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Original Article

The role of the albumin/globulin ratio on predicting post-operative pancreatic fistula in pancreaticoduodenectomy patients

Pankreatikoduodenektomili hastalarda albümin/globulin oranının postoperatif pankreas fistülünü öngörmedeki rolü

Ahmet Burak Ciftci*, Kursat Yemez, Huseyin Eraslan

General Surgery Department, Samsun University, Faculty of Medicine, Samsun Training and Research Hospital, Samsun, Turkey.

Abstract

Aim: The albumin/globulin ratio (AGR) is one of several indicators of inflammation and immunity. This ratio has a prognostic significance in many malignant diseases. Previous studies have demonstrated a relationship between inflammatory mediators and post-operative pancreatic fistula (POPF). This study aimed to evaluate the relationship of AGR, a relatively new indicator, with post-operative pancreatic fistula (POPF).

Materials and Methods: Pancreaticoduodenectomy (PD) patients between 2017 and 2020 were retrospectively analyzed and divided into two groups: (1) with and (2) without clinically relevant POPF (CR-POPF). The two groups were compared in terms of pre-operative–post-operative AGR and clinicodemographic characteristics. AGR was calculated as albumin/total protein–albumin, and the cutoff point for AGR was determined according to Youden's index.

Results: CR-POPF developed in 21% of 121 patients who underwent PD. No differences between the groups in terms of age, gender, comorbid disease status, pancreatic duct width, and anastomosis technique were found. Pre- and post-operative day-3 (POD3) albumin levels and AGR were found to be significantly lower in the CR-POPF group. Multivariate analysis showed that AGR and pancreatic tissue stiffness are independent risk factors for POPF development.

Conclusion: Low AGR is an independent risk factor for the development of CR-POPF. To reduce the incidence of POPF, this ratio should be maintained at an optimal level. The use of AGR as a useful tool for predicting POPF in pancreaticoduodenectomy patients is suggested.

Keywords: Albumin, albumin/globulin ratio, postoperative pancreatic fistula, pancreaticoduodenectomy

Corresponding Author*: Ahmet Burak Ciftci, Department of General Surgery, Samsun Training and Research Hospital, Baris Bulvari, No:199 İlkadım, Samsun, Turkey
E-mail: ciftci.burak@yahoo.com
ORCİD: 0000 0002 1814 4008
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Öz

Amaç: Albümin/globulin oranı (AGR), inflamasyon ve bağışıklığın göstergelerinden biridir. Bu oran birçok malign hastalıkta da prognostik öneme sahiptir. Önceki çalışmalar, inflamatuar aracılar ile postoperatif pankreas fistülü (POPF) arasında bir ilişki olduğunu göstermiştir. Bu çalışmada, nispeten yeni bir gösterge olan AGR'nin postoperatif pankreas fistülü (POPF) ile ilişkisinin değerlendirilmesi amaçlandı.

Gereç ve Yöntem: 2017 ve 2020 yılları arasında pankreatikoduodenektomi (PD) hastaları geriye dönük olarak analiz edildi ve iki gruba ayrıldı: (1) klinik olarak anlamlı POPF'si (CR-POPF) olan ve olmayan (2). İki grup ameliyat öncesi ve sonrası AGR ve klinik, demografik özellikler açısından karşılaştırıldı. AGR, albümin/ (toplam protein-albümin) olarak hesaplandı ve AGR için kesim noktası Youden indeksine göre belirlendi.

Bulgular: PD uygulanan 121 hastanın %21'inde CR-POPF gelişti. Gruplar arasında yaş, cinsiyet, ek hastalık durumu, pankreas kanalı genişliği ve anastomoz tekniği açısından fark bulunmadı. Ameliyat öncesi ve sonrası 3. gün (POD3) albümin seviyeleri ve AGR, CR-POPF grubunda anlamlı derecede düşük bulundu. Çok değişkenli analiz, AGR ve pankreas dokusu sertliğinin POPF gelişimi için bağımsız risk faktörleri olduğunu gösterdi.

Sonuç: Düşük AGR, CR-POPF gelişimi için bağımsız bir risk faktörüdür. POPF insidansını azaltmak için bu oran optimal seviyede tutulmalıdır. AGR'nin pankreatikoduodenektomi hastalarında POPF'yi öngörmede yararlı bir araç olarak kullanılması önerilmektedir.

Anahtar Kelimeler: Albümin, albümin/globulin oranı, postoperatif pankreas fistülü, pankreatikoduodenektomi

Introduction

Pancreaticoduodenectomy (PD) is a complicated, high-risk surgical approach that is the only curative treatment in periampullary region tumors (pancreatic head, duodenum, distal bile duct, or ampulla origin carcinomas). It may also be indicated for chronic pancreatitis, pancreatic cysts, and complex pancreaticoduodenal injuries1. Although the first successful PD was performed by Kausch in 1912, it was popularized by Whipple in 1935 and thereafter was also called by his name2.

Postoperative pancreatic fistula (POPF) is a common and worrisome complication that can develop after PD and other pancreatic surgeries. It can be associated with morbidities such as delayed gastric emptying, postoperative bleeding, intra-abdominal infection, increased hospital stays and costs, and even mortality3. Despite advances in surgical technique and technology, POPF remains a problem for surgeons. Even in high-volume centers, 10-30% morbidity and 3% -45% pancreatic fistula rates are reported after PD4,5.

Many studies have been conducted to predict POPF, and many risk scores have been developed6–9. The most widely known and used score system is a 10-point fistula risk score (FRS), which consists of 4 parameters (gland texture, pathology, pancreatic duct diameter, and intraoperative blood loss) designed by Callery et al6. However, due to its' difficulties in clinical use, Mungroop et al7. developed an alternative fistula risk score (a-FRS) with 3 parameters; consisting of pancreatic tissue, pancreatic duct diameter and body mass index (BMI). Additionally, in 2019, You et al8. created a nomogram consisting of 6 variables (sex, body mass index, ASA score, preoperative albumin, pancreatic duct diameter, and location of tumor) to predict POPF, and web-based calculation was so enabled.

Albumin and globulin, the two main components of serum proteins, have an important role in immunity and inflammation systems and are important determinants of the prognosis of diseases. Serum albumin is a negative acute phase reactant and is also closely related to nutritional status10. Previous studies have demonstrated that low albumin levels showed poor prognosis in various cancers such as stomach, colorectal, pancreatic, and esophageal cancer11–13. Also, prior studies showed that preoperative hypoalbuminemia increases the infectious complications and intraabdominal abscesses in PD patients14. However, both serum albumin and globulin levels alone are simply affected by dehydration and edema, which may debilitate its effectiveness and correctness in predicting the prognosis of cancer patients. To defeat this defect, many recent studies have attempted to investigate the prognostic significance of the albumin/globulin ratio (AGR) in cancer patients. Many studies have shown that AGR, like albumin levels, has a prognostic factor in several cancers including gastric, colorectal, breast, ovarian, and nasopharyngeal cancers15,16. On the other hand, in the only study of the literature investigating the significance of AGR

on perioperative and long-term outcomes of patients who underwent PD, Shinde et al17. found no adverse effects on perioperative and oncological outcomes at the cut off value of ≥1. This finding was inconsistent with other studies in the literature, and each study used different cut-off values. Therefore, with this study, we aimed to identify the possible effect of AGR on pancreatic fistula after PDs.

Materials and Methods

This study was conducted at the Samsun University, Samsun Training and Research Hospital after the approval of the ethical committee of our institution (protocol number: GOKA/2020/12/8, date: 20.08.2020).

Patients who underwent pancreaticoduodenectomy for any reason between 2017 and 2020 at our general surgery department were analyzed retrospectively. Patients with a missing data and who underwent emergency pancreaticoduodenectomy were excluded from the study.

By reviewing the hospital computer records and patient files, demographic characteristics (age and gender), accompanying comorbid diseases (diabetes mellitus-DM and hypertension-HT), laboratory data; preoperative and postoperative day 3 (POD3) blood tests (glucose, albumin, total protein, globulin, amylase, prealbumin, C reactive protein-CRP, and AGR), drain amylase levels on POD3, length of hospital stay, postoperative pathology findings (tumor origin and benign/malign character) and in-hospital mortality status were recorded. According to the pre-operative contrast-enhanced abdominal tomography findings, the pancreatic duct diameter was recorded as <3mm and >3mm. Pancreatic tissue stiffness was classified as hard and soft owing to intraoperative palpation. The technique of the anastomosis of the pancreatic stump used in the surgery was categorized as follows; ductomucosal (Cattel Warren anastomosis), invagination (conventional invaginated end to side anastomosis), and Blumgart technique (duct-to-mucosal Blumgart modification)18.

POPF was diagnosed and graded under the 2016 update of the International Study Group Pancreatic Surgeons' (ISGPS) definition and grading system5. In predicting the diagnosis of pancreatic fistula, the amylase levels in the drainage fluid were taken as the basis. When the drain amylase level is more than 3 times the upper limit of our hospital's serum amylase level, and no clinical signs, it is considered as a biochemical leak (formerly grade A). Grade B refers to the conditions in which the treatment lasts for over 3 weeks with the biochemical leak stated in grade A and there is a significant change in the management of pancreatic fistula (e.g., Percutaneous/endoscopic drainage). We used grade C for signs of organ failure or mortality besides all these conditions. In the current study, we regarded grade B or C as clinically relevant pancreatic fistula (CR-POPF). Patients were divided into two cohorts: POPF (-) and grade A fistula as group 1 and CR-POPF group (grade B and C) as group 2.

The AGR was calculated as dividing the albumin levels by total protein minus albumin. The cut-off value for AGR was defined as 1.15076 according to the receiver operating characteristic (ROC) curve analysis.

Statistical Analysis

Statistical analysis was performed using the Statistical Product and Service Solutions, version 22 (SPSS Inc., Chicago, IL, USA). Data were presented as mean ± standard deviation or median [Inter Quantile Range (minimum-maximum)] values and as frequencies with percentages where appropriate. According to Shapiro-Wilk test of normality, Student's t test was used when normal distribution was achieved, and Mann-Whitney U test was used when it was not. The chi-square and/or Fisher's exact test was used to compare groups among the categories of variables. In order to define risk factors of outcome variable (POPF) multiple logistic regression analysis and adjusted odds ratios with their confidence intervals were calculated. The diagnostic power of AGR was evaluated by ROC analysis and after observing the significant area under the curve (AUC), the cutoff point was determined according to the Youden's index. A p value of less than 0.05 was considered statistically significant for all statistical process.

Results

121 out of a total 133 patients who underwent pancreaticoduodenectomy (PD) were included in the study. 7 patients were excluded from the study because of emergency PD, and 5 patients due to missing data. The figure 1 shows the flowchart of the study. There was 78 male and 43 female patients (gender ratio:1.8/1). The median age (range) of the study group was 65 years (23-87 years) and the rate of CR-POPF was 21.5%. Nine patients were considered as a biochemical leak (formerly grade A) and recovered without additional intervention. 22.3% of the cases were patients with preoperative diabetes mellitus (DM) (n= 27) and 36.4% patients with hypertension (HT) (n= 44). 94.2% of the cases were elective in setting and the majority of pancreatic anastomoses (47.9%) were of the ductomucosal type. Malignant pathologies were detected in 86.8% of the patients and pancreatic head carcinomas were the first among them (54.5%). 83 patients (68.6%) had hard and 38 patients (31.4%) had soft pancreatic parenchyma. The median length of hospital stay in the total study group was 12 days ranging from 3 to 51 days. The overall 30-day mortality rate was 4.1% in the study group. General descriptive statistics of PD patients are depicted in Table 1 and Table 2.

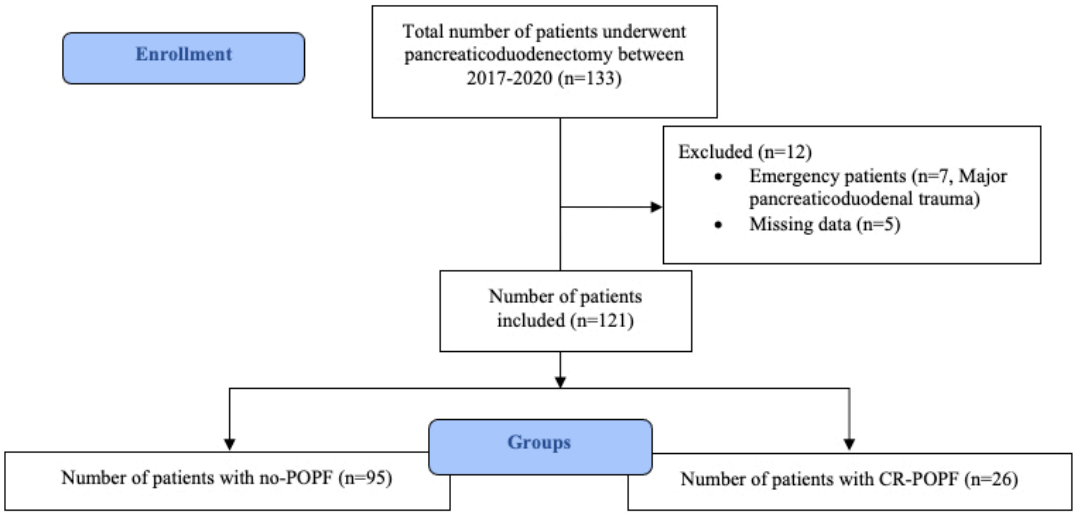

Fig. 1. Study flow diagram.

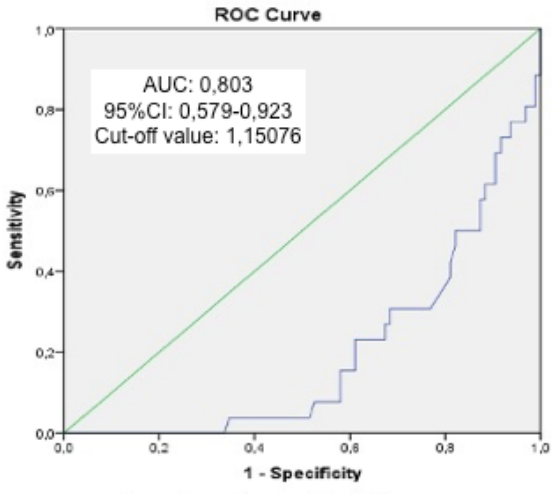

Fig. 2. Receiver operating characteristic curves for cut-off values of AGR (AUC: 0.803).

Risk Factors for POPF

The comparison of possible risk factors as continuous variables for the development of CR-POPF (POPF Grade B/C) is presented in table 3. No significant relationship was seen between CR-POPF and the following factors: age, pre-op and POD3 fasting blood glucose, serum amylase levels, total protein levels, POD3 prealbumin, CRP, and procalcitonin levels. Pre-op albumin and AGR, as well as post-op albumin and AGR, were significantly lower in CR-POPF group (P=0,004, P<0,001, P<0,001, and p<0,001 respectively). Drain amylase level on POD3 and LOHS was significantly higher in the CR-POPF group.

Table 1. General descriptive statistics of PD patients

		n-%
Gender	Female	43-35.5
	Male	78-64.5
CR-POPF	Negative	95-78.5
	Positive	26-21.5
Fistula Grade	A	9-25.7
	B	14-40
	C	12-34.3
Preoperative blood glucose (mg/dl)	<110	48-39.7
	≥110	73-60.3
DM	Negative	94-77.7
	Positive	27-22.3
HT	Negative	77-63.6
	Positive	44-36.4
Mortality	Negative	116-95.9
	Positive	5-%4.1
Pancreatic duct size	<3 mm	21-17.4
	≥3 mm	100-82.6
Pancreatic tissue	Soft	38-31.4
	Hard	83-68.6
Pancreatic anastomosis	Ductomucosal	58-47.9
	Invaginasyon	20-16.5
	Blumgart	43-35.5
Pathology	Ampulla of Vater	27-22.3
	Duodenum	8-6.6
	Distal choledochus	4-3.3
	Pancreas	66-54.5
	Trauma/Pancreatitis	16-13.2
Benign/Malign	Benign	16-13.2
	Malign	105-86.8

PD: pancreaticoduodenectomy, CR-POPF: clinically relevant postoperative pancreatic fistula, DM: diabetes mellitus, HT: hypertension.

Table 2. General descriptive statistics of PD patients continued, laboratory results	
	median[IQR], (min-max)
Age (years)	65[54-75], (23-87)
Pre-op albumin (gr/dl)	3.1[2.6-3.7]
Pre-op AGR	1.1[0.97-1.30]
Post-op albumin (gr/dl), POD3	2.4[2.1-2.7]
Post-op AGR, POD3	1.0[0.91-1.14]
Length of hospital stay (days)	12[8-18], (3-51)
AGR: albumin-globulin ratio, POD3: post-op day3.	

The comparison of possible categoric risk factors for development for CR-POPF is presented in table 4. Univariate analysis showed no significant relationship between CR-POPF and the following factors: gender, pre-op blood glucose, the presence of DM or HT, main pancreatic duct (MPD) size, and pancreatic anastomosis type. Pancreatic tissue was found to be hard with an 85.5 ratio in no POPF group, whereas in the CR-POPF group it was 14.5%. So, there was a significant difference in terms of pancreatic tissue stiffness between the groups (p=0,005). The pathologic origins, the ratio of benign/malign pathologies, and the ratio of emergent/elective operations were similar between the groups (p=0,825, p=0,746, and p=0,169 respectively).

Table 3. Continuous variables associated with the presence of POPF			
	no POPF/ Grade A n=95	POPF (Grade B/C) n=26	p-value
Age (years)	66[54-76]	62[52-70]	0,115
LOHS (days)	11[8-14]	21[16-28]	<0,001
Pre-op laboratory			
Fasting blood glucose (mg/dl)	124[99-158]	131[97-147]	0,882
Serum amylase (IU/L)	52[28-93]	39[25-120]	0,534
Total protein (g/dl)	5.95±1.11	5.71±1.02	0,316*
Albumin (g/dl)	3.2[2.7-3.9]	2.75[2.4-3.2]	0,004
Globulin(g/dl)	2.6[2.3-3.0]	2.9[2.7-3.4]	0,017
AGR	1.2[1.03-1.35]	0.95[0.89-1.06]	<0,001
Post-op laboratory (POD3)			
Fasting blood glucose (mg/dl)	177[141-235]	184[148-230]	0,399
Drain amylase (IU/L)	24[14-77]	2468[232-14553]	<0,001
Total protein (g/dl)	4.83±0.96	4.64±0.62	0,427*
Albumin (g/dl)	2.5[2.1-2.8]	2.1[1.9-2.4]	<0,001
Globulin (g/dl)	2.3[2.0-2.6]	2.5[2.3-2.7]	0,032
AGR	1.04[0.95-1.19]	0.85[0.78-0.94]	<0,001
Prealbumin	6.9[4.8-8.5]	6.3[2.4-8.4]	0,458
CRP (mg/dl)	61.01±90.63	64.35±98.53	0,119*
Procalcitonin	2.86[0.46-7.5]	3.21[1.09-4.45]	0,891
*Student's t test, all others Mann Whitney U test. Values are presented as median[interquartile range, IQR] and mean±Standard deviation (SD). LOHS: length of hospital stay; POPF: postoperative pancreatic fistula; AGR: albumin globulin ratio; POD3: post-op day3; CRP: C reactive protein. Bold values show significance.			

The albumin-globulin ratio was examined in terms of its diagnostic power on the presence of POPF with receiver operating characteristics (ROC) curve analysis and the area under the curve (AUC) was found to be significant (AUC: 0.803, p <0.001). And according to the Youden index, the value of 1.15076 corresponding to 0.923 specificity and 0.579 sensitivity point was determined as a cut-off point (Fig 2). Accordingly, the risk of developing POPF increased for the albumin globulin ratio values of 1.15076 and below.

The albumin-globulin ratio and pancreas tissue stiffness, which affect the presence of POPF, were evaluated by multiple logistic regression analysis. Accordingly, albumin-globulin ratio less than 1.15076 value and absence of pancreatic tissue stiffness (soft pancreas) are found to be independent risk factors for POPF (OR=20.51; 95% confidence interval; 3.538-118.94; p=0.001 and OR=7.209; 95% confidence interval; 2.126-24.439; p=0.002 respectively) (Table 5).

Table 4. Categoric variables affecting the presence of POPF			
[n-%]	No-POPF/ Grade A n=95	POPF (Grade B/C) n=26	p-value
Gender			0,725
Female	33-76.7	10-23.3	
Male	62-79.5	16-20.5	
DM			0,524
No	75-79.8	19-20.2	
Yes	20-74.1	7-25.9	
HT			0,834
No	60-77.9	17-22.1	
Yes	35-79.5	9-20.5	
Main pancreatic duct size			1,000
<3mm	17-81	4-19	
≥3mm	78-78	22-22	
Pancreatic tissue			0,005
Soft	24-63.2	14-36.8	
Hard	71-85.5	12-14.5	
Pancreatic anastomosis			0,969
Ductomucosal (Cattel Warren)	45-77.6	13-22.4	
Invagination	16-80	4-20	
Blumgart	34-79.1	9-20.9	
Pathology			0,825
Ampulla of Vater	23-85.2	4-14.8	
Duodenum	7-87.5	1-12.5	
Distal choledochus	3-75	1-25	
Pancreas	50-75.8	16-24.2	
Pancreatitis	12-75	4-25	
Benign/Malign			0,746
Benign	12-75	4-25	
Malign	83-79	22-21	
Values are presented as numbers-percentages. POPF: postoperative pancreatic fistula; DM: diabetes mellitus; HT: hypertension. Bold values show significance.			

Table 5. Multiple logistic regression analysis

					95% Confidence Interval	
	B	S.Error	p	O.R.	Lower Bound	Upper Bound
Albumin-globulin ratio (<1.15076)	3.021	0.897	0.001	20.51	3.538	118.94
Pancreatic tissue stiffness (-)	1.975	0.623	0.002	7.209	2.126	24.439

Discussion

POPF is one of the main problems that preoccupy surgeons after PD surgeries. Various reasons and risk scores have been proposed in terms of predicting the development of POPF. Although there is no absolute consensus in the literature; body mass index, pancreatic tissue texture, intraoperative bleeding volume, nutritional status, and main pancreatic duct diameter are among the generally accepted risk factors associated with POPF4,6,19. Despite the determination of many risk factors and advances in treatment, even in high-volume centers, the incidence of pancreatic fistula after PD remains high.

In this study, the albumin-globulin ratio was investigated as a new biomarker in predicting the development of CR-POPF. And we found that a low albumin-globulin ratio was associated with a high risk of developing pancreatic fistula. In multiple logistic regression analysis, a low albumin-globulin ratio was found to be an independent risk factor in the diagnosis of POPF. Unlike our study, Shinde et al. found no association between AGR and CR-POPF development17. In their study, patients with a serum albumin < 3gr/dl were not subjected to surgery and cutoff value for AGR was set at 1 (area under curve,0.53). They compared the perioperative outcomes between the groups AGR≥1 and AGR<1. However, in our study, median albumin levels and AGR were compared in patients who developed CR-POPF with those who did not. Also, cutoff point of AGR in our study was 1.15. We think that the differences in the methodology and albumin levels of patients as well as the calculation of different AGR cutoff values may have affected the results between these studies.

In previous studies, there are different arguments between albumin levels and the development of POPF14,20,21. Fujiwara et al. 14 and Gruppo et al. 20 found in their studies that there was no relationship between preoperative albumin levels and postoperative pancreatic fistula development. In these studies, they also emphasized that the albumin levels measured on the first postoperative day were significantly lower in the group with pancreatic fistula. Contrary to these studies, the study of Xu et al. 21 showed that the decrease in albumin levels after pancreaticoduodenectomy did not affect the development of pancreatic fistula. In another study investigating the effects of albumin levels and malnutrition on curative PD patients, the proportions of patients with CR-POPF were not significantly different between the groups (malnutrition vs no-malnutrition)22. In aforementioned study, malnutrition was accepted as serum albumin levels <3.5gr/dl or body mass index (BMI) <18kg/m2.

Also, in the study of Azab et al. 23, which evaluates the predictive value of AGR on survival of breast cancer patients, it is suggested that the AGR is superior to serum albumin level alone. In this paper the reason for this is suggested that albumin levels are easily affected by some physiological and pathological conditions (e.g., dehydration and fluid retention), whereas albumin globulin ratio is not affected by such conditions. In addition, AGR is accepted as a prognostic factor for many cancers in several studies15,16,23. In the light of these, we studied AGR as a predictive factor for POPF.

In our study, no significant relationship was found between age or gender and POPF. While this finding is compatible with some studies in the literature20, some other studies have suggested that advanced age and male gender increase the development of pancreatic fistula24. It was observed that neither diabetes mellitus nor hypertension did not increase POPF in this work.

The mortality rate was 4.1% and the rate of CR-POPF was 21.5% in this study. Similarly the mortality rate after PD is reported to be around 5% in high volume centers today25. Additionally CR-POPF rates after PD are reported to be 19%, 26.7% and 30.8% in different studies20,25,26.

In this study, hard pancreatic tissue was found to be associated with low POPF rates. And this finding was similar to most of the studies in the literature6,19,20,27. However, this feature cannot be used frequently and practically in the clinic because it cannot be determined objectively. It is generally interpreted depending on the surgeon's experience in the operation and therefore its reliability remains limited.

In our study, the malignancy rate was found to be 86.8%, and no significant relationship was found between the presence of malignancy and POPF. This situation supported the studies in the literature28. When evaluating the anastomosis of the pancreatic stump it was observed that the most common type of anastomosis was Cattel Warren ductomucosal in our hospital. And there was no significant difference between anastomosis types and POPF. Many anastomosis

techniques have been described to date. But there is no clear consensus on which anastomosis technique is best after pancreaticoduodenectomies. In many studies, similar to our findings, it has been reported that there is no clear relationship between anastomosis technique and pancreatic fistula29,30.

In previous studies, it was stated that the risk of POPF increases when the diameter of the main pancreatic duct is less than 3mm6. Furthermore, the main pancreatic duct parameter is included in the fistula risk scoring system6. In contrast to these studies in the literature, no significant relationship was found between pancreatic duct diameter and pancreatic fistula in our study. The reason why this result occurred is possibly because, our clinic surgeons are routinely using pancreatic stenting and telescopic anastomosis technique in cases with the narrow pancreatic duct. In addition, we think that the fact that biochemical leakage (formerly Grade A fistula) is not considered as a true pancreatic fistula may contribute to this result.

Our study has some limitations. Firstly, this is a single-center retrospective study. Because the study was retrospective, some patient data that may affect the development of pancreatic fistula (BMI and estimated blood loss) could not be reached, and thus comparisons could not be made in terms of these variables. Since it is single-centered, a broad generalization cannot be made with these results. Secondly, in calculating the albumin globulin ratio, "the total protein minus the albumin" value was taken as the basis for the globulin value. This value may not fully reflect the globulin itself. However, we believe that a valuable result has been obtained as it is evaluated proportionally. Lastly, in this study we investigated the perioperative outcomes, not long-term oncological outcomes.

Conclusions

Strategies to reduce the incidence of POPF remain important in pancreatic surgery. The albumin-globulin ratio is a relatively new, easily applicable and inexpensive marker associated with POPF. Keeping the albumin-globulin ratio in the optimal range may be able to reduce the risk of POPF development. We think AGR might be added to new risk stratification systems that predict the development of POPF in future studies.

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Statement of Ethics

This current study was conducted ethically in accordance with the 1964 Helsinki Declaration and its later amendments. The study protocol was approved by the Institutional Review Board (IRB) of Samsun University, Samsun Education and Research Hospital. IRB protocol approval number is GOKA/2020/12/8. Written informed consent was not required in this study because it was retrospective.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Data analysis, manuscript preparation and critical review: Ahmet Burak Çiftci, Data acquisition, study concept and analysis: Kürşat Yemez, Data acquisition and study design: Hüseyin Eraslan

Data Availability Statement

The datasets generated during the current study are available from the corresponding author on reasonable request.

References

1. Peters JH, Carey LC. Historical review of pancreaticoduodenectomy. Am J Surg 1991; 161: 219–225.
2. Are C, Dhir M, Ravipati L. History of pancreaticoduodenectomy: early misconceptions, initial milestones and the pioneers. HPB 2011; 13: 377–384.
3. Frymerman AS, Schuld J, Ziehen P, et al. Impact of Postoperative Pancreatic Fistula on Surgical Outcome—The Need for a Classification-driven Risk Management. J Gastrointest Surg 2010; 14: 711–718.
4. Vallance AE, Young AL, Macutkiewicz C, et al. Calculating the risk of a pancreatic fistula after a pancreaticoduodenectomy: a systematic review. HPB 2015; 17: 1040–1048.
5. Bassi C, Marchegiani G, Dervenis C, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surgery 2017; 161: 584–591.
6. Callery MP, Pratt WB, Kent TS, et al. A Prospectively Validated Clinical Risk Score Accurately Predicts Pancreatic Fistula after Pancreatoduodenectomy. J Am Coll Surg 2013; 216: 1–14.
7. Mungroop TH, van Rijssen LB, van Klaveren D, et al. Alternative Fistula Risk Score for Pancreatoduodenectomy (a-FRS): Design and International External Validation. Ann Surg 2019; 269: 937–943.

8. You Y, Han IW, Choi DW, et al. Nomogram for predicting postoperative pancreatic fistula. HPB 2019; 21: 1436–1445.
9. Tabchouri N, Bouquot M, Hermand H, et al. A Novel Pancreatic Fistula Risk Score Including Preoperative Radiation Therapy in Pancreatic Cancer Patients. J Gastrointest Surg 2021; 25: 991–1000.
10. Aydin A, Kaçmaz O, Öterkuş M, et al. MPV, RDW, LAKTAT, NA ve Albumin Düzeyleriyle Yoğun Bakım Hasta Mortalitesi Arasındaki İlişki. Dicle Tıp Derg 2022; 168–175.
11. Boonpipattanapong T, Chewatanakornkul S. Preoperative Carcinoembryonic Antigen and Albumin in Predicting Survival in Patients With Colon and Rectal Carcinomas: J Clin Gastroenterol 2006; 40: 592–595.
12. Siddiqui A, Heinzerling J, Livingston EH, et al. Predictors of early mortality in veteran patients with pancreatic cancer. Am J Surg 2007; 194: 362–366.
13. Li X-H, Gu W-S, Wang X-P, et al. Low Preoperative albumin-to-globulin ratio Predict Poor Survival and Negatively Correlated with Fibrinogen in Resectable Esophageal Squamous Cell Carcinoma. J Cancer 2017; 8: 1833–1842.
14. Fujiwara Y, Shiba H, Shirai Y, et al. Perioperative Serum Albumin Correlates with Postoperative Pancreatic Fistula After Pancreaticoduodenectomy. ANTICANCER Res 2015; 5.
15. Oki S, Toiyama Y, Okugawa Y, et al. Clinical burden of preoperative albumin-globulin ratio in esophageal cancer patients. Am J Surg 2017; 214: 891–898.
16. Azab B, Kedia S, Shah N, et al. The value of the pretreatment albumin/globulin ratio in predicting the long-term survival in colorectal cancer. Int J Colorectal Dis 2013; 28: 1629–1636.
17. Shinde R, Bhandare MS, Chaudhari V, et al. Preoperative Albumin-Globulin Ratio and Its Association with Perioperative and Long-Term Outcomes in Patients Undergoing Pancreatoduodenectomy. Dig Surg 2021; 38: 275–282.
18. Hackert T, Hinz U, Pausch T, et al. Postoperative pancreatic fistula: We need to redefine grades B and C. Surgery 2016; 159: 872–877.
19. Eshmuminov D, Schneider MA, Tschuor C, et al. Systematic review and meta-analysis of postoperative pancreatic fistula rates using the updated 2016 International Study Group Pancreatic Fistula definition in patients undergoing pancreatic resection with soft and hard pancreatic texture. HPB 2018; 20: 992–1003.
20. Gruppo M, Angriman I, Martella B, et al. Perioperative albumin ratio is associated with post-operative pancreatic fistula: Serum albumin predicts pancreatic fistula. ANZ J Surg 2018; 88: E602–E605.
21. Xu W, Peng X, Jiang B. Hypoalbuminemia after pancreaticoduodenectomy does not predict or affect short-term postoperative prognosis. BMC Surg 2020; 20: 72.
22. Lee B, Han H, Yoon Y, et al. Impact of preoperative malnutrition, based on albumin level and body mass index, on operative outcomes in patients with pancreatic head cancer. J Hepato-Biliary-Pancreat Sci 2021; 28: 1069–1075.
23. Azab BN, Bhatt VR, Vonfrolio S, et al. Value of the pretreatment albumin to globulin ratio in predicting long-term mortality in breast cancer patients. Am J Surg 2013; 206: 764–770.
24. Mungroop TH, Klompmaker S, Wellner UF, et al. Updated Alternative Fistula Risk Score (ua-FRS) to Include Minimally Invasive Pancreatoduodenectomy: Pan-European Validation. Ann Surg 2021; 273: 334–340.
25. Lapshyn H, Petruch N, Thomaschewski M, et al. A simple preoperative stratification tool predicting the risk of postoperative pancreatic fistula after pancreatoduodenectomy. Pancreatology 2021; 21: 957–964.
26. Sakamoto T, Yagyu Y, Uchinaka E, et al. Predictive Significance of C-reactive Protein-to-albumin Ratio for Postoperative Pancreatic Fistula After Pancreaticoduodenectomy. Anticancer Res 2019; 39: 6283–6290.
27. Fuks D, Piessen G, Huet E, et al. Life-threatening postoperative pancreatic fistula (grade C) after pancreaticoduodenectomy: incidence, prognosis, and risk factors. Am J Surg 2009; 197: 702–709.
28. Dutch Pancreatic Cancer Group, Gerritsen A, Molenaar IQ, et al. Preoperative Characteristics of Patients with Presumed Pancreatic Cancer but Ultimately Benign Disease: A Multicenter Series of 344 Pancreatoduodenectomies. Ann Surg Oncol 2014; 21: 3999–4006.
29. Yildirim OY, Özer N. Effect of Anastomosis Technique on Pancreatic Fistula Formation in Proximal Pancreaticoduodenectomy. J Coll Physicians Surg Pak 2020; 30: 480–484.
30. Yang YM, Tian XD, Zhuand Y, Wang WM, Wan YL, Huang YT. Risk factors of pancreatic leakage after pancreaticoduodenectomy. World J Gastroenterol 2005; 11: 2456.