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YKL-40 as a risk stratification marker in acute pancreatitis: A prospective study

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ABSTRACT

Background/objectives: Increased systemic concentrations of YKL-40 are seen in various inflammatory conditions. We explored the relationship between the serum YKL-40 concentrations and subsequent disease severity in patients with acute pancreatitis (AP).

Methods: Consecutive adults with AP were prospectively enrolled, and classified as having mild, moderate or severe disease. On admission and 48 h later, C-reactive protein (CRP), YKL-40, interleukin-6 and 8 (IL-6, IL-8), and tumor necrosis factor alpha (TNF-α) concentrations were measured. Patients were also classified as those with low (<50 ng/mL, in the range seen in 30 age and sex-matched non-AP subjects), high (≥190 ng/mL, seen in most of the other inflammatory conditions), and intermediate YKL-40 (50–189 ng/mL).

Results: Incidence of mild, moderate and severe AP among the 150 enrolled patients was 80 (53.3 %), 59 (39.3 %), and 11 (7.4 %), respectively. Both on admission and 48 h later, high YKL-40 (vs. intermediate or low) was strongly associated with higher odds of a more severe AP, independently of the concurrent IL-8 and TNF-α concentrations (OR around 3.5–4.0, or higher). On admission, the association was independent also of the concurrent CRP, whereas the association between the later concentrations and the outcome was conditional on CRP – uncertain at low, strong at high CRP. The high YKL-40 – outcome association at both time-points was conditional on concurrent IL-6: uncertain if IL-6 was low, strong if IL-6 was high.

Conclusions: Serum YKL-40 is a plausible candidate for further evaluation as an early biochemical indicator of subsequent AP severity, particularly if considered jointly with CRP and/or IL-6.

1. Introduction

Acute pancreatitis (AP) is a complex inflammatory disease with often unpredictable clinical course and outcomes. In Europe, annual incidence is estimated at 4.6–100 per 100000 population, and rising [1–3]. AP is defined by clinical, biochemical and radiological criteria summarized in the revised Atlanta classification 2012 [4]. The most common etiologies are related to the biliary system and alcohol consumption [5,6], whereas 15 % of the cases are considered idiopathic [7,8]. Clinically, AP is marked by systemic inflammation characterized by leukocyte recruitment and excessive cytokine production [interleukin 1β (IL-1β), IL-6, IL-8, tumor necrosis factor alpha (TNF-α)] [4,9–12]. The severity of the disease is defined based on the development of local complications (e.g., acute peripancreatic fluid collection/necrotic collection within the first 4 weeks and pseudocyst/walled-off necrosis after 4 weeks), and function of the vital organs, and is categorized as: (i) mild

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disease - absence of local/systemic complications and organ failure; (ii) moderately severe disease - local or systemic complications and/or transient (up to 48 h) organ failure (e.g. cardiovascular system, lungs and/or kidneys); (iii) severe disease (in up to 20 % of the cases) - persistent (>48 h) failure of one or more organ systems, alone or (more commonly) in combination with more extensive local changes [4]. Although majority of the cases have a mild course, AP may have high morbidity and case fatality (up to 30–50 %, or higher), particularly in the presence of concomitant infections [13]. One of the greatest challenges in AP management is the fact that the final severity classification is done *post-hoc*. Regardless of the presence of organ failure on admission, the disease can rapidly evolve over a few subsequent days. Hence, regular patient assessment is mandatory, usually 24 and 48 h, and 7 days after admission. Timely recognition of the imminent disease severity is essential for adequate patient management resulting in favorable outcomes [14]. For this purpose, several clinical and radiological scoring systems have been developed, although with limited individual or overall predictive value. Among the former, the Ranson score [15], the Acute Physiology And Chronic Health Evaluation II (APACHE II) score [16], and the Bedside Index for Severity in Acute Pancreatitis (BISAP) system are most frequently used [17]. Radiological scoring systems are mostly based on contrast-enhanced computed tomography (CECT), followed by magnetic resonance imaging (MRI), endoscopic ultrasound and contrast-enhanced ultrasound, methods that are not routinely used [18,19]. A number of biochemical indicators have been suggested as predictive of a severe disease, particularly C-reactive protein (CRP) concentrations >150 mg/L measured around 48 h since the AP onset, and even more so, serum procalcitonin (PCT) concentrations >0.95 ng/mL or IL-6 concentrations >50 pg/mL [20–23]. On the other hand, serum concentrations of some of the pro-inflammatory cytokines, like IL-8 and TNF-α, do not seem to be of use for the purpose [24]. Thus far, however, no single biochemical indicator or a combination thereof has been developed to the level of routine clinical applicability, and the search for novel potential biomarkers in AP is evolving.

Chitinase-3-like-protein 1 or YKL-40 is a highly conserved glycoprotein secreted by various cell types, previously studied in inflammation and malignant disease, but not extensively in AP [25–30]. Markedly increased serum concentrations were reported in patients with different tumors or inflammatory conditions [31–33], but only two smaller studies indicated higher serum YKL-40 concentrations in patients with severe AP vs. those with a milder disease [34,35]. We aimed to undertake a more detailed early exploration of serum concentrations of YKL-40 as a potential risk stratification aid in AP. Having in mind the likely complex and not fully understood interplay between various cytokines in AP [36], we intended to evaluate possible associations between YKL-40 concentrations determined on admission and 48 h after admission and AP severity, while accounting for concurrent concentrations of some of the cytokines suggested as predictive (CRP, IL-6) or not predictive (IL-8, TNF-α) in this setting.

2. Patients and methods

Between June 1, 2020 and June 30, 2023, 150 adult patients (age ≥18 years) with AP and 30 subjects without AP (non-AP) were included in this prospective observational study. The study complied with the principles of the Declaration of Helsinki [37], and was approved by the Ethics committees of the two participating institutions – University Hospital Center Sestre milosrdnice (clinical part; approval EP-19438/19-13, December 5, 2019), and University Hospital Center Zagreb (bioanalytical part; approval 02/21 AG, January 27, 2020). All study participants gave written informed consent for participation, and the use of medical data for research and publication purposes. Except for the donation of two extra blood samples (one in the case of the non-AP subjects) for cytokine quantification, no other procedure deflected from the standard management of the patients with AP.

2.1. Study subjects and procedures

Patients were considered to suffer an episode of AP if at least two of the following were met [4]: i) typical upper abdominal pain; ii) serum concentrations of amylase or lipase >3 time the upper limit of normal; iii) characteristic imaging appearance of the acute pancreatic inflammation (e.g., CECT, transabdominal ultrasonography or MRI). They were included in the study if they provided a written informed consent, and were free of the conditions reported to be associated with dysregulated expression of YKL-40: i) active or previously treated malignant disease (e.g. osteosarcoma, glioblastoma, melanoma, hematological malignancies, gastric, pancreatic, colorectal, breast, ovarian, uterine, lung, kidney, urinary bladder, prostate or thyroid cancer); ii) other inflammatory disease (e.g. meningoencephalitis, human immunodeficiency virus infection, asthma, chronic obstructive pulmonary disease, inflammatory bowel disease, coeliac disease, pyoderma gangrenosum, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, systemic lupus erythematosus, systemic sclerosis, vasculitis); iii) sepsis of other than the pancreatic origin; iv) treatment with immunosuppressants or immunomodulators; v) pregnancy; vi) end-stage renal disease; vii) liver cirrhosis, liver fibrosis, viral hepatitis; viii) Alzheimer's disease or multiple sclerosis.

On admission, detailed medical history was taken, followed by physical examination, standard imaging and laboratory procedures. The comprehensive clinical, laboratory and radiological monitoring of all patients was performed prospectively until the discharge from the hospital, in accordance with the good clinical practice and guidelines for the management of AP patients [4]. The clinical risk scores - Ranson and APACHE II [15,16] – were determined on admission and 48 h later. At the end of the hospitalization, the severity of AP was categorized as “mild”, “moderate” and “severe”, in line with the revised Atlanta criteria [4].

Once classification of the AP patients by the disease severity had been completed, 10 patients from each severity level were randomly selected (30 overall), and 30 patients admitted to the hospital for reasons other than AP (non-AP subjects), who provided an informed consent and met the same exclusion criteria as the AP patients, were selected so as to match the AP patients (1:1) by age (±3 years) and sex.

2.2. Laboratory evaluation

Standard clinical chemistry/biochemistry parameters (including CRP) were determined in AP patients on admission and 48 h later, and on the as-needed basis thereafter. Additionally, on admission and 48 h later, 7 mL of the peripheral blood was withdrawn (EDTA vacutainer tubes) for quantification of YKL-40, IL-6, IL-8, and TNF-α. Non-AP subjects provided a single blood sample for the purpose. Serum was standardly separated, aliquoted (triplicates per sample) and stored at −80 °C until the analysis. The cytokines were quantified using commercially available enzyme-linked immunosorbent assays (ELISA) kits – Human CHI3L1 Quantaike, Human IL-6 Quantakine, Human IL-8/CXCL9 Quantakine and Human TNF-α Quantikine (R&D Systems, Minneapolis, USA) – and the ELISA plate reader Sunrise (Tecan, Mannedorf, Switzerland), as per manufacturers' instructions. As declared by the manufacturer, method imprecision for all ELISA assays is below 5 %. Serum concentrations of YKL-40 were expressed in ng/mL, and concentrations of IL-6, IL-8, and TNF-α were expressed in pg/mL.

2.3. Data analysis

Data analysis was conceived as follows: i) AP severity is a three-level ordered categorical outcome; ii) based on a detailed review [33], we expected YKL-40 concentrations to widely vary in the AP patients, both on admission and 48 h later. We considered that the possible association between YKL-40 and the outcome would be more intuitive for interpretation if the YKL-40 concentrations were considered as a categorical (potential) predictor. Hence, AP patients with YKL-40 concentrations in the range of values measured in the non-AP subjects were to be considered as having "low YKL-40". YKL-40 concentrations ≥190 ng/mL were to be considered "high", since the values in this range have been most commonly reported as associated with the severity of other inflammatory conditions [33]. AP patients with YKL-40 concentrations in-between these values were to be considered as having "intermediate" YKL-40 concentrations. Patients were classified into YKL-40 categories separately on admission and 48 h after admission; iii) concurrent CRP, IL-6, IL-8, and TNF-α concentrations were considered as covariates. Since heavily right-skewed, they were $\log_{(e)}$-transformed and mean-centered; iv) the relationship between the 3-level independent of interest (YKL-40) and the outcome was estimated by fitting cumulative logit models, separately regarding YKL-40 on admission and 48 h after admission. First, a model without covariates was fitted, and then CRP, IL-6, IL-8, and TNF-α were, individually, included as covariates in models without and with YKL-40 – covariate interaction. The no-interaction models were used to generate "the main" adjusted estimates of the YKL-40 – outcome association, whereas the models with the interaction term were used to generate YKL-40 – outcome association at "lower" and "higher" covariate concentrations. Estimates are expressed as odds ratios (OR), for the YKL-40 "high" vs. "low" and vs. intermediate" contrasts (OR >1.0 indicates higher odds of having a more severe AP, i.e., severe vs. moderate, moderate vs. mild). From these models we also generated estimates of the covariate-outcome association at each of the three YKL-40 concentrations (ORs for a more severe disease associated with a 2.72-fold increase in the covariate values). In a secondary analysis, we intended to explore whether the YKL-40 – AP severity association observed in the main analysis held with further adjustments for age, sex, diabetes or dyslipidemia, time since symptom onset to admission, Charlson Comorbidity Index and whether the AP episode was recurrent/associated with cholelithiasis. The three YKL-40 categories (separately on admission and 48 h after admission) were mutually balanced using optimization-based weighting [38] [package *optweight* [39] in R [40], and the same procedures as in the main analysis were repeated. We used SAS for Windows 9.4 software for statistical computations (SAS Inc., Cary, NC).

3. Results

3.1. Subjects

The 30 non-AP subjects (15 men, age mean ± SD 64 ± 14 years, range 35–87 years) had YKL-40, IL-6, IL-8, and TNF-α concentrations <50 ng/mL, <15 pg/mL, <20 pg/mL and <10 pg/mL, respectively (Fig. 1A). On admission, the prevalence of the AP patients with Low YKL-40 (<50 ng/mL) was 40/150 (26.7 %), the prevalence of those with Intermediate YKL-40 (50–189 ng/mL) was 46/150 (30.7 %), and the prevalence of patients with High YKL-40 (≥190 ng/mL) was 66/150 (42.6 %) (Fig. 1B). At 48 h after admission, the patients with Intermediate YKL-40 prevailed (70/150, 46.7 %) (Fig. 1B). Their CRP concentrations shifted to the higher values from the admission to 48 h after admission (Fig. 1C). IL-6, IL-8, and TNF-α concentrations in the 150 AP patients varied from very low (non-AP range) to very high, and were fairly similar on admission and 48 h after admission (Fig. 1D–F). Bivariate correlations between YKL-40, IL-6, IL-8, TNF-α, and CRP were modest to moderate at both time points (Supplemental Information Fig. S1).

Of the 150 AP patients, 80 (53.3 %) had a mild disease, 59 (39.3 %) had a moderate disease, and 11 (7.4 %) had a severe disease.

Similar numerical trends across the patient subsets with increasing YKL-40 concentrations (Low – Intermediate - High) were observed on admission (Table 1) and 48 h after admission (Table 2): i) patients in higher YKL-40 categories tended to be older, more commonly with hypertension, diabetes or dyslipidemia, chronic heart or kidney failure, have a history of neuro-/cardiovascular incidents, higher Charlson comorbidity index, and higher lactate dehydrogenase concentrations than the patients at lower YKL-40 categories, ii) CRP and IL-6 markedly increased with higher YKL-40 category, while increases in IL-8 and TNF-α were less prominent; iii) baseline and total Ranson scores tended to be higher with increasing YKL-40 category; iv) incidence of mild AP decreased, and incidence of moderate or severe AP increased with higher YKL-40 categories (Table 1, Table 2).

3.2. Association between admission YKL-40 and AP severity

In the unadjusted analysis, odds of more severe AP were around 3.56 and around 3.96-fold higher in patients with High vs. Low or Intermediate YKL-40 concentrations, respectively (Fig. 2). Similar associations were observed with the adjustment for admission CRP (ORs around 3.09 and 3.76, respectively) (Fig. 2). The association was consistent at both "low" (40 mg/L) and "high" (160 mg/L) CRP concentrations (Fig. 2). With the adjustment for YKL-40, higher CRP did not appear associated with more severe AP, and this was consistent across the concentrations of YKL-40 (Fig. 2). With the adjustment for IL-6 concentrations, the association between high(er) YKL-40 and more severe AP was less straightforward – only the OR for High vs. Intermediate YKL-40 was clearly >1.0 (OR = 2.66, 95%CI 1.15–6.13) (Fig. 2). At "low" IL-6 (20 pg/mL), YKL-40 did not appear associated with AP severity, whereas at "high" IL-6 (100 pg/mL), the association was clear-cut (ORs around 3.74 and 3.31, respectively) (Fig. 2). Conversely, higher IL-6 did not appear associated with a more severe AP at Low YKL-40, tended to be associated at Intermediate YKL-40, and was clearly associated with a more severe AP in the patients with High YKL-40 (Fig. 2). With the adjustment for IL-8, high(er) YKL-40 was associated with a more severe AP, both at "low" IL-8 concentrations (45 pg/mL), and (more so) at "high" IL-8 concentrations (100 pg/mL) (Fig. 2). Higher IL-8 was clearly associated with a more severe AP only in the patients with High YKL-40 (Fig. 2). With the adjustment for TNF-α, high(er) YKL-40 was clearly associated with a more severe AP, consistently at "low" and "high" TNF-α concentrations (Fig. 2). TNF-α did not appear associated with AP severity (Fig. 2).

3.3. Association between YKL-40 48 h after admission and AP severity

In the unadjusted analysis, odds of more severe AP were around 6.10 and around 2.99-fold higher in the patients with High vs. Low or Intermediate YKL-40 concentrations, respectively (Fig. 3). Somewhat weaker associations were observed with adjustment for CRP (ORs around 2.50 and 2.28, respectively) (Fig. 3). At "low" CRP, YKL-40 did not appear clearly associated with AP severity (Fig. 3), but the association was clear-cut at "high" CRP (Fig. 3). Conversely, higher CRP was associated with a more severe AP only in the patients with Intermediate and High YKL-40 (Fig. 3). With the adjustment for IL-6, high(er) YKL-40 was associated with a more severe AP, but apparently not if IL-6 was "low", and strongly if IL-6

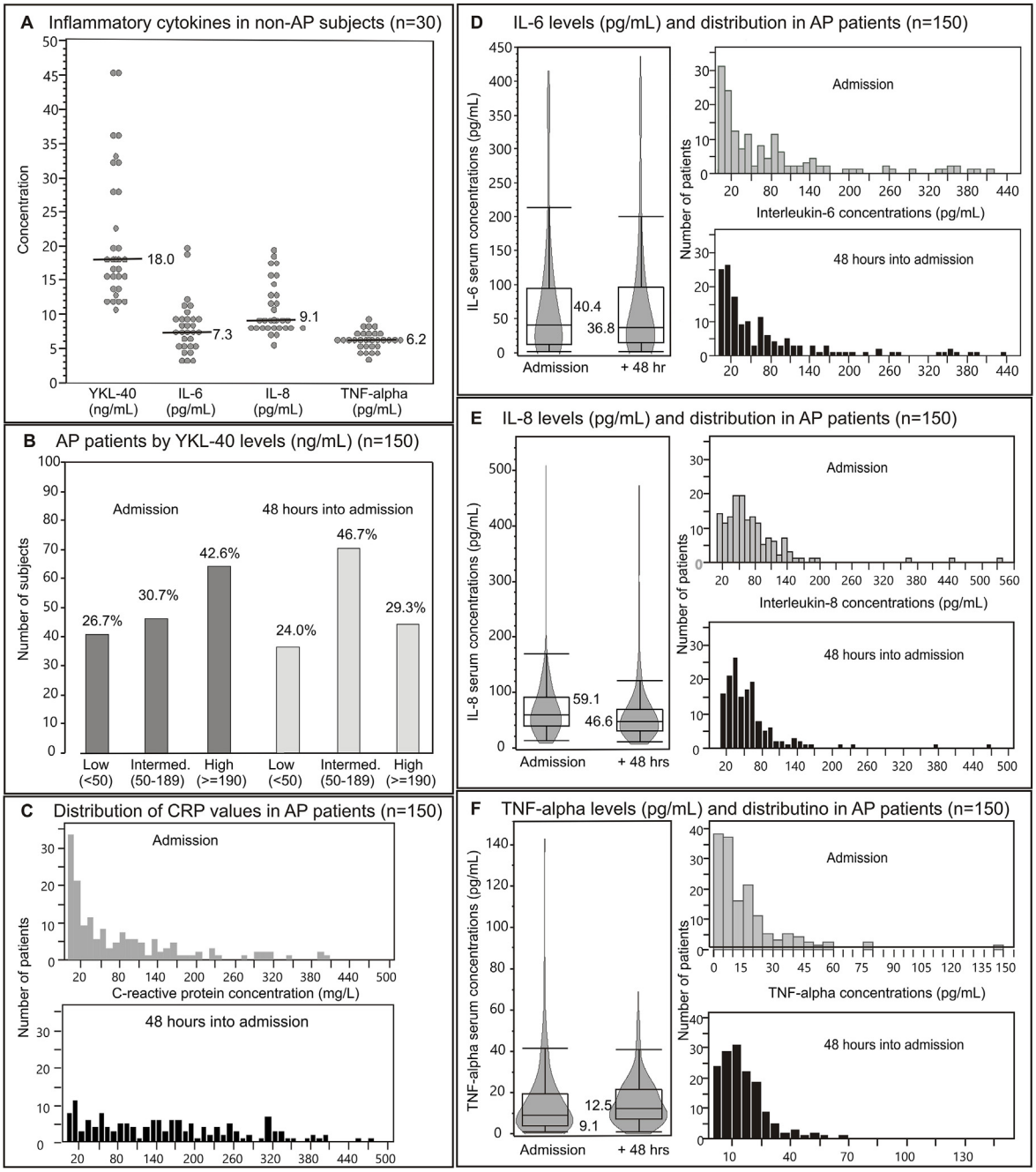

Fig. 1. Measured inflammation markers. **A**. YKL-40, interleukin (IL)-6, IL-8 and tumor necrosis factor alpha (TNF-α) concentrations measured in 30 adults without acute pancreatitis (non-AP). Subjects were matched by age and sex to randomly selected AP patients (1:1, 10 non-AP subjects to 10 AP patients from each of the three AP severity groups). Depicted are individual data and medians. **B**. Distribution of AP patients across the concentrations of YKL-40 determined on admission and 48 h after admission (up to <50 ng/mL = Low, 50–189 ng/mL = Intermediate, and ≥190 ng/mL = High). Depicted are absolute numbers (bars) and percentages. **C**. Distribution of C-reactive protein (CRP) concentrations (mg/L) measured on admission and 48 h after admission in AP patients. Depicted are absolute numbers. **D-F.** Concentrations (pg/mL) (left, box plots represent medians with numerical values, 1st and 3rd quartiles, and inner fences) and distribution of measured values (absolute numbers) (right) of IL-6 (D), IL-8 (E), and TNF-α (F) measured on admission and 48 h after admission in AP patients.

was high (Fig. 3). Conversely, higher IL-6 was associated with a more severe AP only in the patients with Intermediate or High YKL-40 (Fig. 3). With the adjustment for IL-8, high(er) YKL-40 was associated with a more severe AP, both at "low" and (more so) at "high" IL-8 concentrations (Fig. 3). Higher IL-8 was clearly associated with a more severe AP only in the patients with High YKL-40 (Fig. 3). With the adjustment for TNF-α, high(er) YKL-40 was clearly associated with a more severe AP, consistently at "low" and "high" TNF-α concentrations (Fig. 3). TNF-α did not appear associated with AP severity (Fig. 3).

3.3.1. *Secondary analysis*

When the patients with Low, Intermediate and High YKL-40 on admission and 48 h after admission were mutually balanced regarding age, sex, Charlson Comorbidity Index, presence of diabetes or dyslipidemia, time elapsed between symptom onset and admission, and whether the index AP episode was recurrent/associated with cholecystitis/cholelithiasis, the association

Table 1
Patient characteristics at baseline across the concentrations of YKL-40 (<50 ng/mL = Low; 50–189 ng/mL = Intermediate; ≥190 ng/mL = High). Data are mean ± SD, median (range) or count (%).

	YKL-40 Low	YKL-40 Intermediate	YKL-40 High
N	40	46	64
Age	53 ± 16	60 ± 16	66 ± 16
Male	16 (40.0)	18 (46.0)	36 (56.3)
Body mass index (kg/m^2)	28.8 ± 4.6	30.8 ± 4.4	27.5 ± 4.9
Comorbidities/medical history			
Hypertension	12 (32.5)	29 (63.0)	40 (62.5)
Diabetes or dyslipidemia	3 (7.5)	11 (23.9)	21 (32.8)
Chronic heart or kidney failure	3 (7.5)	2 (4.3)	10 (15.6)
Cerebro- or cardiovascular incidents	1 (2.5)	4 (8.7)	8 (12.5)
Charlson comorbidity index	1 (0–7)	2 (0–6)	3 (0.7)
0–1	25 (62.5)	19 (41.3)	16 (25.0)
2–3	12 (30.0)	17 (37.0)	21 (32.8)
≥4	3 (7.5)	10 (21.7)	27 (42.2)
Index acute pancreatitis (AP)			
Time onset to admission (days)	2 [1–9]	2 [1–15]	2 [1–23]
Within 24 h	10 (25.0)	9 (19.6)	17 (26.6)
Within 24–48 h	15 (37.5)	19 (41.3)	25 (39.1)
Time elapsed >48 h	15 (37.5)	18 (39.1)	22 (34.4)
Recurrent AP	11 (27.5)	13 (28.3)	18 (28.1)
Cholecystitis/lithiasis	5 (12.5)	6 (13.0)	11 (17.2)
Laboratory tests on admission			
Hemoglobin (g/L)	142 ± 14	139 ± 16	140 ± 20
Creatinine (μg/L)	69.5 (58.0–83.0)	73.5 (59.8–88.2)	83.0 (70.0–108)
Serum glucose (mmol/L)	6.5 ± 1.6	7.9 ± 3.8	8.1 ± 2.9
Total bilirubin (μmol/L)	23 [16–43]	25 [13–44]	28 (16–53)
Lactate dehydrogenase (U/L)	234 (179–318)	266 (194–436)	272 (193–396)
Potassium (mmol/L)	4.2 ± 0.4	4.1 ± 0.6	4.0 ± 0.9
Sodium (mmol/L)	140 ± 2.9	138 ± 12.5	136 ± 17.2
Red blood cells (x10^9/L)	4.8 ± 0.5	4.8 ± 0.6	4.6 ± 0.7
Platelets (x10^9/L)	255 (206–287)	226 (197–281)	220 (183–261)
White blood cells (x10^9/L)	11.8 ± 4.9	13.1 ± 5.0	14.5 ± 4.7
C-reactive protein (mg/L)	17.3 (7.0–73.7)	40.4 (11.9–89.8)	85.1 (16.3–161.4)
Interleukin 6 (IL-6) (pg/mL)	11.2 (0.2–167.9)	29.2 (1.5–160.6)	82.9 (2.1–410)
Interleukin 8 (IL-8) (pg/mL)	45.0 (14.1–180.4)	56.8 (12.6–134.1)	67.6 (16.2–531.2)
Tumor necrosis factor alpha (TNF-α,pg/mL)	5.0 (1.0–23.8)	7.8 (2.0–57.1)	16.2 (2.0–141.4)
Ranson score on admission			
0-2 (1 % predicted mortality)	35 (87.5)	30 (65.2)	45 (70.3)
3-4 (15 % predicted mortality)	5 (12.5)	16 (34.8)	17 (24.6)
≥5 (40 % predicted mortality)	0	0	2 (3.1)
Final outcome - AP severity			
Mild	26 (65.0)	31 (67.4)	23 (35.9)
Moderate	13 (32.5)	14 (30.4)	32 (50.0)
Severe	1 (2.5)	1 (2.2)	9 (14.1)

between high(er) YKL-40 (contrasts between High and Low, and High and Intermediate YKL-40 categories) and a more severe AP remained similar to that in the main analysis depicted in Figs. 2 and 3 (see Supplemental Information – Secondary analysis, Table S1, Table S2).

4. Discussion

The development of a clinically reliable valid biomarker is a complex and extensive work [41]. To the best of our knowledge, the present study is the largest one thus far that addressed the serum concentration of the YKL-40 in AP, but it is only an early exploration intended to evaluate whether it would be at all feasible to engage into comprehensive evaluation of the YKL-40 as a risk stratification aid in this setting. The present data suggest that high(er) YKL-40 serum concentrations, i.e., those in the range of "average and higher than average" of those reported in various active inflammatory conditions [33] (≥190 ng/mL) – as opposed to lower values [those in the range of the "non-AP" subjects, or similar to those typically reported in the healthy individuals [33]; or the "intermediate" ones] - are rather strongly associated with higher odds of a more severe AP (i.e., moderate over mild, sever over moderate over mild). The association appears to hold for the YKL-40 concentrations at hospital admission and at 48 h after admission. The secondary analysis suggests that this association might be unconditional on age, sex, comorbidities (at least those that have thus far not been associated with increased YKL-40 serum concentrations), and the time elapsed between initial symptoms onset and hospital admission (i.e., whether admitted on day 1, days 2–3 or later than that).

What we find to be of a particular interest is the relationship between the YKL-40-outcome association and the concurrent concentrations of CRP, IL-6, IL-8, and TNF-α. With respect to the CRP, the situation appears to be different on admission and at 48 h after admission. On admission, high(er) YKL-40 concentrations were associated with the worse outcome independently of the concurrent CRP concentrations, and were similar at "low" (40 mg/L) and "high" (160 mg/L) CRP concentrations. At the same time, CRP did not appear associated with the outcome at any (low, intermediate, high) concentration of YKL-40. At 48 h after admission, a time point at which CRP is considered more informative about the outcome than when taken on admission [42] – adjusting for CRP "weakened" the YKL-40-outcome association: it was uncertain at "low" CRP, but clear-cut at "high" CRP. At the same time, association between "higher" CRP and the outcome was conditional on the YKL-40 concentration: there was none at low YKL-40, and it was

Table 2
Patient characteristics 48 h after admission across the concentrations of YKL-40 (<50 ng/mL = Low; 50–189 ng/mL = Intermediate; ≥190 ng/mL = High). Data are mean ± SD, median (range) or count (%).

	YKL-40 Low	YKL-40 Intermediate	YKL-40 High
N	36	70	44
Age	53 ± 15	61 ± 18	65 ± 15
Male	16 (44.4)	31 (44.3)	23 (52.3)
Body mass index (kg/m^2)	29.5 ± 4.4	29.3 ± 5.0	27.7 ± 4.8
Comorbidities/medical history			
Hypertension	14 (38.9)	39 (55.7)	29 (65.9)
Diabetes or dyslipidemia	2 (5.6)	18 (25.7)	15 (34.1)
Chronic heart or kidney failure	2 (5.6)	5 (7.1)	8 (18.2)
Cerebro- or cardiovascular incidents	1 (2.8)	5 (7.1)	7 (15.9)
Charlson comorbidity index	1 (0–7)	2 (0–7)	3 (0–6)
0–1	20 (55.6)	28 (40.0)	12 (27.2)
2–3	13 (36.1)	21 (30.0)	16 (36.4)
≥4	3 (8.3)	21 (30.0)	16 (36.4)
Index acute pancreatitis (AP)			
Time onset to admission	2 (1–3. 1–7)	2 (2–4. 1–23)	2 (1–3. 1–7)
Within 24 h	9 (25.0)	12 (17.1)	15 (34.1)
Within 24–48 h	13 (36.1)	31 (44.3)	15 (34.1)
Time elapsed >48 h	14 (38.9)	27 (38.6)	14 (31.8)
Recurrent AP	11 (30.6)	17 (24.3)	14 (31.8)
Cholecystitis/lithiasis	4 (11.1)	11 (15.7)	7 (15.9)
Laboratory tests at 48 h			
Hemoglobin (g/L)	130 ± 15	126 ± 15	121 ± 17
Creatinine (μg/L)	63 (56–81)	61 (56–71)	71 (58–89)
Serum glucose (mmol/L)	5.0 (4.2–5.9)	5.0 (4.1–5.9)	5.4 (4.3–6.9)
Total bilirubin (μmol/L)	18 [14–27]	19 [14–26]	21 [16–29]
Lactate dehydrogenase (U/L)	195 (157–247)	193 (153–241)	281 (160–396)
Potassium (mmol/L)	4.1 ± 0.4	4.0 ± 0.4	4.1 ± 0.4
Sodium (mmol/L)	138 ± 3	139 ± 3	137 ± 4
Red blood cells (x10^9/L)	4.4 ± 0.4	4.2 ± 0.6	4.0 ± 0.6
Platelets (x10^9/L)	208 (173–265)	209 (181–249)	169 (134–208)
White blood cells (x10^9/L)	8.8 ± 4.4	10.1 ± 4.3	11.3 ± 5.3
C-reactive protein (mg/L)	42.2 (12.2–156)	155 (66.7–227)	180 (124–320)
Interleukin 6 (IL-6) (pg/mL)	15.5 (0.1–224.9)	34.2 (0.3–387)	84.4 (7.7–432)
Interleukin 8 (IL-8) (pg/mL)	41.9 (12.6–237.0)	44.9 (10.1–370.4)	60.8 (13.3–467.9)
Tumor necrosis factor alpha (TNF-α, pg/mL)	9.0 (2.0–32.1)	13.4 (1.0–68.0)	15.5 (2.0–45.8)
Ranson score at 48 h (total)			
0-2 (1 % predicted mortality)	23 (63.9)	32 (45.7)	12 (27.3)
3-4 (15 % predicted mortality)	8 (22.2)	27 (38.6)	18 (40.9)
≥5 (40 % predicted mortality)	5 (13.9)	11 (15.7)	14 (31.8)
Final outcome - AP severity			
Mild	26 (72.2)	40 (57.1)	14 (31.8)
Moderate	10 (27.8)	26 (37.1)	23 (52.3)
Severe	0	4 (5.7)	7 (15.9)

strong at intermediate and high YKL-40 concentrations. These observations imply a few points about possible CRP-YKL-40 relationship in AP: i) according to the present knowledge, both are more likely to be "just" inflammation markers than "effectors"; ii) their dynamics between admission and +48 h is somewhat different – the YKL-40 concentrations apparently tend to decrease (as indicated by the reduced proportion of "high" and increased proportion of "intermediate" values), whereas there is a clear shift of CRP to the higher values. Hence, in a way, they are "discordant". This is supported also by the very modest correlation between the two, both on admission and 48 h later (Fig. S1); iii) if both illustrate the same "latent variable" (i.e., intensity of inflammation), then after adjustment for CRP on admission, one would expect the strength of association betweenYKL-40 and the outcome to be reduced (a "part of the association" would be "taken" by CRP) – but it was not. This might imply that the dynamics of YKL-40 and CRP differs also during the time before hospital admission. It appears as if increase in YKL-40 might be an earlier event, hence on admission it is at its "peak" or already declining, whereas increase in CRP is somewhat lagged – and "peaks" at a later time. In such a sequence of events, one could speculate that the YKL-40 might, for example, be an "effector" that stimulates the CRP concentrations – a "part" of the link between YKL-40 and the outcome might "go via" the CRP concentrations at a later time (e.g., 48 h). The fact that at 48 h after admission the YKL-40 – outcome "link" was reduced upon adjustment for the CRP is actually what one sees when adjustment is made for a "mediator"; iv) while the previous consideration is highly speculative, it is rather obvious that YKL-40 taken on admission provides additional information (i.e., "on top" of that acquired by knowing the CRP concentrations) about the subsequent events (disease severity), and that its "informative value" is unconditional on CRP. It is also rather obvious that there is mutual modification of their individual associations with the outcome when taken at 48 h after admission – it appears that without knowing the value of the other, none of the two is actually adequately informative about the final disease severity. A similar situation appears to hold for the YKL-40 – IL-6 – outcome relationship, and for both on admission and later YKL-40 and IL-6 concentrations. The observed patterns of associations were practically identical at both time points: high(er) YKL-40 was associated with the outcome only at high IL-6, high(er) IL-6 was associated with the outcome only at high(er) YKL-40, that is, neither cytokine alone was adequately informative without knowing the values of the other one. Of interest, there appears to be a mechanistic link between IL-6 and YKL-40. Macrophages are considered to have an important role in evolution of the AP, both regarding the local and

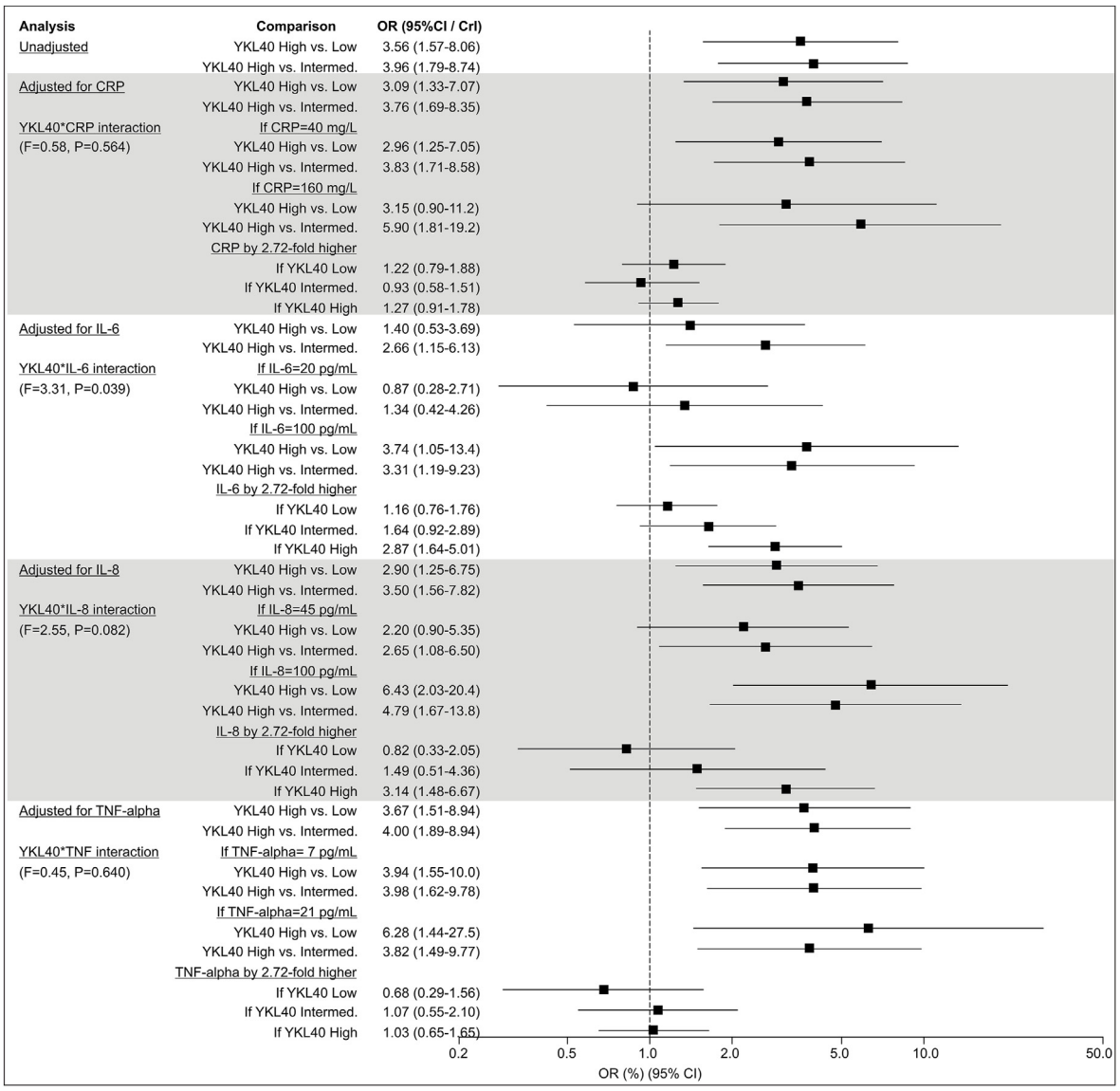

Fig. 2. Association between YKL-40 concentrations measured on admission and severity of acute pancreatitis (AP). Several cumulative logit models were fitted to probability of mild, moderate or severe AP: i) unadjusted model, with YKL-40 category as the only independent (to yield unadjusted "main effects" of YKL-40); ii) four separate models, each with adjustment for one of the inflammation markers determined on admission – C-reactive protein (CRP), interleukin-6 (IL-6), IL-8 and tumor necrosis factor alpha (TNF-α) (to yield YKL-40 adjusted "main effects"); iii) four separate models with interaction terms between YKL-40 category and each of the four inflammation markers (ln-transformed and centered continuous variables) to estimate association between YKL-40 and AP severity at different concentrations ("low" or "high") of other 4 inflammation markers, and associations between these inflammation markers and the outcome at different concentrations of YKL-40 (Low, Intermediate, High). Odds ratios (OR) > 1.0 indicate higher odds of more severe AP (moderate vs. mild, severe vs. moderate).

systemic events [43]: local macrophages (pancreas and related organs) activated by the stressful stimuli mostly differentiate into a pro-inflammatory M1 phenotype that secrete a range of cytokines (including IL-6 and TNF-α) that mediate local events and events in other organs. In the present study, IL-6 and YKL-40 showed a similar dynamics (a tendency of somewhat lower values at 48 h after the admission vs. admission), but their correlation at both time points was modest. However, in a study in healthy young volunteers (n = 6), infusion of the recombinant human IL-6 resulted in a doubling of the circulating concentrations of YKL-40 (from average 30–57 ng/mL), which returned to the starting concentrations after 48 h [44]. Nevertheless, regarding the issue of predicting the AP outcome, the association of each of these cytokines with the outcome was conditional on the concentration of the other one. Overall, it appears that a system that would combine information conveyed by CRP, YKL-40 and IL-6 (IL-6 and CRP at 48 h after admission were strongly correlated) – and possibly also combined with some clinical/imaging system - seems as a feasible option that could be a more accurate and reliable predictor of the disease severity than any of its individual elements.

Although infusion of the recombinant human TNF-α to healthy volunteers [44] did not induce changes in the circulating YKL-40 concentrations, there is compelling evidence that TNF-α also stimulates the YKL-40 production in the macrophages [45]. In the present analysis, both on-admission and later on, the YKL-40 concentrations were associated with the outcome independently of the TNF-α concentrations, and TNF-α was not associated with the outcome at any YKL-40 concentration. This is in the line with the reported lack of the association of the "early" TNF-α concentrations and the AP severity [24]. From the biological standpoint, this is

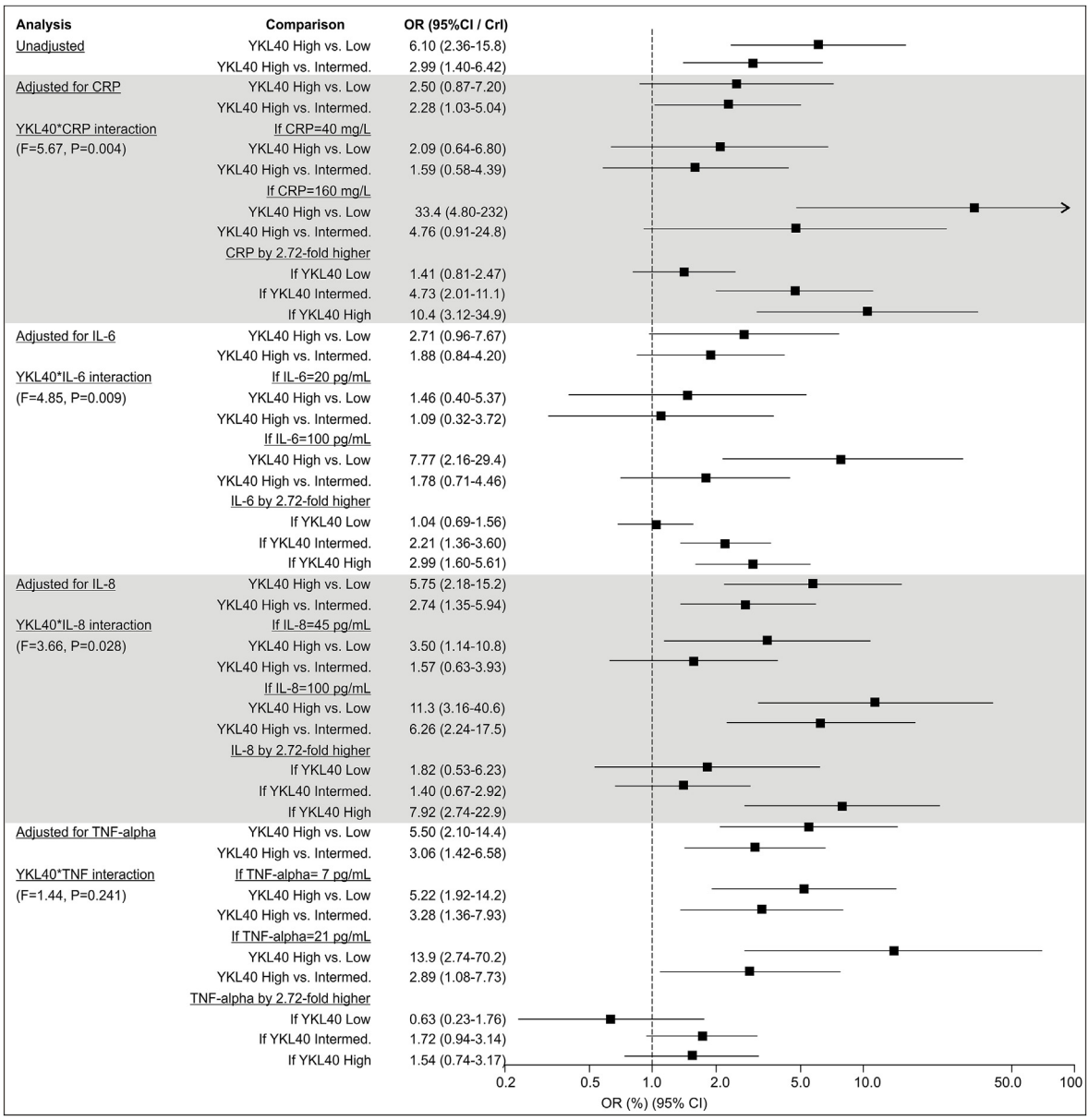

Fig. 3. Association between YKL-40 concentrations measured 48 h after admission and severity of acute pancreatitis (AP). Several cumulative logit models were fitted to probability of mild, moderate or severe AP: i) unadjusted model, with YKL-40 category as the only independent (to yield unadjusted "main effects" of YKL-40); ii) four separate models, each with adjustment for one of the inflammation markers determined 48 h into admission – C-reactive protein (CRP), interleukin-6 (IL-6), IL-8 and tumor necrosis factor alpha (TNF-α) (to yield YKL-40 adjusted "main effects"); iii) four separate models with interaction terms between YKL-40 category and each of the four inflammation markers (ln-transformed and centered continuous variables) to estimate association between YKL-40 and AP severity at different concentrations ("low" or "high") of other 4 inflammation markers, and associations between these inflammation markers and the outcome at different concentrations of YKL-40 (Low, Intermediate, High). Odds ratios (OR) > 1.0 indicate higher odds of more severe AP (moderate vs. mild, severe vs. moderate).

rather understandable [46]: i) the early phase of AP is characterized by a substantial expression of TNF-α in the pancreatic acinar cells, followed by its expression in the infiltrating macrophages; ii) TNF-α stimulates local (resident), peritoneal and circulating macrophages and other cells to produce a range of pro-inflammatory cytokines to exert local and systemic effects; iii) it also stimulates the acinar cell death by necrosis and/or apoptosis; iv) finally, it is rapidly cleared from the systemic circulation. Hence, the TNF-α "activation" appears to be considerably upstream of the process that could be "snap-shot" by the systemic cytokine concentrations as late as at the time of hospital admission, or even later.

Although commonly reported increased in patients with the AP, IL-8, which is thought to participate in local fibrosis after the acute phase [47], is typically not predictive or is only weakly predictive of the AP severity [24,47]. The present observations are in agreement with these findings: both on admission and 48 h later, YKL-40 was associated with the outcome independently of the IL-8 concentrations. On the other hand, high(er) IL-8 was associated with a more severe AP only at high YKL-40. Hence, like in the case of on-admission CRP, the YKL-40 concentrations taken on admission provide additional information about future developments, i.e, "on top" of what could be inferred based on the IL-8 concentrations.

Overall, considering the associations between YKL-40 concentrations and the outcome (AP severity), the TNF-α and IL-8 concentrations determined on admission or 48 h after admission do not seem to provide relevant information.

It could be objected that we considered the AP severity as a three-level ordered variable, and not as a dichotomy ("severe" vs. "moderate or mild") as it is commonly done (reviewed in 23), and that the incidence of the severe AP in this cohort was low (7.3 % - 11 patients). However, we do not see these facts as important limitations. There is a clinical and biological rationale to classify AP into 3 levels, and using the dichotomy of "severe" vs. "other" appears to be preferred for convenience, not for medical reasons (binary outcomes are simpler for analysis than multinomial ones) – we believe that using the AP severity as a 3-level outcome is actually a strength of the present study, not a limitation. Indeed, there were only 11 severe AP patients, and a larger number would likely improve the precision of some estimates, but when the outcome has 3 levels, the rather low number of the patients with the "most severe level" is not as problematic as it would be in an analysis of 11 events vs. 139 non-events. The major limitation of the present study, as one would expect form an exploratory investigation, is its limited generalizability which is due to two major elements: the number of included patients was limited, and all were enrolled at a single institution, and we excluded patients with the conditions known to be associated with high(er) YKL-40, since with a limited sample of patients it would have been practically impossible to evaluate the relationship between YKL-40 and AP severity at different levels of a large number of the possibly interfering conditions. Consequently: i) the YKL-40 concentration cut-off that we used for the present exploratory purposes, although apparently reasonable, might not correspond to what could be considered "low", "intermediate" and "high" (YKL-40) in the target population, hence the observed YKL-40-outcome associations might be over- or underestimates of the reality; ii) by the same logic, the observed relationship between CRP values and the outcome, and the YKL-40 – CRP interrelationshi p having in mind also the known high variability of CRP in AP, and limited predictive values [48] might not hold in the target population, particularly if one were to consider clinical, imaging and other biochemical indicators. Such questions need to be addressed in larger (probably multicenter) samples.

In conclusion, the present data suggest serum YKL-40 concentrations determined at early stages of AP presentation as a feasible candidate biochemical marker that could improve prediction of the disease severity, particularly if considered jointly with CRP and/or systemic IL-6 concentrations, or combined with risk scoring systems based on other biochemical, clinical and imaging indicators, such as EASY-APP [49].

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Declaration of competing interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2024.11.024.

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