG (24 vs. 30 months; $p=0.92$). The 5-year survival rate for the entire cohort was 25.3%.

During the observation period, there was tumor recurrence in 236 (57.7%) patients. There was no difference between EC and AEG regarding the incidence of tumor recurrence (110/197 [55.8%] vs. 126/212 [59.4%]; $p=0.46$). There was a significant difference in recurrence rate dependent on the TNM stage (TNM III/IV vs. TNM I/II; 221 [64.6] vs. 8 [20%]; $p<0.001$).

On Kaplan–Meyer analysis, perioperative transfusion was associated with a significantly decreased OS (21.0 vs. 30.0 months, log-rank chi-square 4.90; $p=0.027$). However, there was no difference in the median DFS among the transfused and nontransfused patients (24.0 vs. 29.0 months; log-rank chi-square 1.90; $p=0.168$; Fig. 1).

Univariate analysis revealed that in addition to transfusion, tumor grade, lymphovascular invasion, venous invasion, perineural invasion, tumor size, N stage, TNM stage, major complications, and comorbidity were significant predictors of OS. Multivariate analysis using Cox regression proportional hazard model demonstrated that the independent predictors of survival were tumor grade, perineural invasion, N stage, major complications, and comorbidity. Transfusion was not identified as an independent prognostic variable for OS in the entire cohort (HR 1.10; 95% CI 0.82–1.48; $p=0.50$; Table 2).

A stratified subanalysis of OS for histological tumor type, operative approach, TNM stage, N stage, and

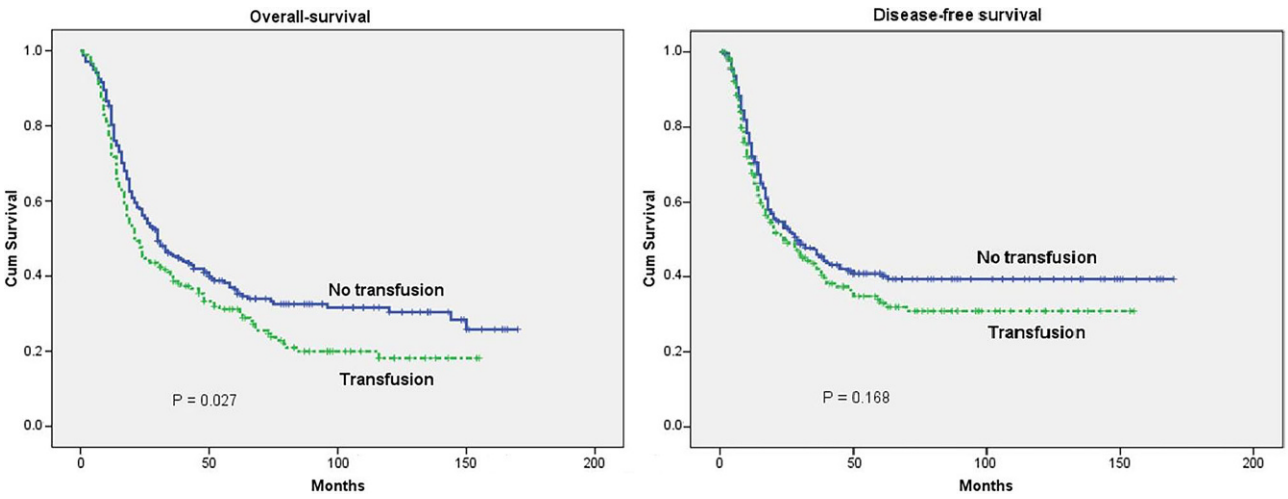

Fig. 1 Kaplan–Meyer plots of overall survival and disease-free survival according to the transfusion status. Time period in months after the operation

Table 2 Multivariate analysis of prognostic factors for overall survival of 409 patients with EC and AEG (Cox proportional hazard model)

Variable	HR (95% CI)	*p*
Grade		
G2 vs. G1	1.02 (0.74–1.41)	0.89
G3 vs. G1	2.34 (1.35–4.06)	0.002
Lymphovascular invasion (+/–)	1.06 (0.63–1.79)	0.82
Venous invasion (+/–)	1.14 (0.80–1.63)	0.47
Perineural invasion (+/–)	1.80 (1.27–2.55)	0.001
Transfusion	1.10 (0.82–1.48)	0.50
TNM stage		
III/IV vs. I/II	1.73 (0.93–3.19)	0.08
N stage		
N1 vs. N0	1.74 (1.00–3.03)	0.05
N2 vs. N0	2.65 (1.40–5.00)	0.003
N3 vs. N0	4.44 (2.28–8.65)	<0.001
Tumor size		
≥3.5 cm vs. <3.5 cm	0.95 (0.64–1.40)	0.79
Major complications	1.76 (1.14–2.71)	0.01
Comorbidity	1.36 (1.02–1.81)	0.04

HR adjusted hazard ratio, *CI* confidence interval, $p < 0.05$ statistical significance, *AEG* adenocarcinoma of the esophagogastric junction cancer, *EC* esophageal cancer

transfusion was performed subsequently (Table 3). Interestingly, the analysis showed a significant difference in OS among transfused and nontransfused patients with squamous cell carcinoma ($p = 0.005$) and also in patients operated on via a thoracoabdominal approach ($p = 0.03$). Therefore, we conducted univariate and multivariate Cox regression analysis to find the independent predictors of OS in these patient subgroups. Besides transfusion, univariate analysis identified tumor grade, lymphovascular invasion, venous invasion, perineural invasion, N stage, and preoperative hemoglobin level as variables associated with the OS in 191 patients with squamous cell cancer. However, only tumor grade, venous invasion, perineural invasion, N stage, and perioperative hemoglobin level were shown to be independent predictors of OS in the squamous cell cancer group.

Among seven variables verified by univariate analysis, the independent predictors, as determined by multivariate Cox regression, of OS in 263 patients who underwent thoracoabdominal surgery for treatment of EC and AEG were: tumor grade (HR 2.34; 95% CI 1.35–4.06, $p = 0.002$), perineural invasion (1.80; 1.27–2.55; $p = 0.001$) and N stage (N3 vs. N0; 4.44; 2.28–8.65; $p < 0.001$).

Allogeneic blood transfusion was demonstrated not to be an independent predictor of OS, neither in the squamous cell group (HR 1.32; 95% CI 0.88–1.97; $p = 0.18$) nor in the thoracoabdominal approach group (HR 1.35; 95% CI 0.98–1.86; $p = 0.07$) when adjusted for the aforementioned variables (Tables 4 and 5).

Table 3 Stratified subanalysis of tumor characteristics, transfusion, and overall survival

Variable	Overall survival Median (95% CI)		*p*
	Transfusion	No transfusion	
Histology			
Squamous cell	18.0 (14.6–21.4)	30.0 (17.4–42.6)	0.005
Adenocarcinoma	24.0 (13.1–34.9)	30.0 (21.9–38.1)	0.743
Approach			
Thoracoabdominal	22.0 (17.6–26.4)	30.0 (20.3–39.7)	0.029
Transhiatal	21.0 (14.1–27.9)	30.0 (13.8–46.2)	0.392
TNM stage			
I, II	71.7 (53.4–90.0)[a]	108.2 (86.5–130.0)	0.164
III, IV	46.4 (37.6–55.1)	62.1 (52.7–71.5)	0.038
N stage			
$N = 0$	73.1 (54.7–91.4)[a]	116.0 (97.5–134.5)	0.153
$N > 0$	20.0 (15.8–24.2)	24.0 (18.0–30.0)	0.256

CI confidence interval, *p* value indicates significance according to the log-rank test
[a]Mean survival in months, median was not reached

Table 4 Multivariable analysis of overall survival of 191 patients with squamous cell cancer

Variable	HR (95% CI)	*p*
Tumor grade		
G2 vs. G1	1.29 (0.87–1.92)	0.21
G3 vs. G1	2.21 (1.13–4.33)	0.02
Lymphovascular invasion (+/–)	0.94 (0.53–1.65)	0.83
Venous invasion (+/–)	1.64 (1.05–2.57)	0.03
Perineural invasion (+/–)	2.47 (1.58–3.87)	<0.001
N -stage		
N1 vs. N0	2.42 (1.33–4.41)	0.004
N2 vs. N0	4.05 (1.97–8.34)	<0.001
N3 vs. N0	4.90 (2.25–10.67)	<0.001
Preoperative hemoglobin g/l	0.98 (0.97–0.99)	0.007
Transfusion	1.32 (0.88–1.97)	0.18

HR hazard ratio, *CI* confidence interval, *p* value indicates significance according to Cox regression analysis

Table 5 Multivariate analysis of overall survival of 263 patients treated via a thoracoabdominal approach

Variable	HR (95% CI)	*p*
Tumor grade		
G2 vs. G1	1.26 (0.88–1.80)	0.21
G3 vs. G1	2.24 (1.18–4.25)	0.01
Lymphovascular invasion (+/–)	0.93 (0.54–1.59)	0.79
Venous invasion (+/–)	1.36 (0.90–2.05)	0.14
Perineural invasion (+/–)	1.87 (1.25–2.81)	0.003
N stage		
N1 vs. N0	1.92 (1.09–3.39)	0.02
N2 vs. N1	3.30 (1.70–6.38)	<0.001
N3 vs. N0	4.73 (2.33–9.60)	<0.001
Transfusion	1.35 (0.98–1.86)	0.07
Comorbidity	1.19 (0.57–2.48)	0.65

HR hazard ratio, *CI* confidence interval, *p* value indicates significance according to Cox regression analysis

Discussion

Our study showed that aBT was not independently associated with worse OS. Perioperative aBT after esophagectomy remains very common. The rate of perioperative aBT in this study was 41.6%, while the rates of aBT in the majority of other studies varied considerably (7–83.5%; [9]). At present, there is no consensus concerning the indications for blood transfusion after esophagectomy nor the type or volume of blood products to be administered. Surgeons are often concerned about perfusion of the gastric conduit, and therefore may be more likely to administer aBT to the patient, even though there is no evidence suggesting a relationship between transfusion and prevention of anastomotic leakage. Conversely, a recent study demonstrated an increased risk of anastomotic complications after surgery for AEG associated with perioperative aBT [17]. Besides, if intraoperative blood loss is not precisely measured, which was the case in the current study, surgeons and anesthesiologists can easily overestimate intraoperative blood loss and suggest aBT, even if there were no clear indications [18]. The old surgical dogma that a patient should not be discharged if their hemoglobin level is under 100 g/l should also not be ignored. This routine practice has been modified in our department by introducing a restrictive transfusion policy. Furthermore, in the era of various alternatives to aBT, such as intravenous iron therapy, patients with severe anemia are no longer being scheduled for elective surgery.

The impact of aBT on outcomes has been investigated in patients with various tumor types. Perioperative aBT was associated with adverse outcome in patients with lung, gastric, pancreatic, colon, and hepatocellular cancer [19–23]. The exact mechanism by which aBT may affect the outcome in cancer patients has not been unequivocally explained. One hypothesis involves immunomodulation induced by aBT [13–15, 24–29]. Independent of the effect of aBT and cancer-related factors, profound surgical stress has also been linked to immunosuppression [9].

Several studies that investigated the association between aBT and perioperative or long-term outcome in patients with EC and AEG reported conflicting results [6, 9–12, 16, 30–32].

In our study, univariate analysis demonstrated that patients who received an aBT had significantly decreased OS compared with nontransfused patients. On multivariate analysis, aBT was not found to be the

independent predictor of OS in the entire cohort or in the stratified subanalysis. This result is consistent with results of other authors [11, 16, 30, 31, 33]. Most of them expressed doubt regarding the independent influence of aBT on long-term outcome and hypothesized that the adverse outcome was derived from the clinical circumstances necessitating the aBT.

By contrast, other reports revealed that perioperative aBT was associated with adverse perioperative or long-term outcome in patients with EC [6, 10, 12, 31–34]. One of the studies found that perioperative aBT was associated with worse 1-year survival rates in stage III EC, but not with 3- to 5-year survival [32]. Interestingly, a significant independent relationship between a specific threshold of the transfused blood and decreased OS has been demonstrated. The identified thresholds varied (two to four units of PRBC) among different studies [31, 33, 34]. Lee et al. founded that long-term mortality gradually increased by 6% with one unit increase in transfused PRBC [10]. Moreover, a recently published meta-analysis revealed that perioperative aBT was associated with significantly worse OS in patients undergoing esophagectomy for EC [9].

There might be several possible explanations for such conflicting results. In some studies, the variables of the compared groups (aBT+ vs. aBT-) were extremely unbalanced, which may have impacted the results [6, 31]. There is also a notable difference between cohorts regarding the proportion of patients with advanced disease, comorbidities, the incidence of preoperative anemia, amount of intraoperative blood loss, and aBT units received. Furthermore, definitions of the postoperative period, mortality rates, and the incidence of postoperative complications differed substantially across studies.

Our study population was characterized by a more advanced stage of disease and more comorbidities than most other studies, which is probably a reflection of the health-care system in developing countries like Serbia [6, 10, 31, 33]. We strongly believe that the relatively low overall 5-year survival rate of 25.3% in the current study is the result of the advanced stage of the disease at the time of diagnosis. Nevertheless, the mortality rate of 2.1% and the incidence of major complications of 11.2% were among the lowest published [6, 10, 16, 31, 33].

There was a significantly higher proportion of more advanced disease, comorbidities, and major complications in the group of transfused patients. We assume that difficult surgical dissection of more advanced tumors led to greater intraoperative blood loss and consequently a higher aBT requirement. The study design makes it very difficult to completely exclude the possibility that the need for aBT was merely a consequence of more advanced disease, complications, and comorbidity. This is of great importance because each of these factors alone may independently influence OS [9].

There are numerous factors reported to have an impact on long-term outcome in patients with EC or AEG [35]. In our study, multivariate analysis identified tumor grade, perineural invasion, N stage, major complications, and comorbidity as independent predictors of OS in patients with EC and AEG.

This study has some limitations that should be considered. Our study was a retrospective observational study with all limitations imposed by the study design. Intraoperative blood loss was not precisely measured and therefore was not incorporated in our analysis.

Conclusion

In conclusion, we found that perioperative aBT was not associated with long-term survival in patients with EC and AEG. As expected, an advanced stage of the disease at the time of operation, postoperative complications, and comorbidities had the most significant impact on prognosis. Therefore, an early diagnosis, careful patient selection, and meticulous surgical technique along with proper postoperative care seem to be the most important determinants of survival in patients with EC and AEG.

Conflict of interest D. Velickovic, P. Sabljak, D. Stojakov, J. Velickovic, K. Ebrahimi, V. Sljukic, and P. Pesko declare that they have no competing interests.

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