Clinical and translational markers of severity and prognosis in chronic pancreatitis

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Purpose of review
The incidence of chronic pancreatitis as a progressive inflammation and fibrosis syndrome is on the rise due to increasing awareness and improved imaging modalities. Numerous classification systems have been suggested in recent years to describe the disease, but only few of them have been used to classify the severity and prognostic significance of the disease. Biomarkers for severity and (early) chronic pancreatitis diagnosis are not yet ready for clinical application.

Recent findings
In using the M-ANNHEIM and Chronic Pancreatitis Prognosis Score (COPPS) classification system, the severity assessment and short- and medium-term disease progression is available. A prospectively validated biomarker for early chronic pancreatitis diagnosis is not yet available, metabolome-based approaches seem to have the greatest potential for clinical translation.

Summary
Currently, due to the lack of universal definition for the early disease stage of chronic pancreatitis, it is difficult to accurately classify these patient cohorts in existing scoring systems. In principle, setting up a suitable scoring system would allow surveillance and establish a therapy approaches flanked by corresponding biomarker panel development. Therapy management of chronic pancreatitis and monitoring by means of scoring systems (such as the COPPS) would make a decisive contribution to improving patient treatment.

Keywords
biomarker, chronic pancreatitis, Chronic Pancreatitis Prognosis Score

INTRODUCTION

Chronic pancreatitis is defined as a fibroinflammatory syndrome of the pancreas in which recurrent episodes of inflammation lead to progressive fibrotic organ remodelling with multiple sequelae [1]: chronic pain, exocrine and/or endocrine insufficiency and complications requiring endoscopic intervention or surgery all of which lead to a reduced quality of life and shorter life expectancy. The 20-year survival rate of affected individuals is decreased by approximately 20% compared with age-adjusted cohorts [2]. The lifetime risk for developing pancreatic cancer is significantly increased in patients with chronic pancreatitis but varies greatly between individuals, depending on the cause of chronic pancreatitis, tobacco use and the presence of diabetes [3]. The socioeconomic importance of the disease is highlighted by the fact that nearly half of all patients become permanently disabled during the course of their illness [4]. Unlike in acute pancreatitis, the diagnosis of chronic pancreatitis is not based on a laboratory value and corresponding clinical symptoms but requires the integration of imaging findings and pancreatic function tests with the patient's disease history and symptoms. This results in an often disproportionately long period from onset of symptoms to diagnosis, even in 2022. Moreover, no consensus on unifying, internationally accepted criteria for the diagnosis of chronic pancreatitis especially in its early phase has been reached so far. Developing targeted treatments for fibrosing diseases has proven to be difficult for numerous reasons two of which are a lack of validated prognostic markers and well defined endpoints thus preventing clinical trials that might

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KEY POINTS

- The M-ANNHEIM system allows for comprehensive classification of chronic pancreatitis cause, diagnostic certainty and disease stage, but prospective data with regard to its value in severity grading are lacking.
- COPPS, is the first prospectively developed and independently validated scoring tool, that allows reliable severity grading based on a 12-month prognosis. Its value in guiding treatment decisions needs further investigation.
- In the future, biomarker panels might play an important role in the early detection of individuals at risk for developing chronic pancreatitis and pancreatic insufficiency.
- Improved diagnostic tools will hopefully help to shorten the time interval from symptom onset to diagnosis.

lead to anticipatory and targeted treatment strategies [5].

Therefore, treatment options for chronic pancreatitis currently remain 'reactive' or symptom driven, and management requires a multiprofessional approach with seamless interaction from primary care to the expert centre level. The variable course and slowly progressing nature of the disease, make this task challenging and accurate and reliable severity assessment as well as prediction of prognosis are of utmost importance to guide patients. Thus, clinical markers for the assessment of severity and prognosis play a crucial role in both the symptom-oriented management of patients today and the successful development of better treatment options tomorrow. A comprehensive literature search shows, that the M-ANNHEIM classification and the Chronic Pancreatitis Prognosis Score (COPPS) are the only two clinical classification systems that determine a multidimensional clinical severity index, and therefore these two classification systems will be specifically addressed in this review [6,7].

CLINICAL MARKERS FOR SEVERITY ASSESSMENT AND PROGNOSIS

As in most patients the diagnosis of chronic pancreatitis is based on imaging, it is intuitive to use imaging for grading severity as well. Widely applied systems are the Cambridge Endoscopic retrograde cholangiopancreatography (ERCP), ultrasound, computed tomography (CT) and MRI] and Rosemont (EUS) classification which are used for a standardized description of pancreatic morphology and for making an imaging based diagnosis [8,9]. But as morphology, symptoms and pancreatic function do not correlate in chronic pancreatitis, imaging-based classifications are not suited to assess severity and prognosis [10,11,12▪]. Although a variety of clinical classification systems have been published since the first Marseille Symposium in 1963 [13], none of those have been validated in prospective studies for clinical endpoints relevant to disease prognosis or disease-associated morbidity [14]. Moreover, most are nondynamic descriptive classification systems suited to estimate a patient's current status with regard to the anticipated natural disease course, but unable to predict any short-term to medium-term outcomes, which in turn potentially alters management. In other words, grading the severity of chronic pancreatitis should rather be perceived as a complex integration of pancreatic function, morphology and patient-reported outcomes.

The fundamental importance of severity and prognosis assessment in the context of chronic pancreatitis is derived from the fact that only an accurate assessment of severity in the appropriate clinical context without misweighting individual aspects (such as impressive parenchymal calcifications) can take into account the biological variability of the clinical picture. The importance of a valid prognosis score for chronic pancreatitis would furthermore enable the possibility of monitoring response to therapy. The M-ANNHEIM classification (severity assessment) and COPPS (prognosis score) so far are the most promising tools to meet these requirements [6,7].

THE M-ANNHEIM CLASSIFICATION

First published in 2007, the M-ANNHEIM classification addressed for the first time the need of a severity classification with a direct impact on the treatment strategy of patients in chronic pancreatitis through acute disease staging. Based on a comprehensive review of the literature and expert consensus, multiple (M) risk factors were combined into one acronym (M-ANNHEIM: alcohol consumption (A), nicotine consumption (N), nutritional factors (N), hereditary factors (H), efferent pancreatic duct factors (E), immunological factors (I), and various rare miscellaneous and metabolic (M) factors) – an approach previously also used by the North American TIGAR-O risk and cause checklist for pancreatitis [15,16].

For the first time, the M-ANNHEIM classification reflected the assumption that an accurate severity assessment can only be made based on the interaction of organ morphology and function, pain behaviour, and disease modulation by intervention or surgery. In accordance with the 1997 Consensus Meeting in Zurich, the diagnosis is divided into the categories definite, probable and borderline chronic pancreatitis [17].

The proposed M-ANNHEIM clinical staging algorithm recommended clinical staging [asymptomatic phase (Stage 0) versus symptomatic phases (Stages I–IV)] to initially determine chronic pancreatitis severity. Due to the lack of internationally agreed recommendations on the definition of the asymptomatic/early phase of chronic pancreatitis at that time, for example, acute pancreatitis was also considered a possible starting event of chronic pancreatitisin the sense of a disease continuum from acute to chronic pancreatitis (Stage 0 b). At Stages I–III, the primary classification was based on the presence of no (I), partial (II), or complete exocrine or endocrine pancreatic insufficiency, subcategorized as Ia–c, IIa–c and III a + b. Symptomatic chronic pancreatitis Stage I distinguishes the presence of recurrent episodes of acute pancreatitis (Stage Ia) and recurrent or chronic abdominal pain (Ib). Stage Ic is reached as soon as serious complications such as ascites or common bile duct stricture occur. In contrast to Stage II, functional organ compromise does not play a role in Stage I. In Stage II, on the other hand, functional impairment is taken into account (exocrine or endocrine insufficiency) and divided into IIa (no pain) and IIb (pain). In Stage IIIa, there is a combined exocrine and endocrine pancreatic insufficiency with pain requiring analgesics. Stage IIIb is reached as soon as additional complications occur (e.g. chronic pancreatitis-related duodenal stenosis, pseudoaneurysms etc.). Stage IV was defined as a painless late stage of chronic pancreatitis with exocrine and endocrine functional impairment. For image-based morphological staging, the M-ANNHEIM classification used the Cambridge classification for all imaging modalities (ultrasound, CT, magnetic resonance imaging/Magnetic Resonance Cholangiopancreatography (MRI/MRCP) and endosonography) and referred to the use of endosonography to specify between mild and moderate parenchymal and ductal changes. In the M-ANNHEIM scoring system, scores are assigned based on clinical features in the categories of pain report (0–4 points), pain control (0–2 points), pancreatic surgery (0 or 4 points), exocrine insufficiency (0–2 points), endocrine insufficiency (0 or 4 points), Cambridge organ morphology (0–4 points) and presence of severe organ complications not covered by the Cambridge classification (0–4 points). The scoring results in the M-ANNHEIM severity index with categories ranging from M-ANNHEIM A (minor severity level; 0–5 points) to M-ANNHEIM E (exacerbated severity level; more than 20 points; see Fig. 1) [6].

M-ANNHEIM SEVERITY INDEX AND CLINICAL TRANSLATION

Various external validation cohorts have investigated the M-ANNHEIM classification with regard to severity assessment in chronic pancreatitis. An Italian cohort of 302 chronic pancreatitis patients demonstrated that assigning the M-ANNHEIM clinical staging [Stage 0 (17%), Stage I (43%), Stage II (25%), Stage III (13%), Stage IV (2%)] and the M-ANNHEIM score is possible [M-ANNHEIM A (41%), B (32%), C (22%), D (7%), E (1%)], but noted that a reduction in the number of categories would facilitate the practical handling of the classification system. A correlation of singular or multiple etiologic risk factors to specific severity scores could not be ascertained ([18]; Abstract). In 2013 a Dutch/Danish cohort was used to investigate whether the M-ANNHEIM severity index of patients with chronic pancreatitis (60 patients) differed from healthy controls (15 patients) with respect to pain sensitivity and pain modulation. In total, 34 patients with less than 10 points in the severity index were classified as moderate chronic pancreatitis group (including: minor and increased severity level; M-ANNHEIM A + B). 26 patients scored more than 10 points and were categorized as severe chronic pancreatitis group (including: advanced and marked severity level; M-ANNHEIM C + D). In the categories pressure pain detection threshold (pPDT) and electric pain detection (ePDT) it could be shown that the predefined disease severity in the M-ANNHEIM classification could be accurately reflected in the study design. For pPDT, a significantly lower threshold was found for the group of severe chronic pancreatitis patients compared with the healthy controls ($P = 0.001$) and the group of moderate chronic pancreatitis patients ($P = 0.001$). Similarly, for ePDT, this threshold gradation could be detected with significantly lowered threshold for the severe chronic pancreatitis patients group compared with the healthy control subjects ($P = 0.007$) and the moderate chronic pancreatitis group ($P = 0.03$) [19]. One year later, a Chinese group published a retrospective analysis of 89 patients who had undergone endoscopic treatment of chronic pancreatitis for pain relief. They found, that a less advanced M-ANNHEIM clinical stage (Ia vs. Ib) was associated with more profound and longer lasting pain relief measured on the Izbicki pain score (complete or partial pain relief after 2-year follow-up 95.2 vs. 78.0%, $P = 0.021$) [20]. Similarly, a multicentre retrospective cohort was able to show in 2015 that the classification also correlated to the risk of undergoing pancreatic surgery, indicating a potential prognostic or even predictive role. A preoperative severity index value of 11 could be identified as a cut-off value for surgical rather than conservative management [median 12 (range: 11–16) vs. median 6 (range: 3–9), $P < 0.001$, Mann–Whitney U test]. Using logistic regression, the M-ANNHEIM severity score was used to calculate the M-ANNHEIM surgery

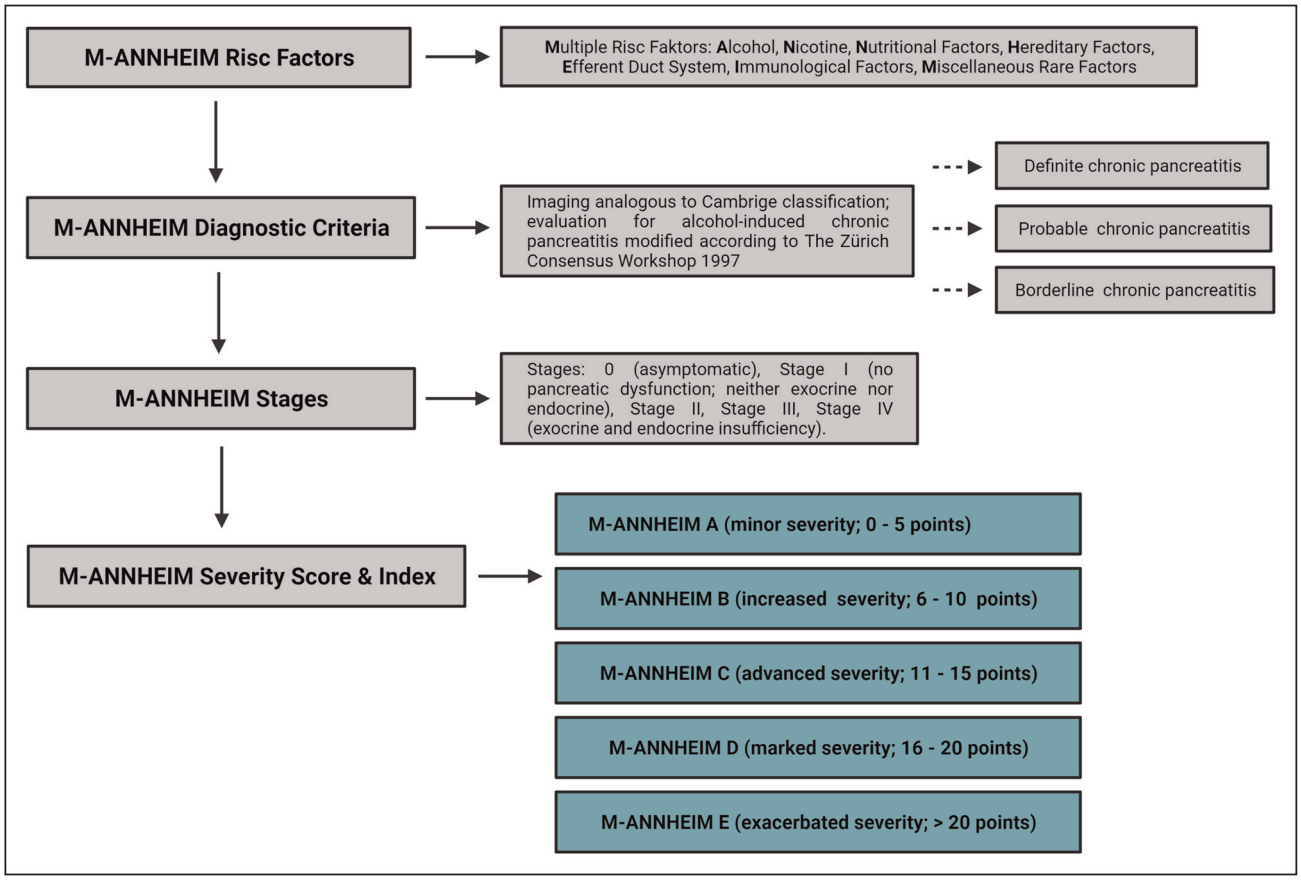

FIGURE 1. M-ANNHEIM severity index of chronic pancreatitis. Multilevel classification system for the severity of chronic pancreatitis. Categorization as definitive chronic pancreatitis is based on the Cambridge classification and if more than one of the following features is present: pancreatic calcifications, moderate or marked ductal lesions (according to the Cambridge classification), marked and persistent exocrine insufficiency defined as pancreatic steatorrhea markedly reduced by enzyme supplementation, typical histology of an adequate histological specimen. Categorization as probable chronic pancreatitis is based on one or more of the following features: mild ductal alterations (according to the Cambridge classification), recurrent or persistent pseudocysts, pathological test of pancreatic exocrine function, endocrine insufficiency. Borderline chronic pancreatitis was classified as a typical clinical history without fulfilled criteria from the group of definite or chronic pancreatitis, as well as an expired episode of acute pancreatitis. A prognostic assessment of which patient is more likely to benefit from intervention/surgery is possible. Adapted from Schneider *et al.* [6].

score, which is intended to serve as a decision tool for a surgical therapeutic approach based on pain, pancreatic imaging and pancreatic complications (where nine points with 78.7% sensitivity and 91% specificity were calculated as cut-off) [21]. Prospective evaluation of this tool is pending.

Although never prospectively validated with regards to relevant clinical endpoints, the comprehensive M-ANNHEIM clinical staging and severity index score seem to be quite suitable for mapping stage and severity in patients with chronic pancreatitis, but clinical implications remain vague. Limitations of the comprehensive M-ANNHEIM severity index score are mainly the diagnostic multidimensional and therefore complex system as well as the lack of detection of relevant chronic pancreatitis-associated sequelae such as malnutrition or osteoporosis [14,22].

SEVERITY CLASSIFICATION AND PROGNOSIS BY USING THE CHRONIC PANCREATITIS PROGNOSIS SCORE

Developed in 2017 by our group and validated in collaboration with partners from Denmark, the COPPS aimed to fill a gap that previously existed for clinical chronic pancreatitis scores: to predict the short-term to mid-term prognosis by using routinely assessable multidimensional data (imaging, functional tests, laboratory values and patient-reported outcomes) and thus also grade severity [7]. Moreover, COPPS was the first classification system for

chronic pancreatitis, that was prospectively developed following a standardized clinical study protocol according to the guidelines for Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis [23]. In the development cohort 91 patients with chronic pancreatitis were prospectively included and followed for 12 months. Primary endpoints were hospital admission rates and length hospital of stays as surrogates for disease severity. Based on correlation analyses with those primary endpoints, four easy-to-survey parameters (HbA1c, BMI, C-reactive protein, platelets) supplemented by the numeric rating scale (0–10) for most severe pain intensity within the last 7 days were used for model calculation. These five parameters were combined into a score that allows grouping into three severity categories A, B or C, similar to the Child–Pugh–Turcotte score for liver cirrhosis (see Fig. 2). Patients especially in the COPPS B and C category experience significantly more inpatient treatment days within 12 months, underscoring the prognostic value of the score. COPPS as validated in a larger independent cohort, including patients from Germany and Denmark and another prospective validation study from India also detected a correlation between higher COPPS categories and the number and length of hospitalizations in this geographically divergent patient population of 171 patients [24]. An international multicentre, prospective COPPS validation study has finished recruitment, data being currently analysed, preliminary results validating previous findings and the ongoing ESGE endorsed ESCOPA trial initiated by the Dutch Pancreatitis Study Group is investigating a potential role of COPPS in predicting response to endoscopic therapy and as a surrogate for treatment success.

BIOMARKERS FOR SEVERITY AND PROGNOSIS ASSESSMENT

Biomarkers for the detection of early stages

Biomarkers routinely used in severity assessment during chronic pancreatitis management are faecal elastase 1 and HbA1c, as markers of exocrine and endocrine pancreatic function, and 25-OH-vitamin D, calcium, albumin and phosphate to assess nutritional failure and risk for osteopenia [25,26]. In terms of biomarker-based prediction of whether a patient will develop chronic pancreatitis, the difficulty in particular for the early stages of chronic pancreatitis is that, unlike late disease stages with clear disease-specific organ manifestations (calcifications and duct distortion), the underlying pathophysiological mechanisms that distinguish health from disease are not yet well understood [1,27]. This is further complicated by the fact that for the early stage of chronic pancreatitis no clearly defined

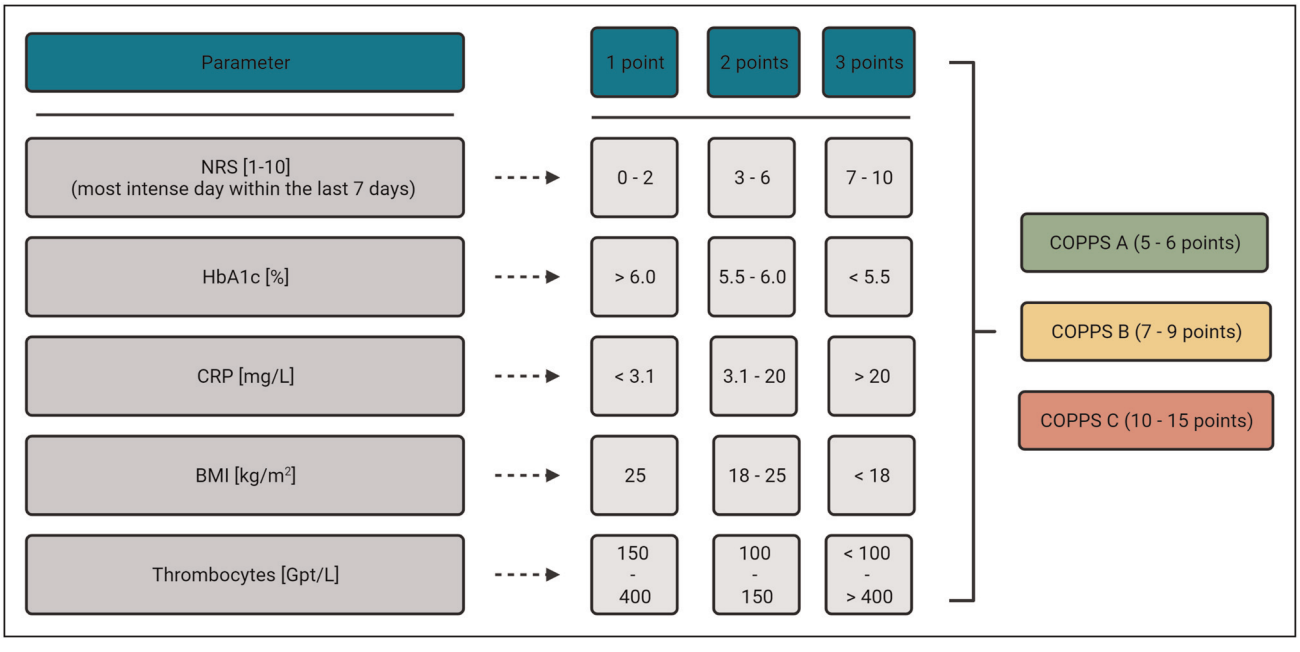

FIGURE 2. Chronic Pancreatitis Prognosis Score. Three stages (Chronic Pancreatitis Prognosis Score A–C) describe the severity of the disease in ascending order using a point system. With the help of the pain assessment (Numeric Rating Scale), HbA1c, C-reactive protein, BMI and platelet count, a prognosis can be made about the expected duration of hospitalization and probability of rehospitalization within the following 12 months. Adapted from Beyer *et al.* [7].

clinicopathological symptom complex could be consented in expert panels so far [28]. Thus, no prospectively validated biomarker is currently available for early diagnosis in the sense of severity assessment, let alone as a progression parameter for prognosis prediction in routine clinical practice. Nevertheless, biomarker-based early detection of chronic pancreatitis is seen as a research opportunity, as in case of a robust detection rate the often years-long odyssey of patients from symptom onset to diagnosis at an often only advanced stage could be shortened and disease-related secondary complications such as malnutrition, osteoporosis or diabetes mellitus could potentially be prevented [29,30]. Amylase, the best-known pancreas-specific laboratory value besides lipase, was investigated in a chronic pancreatitis cohort classified according to M-ANNHEIM with regard to its diagnostic significance. It was possible to detect an excellent ROC-AUC receiver operating characteristic (ROC) curve and the area under the ROC curve (AUC) in the discovery cohort (121 patients) especially in the advanced disease stages (M-ANNHEIM III + IV) in case of decreased amylase levels (M-ANNHEIM III + IV: amylase level: 15.4 U/l, ROC-AUC (95% CI): 0. 95 (0.88–1.00), sensitivity 92%, specificity 95%) and to replicate the diagnostic performance in a validation cohort of 57 patients [ROC-AUC in the validation cohort 0.69 (0.59–0.79) with a corresponding accuracy of 77%, sensitivity 51%, specificity 94%]. A decreased amylase level thus has its value as a biomarker for the diagnosis of chronic pancreatitis and should prompt further investigations (endoscopic ultrasound, pancreatic function assessment, screening for risk factors) [31]. However, it has to be highlighted that the diagnostic accuracy relates mainly to more advanced disease stages and low amylase has not been investigated as a singular diagnostic tool for early stages.

Primarily based on the statistical discrimination tool area under the receiver operator curve (AUROC), a systemic literature review has attempted to determine which biomarkers have the greatest potential with respect to clinical translation [32]. Of 81 biomarkers studied, 61 showed only modest or moderate effect sizes, so that after subtracting the 15 biomarkers with no detected effect, only five biomarkers were categorized as promising (AUROC > 0.96). Using nuclear magnetic resonance spectroscopy, it was shown in 2013 that urinary adenosine is significantly increased in patients with chronic pancreatitis compared with healthy controls subjects [33]. A prospective validation study mainly on diagnostic performance in differentiation from acute pancreatitis is pending.

Adiponectin has not yet gained widespread clinical use as a diagnostic marker to differentiate pancreatic cancer patients from chronic pancreatitis patients due to lack of differentiation [34]. Diagnostic interference and grey areas in the separation to acute pancreatitis have made it difficult to focus on blood-based laboratory parameters such as IL-6 or des-Leu-albumin [35,36]. Oxidized fatty acids have so far not been able to contribute any clear added value to earlier chronic pancreatitis diagnosis [37]. Given the heterogeneous nature of the disease, finding a single, sufficiently accurate diagnostic and prognostic biomarker is unlikely. Therefore composite biomarkers and signature score have moved into the focus. Evaluated in a relatively small cohort of chronic pancreatitis patients, a specific miRNA expression pattern was detected for early chronic pancreatitis (hsa-miR-199a-3p, hsa-miR-221, hsa-miR-130a and hsa-miR-1471), the diagnostic viability of which has to be demonstrated in prospective validation studies supplemented by further diagnostic methods in the future [38].

Already validated in two independent cohorts, a metabolome signature consisting of 8 different metabolomes (beta-carotene, cryptoxanthin, behenic acid (C22 : 0), indole-3-acetic acid, hippuric acid, mannose, ceramides (d18 : 1, C24 : 1), *N*-acetylcytidine) was identified by our group, which can robustly discriminate between chronic pancreatitis patients and healthy controls subjects based on EDTA and serum samples (AUC > 0.8). Whether the metabolome signature is also suitable for diagnosing early stages of chronic pancreatitis needs to be investigated prospectively, as only confirmed chronic pancreatitis patients had been studied due to the aforementioned obstacles [39▪]. However, it could be shown, that the metabolome signature score correlates well with the presence or absence of exocrine and/or endocrine pancreatic insufficiency without dropping its diagnostic performance in any of those subgroups, pointing towards a role of metabolomics as both an early diagnostic as well as a severity marker in chronic pancreatitis. Different biomarker panels have theoretical and partly practical potential, but need to be studied prospectively and under clearly predefined diagnostic criteria of chronic pancreatitis and its early stage. Such successful clinical translation would provide a target for antifibrotic and anti-inflammatory drug-based therapeutic strategies.

CONCLUSION

The main problem of all chronic pancreatitis classification systems is that none of them have been

investigated in prospective randomized trials with regard to morbidity and mortality or other established relevant clinical endpoints. Using the M-ANNHEIM severity index and the COPPS, the need for interventions/surgeries as well as hospital readmission and length of stay at 12-month follow-up can be assessed. Further studies are necessary to evaluate whether COPPS can be used to predict the response to therapy. Metabolome signatures are generally suitable for blood-based discrimination of chronic pancreatitis patients and healthy control individuals, although it is currently unclear to what extent such signatures are viable as an early diagnostic tool.

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Conflicts of interest

There are no conflicts of interest.

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- ■■ of outstanding interest

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First successful valdation of a metabolome signature to discriminate chronic pancreatitis patients to healthy control subjects.