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Original Article

Pancreatic Fistula after D1+/D2 Radical Gastrectomy according to the Updated International Study Group of Pancreatic Surgery Criteria: Risk Factors and Clinical Consequences. Experience of Surgeons with High Caseloads in a Single Surgical Center in Eastern Europe

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ABSTRACT

Purpose: Incidence, risk factors, and clinical consequences of pancreatic fistula (POPF) after D1+/D2 radical gastrectomy have not been well investigated in Western patients, particularly those from Eastern Europe.
Materials and Methods: A total of 358 D1+/D2 radical gastrectomies were performed by surgeons with high caseloads in a single surgical center from 2002 to 2017. A retrospective analysis of data that were prospectively gathered in an electronic database was performed. POPF was defined and graded according to the International Study Group for Pancreatic Surgery (ISGPS) criteria. Uni- and multivariate analyses were performed to identify potential predictors of POPF. Additionally, the impact of POPF on early complications and long-term outcomes were investigated.
Results: POPF was observed in 20 patients (5.6%), according to the updated ISGPS grading system. Cardiovascular comorbidities emerged as the single independent predictor of POPF formation (risk ratio, 3.051; 95% confidence interval, 1.161–8.019; P=0.024). POPF occurrence was associated with statistically significant increased rates of postoperative hemorrhage requiring re-laparotomy (P=0.029), anastomotic leak (P=0.002), 90-day mortality (P=0.036), and prolonged hospital stay (P<0.001). The long-term survival of patients with gastric adenocarcinoma was not affected by POPF (P=0.661).
Conclusions: In this large series of Eastern European patients, the clinically relevant rate of POPF after D1+/D2 radical gastrectomy was low. The presence of co-existing cardiovascular disease favored the occurrence of POPF and was associated with an increased risk of postoperative bleeding, anastomotic leak, 90-day mortality, and prolonged hospital stay. POPF was not found to affect the long-term survival of patients with gastric adenocarcinoma.

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Keywords: Radical gastrectomy; Gastric cancer; Pancreatic fistula; Complications; Survival

INTRODUCTION

With an incidence of over 1 million in 2018, gastric cancer (GC) exerts a significant burden on healthcare systems [1]. The prevalence of GC shows considerable geographical variation. More than 70% of the cases of GC are from the eastern, southeastern, and central parts of Asia, while only 15% are from European countries [1,2]. Different geographical patterns of GC incidence have also been observed within Europe [3,4]. For instance, the incidence of GC in Eastern Europe which accounts for 8% of all GC cases worldwide [2], is almost twice that of Western Europe [4].

Surgery is generally considered the sole curative treatment for patients diagnosed with GC. The stage of GC at the time of diagnosis varies significantly between different geographical regions. For instance, most patients with GC are diagnosed at an early stage in Eastern Asia [5-8], while most of the patients in Western countries are diagnosed at an advanced stage [7,9-12]. The stage at diagnosis may account for the significant differences in survival between patients with GC from Eastern Asia and those from Western countries (5-year survival rate of 79.8% in Eastern Asia versus 40.1% in Western countries) [7]. The differences in survival are not only explained by the differences in patient characteristics but also by the higher number of lymph nodes examined in the Eastern Asian patients, as shown by a recent comparative study [7]. The number of examined lymph nodes considerably affects stage migration [7]. Examination of a greater number of lymph nodes is associated with more accurately staged disease. Nevertheless, the number of lymph nodes examined is highly dependent on the method used in the assessment of lymph node involvement [13].

In Eastern Asia, lymphadenectomy extending beyond D1 in curative surgical resection of GC has long been in practice [14,15]. In contrast, the Western surgical centers were initially reluctant to adopt this technique owing to the lack of proven survival benefits and the high morbidity and mortality rates that were reported in initial procedures [9,10,16,17]. Nowadays, the oncological benefits of lymph node dissection extending beyond D1 in GC have been shown in several European centers [12,18-20], with no increase in morbidity and mortality rates [18,20,21]. Although a recent European randomized study has shown no difference in survival between patients with D1 and D2 gastrectomies for GC [11], a subgroup analysis has demonstrated a significant survival benefit of D2 lymphadenectomy in patients with advanced disease [11,22], who are predominant in Europe. Nevertheless, D2 lymphadenectomy is currently recommended for curative-intent surgery in advanced GC in high-volume European surgical centers [23,24].

Formation of a postoperative pancreatic fistula (POPF) is an important source of morbidity after radical gastrectomy with lymph node dissection extending beyond D1 [23,25]. A POPF may potentially result from an extended lymphadenectomy accompanied by bursectomy. Although several studies have explored potential predictors of the development of POPF after a radical gastrectomy with lymph node dissection extending beyond D1 [8,26-48], few of them have used the International Study Group for Pancreatic Surgery (ISGPS) definition and grading system [8,28,29,32,33,35,37-39,41-48], and none of them has used the updated grading system [49]. Interestingly, the number of studies performed on Western patients is limited [26,35], and none of those studies includes Eastern European patients. Furthermore,

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the impact of POPF on early morbidity and long-term survival after a radical gastrectomy with lymph node dissection extending beyond D1 for GC has been poorly investigated [28,30,39,40,45,47,48].

The present study aimed to evaluate the incidence, risk factors, and clinical consequences of a POPF following D1+/D2 gastrectomy, in a relatively large series of Eastern European patients.

MATERIALS AND METHODS

Inclusion of patients

The data of all patients who underwent a D1+/D2 radical gastrectomy between January 1, 2002, to December 31, 2017, and who were operated by 1 of 3 surgeons (M.I., C.V., and T.D.) with high caseloads (a minimum of 100 radical gastrectomies) were prospectively gathered in an electronic database established at our Department of Surgery and retrospectively analyzed. Our previous analysis found that a larger number of radical gastrectomies performed (at least 100 procedures per surgeon) was associated with significantly improved outcomes [20]. The demographic, clinical, and pathological characteristics of all the participants are shown in **Tables 1-3**.

Operative data

We employed the definition of a D1+/D2 gastrectomy set out by the Japanese Gastric Cancer Association [14], which takes into consideration the tumor location. No distinction was made between D1+ and D2 gastrectomies based on data that showed no oncologic differences between the 2 types of lymph node dissection [50,51]. A splenectomy was performed only when tumor invasion of the spleen was suspected or when the tumor was present in the upper part of the stomach. A distal pancreatectomy was only performed in patients with suspected tumor invasion of the pancreas.

Reconstruction after resection was performed through a Roux-en-Y esophago/gastrojejunostomy. The operative data of the patients in the study are shown in **Table 2**.

Table 1. Demographic and clinical characteristics of 358 patients who underwent D1+/D2 radical gastrectomy

Parameter	All patients (358 patients)	POPF (20 patients)	No POPF (338 patients)	P-value
Age (yr)	62±10.6	65±8.5	62±10.7	0.201†
Male (sex)	246 (68.7)	16 (80.0)	230 (68.0)	0.327*
Diabetes mellitus	42 (11.7)	0 (0.0)	42 (12.4)	0.147*
Cardiovascular diseases	135 (37.7)	12 (60.0)	123 (36.4)	0.054*
HBV infection	10 (2.8)	1 (5.0)	9 (2.7)	0.560*
HCV infection	5 (1.4)	0 (0.0)	5 (1.5)	1*
Upper digestive hemorrhage	154 (43.0)	10 (50.0)	144 (42.6)	0.643*
Upper digestive stenosis	84 (23.5)	2 (10.0)	82 (24.3)	0.180*
Abdominal pain	233 (65.1)	11 (55.0)	222 (65.7)	0.342*
Weight loss	162 (45.3)	6 (30.0)	156 (46.2)	0.173*
Neoadjuvant treatment	15 (4.2)	0 (0.0)	15 (4.4)	1*
Tumor location				0.608*
Upper third	58 (16.2)	3 (15.0)	55 (16.3)	
Middle third	200 (55.9)	13 (65.0)	187 (55.3)	
Lower third	92 (25.7)	4 (20.0)	88 (26.0)	
Pangastric	8 (2.2)	0 (0.0)	8 (2.4)	

Data are shown as mean±standard deviation or number (%).
POPF = postoperative pancreatic fistula; HCV = hepatitis C virus; HBV = hepatitis B virus.
*Fisher's exact test (2-tailed); †Mann-Whitney U test (2-tailed).

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Table 2. Operative data of 358 patients who underwent D1+/D2 radical gastrectomy

Parameter	All patients (358 patients)	POPF (20 patients)	No POPF (338 patients)	P-value
Type of gastrectomy				0.775*
Total gastrectomy	286 (79.9)	17 (85.0)	269 (79.6)	
Distal gastrectomy	71 (19.8)	3 (15.0)	68 (20.1)	
Proximal gastrectomy	1 (0.3)	0 (0.0)	1 (0.3)	
D2 lymph node dissection	243 (67.9)	14 (70.0)	229 (67.8)	1*
Distal pancreatectomy	21 (5.9)	3 (15.0)	18 (5.3)	0.103*
Splenectomy	106 (29.6)	8 (40.0)	98 (29.0)	0.317*
Bursectomy	188 (52.5)	11 (55.0)	177 (52.4)	1*
Associated surgical procedures	57 (15.9)	5 (25.0)	52 (15.4)	0.339*
Type of esophago/gastrojejunal anastomosis				1*
Hand-sewn	259 (72.3)	15 (75.0)	244 (72.2)	
Stapled	99 (27.7)	5 (25.0)	94 (27.8)	
Minimally invasive approach	30 (8.4)	1 (5.0)	29 (8.6)	1*
Operative time (min)	196±52.3	214±44.3	195±52.6	**0.041**†‡
Estimated blood loss (mL)	349±168.6	413±184.9	346±167.1	0.118†

Data are shown as mean±standard deviation or number (%).
POPF = postoperative pancreatic fistula.
*Fisher's exact test (2-tailed); †Mann-Whitney U test (2-tailed); ‡Statistically significant.

Table 3. Pathological data of 358 patients who underwent D1+/D2 radical gastrectomy

Parameter	All patients (358 patients)	POPF (20 patients)	No POPF (338 patients)	P-value
Macroscopic type				0.484*
Mass (type 1)	39 (10.9)	1 (5.0)	38 (11.2)	
Ulcerative (type 2)	118 (33.0)	9 (45.0)	109 (32.2)	
Infiltrative-ulcerative (type 3)	171 (47.8)	9 (45.0)	162 (47.9)	
Diffuse-infiltrative (type 4)	27 (7.5)	0 (0.0)	27 (8.0)	
NA	2 (0.8)	1 (5.0)	1 (0.7)	
Tumor diameter (cm)	5.6±3.2	6.3±4.5	5.6±3.1	0.649†
Adenocarcinoma	311 (86.9)	18 (90.0)	293 (86.7)	1*
Lymphoma	28 (7.8)	1 (5.0)	27 (8.0)	1*
Grade of differentiation				1*
G1	85 (23.7)	4 (20.0)	81 (24.0)	
G2	95 (26.5)	8 (40.0)	87 (25.7)	
G3	124 (34.6)	4 (20.0)	120 (35.5)	
NA	54 (15.2)	4 (20.0)	50 (14.8)	
T stage				1*
T1	20 (5.6)	1 (5.0)	19 (5.6)	
T2	70 (19.6)	4 (20.0)	66 (19.5)	
T3	162 (45.3)	7 (35.0)	155 (45.9)	
T4	82 (22.9)	6 (30.0)	76 (22.5)	
NA	24 (6.6)	2 (10.0)	22 (6.5)	
Positive lymph nodes	224 (62.6)	15 (75.0)	209 (61.8)	0.337*
No. of harvested lymph nodes	25±12	24.6±12	25.2±12	0.967†
TNM stage				0.090*
Stage IA	16 (4.5)	1 (5.0)	15 (4.4)	
Stage IB	41 (11.5)	2 (10.0)	39 (11.5)	
Stage IIA	65 (18.2)	1 (5.0)	64 (18.9)	
Stage IIB	59 (16.5)	2 (10.0)	57 (16.9)	
Stage IIIA	54 (15.1)	5 (25.0)	49 (14.5)	
Stage IIIB	59 (16.5)	2 (10.0)	57 (16.9)	
Stage IIIC	38 (10.6)	5 (25.0)	33 (9.8)	
Stage IV	5 (1.4)	0 (0.0)	5 (1.5)	
NA	21 (5.7)	2 (10.0)	19 (5.6)	
Negative resection margins	317 (88.5)	16 (80.0)	301 (89.0)	0.266*

Data are shown as mean±standard deviation or number (%).
POPF = postoperative pancreatic fistula, NA = not applicable.
*Fisher's exact test (2-tailed); †Mann-Whitney U test (2-tailed).

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Table 4. Postoperative data of 358 patients who underwent D1+/D2 radical gastrectomy

Parameter	All patients (358 patients)	POPF (20 patients)	No POPF (338 patients)	P-value
Postoperative hemorrhage	17 (4.7)	3 (15.0)	14 (4.1)	0.061*
Postoperative hemorrhage requiring re-laparotomy	13 (3.6)	3 (15.0)	10 (3.0)	**0.029***‡
Eso-jejunal/gastro-jejunal leak	19 (5.3)	6 (30.0)	13 (3.8)	**0.002***‡
Eso-jejunal/gastro-jejunal leak requiring re-laparotomy	4 (1.1)	0 (0.0)	4 (1.2)	1*
Chyle leak	14 (3.9)	0 (0.0)	14 (4.1)	1*
Severe complications (Dindo-Clavien grades 3–4)	22 (6.1)	3 (15.0)	19 (5.6)	0.115*
Re-laparotomy for complications	19 (5.3)	3 (15.0)	16 (4.7)	0.081*
90-day mortality	14 (3.9)	3 (15.0)	11 (3.3)	**0.036***‡
Hospital stay (days)	13±7.5	22±10.8	12±6.9	**<0.001**†‡
Adjuvant treatment	132 (36.9)	6 (30.0)	126 (37.3)	0.636*

Data are shown as mean±standard deviation or number (%).
POPF = postoperative pancreatic fistula.
*Fisher's exact test (2-tailed); †Mann-Whitney U test (2-tailed); ‡Statistically significant.

Postoperative data

The ISGPS definition and grading system were used for POPF [49]. The severity of complications was assessed using the Dindo-Clavien classification [52]. Postoperative mortality was corresponded to the 90-day mortality rate. The postoperative data of the patients are presented in **Table 4**.

Statistical analyses

Categorical variables are expressed as a number (percentage), while continuous variables are expressed as the mean±standard deviation. Overall survival (OS) time is expressed as the median (range). Fisher's exact test (2-tailed) and the Mann-Whitney U test (2-tailed) were used to compare categorical and continuous variables, respectively. Potential predictors for the formation of a POPF were tested in univariate analyses. Risk factors with a P-value <0.1 were included in a multivariate binary logistic regression model with a forward stepwise method.

The median OS time was estimated using the Kaplan-Meier actuarial survival curves, and the results were compared using the log-rank test. The OS time was defined as the time from surgical resection to either death or the last follow-up which took place on March 1, 2019.

A P-value <0.05 was considered statistically significant. Statistical analyses were performed using the Statistical Packages for Social Sciences (SPSS) version 20.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

According to the updated definition and grading system for POPF set out by the ISGPS [49], a clinically relevant (grades B–C) POPF was observed in 20 patients (5.6%) of the present cohort.

Assessment of potential predictors of POPF formation after D1+/D2 radical gastrectomy

Several preoperative, intraoperative, and pathological factors were analyzed as potential predictors of POPF formation (**Tables 1-3**). Increased operative time was the only statistically significant risk factor for POPF formation after D1+/D2 radical gastrectomy (P=0.041) that was identified through the univariate analyses performed, as shown in **Table 2**.

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Table 5. Multivariate analysis of potential predictors of postoperative pancreatic fistula formation in 358 patients who underwent D1+/D2 radical gastrectomy

Risk factor	Risk ratio	95% CI	P-value
Cardiovascular comorbidities	3.051	1.161–8.019	**0.024***
Increased operative time	1.009	1.000–1.017	0.053
TNM stages III–IV	2.491	0.932–6.661	0.069

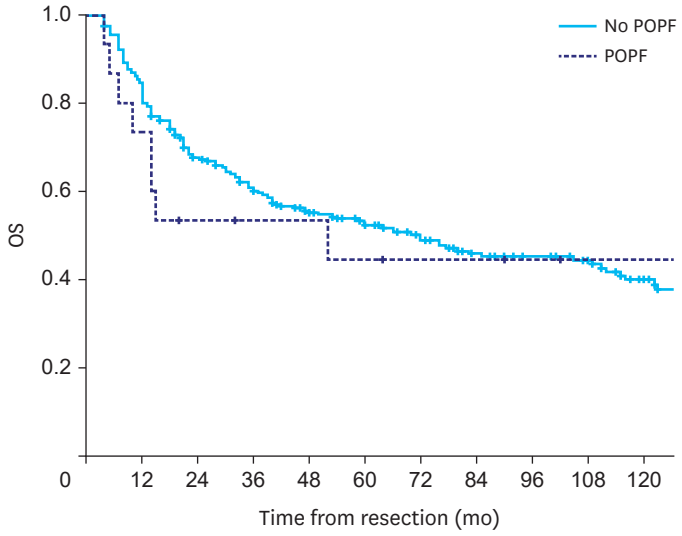
CI = confidence interval.
*Statistically significant.

The multivariate analysis included operative time (P=0.041), cardiovascular comorbidities (P=0.054) and TNM staging (P=0.090). Cardiovascular comorbidities were identified as an independent risk factor for POPF formation after D1+/D2 gastrectomy, as shown in **Table 5**.

Clinical consequences of POPF formation after D1+/D2 radical gastrectomy

The impact of POPF formation on early postoperative complications, including 90-day mortality, completion of adjuvant therapy, and long-term survival, was also explored (**Table 4** and **Fig. 1**). We found that POPF formation after D1+/D2 radical gastrectomy was associated with statistically significant increased rates of postoperative hemorrhage requiring re-laparotomy (P=0.029), esophago/gastrojejunal anastomotic leak (P=0.002), 90-day mortality (P=0.036), and hospital stay (P<0.001), as shown in **Table 4**.

Survival was calculated only for patients with pathologically confirmed gastric adenocarcinoma. Patients with a type of gastric tumor other than gastric adenocarcinoma (47 patients), those who passed away within 90 days postoperatively (14 patients), and those lost to follow-up (8 patients) were excluded. As shown in **Fig. 1**, the median OS for patients who underwent D1+/D2 radical gastrectomy for gastric adenocarcinoma was 70 months (3–201 months), with no significant difference between the patients with a POPF and those without one: 52 months (4–173 months) versus 72 months (3–201 months) (P=0.661).



No. of patients at risk				
No POPF	274	229	102	39
POPF	15	11	5	4

Fig. 1. The Kaplan-Meier actuarial OS curves for patients who underwent D1+/D2 radical gastrectomy for gastric adenocarcinoma with and without POPF.
POPF = postoperative pancreatic fistula, OS = overall survival.

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The 1-year, 5-year, and 10-year survival rates were 85%, 54%, and 40%, respectively, for the entire group of patients who had undergone D1+/D2 radical gastrectomy for gastric adenocarcinoma. The 1-year, 5-year, and 10-year survival rates were 73%, 45%, and 45%, respectively, for patients with a POPF and 85%, 53%, and 38%, respectively, for patients without a POPF.

DISCUSSION

Recent studies have shown that D1+/D2 radical gastrectomy may result in morbidity and mortality rates of 14.2%–41% and 0%–8.6%, respectively [6,8,15,18,20,21,34,37,40,44,51,53-57].

Previous studies of patients who underwent D1+/D2 radical gastrectomy have found the incidence of POPF to be largely variable, ranging between 0 and 55.8%. This variation could be attributed to the different definitions used for POPF [6,8,15,16,20,21,25,26,28-30,32,34,35,37-41,44,48,53,58,59]. The introduction of the ISGPS definition and grading system for POPF in 2005 has played an important role in surgical audit and comparison of the different experiences of surgical centers worldwide [60]. The updated ISGPS grading system introduced in 2016 has allowed a better evaluation of POPF, with important clinical implications [49].

The current study is the most significant Western study investigating the incidence, risk factors, and clinical consequences of POPF defined using the ISGPS criteria, after D1+/D2 radical gastrectomy, with all surgeries being performed by surgeons with high caseloads.

One might associate the occurrence of POPF after D1+/D2 radical gastrectomy with close dissection and potential injury to the pancreas. POPF may be caused by thermal, direct manipulative and vascular injury during lymph node dissection; bursectomy; freeing of the duodenum from the pancreas; and inadvertent closure of the duodenum [25]. Pancreatic safety during D1+/D2 radical gastrectomy has previously been demonstrated in Eastern Asian [15], and in Western European patients [35]. In this study, we have replicated those findings in Eastern European patients.

Dissection of the peritoneal sheet overlying the anterior surface of the pancreas during bursectomy may cause parenchymal damage to the pancreas, which may lead to the formation of a POPF. In the present study, bursectomy did not emerge as a risk factor for POPF formation. This finding has been replicated by previous studies [27,35]. Nonetheless, some authors have found an association between bursectomy and increased rates of POPF [33,44,61].

Similar to previous studies, this study has found that the number of harvested lymph nodes did not influence the rate of POPF formation [28,41,45,48]. However, an increased number of retrieved lymph nodes has been identified as an independent risk factor for POPF formation after D1+/D2 radical gastrectomy, in one study [39].

The present study has identified cardiovascular comorbidities as the single independent predictor of POPF occurrence after D1+/D2 radical gastrectomy. This might be explained in part by ischemia of the pancreas which may result from cardiovascular disease. Thus, vascular degenerative changes including arteriosclerosis of the microvessels in the pancreas

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are likely to lead to the formation and exacerbation of POPF, particularly in the context of vascular injuries that may cause some degree of compromise of the local blood supply [36]. Moreover, prolonged vasospasm and local inflammatory responses may also contribute to compromised local blood supply [25,35,58]. No influence of cardiovascular comorbidities on POPF occurrence has been reported by previous studies [37,47]. However, cardiovascular comorbidities have been previously correlated with increased overall morbidity rates after D2 radical gastrectomy [54]. Overall comorbidities have also been identified as an independent risk factor for POPF formation in one study [36] but not in others [28,33,45,46,48].

While age might be considered as a risk factor for POPF formation [26,30,35,36,39], most studies have failed to show any correlation between age and POPF formation [28,31,33-35,37,38,40-42,44-48]. The latter finding has been replicated in our study.

The analyses performed in this study did not reveal any association between male sex and increased rates of POPF. This finding is supported by a few studies [28-30,36-38,40,47], and refuted by others [8,26,31,33-35,39,41,42,44-46,48].

Neoadjuvant chemotherapy has not been identified as an independent risk factor for POPF formation in our study. While this finding has been replicated in one study [33], it has been disproven by others [35,40,41].

Visceral fat area [41-43] and body mass index [8,28-31,36,39,40,42,43] have been previously associated with a high risk of POPF formation. However, a few studies have not shown any correlation between body mass index and POPF formation [34,35,37-39,41,44-48].

Tumor location was not found to influence the rate of POPF formation in the present study, as confirmed by previous studies [26,28,45].

Although total gastrectomy has been previously associated with increased rates of POPF [8,29,46,48], we did not find any correlation between total gastrectomy and the rate of POPF formation. Our finding is supported by other studies [26,31,33,35,37,41,47].

Increased rates of POPF have been linked to distal pancreatectomy [8,35,40,48] and splenectomy [8,29,35,40,43,44,46,48]. Furthermore, a recent meta-analysis found an association between splenectomy during radical gastrectomy and increased rates of POPF [62]. We did not find any difference in POPF rates between patients who had undergone a distal pancreatectomy or splenectomy and those who had not. A previous study has shown no increase in the rate of POPF formation with splenectomy [41].

Associated procedures were not found to have an impact on POPF formation after D1+/D2 radical gastrectomy in the present study, in accordance with previously published data [37].

Our study did not reveal any difference in POPF formation between patients who underwent D1+ and D2 lymphadenectomies, as shown by previous studies [8,28,39,41,42,44-46]. However, a few studies have demonstrated a higher rate of POPF formation with D2 gastrectomy than with D1+ gastrectomy [30,40,48].

A higher incidence of POPF was observed after laparoscopic radical gastrectomy than after open radical gastrectomy in a recent Japanese nationwide study [6]. Similarly, a recent meta-

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analysis has found an association between minimally invasive gastrectomy and an increased risk of POPF [25]. Nonetheless, some studies did not identify any significant difference in the rates of POPF formation between gastrectomies performed using open and minimally invasive approaches [29,41,44,46,53,59,63], as was the case in the present study. Modified techniques of laparoscopic gastrectomy such as pancreas-compressionless gastrectomy [64] and robotic gastrectomy [65] have been suggested to mitigate pancreatic complications. A recent meta-analysis has shown no significant difference in the formation of clinically relevant POPF after laparoscopic and robotic radical gastrectomy [25]. It is also worth mentioning that 2 studies have found an increased risk of POPF formation with the open surgical approach [8,48].

Similar to previous studies, we found that longer operative times were associated with increased rates of POPF in univariate analyses [28,29,31,39,40,44,48]. A longer operative time may reflect a more difficult operation that involves technically challenging lymph node dissection, bursectomy, or freeing of the duodenum. In the presence of local fibrosis and/or inflammation when the border between fat and the pancreas might be unclear, the risk of vascular injuries and pancreatic trauma might be higher during the abovementioned maneuvers [33]. The technical difficulty and the high risk of injury might explain the fact that a longer operative time increases the risk of POPF [39]. A few studies have not shown any association between the operative time and POPF formation [33,35-38,42,45,47].

Blood loss did not influence POPF formation in this study. This finding is supported by other studies [28,31,35,36,38,39,42,45,47]. However, increased blood loss has previously been associated with higher rates of POPF [8,29,33,37,40,43,48].

Several pathological parameters were investigated as potential risk factors for POPF in the present study. As has been previously reported, we found that neither T staging [28,31,33,35,37,38,40,41,44,45,47] nor N staging [15,28,31,35,37,38,40,44,45,47] of the tumor affected the rate of POPF formation. However, increased rates of POPF have been associated with an advanced T stage in 2 studies [30,48] and with positive lymph nodes in one study [48]. Nevertheless, similar to previous studies [8,30,35], no correlation between resection margins and POPF was found in the present study.

In this study, POPF occurrence was associated with statistically significant increased rates of postoperative bleeding requiring re-laparotomy (P=0.029), anastomotic leak (P=0.002), 90-day mortality (P=0.036) and prolonged hospital stay (P<0.001). It is widely accepted that a POPF can lead to other serious complications such as bleeding, intra-abdominal sepsis, and anastomotic leak, which are all associated with prolonged hospital stays [16,17,49,64] and increased mortality rates [66,67]. Enzymatic, local septic vascular, or visceral erosions in the setting of POPF formation might explain the increased rates of late hemorrhage and anastomotic leak. Furthermore, pseudoaneurysms and other vascular irregularities that may arise as complications of POPF might lead to disastrous bleeding [67]. The association of POPF with increased morbidity [48] and an extended hospital stay has been previously observed [28,40,45,47,48]. On the other hand, one study has identified no such correlation [39]. POPF has also been linked to increased mortality [30,40] and re-operation rates [30]. We did not find any difference in the re-laparotomy rates between the patients with and without POPF. This finding is supported by previous research [28]. No association has been identified between POPF and increased rates of postoperative bleeding or anastomotic leak [28,39].

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The present study has demonstrated that POPF occurrence does not affect long-term survival after D1+/D2 radical gastrectomy for gastric adenocarcinoma. While some studies have shown no effect of postoperative complications on long-term survival after curative resection of GC [68], others have shown their detrimental effect on long-term outcomes [55,69]. Postoperative complications may potentially induce a prolonged inflammatory state in immunosuppressed hosts, which may lead to the proliferation of micrometastatic tumor cells. This, in turn, can cause disease recurrence and poorer long-term survival [55,69]. Increased and prolonged inflammatory states have been demonstrated in patients who developed postoperative complications after gastrectomy [69].

The limitations of the present study include its retrospective design and the relatively small number of patients in several subgroup analyses such as for neoadjuvant therapy and minimally invasive surgical approach.

In conclusion, in this large series of Eastern European patients, clinically relevant POPF rates after D1+/D2 radical gastrectomy were low. Cardiovascular comorbidities were found to be an independent risk factor for POPF formation. POPF was associated with an increased risk of postoperative bleeding requiring re-laparotomy, anastomotic leak, 90-day mortality, and prolonged hospital stay. Lastly, POPF had no impact on the long-term survival of patients with gastric adenocarcinoma.

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