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The Preoperative Prognostic Nutritional Index Predicts the Development of Deep Venous Thrombosis After Pancreatic Surgery

TOMOHIRO IGUCHI[1], KEISHI SUGIMACHI[1], YOHEI MANO[1], MIHOKO KONO[2], MASAKI KAGAWA[3], TOMONORI NAKANOKO[3], HIDEO UEHARA[3], MASAHIKO SUGIYAMA[3], MITSUHIKO OTA[3], MASAHIKO IKEBE[3], MASARU MORITA[3] and YASUSHI TOH[3]

[1]Department of Hepato-Biliary Pancreatic Surgery, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan;
[2]Department of Cardiovascular Medicine, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan;
[3]Department of Gastroenterological Surgery, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan

Abstract. *Background/Aim: Pancreatic surgery is associated with a high risk of developing deep venous thrombosis (DVT) and malnutrition. We aimed to evaluate the factors predicting the development of DVT, focusing on nutrition assessment tools. Patients and Methods: One hundred patients who underwent pancreatic surgery were postoperatively examined for DVT. We assessed the risk factors for the development of DVT after surgery. Results: Postoperative DVT was detected in 11 patients (11%). Patients who developed DVT after surgery were significantly older ($p=0.016$) and had higher preoperative D-dimer levels ($p=0.005$) than those who did not. The preoperative prognostic nutritional index (PNI) was mostly associated with the development of DVT ($p=0.079$). Furthermore, PNI ≤ 44.3, BUN >20 mg/dl, D-dimer ≥ 1.9 $\mu g/ml$ were independent predictors for the development of DVT after surgery. Conclusion: A poor nutrition status and dehydration should be preoperatively improved for patients who are identified, as having a high risk of developing DVT after pancreatic surgery.*

Venous thromboembolism (VTE), which consists of pulmonary embolism (PE) and deep venous thrombosis (DVT) is a leading cause of morbidity and mortality in patients undergoing abdominal oncological surgery (1, 2). In particular, the incidence of VTE after pancreatic surgery is considered to be high (3, 4). The induction of pharmacologic prophylaxis after surgery is recommended by the 9th edition of American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (5) and prevents the development of postoperative VTE (6): however, it is not yet routinely performed in the field of pancreatic surgery because postoperative bleeding is a potentially fatal complication. Thus, identifying patients at high risk for VTE development after pancreatic surgery is a significant clinically relevant problem.

Although D-dimer has been recognized as a sensitive laboratory test for predicting VTE (7, 8), the D-dimer level is commonly elevated in patients with advanced cancer (9). Several studies have reported that preoperative serum D-dimer levels are associated with the development of DVT (10, 11); however, challenges remain in determining the prevalence of DVT before surgery.

Pancreatic surgery, particularly pancreaticoduodenectomy, is a high-risk procedure in comparison to other abdominal surgeries and patients who undergo pancreatic surgery often show a poor nutrition status. It is well known that a poor nutrition status is a risk factor of postoperative complication after surgery (12). It was recently reported that hypoalbuminemia was associated with the development of DVT in patients with liver disease (13), and gastric cancer (14). Malatino *et al.* demonstrated that DVT could be accurately diagnosed in hospitalized patients based on hypoalbuminemia and decreased protein S (15); thus, we hypothesized that malnutrition may be associated with DVT. However, little is known on the association between the nutritional status and incidence of DVT in patients after pancreatic surgery. Besides

Correspondence to: Tomohiro Iguchi, MD, Hepato-Biliary Pancreatic Surgery, National Hospital Organization Kyushu Cancer Center, 3-1-1 Notame, Fukuoka, 811-1395, Japan. Tel: +81 925413231, Fax: +81 925413262, e-mail: tomo@surg2.med.kyushu-u.ac.jp

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serum albumin, several inflammatory and nutritional scores, such as the neutrophil-to-lymphocyte ratio (NLR) (16), platelet-to-lymphocyte ratio (PLR) (17), controlling nutritional status (CONUT) score (18), modified Glasgow prognostic score (GPS) (19) and prognostic nutritional index (PNI) (20) were reported to be associated with the short-term and long-term outcomes after pancreatic surgery.

The present study aimed to evaluate factors predicting the development of DVT, with a focus on nutrition assessment tools.

Patients and Methods

Patients. Between April 2015 and August 2018, 100 consecutive patients who underwent pancreatic surgery (pancreaticoduodenectomy, n=62; distal pancreatectomy, n=35; total pancreatectomy, n=3) at our Institute were enrolled in this study. Six patients who were preoperatively diagnosed with DVT and 3 patients who did not undergo postoperative US were excluded. This project was approved by the Ethics and Indications Committee of National Hospital Organization Kyushu Cancer Center (2017-33). The mean age of the patients was 68.1 years (range=24-85 years). The male-to-female ratio was 61:39. The final diagnoses were pancreatic cancer (n=56), biliary tract cancer (n=16), other cancer (n=6), intraductal papillary mucinous neoplasm (n=13), neuroendocrine tumor (n=3), and other non-cancerous lesion (n=6). Among 78 patients who were diagnosed with cancer, 66 patients had advanced cancer (Stage ≥2) according to the Union for International Cancer Control. The mean (±standard deviation) operative time and blood loss were 284.9±90.8 min and 251.4±268.2 g, respectively.

Perioperative management. Among 100 patients, 10 patients received induction chemotherapy prior to surgery. With the exception of one laparoscopically-treated case, all patients underwent laparotomy *via* a midline incision under endotracheal general anesthesia. A central venous catheter was preoperatively inserted from the right internal jugular vein into the superior vena cava in all cases. Postoperative pain was controlled by epidural analgesia or intravenous patient-controlled analgesia, in conjunction with other analgesic medication. Graduated compression stockings and a foot pump were used for mechanical prophylaxis in all cases. All patients received a physical examination. In addition, in 57 cases, enoxaparin was initiated as pharmacologic prophylaxis against VTE on postoperative day 1 or after the removal of the epidural catheter, until postoperative day 7. All patients were routinely examined for VTE on postoperative day 7 using US and enhanced computed tomography.

Sonography. DVT of the whole leg was diagnosed by duplex scanning. Sonography was performed using a Prosound F75 instrument with a 13 MHz high-resolution linear array transducer (Hitachi, Tokyo, Japan). The area of the upper leg, including the common femoral vein, femoral vein and popliteal vein, was evaluated with the venous compression method, with the patient in the supine position. The area of the lower leg, including the peroneal vein, anterior tibial vein, posterior tibial vein, soleal vein and calf vein, was evaluated by the blood flow induction method, with the patient in a sitting position.

Nutrition assessment tools. We assessed some inflammatory and nutritional scores, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), controlling nutritional status (CONUT) score, modified Glasgow prognostic score (GPS) and prognostic nutritional index (PNI). The NLR was calculated by dividing the neutrophil count by the lymphocyte count. The PLR was calculated by dividing the platelet count by the lymphocyte count. The CONUT score is an index calculated based on the serum albumin concentration, total lymphocyte count, and total cholesterol concentration, and classifies undernutrition into 4 degrees. The modified GPS classifies undernutrition into 3 degrees based on the combination of the serum albumin level and C-reactive protein concentration. The PNI was calculated as 10× the serum albumin concentration (g/dl) + 0.005 × the lymphocyte count (/mm^3).

Statistical analysis. The clinical records of the 100 patients were collected and retrospectively reviewed. The clinical values of the DVT and non-DVT groups were compared using the $\chi 2$ test and Student's *t*-test. The association between clinical factors (including factors identified in this study as being positively associated with DVT), known risk factors for the development of DVT, and the PNI (the nutritional index most strongly associated with DVT) and the development of DVT was evaluated using a multiple regression analysis. The cut-off values of continuous variables were estimated based on a receiver-operating characteristic (ROC) curve analysis. The results were analyzed using the JMP 13.0.0 software program (SAS Institute Inc., Cary, NC, USA). *p*-Values<0.05 were considered statistically significant.

Results

Postoperative development of DVT. Eleven of 100 patients developed DVT in the postoperative period. The diameter of DVT detected in 10 patients ranged from 1.4 to 11.0 mm, with an average diameter of 4.5 mm. DVT was detected in the soleus vein (n=8) and fibular vein (n=2). After surgery, one patient developed massive DVT in the common femoral vein to the fibular vein. No PE events were diagnosed during the perioperative period.

Clinical characteristics of the DVT and non-DVT groups. The clinical findings of the DVT group were compared to those of the non-DVT group (Table I). Patients in the DVT group were significantly older (p=0.005) and had lower preoperative serum D-dimer levels (p=0.032) than those in the DVT group. The preoperative blood urea nitrogen (BUN) levels in the DVT group were higher in comparison to the non-DVT group; however, the difference was not statistically significant. Among the nutrition assessment tools, the preoperative PNI was most strongly associated with a higher risk of DVT development, and the preoperative PNI in the DVT group was lower than that in the non-DVT group (p=0.079). There were no differences in the clinical factors of the two groups, including sex, body mass index, American Society of Anesthesiologists physical status, preoperative chemotherapy, stage of cancer progression, operative procedure, operative time, blood loss or other preoperative laboratory levels.

Table I. *Comparison of clinical factors between non-DVT group and DVT group.*

Factors	non-DVT group (n=89)	DVT group (n=11)	*p*-Value
Age (years)	67.0±11.1	76.7±4.3	0.005
Gender (male/female)	54/35	7/4	0.999
BMI (kg/m^2)	22.6±3.2	22.1±2.4	0.638
ASA-PS scale (1/2/3)	7/77/5	0/10/1	0.582
Preoperative chemotherapy	9 (10.1%)	1 (9.1%)	0.999
Advanced stages of cancer (UICC, Stage ≥2)	55 (61.8%)	9 (81.8%)	0.319
Operative procedure (PD/DP/TP)	54/32/3	8/3/0	0.667
Operative time (min)	283.1±89.0	299.2±107.6	0.583
Blood loss (g)	257.6±275.2	200.9±205.4	0.511
Preoperative laboratory data			
White Blood Cell (/µl)	5390.8±1550.3	5220.9±2009.2	0.741
Hemoglobin (g/dl)	12.9±1.4	12.9±1.3	0.977
Hematocrit (%)	38.2±3.7	38.3±3.4	0.970
Platelet (×10^4/µl)	25.9±32.7	22.6±8.1	0.741
Prothrombin time (%)	104.6±17.2	98.7±17.9	0.290
Activated partial thromboplastin time (s)	33.7±9.9	31.0±1.8	0.376
Fibrinogen (mg/dl)	345.9±80.2	345.6±70.7	0.991
Albumin (g/dl)	3.9±0.4	3.7±0.4	0.169
Blood urea nitrogen (mg/dl)	14.1±3.6	15.9±4.7	0.131
Creatinine (mg/dl)	0.7±0.2	0.8±0.2	0.545
Natrium (mmol/l)	139.9±2.0	139.4±2.1	0.406
Total cholesterol (mg/dl)	194.7±35.9	183.6±36.3	0.337
C-reactive protein (mg/dl)	0.3±0.9	0.5±0.7	0.631
D-dimer (µg/ml)	1.2±1.7	2.5±3.2	0.032
Nutrition assessment tool			
NLR	2.4±1.2	2.6±1.2	0.590
PLR	176.1±153.5	173.6±50.0	0.958
CONUT (normal/light/moderate/severe)	50/33/6/0	3/6/2/0	0.391
Modified GPS (0/1/2)	68/17/4	6/4/1	0.296
PNI	46.4±5.0	43.7±3.2	0.079
Pharmacologic DVT prophylaxis	50 (56.2%)	7 (63.6%)	0.915

DVT, Deep venous thrombosis; BMI, body mass index; ASA-PS, American Society of Anesthesiologists physical status; UICC, Union for International Cancer Control; PD, pancreaticodeodenectomy; DP, distal pancreatectomy; TP, total pancreatectomy; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; CONUT, controlling nutritional status; GPS, Glasgow prognostic score; PNI, prognostic nutrition index.

Predictive factors for postoperative DVT development. In multiple regression analysis, the following variables were independently associated with the risk of postoperative DVT development: PNI ≤44.3, BUN >20 mg/dl and D-dimer ≥1.9 µg/dl (p=0.014, p=0.033 and p=0.036, respectively; Table II).

Table II. *Multivariate analysis of risk factors associated with the incidence of postoperative DVT.*

Variable	HR (95% CI)	*p*-Value
PNI ≤44.3	31.3 (2.0-486.4)	0.014
BUN >20 mg/dl	25.2 (1.3-484.9)	0.033
D-dimer ≥1.9 µg/dl	12.2 (1.1-136.2)	0.036

HR: Hazard ratio; CI, confidence interval; PNI, prognostic nutrition index; BUN, blood urea nitrogen.

Discussion

There have been numerous studies on VTE, including the prevalence and risk factors for DVT in patients undergoing surgery (10, 21). Pancreatic surgery is known to be associated with a high risk of DVT after surgery (3, 4). Nevertheless, the clinical relevance of DVT after pancreatic surgery has not been fully elucidated. In this study, we showed that the frequency of DVT after pancreatic surgery was 11.0%. In general, the frequency of VTE after surgery is reported to be 0.63-1.6% (22, 23). Our data also support that the incidence of DVT was high after pancreatic surgery. We also showed that a preoperative low PNI, high BUN and high D-dimer influenced the development of DVT after pancreatic surgery.

In the present study, we showed that the preoperative PNI, a nutrition assessment tools, was a significant risk factor for the development of DVT after pancreatic surgery. To the best of our knowledge, this study was the first to evaluate the risk factors for DVT after pancreatic surgery with a focus on nutrition assessment tools. It is well recognized that Virchow's triad, including a hypercoagulable state, stasis and endothelial injury contribute to the development of DVT (24). Patients with vascular endothelial injury caused by malnutrition may develop venous thrombosis through the aggregation of platelets or the release of cytokines from subendothelial tissue.

Dehydration induces hemoconcentration and hyperviscosity of total plasma and the development of a hypercoagulable state. Dehydration has been reported as a significant risk factor for the development in relation to air flights, bariatric surgeries and seasonal variation (25, 26). Tanira *et al*. demonstrated that dehydration caused changes to the coagulation system, including platelet aggregation and the accelerated formation of thrombosis in mice (27). Consistent with these findings, the preoperative BUN level was a risk factor for the development of DVT after pancreatic surgery in this study. Thus, hypovolemia attributed to vascular permeability following surgical stress, in addition to preoperative dehydration, could induce a severe hypercoagulable state in the perioperative period.

Several factors, including infection, surgery, age and malignancy can lead to D-dimer elevation, irrespective of the development of VTE (28). Hence, the non-specific elevation of D-dimer was observed after surgery. On the other hand, several studies showed that preoperative serum D-dimer elevation was associated with a higher cumulative incidence of postoperative DVT (10, 11). In our study, the preoperative serum D-dimer level was also a risk factor for the development of DVT after surgery, suggesting that a hypercoagulable state already existed in such patients who developed DVT after surgery.

Our study was associated with several limitations. First, this study was a retrospective study that was performed in a single center. Second, it was unclear whether DVT was present before surgery or not. A larger prospective multicenter study performed according to appropriate protocols is needed to validate our results.

In conclusion, this study shows that preoperative PNI, BUN and D-dimer value were associated with the development of DVT and a poor nutrition status and dehydration should be preoperatively improved for patients undergoing pancreatic surgery who are considered to be at increased risk for the development of DVT.

Conflicts of Interest

The Authors declare no conflicts of interest associated with this manuscript.

Authors' Contributions

Tomohiro Iguchi: study concept and design, drafting of manuscript; Keishi Sugimachi: study concept and critical revision of the manuscript; Yohei Mano: data collection; Mihoko Kono: study concept; Msaki Kagawa: data collection; Tomonori Nakanoko: statistical analysis; Hideo Uehara: data collection; Masahiko Sugiyama: data collection; Mitsuhiko Ota: statistical analysis; Masahiko Ikebe: critical revision of the manuscript; Masaru Morita: critical revision of the manuscript; Yasushi Toh: final approval of the manuscript.

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