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Commentary

High risk of complications and mortality in cirrhotic patients with acute pancreatitis

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Acute pancreatitis is one of the most common gastrointestinal diseases requiring acute hospital admission. Gallstones (50%) and alcohol (20%) are the most frequent underlying causes. Medication, endoscopic retrograde cholangiopancreaticography (ERCP), hypercalciemia, hypertriglyceridaemia, autoimmune pancratitis, infection, genetic mutations and trauma are responsible for the remaining 30%. In most patients, the disease has a mild and self-limiting course, but in approximately 20% moderate or severe pancreatitis develops, with (peri)pancreatic necrosis, organ failure, formation of collections, infectious complications and a substantial mortality. During the last decade, treatment of acute pancreatitis has changed considerably. Several large multicenter randomized trials in patients with severe pancreatitis have provided conclusive evidence concerning major issues that were previously controversial: early (<24 h) versus late enteral tube feeding (no beneficial effects [1]), urgent ERCP with sphincterotomy within 24 h after hospital admission in case of biliary cause (no beneficial effects unless concomitant cholangitis [2]) as well as timing and approach for drainage in case of infected pancreatic necrosis or pseudocysts (in general preference for radiologic and/or endoscopic rather than surgical approach, with step-up approach and delayed intervention [3–5]). For more information on acute pancreatitis we refer to a recent review of the Dutch Pancreatitis Study Group [6].

In this issue of the Journal, Vogel et al. report that acute pancreatitis runs a more severe course in case of coexistent liver cirrhosis [7]. In their retrospective monocenter study, all 52 cirrhotic patients admitted for acute pancreatitis between 2011 and 2020 (3.5% of all acute pancreatitis patients in their database) were compared to 104 patients without cirrhosis admitted with acute pancreatitis (1:2 matched-pair analysis). Despite similar predictive severity scores at baseline, infections (>50% versus 13%), sepsis (30% versus <5%) and other complications were more frequent, and medical interventions were more often performed with higher risk of periprocedural complications in case of coexistent cirrhosis. Also, organ failure was more frequent (48% versus 12%, with acute on chronic liver failure in 44% of the cirrhosis group), and 6-month mortality much higher (25% versus 1.9%). Patients with portal hypertension (73% of total) seemed particularly prone for an unfavorable course. It should be noted that the cirrhosis patients that were included in this study had relatively advanced disease with a median MELD score of 16. The publication of Vogel et al. [7] is timely and interesting since previous available literature is scarce. Another recent smaller retrospective single-center study [8] compared 40 cirrhotic patients with acute pancreatitis (4.9% of all patients with acute pancreatitis in their database) with 80 non-cirrhotic acute pancreatitis patients (selected by 1:2 propensity score matching). The authors conclude from their data, that cirrhotic patients had similar morbidity and mortality. Nevertheless, severe acute pancreatitis (17.5% vs. 7.5%), need for intensive care unit (15% vs. 6.3%) and hospital mortality (7.5% vs. 1.3%) tended to be higher for cirrhotics, although statistical significance was not reached. Also decompensated cirrhotics appeared to be at particular risk for an unfavorable course. The same authors also

Abbreviations: ERCP, endoscopic retrograde cholangiopancreaticography.

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explored the 2.8 million patients with a discharge diagnosis of acute pancreatitis in the USA National Inpatient Sample (NIS) database (2003–2013). Cirrhosis prevalence was 2.8%, with significantly higher morbidity and mortality [9]. In the last available retrospective study, coexistent cirrhosis (in 32 (13%) of 242 patients with acute alcoholic pancreatitis) was independently associated with a severe course of the pancreatitis [10].

Several limitations apply to the publication by Vogel et al. [7]. Due to the retrospective design there is an inevitable risk of bias. The fact that more patients in the cirrhotic group (21% versus 11%, $P = 0.16$) were late referrals to a large tertiary referral center, is another potential cause of bias. Also, numbers of included patients are quite limited. For future studies, a prospective multicenter approach with more patient numbers could improve generalizability of findings. Also, it should be noted that a significant proportion of cirrhotic and non-cirrhotic patients (25% resp. 32%) were known with pre-existing chronic pancreatitis, which is an exclusion criterion in most studies on acute pancreatitis. Furthermore, the identical BMI in the two groups and the absence of any association between obesity and a complicated course in the current study are not in line with previous data [9,11]. In addition, treatment was not always according to current state of the art [6], possibly due to changed insights during the long inclusion period (2011–2020). For example, a large number of patients underwent drainage of collections relatively early in the disease course (< 1 months after onset of disease). According to a recent nationwide prospective multicenter randomized controlled trial in the Netherlands [5], postponing drainage could lead to more successful conservative management, with a reduced need for re-interventions. Although it remains to be seen whether such policy is generalizable to a population of patients with acute pancreatitis and cirrhosis, it may well be that an approach with preference for late interventions could have led to better results in the study of Vogel et al. [7]. Another example that treatment in the study of Vogel et al. [7] was not always according to current insights [2], are the high numbers of early ERCP (performed in 70–80% of patients with suspected biliary cause in both groups, with more procedural complications in the cirrhotic group). Finally, the multivariable analyses in this report are not in line with the recommendations for etiological research versus prediction research [12,13], resulting in limited interpretability and applicability of the data. Although both types of research are often confused, their distinction is not trivial. Both types of modeling avail of multivariable analyses, but their approaches and interpretation of results differ. Etiological research aims to uncover a causal role of a specific risk factor (e.g. cirrhosis) for a certain outcome, adjusting for confounding factors that are selected based on pre-existing knowledge of causal relations. In contrast, prediction research aims to accurately predict the risk of a certain outcome (e.g. mortality) based on statistically significant, but not necessarily causal, associations in the data at hand [12,13]. Although the aim in the current work seems to be predicting outcomes, one could also easily propose cirrhosis as an etiological factor in complications and mortality (possibly mediated by increased bacterial infection risk due to high intestinal permeability). If cirrhosis would be an etiological factor contributing to an unfavorable course of pancreatitis, further research should be performed as to whether a short early period of prophylactic antibiotics could improve outcome when a patient with cirrhosis develops acute pancreatitis. This approach has already been shown to reduce infection rates and mortality in case of cirrhotic patients with variceal bleeding [14]. Also in case of an infectious complication, adding intravenous albumin suppletion to appropriate antibiotic therapy could prevent further underfilling of the systemic circulation, ameliorate decreases of effective circulating volume and reduce risk of acute kidney injury. This approach reduces mortality in cirrhotics with spontaneous bacterial peritonitis [15]. Other areas of future research could be, whether treatment of portal hypertension (a major risk factor for unfavorable outcome in the Vogel study [7]) using octreotide or beta-blockers could have a beneficial impact on outcome. In absence of further data, the clinician should be aware that the combination of cirrhosis with acute pancreatitis is relatively rare but potentially very hazardous. This hold true both for the 'natural course' of the disease, as well as the risk for complications of interventions. Immediate antibiotic treatment in case of suspected bacterial infections and early referral to a center of expertise are warranted under these circumstances. Finally, the present findings will help in patient counseling and risk-stratification and this all adds to the value of the work by Vogel et al. [7] in this issue.

Declaration of Competing Interest

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