CAN PREOPERATIVE BIOCHEMICAL INVESTIGATIONS PREDICT POSTOPERATIVE PANCREATIC FISTULA AFTER PANCREATICODUODENECTOMY?

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Article History: Received: 10.06.2023 **Revised:** 20.07.2023 **Accepted:** 01.08.2023

Abstract

Aim:

To evaluate different risk factors of postoperative pancreatic fistula (POPF) after Pancreaticoduodenectomy (PD) procedure with special attention to the preoperative laboratory investigations that may have a role on incidence of POPF. And its post operative consequences.

Patients and methods:

A total number of 119 patient who underwent PD procedure and pancreaticojejunostomy (PJ) reconstruction of the pancreatic remnant at the NCI- Cairo university-Egypt, by different surgeons between March 2021 and May 2023. The International Study Group on Pancreatic Fistula Definition was consistently used for evaluation and diagnoses of clinically relevant (CR) POPF after PD. Univariate analysis was performed to analyze the following factors: patient age, sex, hypertension, diabetes mellitus, clinical presentation, serum albumin and bilirubin levels, pancreatic texture and duct diameter, pancreatic drainage, PJ and postoperative morbidity and mortality.

Results:

21 cases developed CR-POPF (17.65%). The most common co-morbidity in our study was DM (32.8%). followed by HTN (22.7%). None of those risk factors showed statistically significant difference between fistula and no-fistula groups. Smoking prevalence was 8.4 % among our cases. 30% of smokers developed POPF Vs 15.1 % of non-smokers (P= 0.397). The most common main presentation among our cases was obstructive Jaundice in 76.5 % of cases. 84 % of cases underwent upfront surgery while 16 % (n=19) received NACT. Only 1 case (5.3%) of the NACT group suffered POPF vs 20 cases (20%) of the upfront surgery group. P value = 0.19.

76.1% of cases had normal albumin levels (> 3.5gm/dl), 22.1% had mild depletion (2.8-3.5 gm/dl) while only 1.8% had moderate depletion (2-2.7 gm/dl). By comparing those 3 groups there was no significant difference regarding the post operative course and complications. 84.8% of our cases had normal serum bilirubin levels (<2 mg/dl), 6.3% had serum bilirubin between 2 and 3 mg/dl while 8.9% had serum bilirubin levels >3 mg/dl. Also, there was not statistically significant difference between those groups regarding post operative course and complications.

According the ISGPS classification depending on the pancreatic texture and duct diameter, 37.8% of our patients were category A (not soft and duct diameter >3ml), 26.9% were category B (not soft and duct diameter <3ml), while 2.5% were of category C (soft and duct diameter >3ml) and 32.8% were category D (soft and duct diameter <3ml). The least category to develop POPF was category A 6.7% (P=0.043).

Time to remove drains and to start enteral feeding and overall hospital stay were significantly lower in the no-fistula group. Also, post operative complications such as chest infection, wound infection, bile leak, incisional hernia and relaparotomy were more prevalent in fistula group with statistically significant differences. DGE and PPH were more prevalent in the fistula group but with no statistically significant differences. Also, the overall mortality rate was 8.2% and it was significantly higher in fistula group 38.1% Vs 2% in no-fistula group (P value= <0.001).

Conclusions:

The POPF is the main factor affecting post operative course after PD. In our study, the only factor that showed statistically significant difference that predict POPF was the ISGPF classification according to pancreatic texture and duct diameter. None of the routine preoperative laboratory investigations showed statistically significant differences that suggest a major effect on incidence of POPF.

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DOI: 10.48047/ecb/2023.12.Si8.663

Introduction

For malignancies coming from the periampullary region, lower common bile duct, and pancreatic head, a pancreatoduodenectomy (PD) is a typical procedure(1).) With significant mortality and morbidity, PD has always been a difficult procedure. The postoperative morbidity might reach up to 30% to 50%, despite the fact that the mortality rate for PD has decreased to roughly 2%. (2)

Multiple complications may arise following surgery. Postoperative pancreatic fistula (POPF), delayed gastric emptying, bleeding, hepatic abscess, and biliary stricture are some of the main complications that can occur (3). POPF is a frequent and serious complication that can result in bleeding or infection and, in some circumstances, necessitate an additional surgical procedure (3, 4). Leakage of pancreatic enzymes into the abdominal cavity is known as POPF. When the amylase activity in the drain fluid is three times higher than the normal upper value, it is recognized. It might be caused by a pancreatic anastomosis that failed to heal or by a raw pancreatic surface.(5)

One of the most significant side effects of PD is pancreatic fistula (PF), which occurs between 10% and 28% of all cases (6). Grade A PF was replaced by biochemical leak in the definition provided by the International Study Group on Pancreatic Fistula (ISGPF) in 2016 because it had no clinical impact, and grades B and C PF were also referred to as clinically relevant postoperative PF (CR-POPF)) (7). When compared to grade A PF, CR-POPF can lengthen hospital stays and raise costs while also raising the risk of secondary morbidities like postoperative bleeding, abdominal infections, and even mortality (8-10). Consequently, preventing the development of CR-POPF following PD is of utmost importance. The understanding of CR-POPF's potential mechanisms is improved by identifying risk factors, which is also helpful for management and prevention. Numerous studies have looked closely at the risk variables for PF, including body mass index (BMI), pancreatic duct width, texture, serum albumin levels, surgical methods, and others (11-13). However, most past studies on PF risk factors did not rule out grade A PF, and it was still unclear how various factors affected CR-POPF. In the current paper, we conducted a retrospective study to determine the impact of preoperative laboratory investigations and other factors on CR-POPF following PD, establishing an approach for its management and prevention.(2)

To avoid POPF, it may be helpful to estimate surgical risks by assessing perioperative nutritional or inflammatory condition. Lower postoperative serum albumin, according to Ryan et al., may be a risk factor for postoperative problems in individuals having esophagectomy (14). In patients having PD, preoperatively elevated blood urea nitrogen (BUN) and preoperatively low serum albumin have been linked to an increased risk of morbidity and mortality (15, 16).

Patients and Methods

Between March 2021 and May 2023, (119) patients underwent pancreaticoduodenectomy for various primary diseases in the Department of Surgery, National Cancer Institute.

All patients underwent PD procedure and reconstruction with pancreaticojejunotomy (PJ) with or without internal pancreatic duct stenting.

At first, to assess the risk factors for POPF, we investigated the relation between clinical variables and POPF after PD by univariate and analyses. The following factors were included for analysis: age, gender, diagnosis, duration of operation, intraoperative blood loss, perioperative transfusion of red blood cell (RCC), concomitant resection of the portal vein or other organs, co-existent disease of cardiovascular nature, coexistent disease of diabetes mellitus.

Hemoglobin level, Absolute white blood cell (WBC), as well as serum total bilirubin, and albumin were routinely determined in peripheral venous samples.

Pancreatic fistula was defined by the guideline of the International Study Group on Pancreatic Fistula (ISGPF) (7). Pancreatic fistula was classified into three categories by ISGPF as follows: biochemical leak (no clinical impact) (previously described as grade A); requiring a change in management or adjustment in the clinical pathway (grade B); needing a major change in clinical management or deviation from the normal clinical pathway (grade C). In the present study, grade B and C were defined as “postoperative pancreatic fistula (POPF)”. Hemogram and chemistry profile were routinely measured for each patient preoperatively.

We did not use prophylactic octreotide as a routine unless in cases of a documented pancreatic leakage. We planned to start clear oral fluids at POD2, and regular diet at POD5. NGT to be removed at POD4 unless there was persistent vomiting. At POD4 an amylase level from drains to be performed, and drains are routinely removed if the level is less than 300 IU/L and if amount does not exceed 200 ml. Prophylactic use of low molecular weight heparin is considered in all patients till the day of discharge.

Parenteral nutrition was started in patients with delayed gastric emptying or other complications that delayed enteral feeding more than 5 days.

Statistical analysis

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). Data was summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were

done using the non-parametric Mann-Whitney test (17). For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5 (18). Logistic regression was done to detect independent predictors of pancreatic fistula (19). P-values less than 0.05 were considered statistically significant.

Results

In our study we reviewed a total of 119 cases who underwent pancreaticoduodenectomy at National Cancer Institute (NCI), Cairo university, both sex and all age groups were included, we excluded inoperable cases and cases with very small pancreatic duct who underwent pancreaticogastrostomy instead of pancreaticojejunostomy.

Among our 119 cases, 21 cases developed CR-POPF (17.65%). When comparing fistula and no fistula groups regarding preoperative, intraoperative and post operative factors the following data were described:

Among the total 119 cases, 64 cases (53.8%) were males, and 55 cases (46.2%) were females. POPF occurred in 17.2% in male patients and in 18.2% of female patients with P value = 0.887. The mean age in the fistula group was 57.76 years and in no-fistula group was 53.7 years with no significant difference. The most common co-morbidity in our study was DM (32.8%). followed by HTN (22.7%). Other comorbidities included HCV infection in 5.9 % of cases, IHD in 4.2 % of cases, previous stroke in 2.5 % of cases, liver cirrhosis in of 1.7 % cases and AF in 0.8 % of cases. None of those risk factors showed statistically significant difference between fistula and no-fistula groups.

Smoking prevalence was 8.4 % among our cases. 30% of smokers developed POPF Vs 15.1 % of non-smokers, this difference is not statistically significant P= 0.397.

39 cases of our study were known diabetics. POPF in diabetic cases occurred in 15.4% of cases while the percentage in non-diabetics was 18.8%, the p value was 0.651. Among those 39 cases, 30 cases were on OHD, and 9 cases were on Insulin injection. It is worth mentioning that POPF developed in 20% of the OHD group Vs 0% in insulin group. However, P value= 0.358 which is not statistically significant.

Table 1 *Preoperative factors and their effect on POPF*

		POPF				
		yes		no		P value
		Count	Row N %	Count	Row N %	
sex	**M**	11	17.2%	53	82.8%	0.887
	F	10	18.2%	45	81.8%	
DM	**Yes**	6	15.4%	33	84.6%	0.651
	No	15	18.8%	65	81.3%	
HTN	**Yes**	4	14.8%	23	85.2%	0.780
	No	17	18.5%	75	81.5%	
cirrhosis	**Yes**	0	0.0%	2	100.0%	1.000
	No	21	17.9%	96	82.1%	
IHD	**Yes**	2	40.0%	3	60.0%	0.213
	No	19	16.7%	95	83.3%	
AF	**Yes**	0	0.0%	1	100.0%	1.000
	No	21	17.8%	97	82.2%	
smoking	**Yes**	3	30.0%	7	70.0%	0.379
	No	18	16.5%	91	83.5%	
Stroke	**Yes**	1	33.3%	2	66.7%	0.445
	No	20	17.2%	96	82.8%	
HCV	**Yes**	0	0.0%	7	100.0%	0.351
	No	21	18.8%	91	81.3%	
insulin	**Yes**	0	0.0%	9	100.0%	0.358
	No	21	19.1%	89	80.9%	
OHD	**Yes**	6	20.0%	24	80.0%	0.696
	No	15	16.9%	74	83.1%	
steroids	**Yes**	0	0.0%	2	100.0%	1.000
	No	21	17.9%	96	82.1%	
Anti-platelets	**Yes**	3	18.8%	13	81.3%	1.000
	No	18	17.5%	85	82.5%	

anti HTN	**Yes**	4	16.0%	21	84.0%	1.000
	No	17	18.1%	77	81.9%	
BB	**Yes**	0	0.0%	6	100.0%	0.589
	No	21	18.6%	92	81.4%	
OJ	**Yes**	16	17.6%	75	82.4%	1.000
	No	5	17.9%	23	82.1%	
abdominal pain	**Yes**	8	25.8%	23	74.2%	0.166
	No	13	14.8%	75	85.2%	
GOO	**Yes**	1	33.3%	2	66.7%	0.445
	No	20	17.2%	96	82.8%	
Weight loss	**Yes**	0	0.0%	4	100.0%	1.000
	No	21	18.3%	94	81.7%	
others	**Melena**	1	50.0%	1	50.0%	0.445
	Hematemesis	0	0.0%	1	100.0%	
	No	20	17.2%	96	82.8%	

The most common main presentation among our cases was obstructive Jaundice in 76.5 % of cases. Other less common presentations were abdominal pain, gastric outlet obstruction, significant weight loss and Gi bleeding. None of these presentations correlates with the development of POPF.

84 % of cases underwent upfront surgery while 16 % (n=19) received NACT. Only 1 case (5.3%) of the NACT group suffered POPF vs 20 cases (20%) of the upfront surgery group. P value = 0.19.

71.4 % of our cases underwent preoperative biliary drainage. The main method of drainage was plastic stent insertion (81.2%) followed by simple sphincterotomy (7.1%), metallic stent insertion (7.1%), preoperative hepaticojejunostomy (2.4%) and PTD insertion (2.4%). Also in our study group, none of these factors showed statistically significant difference that correlates with the development of POPF P value = 0.331.

Regarding preoperative laboratory investigations, comparison between fistula and no-fistula groups is described in table and it showed that there is no statistically significant difference between both groups.

Table 2 *Preoperative laboratory investigations and their effect on POPF*

	POPF						
	Yes			**No**			**P value**
	Mean	**SD**	**Median**	**Mean**	**SD**	**Median**	
Hb (pre)	12.50	1.72	12.50	12.19	1.72	12.40	0.435
TLC (pre)	7.39	2.16	7.22	7.50	2.79	7.15	0.849
Alb (pre)	3.90	0.44	3.90	3.90	0.57	4.00	0.813
AST (pre)	38.10	23.21	30.00	41.46	31.32	31.00	0.898
ALT (pre)	43.86	31.07	37.00	49.76	66.97	29.00	0.624
BIL T (pre)	0.85	0.43	0.80	1.84	2.81	1.00	0.100
BIL D (pre)	0.65	0.49	0.60	1.38	2.28	0.54	0.792

In our study, we stratified our patients according to albumin and bilirubin levels to be able to study the effect of abnormal levels of albumin and bilirubin specifically on post operative course and morbidity. Among our cases, 76.1% of cases had normal albumin levels (> 3.5gm/dl), 22.1% had mild depletion (2.8-3.5 gm/dl) while only 1.8% had moderate depletion (2-2.7 gm/dl). By comparing those 3 groups there was no significant difference regarding the post operative course and complications.

Regarding the serum bilirubin levels, 84.8% of our cases had normal serum bilirubin levels (<2 mg/dl), 6.3% had serum bilirubin between 2 and 3 mg/dl while 8.9% had serum bilirubin levels >3 mg/dl. Also, there was not statistically significant difference between those groups regarding post operative course and complications. To be noted that

the maximum level of serum bilirubin in our cases was 16 mg/dl.

7 cases underwent SMV/PV resection and reconstruction none of them developed POPF.

Regarding pancreatic texture, 35.3% of the patients had soft pancreas, while 47.9 % had intermediate Pancreas and 16.8% had hard pancreas. As expected, the most common type that developed POPF was soft pancreas (21.4%) followed by intermediate pancreas (17.5%) then the hard pancreas (10%). The P value was not significant 0.623. Mean pancreatic duct diameter was 3 mm in fistula group and 3.7 mm in no-fistula group, this difference is not statistically significant.

According the ISGPS classification depending on the pancreatic texture and duct diameter, 37.8% of our patients were category A (not soft and duct diameter >3ml), 26.9% were category B (not soft and duct diameter <3ml), while 2.5% were of category C (soft and duct diameter >3ml) and 32.8% were category D (soft and duct diameter <3ml).

Th least category to develop POPF was category A 6.7% followed by category D 20.5% then category B 28.1% then category C 33.3%. P value was significant 0.043.

The mean operative time was 5.28 hours in fistula group Vs 5.12 hours in no-fistula group.

Pancreatic duct anastomosis stenting was performed in 67.2% of cases, 20% of them developed POPF. While 12.8% only in cases without pancreatic duct stenting, P value = 0.129.

The most common postoperative pathology was adenocarcinoma in 80.9% of cases, followed by Solid pseudopapillary neoplasm 10.4%, Neuroendocrine tumor 2.6%, GIST 1.7%, mucinous cystadenocarcinoma 0.9 % IPMN 0.9% and inflammation and fibrosis 0.9%. 1.7% of cases showed negative pathology for residual cancer.

T stage of our cases was distributed as follows, 0.9% T1, 31%T2, 58.4% T3, 3.5% T4 and 5.3% Tx. When comparing type of pathology and T stages no statistically significant difference was found.

Table 3 *NACT, preoperative biliary drainage, intraoperative factors and pathological factors affecting POPF:*

		POPF				
		Yes		No		P value
		Count	Row N %	Count	Row N %	
NACTH	**Yes**	1	5.3%	18	94.7%	0.190
	No	20	20.0%	80	80.0%	
Pre-Operative Biliary Drainage	**Yes**	15	17.6%	70	82.4%	1.000
	No	6	17.6%	28	82.4%	
Type of Biliary Drainage	**Sphincterotomy**	0	0.0%	6	100.0%	0.331
	PTD	0	0.0%	2	100.0%	
	Hepatico-jejunostomy	1	50.0%	1	50.0%	
	Plastic Stent	12	17.4%	57	82.6%	
	Metallic Stent	2	33.3%	4	66.7%	
Vein Resection	**Yes**	0	0.0%	7	100.0%	0.351
	No	21	18.8%	91	81.3%	
Pancreatic Texture	**Soft**	9	21.4%	33	78.6%	0.623
	Intermediate	10	17.5%	47	82.5%	
	Hard	2	10.0%	18	90.0%	
ISGPS Category	**A**	3	6.7%	42	93.3%	0.043
	B	9	28.1%	23	71.9%	
	C	1	33.3%	2	66.7%	
	D	8	20.5%	31	79.5%	
Pancreatic Stent	**Yes**	16	20.0%	64	80.0%	0.335
	No	5	12.8%	34	87.2%	
Origin (Post)	**Stomach**	0	0.0%	1	100.0%	0.369
	Pancreatic Duct	6	13.3%	39	86.7%	
	Duodenum	2	25.0%	6	75.0%	
	Distal CBD	2	66.7%	1	33.3%	
	Colon	0	0.0%	1	100.0%	
	Ampullary	9	20.9%	34	79.1%	
	N/A	2	15.4%	11	84.6%	

Pathology Type (Post)	**Solid Pseudopapillary Neoplasm**	2	16.7%	10	83.3%	0.349
	NET	2	66.7%	1	33.3%	
	Negative For Residual	0	0.0%	2	100.0%	
	MCN	0	0.0%	1	100.0%	
	IPMN	0	0.0%	1	100.0%	
	Inflammation And Fibrosis	0	0.0%	1	100.0%	
	GIST	1	50.0%	1	50.0%	
	ADC	16	17.2%	77	82.8%	
T Stage (Post)	**Tis**	0	0.0%	1	100.0%	0.767
	T1	0	0.0%	1	100.0%	
	T2	8	22.9%	27	77.1%	
	T3	13	19.7%	53	80.3%	
	T4	0	0.0%	4	100.0%	
	Tx	0	0.0%	6	100.0%	
Surgical Margins	**Positive Sm**	0	0.0%	3	100.0%	1.000
	Negative Sm	21	18.9%	90	81.1%	

Regarding the effects of POPF on the postoperative course, time to remove drains and to start enteral feeding and overall hospital stay were significantly lower in the no-fistula group. Also, post operative complications such as chest infection, wound infection, bile leak, incisional hernia and relaparotomy were more prevalent in fistula group with statistically significant differences. DGE and PPH were more prevalent in the fistula group but with no statistically significant differences. Also, the overall mortality rate was 8.2% and it was significantly higher in fistula group 38.1% Vs 2% in no-fistula group (P value= <0.001).

Table 4 *Postoperative morbidity and mortality*

		POPF				
		Yes		**No**		**P Value**
		Count	**%**	**Count**	**%**	
Chest Infection	**Yes**	6	28.6%	8	8.2%	0.018
	No	15	71.4%	90	91.8%	
Bile Leak	**Yes**	7	33.3%	4	4.1%	< 0.001
	No	14	66.7%	94	95.9%	
Bile Leak Grade	**Grade B**	4	57.1%	1	25.0%	0.545
	Grade C	3	42.9%	3	75.0%	
DGE	**Yes**	6	28.6%	16	16.3%	0.218
	No	15	71.4%	82	83.7%	
DGE Grade	**Grade A**	2	33.3%	11	68.8%	0.262
	Grade B	3	50.0%	3	18.8%	
	Grade C	1	16.7%	2	12.5%	
Enteric Leak	**Yes**	1	4.8%	2	2.0%	0.445
	No	20	95.2%	96	98.0%	
PPH	**Yes**	4	19.0%	7	7.1%	0.103
	No	17	81.0%	91	92.9%	
Type of PPH	**Intraluminal**	1	25.0%	3	37.5%	1.000
	Extraluminal	3	75.0%	5	62.5%	
Grade of PPH	**Grade A**	0	0.0%	1	12.5%	0.697
	Grade B	1	25.0%	4	50.0%	
	Grade C	3	75.0%	3	37.5%	

Wound Infection	**Yes**	14	66.7%	27	27.6%	0.001
	No	7	33.3%	71	72.4%	
Incisional Hernia	**Yes**	3	14.3%	2	2.0%	0.038
	No	18	85.7%	96	98.0%	
Relaparotomy	**Yes**	6	28.6%	6	6.1%	0.007
	No	15	71.4%	92	93.9%	
Mortality	**Yes**	8	38.1%	2	2.0%	< 0.001
	No	13	61.9%	96	98.0%	

Discussion:

The overall POPF rate in our study was 17.65% which is comparable to literature, there was no significant difference that suggests that any of these preoperative factors has significant effect on POPF including Age, gender and comorbidities as DM and HTN. Although some literature suggested male age as a risk factor and others suggested DM as protective factor for POPF. Smoking is suggested by previous literature as a risk factor for POPF, in our study also POPF was more prevalent in smokers but without significant P value which may be related to low prevalence of smokers in our study (8.4%). Also, POPF did not develop in any of our diabetic patients who were on insulin therapy. However, the difference between the patients on insulin Vs OHD was not statistically significant. Also, preoperative biliary drainage had no significant relation to the development of POPF.

Regarding routine preoperative laboratory investigations, none of the routine preoperative laboratory showed statistically significant difference between fistula and no-fistula group. Even after stratification of the patients to multiple categories according to levels of serum albumin and bilirubin, there was no significant affection on POPF. However, we did not operate on patients with severe albumin depletion or patients with very high Albumin levels.

When concerning the operative factors, neither the extent of local resection including venous resection, nor the extent of lymphadenectomy showed significant effect on development of POPF.

Most literatures defined Pancreatic duct diameter and pancreatic texture as the most important factors that affect the POPF. In our study there was more prevalence of fistula in soft pancreas and small duct diameter, but the difference of each factor alone was not significant. When combining both factors according to the categories of the ISGPS, Category A (not soft pancreas and duct > 3m) had significantly lesser POPF than other categories.

Regarding rate of fistula that was associated with pancreatic duct stent placement, which was more than other cases without stent placement. That is most probably due to selection bias as we selectively inserted stent in cases with small duct size. None of the pathological factors were found to have significant effect on POPF including type of tumor or stage of the tumor. Even the 3 cases with positive surgical margin did not develop POPF.

Regarding postoperative complications, most of the complications and mortality were directly related to POPF as bile leakage, wound infection, incisional hernia, and relaparotomy. Other complications were related to increased hospital stays such as chest infection. However, chest infection was more common in fistula group due to prolonged hospital stay in this group.

Conclusion:

The POPF is the main factor affecting post operative course after PD. Most of the postoperative complications as biliary leakage, wound infection, chest infection, incisional hernia and relaparotomy are direct sequalae of POPF. Also 90 days mortality after PD is mainly depending on POPF and its`s related complications and management. So, Avoiding, prediction and early effective management of POPF plays a crucial role for improvement of post operative outcomes after PD.

In our study, the only factor that showed statistically significant difference that predict POPF was the ISGPF classification according to pancreatic texture and duct diameter.

Other factors that showed a difference that was suggestive but not conclusive effect were smoking as a risk factor and insulin treatment in diabetic patients and neoadjuvant chemotherapy as a protective factor. But further dedicated studies with larger sample size are needed for confirmation.

None of the routine preoperative laboratory investigations showed statistically significant differences that suggest a major effect on incidence of POPF, making sure that serum albumin is not severely depleted, and serum bilirubin is not markedly elevated. So, it is safe to operate upon these cases and avoid patient delay to correct their values preoperatively.

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