Clinics in Surgery

Research Article
Published: 20 Sep, 2018

Clinical Impact of the Perioperative Inflammatory Status in Pancreatic Surgery: Data from a High-Volume Center

Matteo De P[1], Paiella S[1], Ciprani D[1], Landoni L[1], Salvia R[1], Fumagalli L[2] and Bassi C[1]*

[1]Department of General and Pancreatic Surgery, University and Hospital Trust of Verona, Italy

[2]Department of General Surgery, Hospital of Lecco, Lecco, Italy

Abstract

Purposes: The inflammatory status is related to postoperative outcomes, and its response to surgical trauma is a significant determinant of surgical outcome, especially for infectious postoperative complications. This study aims to analyze the relationship between the immune and inflammatory indexes, assessed perioperatively, and the postoperative course after pancreatic surgery.

Methods: Data of consecutive pancreatoduodenectomies and total pancreatectomies performed at the General and Pancreatic Surgery Department of Verona from 2014 to 2016 were retrieved from a prospectively maintained electronic database and evaluated. Perioperative variations of blood count cells were recorded and then compared with postoperative outcomes.

Results: The final population consisted of 554 patients. Post Operative Pancreatic Fistula (POPF), infectious complications, major complications, and mortality occurred in 75(13.5%), 261(47.1%), 85(15.3%), and 17(3%) patients, respectively. Patients with absolute and median postoperative low lymphocyte counts were associated with a worse postoperative clinical course ($p<0.05$). Furthermore, a preoperative Systemic-Immune-Inflammation Index (SIII) higher than 900 correlated with mortality.

Conclusion: The unpaired recovery of immune effectors in the early postoperative days, expressed by low lymphocyte count and a high preoperative SIII are associated with a complicated postoperative course.

Keywords: Pancreaticoduodenectomy; Total pancreatectomy; Systemic-immune-inflammation index; Infectious complications; Lymphocyte count

OPEN ACCESS

Correspondence:

Matteo De P, Department of General and Pancreatic Surgery, Pancreas Institute, University of Verona Hospital Trust, Policlinico GB Rossi, Piazzale L.A. Scuro, 10, 37134, Verona, Italy, Tel: +390458124553; Fax +390458124826;

E-mail: m.depastena@gmail.com

Received Date: *18 Aug 2018*

Accepted Date: *17 Sep 2018*

Published Date: *20 Sep 2018*

Citation:

Matteo De P, Paiella S, Ciprani D, Landoni L, Salvia R, Fumagalli L, et al. Clinical Impact of the Perioperative Inflammatory Status in Pancreatic Surgery: Data from a High-Volume Center. Clin Surg. 2018; 3: 2121.

Introduction

The morbidity and mortality rates after pancreatic surgery are still high. Post Operative Pancreatic Fistula (POPF) and Infectious Complications (ICs) are the most threatening complications of pancreatic resections [1,2]. Whilst POPF is usually related to pancreatic texture, main pancreatic duct size and intraoperative variables [3], on the other hand, the impact of ICs on postoperative course might be related to an impairment of pro- and anti-inflammatory processes that could ultimately lead to the development of infectious events. The direct association between ICs and patients' immune impairment has been already described [4]. The hosts' immune response to tissue injury and surgery is complex and poorly understood, especially during major surgery such as pancreatic resections. Up to now, the host response was believed to follow a bimodal response, with a subtle equilibrium between systemic inflammatory and anti-inflammatory response syndromes [5]. Recent data, however, suggest that his paradigm may not be correct [6]. The physical stress related to surgical increases the expression of T-helper 2 lymphocytes which causes an impaired cell-mediated immunity. Then, the activation of the hypothalamic-pituitary-adrenal axis and the sympatho-adrenal system with the release of cortisol and catecholamines appear to be responsible for the alteration of the lymphocyte count [7]. Furthermore, the activation of the hypothalamic-pituitary-adrenal axis generates a rapid and massive influx in bloodstream of neutrophil granulocytes mobilized by the spleen, a depletion of blood lymphocytes by homing from blood into lymphatic organs (bone marrow, nodes and gut) and their recovery in peripheral blood from 36 hrs to 72 hrs after surgery [8,9]. Furthermore, the increased expression of arginase-1, due to the pro-inflammatory cytokines, causes an arginine deficient state, which further impairs the functions of the lymphocytes [10]. Recently, the Systemic-Immune-Inflammation Index (SIII), based on lymphocyte, neutrophils, and platelet counts, has been described as a predictor of survival in patients affected by pancreatic

Table 1: Demographic data.

Study Population N° = 554	
	Total n° (%)
Age (years, SD)	63,2 (±10.9)
Sex (Male)	308 (55.6%)
BMI (Kg/m^2, IQR)	24 (21.6 - 26.7)
Diabetes	124 (22.3%)
ASA score	
I-II score	438 (79.1%)
III-IV score	116 (20.9%)
CACI (SD)	4.4 (±1.6)
Jaundice	280 (50.5%)
Preoperative Biliary Drain	256 (46.2%)
Neoadjuvant chemotherapy	79 (14.3%)
Type of resection	
Pancreaticoduodenectomy	474 (85.6%)
Total pancreatectomy	80 (14.4%)
Vascular resection	80 (14.4%)
Estimates blood loss (ml)	350 (300 - 500)
Operative time (min)	422 (370 - 480)
Pathology	
PDAC	313 (56.5%)
Ampullary tumor	56 (10.1%)
Cholangiocarcinoma	15 (2.7%)
IPMN	65 (11.7%)
pNET	52 (9.4%)
Other	53 (9.6%)

BMI: Body Mass Index; PDAC: Pancreatic Ductal Adenocarcinoma; pNET: Pancreatic Neuroendocrine Tumor; IPMN: Intraductal Papillary Mucinous Neoplasm

cancer [11,12]. In this setting, major complications and, particularly, ICs might be related to an impaired immune response of the patient, with an impaired immune host response. This study aimed to analyze the relationship between perioperative blood cell count patterns and surgical outcomes of patients submitted to pancreatic surgery.

Methods

The study was conducted, after the Institutional Review Board approval (CESC-VR 1101), according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [13]. The Institutional electronic prospectively maintained database was queried and all consecutive Pancreatoduodenectomies (PD) and Total Pancreatectomies (TP) performed from 2014 to 2016 were retrieved. An observational study was conducted collecting clinical and laboratory data of patients submitted to pancreatic resection. Demographic and clinical details included age, gender, ASA score, Body Mass Index (BMI), diabetes mellitus, Charlson Age-adjusted Comorbidity Score Index (CACI) [14], jaundice, and preoperative biliary drain. Blood cell counts were taken at baseline and on postoperative days 1,2 and 3. All blood cell counts were performed with the automated counter. Furthermore, the median value of each differential cell type was calculated through the values collected on postoperative days 1,2 and 3. The SIII was defined as platelet count multiplied by neutrophil-to-lymphocyte ratio (absolute neutrophil count divided by absolute lymphocyte count). POPF was recorded according to the updated ISGPS definition, and only grades B and C were considered [15]. All postoperative complications and mortality rates were collected at 90th postoperative day and graded according to Clavien-Dindo classification [16]. Major complications were defined as a Clavien-Dindo grade higher than 3. Infectious Complications (IC) included SSI, septic events, pneumonia, urinary tract infections and blood infections. ICs were also considered as those clinical conditions related to infection by bacterium or fungi in a specific organ/compartment when this was demonstrated bacteriologically by positive cultures. Statistical analyses were performed using SPSS software® version 22.0 (IBM corp., Armonk, NY, USA). Normally distributed data were presented as mean with Standard Deviation (SD) and non-normally distributed data were presented as median with Interquartile Range (IQR). Categorical variables were presented as counts and proportions. The group differences were assessed using a Chi-square test or Fisher's exact test for categorical variables. For non-normally distributed continuous variables the Mann-Whitney U test was applied. Factors found to be a value of $p \leq 0.05$ on univariate analysis were subjected to multivariate analysis with logistic regression models. The p values were presented as odds ratios or hazard ratios and 95% CIs, as appropriate. Statistical significance was determined by a p-value of <0.05.

Results

A total of 648 patients were submitted to pancreatic resection, PDs and TPs, during the study period. The perioperative clinical and laboratory data were available only on 554 (85.5%) patients that were the final population. (Table 1) shows demographic and pathological data. POPF occurred in 75 (13.5%) patients. The analysis of the risk factors for the development of POPF is shown in (Table 2). The absolute preoperative lymphocyte count, the absolute neutrophil and lymphocyte count on POD II, and the median of postoperative lymphocyte count were correlated to POPF ($p<0.05$). The absolute lymphocyte count on POD II was also associated with the development of ICs ($p=0.032$), as reported in (Table 3). The absolute white blood cell, the neutrophil and lymphocytes count, as well as the median postoperative lymphocyte count were related to the occurrence of major complication and mortality ($p<0.05$), as showed in (Table 4 and 5). Furthermore, the mortality rate was increased in patient with a preoperative SIII higher than 900 ($p=0.039$). The multivariate analysis presented in (Table 6) shows that a low lymphocyte counts on POD II and a low median of postoperative lymphocyte count were independent risk factors for the development of a complicated postoperative course.

Discussion

The occurrence of complications after pancreatic surgery is a suffering event. Despite the improved surgical technique, the accurate preoperative patient selection, and the strict postoperative surveillance, the overall morbidity and mortality rates are still high [17]. Some variables are well known risk factors for the development of postoperative complications after pancreatic surgery (a small main pancreatic duct size, a soft gland texture, the presence of jaundice and/or biliary stent) [3,18]. Other risk factors are mainly patient-related, such as performance status, body mass index, and the presence of comorbidities [19]. The study reports a postoperative absolute low lymphocyte count and a low median lymphocyte count are risk factors for the development of POPF, major complication, ICs and mortality. These data are in line with the literature [20]. Particularly,

Table 2: Variables associated with the development of POPF.

Study Population N°=554				
	Total median (IQR)	**POPF 75 (13.5%)**	**No POPF 479 (86.5%)**	**P value**
Preoperative variables				
WBC count	7.4 (5.8-12.9)	7.7 (6.1-13.1)	7.3 (5.7-12.8)	0.534
Neutrophils	3.9 (2.9-5.1)	4 (3.2-4.9)	3.8 (2.8-5.1)	0.517
Lymphocytes	1.7 (1.3-2.2)	1.9 (1.6-2.3)	1.6 (1.3-2.1)	0.004*
SSI>900	127 (22.9%)	20 (26.7%)	107 (22.3%)	0.224
Postoperative variables				
WBC count I POD	12.6 (10.5-15.9)	13 (10.4-15.6)	12.5 (10.5-16)	0.779
Neutrophils I POD	10.8 (8.8-14)	11.3 (8.9-13.5)	10.8 (8.8-14)	0.692
Lymphocytes I POD	0.9 (0.7-1.3)	0.9 (0.7-1.4)	1 (0.7-1.3)	0.979
WBC II POD	12.1 (9.6-15.6)	13 (10.4-16.3)	11.9 (9.4-15.4)	0.254
Neutrophils II POD	10.1 (7.8-13.3)	10.8 (8.7-14.5)	10 (7.6-12.9)	0.05*
Lymphocytes II POD	0.8 (0.5-1.3)	0.7 (0.5-1.1)	1 (0.7-1.3)	0.017*
Lymphocytes median I-II-III POD	0.8 (0.6-1.3)	0.7 (0.6-1.1)	1.1 (0.8-1.3)	0.007*

*Statistically significant

POPF: Post-Operative Pancreatic Fistula; IQR: Interquartile Range; POD: Postoperative Day; WBC: White Blood Cell

Table 3: Variables associated with the development of Infectious Complication.

Study Population N°=554				
	Total median (IQR)	**Infectious Complication 261 (47.1%)**	**No Infectious Complication 293 (52.9%)**	**P value**
Preoperative variables				
WBC count	7.4 (5.8-12.9)	8.5 (5.9-13.7)	7.3 (5.8-12.5)	0.273
Neutrophils	3.9 (2.9-5.1)	3.8 (3.0-4.9)	3.7 (2.8-5.3)	0.955
Lymphocytes	1.7 (1.3-2.2)	1.7 (1.3-2.0)	1.8 (1.4-2.1)	0.726
SSI>900	127 (22.9%)	64 (24.8%)	63 (21.5%)	0.141
Postoperative variables				
WBC count I POD	12.6 (10.5-15.9)	12.5 (10.2-15.9)	12.5 (10.5-16)	0.807
Neutrophils I POD	10.8 (8.8-14)	10.8 (8.5-13.9)	10.8 (8.9-14.1)	1.000
Lymphocytes I POD	0.9 (0.7-1.3)	0.9 (0.7-1.3)	1 (0.7-1.3)	0.285
WBC II POD	12.1 (9.6-15.6)	12.5 (9.6-15.4)	11.6 (9.4-15.5)	0.264
Neutrophils II POD	10.1 (7.8-13.3)	10.5 (7.8-13.2)	9.9 (7.6-13.5)	0.585
Lymphocytes II POD	0.8 (0.5-1.3)	0.7 (0.5-1.3)	1.1 (0.8-1.4)	0.032*
Lymphocytes median I-II-III POD	0.8 (0.6-1.3)	0.8 (0.6-1.3)	1.1 (0.8-1.4)	0.073

*Statistically significant

POPF: Post-Operative Pancreatic Fistula; IQR: Interquartile Range; POD: Postoperative Day; WBC: White Blood Cell

the variations of lymphocytemia seem to represent an interesting marker of the host response following surgery [21]. Generally, the activation of the hypothalamus-pituitary gland-adrenal gland axis following the surgical trauma generates the acute lymphocytopenia occurring in the early postoperative days, with a restore in 24 hrs to 36 hrs after surgery [9,22]. The data of the literature, confirmed by this series, could be explained by an ineffective host response to the surgical trauma due to a single pathway failure, such as a deficient gene expression of gammac cytokines [23] or alterations of a suppressor of cytokine signaling family of proteins [21], or evenly to a multisystem failure that involving the autonomic nervous, the endocrine, and immune system [24]. In patients suffering from cancer, the perioperative inflammatory status, e.g. the blood lymphocyte counts and the SIII, is a strong predictor of survival [12,25]. Clark et al. reports that in patients undergoing pancreaticoduodenectomy, a low preoperative lymphocyte count retains significance on multivariate analysis towards overall survival [26]. Fogar find that the number of circulating lymphocytes impacts on survival of pancreatic cancer patients, suggesting that the immune system plays a pivotal role in pancreatic adenocarcinoma immune-surveillance [27,28]. Our results show that SIII and lymphocytopenia are associated with postoperative mortality after pancreatic resections. This study has several limitations. First, it was carried out using a prospectively maintained database but it was retrospectively analyzed, generating information/selection bias. Second, we included either pancreaticoduodenectomy or total pancreatectomy and it might be speculated that the surgical trauma of these two surgeries is not equal, especially considering the endocrine function of the pancreas that is acutely aborted following total pancreatectomy. Third, we included either patients suffering from malignancies and not, and it is well

Table 4: Variables associated with the development of Major Complication.

Study Population N°=554				
	Total median (IQR)	**Major Complication 85 (15.3%)**	**No/Minor Complication 469 (84.7%)**	**P value**
Preoperative variables				
WBC count	7.4 (5.8-12.9)	8.2 (6-14.1)	7.2 (5.7-11.6)	0.134
Neutrophils	3.9 (2.9-5.1)	3.9 (3.2-5.2)	3.9 (2.9-5)	1.000
Lymphocytes	1.7 (1.3-2.2)	1.9 (1.2-2.2)	1.7 (1.3-2.1)	0.479
SSI>900	127 (22.9%)	23 (27.1%)	104 (22.2%)	0.128
Postoperative variables				
WBC count I POD	12.6 (10.5-15.9)	12.7 (10.2-16.2)	12.5 (10.5-15.8)	0.634
Neutrophils I POD	10.8 (8.8-14)	11.2 (8.7-14.2)	10.8 (8.8-14)	0.546
Lymphocytes I POD	0.9 (0.7-1.3)	0.9 (0.7-1.3)	1 (0.7-1.3)	0.390
WBC count II POD	12.1 (9.6-15.6)	13.2 (10.8-17)	11.8 (9.4-15.4)	0.032*
Neutrophils II POD	10.1 (7.8-13.3)	11.3 (9.1-15.1)	9.9 (7.6-13)	0.026*
Lymphocytes II POD	0.8 (0.5-1.3)	0.7 (0.5-1.2)	1 (0.7-1.3)	0.028*
Lymphocytes median I-II-III POD	0.8 (0.6-1.3)	0.7 (0.6-1.2)	1.1 (0.8-1.4)	0.027*

*Statistically significant
IQR: Interquartile Range; POD: Postoperative Day; WBC: White Blood Cell

Table 5: Variables associated with Mortality.

Study Population N°=554				
	Total median (IQR)	**Mortality rate 17 (3%)**	**Survival rate 537 (97%)**	**P value**
Preoperative variables				
WBC count	7.4 (5.8-12.9)	11 (6-14)	7.3 (5.8-12.9)	0.045*
Neutrophils	3.9 (2.9-5.1)	4.2 (3.4-5.2)	3.9 (2.9-5)	0.622
Lymphocytes	1.7 (1.3-2.2)	2 (1.6-2.8)	1.7 (1.3-2.1)	0.324
SSI>900	127 (22.9%)	7 (41.2%)	120 (22.3%)	0.039*
Postoperative variables				
WBC count I POD	12.6 (10.5-15.9)	13.3 (10.5-18.6)	12.6 (10.5-15.9)	1.000
Neutrophils I POD	10.8 (8.8-14)	11.8 (9-16.7)	10.8 (8.8-14)	0.840
Lymphocytes I POD	0.9 (0.7-1.3)	0.9 (0.7-1.3)	1 (0.7-1.3)	0.800
WBC II POD	12.1 (9.6-15.6)	15 (11-18)	11.8 (9.6-15.4)	0.03*
Neutrophils II POD	10.1 (7.8-13.3)	14.3 (9.1-15.1)	10 (7.7-13.2)	0.018*
Lymphocytes II POD	0.8 (0.5-1.3)	0.8 (0.5-1.3)	1 (0.7-1.5)	0.025*
Lymphocytes median I-II-III POD	0.8 (0.6-1.3)	0.7 (0.6-1.2)	1.2 (0.8-1.4)	0.02*

*Statistically significant
IQR: Interquartile Range; POD: Postoperative Day; WBC: White Blood Cell

known that in the first there is an intrinsic impairment of the immune system, due to the tumor itself. Furthermore, this subgroup of patients included subjects that received preoperative chemotherapy and this somehow might have been impacted on lymphocytes counts. Our study describes for the first time the correlation between SIII and postoperative mortality, confirming the direct role of the lymphocyte pattern on the postoperative clinical course. The perioperative identification of patients at risk of developing postoperative complications, using laboratory information easily retrievable, might allow applying a strict postoperative surveillance, with a dedicated postoperative management following pancreaticoduodenectomy and total pancreatectomy. Our results do not allow us to draw a definitive conclusion concerning the reliability of lymphocyte count changes after surgery. Conversely, our findings suggest that a further exploration of the host response to surgery, using easily available measurements, such as blood cell differential count, is worthwhile. In addition, on the basis of present and future findings, a proper analysis of the immune system before surgery could be useful to select patients that might benefit from a perioperative immune treatment, such as cytokine administration or immunonutrition, to rebalance the inflammatory status and to improve the restore of a favorable leucocytes pattern [29,30].

Conclusion

The unpaired recovery of immune effectors in the early postoperative days, expressed by a low lymphocyte count and a higher preoperative SIII, is associated with a complicated postoperative course and with mortality. Further exploration of the host response to surgery is needed to confirm the power of these reliable, feasible and reproducible inflammatory markers.

Table 6: Multivariate Analysis of predictor of postoperative complication.

	POPF Odds ratio (95% CI)	Major Complication Odds ratio (95% CI)	Mortality Odds ratio (95% CI)
Preoperative variables			
White blood cell count	\	\	1.34 (0.73-1.77)
Lymphocytes	**2.38 (1.48-3.83)**	\	\
SSI>900	\	\	**1.91 (1.71-3.14)**
Postoperative variables			
White blood count II POD	\	1.1 (0.86-1.34)	0.77 (0.39-1.51)
Neutrophils II POD	**1.13 (1.1-1.24)**	0.99 (0.79-1.25)	1.4 (0.67-2.89)
Lymphocytes II POD	**0.17 (0.04-0.72)**	**0.22 (0.05-0.83)**	0.83 (0.28-6.4)
Lymphocytes median I-II-III POD	0.81 (0.35-1.32)	0.59 (0.46-1.97)	**0.57 (0.11-0.97)**

POPF: Post-Operative Pancreatic Fistula; POD: Postoperative Day

References

1. Cameron JL, He J. Two thousand consecutive pancreaticoduodenectomies. J Am Coll Surg. 2015;220(4):530-6.
2. De Pastena M, Paiella S, Marchegiani G, Malleo G, Ciprani D, Gasparini C, et al. Postoperative infections represent a major determinant of outcome after pancreaticoduodenectomy: Results from a high-volume center. Surgery. 2017;162(4):792-801.
3. Callery MP, Pratt WB, Kent TS, Chaikof EL, Vollmer CM Jr. A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreatoduodenectomy. J Am Coll Surg. 2013;216(1):1-14.
4. Gennari R, Dominioni L, Imperatori A, Bianchi V, Maroni P, Dionigi R. Alterations in lymphocyte subsets as prognosticators of postoperative infections. Eur J Surg. 1995;161(7):493-9.
5. Moore FA, Sauaia A, Moore EE, Haenel JB, Burch JM, Lezotte DC. Postinjury multiple organ failure: a bimodal phenomenon. J Trauma. 1996;40(4):501-10.
6. Mannick JA, Rodrick ML, Lederer JA. The immunologic response to injury. J Am Coll Surg. 2001;193(3):237-44.
7. Kirchhoff C, Biberthaler P, Mutschler WE, Faist E, Jochum M, Zedler S. Early down-regulation of the pro-inflammatory potential of monocytes is correlated to organ dysfunction in patients after severe multiple injury: a cohort study. Crit Care. 2009;13(3).
8. Toft P, Tonnesen E, Helbo-Hansen HS, Lillevang ST, Rasmussen JW, Christensen NJ. Redistribution of granulocytes in patients after major surgical stress. APMIS. 1994;102(1):43-8.
9. Toft P, Hokland M, Hansen TG, Tonnesen E. Changes in lymphocyte subpopulations and adhesion/activation molecules following endotoxemia and major surgery. APMIS. 1995;103(4):261-6.
10. Ochoa JB, Strange J, Kearney P, Gellin G, Endean E, Fitzpatrick E. Effects of L-arginine on the proliferation of T lymphocyte subpopulations. JPEN J Parenter Enteral Nutr. 2001;25(1):23-9.
11. Hu B, Yang XR, Xu Y, Sun YF, Sun C, Guo W, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res. 2014;20(23):6212-22.
12. Aziz MH, Sideras K, Aziz NA, Mauff K, Haen R, Roos D, et al. The Systemic-Immune-Inflammation Index Independently Predicts Survival and Recurrence in Resectable Pancreatic Cancer and its Prognostic Value Depends on Bilirubin Levels: A Retrospective Multicenter Cohort Study. Ann Surg. 2018.
13. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453-7.
14. Chang CM, Yin WY, Wei CK, Wu CC, Su YC, Yu CH, et al. Adjusted Age-Adjusted Charlson Comorbidity Index Score as a Risk Measure of Perioperative Mortality before Cancer Surgery. PLoS One. 2016;11(2).
15. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surgery. 2017;161(3):584-91.
16. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009;250(2):187-96.
17. Ho V, Heslin MJ. Effect of hospital volume and experience on in-hospital mortality for pancreaticoduodenectomy. Ann Surg. 2003;237(4):509-14.
18. Costi R, De Pastena M, Malleo G, Marchegiani G, Butturini G, Violi V, et al. Poor Results of Pancreatoduodenectomy in High-Risk Patients with Endoscopic Stent and Bile Colonization are Associated with E. coli, Diabetes and Advanced Age. J Gastrointest Surg. 2016;20(7):1359-67.
19. Dias-Santos D, Ferrone CR, Zheng H, Lillemoe KD, Fernandez-Del Castillo C. The Charlson age comorbidity index predicts early mortality after surgery for pancreatic cancer. Surgery. 2015;157(5):881-7.
20. Edwards MR, Sultan P, del Arroyo AG, Whittle J, Karmali SN, Moonesinghe SR, et al. Metabolic dysfunction in lymphocytes promotes postoperative morbidity. Clin Sci (Lond). 2015;129(5):423-37.
21. Fumagalli LA, Vinke J, Hoff W, Ypma E, Brivio F, Nespoli A. Lymphocyte counts independently predict overall survival in advanced cancer patients: a biomarker for IL-2 immunotherapy. J Immunother. 2003;26(5):394-402.
22. Heffernan DS, Monaghan SF, Thakkar RK, Machan JT, Cioffi WG, Ayala A. Failure to normalize lymphopenia following trauma is associated with increased mortality, independent of the leukocytosis pattern. Crit Care. 2012;16(1).
23. White M, Mahon V, Grealy R, Doherty DG, Stordeur P, Kelleher DP, et al. Post-operative infection and sepsis in humans is associated with deficient gene expression of gammac cytokines and their apoptosis mediators. Crit Care. 2011;15(3):R158.
24. Lissoni P, Fumagalli L, Brivio F, Rovelli F, Messina G, Di Fede G, et al. Cancer chemotherapy-induced lymphocytosis: a revolutionary discovery in the medical oncology. J Biol Regul Homeost Agents. 2006;20(1-2):29-35.
25. Giardino A, Spolverato G, Regi P, Frigerio I, Scopelliti F, Girelli R, et al. C-Reactive Protein and Procalcitonin as Predictors of Postoperative Inflammatory Complications After Pancreatic Surgery. J Gastrointest Surg. 2016;20(8):1482-92.
26. Clark EJ, Connor S, Taylor MA, Madhavan KK, Garden OJ, Parks RW. Preoperative lymphocyte count as a prognostic factor in resected pancreatic ductal adenocarcinoma. HPB (Oxford). 2007;9(6):456-60.
27. Bhatti I, Peacock O, Lloyd G, Larvin M, Hall RI. Preoperative hematologic

markers as independent predictors of prognosis in resected pancreatic ductal adenocarcinoma: neutrophil-lymphocyte versus platelet-lymphocyte ratio. Am J Surg. 2010;200(2):197-203.

28. Fogar P, Sperti C, Basso D, Sanzari MC, Greco E, Davoli C, et al. Decreased total lymphocyte counts in pancreatic cancer: an index of adverse outcome. Pancreas. 2006;32(1):22-8.

29. Brivio F, Lissoni P, Tisi E, Erba L, Barni S, Tancini G, et al. Effects of a preoperative therapy with interleukin-2 on surgery-induced lymphocytopenia in cancer patients. Oncology. 1992;49(3):215-8.

30. Gade J, Levring T, Hillingso J, Hansen CP, Andersen JR. The Effect of Preoperative Oral Immunonutrition on Complications and Length of Hospital Stay After Elective Surgery for Pancreatic Cancer--A Randomized Controlled Trial. Nutr Cancer. 2016;68(2):225-33.