To the Editor:

Pancreatic cancer is one of the most aggressive cancers. Accumulating epidemiological studies suggested a link between human blood group antigens and carcinogenesis or progression of various human tumors including pancreatic cancer. So far, there are few large studies of this kind in China. To understand more about the relationship between ABO blood group and the risk of developing pancreatic cancer, we collected data from pancreatic cancer patients of the Han Chinese people diagnosed in our institution between February 1, 2010, and May 31, 2017, and evaluated whether ABO blood type was a risk factor for pancreatic cancer. Meanwhile, we investigated whether there is a link between ABO blood group and pancreatic neuroendocrine tumors (pNETs) and other types of pancreatic masses. In addition, correlations between ABO blood group and carbohydrate antigen (CA) 19-9, CA 125, and carcinoembryonic antigen (CEA) were also investigated.

We included patients with definite pathological diagnosis and blood types. The results of CA 19-9, CA 125, and CEA were collected within 1 week before surgery or puncture. Because there are no authoritative reports describing the definite distribution ratios of different blood types in Han Chinese people, we quoted the data reported by Sun et al. which included up to 200,660 Han Chinese people, as the control group in our study.

In total, 4099 patients were eligible for this analysis, including 3063 cases of pancreatic cancer, 222 cases of pNETs, and 814 cases of other types of pancreatic masses. Distributions of ABO blood types were displayed in the form of pie charts in Figure 1. The odd ratio (OR) and 95% confidence intervals (CIs) for pancreatic cancer, pNETs, and other types of pancreatic masses by ABO blood group were listed in Table 1, and blood type O was used as the referent group. For the combined study population, compared with patients with blood group O, those with blood group A were more likely to develop pancreatic cancer (OR for incident pancreatic cancer, 1.522 [95% CI, 1.388–1.668], P < 0.001), whereas those with blood group B were less likely to develop pNETs and other types of pancreatic masses (OR for incident pNETs and other types of pancreatic masses, 0.620 [95% CI, 0.430–0.894], 0.711 [95% CI, 0.593–0.852], P < 0.001, respectively). The levels of CA 19-9 and CA 125 in pancreatic cancer patients did not differ significantly between different blood groups (P = 0.779 and P = 0.253, respectively), whereas the rate of elevated expression of CEA was significantly lower in pancreatic cancer patients with blood type A than those with blood types B, AB, and

**TABLE 1.** Odds Ratios and 95% Confidence Intervals for Different Patients With Pancreatic Cancer, pNETs, and Other Types of Pancreatic Masses by ABO Blood Group

| Blood Group | Pancreatic cancer | pNETs | Other masses |
|-------------|------------------|-------|-------------|
| O (Referent) | 1.00             | 1.00  | 1.00        |
| A            | 1.522 (1.388–1.668)* | 1.187 (0.862–1.636) | 1.035 (0.872–1.229) |
| B            | 1.002 (0.909–1.104) | 0.620 (0.430–0.894)† | 0.711 (0.593–0.852)* |
| AB           | 1.125 (0.984–1.287) | 1.004 (0.633–1.595) | 0.889 (0.693–1.142) |

*P < 0.0001.
†P < 0.05.

**FIGURE 1.** Distributions of ABO blood types in people of different subgroups. A, Pancreatic cancer, (B) pNETs, (C) other types of pancreatic masses, and (D) patients discharged from Peking Union Medical College Hospital (Beijing, China) between January 2010 and June 2016.
The ABO blood group system was first discovered more than one century ago, and until now, it is still the most important blood group system in immunohematology, transfusion, and transplantation medicine. In recent years, there is increasing evidence of an important role of ABO blood group system in pancreatic cancer. In this study, we reported the blood group distributions of patients with pancreatic cancer in our center, and we found that there is an association between ABO blood type and pancreatic cancer in Han Chinese people. Han Chinese people with blood type A had an increased likelihood of developing pancreatic cancer than people with blood type O, which is in accordance with the study by Wolpin et al. However, unlike the results of Wolpin et al., our study revealed that the risks of pancreatic cancer in blood types B and AB were lower than people with blood type O. In fact, the results were not exactly the same between our study and previous reports either. This may be owing to racial and ethnic differences in blood type distributions.

A number of studies have investigated the mechanisms of how blood type affects pancreatic cancer. Hofmann et al. reported that blood group IgM isoagglutinins and O-GalNAc glycoproteins may play a role in the pathogenesis and progression of pancreatic cancer, and it was reported that ABO antigen expression is indeed altered in primary and metastatic pancreatic cancers compared with normal pancreatic tissues.

In addition, large amounts of reports suggest that there is a link between blood group antigens and the systemic inflammatory response, which has been demonstrated to be important mechanisms during the initiation and development of tumors, including pancreatic cancer. However, more studies on this issue are still warranted to explore the underlying mechanisms involved.

Overall, our findings confirmed once again that the ABO blood group was associated with the risk of pancreatic cancer from the perspective of the Han Chinese people. This will help to identify high-risk population subsets of pancreatic neoplasms in China. In addition, clarifying the etiology mechanisms linking pancreatic cancer risk to ABO blood group may provide a new perspective for the treatment of pancreatic cancer.

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M.L. and S.J. contributed equally to this article. The authors declare no conflict of interest.

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TABLE 1. Demographic and Clinical Data Among AAs and Whites With Index Acute Pancreatitis

|                                | AAs (n = 131) | Whites (n = 122) | P      |
|--------------------------------|---------------|------------------|--------|
| Age, mean (SD), y              | 48.9 (15.8)   | 50.8 (17.6)      | 0.42   |
| Sex, female, n (%)             | 77 (58.8)     | 58 (47.5)        | 0.08   |
| BMI, mean (SD), kg/m²          | 29.8 (15.8)   | 29.7 (8.5)       | 0.14   |
| Location of residence, n (%)   |                |                  | 0.02   |
| Southern suburbs               | 74 (56.5)     | 58 (47.5)        |        |
| Northern suburbs               | 43 (32.8)     | 36 (29.5)        |        |
| Western suburbs                | 14 (10.7)     | 28 (23)          |        |
| Predicted mean income, mean (SD), $ | 37,924 (16,111) | 58,502 (24,978) | <0.0001|
| Transferred to UIC for higher level of care, n (%) | 27 (20.6) | 45 (36.9) | 0.005  |
| Medical history, n (%)         |               |                  |        |
| Diabetes mellitus              | 22 (16.8)     | 27 (22.1)        | 0.34   |
| Coronary artery disease        | 21 (16)       | 9 (7.4)          | 0.05   |
| Chronic kidney disease         | 10 (7.6)      | 9 (7.4)          | 1.0    |
| Hypertension                   | 57 (43.5)     | 39 (32)          | 0.07   |
| Family history of pancreatitis | 4 (3.1)       | 1 (0.8)          | 0.37   |
| No. alcoholic drinks per week, mean (SD)  | 11 (20)     | 13 (28)         | 0.37   |
| Duration of tobacco exposure, mean (SD), y  | 6 (10.4)    | 4.7 (10.9)       | 0.09   |
| Etiologies, n (%)              |               |                  | 0.19   |
| Gallstones                     | 43 (33.1)     | 51 (41.8)        |        |
| Alcohol                        | 33 (25.4)     | 22 (18.0)        |        |
| Idiopathic                     | 40 (30.8)     | 29 (23.8)        |        |
| Hypertriglyceridemia-induced   | 2 (1.5)       | 7 (5.7)          |        |
| Post-ERCP                      | 2 (1.5)       | 3 (2.5)          |        |
| Other                          | 10 (7.7)      | 10 (8.2)         |        |
| SBP at presentation, mean (SD), mm Hg | 141 (23)   | 132 (24) (n = 121) | 0.003  |
| DBP at presentation, mean (SD), mm Hg | 81 (15)     | 74 (12) (n = 121) | <0.0001|
| Creatinine level, mean (SD), mg/dL | 1.6 (2.2)    | 1.2 (1.2)        | 0.02   |
| Disease severity, n (%)*       |               |                  | 0.66   |
| Mild                            | 90 (68.7)     | 70.5 (86)        |        |
| Moderate                       | 33 (25.2)     | 21.3 (26)        |        |
| Severe                         | 8 (6.1)       | 8.2 (10)         |        |
| Mortality, n (%)               | 5 (3.8)       | 3 (2.5)          | 0.15   |
| ICU admission rate, n (%)      | 21 (16.0)     | 14.8 (18)        | 0.86   |
| ICU length of stay, mean (SD), d | 1 (3.8)     | 1.1 (3.5)        | 0.87   |
| Hospital length of stay, mean (SD), d | 6 (5.9)  | 6.8 (7.6)        | 0.21   |
| 30-Day readmission rate, n (%) | 25 (19)       | 15 (12.3)        | 0.14   |

Bold value are statistically significant.

*Disease severity based on the Revised Atlanta Classification.

DBP indicates diastolic blood pressure; ERCP, endoscopic retrograde cholangiopancreatography; SBP, systolic blood pressure; SD, standard deviation; UIC, University of Illinois at Chicago.

for continuous variables and Fisher exact test or analysis of variance for categorical data were used with two-sided tests with a priori significance level of α of level of 0.05. A multivariate regression analysis was completed to determine independent predictors of creatinine by adjusting for race, body mass index (BMI), age, and comorbidities. There were 253 subjects analyzed, of which 131 were AAs and 122 whites (Table 1); 135 were female. There were no significant differences among AAs and whites (Table 1) for many variables including in age, BMI, or sex (P = 0.42, P = 0.14, and P = 0.08, respectively), alcohol, tobacco, and illicit drug consumption (P = 0.37, P = 0.09, and P = 1.0, respectively), nonsteroidal anti-inflammatory, opioid, or statin use (P = 0.69, P = 0.48, and P = 0.89, respectively), with similar rates of diabetes mellitus, chronic kidney disease, and hypertension; nor were there differences in family history of AP and underlying etiologies (P = 0.37 and P = 0.19, respectively). However, compared with whites, AAs were more likely to have coronary artery disease (P = 0.05). In addition, AAs were more likely to live in underserved neighborhoods of Chicago (P = 0.02), had significantly lower predicted mean annual income (P < 0.0001), and the percentage of subjects transferred to University of Illinois at Chicago for higher level of care was significantly lower in AAs compared with whites (20.6% vs 36.9%, P = 0.005) (Table).

Despite having higher mean systolic and diastolic blood pressures at presentation (P = 0.003 and P < 0.001, respectively), AAs had significantly higher creatinine level at admission compared with whites (1.6 mg/dL vs 1.2 mg/dL, P = 0.02). In a multivariate regression analysis, only race was found to be an independent predictor of creatinine (P = 0.037) when additional adjustments were made for age, BMI, and comorbidities.

African Americans and whites received similar amounts of intravenous fluids within 8 hours (1.3 [SD, 0.6] vs 1.4 [SD, 0.8] liters, P = 0.77) and 24 hours of admission (5.3 [SD, 2] vs 5.0 [SD, 2.1] L, P = 0.19). Disease severity was similar between 2 groups (P = 0.66). Mortality rate was numerically higher in AAs compared with whites (3.8% vs 1.6%, P = 0.29), and there were no significant differences in intensive care unit (ICU) admission rate, ICU length of stay, and hospital length of stay (P = 0.86, P = 0.87, and P = 0.21, respectively) between 2 groups. However, there was a positive correlation between creatinine levels and ICU admissions (P = 0.002) and AAs had higher 30-day readmission rate compared with whites (18.9% vs 12.3%, P = 0.14).

We identified significantly higher creatinine levels on admission in AAs compared to whites. Race remained an independent predictor of creatinine in the multivariate regression analysis when adjusted for covariables. Therefore, this finding truly reflects the presence of end-organ damage in an acute setting. There were no significant differences in total intravenous fluids administration and disease severity between 2 groups. African Americans had higher mortality and 30-day readmission rates compared with whites, but these did not reach statistical significance, most likely because of small study size.

African Americans with AP were more likely to live in underserved neighborhoods and have significantly lower predicted income levels. In addition, percentage of transfer among subjects who received care at our institution for AP was significantly lower in AAs compared with whites and this is consistent with previous reports. This finding along with limited access to care in disadvantaged, lower income populations can explain part of existing disparities.

Our study has several limitations. It is (a) a retrospective study, which prevented...
longitudinal collection of key variables, (b) used International Classification of Disease codes, which may have resulted in under detection of AP cases, and (c) focused on AAs and whites which decreased the study size. A larger study with an increased power may allow more in depth investigation of actionable factors, which can be used to develop preventive strategies, improve access to care and optimize delivery of the care especially at high-risk groups.

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RESULTS
We included 58 consecutive patients with WON treated in our ICU during the inclusion period. Most patients were men (59%) and the median age was 60 years (range, 26–78 years). Gallstones were the predominant etiology, comprising approximately half of the cases. Twenty-five (43%) had culture-verified sepsis before the index endoscopy.

At the time of index endoscopy, 54 patients (96%) had infected WON. The most common findings at the index endoscopy were Enterococci (80%), fungi (30%), and gram-negative bacteria (20%). In total, 27 patients (47%) developed culture-verified sepsis during their stay in ICU, with Enterococci being the most predominant finding (37%), followed by fungi (30%), and gram-negative bacteria (26%). Both SOFA, APACHE II, and mMarshall were significantly higher in nonsurvivors than patients who survived their ICU stay (Table 1).

In total, 22 patients (38%) died during their stay in ICU, predominantly because of multigorgan failure. Additional 2 patients died within 6 months after admission to the ICU. There was no difference in age and sex between survivors and nonsurvivors. The median length of stay in the ICU was 30 days (range, 1–239 days). The median

To the Editor:

Walled-off pancreatic necrosis (WON) is a late manifestation of severe necrotizing pancreatitis and is often associated with the development of local and systemic complications, resulting in sepsis, multiple organ dysfunction, extended stay in intensive care unit (ICU), and moreover death. Several minimally invasive techniques have replaced open surgery as a primary treatment resulting in improved survival. A number of patient series focusing on outcome have been published with inhospital mortality rates ranging from 5% to 15%. However, no studies have focused on a specific subgroup of patients with WON admitted to ICU. We evaluated the clinical outcome and possible predictors of mortality in ICU patients with WON undergoing endoscopic, transgastric drainage, and necrosectomy.
length of stay in hospital was 121 days (range, 16–543 days).

In adjusted Cox regression analyses, the following variables predicted mortality at the index endoscopy: APACHE II score (hazard ratio [HR], 3.30; 95% confidence interval [CI], 1.32–8.25, \( P = 0.011 \)), SOFA score (HR, 3.76; 95% CI, 1.45–9.71, \( P = 0.006 \)), mMarshall score (HR, 4.30; 95% CI, 1.71–10.68, \( P = 0.002 \)), use of mechanical ventilation (HR, 7.09; 95% CI, 1.61–31.29, \( P = 0.011 \)), renal replacement therapy (HR, 5.84; 95% CI, 2.25–15.12, \( P < 0.001 \)), vasoactive drugs (HR, 1.70; 95% CI, 1.05–2.67, \( P = 0.026 \)), and WBC (HR, 1.08; 95% CI, 1.02–1.08, \( P = 0.001 \)). In the recently published TENSION trial, the mortality rate was 18% in the endoscopic step-up approach. However, no studies have specifically focused on the subgroup of patients treated with the same endoscopic procedure and in need of treatment in ICU.

Infected WON at the time of intervention has a great impact on subsequent disease course and prognosis. In our study, 96% had culture-proved infected necrosis at the time of index endoscopy, a percentage that is similar to findings in the TENSION trial, but considerably higher than the rates (38%–54%) reported in some of the largest studies to date. In addition, the median CTSI in our study was 8 points, and the median mCTSI was 10 points, thus reflecting the extension and complexity of WON in our cohort.

Our findings suggest that APACHE II, SOFA, and mMarshall scores are not only useful in the early phase of acute pancreatitis but also reliable predictive tools in the late stage of the disease. Especially, the relative simplicity of mMarshall score as compared with both APACHE II and SOFA score makes this scoring system suitable for monitoring of WON patients in ICU setting.

**DISCUSSION**

This study reports clinical outcome and evaluates potential prognostic predictors in a consecutive group of ICU patients with WON who underwent same treatment modality.

In this retrospective study, the ICU mortality rate was 38%. Several studies have reported overall mortality rates in endoscopically treated WON patients ranging from 5% to 15%. In the recently published TENSION trial, the mortality rate was 18% in the endoscopic step-up approach. However, no studies have specifically focused on the subgroup of patients treated with the same endoscopic procedure and in need of treatment in ICU.

Infected WON at the time of intervention has a great impact on subsequent disease course and prognosis. In our study, 96% had culture-proved infected necrosis at the time of index endoscopy, a percentage that is similar to findings in the TENSION trial, but considerably higher than the rates (38%–54%) reported in some of the largest studies to date. In addition, the median CTSI in our study was 8 points, and the median mCTSI was 10 points, thus reflecting the extension and complexity of WON in our cohort.

**TABLE 1. The Baseline Data at Index Endoscopy**

| Parameter          | Overall   | Nonsurvivors | Survivors | \( P \)  |
|--------------------|-----------|--------------|-----------|---------|
| SOFA score         | 11 (6–18) | 14 (6–18)    | 8 (6–16)  | 0.0008  |
| APACHE II score    | 17 (6–34) | 19.5 (6–34)  | 15.5 (8–29) | 0.0095  |
| mMarshall score    | 6 (0–12)  | 8 (0–12)     | 5 (0–10)  | 0.0007  |
| CTSI               | 8 (3–10)  | 7 (3–10)     | 8 (3–10)  | 0.813   |
| mCTSI              | 10 (6–10) | 10 (6–10)    | 10 (6–10) | 0.948   |
| CRP, mg/L          | 142 (28–376) | 145 (65–290) | 142 (28–360) | 0.822   |
| WBC, \( \times 10^9 \)/L | 11 (6–68.2) | 29 (8.9–68.2) | 11 (3.8–54.7) | 0.020   |
| Sepsis, n (%)      | 25 (43.1) | 11 (50)      | 14 (39)   | 0.430   |
| Albumin, g/L       | 17 (9–30) | 16.5 (11–25) | 18 (9–30) | 0.501   |

Values are given as median (range), unless otherwise indicated. Significant findings are presented in bold.

**FIGURE 1.** Evaluation of possible predictors of mortality at the index endoscopy.

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A Better Way to Predict the Severity of Acute Pancreatitis?

To the Editor:

Acute pancreatitis (AP) is a common reason for hospitalization costing lots of resources annually. Severe AP cases are often associated with severe complications and high mortality, although mild AP cases can be successfully improved quickly but have unnecessarily long hospital stays. So what can we do to reduce resource utilization without a detrimental impact on safety? Prediction of the severity of AP is the key to the problem, for it is important for determining early triage, aggressive resuscitation of the patient, and the need to refer to an intensive care unit. However, all prognostic systems in current use, which are developed in groups of patients, fall short of what is required.

We read with great interest the article by Gonzalez et al where they suggest that free thyroxine (FT4) level determination during the initial clinical evaluation of patients admitted to the emergency service with AP can be included as a severity indicator to help determine the differential care of these cases, and the conclusion in the well-designed prospective trial is indeed encouraging for it may be a new method to predict the severity of AP.

However, we find that the gradation of severity was made according to the classification defined at the 1992 Atlanta International Symposium, whose recently revised grades are moderate, moderate-severe, and severe, and moderate and moderate-severe stages were combined in the study. In other words, 2 levels were considered in the analysis: moderate AP (MAP) and severe AP (SAP). As the study suggested, with this method, FT4 level determination can be included as an indicator to differentiate SAP with MAP and help determine the differential care of patients with AP. However, the study did not explore whether the method can pick out the mild AP cases, which may be successfully improved quickly but have unnecessarily long hospital stays.

Can FT4 level determination help us pick out the mild AP cases? In this purpose, we screened the relevant studies and did the meta-analyses.

We searched the Embase, MEDLINE, Pubmed, and Google Scholar databases from inception to identify all studies that using FT4 to predict the severity of AP. Two independent reviewers extracted data and assessed the quality of publications; a third investigator resolved any discrepancies. This resulted in 4 studies, including 339 patients, were included in this analysis. Baseline characteristics of included studies are displayed in Table 1. As Figure 1 showed, there was no evidence of heterogeneity (P = 0.40, I² = 0%), and FT4 level determination cannot differentiate mild AP with MAP and SAP with a mean difference of 0.33 (95% confidence interval, −0.18 to 0.84; P = 0.20).

In conclusion, FT4 level determination can be included as an indicator to differentiate MAP with SAP. However, there is a long way to make it an accurate method for us to pick out the mild cases, which may reduce resource utilization without a detrimental impact on safety.

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TABLE 1. List of the Studies Included in the Systematic Review and the Characteristics

| Study       | Style | Cohort Size | Sex, Male/Female | Etiology, n |
|-------------|-------|-------------|------------------|-------------|
| Xie et al, 2012 | P     | 52          | 28/24            | BAP         |
| Zhang et al, 2016 | P     | 50          | 40/10            | AAP + HLAP  |
| Yang et al, 2016 | R     | 76          | 54/22            | Others      |
| Yang et al, 2018 | R     | 161         | 97/64            |            |

P indicates prospective cohort study; R, retrospective cohort study; BAP, biliogenic acute pancreatitis; AAP, alcoholic acute pancreatitis; HLAP, hyperlipidemic acute pancreatitis.
Fate of Autophagic Vacuoles in Acinar Cells During Pancreatitis

To the Editor:

The focus of this letter is to provide electron micrographs that support evolving concepts of the pathogenesis of acute pancreatitis. These micrographs were made years ago when we were studying pancreatitis induced in rats by puromycin treatment and extended the model to include duct obstruction. In earlier studies of puromycin-induced acinar cell injury, there was evidence of extrusion of autophagic vacuoles into the lumen of acini and the duct system of the pancreas. The formation of autophagic vacuoles is a common and often florid response of the pancreatic acinar cells to injury by chemical agents, nutritional insult, radiation, and duct ligation. Furthermore, a low incidence of autophagic vacuoles is seen in the pancreatic acinar cells from normal pancreas of human and animal origin. Pancreatic acinar cells do not typically accumulate lipofuscin pigment during aging as is the case in liver, myocardium, and some other cells (personal observation).

The fact that lipofuscin does not accumulate in pancreatic acinar cells suggests that the pancreas has a mechanism for clearing residual bodies (secondary lysosomes) from the cell. More recently, there have been observations in newer models of pancreatitis demonstrating basolateral exocytosis of zymogen granules and autophagic vacuoles. If extrusion into the duct systems is the normal mechanism for clearing of autophagic vacuoles from the cells, then it is reasonable to ask what the effect of duct obstruction would be on this excretory mechanism and to hypothesize that in the face of duct obstruction there might be increased interstitial extrusion of autophagic vacuole contents including pancreatic enzymes. The studies described here were undertaken to see if basolateral exocytosis of autophagic vacuoles would be increased by duct obstruction.

These studies were carried out in male Wistar rats weighing 95 to 250 g that had been maintained on Purina Laboratory Chow. Puromycin was given by intraperitoneal injection of an aqueous solution, 10 mg/mL adjusted to pH 7 to 8 with NaOH. Four doses of 40 mg/kg were given at 1 hour intervals in all puromycin-treated rats used in these studies.

The common bile duct of 17 of the rats was ligated near the duodenum using 4-0 surgical silk. The efficacy of ligation was judged at the time of autopsy by observing duct distension. Six sham-operated control rats were subjected to laparotomy, and a suture was placed about the common bile duct near the duodenum but was not tied. Intraperitoneal injection of Nembutal (50 mg/kg) was used.
to achieve anesthesia for these surgical procedures and for perfusion fixation described hereafter. The abdominal incisions were closed with 4-0 silk suture in the muscular wall and steel clips in the skin.

At the time of autopsy, tissue for light microscopy was fixed in Susa's solution, and tissue for electron microscopy was fixed by primary glutaraldehyde fixation and osmium postfixation. In some experiments, initial fixation was done by perfusing the pancreas through the abdominal aorta with a solution consisting of 2.5% glutaraldehyde in Millonig's phosphate buffer, containing 5 units per milliliter of heparin and sufficient trypan blue to stain the tissue slightly. Perfusion fixation was undertaken to avoid rupture of fragile cells during dicing for fixation. In the most successful perfusion routine, the abdomen of the anesthetized animal was opened and the aorta was cannulated with a 22-gauge needle, perfusion fluid was pumped at a rate of 5 mL/min using an LKB Varioperpex pump, the chest of the animal was then opened and the heart was opened to reduce the systolic pressure in the aorta, the aorta was then clamped at the level of the diaphragm to prevent perfusion of the cephalic and thoracic regions, and the hepatic artery was clamped in the porta hepatis to prevent perfusion of the liver. Perfusion was continued for 5 to 10 minutes. Successful perfusion was marked by blue staining of the pancreas. After perfusion, a block of tissue measuring 2 × 3 × 5 mm was excised from the body or tail of the pancreas, immersed in 2.5% buffered glutaraldehyde continuing fixation for 1 hour before dicing into 1 mm cubes. The tissue was then rinsed, postfixed in 1% osmic acid, dehydrated, and embedded. Several experiments were done without perfusion by simply excising tissue from ether anesthetized animals with immediate immersion and dicing in glutaraldehyde. The Susa-fixed pancreas was embedded in paraffin, and sections were stained with hematoxylin and eosin. For electron microscopy, all tissues were stained with uranyl acetate and lead citrate.

In preliminary experiments, duct-ligated rats were injected 2 or 3 times with 0.08 mg/kg of methacholine in an effort to increase the pressure within the pancreatic duct system. Such rats developed gross evidence of pancreatitis (fat necrosis, ascites, pancreatic edema) within 12 hours; however, ultrastructural changes were qualitatively no different from experiments in which no methacholine was given. The common bile ducts were ligated 6, 9, or 12 hours before killing, and we found that formation of autophagic vacuoles in acinar cells was a prominent change.

Changes in acinar cells attributable to puromycin injury in both sham-operated and duct-ligated groups included the presence of numerous autophagic vacuoles (Figs. 1, 2), the presence of intracisternal granules (Figs. 1, 2), marked clumping of chromatin in nuclei, and death of scattered cells. Autophagic vacuoles were also seen in acinar cells of duct-ligated rats (Fig. 3). In animals treated with puromycin alone,
we observed debris apparently from autophagic vacuoles in the lumen of pancreatic acini (Fig. 4) and in the duct system after duct ligation (Fig. 5). Such debris was particularly conspicuous 18 hours after the initiation of puromycin treatment in a sham-ligated animal. There was also evidence of interstitial extrusion of cytoplasmic debris in this group of rats.

In several groups, a course of puromycin injections was followed by duct ligation 4 hours after the first of the puromycin injections. The animals were then sacrificed 14, 16, or 22 hours after duct ligation. Ultrastructural studies of the pancreas of these rats showed evidence of dilatation of the ducts and acinar lumens (Fig. 6). We saw debris similar to that in the autophagic vacuoles in interstitial spaces as early as 6 hours after duct ligation, although this was more prominent in longer experiments (Fig. 7). Debris was present in the duct system (Figs. 5, 6); however, there was more extensive interstitial extrusion of cell debris with phagocytosis by invading macrophages (Figs. 8, 9) than was noted in sham-ligated puromycin-treated rats.

Acinar cells from animals that had undergone duct ligation after a series of saline injections lacked the stigmata of puromycin-induced injury; however, there was an increased incidence of cytoplasmic autophagic vacuoles in the acinar cells together with evidence of dilatation of acinar and duct lumens and interstitial extrusion of the contents of autophagic vacuoles.

We occasionally encountered evidence of rupture of acinar cells into the interacinar space that we felt was an artifact attributable to the trauma of dicing the tissue. Such areas contained dispersed cell organelles, which did not appear to be held together within vacuolar membranes and showed less evidence of degradation than the debris commonly seen within autophagic vacuoles. Because we saw evidence of intraluminal and interstitial extrusion of cell debris in perfusion-fixed samples of pancreas, we feel that the findings illustrated here are not artifactual.

There have been previous ultrastructural studies of changes induced in pancreas after common duct ligation. Walters et al looked for changes during the first 24 hours. They saw autophagic vacuoles as early as 6 hours after common duct ligation in mice and also observed interstitial and intraluminal osmiophilic debris, apparently extruded from acinar cells, beginning 4 days after ligation. These findings are similar to our observations in rats. Diffuse or multifocal leakage from the duct system has been documented in cats after pancreatic duct ligation with elevation of intraductal pressure, and Herriott...
and Palmer found histologic evidence of rupture of the pancreatic duct system in duct-ligated rats.

The concept of function of lysosomes provides a framework into which the hypothesized mechanism for induction of pancreatitis by interstitial extrusion of autophagic vacuoles fits, that is, that pancreatic duct obstruction gives rise to a cellular disorder in the exocrine pancreas associated with lysosome malfunction—specifically increased autophagy and subsequent damage to extracellular structures as a result of interstitial extrusion of cytoplasmic debris and hydrolytic enzymes. Several examples of extrusion of lysosomes from other cell types are reported, especially in organs served by excretory ducts. Thus, it seems to be established that some cells use exocytosis to clear their cytoplasm of residual bodies. It is not surprising to find that this occurs in the pancreas where autophagy is a common result of injury. We would anticipate that any agent that causes acinar cell injury with prominent autophagic vacuole formation might be synergistic with duct obstruction in inducing a significant pancreatitis. Our experiments using combined puromycin treatment and duct ligation suggest that such synergism exists and supports the hypothesis that interstitial extrusion of debris from injured but surviving cells may play a pathogenetic role in the evolution of pancreatitis.

Pancreatitis is a disease with multiple causes. It appears that the incidence of human pancreatitis is sporadic among individuals in whom one or more of the predisposing factors is present. One explanation for such sporadic incidence is that pancreatitis results from the coincidence of 2 or more etiologic factors. The experimental evidence presented previously suggests that, although duct obstruction alone leads to pancreatitis, the combination of duct obstruction with another injury that induces autophagic vacuole formation in acinar cells sets the stage for the evolution of more florid pancreatic inflammation.

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FIGURE 7. Osmiophilic debris lies in the intercellular and interstitial space surrounding the base of an apparently viable acinar cell. Leukocytes lie in the interacinar space. Note the lipid deposits in the base of the acinar cell at the top of the field. All cells contain a few intracisternal granules. From the same rat as Figure 1. Bar, 0.46 μm.

FIGURE 8. This interstitial macrophage contains osmiophilic debris, which has the same configuration as lipid deposits seen in acinar cells in other micrographs from the same rat. Bar, 1.02 μm.
FIGURE 9. This phagocytic cell (probably a mononuclear phagocyte or centroacinar cell) contains a large vacuole containing zymogen granules, degenerating mitochondria and other debris consistent with acinar cell origin. From a rat in which the common duct had been ligated 12 hours before killing. Bar, 0.82 μm.

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Factors Affecting Nonalcoholic Fatty Liver Disease After Pancreatic Head Resection

To the Editor:

Pancreatic head resection (PHR), including pancreaticoduodenectomy (PD) or total pancreatectomy (TP), has become an established treatment with low morbidity and mortality for periampullary diseases, so long-term metabolic disorders have attracted considerable interest. Several reports have demonstrated that nonalcoholic fatty liver disease (NAFLD) occasionally develops in the patients who underwent PD and the prevalence was reported to range from 23% to 38%.1–4 Our former report documented that this prevalence was 12% at 1 month, 21% at 6 months, and 15% at 1 year after PD, respectively, and the risk factors were female sex and a decrease in serum copper (Cu), and this complication was improved or recurred sequentially.5 However, few data are available on the factors affecting improvement or exacerbation of this complication,6 so we retrospectively studied the patients undergoing PHR.

From 2003 to 2016, 313 patients underwent PHR for periampullary disease in our hospital. Two hundred eighteen patients received a computed tomography, until 1 year after surgery, and the remainder who either did not or died within 1 year were excluded from this study. Seven patients with hepatitis B virus surface antigen or hepatitis C virus antibody were also excluded. Thus, 211 patients were enrolled and underwent physical, radiological, and blood examinations at 6 months and 1 year after PHR. We summarized 2 types of diseases: pancreatic ductal cancer in 78 and other periampullary diseases in 133. Surgical procedures included pylorus-preserving PD in 154, subtotal stomach-preserving PD in 35, conventional PD (Whipple PD) in 17, and TP in 5. Twenty patients underwent portal vein resection (PVR) with reconstruction.

We classified them into the 2 groups: 46 in whom NAFLD developed 6 months after surgery (NAFLD G) and 165 in normal then (Normal G). The NAFLD G was classified into the 2 subgroups (SG): 20 in whom NAFLD was improved 1 year after surgery (Recovery SG) and 26 who did not recover (No change SG). The Normal G was classified into the 2 SGs: 10 in whom NAFLD developed 1 year after surgery (Exacerbation SG) and 155 in normal continuously (Normal SG). We compared the clinical parameters between the respective SGs (Fig. 1). Informed consent was obtained by the opt-out method, and this study was approved by the institutional review board at Miyazaki University in 2018 (Approval Number #2017-137).

The clinical parameters to be compared were the following: preoperatively: age, sex, body mass index, disease, diabetes mellitus, and dyslipidemia; perioperatively: surgery, PVR, and frequency of defecation; and postoperatively: pancreatic enzyme supplements and blood tests. Blood tests included total protein (g/dL), total cholesterol (mg/dL), hemoglobin A1c (%), pancreatic function
diagnostic test (%), zinc (µg/dL), and Cu (µg/dL).

Pancreatic enzymes supplements, such as Toughmac (Ono Pharmaceutical Co, Ltd, Osaka, Japan) or Berizym (Shionogi & Co Ltd, Osaka, Japan) were routinely administered in 130 patients. We have used the pancrelipase delayed-release supplement LipaCreon (Eisai Co Ltd, Tokyo, Japan) in 69 patients since 2012. The remaining 12 patients did not receive any kinds of supplements at the attending physician's discretion.

Details of the methods to define NAFLD were described previously.5

Clinical parameters are expressed as the number (percentage) or median (range). Comparisons between groups were made using the χ² test or the Mann-Whitney U test. All P values were based on a two-sided test, and a P value of less than 0.05 was considered to be statistically significant. Statistical analyses were performed using SPSS software Version 18.0 (SPSS, Chicago, Ill).

By univariate analysis, age (P = 0.002), sex (P = 0.047), frequency of defecation (P = 0.013), and total protein at 1 year (P = 0.044) were significantly different between Recovery SG and No change SG. Sex (P = 0.023), disease (P = 0.035), surgery (P = 0.001), PVR (P = 0.001), and Cu at 1 year (P = 0.033) were significantly different between Exacerbation SG and Normal SG by univariate analysis. By multivariate analysis, higher age (P = 0.006) was the factor affecting improvement of NAFLD and a decrease in Cu at 1 year (P = 0.032) was related to exacerbation of NAFLD (Table 1).

Our results suggested that elderly men were subjected to a recovery from NAFLD. We assume that menopausal women may have an imbalance in sex hormone, a change in body fat distribution, and the markedly accelerated accumulation of visceral fat. This hormonal change in fat distribution is not related to male sex, which may be one of the improvement factors of NAFLD.

We found that a decrease in Cu was associated with development of NAFLD. Copper has essential roles in the mitochondrial electron transport chain, in the detoxification of reactive oxygen species, in neurotransmitter synthesis, and in the modulation of cellular energy metabolism and epigenetic modifications.5 Copper deficiency affects the antioxidant defense system resulting in increased reactive oxygen species levels and the related oxidative damage of lipid, DNA, and proteins.10,11 We presume that Cu supplementation might be a potential therapy. Moreover, antioxidant molecules are likely to be an option of the treatment, because oxidative stress has a key role in this pathogenesis.

In conclusion, 1 year after PHR, NAFLD could improve in elderly men, whereas it might newly develop in women with a decrease in serum Cu. We hope that this retrospective evaluation will be helpful to treat this complication in the near future.

The authors declare no conflict of interest.

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TABLE 1. Factors Affecting Improvement or Exacerbation of NAFLD From 6 Months to 1 Year After PHR by Multivariate Analysis

|                          | SE       | Odds Ratio (95% CI) | P         |
|--------------------------|----------|---------------------|-----------|
| Improvement              |          |                     |           |
| Age, elderly             | 0.038    | 0.924 (0.857–0.995) | 0.037     |
| Sex, male                | 0.802    | 2.260 (0.469–10.894)| 0.309     |
| Frequency of defecation  | 0.302    | 1.201 (0.642–2.247) | 0.566     |
| Total protein, 1 y       | 0.711    | 0.582 (0.144–2.345) | 0.446     |
| Exacerbation             |          |                     |           |
| Sex, female              | 1.213    | 5.226 (0.485–56.286)| 0.173     |
| Disease, PDC             | 1.172    | 1.278 (0.128–12.721)| 0.834     |
| Surgical method, TP      | 1.191    | 5.114 (0.496–52.759)| 0.170     |
| Portal vein resection    | 1.445    | 1.516 (0.089–25.721)| 0.773     |
| Copper, 1 y              | 0.032    | 0.940 (0.883–1.000) | 0.049     |

CI indicates confidence interval; PDC, pancreatic ductal cancer; SE standard error.
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