Needle-Based Confocal Laser Endomicroscopy Examination of Autoimmune Pancreatitis With Cystic Lesions (With Video)

To the Editor:

Autoimmune pancreatitis (AIP) is a benign disease recognized as a distinctive type of pancreatitis with a presumed autoimmune etiology. The typical pancreatic imaging features of AIP include diffuse and irregular narrowing of the main pancreatic duct (MPD) and enlargement of the pancreas. The presence of cystic lesions in AIP is rare. There are approximately 20 case reports of AIP presenting with pancreatic cysts.[1] Among patients with available histology, 4 cases had immunoglobin G4 (IgG4) lymphoplasma cell infiltration in the pancreatic pseudocyst wall; however, 3 of them received corticosteroids, without any clinical or radiographic response. The pathomechanism of their formation is not clear because of limited data. Needle-based confocal laser endomicroscopy (nCLE) is a novel imaging technique, which enables real-time in vivo microscopic imaging of the cyst wall during endoscopy with a promising diagnostic yield. The nCLE examination may improve our understanding of pancreatic cystic lesions (PCLs) in AIP patients.

We included 2 cases with remarkably elevated serum IgG4 and multiple PCLs. The largest cystic lesions of both cases underwent endoscopic ultrasound–guided nCLE. During the procedure, nCLE preloaded 19-gauge fine-needle aspiration (FNA) needle was advanced into the cystic lesions under endoscopic ultrasound guidance. The data were stored digitally for postprocedural analysis. Endoscopic ultrasound-FNA was performed immediately after from the same location. Videos of nCLE were reviewed by the endoscopists (Y.F. and A.Y.) and pathologists (Y.Z. and Z.M.), who were not blinded to the clinical or histopathologic features.

Both patients consented to the use of intravenous fluorescein and to the performance of nCLE prior to FNA. Antibiotics were routinely administered before the procedure. The study was approved by the institutional review board of our hospital.

Table 1 demonstrates the characteristics of the included patients and the cystic lesions. Elevated serum IgG4 levels more than 4 times the upper limit of normal were found in both patients. One patient had focal pancreatic swelling, whereas the other had no pancreatic swelling at all. Pancreatic duct narrowing could be found in both cases.

Multiple cystic lesions were both located in the body and tail of the pancreas. The cystic lesions were less than 3 cm in 1 patient, whereas 1 cyst was greater than 3 cm in the other. Analysis of the cystic fluid showed elevated level of amylase and normal carcinoembryonic antigen in both patients. Cytological results were unremarkable. For the first patient, nCLE showed heterogeneous-sized bright-white particles, which suggested pseudocyst (Supplemental Digital Content 1, Video 1, http://links.lww.com/MPA/A765 and Supplemental Digital Content 2, video descriptions, http://links.lww.com/MPA/A766), and removal of these cystic lesions was quickly achieved by steroid treatment (Figs. 1A, B). However, nCLE showed interlaced superficial vascular network of the largest cyst in the other patient (Supplemental Digital Content 3, Video 2 and Supplemental Digital Content 2, video descriptions, http://links.lww.com/MPA/A766), and it persists despite adequate treatment (Figs. 1C, D). Definitive exclusion of neoplastic cystic lesion in this patient can be difficult, and long-term follow-up is needed.

To our knowledge, this is the first study that describes the nCLE findings of pancreatic cystic wall in patients with AIP.

Comprehensive nCLE criteria have been established for the characterization of the most frequent types of PCLs (serous and mucinous cystadenomas, intraductal papillary mucinous neoplasm (IPMN), neuroendocrine neoplasm, and pseudocysts) in several studies.[2–4] The PCLs of the first patient in our study were diagnosed as pseudocysts based on cystic fluid analysis and nCLE findings, which were fields of bright particles. Removal of these pseudocysts was quickly achieved by steroid treatment.

Formation of pancreatic cyst in patients with AIP has been reported in 21 cases to date.[1] Most of them were clinically or surgically diagnosed as pseudocysts. Therapy with steroids was initiated in 14 patients. Cystic lesions in 4 patients resolved completely with steroid, whereas 4 large cystic lesions had partial response, and 6 patients had no response. D'Egidio and Schein[5] classified pseudocysts in 1991. The pseudocyst in AIP can be classified as type II or type III. Narrowing of the MPD might be responsible for the pseudocyst growth. Responsiveness to corticosteroid treatment possibly ameliorates the narrowing of the MPD causing pancreatic juice release, which induces rapid resolution of the pancreatic cyst.

The nCLE findings of the other patient in our study were interlaced superficial vascular network of the largest cyst, which has not been described in nCLE criteria before. The small cystic lesions had response to steroids, whereas the largest one had no response. Definitive exclusion of neoplastic cystic lesion in this patient can be difficult. There are some articles concerned with the association of AIP with IPMN,[6] as well as with pancreatic malignancy.[7,8] The typical nCLE findings of IPMN are papillary projections.[9] The pattern of dark aggregates of cells surrounded by small vessels may be a promising characteristic in identification of malignant PCLs.[10] Although the nCLE findings of the other AIP patients were not in accord with any of the patterns described above, long-term follow-up is needed for neoplastic surveillance.

Development of PCLs in AIP is a rare phenomenon, with only a few cases reported in the literature. The variable response to steroid may be due to different histological nature of the PCLs. Endoscopic ultrasound with nCLE could be a promising diagnostic modality in identification of PCLs of AIP patients. Further studies are needed to confirm these findings.

TABLE 1. Patients and Cystic Lesions Characteristics

Patient	Sex	Age, y	Clinical Manifestations	sIgG4, mg/L	Pancreatic Swelling	No. Cysts	Location	Size, cm
1	Male	56	Abdominal pain	5420	Focal swelling	Multiple	Body, tail	<3
2	Male	62	Jaundice	21,700	No	Multiple	Body, tail	>3

Reference range of serum IgG4 is 0 to 1350 mg/L.

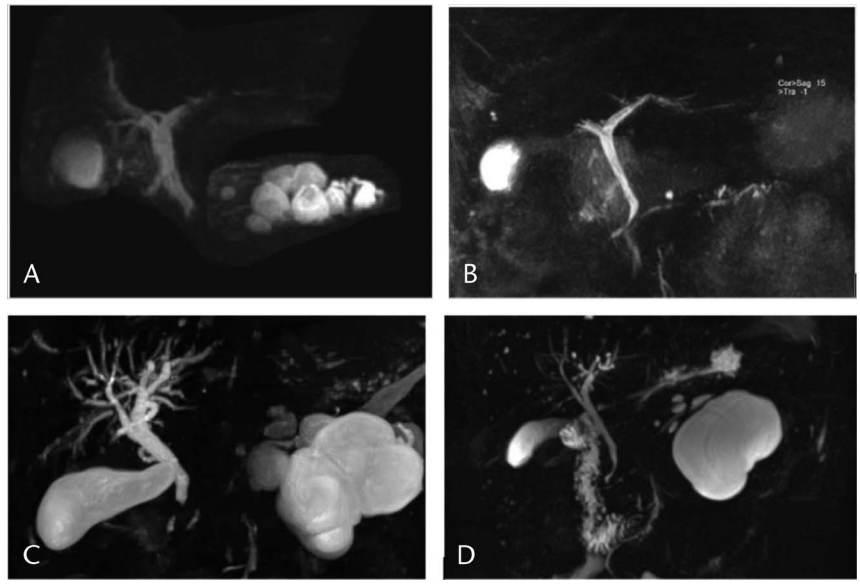

FIGURE 1. A and B, Magnetic resonance imaging scans showing presence and removal of PCLs in the first patient before and after steroid. C and D, Magnetic resonance imaging scans showing presence and partial response of PCLs in the other patient before and after steroid.

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Nonfunctional Pancreatic Neuroendocrine Carcinoma With Isolated Retroperitoneal Metastasis
A Case Report and Literature Review

To the Editor:

Pancreatic neuroendocrine tumors (pNETs) are rare neuroendocrine neoplasms, with an estimated incidence of approximately 1 per million per year, about 3% of primary pancreatic tumors.[1] Most of them are nonfunctional tumors (50%–75%).[2] Newly published 2010 World Health Organization (WHO) classification classified them into three distinct types: neuroendocrine tumor grade 1 (G1), neuroendocrine tumor grade 2 (G2), and neuroendocrine carcinoma (G3).[3] Pancreatic neuroendocrine carcinoma (pNEC) only amounts to about 2% to 3% of all pNETs. Here we demonstrated a rare case of pNEC with isolated retroperitoneal metastasis. It served as the only

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reported case of pNEC metastases spread to the retroperitoneal preceded to other organs.

CASE REPORT

A 61-year-old female was referred to our hospital with gallbladder polyps and right upper quadrant pain. We discovered a 3.55-cm mass in the tail of the pancreas, a 3.92-cm mass in the right retroperitoneal, and right retroperitoneal lymph node enlargement (Figs. 1A-C). Tumor markers showed that carcinoembryonic antigen was 17.48 ng/mL (reference range, 0–5 ng/mL) and alpha-fetoprotein was 7.99 IU/mL (reference range, 0–5.8 IU/mL). The patient underwent distal pancreatectomy + splenectomy + regional lymph nodes dissection + retroperitoneal mass resection + cholecystectomy in our hospital. Upon microscopic analysis, the pancreatic tail was nodule confirmed as pNEC, and the retroperitoneal mass was distant metastasis (Figs. 1D-E). The mitotic count was 5 to 8 per 10 high-power field. Immunohistochemical staining revealed CD117, (+); CD56(NK-1), (+); CK19, (partially +); CK7, (−); CgA, (+); Ki-67, (20%–30%); Syn, (+). There were no lymph node metastases. The pathological diagnosis was T2, N0, M1, stage IV, with an R0 resection.

After 20 months of regular follow-up, some liver, bone, and right kidney lesions with retroperitoneal metastasis recurrence were found by abdominal computed tomography (CT). Further fluorine-18-fluorodeoxyglucose (^{18}F-FDG) and fluorine-18-octreotide (^{18}F-Octreotide) positron emission tomography (PET)/CT showed abnormal uptake of ^{18}F-Octreotide was observed in newly found lesions and retroperitoneal metastasis recurrent, which were considered as NEC metastasis tumors (Fig. 1F). Hardly any uptake of ^{18}F-FDG is evident at the same sites. The patient underwent further medical treatment (everolimus, 10 mg/d) in oncology. Unfortunately, the effect of medical treatment was minimal and the patient ultimately succumbed 25 months after the surgery.

DISCUSSION

Pancreatic neuroendocrine tumors are extremely rare, and the biological behavior of pNETs is unpredictable. Neuroendocrine carcinoma is defined as carcinomas that have been reckoned as poorly differentiated tumors with highly invasive nature and high proclivity for metastatic dissemination. Making early diagnosis and treatment seems complicated if they are nonfunctional and thus have no special symptoms or signs at an early stage. Most of them are incidentally detected on imaging and the patients already have distant metastases, as in this case. Computed tomography and magnetic resonance imaging can be used to establish the location of the primary NETs and help guide the proper surgical or medical treatment. Recent various meta-analyses or series show that (68)Ga-labeled somatostatin analogs PET/CT have higher sensitivity (92%), higher specificity (88%), higher accuracy (93%), and empowers whole-body assessment of disease extent.[4] The functional imaging of NETs can be also used to evaluate malignancy because different grades of NETs exhibit different receptor expression or metabolic pathways.[5]

The microscopic analysis combined with immunohistochemistry is the "gold standard" for the diagnosis of pNETs. Chromogranin A (CgA) and synaptophysin (Syn) are neuroendocrine markers.[6] Histopathological classification of pNETs can be categorized based on the mitotic count and the Ki-67 proliferation index according to 2010 WHO classification of gastropancreatic-neuroendocrine neoplasms. On this measure, the high of two is adopted for categorization, our case can be classified as G3. Some authors speculate that NEC with a Ki-67 index below 55%, can be called a new category, had better survival and lower relative risk.[7] Many scholars hold the view that NEC may not have only 1 entity. By analyzing 2158 cases from the Surveillance, Epidemiology, and End Results database, grading and systemic metastases are considered to have a significant impact on survival.[8]

Surgical resection with regional lymph node dissection is the only cure for patients with pancreatic NETs, but the role of chemotherapy after curative resection is still unclear. The National Comprehensive Cancer Network guideline recommends if complete resection is possible, resect the primary tumor and metastases with a regular postoperative review is enough.[9] In contrast, for poorly differentiated (high-grade) extrapulmonary NECs, the North American Neuroendocrine Tumor Society guideline believes that it is unlikely to be curative by surgery alone. Chemotherapy (4 to 6 cycles of carboplatin and etoposide or cisplatin) after surgery is recommended.[10]

In summary, owing to the nonfunction, most of the pNETs can only be incidentally discovered by imaging. Surgical resection remains the only cure. Positron emission tomography/CT is one of best imaging techniques for whole body assessment of disease extent and valuable surgical or medical treatment. Chemotherapy after curative resection of pNEC may influence their prognosis. Medical management for advanced pNETs is of equal importance.

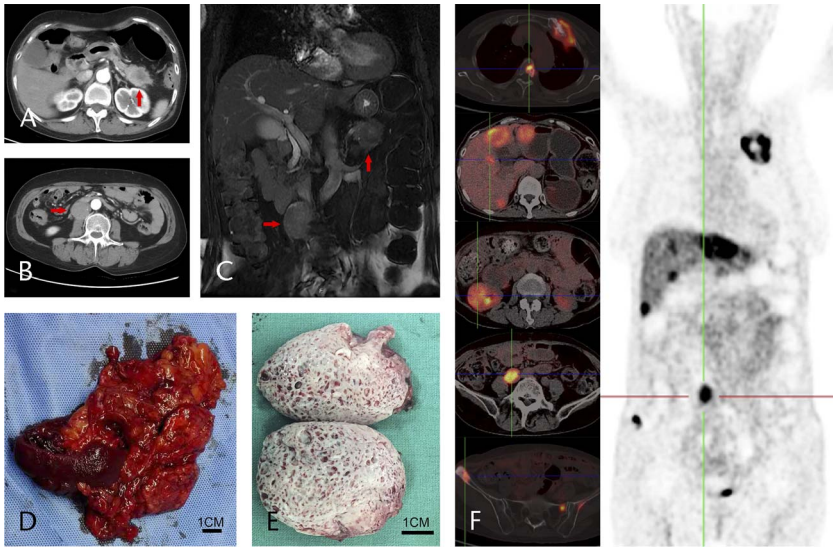

FIGURE 1. A, Pre-operative arterial phase CT image reveals a 2.82 × 3.71 cm poorly enhancing mass is defined in the pancreatic tail portion (↑). B, A 3.09-cm poorly enhanced nodule is seen in the right retroperitoneal, in front of right lumbar muscle (→). C, Pancreatic tail mass (↑) and retroperitoneal nodule (→) showed in preoperative magnetic resonance imaging. Resected specimens: (D) Pancreatic tail mass and (E) cutout view of the retroperitoneal nodule. F, ^{18}F-Octreotide PET/CT showing increased tracer uptake in bones, liver, right kidney, and retroperitoneal. Hardly any uptake of ^{18}F-FDG is evident at the same sites.

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Resection of Replaced Common Hepatic Artery in Locally Advanced Pancreatic Cancer
A Case Report and Analysis of Technical and Oncological Implications

To the Editor:

Current evidence suggest that management of locally advanced pancreatic cancer (LAPC) with neoadjuvant treatment followed by radical resection may confer survival similar to earlier stages of the disease.[1] In this setting, the benefits of arterial resections remain controversial. We report a case of successful resection of a replaced common hepatic artery (rCHA) completely encased by a pancreatic head tumor and reconstruction with the use of transposed splenic artery (SA).

CASE PRESENTATION

A 43-year-old woman with no medical history was diagnosed with a biopsy-confirmed 30 × 35-mm pancreatic adenocarcinoma. The tumor abutted the superior mesenteric vein just inferior to the splenic vein confluence and the superior mesenteric artery for 180 degrees. A rCHA arising from the superior mesenteric artery was encased by the tumor. There was no evidence of metastatic disease on staging scans. The patient received 6 cycles of neoadjuvant leucovorin, 5-fluorouracil, irinotecan and oxaliplatin chemotherapy, and restaging imaging showed a modest reduction in the local volume of the disease. Carbohydrate antigen 19-9 levels dropped from 591 to 119 U/mL. The anatomical variant of the rCHA completely encased by the tumor was the determining factor for staging the disease radiologically as locally advanced. The relatively small size of the tumor, absence of metastatic disease, disease response to neoadjuvant treatment, and the patient's clear medical history and excellent performance status were positive factors in the decision to proceed to resection.

The resection initially followed the stages of standard pancreaticoduodenectomy. After periadventitial dissection and skeletonization of the rCHA proximally and distally, tumor encasement was identified within approximately 5 mm from its origin and for approximately 3 cm. An arterial resection was deemed necessary for complete tumor clearance. The resection continued as a total pancreatectomy and splenectomy to eliminate the risks from a pancreatic leak in the presence of an arterial reconstruction. Appropriate length of SA was preserved. Wedge resection of the superior mesenteric vein was also performed. At the end of the resection, the arterial reconstruction was performed by means of transposition of the SA and end-to-end anastomosis with the rCHA, followed by a hepaticojejunostomy and gastrojejunostomy (Fig. 1). Arterial and portal flow into the liver was confirmed with ultrasound Doppler.

The patient marked an uncomplicated recovery and was discharged on the 15th postoperative day on warfarin. Histopathology confirmed a moderately differentiated pancreatic ductal adenocarcinoma, with vascular and perineural invasion and stage pT2N0 (0 of 41 lymph nodes) with clear margins.

DISCUSSION

Recent advances in LAPC management have led to a change in the understanding of disease resectability. Arterial resections remain controversial, as the literature suggests higher risks of morbidity and mortality in the absence of proof of oncological benefit for these patients.[2,3] Various studies have reported results in pancreatectomies with arterial resections (celiac, hepatic, and superior mesenteric arteries). As most common hepatic artery resections have been reported within a group of arterial resections, it is difficult to delineate the common hepatic artery resection–specific results. A meta-analysis of retrospective studies identified longer operative time, higher blood loss, perioperative morbidity (17%–100%), and reoperation rate (0–75%).[2] Postoperative mortality has been reported between 0% and 45% with a 5-fold increased risk compared with standard resections and 8-fold increased risk compared with venous only resections.[2] With regard to the reconstruction, various methods have been used, including autologous venous[4,5] or arterial[6,7] interposition graft, transposition of native arteries,[6–8] or use of cryopreserved vessels.[5] Preoperative embolization of the hepatic artery without arterial reconstruction has also been reported with promising short-term results.[9] The paucity of data on long-term outcomes, with one study reporting 97% patency of reconstruction in a median follow-up time of approximately 1.5 years,[4] perhaps may be explained by the relatively short survival of patients with LAPC. It is the authors' opinion that with the current trend toward increasing survival, an arterial reconstruction should be preferred whenever hepatic artery resection is performed during pancreaticoduodenectomy or total pancreatectomy. Primary reconstruction is favored when possible (length of artery adequate for a tension-free repair); otherwise, SA transposition is favored over venous

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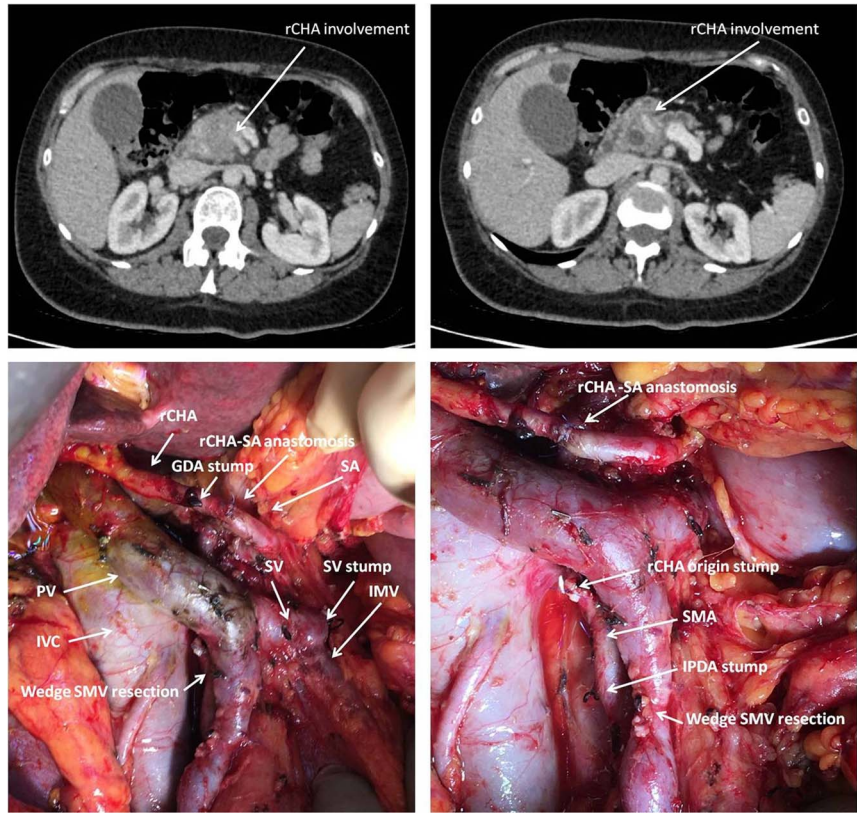

FIGURE 1. Preoperative computed tomographic scan demonstrating rCHA involvement by the tumor and operative field after resection and reconstruction. GDA, gastroduodenal artery; IMV, inferior mesenteric vein; IPDA, inferior pancreaticoduodenal artery; IVC, inferior vena cava; SMA, superior mesenteric artery; SMV, superior mesenteric vein; SV, splenic vein; PV, portal vein.

interposition graft owing to the usual size match and the higher patency rates with use of arterial grafts. The use of cryopreserved cadaveric arteries in the absence of immunosuppression has not been adequately studied and carries the theoretically higher risk of thrombosis due to rejection. Nonetheless, cryopreserved cadaveric or artificial grafts should be considered in the absence of better options.

From the oncological perspective, histological evidence of arterial invasion was found only in 44% of the published cases with a median R0 resection rate of 60%.[2] Although true involvement of the arterial wall is not always present, in cases of complete vessel encasement, an R0 resection would be impossible without an arterial resection. With regard to lymph node metastasis, no difference has been identified.[2] The local recurrence rate after arterial resection was lower compared with standard pancreaticoduodenectomy (20% vs 47%, $P = 0.02$).[4] Nonetheless, 1-year (47%–50%; range, 16%–83%), 3-year (8.3%; range, 0%–30%), and 5-year (0%; range, 0%–42%) survival rates, as well as median overall survival (range, 7–25 months) were significantly lower than that of standard pancreatectomy.[2,4] Of note, 1-year (odds ratio, 3; $P = 0.03$) and 2-year (odds ratio, 6; $P = 0.23$) survival rates were better compared with patients who received palliative treatment.[2] These results suggest that the locally advanced stage may also depict unfavorable tumor biology with potential presence of micrometastatic disease at the time of the resection. An exception to this may be the cases where arterial anatomy is responsible for the locally advanced stage of the disease.[10]

CONCLUSIONS

Our case argues in favor of arterial resections been considered during pancreaticoduodenectomy in an effort to achieve a complete resection. Good patient selection, assessment of tumor biology, surgical expertise, and multidisciplinary specialized management in high-volume tertiary setting are necessary for successful outcomes.

J.A.A. and N.A.C. reviewed the literature and drafted the manuscript. All remaining authors contributed in manuscript revision and editing.

Informed written consent was obtained from the patient for publication of this report and any accompanying images.

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Factors Causing Abnormal Heart Failure After Successful Fluid Resuscitation on Acute Pancreatitis Patients

To the Editor:

In the early stages of acute pancreatitis (AP), the large amount of fluid entering the interstitial space due to capillary leakage syndrome can lead to hypovolemic shock, which may subsequently manifest as perfusion abnormalities and multiple-organ dysfunction.[1–3] To restore organ perfusion, fluid resuscitation has gradually been recognized over the last 20 years as a very important treatment.[4] After inflammation improves, the large amount of fluid that has accumulated in the interstitial space gradually returns to systemic circulation and becomes a mechanism of organ function recovery. However, the speed of liquid self-return is difficult to estimate and excessive liquid self-return still may lead to cardiac insufficiency, which we refer to as abnormal heart failure (AHF). This study used a data set to analyze related factors, diagnosis methods, and prognosis of AP + AHF.

Between June 2005 and June 2017, 1834 patients with AP who were admitted to the First Affiliated Hospital of the Medical College, Zhejiang University, were reviewed. Among them, 136 patients who had hypovolemic shock in the early stages recovered successfully after fluid resuscitation, of whom 22 patients exhibited AHF. The diagnostic criteria for AHF were as follows: during the improvement period after successful fluid resuscitation, the patient exhibited various manifestations of heart failure, along with increased urine volume, decreased body weight, and decreased corrected cumulative net input (CCNI); the specific indicators of heart failure were cardiac index (CI) <3.0, global end-diastolic volume index >700, intrathoracic blood volume index >850, and extravascular lung water index (ELWI) >10 (provided by transpulmonary thermodilution). A comparative assessment of general characteristics (age, sex, and baseline weight), AP severity (severe AP [SAP]% and severity of organ failure),[5] liquid exudation intensity (CCNI and weight loss ratio [WLR]), and prognosis (mortality, intensive care unit [ICU] stay duration, and peripancreatic infection rate) was performed.

There was no significant difference in the sex distribution or basal body weight between the AHF (n = 22) and non-AHF (n = 114) groups. Patient age was significantly greater in the AHF group than in the non-AHF group ($P < 0.0001$). Acute pancreatitis severity ($P = 0.0156$), developed rate of organ failure ($P = 0.0352$), and number of organs involved ($P = 0.0370$) were greater in the AHF group than in the non-AHF group. The CCNIs ($P = 0.0168$) during fluid resuscitation and WLR ($P = 0.0035$) in the healing period were both significantly greater in the AHF group than in the non-AHF group, although there was no significant difference in the debridement surgery rate and mortality between the two groups. The incidence of peripancreatic infection was higher ($P = 0.0032$) and the ICU stay duration was greater ($P < 0.0001$) in the AHF group than in the non-AHF group (Table 1).

TABLE 1. Risk Factors and Prognosis of AHF

	AHF Group (n = 22)	Non-AHF Group (n = 114)	*P*
Age, mean ± SEM, y	64.14 ± 1.142	55.34 ± 0.889	<0.0001
Sex, male, n (%)	7 (31.8)	47 (41.2)	0.40888
Basic weight, mean ± SEM, kg	65.27 ± 1.394	67.44 ± 0.6467	0.1768
Speed of organ failure, mean ± SEM, d	2.773 ± 0.2175	3.474 ± 0.1383	0.0352
Organ involvement, n			0.03703
Shock	2	35	
Shock + ARDS	20	79	
Severity, n			0.01568
SAP	20	74	
MSAP	2	40	
CCNI, mean ± SEM	0.1125 ± 0.005501	0.09779 ± 0.002439	0.0168
WLR, mean ± SEM, ×100%	0.8728 ± 0.008299	0.9009 ± 0.003722	0.0035
Peripancreatic infection, n (%)	14 (63.6)	35 (30.7)	0.00322
ICU hospital stay, mean ± SEM, d	18.37 ± 1.624	9.419 ± 0.6587	<0.0001
Debridement surgery, n (%)	7 (31.8)	17 (14.9)	0.10983
Death, n (%)	3 (13.6)	9 (7.8)	0.64638

Corrected cumulative net input is measured as cumulative net input (*n*)/baseline weight (day *n*); cumulative net input (*n*) is measured as net amount on day 1 + net amount on day 2 + … + net amount on day *n*. Net input on day *n* is measured as liquid intake (*n*) − liquid output (*n*) (day *n*); WLR is measured as (baseline weight − lightest weight)/baseline weight; lightest weight is measured as the weight of a patient who underwent fluid resuscitation and entered a stable phase after tissue edema regression.

ARDS indicates respiratory distress syndrome.

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Patients with AHF were older, had more severe organ failure or more organ involvement, and had more fluid accumulation in the interstitial space during fluid resuscitation compared with non-AHF patients. These factors may inevitably have led to a greater intertissue fluid load and decreased cardiopulmonary and renal ability to adjust the volume of circulating fluid. To understand the physiological process easily, we created a diagram to explain the changes in the distribution of the fluid volume in the circulation and tissue (C/T ratio; Fig. 1). During the shock phase (Fig. 1A), a large circulating volume entered the tissue, leading to a significant reduction in the C/T ratio, global end-diastolic volume index (GEDI), and CI. During the rapid resuscitation phase of fluid resuscitation (Fig. 1B), the circulation volume returned to a normal state, although a greater volume of liquid was distributed in the tissues; as a result, the body weight and CCNI, GEDI, and CI accordingly increased to some extent. During the AHF phase (Fig. 1C), a large volume of tissue fluid returned to the circulation owing to microcirculation recovery. Although the urine volume increased, there may have unexpectedly been more liquid in the circulation. This manifested as a decrease in body weight and CCNI; however, the C/T ratio, GEDI, and ELWI gradually exceeded the normal value, eventually leading to AHF. When AHF patients experience shortness of breath, have large shadows in the lungs on x-ray, and experience hypoxemia after early shock and successful fluid resuscitation, they are easily misdiagnosed as having pulmonary infection (18/22 AHF patients); if needed, empiric diuretics can be used to further confirm the diagnosis.[6] During the recovery phase (Fig. 1D), along with the additional volume of liquid that has been excreted from the body, with or without medical treatment, the body

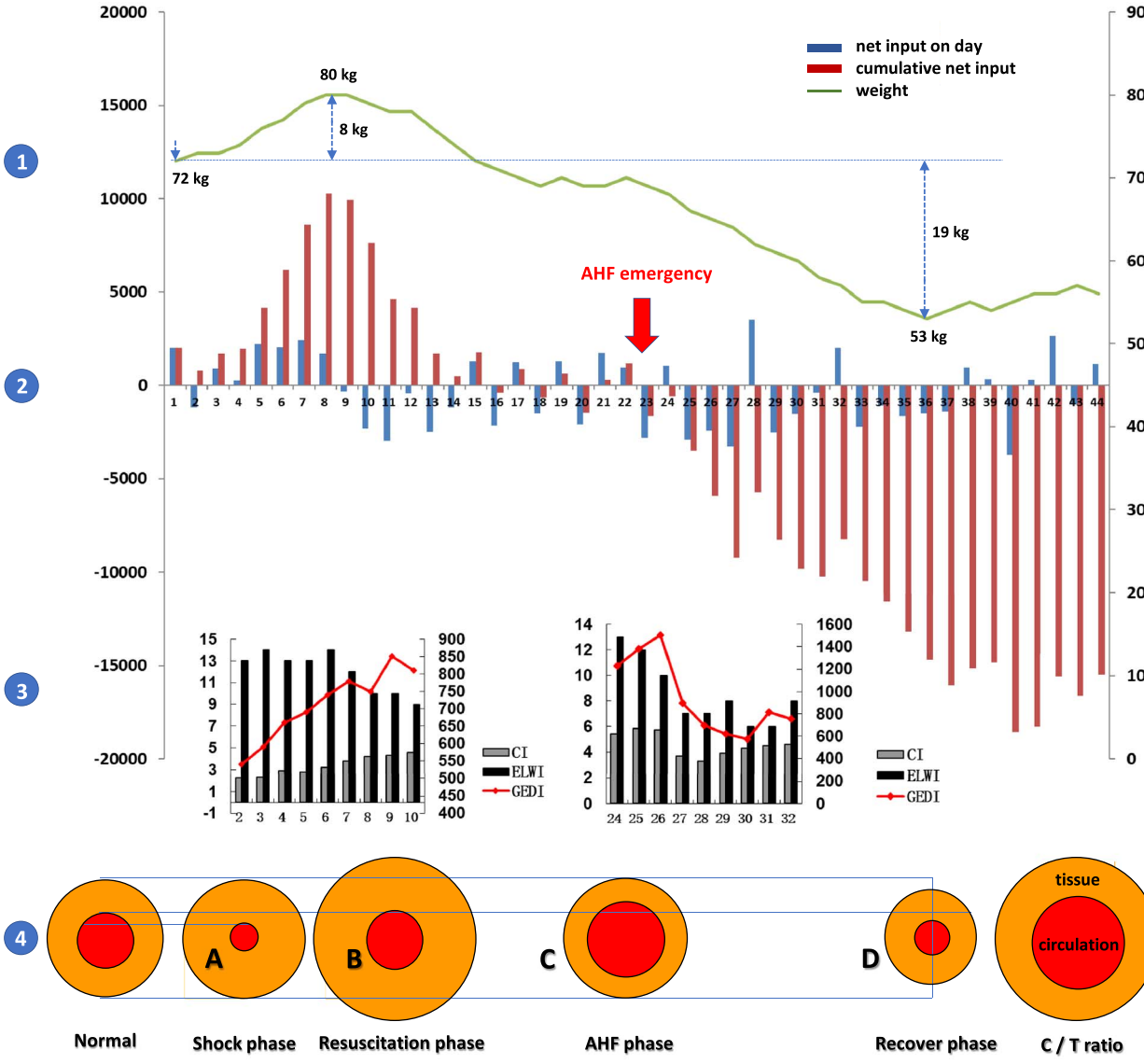

FIGURE 1. (1) The green curve indicates the weight change. (2) Liquid net divergence is depicted, including the net input on day *n* (blue column) and cumulative net input (*n*) (red column). A positive number suggests that the input quantity is greater than the output quantity, and a negative number suggests that the output quantity is greater than the input quantity. (3) With regard to TDTP monitoring, the left image shows the trend in the CI/ELWI/GEDI values during the liquid resuscitation stage, whereas the right image shows the trend in the CI/ELWI/GEDI values after the patient developed AHF. (4) Relationship between circulation capacity (red circle) and tissue interstitial fluid volume (yellow circle): normal, shock (A), resuscitation (B), AHF (C), and recovery (D) phases. TDTP, transpulmonary thermodilution.

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weight and CCNI decreased further, and the C/T ratio, CI, ELWI, and GEDI values returned to normal. Thus, the loss of an equal proportion of tissue quality and circulation capacity is the cost of recovery from SAP.

Abnormal heart failure itself will affect the prognosis of SAP to a certain extent, and its delayed diagnosis and treatment will produce further adverse consequences; therefore, it is vital for clinicians to identify the early occurrence of AHF during the treatment of SAP. We believe that the close monitoring of important parameters such as transpulmonary thermodilution measures in high-risk patients, assessment of CCNI and body weight, and excluding a diagnosis of lung infection, myocardial infarction, and lung infarction can facilitate the prompt diagnosis of AHF.

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Trends and In-Hospital Outcomes of Neuroendocrine Neoplasms

To the Editor:

Neuroendocrine cells are distributed widely throughout the body. Neuroendocrine neoplasms (NENs) are epithelial tumors with predominant neuroendocrine characteristics as manifested by immunohistochemical staining and can arise in various organs throughout the body. Although some of the clinicopathologic features are unique to the site of origin, other characteristics are shared regardless of the site.[1] The classification and nomenclature of NENs are confusing, in part because most studies have focused on tumors arising in a specific organ system. Site-specific proposals for nomenclature and classification differ in terminology and in the criteria for histologic grading and staging.

There is evidence that there has been a significant increase in the incidence of NENs from 1973 to 2004.[2] Furthermore, histologic grading, primary tumor site, and disease staging were found to be strong predictors of outcome in these patients by Surveillance, Epidemiology, and End Results database analysis. Despite this, limited evidence exists regarding the trends and in-hospital outcomes among these patients. Although the annual incidence of NENs remains low, the prevalence of NENs is relatively high owing to the long survival of patients with low-grade NENs. Clinicians need to be become familiar with the natural history, trends, patterns, and outcomes for these tumors as well as the financial cost of taking care of patients with NENs.

We studied the trends of hospitalizations, demographics, diagnosis at presentation, and in-hospital outcomes in patients with NENs. We used the National Inpatient Sample data set, a nationally representative weighted sample of all US hospital discharges, for this study.[3] We obtained data from the year 2008 to 2014 and identified the diagnosis of NENs (*International Classification of Diseases, Ninth Revision* code: 209.x). Categorical and continuous variables were tested using the χ^2 test and Student *t* test.

Overall, 38,686 patients with NENs were identified between 2008 and 2014. The NEN subtypes included were as follows: malignant small intestinal carcinoid tumors (11.5%); malignant carcinoid tumors of the appendix, large intestine, and rectum (7%); malignant carcinoid tumors of other and unspecified sites (38.7%); malignant poorly differentiated neuroendocrine tumors (12.6%); benign carcinoid tumors of the small intestine (4%); benign carcinoid tumors of the appendix, large intestine, and rectum (3.7%); and benign carcinoid tumors of other and unspecified sites (13.8%; Fig. 1). There were 179 (0.5%) of the 38,686 patients who had carcinoid syndrome on primary presentation of the diagnosis.

We found a mean age of 62.88 years, female predominance (51.9%), and predominantly

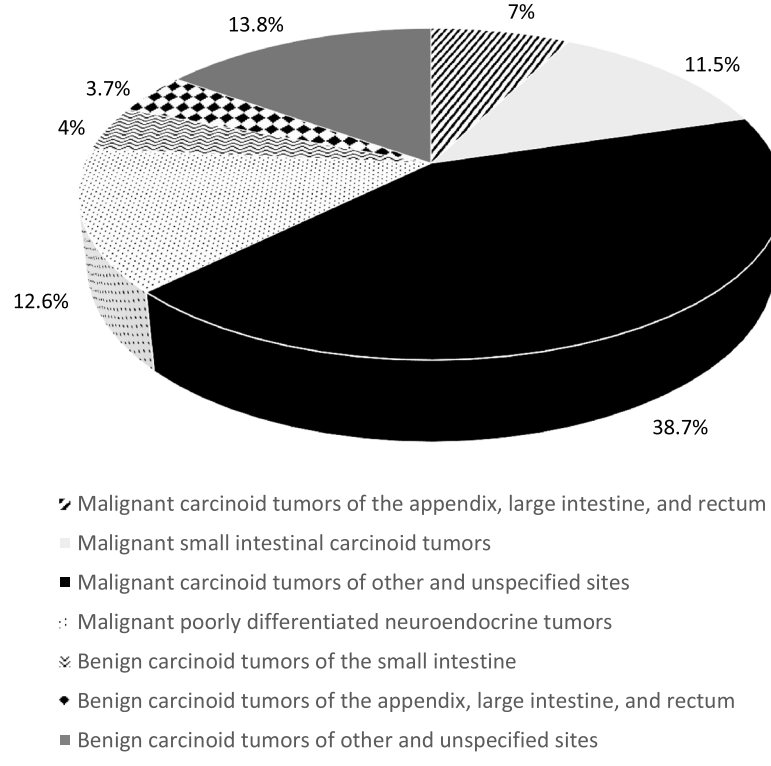

FIGURE 1. Incidence of various types of NENs.

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white ethnicity (75.70%) among the cohort studied. The mean length of stay and incurred cost of hospitalization were found to be ~6.60 days and $18,300.90 US dollars, respectively. Furthermore, the in-hospital mortality across all NENs was found to be 4.77%. In general, the trend of hospitalization for NENs generally increased from 2008 to 2010 but remained relatively unchanged between 2010 and 2014. Our study provides evidence that there is a significant cost and in-hospital mortality associated with this cohort of patients.

Our study was limited by the retrospective nature of the analysis, restriction to in-hospital data, lack of information on therapeutic procedures, and variation in coding and documentation practices. The study cohort was composed of patients with malignancies of very variable prognosis ranging from low-grade, well-differentiated neuroendocrine tumors to poorly differentiated neuroendocrine carcinomas. The in-hospital outcomes of NENs are understudied, and although our study provides an insight into the epidemiologic trends and the substantial financial burden of this disease, more work is needed. Improved and more precise coding as well as more uniform classification of NENs across different organ systems is needed. Better understanding of the cost of inpatient care for patients with NENs will help with the allocation of resources for patient care.

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D-Dimer Could Be a Surrogate Postoperative Prognostic Marker of Resectable Pancreatic Cancer

To the Editor:

Pancreatic cancer (PCA) has a poor prognosis, and its incidence is increasing throughout the world. Although surgery is the most effective therapy, postoperative recurrence remains an issue. Thus, biomarkers for PCA are greatly needed. D-dimer is a fibrin cleavage product that has been shown to be related to tumor progression and recurrence in various cancers. We evaluated D-dimer for its potential in predicting PCA progression and prognosis.

We retrospectively examined the medical records of 105 PCA patients who underwent curative liver resection at our department between 2005 and 2018. Recurrence was observed in 67 (64%) cases, and preoperative venous thromboembolism was detected in 3 cases. All patients provided

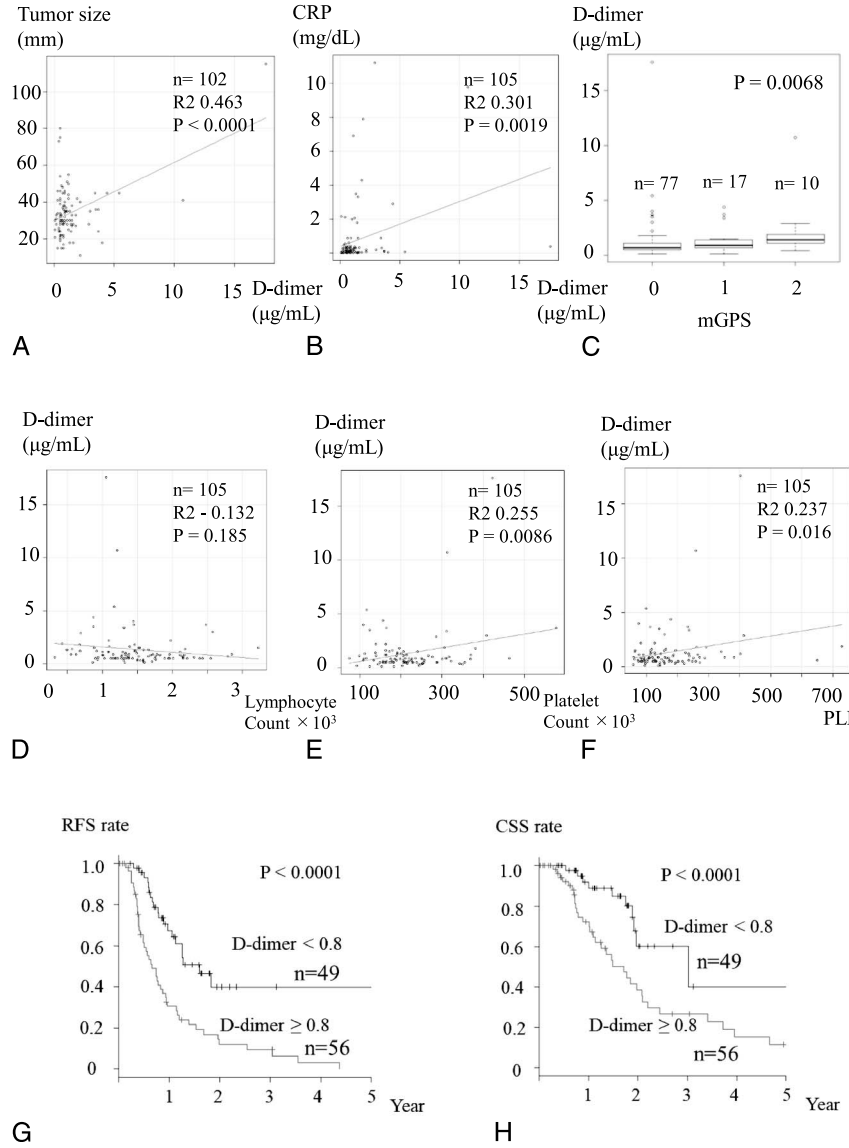

FIGURE 1. A, D-dimer had strongly positive correlation to tumor size ($R^2 = 0.432$; $P < 0.0001$). B, D-dimer had correlation to CRP ($R^2 = 0.301$; $P = 0.0019$). C, D-dimer had a significant difference among modified Glasgow Prognostic Factor (mGPS) by the Kruskal-Wallis test ($P = 0.0068$). D, D-dimer had no correlation to lymphocyte count ($R^2 = 0.132$; $P = 0.182$). E, D-dimer had a correlation to platelet count ($R^2 = 0.255$; $P = 0.0086$). F, D-dimer had correlation to PLR ($R^2 = 0.237$; $P = 0.016$). The correlation of D-dimer to prognosis was evaluated. Kaplan-Meier curves for both low and high D-dimer groups are shown. G, High D-dimer levels were associated with poor RFS ($P < 0.0001$) and (H) poor CSS ($P < 0.0001$).

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informed consent using the opt-out methods, and the study design was approved by our Clinical Ethics Committee (HS2019-107).

The average preoperative D-dimer level was 1.32 μg/mL (range, 0.1–17.6 μg/mL). Preoperative D-dimer had positive correlation to tumor size ($P < 0.0001$; Fig. 1A), CRP ($P = 0.0019$; Fig. 1B), modified Glasgow Prognostic Score ($P = 0.0068$; Fig. 1C), platelet count ($P = 0.0086$; Fig. 1E), and platelet-lymphocyte ratio ($P = 0.016$; Fig. 1F). The level of D-dimer was also measured in 24 patients who developed postoperative recurrence. The average D-dimer level in the postoperative state was 3.21 μg/mL (range, 0.5–14.0 μg/mL), which was significantly higher than that in the preoperative state ($P = 0.0035$). The optimal cutoff value related to both recurrence and cancer-related death was calculated to be 0.8 μg/mL. The high D-dimer group (≥0.8 μg/mL) related to poor recurrence-free survival (RFS, $P < 0.0001$, Fig. 1G) and cancer-specific survival (CSS, $P < 0.0001$, Fig. 1H). In multivariate analysis, a correlation between D-dimer and the prognosis of PCA was observed and became an independent predictor of postoperative survival (RFS, $P = 0.001$; CSS, $P = 0.013$, Table 1).

Recent retrospective studies have reported the relation between D-dimer and PCA prognosis. Our study revealed that D-dimer also correlated with inflammatory factors, which could reflect not only prognosis but also inflammatory state. Previous studies had reported the correlation between pancreatic cancer and inflammation. For example, inflammatory stimulation was related to Kirsten rat sarcoma viral oncogene homolog activation in basic experiments of pancreatic cancer cells.[1] In addition, modified Glasgow Prognostic Score factor had a correlation to the postoperative prognosis of resectable pancreatic cancer patients.[2] Similarly, D-dimer showed a correlation to these inflammatory factors and was the strongest prognostic factor in our multivariate analysis among inflammatory factors. Therefore, D-dimer could be a surrogate marker reflecting the inflammatory state and malignancy on pancreatic cancer.

Recently, certain studies have suggested a correlation between cancer and coagulation, showing that cancer cells promote coagulation by inactivating the fibrinolytic system.[3] The cancer cells then activate coagulation factors, such as D-dimer,

TABLE 1. Univariate and Multivariate Analysis of Prognostic Factors for RFS and CSS Using Cox Proportional Hazards Model

	Univariate Analysis		Multivariate Analysis	
Factors	**RR (95% CI)**	***P***	**RR (95% CI)**	***P***
RFS				
Age, <70/>70, y	1.114 (0.69–1.81)	0.664	—	—
Sex, male/female	0.677 (0.41–1.10)	0.117	—	—
CEA	0.995 (0.98–1.01)	0.589	—	—
CA 19-9	1.000 (1.00–1.00)	0.036*	1.000 (1.00–1.00)	0.096
T factor	1.608 (0.97–2.64)	0.060	1.207 (0.73–1.99)	0.462
Lymphatic metastasis, −/+	1.219 (0.71–2.10)	0.475	—	—
Residual tumor, R0/R1	1.588 (0.91–2.77)	0.103	—	—
Tumor location, head/body or tail	1.230 (0.73–2.09)	0.433	—	—
Neutrophil lymphocyte ratio (cutoff, 2.56)	0.741 (0.45–1.21)	0.228	—	—
Monocyte lymphocyte ratio (cutoff, 0.21)	0.944 (0.58–1.53)	0.817	—	—
Platelet lymphocyte ratio (cutoff, 142)	1.210 (0.74–1.97)	0.446	—	—
mGPS	1.527 (1.08–2.16)	0.017*	1.026 (0.68–1.54)	0.901
D-dimer (cutoff, 0.80)	2.849 (1.68–4.82)	0.001*	3.011 (1.61–5.61)	0.001*
CSS				
Age, <70/>70, y	1.007 (0.55–1.84)	0.981	—	—
Sex, male/female	1.067 (0.56–2.02)	0.842	—	—
CEA	0.999 (0.98–1.01)	0.944	—	—
CA 19-9	1.000 (1.00–1.00)	0.073	1.000 (1.00–1.00)	0.208
T factor	1.603 (0.89–2.86)	0.109	—	—
Lymphatic metastasis, −/+	1.078 (0.53–2.18)	0.835	—	—
Residual tumor, R0/R1	1.036 (0.51–2.12)	0.923	—	—
Tumor location, head/body or tail	1.521 (0.77–2.98)	0.222	—	—
Neutrophil lymphocyte ratio (cutoff, 2.56)	0.810 (0.45–1.47)	0.490	—	—
Monocyte lymphocyte ratio (cutoff, 0.21)	0.944 (0.52–1.72)	0.867	—	—
Platelet lymphocyte ratio (cutoff, 142)	1.064 (0.58–1.93)	0.838	—	—
mGPS	1.507 (1.00–2.26)	0.046*	1.233 (0.80–1.89)	0.336
D-dimer (cutoff, 0.80)	2.852 (1.40–5.83)	0.004*	2.592 (1.22–5.49)	0.013*

*$P < 0.05$.

RR indicates relative risk; 95% CI, 95% confidence interval.

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fibrinogen, interleukin-6, soluble P-selectin, and vascular endothelial growth factor.[4] It has also been suggested that circulating cancer cells trigger blood coagulation via a tissue factor expressed on cancer cells.[5] Sun et al[6] reported that PCA patients expressed high levels of fibrinogen and D-dimer while at the same time expressing low levels of antithrombin-III (AT-III). Furthermore, PCA cells themselves were found to be in a hypercoagulative state. Although it remains unclear how blood coagulation is mechanically related to PCA progression, it is suggested that a hypercoagulative state is important in the pathogenesis of PCA.

We previously reported that the coagulation phenomenon induced by inflammation leads to tumor progression and poor prognosis in cholangiocarcinoma.[7] From the present results, PCA also showed a correlation with inflammation, coagulation, and malignancy. We also hypothesize a cancer progression mechanism in which the inflammation induced by cancer cells occurs through inflammatory factors, such as tissue factor or TNF-α, and these inflammatory factors lead to the coagulation by platelet aggregation. The activation of the coagulation phenomenon related to tumor progression and D-dimer could reflect a series in these mechanisms and be a potential predictive marker for inflammatory state and PCA progression. However, our study did have some limitations, mainly due to its nature as a retrospective study and due to the small number of examined cases. Therefore, further clinical studies are necessary to fully elucidate the mechanical role of the D-dimer.

In conclusion, we showed that high D-dimer levels were significantly associated with both inflammation and poor prognosis in PCA patients. Therefore, D-dimer may be a useful surrogate and predictive biomarker for inflammation and prognosis in PCA patients. Our findings also indicate that coagulation factors, in general, may be promising targets for controlling cancer progression.

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