

# CLINICAL—PANCREAS

## Development and Validation of a Chronic Pancreatitis Prognosis Score in 2 Independent Cohorts



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**BACKGROUND & AIMS:** The clinical course of chronic pancreatitis is unpredictable. There is no model to assess disease severity or progression or predict patient outcomes. **METHODS:** We performed a prospective study of 91 patients with chronic pancreatitis; data were collected from patients seen at academic centers in Europe from January 2011 through April 2014. We analyzed correlations between clinical, laboratory, and imaging data with number of hospital readmissions and in-hospital days over the next 12 months; the parameters with the highest degree of correlation were used to develop a 3-stage chronic pancreatitis prognosis score (COPPS). The predictive strength was validated in 129 independent subjects identified from 2 prospective databases. **RESULTS:** The mean number of hospital admissions was 1.9 (95% confidence interval [CI], 1.39–2.44) and 15.2 for hospital days (95% CI, 10.76–19.71) for the development cohort and 10.9 for the validation cohort (95% CI, 7.54–14.30) ( $P = .08$ ). Based on bivariate correlations, pain (numeric rating scale), level of glycated hemoglobin A1c, level of C-reactive protein, body mass index, and platelet count were used to develop the COPPS system. The patients' median COPPS was 8.9 points (range, 5–14). The system accurately discriminated stages of disease severity (low to high): A (5–6 points), B (7–9), and C (10–15). In Pearson correlation analysis of the development cohort, the COPPS correlated with hospital admissions (0.39;  $P < .01$ ) and number of hospital days (0.33;  $P < .01$ ). The correlation was validated in the validation set (Pearson correlation values of 0.36 and 0.44;  $P < .01$ ). COPPS did not correlate with results from the Cambridge classification system. **CONCLUSIONS:** We developed and validated an easy to use dynamic multivariate scoring system, similar to the Child-Pugh-Score for liver cirrhosis. The COPPS allows objective monitoring of patients with chronic pancreatitis, determining risk for readmission to hospital and potential length of hospital stay.

Chronic pancreatitis, as defined by the German “S3-consensus guidelines,” is a disease of the pancreas in which recurrent inflammatory episodes result in replacement of pancreatic parenchyma by fibrous connective tissue. This fibrotic reorganization of the pancreas leads to a progressive exocrine and endocrine pancreatic insufficiency. In addition, characteristic complications arise, such as pseudocyst formation, pancreatic duct obstruction, duodenal obstruction, vascular complications, bile duct stenosis, malnutrition, and pain syndrome. Pain presents as the main symptom of patients with chronic pancreatitis. Chronic pancreatitis significantly reduces the quality of life and the life expectancy of affected patients.<sup>1,2</sup> Many of the symptoms and complications mentioned previously can be treated and treatment effects need to be monitored.

The first classification system of chronic pancreatitis developed at a symposium in Marseilles in 1963 focused on morphological changes and etiology underlying the disease.<sup>3</sup> In its revised version, published in 1985, these morphological changes were specified and linked to a potential loss of endocrine and exocrine organ function<sup>4</sup> and further subtypes were introduced in the consecutively published Marseilles-Rome classification.<sup>5</sup> The Cambridge classification, which was the first clinical grading system for chronic pancreatitis, was based on changes in ductal morphology on endoscopic retrograde pancreatography and to some extent equivalent findings on ultrasound or computed tomography.<sup>6,7</sup> The Cambridge criteria remain the standard for grading of chronic pancreatitis on imaging, but already

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**Abbreviations used in this paper:** BMI, body mass index; CI, confidence interval; COPPS, chronic pancreatitis prognosis score; ERCP, endoscopic retrograde cholangiopancreatography; HbA1c, glycated hemoglobin A1c; TRIPOD, Individual Prognosis Or Diagnosis statement.

Most current article

**Keywords:** C-reactive Protein; BMI; Pancreas; Clinical Scoring System; Child-Pugh-Turcotte Score.

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**EDITOR'S NOTES****BACKGROUND AND CONTEXT**

The clinical course of chronic pancreatitis is unpredictable. There is no model to assess disease severity or progression or predict patient outcomes.

**NEW FINDINGS**

The researchers developed and validated a chronic pancreatitis prognosis score (COPPS); an easy to use dynamic multivariate system csimilar to the Child-Pugh-Score for liver cirrhosis

**LIMITATIONS**

The system should be tested with a larger set of outpatients as part of an international multicenter cohort that is in development.

**IMPACT**

The COPPS system allows objective monitoring of patients with chronic pancreatitis, determining risk for readmission to hospital and potential length of hospital stay.

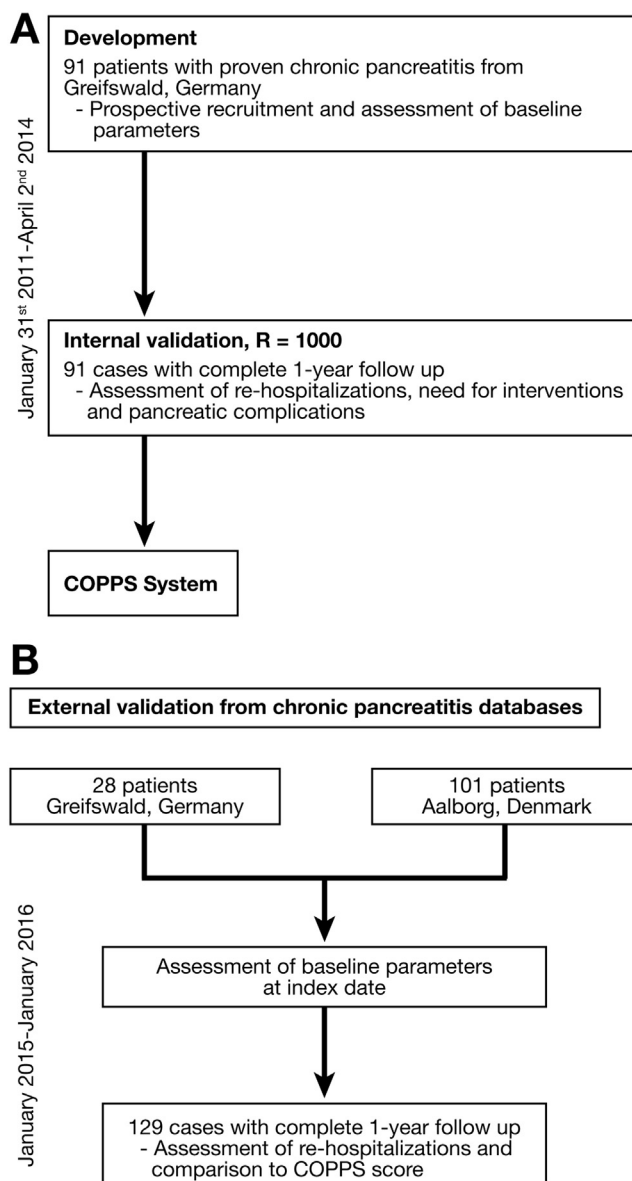
when first introduced, experts stated that morphological changes in chronic pancreatitis might not reflect the functional or histological state of the pancreas and early stages of the disease might be missed.<sup>6,8</sup> More recently proposed classification systems from Zurich, Kerala, Manchester, Heidelberg, and Mannheim help to describe the natural progression of the disease by grading the severity on the basis of imaging, clinical symptoms, need for intervention, and loss of function,<sup>9-13</sup> but are neither suited to assess the current severity nor to evaluate short- to mid-term outcomes of the disease. Furthermore, none of the published severity scoring systems have been developed in a prospective cohort of patients nor have they been evaluated for predicting relevant clinical outcome parameters. We hypothesized that it would be possible to develop and validate a simple and dynamic scoring system, comparable to the Turcotte-Child-Pugh score for liver cirrhosis<sup>14,15</sup> based on routine laboratory parameters, pain symptoms, body mass index (BMI), or imaging. The aim of the study was to test this system in a prospective manner and validate the scoring against clinical variables in 2 independent patient cohorts with the future potential to predict the response to therapy and risk of complications.

## Patients and Methods

### Aims and Study Design

This study was designed according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis statement (TRIPOD).<sup>16</sup> In the first phase, we conducted a prospective single-center cohort study on 91 patients (development cohort) with preexisting chronic pancreatitis to develop a severity scoring system in chronic pancreatitis, by using readily available routine laboratory parameters, BMI, imaging, and standardized assessment of pain symptoms. In the second phase, the score was validated in an independent cohort from 2 prospectively recruited

databases at academic centers (Aalborg, Denmark, and Greifswald, Germany) comprising 129 subjects (validation cohort), see Figure 1. With regard to the TRIPOD recommendation, we performed a type 3 study by developing a prediction model using 1 data set and an evaluation of its performance on separate data.<sup>16</sup> Baseline parameters were collected at the time of inclusion. Twelve months from inclusion, the patients were contacted via phone or approached when in the hospital as an outpatient and endpoints were recorded. For the development cohort, the first patient was recruited on January 31, 2011, and follow-up for the last patient ended in April 2, 2014 (Figure 1A). The study was approved by the institutional ethics committees and conducted in accordance with the declaration of Helsinki. No additional diagnostic or therapeutic procedures were performed as result of study participation nor did inclusion in the study influence medical care of the patients. Except for the study investigators, all medical personnel were blinded to the study results or as to whether a patient was included.



**Figure 1.** Flow chart for development (A) and external validation (B) of COPPS.

## End points

As primary endpoints and surrogates for severity of disease, (re)-admission to hospital, measured as number of hospitalizations and total number of days spent in hospital within 12 months from inclusion, were chosen. Secondary outcomes were pancreatitis-related readmissions, pancreatitis-related complications, and need for endoscopic or surgical interventions. A hospital stay was considered related to pancreatitis if admission was due to an acute episode of pancreatitis, abdominal pain likely caused by pancreatitis, pancreatic endoscopy or surgery, or infectious complications including the pancreas. Although long-term mortality is increased in patients with chronic pancreatitis with a hazard ratio (HR) 3.6 to 5.0 when compared with the normal population,<sup>17</sup> we could not use mortality as the primary endpoint for the development of a scoring system due to a low annual event rate.

## Inclusion Criteria

Inclusion criteria for the development cohort included written informed consent given by patients and preexisting chronic pancreatitis. The diagnosis of chronic pancreatitis was made if 1 or more of the following criteria were met and no other diagnosis was more likely<sup>2</sup>:

- recurrent bouts of pancreatic pain with documented rise in amylase or lipase activity for a duration of more than 1 year and radiological evidence supporting the diagnosis
- pancreatic calcifications
- histological proof of chronic pancreatitis
- unequivocal changes in pancreatic duct morphology
- severely abnormal pancreatic function tests with maldigestion

The validation patients from Germany had identical inclusion criteria, whereas for Danish patients the diagnosis

of chronic pancreatitis was established according to the Lüneburg score.<sup>18,19</sup>

## Assessment of Prognostic Factors

Initial screening included a list of 14 routine laboratory parameters, which were measured using the clinical standard procedure of the respective institutional clinical chemistry department, BMI (measured as body weight in kilograms divided by square height in meters), pain severity as worst pain on numeric rating scale (0–10; 0 = no pain; 10 = worst imaginable pain) within the past 7 days, and grading of pancreatic morphology based on the available imaging according to the modified Cambridge Score.<sup>2,6,7,20</sup> Analysis of imaging was conducted by expert endoscopists with experience in more than 1000 endoscopic retrograde cholangiopancreatographies (ERCPs) or diagnostic radiologists with expertise in abdominal imaging, who were blinded to any other study related information. Values were expressed using SI units. Reference ranges for development and validation cohort as well as in between centers were identical and are displayed in Table 1.

## Statistical Analysis

Data analysis began after the follow-up period of the last patient was completed. To identify single variables for score development, linear correlation (parametric and nonparametric) analysis was performed and parameters that would show the best fit with closest correlation to both primary endpoints were included in further analysis. Cases with missing data were excluded pairwise from the analyses (Table 1). Each of the best-fitting 5 parameters were graded into 3 categories (1 = within normal range, 2 = moderately altered, 3 = significantly abnormal) according to the parameter values, and the numbers were summed to achieve the final composed score value of 5 to 15. Scores of all patients were again

**Table 1.** Baseline Parameters Used for Score Development

Parameter	Reference value	Mean value	95% CI	SD	Missing data
HbA1c	<6.5%	5.9	5.54–6.30	1.82	0
Conjugated bilirubin	0–5 $\mu\text{mol/L}$	8.0	4.53–11.49	14.80	19
NRS	$\leq 3$	3.1	2.50–3.67	2.80	0
BMI	18–24.99 $\text{kg/m}^2$	24.3	23.34–25.29	4.67	0
Stool elastase	>200 $\mu\text{g/g}$	220.0	182.57–257.52	179.95	0
ALAT	0.18–0.60 $\mu\text{katal/L}$	0.7	0.52–0.97	1.08	1
gGT	0–0.65 $\mu\text{katal/L}$	3.9	2.38–5.47	7.39	1
INR	1.0–1.2	1.1	1.06–1.18	0.28	0
Quick	70%–130%	92.9	87.93–97.78	23.65	0
Albumin	34–50 $\text{g/L}$	37.2	30.62–37.73	17.07	0
CRP	<5.0 $\text{mg/L}$	24.6	15.99–33.25	41.43	0
Platelets	140–440 $\text{Gpt/L}$	269.8	245.29–294.25	117.6	0
Urea	2.5–6.4 $\text{mmol/L}$	5.8	4.71–6.48	4.75	0
MCV	80–95 $\text{fl}$	91.4	89.69–93.01	7.97	0
Triglycerides	0–1.9 $\text{mmol/L}$	2.1	1.57–2.65	2.56	3
Total bilirubin	0–17 $\mu\text{mol/L}$	15.7	9.67–21.74	28.96	0
CS	<1	2.6	2.31–2.86	1.24	9

ALAT, alanine transaminase; CRP, C-reactive protein; CS, Cambridge Score; gGT, gamma-glutamyl transaminase; INR, international normalized ratio; MCV, mean corpuscular volume; NRS, numeric rating scale for pain: 0 = no pain, 10 = worst imaginable pain.

correlated against primary endpoints using linear correlation, but score values were then grouped into 3 categories (A, B, C) indicating increasing risk for readmission. The final score was internally validated by using ordinary nonparametric bootstrapping for linear Pearson correlation with 1000 repeats. As for the external validation cohort, both sum of the individual scores (5 to 15) as well as grouped categories A, B, and C were correlated to the primary endpoints. Cohort comparison was conducted pairwise using unpaired *t* test for comparison of means and  $\chi^2$  test for comparison of distribution. Hospital admission rates and days spent in hospital according to chronic pancreatitis prognosis score (COPPS) category were compared using Kruskal-Wallis test and Dunn's multiple comparison test. The model was not adjusted during the validation process. Data and statistics were handled using R 2.1.0 (<http://cran.r-project.org/src/base/R-2/R-2.1.0.tar.gz>) and R-studio 1.0.153 (<https://github.com/rstudio/rstudio/tarball/v1.0.153>). Before final submission for publication, all authors declared to have proofread the manuscript and approved draft submission.

## Results

### Baseline Parameters Development Cohort

Between January 2011 and January 2013, 91 patients with unequivocal evidence of chronic pancreatitis were prospectively included. Four of these cases were recruited from the outpatient clinic, all others were hospitalized at the time of inclusion. The median age was 55 (range, 25–88 years), 20 cases (22.0%) were women and 71 cases (78%) were men. Suspected etiology of pancreatitis was alcoholic (67.0%), obstructive (2.2%), hereditary (3.3%), and autoimmune (1.1%); the remaining cases were classified as idiopathic (26.4%). Exocrine pancreatic insufficiency, determined by low fecal elastase activity, was present in 62.9%, and 41.0% were diabetics (1.3% type 1, 17.5% type 2, 16.4% type 3.c, 5.8% unknown). Relevant comorbidities included fatty liver disease and cirrhosis, gastroesophageal reflux, hyperlipidemia, and hypertension. The modified Cambridge Score could be calculated for 82 (90.1%) cases using endoscopic ultrasound, ERCP, or computed tomography imaging and reached an average value of 2.6 (95% confidence interval [CI], 2.31–2.86; SD 1.24). Five (5.5%) were categorized Cambridge 0, 9 (9.9%) reached Cambridge I, 29 (31.9%) reached Cambridge II, 11 (12.1%) reached Cambridge III, and 28 (30.8%) were classified as

Cambridge IV. The average length of the initial hospital stay at the time of inclusion was 11.6 days (95% CI, 7.59–15.64; SD 19.336). In 83% of the cases, chronic pancreatitis was the reason for admission. Demographics and all other baseline parameters used for score development are displayed in [Tables 1 and 3](#).

### Primary and Secondary End points

During the 1-year follow-up period, subjects were admitted 1.9 times to the hospital on average (95% CI, 1.39–2.44), making up for a total of 257 admissions within 12 months' time, 137 of which could be directly linked to chronic pancreatitis. The average time spent in hospital was 15.24 days per patient within 12 months, adding to 1856 days total, of which 1050 days were directly pancreatitis related. During the follow-up period, one 87-year-old patient with newly suspected pancreatic malignancy died of pulmonary embolism (1.1% overall mortality). During the follow-up period, 20 patients (22.0%) underwent pancreatic surgery for chronic pancreatitis and 39 patients (42.9%) had at least 1 therapeutic endoscopic procedure with a total of 17 common bile duct and 29 pancreatic duct stent insertions. An additional 66 therapeutic ERCPs were performed without stenting (eg, for stent removal).

### Correlation Analysis and Score Development

In a first step, all evaluated baseline parameters were correlated to the primary endpoints. Of those initially recorded, 4 showed significant ( $P < .05$ ) correlation with either the number of hospitalizations or combined length of hospital stays (glycated hemoglobin A1c [HbA1c], BMI, C-reactive protein, platelets). These parameters were considered for the development of a scoring system. Details of the individual statistics are found in [Supplementary Table 1](#). Additionally, the numeric rating scale for worst pain within the past 7 days ranging from 0 to 10 was included despite the lack of significant correlation, as it is the factor most significantly linked to quality of life in these patients. Using these 5 parameters, we developed a score by adopting a grading system similar to the Child-Pugh-Turcotte score for liver cirrhosis,<sup>14</sup> as described previously. The final score can be found in [Table 2](#). As for HbA1c and BMI, a negative correlation was seen; lower values

**Table 2.** Chronic Pancreatitis Prognosis Score (COPPS)

	1 point	2 points	3 points
NRS (1–10), most intense day within the past 7 d	0–2	3–6	7–10
HbA1c, %	>6.0	5.5–6.0	<5.5
CRP, mg/L	<3.1	3.1–20	>20
BMI, kg/m <sup>2</sup>	>25	18–25	<18
Thrombocytes, Gpt/L	150–400	100–150	<100, >400

COPPS A = 5–6 points

COPPS B = 7–9 points

COPPS C = 10–15 points

CRP, C-reactive protein; NRS, numeric rating scale for pain: 0 = no pain, 10 = worst imaginable pain.



**Table 3.** Demographic and Clinical Characteristics of Test and Validation Cohort

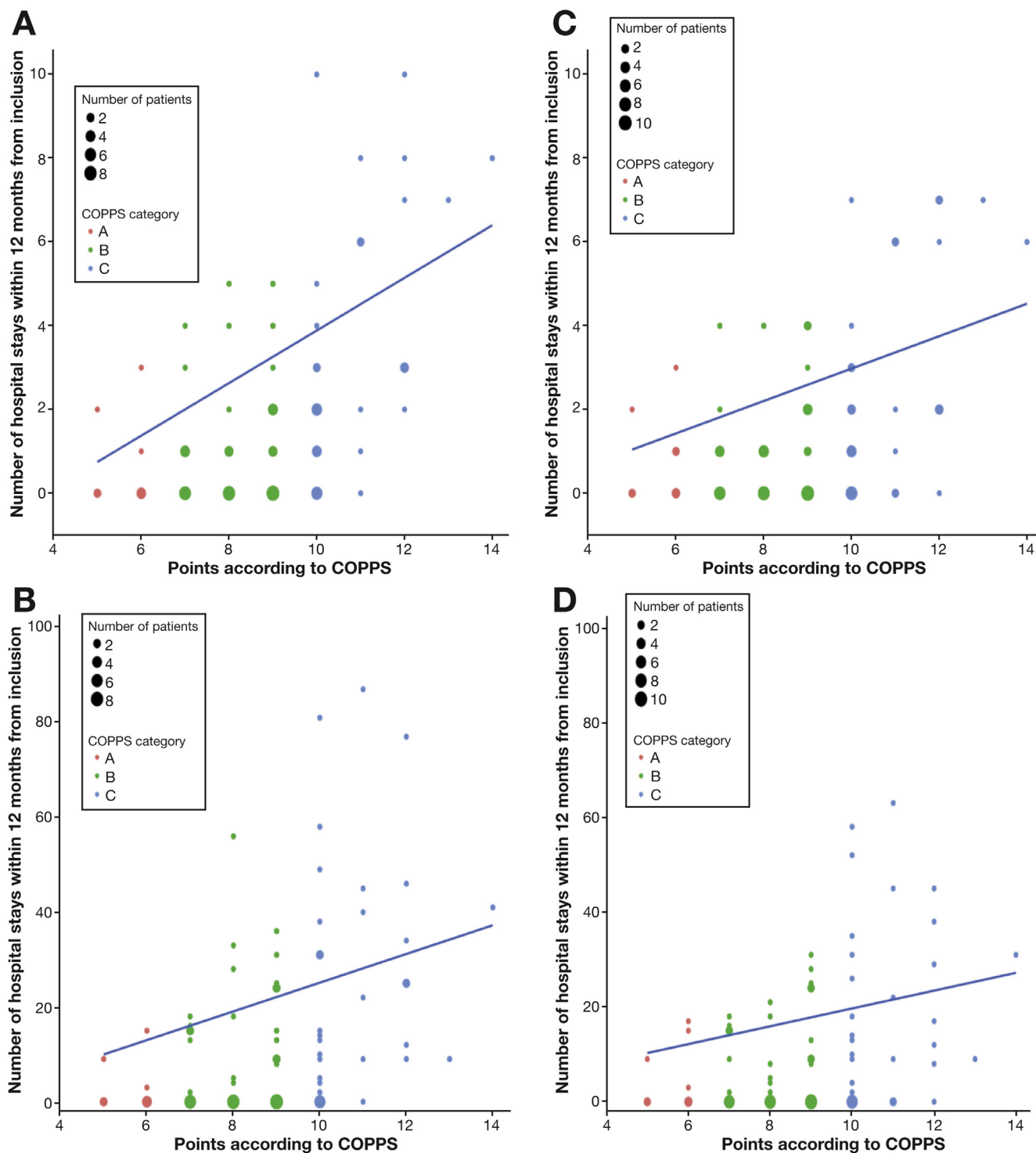
	Development	Validation	Comparison
n	91	129	—
Age, median (range)	55 (25–88)	56 (19–85)	$P = .89$
Female sex (%)	20 (22.0)	31 (24.0)	$P = .75$
Etiology (%)			$P = .74$
Alcoholic	61 (67.0)	78 (60.5)	
Obstructive	2 (2.2)	11 (8.5)	
Hereditary	3 (3.63)	4 (3.1)	
Autoimmune	1 (1.1)	1 (0.8)	
Idiopathic	24 (26.4)	35 (27.1)	
Distribution of score	A 9 B 47 C 35	A 7 B 71 C 51	$P = .50$
Mean no. hospital stays within 12 mo from inclusion (95% CI): all admissions	1.9 (1.39–2.44)	1.5 (1.18–1.90)	$P = .23$
Mean no. hospital stays within 12 mo from inclusion (95% CI): pancreatic admissions	1.5 (1.07–1.94)	1.0 (0.71–1.27)	$P = .05$
Mean no. of days spent in hospital within 12 mo from inclusion (95% CI): all admissions	15.24 (10.76–19.71)	10.9 (7.54–14.30)	$P = .12$
Mean no. of days spent in hospital within 12 mo from inclusion (95% CI): pancreatic admissions	11.5 (7.93–15.15)	8.0 (4.92–11.06)	$P = .14$
COPPS parameters			
NRS (95% CI)	3.1 (2.50–3.67)	4.6 (4.01–5.13)	$P < .01$
HbA1c (95% CI)	5.9 (5.54–6.30)	6.4 (6.09–6.64)	$P = .06$
BMI (95% CI)	24.3 (23.34–25.29)	23.4 (22.70–24.07)	$P = .12$
CRP (95% CI)	24.6 (15.99–33.25)	19.5 (13.56–25.47)	$P = .34$
Platelets (95% CI)	269.8 (245.29–294.25)	315.6 (284.4–346.7)	$P = .03$

predict more severe disease. There was no direct link between low HbA1c and hypoglycemia during the hospital stays of the respective patients ( $P = .47$ ). Although for platelet count the incline of the correlation curve was positive, a large diversion of the distribution was seen in patients with higher hospitalization rates, pointing toward a dichotomous relation. Thus, very high and very low platelet counts were associated with severe disease. The scoring system was calculated for all 91 study subjects (100%) and reached 8.9 points on average (95% CI, 8.50–9.28; SD 1.88) with a minimum of 5 and maximum of 14 points. Nine patients (9.9%) were COPPS category A, 47 (51.6%) were COPPS category B, and the remaining 35 (38.5%) were COPPS category C. The newly developed score values were positively correlated to the total number of hospitalizations (Pearson 0.48; Kendal-Tau 0.36) and to the combined number of days spent in hospital for any reason (Pearson 0.34; Kendal-Tau 0.31) (Figure 2A and B), as well as hospitalizations (Pearson 0.40; Kendal-Tau 0.25) and duration of stays (Pearson 0.25; Kendal-Tau 0.22) that were directly linked to pancreatitis on a significance level of  $<.05$  (Figure 2C and D). Conversely, when grouping the patients by the respective COPPS category (A, B, C), the hospital readmission rate as well as days spent in hospital for either all admissions or pancreas-related admissions were significantly higher in category C when compared with A or B (Figure 3). Linear correlation of COPPS category to primary outcome showed significance on level of  $P = .01$  for readmission (all admissions: Pearson 0.39, Kendal-Tau 0.35; pancreatic admissions: Pearson 0.30, Kendal-Tau 0.24) and

for number of hospital days, respectively (all admissions: Pearson 0.33, Kendal-Tau 0.32; pancreatic admissions: Pearson 0.25, Kendal-Tau 0.23). Of all secondary outcomes analyzed, COPPS showed significant association with the number of therapeutic endoscopies during follow-up (Pearson 0.35; Kendal-Tau 0.26;  $P < .01$ ). There was no significant association with the Cambridge classification grade, number of pancreatic surgical procedures, anxiety, decreased quality of life, continued opioid use, continuation of alcohol consumption, or smoking (Supplementary Table 2). Patients whose initial hospital stay was longer also had higher COPPS scores ( $P < .05$ ).

### Validation

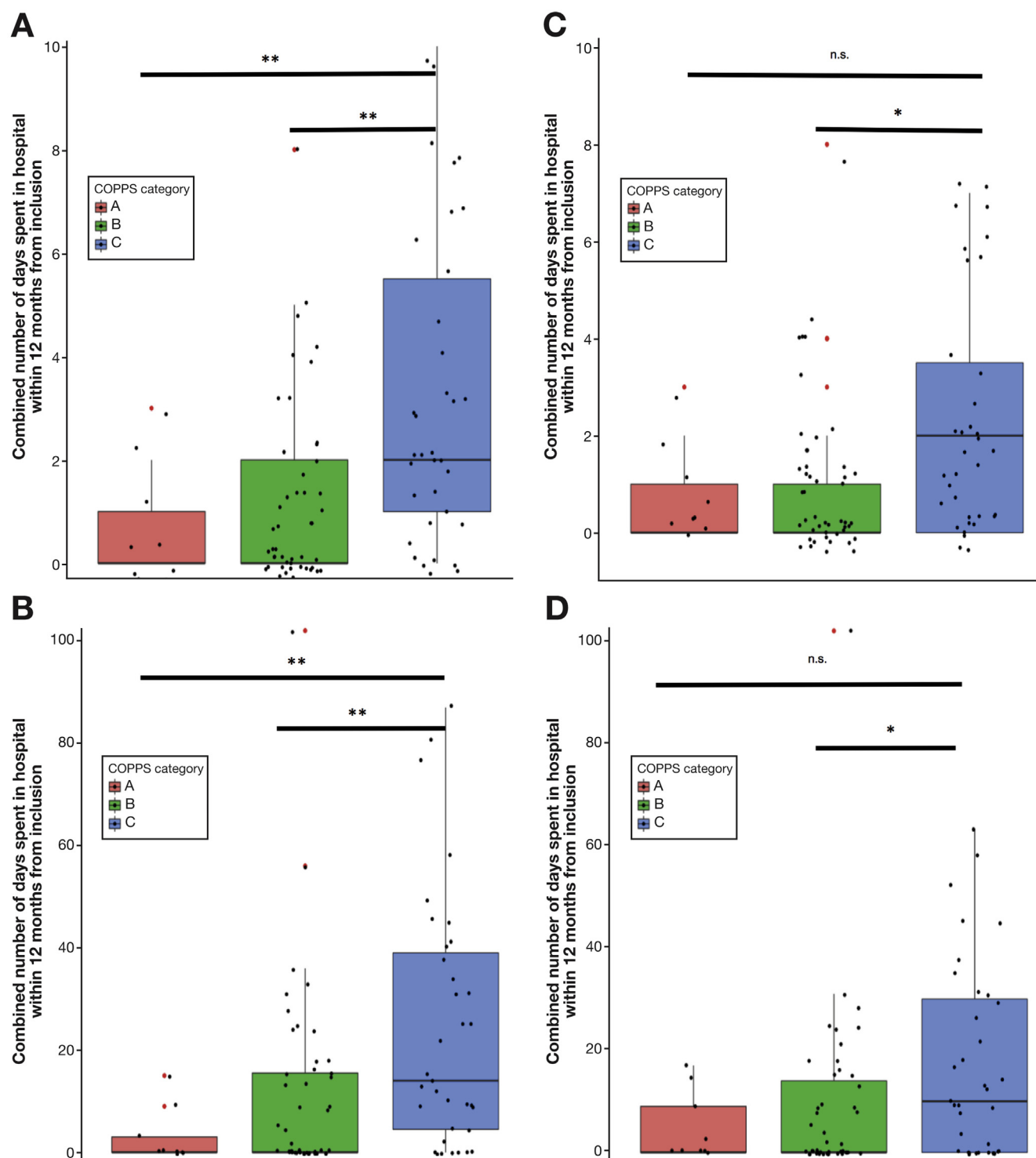
Significant bias and overoptimistic prognosis during score development was excluded by nonparametric bootstrapping, with  $R = 1000$  for Pearson correlation coefficient of COPPS score of both number of hospital stays as well as days spent in hospital (Supplementary Figure 1). To validate the newly developed scoring system, it was used on an independent cohort of 129 patients with confirmed chronic pancreatitis, who were identified from 2 prospective patient databases at 2 tertiary referral centers for pancreatic disease. Laboratory values as well as pain scoring were extracted from the electronic patient record of the respective index stay and the combined length of hospital stays, and number of hospitalizations in the consecutive year were recorded analogously to the development cohort. The characteristics of the validation cohort



**Figure 2.** Linear correlation between number of hospital stays in patients from the development cohort with chronic pancreatitis within 1 year from inclusion and points according to COPPS. All admissions (A): Pearson 0.48; Kendal-Tau 0.36;  $P < .01$ . Pancreatic admissions (C): Pearson 0.40; Kendal-Tau 0.25;  $P < .01$ . Linear correlation between combined number of days spent in hospital in patients from the development cohort with chronic pancreatitis within 1 year from inclusion and points according to COPPS. All admissions (B): Pearson 0.34; Kendal-Tau 0.31;  $P < .01$ . Pancreatic admissions (D): Pearson 0.25; Kendal-Tau 0.22;  $P < .01$ .

did not differ significantly from the development cohort except for platelet count, pain and number of hospital admissions directly related to the pancreas (Table 3). The COPPS distribution was similar to the development cohort (Table 3) and was significantly positively correlated to the

number and length of hospital stays in the year after their inclusion time point ( $P < .05$ ) with similar correlation coefficients in this independent cohort, thus validating the value of COPPS for grading and predicting the severity of chronic pancreatitis (Figure 4).

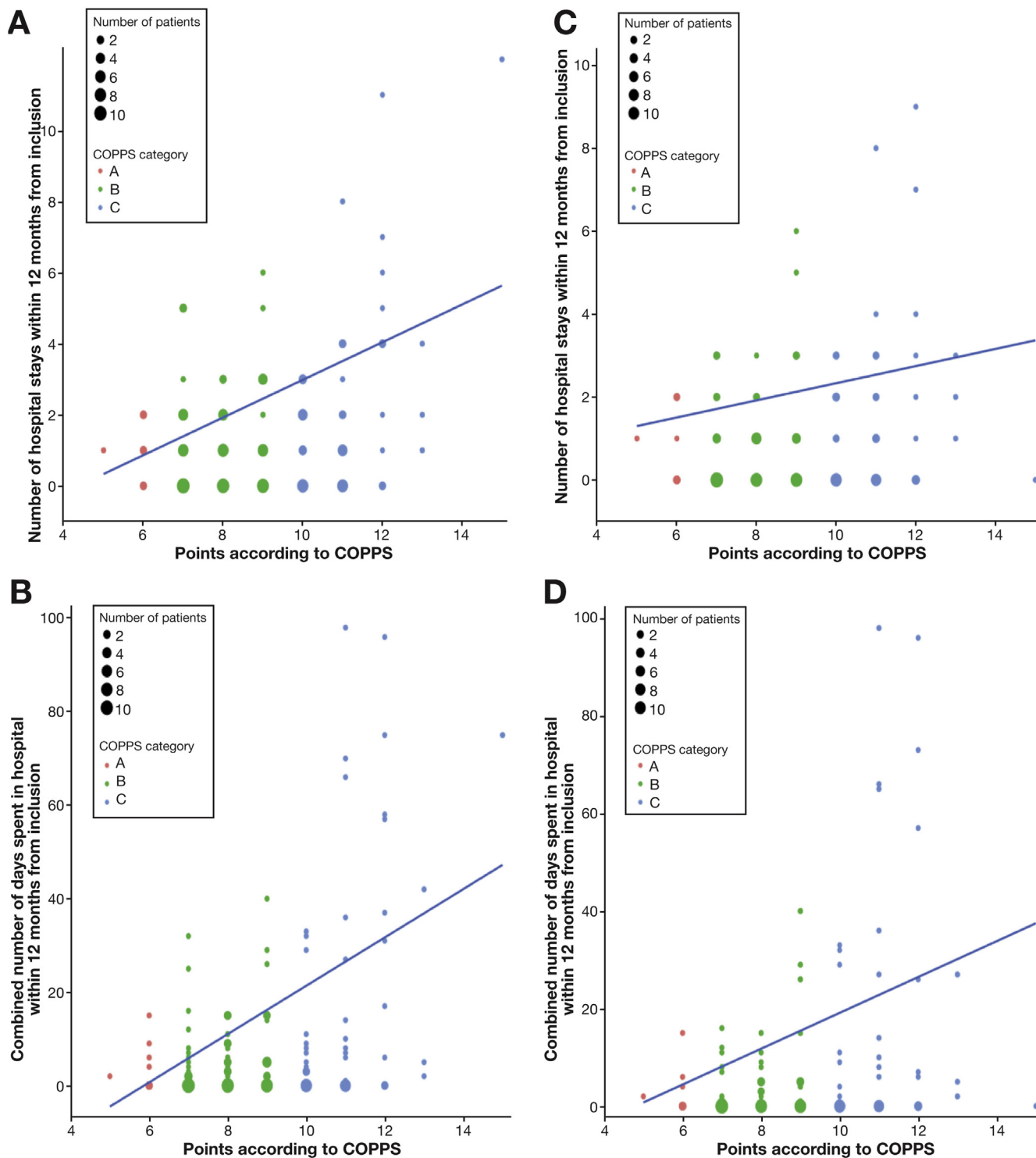


**Figure 3.** Patients from the development cohort grouped by the respective COPPS category plotted against number of hospital stays within 1 year from inclusion. COPPS category C was associated with significantly higher rate of all (A) and pancreatic (C) readmissions. Patients from the development cohort grouped by the respective COPPS category plotted against combined number of days spent in hospital within 1 year from inclusion. COPPS category C was associated with significantly higher number of days spent in hospital for all (B) and pancreatic admissions (C). Dot plot with boxes and whiskers. Individual dots indicate distribution of samples, red dot indicate outliers. \* $P < .05$ , \*\* $P < .01$ .

## Discussion

The worldwide incidence of chronic pancreatitis is reported to be between 1.6 and 23 per 100,000, with an

increasing prevalence.<sup>21</sup> Although most patients with chronic pancreatitis are treated as outpatients, in 2008 there were 10,267 (*International Classification of Diseases*,



**Figure 4.** Linear correlation between number of hospital stays in patients from the validation cohort with chronic pancreatitis within 1 year from index date and points according to COPPS. All admissions (A): Pearson 0.36; Kendal-Tau 0.16;  $P < .01$ . Pancreatic admissions (C): Pearson 0.24; Kendal-Tau 0.13;  $P < .01$ . Linear correlation between combined number of days spent in hospital in patients from the validation cohort with chronic pancreatitis within 1 year from inclusion and points according to COPPS. All admissions (B): Pearson 0.44; Kendal-Tau 0.19;  $P < .01$ . Pancreatic admissions (D): Pearson 0.32; Kendal-Tau 0.15;  $P < .05$ .

10th Revision: K86) hospital admissions for chronic pancreatitis in Germany alone (Federal Statistics Office). This does not include those patients who were coded as

having acute pancreatitis, including those due to an acute episode of chronic pancreatitis (50,673 cases). Evaluating records from the United States, United Kingdom, the



Netherlands, and Finland confirmed an increasing number of annual hospital admissions amounting to a 30% increase within 6 years.<sup>22</sup> This substantiates the high socioeconomic significance of the disease. Mortality from chronic pancreatitis is reported to be 12.8 % to 19.8 % over a mean observation period of 6.3 to 9.8 years.<sup>23–25</sup> Total mortality in the same studies was reported to be 28.8 % to 35 %. Continued alcohol consumption results in a significantly reduced survival rate.<sup>26</sup> Thirty-three percent of patients suffering from chronic pancreatitis are no longer able to pursue their profession.<sup>27</sup> Keeping this in mind, we aimed to establish an objective, dynamic scoring system with the potential to respond to disease-specific treatment and that predicts the natural course of the disease.

### Development of the COPPS

We developed a clinical scoring system to assess the severity and prognosis of patients with chronic pancreatitis. The number of hospital readmissions and total time in hospital within 1 year from inclusion were chosen as primary endpoints and surrogates for disease activity as well as an indirect measure of health care utilization. After screening a total of 14 routine laboratory parameters, BMI, and pain measured as highest score on the numeric rating scale within the past 7 days, we selected the 4 parameters that correlated best with primary endpoints and used them in combination with the numeric rating scale for pain to compose the COPPS 3-level activity scoring system. By including only routine laboratory parameters and pain, COPPS can be used by general physicians in the outpatient setting and hospitalists alike to reliably predict the risk of hospital (re)admission as a measure of disease severity. Margins of the individual laboratory parameters were established by deliberately using simple statistical methods and clinical judgment rather than complicated algorithms. This ensures that COPPS can be easily calculated on the one hand and achieves well-distinguishable ranges for the individual parameters. On the other hand, it may allow physicians to prioritize their treatment strategy by identifying potential factors that most significantly contribute to a high score and to assess the outcome of their treatment choices in the short to medium term. It could therefore meet critical criteria for new grading systems recently demanded in an international draft consensus proposal for a new mechanistic definition of chronic pancreatitis.<sup>28</sup> The question of whether COPPS can help to guide treatment, needs to be tested prospectively. COPPS is in many ways similar to the long-established Child-Pugh-Turcotte score that has proven its value in grading the severity of liver cirrhosis and short- to medium-term mortality,<sup>14,15</sup> with 2 distinct differences. Different outcome criteria were used and parameters contributing to the score were identified by prospective testing; however, the predictive strength of COPPS with regard to the primary endpoint chosen is equal, suggesting that it could be as helpful in clinical decision making as the Child-Pugh-Turcotte score.<sup>29–31</sup>

### Comparison With Previous Scoring Systems

Previously suggested classifications and staging systems for chronic pancreatitis lack these qualities. All classifications for chronic pancreatitis have been developed on the basis of single-center experience or expert consensus, not prospective studies. The first system that included a grading was published by Sarner and Cotton<sup>6</sup> in 1984, known as the Cambridge classification, and is still used today in its revised version.<sup>2,20</sup> It is solely based on modes of ductal and parenchymal imaging, but was later found to be correlated with pancreatic exocrine function,<sup>32,33</sup> quality of life, and pain by some,<sup>34</sup> but imaging results were not well correlated to pain patterns.<sup>35</sup> Ammann and colleagues<sup>9,36</sup> introduced the concept of stage-wise progression in alcoholic pancreatitis with more advanced disease being defined by definite morphological changes and the presence of exocrine with or without endocrine insufficiency. Despite this disease model fitting the clinical experience of many experts, it is not suited to stage chronic pancreatitis on a day-to-day basis, as it does not take short-term outcomes and impact of treatment into account. Three more recent staging systems originating from Kerala, Manchester, and Heidelberg incorporate the use of imaging as a basis of diagnosing chronic pancreatitis and grade disease stage depending on the presence of pancreatic complications, functional impairment (exocrine or endocrine insufficiency), and pain into 3 groups (mild/moderate, severe).<sup>10–12</sup> This kind of classification again seems to be accurately fitted to describe the natural history of disease as seen by a retrospective analysis of the Manchester cohort.<sup>11</sup> A retrospective analysis of patients who underwent surgery included in the study by Büchler et al<sup>12</sup> showed that pancreatic complications and not pain was the most frequent indication for an operation, but failed to define a cutoff for when surgery was indicated to prevent further deterioration. This is a question we will address by using the COPPS score in a prospective multicenter setting currently recruiting. The very complex M-ANNHEIM system includes a scoring system based on symptoms and clinical interventions, but was not correlated against any valid outcome criteria when first developed.<sup>13</sup> A study by He et al<sup>37</sup> in 89 patients with chronic pancreatitis showed that patients with early M-ANNHEIM stage profited better from endoscopic therapy as measured by improvement on the Izbicki pain score, thus demonstrating some prognostic value of the grading system. A recent study from Denmark identified pain and low serum albumin to be predictive for hospital admission in a prospective cohort of 170 outpatients,<sup>19</sup> some of whom were included in the validation cohort of this study. This study by Olesen et al<sup>19</sup> underscores the predictive value of opioid use as surrogate for impairment by pain and nutritional state and how those contribute to frequency of hospitalization. The fact that in our study low BMI, but not low albumin, was a risk factor for frequent hospital stays could be due to cohort differences. In our study, patients were younger, and more likely to be men, and exocrine pancreatic insufficiency was less frequent

with an average BMI of 24.1, pointing toward a better nutritional state where albumin levels are not yet significantly affected, indicating a potentially lower rate of fibrosis.<sup>38</sup> The fact that low, but not high, HbA1c was correlated with increasing risk for hospital admission was surprising. It could indicate that in patients with chronic pancreatitis, hypoglycemia as a result of brittle diabetes rather than consequences of long-lasting hyperglycemia, such as micro- and macrovascular disease, was associated with hospital admission, although we did not find a higher rate of hypoglycemia in the patients' records with low HbA1c. Whether the course of diabetes in chronic pancreatitis is different from other forms of diabetes is still under investigation. Another possibility is that also nondiabetic patients who are underweight or having starvation hypoglycemia with bad pancreatitis flares are contributing to this finding. Interestingly COPPS did not correlate well with previously established morphological scores or the need for surgery, indicating that a composite score for clinical activity and morphology does not correlate well in patients with chronic pancreatitis. The positive correlation with need for therapeutic endoscopy is somewhat expected, as in those endoscopies obviously would lead to higher readmission rates, the primary outcome of this study.

### Strengths and Limitations

All patients included in the development cohort were prospectively recruited and none were lost to follow-up. Also, from the initially screened parameters, some data were missing, all parameters included in the final score were complete, for both development and validation. The composition of the cohort with regard to demographics and etiology was comparable to similar cohorts from the Western hemisphere. Internal validation by bootstrapping excluded significant bias during the development of the score. In a second independent set of patients that was recruited from prospective databases we could externally validate our finding by again demonstrating correlation of COPPS with the number of readmissions and combined length of hospital stays. This was despite differences in cohort composition with regard to mean numeric rating scale and platelets, but similar overall demographic and disease-specific characteristics. Taken together, this further supports the potential value of COPPS. In both the development and validation cohorts, the percentage of patients with low COPPS score (5–6, COPPS A) was low. This might be because most patients were recruited among hospitalized patients with expectedly higher disease activity at tertiary centers. In fact, a long initial hospital stay was independently associated with higher risk for readmission in our cohort. On the other hand, pancreatitis guidelines advocate for management of these patients at high-volume centers; therefore, the potential spectrum bias reflects a desirable situation. By testing COPPS in a larger set of outpatients as part of an international multicenter cohort for which

we are currently recruiting patients, this issue can be resolved.

## Conclusion

In a type 3 study regarding the TRIPOD reporting criteria, we developed a multivariate prediction model to foresee the individual short-term (12-month) prognosis of patients suffering from chronic pancreatitis by using C-reactive protein, platelet count, HbA1c, BMI, and pain.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at [www.gastrojournal.org](http://www.gastrojournal.org), and at <https://doi.org/10.1053/j.gastro.2017.08.073>.

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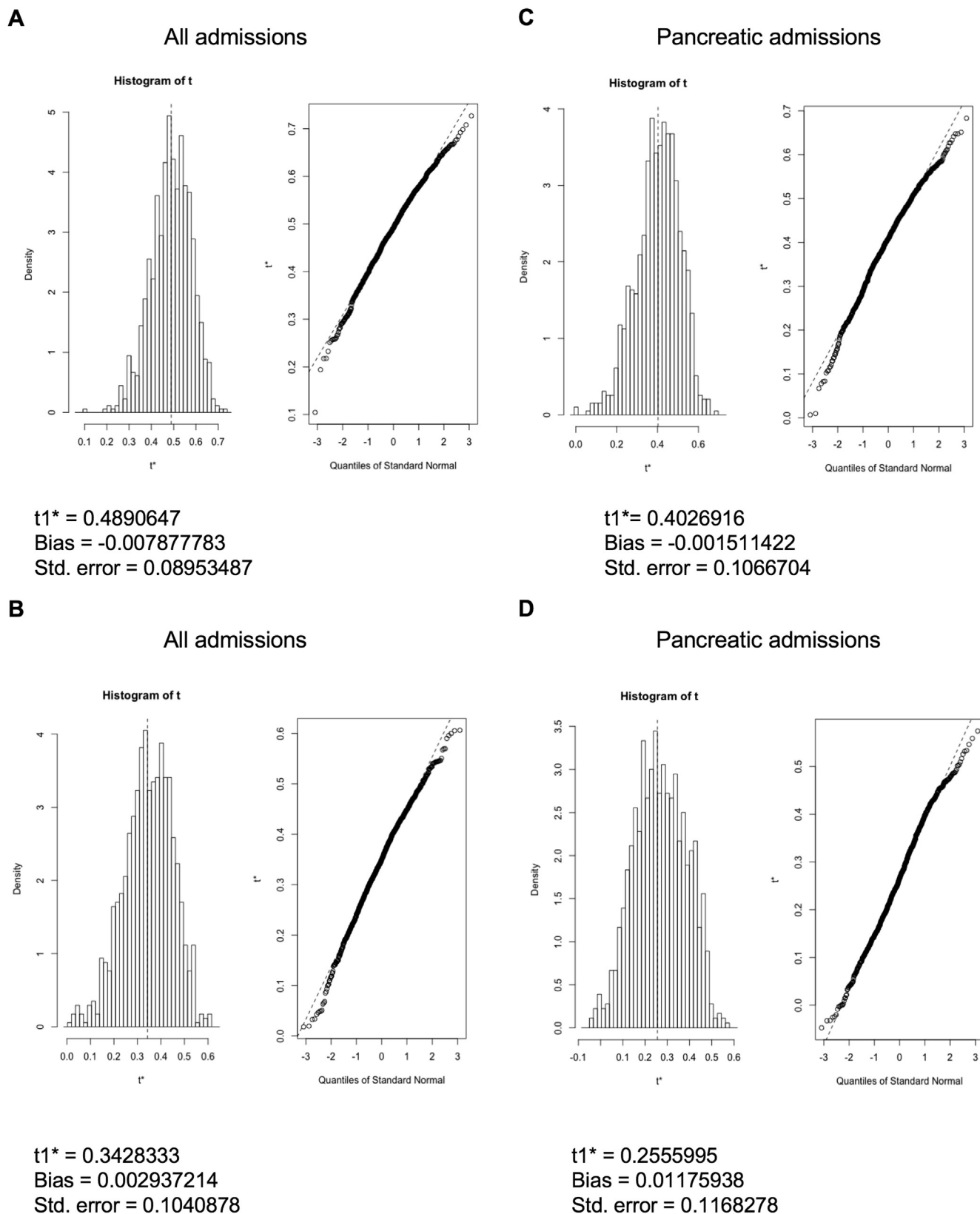
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#### Conflicts of interest

The authors disclose no conflicts.

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**Supplementary Figure 1.** Results from ordinary nonparametric bootstrap for COPPS category A, B, and C and number of hospital stays within 1 year from inclusion for internal validation of development cohort based on 1000 bootstrap replicates ( $R = 1000$ ). All admissions (A): Bias, standard error:  $t1^* -0.007877783, 0.08953487$ . Pancreatic admissions (C): Bias, standard error:  $t1^* -0.001511422, 0.1066704$ . Results from ordinary nonparametric bootstrap for COPPS category A, B, and C and number of days spent in hospital within 1 year from inclusion for internal validation of development cohort based on 1000 bootstrap replicates ( $R = 1000$ ). All admissions (B): Bias, standard error:  $t1^* 0.002937214, 0.1040878$ . Pancreatic admissions (D): Bias, standard error:  $t1^* -0.01175938, 0.1168278$ .

**Supplementary Table 1.** Results From Correlation Analysis for Individual Parameters Showing Significant Results

	HbA1c				BMI				CRP				Platelets				Smoking				Alcohol				NRS			
	HS		HD		HS		HD		HS		HD		HS		HD		HS		HD		HS		HD		HS		HD	
	<i>R</i> <sup>2</sup>	<i>P</i>	<i>R</i> <sup>2</sup>	<i>P</i>	<i>R</i> <sup>2</sup>	<i>P</i>	<i>R</i> <sup>2</sup>	<i>P</i>	<i>R</i> <sup>2</sup>	<i>P</i>	<i>R</i> <sup>2</sup>	<i>P</i>	<i>R</i> <sup>2</sup>	<i>P</i>	<i>R</i> <sup>2</sup>	<i>P</i>	<i>R</i> <sup>2</sup>	<i>P</i>	<i>R</i> <sup>2</sup>	<i>P</i>	<i>R</i> <sup>2</sup>	<i>P</i>	<i>R</i> <sup>2</sup>	<i>P</i>	<i>R</i> <sup>2</sup>	<i>P</i>	<i>R</i> <sup>2</sup>	<i>P</i>
<b>All hospital admissions</b>																												
Pearson	−0.3	<b>.01</b>	−0.2	<b>.04</b>	−0.2	<b>.03</b>	−0.2	<b>.03</b>	0.1	.19	0.1	.19	0.2	<b>.04</b>	0.2	.1	0.29	<b>.006</b>	.024	<b>.02</b>	0.31	<b>.002</b>	0.29	<b>.004</b>	0.15	.2	0.01	.9
Kendall	−0.3	<b>.001</b>	−0.2	<b>.01</b>	−0.2	<b>.003</b>	−0.2	<b>.002</b>	0.2	<b>.02</b>	0.2	<b>.03</b>	0.1	.2	0.1	.3	0.13	.11	0.11	.17	0.13	.11	0.05	.49	0.001	1.0	−0.04	.6
<b>Pancreas specific hospital admissions</b>																												
Pearson	−0.20	.06	−0.15	.15	−0.14	.18	−0.12	.27	0.15	.16	0.08	.41	0.41	<b>.02</b>	0.24	<b>.02</b>	0.16	.12	0.1	.33	0.24	<b>.02</b>	0.2	.05	0.12	.28	0.00	.97
Kendall	−0.14	.07	−0.11	.16	−0.13	.10	−0.11	.14	0.20	<b>.01</b>	0.17	<b>.03</b>	0.13	.09	0.12	.10	0.03	.65	<b>0.02</b>	.74	0.05	.49	0.09	.27	−0.02	.78	−0.03	.64

NOTE. Values in bold depict significant *P* values. CRP, C-reactive protein; HD, total number of days spent in hospital with 1 year from inclusion; HS, number of hospital stays within 1 year from inclusion; NRS, numerical rating scale.

**Supplementary Table 2.** Secondary Outcome Parameters and COPPS

	Cambridge classification		Number of therapeutic endoscopies		No. of pancreatic surgical procedures		Anxiety (categorical)		Continued opioid use (categorical)		Decreased QOL (categorical)		Continued alcohol use (categorical)		Continued tobacco use (categorical)	
	<i>R</i> <sup>2</sup>	<i>P</i>	<i>R</i> <sup>2</sup>	<i>P</i>	<i>R</i> <sup>2</sup>	<i>P</i>	$\chi^2$	<i>P</i>	$\chi^2$	<i>P</i>	$\chi^2$	<i>P</i>	$\chi^2$	<i>P</i>	$\chi^2$	<i>P</i>
<i>COPPS category</i>																
Pearson	−0.09	.91	0.35	.0005	−0.01	.89	3.39	.18	0.77	.06	1.50	.47	1.33	.55	3.47	.17
Kendall	−0.01	.96	0.26	.002	−0.005	.95	—	—	—	—	—	—	—	—	—	—

Cambridge score, endoscopies, and surgery were treated as continues variables using linear regression. All others were considered categorical and generalized linear regression was used.

QOL, quality of life measured as EQ5D<80%.