Chronic pancreatitis (CP) arise from diverse etiologies and can result in significant morbidities, such as pain, exocrine and endocrine insufficiency, and even mortality, with occurrence of unresectable pancreatic cancer. These features may be part of the clinical presentation at diagnosis or develop later. Although considerable progress has been made in terms of understanding the etiopathogenesis, clinical course, and treatment outcomes, significant gaps remain in our knowledge. Even in the area of diagnostic criteria and disease classification, though core elements, especially in advanced disease, are common, differences exist. In 2016, a multi-society group published a proposal for a new mechanistic definition of CP and conceptual model of disease initiation and progression to serve as the foundation for future research on reaching a consensus to a mechanistic definition, diagnostic criteria, and disease classification in terms of subtypes, severity, and prognosis.

In this issue of JGH, two important issues with significant impact on the quality of life of CP patients are explored. Olesen et al. examined the factors associated with the presence and type of pain in CP. Liu et al. analyzed risk factors associated with the development of diabetes mellitus (DM) in idiopathic CP (ICP) and created a predictive nomogram. These results are important to help us better understand the disease process and clinical course of CP.

Olesen et al. performed a cross-sectional, multicenter study based on data derived from the Scandinavian Baltic Pancreatic Club database, with CP defined according to the M-ANNHEIM classification system, to determine the prevalence of pain, risk factors for pain, and associations between pain risk factors and type of pain (intermittent vs constant pain). A total of 1384 patients with CP were enrolled. The prevalence of pain was 57.9%. Multivariate analysis confirmed the independence and significance of the associations for pain and age at diagnosis, current status of smoking, alcohol consumption, exocrine pancreatic insufficiency, pancreatic duct changes, pseudocyst, and duodenal stenosis. Constant pain was more frequently reported in moderate and heavy smokers, whereas alcohol was associated with intermittent pain. The strength of the study is the well-defined large patient population. These findings underline the complexity of pain and specifically emphasize the importance of smoking and alcohol cessation. Given the study design, there are intrinsic limitations such as inability to attribute causality, possibility of recall bias, and inability to provide more detailed information such as pain intensity and whether the findings can be extrapolated to non-Caucasian populations.

Liu et al. utilized data from a single center CP database in Shanghai, China, that was set up retrospectively but maintained prospectively to determine the incidence of DM. The authors also attempted to identify risk factors for DM and develop a nomogram for prediction of DM in patients with ICP. Although the M-ANNHEIM classification system was not used, unlike in the study by Olesen et al., specific morphologic features and complications were systematically captured. A total of 1633 patients were enrolled. The median follow-up duration was 9.8 years. DM was found in 26.3% of patients after the onset of CP. Adult status at onset of ICP, biliary stricture at/before diagnosis of CP, steatorrhea at/before diagnosis of CP, and complex pathologic changes in the main pancreatic duct were identified as risk factors for DM development in these patients. The nomogram demonstrated good accuracy in estimating the risk of DM, with a C index of 0.674. The obvious strengths of this study are the novelty in terms of creation of a nomogram, the large sample size, and amount of data available prospectively. Nonetheless, not all factors related to the development of DM were included in the analysis, and it was difficult to distinguish between pancreatogenic DM and type 2 DM.

Currently, a definite diagnosis of CP is usually achieved at a late disease stage, and the focus of management is then directed towards the detection of and management of complications, such as pain relief, replacement therapies for exocrine and endocrine pancreatic deficiencies, and surgical resection in context of cancer and unremitting pain. These two papers provide important data to further our knowledge in the clinical course of established CP. They address the clinically important issues of lifestyle adjustment in pain management and the need for screening of DM.

There is a need to be able to diagnose CP at an early stage and initiate treatment to limit disease progression and minimize complications. An international working group supported by four major pancreas societies sought to develop a consensus definition and diagnostic criteria for early CP. However, no consensus could be reached for a definition or diagnostic criteria of early CP. However consensus was achieved in other areas, such as the use of the term “early” to describe a disease state with preserved pancreatic function and potentially reversible features rather than disease duration, the importance of genetic variants as important risk factors for early CP, the role of environmental risk factors to provide evidence to support the diagnosis of early CP, and the need to differentiate CP from other disorders with overlapping morphological and functional features. The conclusion was that new approaches to the accurate diagnosis of early CP would require development and validation of a mechanistic definition that considers risk factors, biomarkers, clinical context, and new models of disease.

There is also a need to better stratify patients for prognostication and to guide surveillance for CP related complications. The study by Liu et al. addressed DM development. The M-ANNHEIM classification system provides a comprehensive etiologic, morphologic, and functional description. However, it is not consistently applied in clinical practice. A recent study correlated clinical, laboratory, and imaging data with the number of hospital readmissions and in-hospital days to develop a three-stage chronic pancreatitis prognosis score (COPPS), which was based on a composite of pain (numeric rating scale), level of glycosylated hemoglobin A1c, level of C-reactive protein, body mass index, and...
platelet count. COPPS helped to determine the risk for readmission to hospital and potential length of hospital stay.\(^6\) CP increases the risk of pancreatic cancer. However, in the absence of hereditary predisposition, it remains unclear which subgroup of CP patients would benefit from surveillance.\(^7\),\(^8\) Well-designed multicenter prospective longitudinal cohort studies with a large sample size of well-characterized CP patients are needed to better understand the true natural history of CP and develop predictive nomograms, and one such study is currently underway.\(^9\)

Despite ongoing multi-society efforts to systematically address diagnostic and therapeutic challenges in CP,\(^3\),\(^7\),\(^9\),\(^10\) important gaps in knowledge remain. The search for the Holy Grail continues.

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**References**