VILNIUS UNIVERSITY

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THE VALUE OF INFLAMMATION MARKERS IN EARLY ACUTE PANCREATITIS COURSE PREDICTION: THE RESULTS OF PROSPECTIVE MULTICENTER COHORT STUDY

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VILNIAUS UNIVERSITETAS

ANDRIUS KARPAVIČIUS

UŽDEGIMO ŽYMENŲ REIKŠMĖ ANKSTYVAM ŪMINIO PANKREATITO EIGOS PROGNOZAVIMUI: PERSPEKTYVINIO DAUGIACENTRIO KOHORTINIO TYRIMO REZULTATAI

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ABBREVIATIONS

AP – Acute Pancreatitis

APACHE II – Acute Physiology and Chronic Health Evaluation II

AUC – Area Under the Curve;

BISAP – Bedside Index of Severity in Acute Pancreatitis;

BMI – Body Mass Index

CRP – C-Reactive Protein

CT – Computed Tomography

CTSI – Computed Tomography Severity Index;

HAPS – Harmless Acute Pancreatitis Score;

IL-6 – Interleukin-6

MAP – Mild Acute Pancreatitis

MCTSI – Modified Computed Tomography Severity Index;

MODS – Multiple Organ Dysfunction Score;

MSAP – Moderate Severity Acute Pancreatitis

NPV – Negative Predictive Value

POP – Pancreatitis Outcome Prediction;

PPV – Positive Predictive Value

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-analysis;

QUADAS – Quality Assessment of Diagnostic Accuracy Studies

SAP – Severe Acute Pancreatitis

SIRS – Systemic Inflammatory Response Syndrome

SOFA – The Sequential Organ Failure Assessment score;

INTRODUCTION

Acute pancreatitis (AP) is a disease with a high variable clinical course. Theincidence of AP is about 13-45 cases per 100 000 individuals, with the overall mortality rate of 10%-15%. In Lithuania the morbidity rate in AP is significantly higher in comparison with data submitted by other countries and reaches 113 cases per 100 000 population per year.The mortality rate is 1.5-4.2% in general, but in severe, complicated forms it can reach 30%. Non-complicated forms of AP can be treated in smaller regional hospitals, but the patients with the severe course of AP (SAP) should be timely transferred to the high volume centers.It has been reported that hospitals treating higher number of AP cases have better clinical outcomes. Delay can be fatal for the AP patient, so early prediction of SAP remains very important. Pancreatic enzyme levels poorly correlate with the severity of AP, thus prognosis is commonly based on clinical scores. The first disease specific prognostic score was proposed by Ranson in 1974, which later was complemented by a number of pancreatitis specific and organ failure scores, including Glasgow/Imrie (1984), APACHE II (Acute Physiology and Chronic Health Evaluation II - 1985), MODS (Multiple Organ Dysfunction Score - 1995), SOFA (Sequential Organ Failure Assessment - 1998), POP (Pancreatitis Outcome Prediction - 2007), BISAP (Bedside Index of Severity in Acute Pancreatitis - 2009) and many others. Although, the accuracy of such scores is high enough all of them are multifactorial and rather uncomfortable for everyday use, so a great attention is still given for seeking a single prognostic marker.

The most widely explored and described single predictor is C-reactive protein (CRP), which remains very useful, because it is accurate, cheap, and widely available. However, its concentration reaches a peak on third day of the disease, so it has the greatest prognostic value approximately 48 h after the onset of the symptoms. IL-6 (Interleukin-6) is also introduced in clinical practice and is approved as a reliable prognostic marker in many countries.

The predictive value of adipokines, such as leptin, adiponectin, resistin and visfatin, is less explored. Adipokines are cytokines produced in white adipose tissue as well as in peripancreatic fat and involved in inflammatory response. Increase of fatty tissue due to obesity is associated with the amplified systemic inflammatory response

in AP; furthermore it can be used as a prognostic factor for mortality, local, systemic complications and severity of AP. Peripancreatic fat necrosis in acute pancreatitis causes multisystem organ failure and mortality. It is hypothesized that peripancreatic necrosis can cause the massive release of adipokines into the patient's bloodstream, so adipokines can serve as predictors of clinical course and complications of acute pancreatitis.

THE AIM OF THE STUDY

The aim of the dissertation is to evaluate the prognostic usefulness of inflammation markers and compare it with existing prognostic systems for AP course, necrosis, need for intervention and mortality.

OBJECTIVES

1. To perform and publish the comprehensive review about prognostic possibilities of adipokines in AP;
2. To assess the influence of the obesity and peripancreatic necrosis on the AP course;
3. To determine the clinically significant early laboratory markers for AP course, pancreatic and peripancreatic necrosis, need for intervention and mortality prediction;
4. To compare prognostic possibilities of laboratory markers with routine prognostic systems.

STATEMENTS TO BE DEFENDED

1. Higher BMI (Body Mass Index) and the peripancreatic necrosis volume are associated with more severe AP cases.
2. Resistin and IL-6 could be used as early markers of severe AP.
3. BISAP score is more universal and earlier for AP course, necrosis, need for interventions and mortality prediction than adipokines, IL-6 and CRP.

SCIENTIFIC NOVELTY OF THE STUDY

The prognostic possibilities of adipokines in AP were noticed several years ago. First experimental studies were performed on rats in 2002-2007. The statistically significant differences of leptin concentration were found both between the control and AP groups as well as edemic and necrotic AP groups.

In a few years the significant differences of leptin and resistin concentrations between the control and AP groups were found on the clinical studies. The significance of adiponectin for the SAP prognosis was also confirmed. Research studies published from 2006 to 2010 established that resistin and visfatin may also be used for SAP prognosis. Few years later it was found that leptin concentrations are significantly different in MAP and SAP groups.

Though the total number of studies on adipokines prognostic significance is rather noteworthy, the majority of them are small volume analyses, often performed without control groups and standardized testing directed towards prognostic possibilities of separate adipokines.

All the studies mentioned above were very different in their methodology, diagnostic criteria, classification and evaluation of AP.

In recent years quite many publications have appeared on the influence of obesity and BMI on AP course. Supposedly, obese patients are more inclined to systemic inflammatory response syndrome (SIRS), under the influence of which more complicated AP course and worse outcomes can be expected.

Peripancreatic fat necrosis in acute pancreatitis causes multisystem organ failure and mortality regardless of weather the patient suffers from pancreatic necrosis or not. Adipokines are produced in adipose tissue, so the peripancreatic necrosis can cause the massive release of them into the patient‘s blood. The study published in 2015 found that even 100 ml volume of peripancreatic necrosis is associated with SAP.

The prognostic value of IL-6 has been studied much better. In many centers it is used routinely and has good prognostic characteristics on AP course, necrosis, interventions and prediction of outcomes. Unfortunately most studies on IL-6 and

adipokines were published before 2012. In 2012 the Atlanta classification of AP was revisited and new form – moderate severity AP – was identified. Therefore the criteria of SAP became more stringent and the cut off values of adipokines, as well as CRP and IL-6 must be recalculated.

The history of prognostic studies in AP in Lithuania is very short. Only few papers about the prognostic value of cytokines and different prognostic systems were published. This study is the first attempt to assess the prognostic possibilities of adipokines in AP in Lithuania.

LITERATURE REVIEW

A review of literature presents the definition, epidemiology, etiology and classification of AP, gives the survey of the single predictors and different prognostic systems of AP course and complications. It contains systematic analysis of prognostic possibilities of adipokines and influence of obesity and peripancreatic necrosis on disease course.

PRACTICAL SIGNIFICANCE

This paper contributes to the ongoing worldwide search for prognostic markers in AP so that severe acute pancreatitis is diagnosed as early as possible. Early and appropriate treatment will progress in reducing rates of SAP complications and mortality. It also aims to facilitate the work of medical personnel at non-specialized hospitals by helping to make an early correct assessment of a patient's with AP condition.

MATERIALS AND METHODS

Comprehensive review

We performed the search of PubMed database (service of the United States National Library of Medicine that includes citations from MEDLINE and other life science journals for biomedical articles) and the systemic analysis of the literature for both experimental and human studies on prognostic value of adipokines in AP for period 2002-2012. Keywords for the search were adipokines, adipocitokines, visfatin,

resistin, adiponectin, leptin, acute pancreatitis, pancreatic necrosis, peripancreatic necrosis. Further we searched the references of identified articles to find additional sources of information. Only articles in English language were included in the analysis. Dual publications were excluded. All identified papers (title, abstract and subsequently full text) were independently evaluated by two investigators. Only the papers that described the use of adipokines for prediction of severity and/or complications of AP were selected for further analysis. To be included in the systematic review, each article had to contain information about the levels of measured adipokines, diagnosis and verification of AP, to specify presence of pancreatic necrosis, organ dysfunction and/or mortality rates. All disagreements were resolved by discussion with other two investigators. From the very beginning, study was carried out adhering to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) checklist and flowchart for systemic reviews.

To assess quality of all included human studies the QUADAS (Quality Assessment of Diagnostic Accuracy Studies) tool was used. Quality assessment was performed independently by three researches and all disagreements were resolved by review and discussion with the fourth investigator. Based on the judges' evaluation 8 of 9 studies got seven or more "yes", so the overall quality of included studies was good. However, all studies were very different. Four of them analyzed only one adipokine, two adipokines were analyzed in three studies, and the remaining two studies analyzed three adipokines. In two studies adipokines concentration was measured only in control and AP groups, without distinction of mild and severe acute pancreatitis.

Because of the high heterogeneity between the studies, lack of the uniform diagnostic criteria and high variation of the assessed adipokines profile it was decided to refrain from the statistical processing or meta-analysis of the available data.

Prospective study design and patient population

Our study was conducted in four Lithuanian hospitals during the period between April 2012 and March 2015. The Regional Ethics Committee approved the

study protocol (permission No. L-12-02/1/2/3/4) and all the patients and the control group provided written informed consent.

The diagnosis of AP was established according to the revisited Atlanta classification and based on the presence of at least 2 of the 3 following features: abdominal pain characteristic of acute pancreatitis, serum amylase level ≥3 times up the upper limit of normal and characteristic findings of AP on abdominal computerized tomography scan.

All patients admitted to the hospitals with a diagnosis of acute pancreatitis and onsets of the symptoms within last 72h were included in this study. Pregnant women, patients with the history of necrotizing pancreatitis and underlying chronic pancreatitis were excluded from this study.

Each patient's age, sex, etiological factor, body mass index (BMI), presence of organ failure and local complications, interventions, in-hospital mortality and length of hospital stay were recorded.

SOFA, BISAP and HAPS scores were calculated using data from the first 24h from admission. In 48-72h from admission SOFA score was recalculated.

According to the revisited Atlanta classification, based on organ failure, all the AP patients retrospectively were classified as mild, moderate or severe AP cases.

Blood samples

Peripheral blood samples from AP patients were obtained at the day of the admission and after 48-72 h (3rd day). The blood samples of the control group were obtained only once. All the samples were centrifuged and stored at -20ºC until analysis. Blood sample analysis was performed at the Center of Laboratory Medicine, Vilnius University. Adipokines and IL-6 serum concentrations were measured using ELISA kits (DIAsourceImmunoAssays SA/Adiponectin, IBL/International Leptin Elisa, DIAsourceImmunoAssays SA/Resistin ELISA, BioVendor Human Visfatin (Nampt) ELISA and DIAsourceImmunoAssays SA/IL6) according to the manufacturer's instructions. Compact microplate processor Gemini (Stratec Biomedical AG) was used. Plasma levels of CRP and other tests were measured in accordance with hospitals laboratory routine.

CT scan

Contrast enhanced CT (CECT) scans were performed for patients with acute pancreatitis no earlier than the third day and no later than the seventh day after the onset of symptoms. All CECT examinations were performed in four centers:

1. Vilnius University Hospital "Santariškių Klinikos"
2. Vilnius City Clinical Hospital
3. Republican Vilnius University Hospital
4. Hospital of Lithuanian University of Health Sciences "Kauno Klinikos"

All examinations were performed on a multidetector CT scanners (GE VCT, GE Light Speed Pro and Toshiba Aquilion) and covered abdominal region and if necessary pelvic region. Standard pancreatic scanning protocol was used with late arterial and portovenous phases. CT scans were retrospectively and independently reviewed on workstations (GE Advanced Work station VolumeShare 5 (AW4.6)) by two experienced abdominal radiologists who were unaware of presenting signs and symptoms of patient outcomes. The severity of the pancreatitis for each case was assessed by each observer using the CT severity index (CTSI) and modified CT severity index (MCTSI). Possible pancreatic necrosis and their extent, peripancreatic fluid collections and extrapancreatic findings (pleural effusion, ascites, parenchymal, vascular and GI tract complications) were evaluated. In the cases of disagreement of CT indexes between two radiologists consensus was reached after secondary review of CT scans by the same radiologists and discussion. Up to three biggest peripancreatic fluid collections were measured in three perpendicular dimensions (in cm). The simplified formula of an ellipsoid was used (length x width x thickness/2) to calculate the volume of the peripancreatic fluid collections. This formula enables quick and easy calculation of the volume and is widely used in radiology.

Statistical analysis

Statistical analysis was performed using R v. 3.2.0 package. Categorical variables were expressed as absolute numbers and percent. For the association

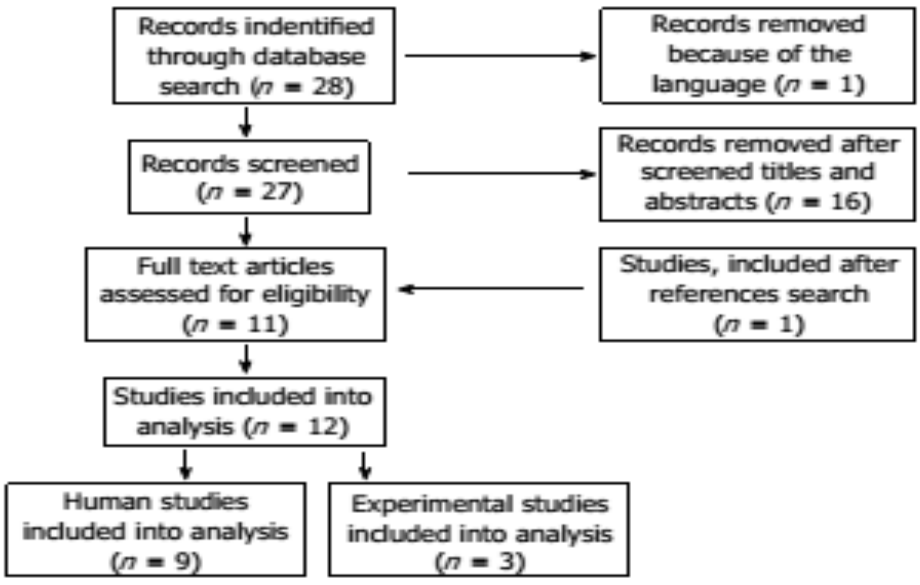
between two variables Pearson's chi-square test or Fisher's exact test were applied, as appropriate. Continuous variables were expressed as mean±standard deviation (SD) and median±interquartile ranges (IQR). Normality of the variables was checked by Shapiro-Wilk statistic. All variables, except age, were not distributed according to the normal distribution; therefore nonparametric hypotheses were tested to detect significant differences between selected categories. ROC curves, area under the curve (AUC) and optimal cut off values were calculated using R plugin pROC. AUC was calculated using the 95% confidence interval (CI). A *p* value less than 0.05 was considered statistically significant.

RESULTS

Comprehensive review

Through database search 28 records were identified. After screening the titles and abstracts, 16 records were removed, because adipokines were not used for prediction of the disease course. One record was removed because of the language. In reference search one additional study was found. So, nine human and three experimental studies were further analyzed (Figure 1).

Fig. 1 Selection of the studies for systematic review (PRISMA flowchart).



All three experimental studies were performed on rats. The only one adipokine leptin was analyzed. In all studies significant differences between leptin concentrations in control and acute pancreatitis groups were found, one study analyzed leptin concentrations in control, acute edematous pancreatitis (AEP) and acute necrotizing pancreatitis (ANP). Significant difference at 12 h was found between controls and ANP group. At 24 and 48 h significant difference was found between controls and both AEP and ANP groups (Table 1).

Table 1. Summary of the experimental studies on the prognostic value of adipokines

Study	Animal	Groups	n	Leptin
Konturek P.C. et al. 2002	Rats	AP Controls	6-8 6-8	The induction of CIP resulted in a significant increase of plasma levels of leptin.
Yavuz N., et al. 2004	Rats	AP CP (chronic) Control	10 10 10	1.92±0.1 1.86±0.13 0.78±0.12 $p<0.001$
Kerem M. et al. 2007	Rats	AEP ANP Controls	30 30 30	At 12h leptin levels in ANP was higher than in controls ($p<0.001$).At 24 and 48h leptin levels in AEP and ANP were higher than in controls ($p=0.027$ and $p<0.001$)

Abbreviations: AP – Acute Pancreatitis; CIP – Cerulein Induced Pancreatitis; CP – Chronic Pancreatitis; AEP – Acute Edeomatous Pancreatitis; ANP – Acute Necrotic Pancreatitis

All nine human studies (Table 2) with adipokines are very different in terms of methodology and objectives, so it is difficult to generalize their results. It seems that concentrations of the leptin and resistin increases significantly in patients with AP compared with controls. Serum levels of adiponectin, visfatin and especially resitin (positive correlation with APACHE II, Ranson and CRP) are significantly different in severe acute pancreatitis and mild acute pancreatitis patients, so, they can serve as a markers for the disease severity prediction. Resistin and visfatin can also be used for prediction of pancreatic and peripancreatic necrosis, intervention needs and possible, outcome.

Table 2. Summary of the human studies on the prognostic value of adipokines

Study (patients & methods)	Results & Conclusions
Konturek et al., 2002: • Prospective observational study; n=45 • Diagnosis of AP based on Atlanta criteria. • Adipokines studied: leptin • Adipokines evaluated between 48-72h of illness onetime • AP (n = 15) Vs Controls (n = 30)	Leptin: AP/Controls- 7.5(4.3-18.4)/2.1-11.8) **Median plasma leptin levels in AP were significantly increased as compared with controls.**
Duarte-Rojo et al., 2006: • Prospective observational study; n=52 • Diagnosis of AP based on typical clinical manifestations with at least a 3-fold increase of serum amylase and/or lipase. Whenever uncertainty about diagnosis existed, CT-scan was performed to confirm/rule out AP. • Severe AP was considered when patients developed one or more local or systemic complications according to the Atlanta classification of AP • Adipokines studied: leptin • Adipokines evaluated onetime during the 1 day of hospital stay • MAP (n=38) Vs SAP (n=14)	There was no statistically significant association between leptin serum levels and severity of AP. There was no difference in leptin measurements between patients favorable and fatal outcomes (p= 0.34). Time of evolution from onset of pain did not alter leptin values. There was a positive correlation of BMI and leptin (r = 0.476, p < 0.001) in the whole group. Predicted severity by modified Ranson's criteria correlated with Atlanta criteria (r = 0.414, p = 0.002); however, it did not correlate with leptin levels. **In summary, our results do not support human leptin as a major pro-inflammatory signal involved in AP, nor as a protective and anti-inflammatory mediator. It seems neither to be the link between obesity and a higher rate of complications in AP; not a prognostic marker.**
Tukiainen et al., 2006: • Prospective observational study (n=24) • AP and SAP defined by Atlanta criteria • Adipokines studied: leptin, adiponectin • Adipokines evaluated on admission, on day 2-4, and on day 5-7 • MAP (n = 12) Vs SAP (n = 12)	In patients with SAP highest value of CRP was 349 mg/l (284-476 mg/l), with MAP – 119 mg/l (11-367 mg/l) Leptin on admission SAP/MAP – 6,1 (1.6-72.9)ng/l/9.0(2.5-36.5)ng/l, (p>0.05); on days 2-4 – 7.7(1.6-13.9)/3.8(1.6-12.9), (p>0.05). Adiponectinon admission SAP/MAP – 5642(1201-19400)ng/l/6314(1980-24340)ng/l, (p>0.05) **Plasma levels of adiponectin and leptin do not correlate with AP severity on admission and during the first week of the disease.**
Schaffler et al., 2006: • Pilot prospective observational study (n=23) • Diagnosis of AP was based on clinical, laboratory and radiological findings during CT and/or ultrasound examination • Adipokines studied: leptin, adiponectin, resistin • Adipokines evaluated daily for 10 days after admission • SAP (n=20) Vs MAP (n=3) and patients with high points Vs Low points on radiological scores	Balthazar score – 4 (1-5), Schroeder score – 5 (1-7), Necrosis score – 2(1-4) Ranson – 3 (0-7), Apache II – 12 (4-37) Resistin has a significant positive correlation with Ranson score (R=0.6, p=0.002) and with Apache II score (r=0.5, p=0.019) Resistin: intervention group/no intervention – 32.4±10.7/15.8±5.1 ng/l, p=0.026 Leptin and relative changes in leptin values were positively and significantly correlated with CRP levels (r=0.6, p=0.007 and p=0.003 respectively) Resistin cut-off value of >9.2ng/ml (10 day mean value) can provide a PPV of 91.9% in predicting Schroder score of >3

Study (patients & methods)	Results & Conclusions
	(specificity 85%, sensitivity 75%, AUC 0.9, p<0.0001) Leptin cut-off value of 15.0ng/ml can provide a PPV of 88% in predicting Schroder score of >3 (specificity 85%, sensitivity 50%, AUC 0.72, p<0.0001) Day 1 resistin proved to predict a Schroder score >3 with a PPV of 93.3%, cut-off 6.95ng/ml, specificity 87.5%, sensitivity 93.3%;AUC 0.9, p=0.002) **Serum adipokines might be the new useful early markers of disease severity in AP.**
Lesniowski et al., 2007: • Prospective observational study (n=79) • All AP was classified as grade B according to Balthazar CT score. • Adipokines studied: adiponectin, resistin • Adipokines evaluated onetime during the first day of hospitalization • AP (n = 39) Vs Controls (n = 40)	Resistin: AP/Controls – 8.38±4.87/3.58 ±1.51 ng/ml; p<0.05 Adiponectin: AP/Controls – 119.38±61.75/133.77±55.38 ng/ml; p>0.05 CRP: AP/Controls – 23.21±8.75/3.95±1.06 mg/l; p<0.01 Weak positive correlation between serum resistin and CRP was observed (r=0.57; p<0.05) No correlation between selected adipocytokines and BMI was noticed **Serum concentrations of resistin may possibly represent the useful early marker of inflammatory response in AP.**
Sharma et al., 2009: •Prospective observational study (n=60) •Diagnosis of AP based on Atlanta criteria. • SAP was defined as the presence of cardiovascular, pulmonary, and/or renal system dysfunction during the initial hospital admission during for at least 48h. • Adipokines studied: adiponectin •Adipokines evaluated on admission and subsequently up to 30th hospital day •MAP (n = 27) Vs SAP (n = 33)	Serum adiponectin levels from days 1 to 3 were significantly lower for patients with SAP (median 3.74 (0.83-8.92)µg/l)than those with MAP (6.58 (1.31-15.37)µg/l)), p=0.02; Serum adiponectin levels from days 4 to 7 were lower for patients with SAP (median 4.53 (0.94-18.2)µg/l)than those with MAP (8.06 (2.11-17.72)µg/l)), p=0.01; 1-3 day serum adiponectin threshold of 4.5µg/ml correctly classified the severity of 81% of patients with AP. This threshold yielded a sensitivity of 70%, specificity 85%, PPV64%, NPV 88%. (AUC 0.75) **Serum adiponectin levels are significantly lower in patients with SAP than those with MAP and could serve as inverse marker of systemic inflammatory response to pancreatic injury.**
Daniel et al., 2010: • Prospective observational study (n=62) • Diagnosis of AP was based on at least threefold elevated serum amylase level, as well as ultrasonography and CT • In all cases AP was classified as C according to Balthazars CT score and as severe according to Ranson"s criteria (3 points) • Adipokines studied: resistin • Adipokines evaluated on 1, 2 ,3 and 5 day of hospitalization. • SAP (n=32) Vs Controls (n=30)	On first day of observation, the median serum CRP level was 51.9±46.1 mg/l, significantly higher than in control group (3.44±3.04 mg/l, p<0.01), and further increased at third day of hospitalization (102.6±55.1 mg/l; p<0.05), slightly decreasing on fifth day of hospitalization (78±47.7 mg/l). The values observed at third and fifth day of hospitalization were significantly higher than in the control group (p<0.001). One day of admission and third day of the hospitalization the mean serum resistin concentration was 12.9±6.38 ng/ml and 17.4±4.23 ng/ml, respectively. Both values were significantly higher than in the control group (4.06±2.63 ng/ml, p<0.05). At fifth day of hospitalization serum resistin concentration increase further to 25.8±8.14 ng/ml, wich was significantly higher than at first and third day (p<0.05) of hospital stay. Significant correlation between CRP and resistin (r=0.43; p<0.05) during the hospital stay was found. **Resistin may be useful early marker in edematous form of AP.**

Study (patients & methods)	Results & Conclusions
Schaffler et al., 2010- 2011: • Prospective observational study (n=50) • Diagnosis of AP was based on clinical, laboratory and radiological findings during CT and/or ultrasound examination • All patients were divided into three groups: first – with higher radiological score's points, second – with lower radiological score's points and third – no CT scan (mild pancreatitis) • Adipokines studied: leptin, adiponectin, resistin, visfatin • Adipokines were measured daily from admission till 10 days of hospital stay. • SAP (n=41) Vs MAP (n=9) and patients with high points Vs low points on radiological scores	Balthazar score – 4.0 (1-5), Schroeder score – 4.5 (1-7), Necrosis score – 1.5(1-4), Ranson – 3 (0-8), Apache II – 12 (0-45) Admission resistin levels has positive an significant correlation with Apache II score (r=6, p<0.001) and with Ranson score (r=0.4, p=0.013) Admission resistin cut-off value of >11.9ng/ml can provide a PPV of 89% in predicting Schroeder score of >3 (specificity 80%, sensitivity 70%, AUC 0.8, p<0.002) Admision resistin cut-off value of >11.9ng/ml can serve as a positive predictor of a Balthazar score >3 and Necrosis score >2. Admission visfatin cut-off value of >1.8ng/ml can provide a PPV of 93.3% in predicting Schroeder score of >3 (specificity 81.8%, sensitivity 93.3%, AUC 0.89, p<0.001, likehood ratio 5.1, post-test probability 93.0%) Admission visfatin concentration can also predict Necrosis score >2 (PPV 48.3, specificity 40.0%, sensitivity 93.8%, AUC 0.77, p<0.004, likehood ratio 1.5, post-test probability 70.0%) and Balthazar score >3 (PPV 79.3, specificity 57.1%, sensitivity 88.9%, AUC 0.74, p<0.011, likehood ratio 2.1, post-test probability 55.0%) **Resistin and visfatin levels are highly elevated in patients with SAP when compared to patients with MAP. Both adipokines levels are positively correlated with clinical severity, clinical end points and needs for interventions. A single measurement of serum resistin or visfatin on the day of admission is a highly significant and positive predictive marker in predicting peripancreatic necrosis.**

Abbreviations: AP - Acute Pancreatitis; SAP - Severe Acute Pancreatitis; MAP - Mild Acute Pancreatitis; BMI - Body Mass Index; CRP - C-Reactive Protein; AUC - Area UnderCurve; PPV - Positive Predictive Value; NPV - Negative Predictive Value; CT - Computed Tomography.

Patients' characteristics

During the study period 119 of AP patients were prospectively assessed for possible inclusion in the study. Seventeen patients were excluded for various reasons (Fig. 2). In the final analysis 102 of AP patients (50 males and 52 females, mean age 55.7±18.1 years) were included. Mean time after onset of the symptoms was 20.3±13.8 hours. The main etiological factors of AP were biliary stones (42.2%) and alcohol (35.3%). Necrosis of the pancreas during CECT was detected in 60 (58.8%)

patients and the peripancreatic necrosis was present in 67 (65.7%) cases. Ninety two (90.2%) patients were treated conservatively and 10 (9.8%) underwent the interventions. Mean length of hospital stay was 20.8±28.3 days. Five patients died during hospitalization (mortality rate – 4.9%).

According to the revisited Atlanta classification, 27 (26.5%) of all patients had mild, 55 (53.9%) - moderate and 20 (19.6%) severe AP (Fig. 2). The main differences of the clinical and biochemical characteristics between SAP and milder forms of the AP are shown in Table 3.

Forty healthy persons were included as a control group: 17 males and 23 females with the mean age of 54.3±16.1 years and BMI of 27.9±4.7 kg/m^2. No significant differences were noted between the AP patients and control group in terms of their gender, age or BMI.

Fig.2 The flow-diagram for patient selection

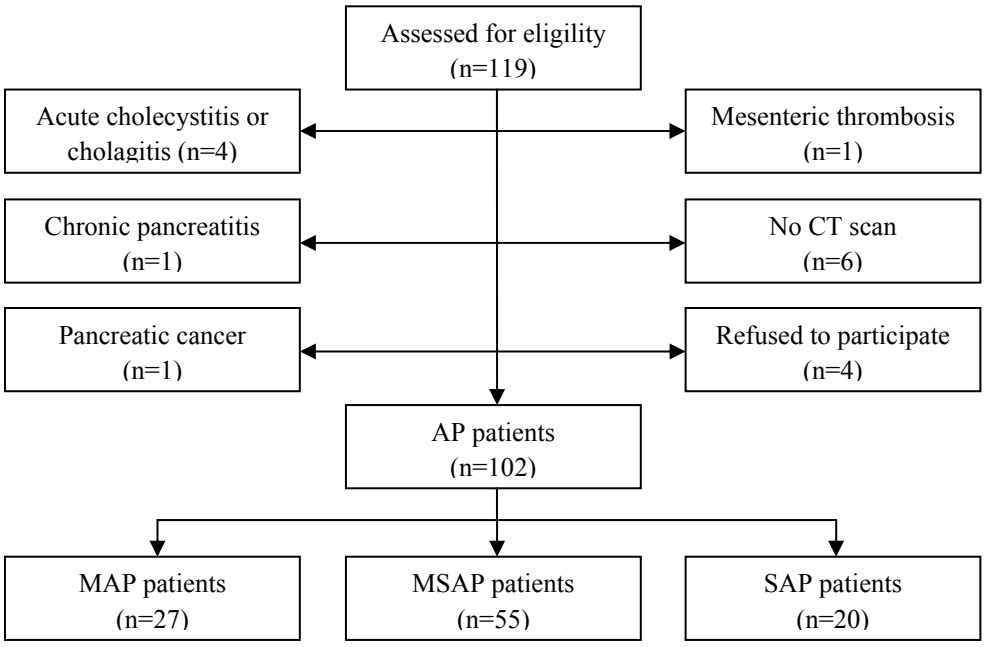


Table 3. Differences in clinical course of mild+moderate and severe AP

	Mild and moderate severity AP (n=82)	**Severe AP (n=20)**	**p value***
Age	55.90±19.02	55.00±14.20	0.814
Sex:			
Male (%)	38 (46.3)	12 (60.0)	
Female (%)	44 (53.7)	8 (40.0)	
BMI	27.99±7.54	31.07±10.02	**0.041**
Adiponectin µg/ml (1st day)	11.10±9.58	7.91±10.07	0.446
Adiponectin µg/ml (3rd day)	10.04±9.14	8.64±6.44	0.870
Leptin ng/ml (1st day)	7.21±11.83	4.17±8.14	0.397
Leptin ng/ml (3rd day)	2.33±3.85	0.84±6.03	0.533
Visfatin ng/ml (1st day)	4.15±5.45	5.42±4.74	0.179
Visfatin ng/ml (3rd day)	2.94±4.58	7.34±5.68	0.059
IL-6 pg/ml (1st day)	133.00±350.47	635.95±634.45	**0.000**
IL-6 pg/ml (3rd day)	94.97±323.86	545.31±574.17	**0.000**
Resistin ng/ml (1st day)	10.70±8.65	20.20±31.75	**0.000**
Resistin ng/ml (3rd day)	11.67±14.87	40.75±28.27	**0.000**
CRP mg/ml (1st day)	9.54±64.79	16.15±74.86	0.220
CRP mg/ml (3rd day)	180.30±224.87	377.13±91.39	**0.000**
SOFA (1st day) (score)	1±2	3±3	**0.000**
SOFA (3rd day) (srore)	1±2	4±2	**0.000**
BISAP (score)	1±2	3.00±1	**0.000**
HAPS (score)	1±2	1±1	**0.018**
CTSI (score)	4±4	6±2	**0.000**
MCTSI (score)	6±4	8±2	**0.000**
Pancreatic necrosis (%)	40(48.8)	20(100)	**0.000**
Peripancreatic necrosis volume (ml) (n)	31.50±518.50 (48)	731.00±2141.50 (19)	**0.000**
Need for surgery (%)	2(2.4)	8(40.0)	**0.000**
Hospital stay (d)	11.00±7.00	30±22.75	**0.000**
Number of deaths (%)	0(0.0)	5(25.0)	**0.000**

Abbreviations: AP – Acute Pancreatitis; BMI – Body Mass Index; IL-6 – Interleukin-6; CRP – C-Reactive Protein; SOFA - The Sequential Organ Failure Assessment score; BISAP - Bedside Index of Severity in Acute Pancreatitis; HAPS - Harmless Acute Pancreatitis Score; CTSI - Computed Tomography Severity Index; MCTSI - Modified Computed Tomography Severity Index;

Age was expressed as mean±standart deviation (SD); sex, pancreatic necrosis, need for surgery and number of deaths by percents, other variables - as median±interquartile ranges (IQR).

*Significant in bold

The predictive value of peripancreatic necrosis and BMI

The median volume of peripancreatic necrosis was lower in milder AP forms (median 31.5 ml, Q1-Q3 0-518.5 ml) than in SAP (median 731.0 ml, Q1-Q3 432.5-2574.0 ml), $p<0.05$. The analysis of the ROC curves has demonstrated, that cut-off value of 112.5 ml is associated with SAP (sensitivity 61.0%, specificity 95.0%, AUC 0.80) and 433.0 ml cut-off value is associated with the need of intervention (sensitivity 68.5%, specificity 100%, AUC 0.87).

The median value of BMI was higher in patients with SAP when compared to patients with MAP+MSAP (31.3 and 28.0 kg/m^2), $p<0.05$.

Comparison of AP patients and controls

The median serum adiponectin levels at admission were higher in AP group (median 10.7 μg/ml, Q1-Q3 6.8-16.8 μg/ml) than in controls (median 8.3 μg/ml, Q1-Q3 5.6-12.3 μg/ml), $p>0.05$. The median serum leptin levels at admission were higher in AP group (median 6.7 ng/ml, Q1-Q3 2.8-14.5 ng/ml) than in controls (median 4.0 ng/ml, Q1-Q3 1.5-8.5 ng/ml), $p>0.05$. The median serum resistin levels at admission were higher in AP group (median 12.6ng/ml, Q1-Q3 7.4-18.2 ng/ml) than in controls (median 5.4 ng/ml, Q1-Q3 4.5-6.7 ng/ml), $p<0.05$. The median serum visfatin levels at admission were higher in AP group (median 4.7 ng/ml, Q1-Q3 2.1-7.4 ng/ml) than in controls (median 1.6 ng/ml, Q1-Q3 1.2-2.2 μg/ml), $p<0.05$. The median serum IL-6 levels at admission were higher in AP group (median 194,3 pg/ml, Q1-Q3 39.8-508.8 pg/ml) than in controls (median 1.5 pg/ml, Q1-Q3 0.3-7.0 pg/ml), $p<0.05$.

Comparison of MAP+MSAP and SAP

Median admission and 3rd day resistin, IL-6 and 3rd day CRP values were significantly higher in SAP group when compared with other patients. No significant differences were noted for admission and 3rd day adiponectin, leptin, visfatin and admission CRP values between SAP and other patients (Table 3). The ROC analysis applied for early SAP prediction showed significant results only for admission resistin and IL-6. The detail results are shown Table 4.

Table 4. Resistin and IL-6 can predict SAP on admission

	AUC	95% CI	Cut-off	Sens., %	Spec., %	PPV, %	NPV, %
IL-6 Admission	**0.78**	**0.6596-0.9075**	**473.4**	**82.9**	**75.0**	**51.7**	**93.2**
IL-6 3rd day	**0.82**	**0.7322-0.9117**	**119.9**	**54.9**	**100.0**	**35.1**	**100.0**
Resistin Admission	**0.76**	**0.6462-0.8782**	**13.7**	**63.4**	**80.0**	**34.8**	**92.9**
Resistin 3rd day	**0.89**	**0.8232-0.9597**	**23.9**	**79.3**	**85.0**	**50.0**	**95.6**
CRP Admission	0.59	0.4542-0.7238	4.4	35.4	90.0	25.4	93.5
CRP 3rd day	**0.79**	**0.6932-0.8873**	**301.1**	**70.7**	**80.0**	**40.0**	**93.5**

Abbreviations: IL-6 – Interleukin-6; AUC - Area Under the Curve; CI – Confidence Interval; Sens. – Sensitivity; Spec. – Specificity; PPV – Positive Predictive Value; NPV – Negative Predictive Value
*Significant in bold

Comparison of patients with and without necrosis

Median admission and 3rd day resistin, IL-6 and 3rd day visfatin and CRP values were significantly higher in necrosis (pancreatic and peripancreatic) group when compared with the patients without necrosis. No significant differences were noted for admission and 3rd day adiponectin, leptin and admission visfatin and CRP values between these two groups (Table 5). The ROC analysis applied to predict the necrosis on admission showed no significant result for adipokines. Only admission IL-6 with a cut-off 157.0 pg/ml could be used for early prediction of necrosis (sensitivity 75.0%, specificity 67.1%, AUC 0.72).

Table 5. There are significant differences of admission resistin and IL-6 concentrations between patients with and without pancreatic/peripancreatic necrosis

	Necrosis (-) n=32 Median (Q1-Q3)	Necrosis (+) n=70 Median (Q1-Q3)	p value*
Adiponectin (µg/ml)			
Admission	11.9 (7.7-17.2)	10.6 (6.5-16.6)	0.632
3rd day	12.3 (7.0-18.9)	8.7 (5.8-13.0)	0.118
Leptin (ng/ml)			
Admission	8.1 (3.8-16.0)	4.6 (2.7-14.0)	0.320
3rd day	2.2 (0.7-3.7)	2.2 (0.5-6.0)	0.994
Resistin (ng/ml)			
Admission	8.0 (5.5-15.5)	14.0 (8.8-24.5)	**0.002**
3rd day	7.0 (4.6-9.3)	22.2 (13.0-86.9)	**0.000**
Visfatin (ng/ml)			
Admission	3.3 (1.5-6.8)	5.0 (3.2-7.5)	0.105
3rd day	2.6 (0.9-3.3)	5.0 (2.0-8.1)	**0.005**
IL-6 (pg/ml)			
Admission	54.7 (12.7-162.3)	282.3 (74.6-627.9)	**0.000**
3rd day	25.0 (6.3-68.8)	345.3 (102.8-629.3)	**0.000**
CRP (mg/ml)			
Admission	9.8 (2.7-49.9)	11.7 (4.7-81.3)	0.216
3rd day	79.6 (36.5-140.5)	319.6 (183.4-393.3)	**0.000**

Abbreviations: IL-6 – Interleukin-6; CRP – C-Reactive Protein;
*Significant in bold

Comparison of patients who were treated conservatively and those who underwent interventions

Median admission and 3rd day resistin, IL-6 and 3rd day CRP values were significantly higher in patients who underwent the interventions for AP when compared with the conservatively treated patients. Admission and 3rd day adiponectin, leptin, visfatin and admission CRP values were not different in these two groups (Table 6). The ROC analysis applied to predict the interventions on admission showed no statistically significant results.

Table 6. Significant differences of admission resistin and IL-6 concentrations between patients who were treated conservatively and those who underwent interventions

	Intervention (-) n=92 Median (Q1-Q3)	**Intervention (+) n=10 Median (Q1-Q3)**	**p value***
Adiponectin (µg/ml)			
Admission	10.7 (6.8-16.8)	9.4 (6.8-15.1)	0.617
3rd day	10.2 (6.2-15.2)	8.3 (4.2-10.4)	0.283
Leptin (ng/ml)			
Admission	7.0 (2.7-14.7)	4.0 (3.1-11.6)	0.605
3rd day	2.3 (0.7-5.1)	1.2 (0.3-4.7)	0.365
Resistin (ng/ml)			
Admission	11.6 (7.2-17.0)	25.3 (9.6-56.0)	**0.046**
3rd day	12.9 (7.3-24.6)	44.7 (36.6-50.0)	**0.000**
Visfatin (ng/ml)			
Admission	4.5 (2.0-7.4)	5.7 (4.0-9.1)	0.253
3rd day	3.2 (1.6-7.6)	4.0 (2.2-6.7)	0.633
IL-6 (pg/ml)			
Admission	166.7 (37.9-470.7)	486.6 (322.2-1087.8)	**0.026**
3rd day	128.4 (31.8-368.8)	832.2 (520.2-1056.3)	**0.000**
CRP (mg/ml)			
Admission	10.7 (3.5-71.4)	11.2 (3.3-107.8)	0.888
3rd day	184.9 (94.5-346.4)	389.6 (353.0-412.2)	**0.002**

Abbreviations: IL-6 – Interleukin-6; CRP – C-Reactive Protein;
*Significant in bold

Comparison of survivors and dead patients

Median admission and 3rd day resistin and 3rd day IL-6 and CRP values were significantly higher in patients who died from AP when compared with survivors group. Admission and 3rd day adiponectin, leptin, visfatin and admission IL-6 and CRP values were not different in these two groups (Table 7). The ROC analysis applied to predict the mortality on admission showed no statistically significant results.

Table 7. Significant differences of admission resistin concentrations between survivors and dead patients

	Died n=5 Median (Q1-Q3)	**Survived n=97 Median (Q1-Q3)**	**p value***
Adiponectin (µg/ml)			
Admission	10.8 (6.9-18.6)	10.6 (6.4-16.7)	0.631
3rd day	7.9 (7.0-10.7)	9.9 (6.1-15.1)	0.816
Leptin (ng/ml)			
Admission	4.2 (0.6-9.6)	6.9 (2.8-14.6)	0.535
3rd day	0.6 (0.1-6.1)	2.2 (0.7-5.0)	0.566
Resistin (ng/ml)			
Admission	26.2 (24.5-44.0)	11.7 (7.2-17.3)	**0.033**
3rd day	48.6 (41.5-58.4)	13.5 (7.5-25.7)	**0.002**
Visfatin (ng/ml)			
Admission	5.0 (3.7-9.0)	4.5 (2.1-7.4)	0.710
3rd day	9.0 (2.0-16.9)	3.2 (1.7-7.5)	0.251
IL-6 (pg/ml)			
Admission	488.4 (484.7-1389.6)	177.1 (38.4-496.6)	0.063
3rd day	753.0 (459.5-1619.2)	159.7 (34.3-376.1)	**0.012**
CRP (mg/ml)			
Admission	4.9 (4.7-35.6)	11.2 (3.3-71.70	0.901
3rd day	394.7 (328.3-411.5)	205.6 (100.1-355.4)	**0.026**

Abbreviations: IL-6 – Interleukin-6; CRP – C-Reactive Protein;

*Significant in bold

The possibilities of BISAP, HAPS, CTSI and MCTSI for AP course, necrosis, need for interventions and mortality prediction

The distribution of patients according to the disease severity and BISAP, HAPS, CTSI and MCTSI scores is showed in tables 8-11. The ROC analysis applied

for SAP prediction showed significant results for BISAP, CTSI and MCTSI scores (Table 12).

Table 8. Course of AP and BISAP score

Course/BISAP	0	1	2	3	4	5
MAP n=27 (%)	10 (37.0)	14 (51.9)	3 (11.1)	0 (0)	0 (0.0)	0 (0.0)
MSAP n=55 (%)	11 (20)	18 (32.7)	19 (34.6)	7 (12.7)	0 (0.0)	0 (0.0)
SAP n=20 (%)	0 (0.0)	0 (0.0)	6 (30.0)	10 (50.0)	3 (15)	1(5)

Abbreviations: BISAP – Bedside Index of Severity in Acute Pancreatitis; MAP – Mild Acute Pancreatitis; MSAP – Moderate Severity Acute Pancreatitis; SAP – Severe Acute Pancreatitis

Table 9. Course of AP and HAPS score

Course/HAPS	0	1	2	3
MAP n=27 (%)	9 (33.3)	16 (59.3)	2 (7.4)	0 (0.0)
MSAP n=55(%)	16 (29.2)	19 (34.5)	19 (34.5)	1 (1.8)
SAP n=20 (%)	1 (5.0)	10 (50.0)	8 (40.0)	1 (5.0)

Abbreviations: HAPS – Harmless Acute Pancreatitis Score; MAP – Mild Acute Pancreatitis; MSAP – Moderate Severity Acute Pancreatitis; SAP – Severe Acute Pancreatitis

Table 10. Course of AP and CTSI score

Course/CTSI	0	1	2	3	4	5	6	7	8	9	10
MAP n=27 (%)	4 (14.8)	2 (7.4)	19 (70.4)	2 (7.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
MSAP n=55 (%)	0 (0.0)	0 (0.0)	6 (10.9)	5 (9.1)	5 (9.1)	12 (21.8)	21 (38.2)	2 (3.6)	3 (5.5)	0 (0.0)	1 (1.8)
SAP n=20 (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.0)	9 (45.0)	0 (0.0)	5 (25.0)	1 (5.0)	3 (15)

Abbreviations: CTSI – Computed Tomography Severity Index; MAP – Mild Acute Pancreatitis; MSAP – Moderate Severity Acute Pancreatitis; SAP – Severe Acute Pancreatitis

Table 11. Course of AP and MCTSI score

Course/MCTSI	0	2	4	6	8	10
MAP n=27 (%)	4 (14.8)	13 (48.2)	9 (33.3)	1 (3.7)	0 (0.0)	0 (0.0)
MSAP n=55 (%)	0 (0.0)	3 (5.5)	2 (3.6)	13 (23.6)	31 (56.4)	6 (10.9)
SAP n=20 (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	11 (55.0)	9 (45.0)

Abbreviations: MCTSI – Modified Computed Tomography Severity Index; MAP – Mild Acute Pancreatitis; MSAP – Moderate Severity Acute Pancreatitis; SAP – Severe Acute Pancreatitis

Table 12. BISAP, CTSI and MCTSI can predict SAP

Score	AUC	p value*	95% CI	Cut-off	Sensitivity, %	Specificity, %	PPV	NPV
BISAP	**0.91**	**9.99E-12***	**0.8607-0.965**	**2**	**64.6**	**100.0**	**40.8**	**100.0**
HAPS	0.66	0.01425*	0.5475-0.7732	1	30.5	95.0	25.0	96.2
CTSI	**0.86**	**1.36E-08***	**0.789-0.9312**	**6**	**67.1**	**90.0**	**40.0**	**96.5**
MCTSI	**0.84**	**3.24E-08***	**0.7703-0.9083**	**8**	**54.9**	**100.0**	**35.1**	**100.0**

*Hypothesis H0: AUC=0.5
**Significant in bold
Abbreviations: BISAP – Bedside Index of Severity in Acute Pancreatitis; HAPS – Harmless Acute Pancreatitis Score; CTSI – Computed Tomography Severity Index; MCTSI – Modified Computed Tomography Severity Index; AUC – Area Under the Curve; CI – Confidence Interval; PPV – Positive Predictive Value; NPV – Negative Predictive Value

The distribution of patients according to necrosis, needs for interventions, outcomes and BISAP, HAPS, CTSI and MCTSI scores is showed in tables 13-16. The ROC analysis applied for necrosis, needs for interventions and mortality prediction showed significant results for BISAP, CTSI ir MCTSI scores (Tables 17-20).

Table 13. BISAP score according to necrosis, needs for interventions and outcomes

BISAP		0	1	2	3	4	5
Pancreatic and peripancreatic necrosis n (%)	**No.** n=32 (31.4)	11 (34.4)	16 (50.0)	5 (15.6)	0 (0.0)	0 (0.0)	0 (0.0)
	Yes. n=70 (68.6)	10 (14.3)	16 (22.9)	23 (32.8)	17 (24.3)	3 (4.3)	1 (1.4)
Interventions n (%)	**No.** n=92 (90.2)	21 (22.8)	31 (33.7)	26 (28.3)	13 (14.1)	0 (0.0)	1 (1.1)
	Yes. n=10 (9.8)	0 (0.0)	1 (10.0)	2 (20.0)	4 (40.0)	3 (30.0)	0 (0.0)
Outcomes n (%)	**Survived** n=97 (95.1)	21 (21.7)	32 (33.0)	26 (26.8)	17 (17.5)	1 (1.0)	0 (0.0)
	Died n=5 (4.9)	0 (0.0)	0 (0.0)	2 (40.0)	0 (0.0)	2 (40.0)	1 (20.0)

Abbreviations: BISAP – Bedside Index of Severity in Acute Pancreatitis

Table 14. HAPS score according to necrosis, needs for interventions and outcomes

HAPS		0	1	2	3
Pancreatic and peripancreatic necrosis n (%)	**No.** n=32 (31.4)	12 (37.5)	16 (50)	4 (12.5)	0 (0.0)
	Yes. n=70 (68.6)	14 (20)	29 (41.4)	25 (35.7)	2 (2.9)
Interventions n (%)	**No.** n=92 (90.2)	26 (28.3)	42 (45.6)	23 (25.0)	1 (1.1)
	Yes. n=10 (9.8)	0 (0.0)	3 (30.0)	6 (60.0)	1 (10.0)
Outcomes n (%)	**Survived** n=97 (95.1)	25 (25.8)	43 (44.3)	27 (27.8)	2 (2.1)
	Died n=5 (4.9)	1 (20.0)	2 (40.0)	2 (40.0)	0 (0.0)

Abbreviations: HAPS – Harmless Acute Pancreatitis Score

Table 15. CTSI score according to necrosis, needs for interventions and outcomes

CTSI		0	1	2	3	4	5	6	7	8	9	10
Pancreatic and peripancreatic necrosis n(%)	**No.** n=32 (31.4)	4 (12.5)	2 (6.3)	25 (78.1)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Yes. n=70 (68.6)	0 (0.0)	0 (0.0)	0 (0.0)	6 (8.6)	5 (7.2)	14 (20.0)	30 (42.9)	2 (2.9)	8 (11.4)	1 (1.4)	4 (5.7)
Interventions n(%)	**No.** n=92 (90.2)	4 (4.3)	2 (2.2)	25 (27.2)	7 (7.6)	5 (5.4)	12 (13.0)	27 (29.4)	2 (2.2)	4 (4.3)	1 (1.1)	3 (3.3)
	Yes. n=10 (9.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (20.0)	3 (30.0)	0 (0.0)	4 (40.0)	0 (0.0)	1 (10.0)
Outcomes n(%)	**Survived** n=97 (95.1)	4 (4.1)	2 (2.1)	25 (25.8)	7 (7.2)	5 (5.2)	14 (14.4)	27 (27.8)	2 (2.1)	8 (8.2)	1 (1.0)	2 (2.1)
	Died n=5 (4.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (60.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (40.0)

Abbreviations: CTSI – Computed Tomography Severity Index

Table 16. MCTSI score according to necrosis, needs for interventions and outcomes

MCTSI		0	2	4	6	8	10
Pancreatic and peripancreatic necrosis n(%)	**No.** n=32 (31.4)	4 (12.5)	16 (50.0)	11 (34.4)	1 (3.1)	0 (0.0)	0 (0.0)
	Yes. n=70 (68.6)	0 (0.0)	0 (0.0)	0 (0.0)	13 (18.6)	42 (60.0)	15 (21.4)
Interventions n(%)	**No.** n=92 (90.2)	4 (4.3)	16 (17.4)	11 (12.0)	14 (15.2)	37 (40.2)	10 (10.9)
	Yes. n=10 (9.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (50.0)	5 (50.0)
Outcomes n(%)	**Survived** n=97 (95.1)	4 (4.1)	16 (16.5)	11 (11.4)	14 (14.4)	39 (40.2)	13 (13.4)
	Died n=5 (4.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (60.0)	2 (40.0)

Abbreviations: MCTSI – Modified Computed Tomography Severity Index

Table 17. BISAP, CTSI and MCTSI can predict necrosis

Score	AUC	p value*	95% CI	Cut-off	Sensitivity, %	Specificity, %	PPV	NPV
BISAP	**0.76**	**3.44E-06***	**0.6768-0.8496**	**2**	**84.4**	**62.9**	**89.8**	**50.9**
HAPS	0.66	**0.004562***	0.558-0.7616	2	87.5	38.6	87.1	39.4
CTSI	**1.00**	**2.20E-16***	**0.9958-1**	**3**	**96.9**	**100.0**	**98.6**	**100.0**
MCTSI	**1.00**	**2.20E-16***	**0.9912-1**	**5**	**96.9**	**100.0**	**98.6**	**100.0**

*Hypothesis H0: AUC=0.5

**Significant in bold

Abbreviations: BISAP – Bedside Index of Severity in Acute Pancreatitis; HAPS – Harmless Acute Pancreatitis Score; CTSI – Computed Tomography Severity Index; MCTSI – Modified Computed Tomography Severity Index; AUC – Area Under the Curve; CI – Confidence Interval; PPV – Positive Predictive Value; NPV - Negative Predictive Value

Table 18. BISAP, CTSI and MCTSI can predict interventions

Score	AUC	p value*	95% CI	Cut-off	Sensitivity, %	Specificity, %	PPV	NPV
BISAP	**0.85**	**5.81E-05***	**0.7216-0.9686**	**3**	**84.8**	**70.0**	**33.3**	**96.3**
HAPS	**0.77**	**0.00136***	**0.6469-0.8955**	**2**	**73.9**	**70.0**	**22.6**	**95.8**
CTSI	**0.80**	**0.0007223***	**0.6851-0.9192**	**5**	**46.7**	**100.0**	**16.9**	**100.0**
MCTSI	**0.82**	**0.0001236***	**0.722-0.9139**	**8**	**48.9**	**100.0**	**17.5**	**100.0**

*Hypothesis H0: AUC=0.5

**Significant in bold

Abbreviations: BISAP – Bedside Index of Severity in Acute Pancreatitis; HAPS – Harmless Acute Pancreatitis Score; CTSI – Computed Tomography Severity Index; MCTSI – Modified Computed Tomography Severity Index; AUC – Area Under the Curve; CI – Confidence Interval; PPV – Positive Predictive Value; NPV - Negative Predictive Value

Table 19. BISAP, CTSI and MCTSI can predict mortality

Score	AUC	p value*	95% CI	Cut-off	Sensitivity, %	Specificity, %	PPV	NPV
BISAP	**0.87**	**0.0001697***	**0.715-1**	**4**	**99.0**	**60.0**	**75.0**	**98.0**
HAPS	0.55	0.701*	0.2867-0.8205	2	70.1	40.0	65,0	95.8
CTSI	**0.83**	**0.003524***	**0.6979-0.966**	**6**	**58.8**	**100.0**	**11.1**	**100.0**
MCTSI	**0.77**	**0.01837***	**0.633-0.9113**	**8**	**46.4**	**100.0**	**8.8**	**100.0**

*Hypothesis H0: AUC=0.5

**Significant in bold

Abbreviations: BISAP – Bedside Index of Severity in Acute Pancreatitis; HAPS – Harmless Acute Pancreatitis Score; CTSI – Computed Tomography Severity Index; MCTSI – Modified Computed Tomography Severity Index; AUC – Area Under the Curve; CI – Confidence Interval; PPV – Positive Predictive Value; NPV - Negative Predictive Value

CONCLUSIONS

1. The comprehensive literature review has shown that adipokines are potential markers of AP severity and complications, but their predictive possibilities are not explored enough.
2. Higher BMI and the peripancreatic necrosis (cut-off value 112.5 ml) are associated with more severe AP cases.
3. Adiponectin and leptin are not useful markers for AP severity, necrosis, need for interventions and mortality prediction.

4. Resistin and IL-6 cut-off values 13.7 ng/ml and 473.4 pg/ml could be used as early markers of severe AP. The IL-6 cut-off value 157.0 pg/ml predicts necrosis. None of explored markers could be used for early prediction of interventions and mortality.
5. BISAP score is more universal and earlier for AP course, necrosis, need for interventions and mortality prediction than adipokines, IL-6 and CRP.

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EDUCATION	
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1997-2003	Master degree in Medicine, Faculty of Medicine, Vilnius University.
1997	Vilnius “Radvilų” secondary school.

SANTRAUKA

Darbo tikslas

Disertacijos tikslas yra įvertinti laboratorinių uždegimo žymenų reikšmę ankstyvam ūminio pankreatito sunkumo prognozavimui bei palyginti ją su jau naudojamomis prognozinėmis sistemomis, kuriomis remiantis būtų galima prognozuoti ūminio pankreatito eigą, komplikacijas bei mirštamumą;

Darbo uždaviniai:

1. Atlikti ir publikuoti sisteminę literatūros apžvalgą apie adipokinų prognozines galimybes sergant ŪP;
2. Įvertinti nutukimo bei peripankreatinės nekrozės įtaką ŪP eigai;
3. Nustatyti laboratorinius uždegimo žymenis, padedančius prognozuoti ūminio pankreatito eigą, kasos ir peripankreatinių audinių nekrozę, intervencijas bei mirštamumą ankstyvajame ligos laikotarpyje;
4. Palyginti tiriamųjų laboratorinių žymenų bei jau naudojamų prognozinių sistemų galimybes.

Darbo naujumas

Adipokinų prognozinės galimybės tyrinėjant ŪP pastebėtos prieš keliolika metų. 2002-2007 metais publikuotos studijos, tyrusios žiurkes, nustatė statistiškai reikšmingus leptino koncentracijų skirtumus tarp kontrolinės ir ŪP grupių bei tarp ūmaus edeminio ir ūmaus nekrozinio pankreatito grupių. Klinikinės studijos taip pat pradėtos 2002 metais, kai buvo nustatyti statistiškai reikšmingi leptino koncentracijų skirtumai tarp kontrolinės ir ŪP grupių. 2007 metais analogiška studija įrodė tą patį skirtumą tirdama resistiną. 2009 metais buvo įrodyta adiponektino prognozinė vertė nustatant SŪP. 2006-2010 metais publikuotos studijos nustatė, jog resistinas ir visfatinas gali būti naudojami SŪP prognozavimui, o jų koncentracijos koreliuoja su intervencijų poreikiu bei ligos išeitimis. 2012-2014 metais buvo nustatyta, jog ir leptino koncentracija statistiškai reikšmingai skiriasi LŪP ir SŪP grupėse, o resistino – ŪP bei kontrolinėje grupėje, tačiau statistiškai reikšmingų skirtumų tarp LŪP ir SŪP grupių nerasta.

Taigi, nors bendras adipokinų prognozines savybes tyrusių studijų skaičius atrodo nemažas, tačiau didžioji jų dalis – tai nedidelių imčių, dažnai be kontrolinių

grupių ir standartizuoto ištyrimo atlikti darbai, tiriantys atskirų adipokinų prognozines galimybes. Studijos labai heterogeniškos, be to neatitinka šiuolaikinės ŪP sampratos, diagnostikos bei ligos eigos sunkumo kriterijų, o SŪP dažniausiai buvo nustatomas remiantis netiesioginiais požymiais.

Paskutiniais metais pasirodė nemažai publikacijų apie nutukimo bei kūno masės indekso (KMI) įtaką ŪP eigai. Manoma, jog nutukusiems pacientams vystosi ryškesnis sisteminio uždegiminio atsako sindromas (SUAS), kas įtakoja sunkesnę ŪP eigą ir blogesnes išeitis. Taip pat pastebėta, jog peripankreatinių riebalų nekrozė sukelia poliorganinį nepakankamumą ir didina mirtingumą, nepriklausomai nuo to, ar pacientui yra kasos nekrozė ar ne. Kadangi adipokinai gaminami riebaliniame audinyje, peripankreatinė nekrozė turėtų sukelti didelio jų kiekio atsipalaidavimą į paciento kraują. Todėl galima spėti, jog jie galėtų būti peripankreatinės nekrozės, o tuo pačiu ir SŪP prognoziniai žymenys. Tai iš dalies patvirtina ir 2015 metais publikuota studija, kuri įrodė, jog 100 ml peripankreatinės nekrozės tūris gali būti siejamas su SŪP. Adipokinų ir peripankreatinės nekrozės ryšį netiesiogiai tyrė ir vokiečių mokslininkų grupė, vadovaujama A. Schaffler. Tačiau šių studijų metodika kelia abejonių, nes nekrozių tūriai skaičiuoti nebuvo, o vertinimui naudotos tam tikros nespecifinės radiologinės skalės.

Kiek geriau ištyrinėta interleukino-6 (IL-6) prognozinė vertė. Daugelyje pasaulinių pankreatologijos centrų jis naudojamas rutiniškai ir pasižymi geromis prognozinėmis savybėmis prognozuojant tiek ligos eigą, tiek kasos bei peripankreatinę nekrozę, intervencijas ir mirštamumą. Publikacijų gausa bei jose pateikiami panašūs rezultatai įrodo, kad IL-6 jau gali būti laikomas vienu iš rutininių prognozinių žymenų. Tačiau nereikia pamiršti, jog dauguma studijų, kaip ir adipokinų atveju, buvo atlikta iki 2012 metų, kuomet pasikeitė ŪP klasifikacija bei SŪP kriterijai „sugriežtėjo“. Todėl natūralu, jog anksčiau nustatytos kritinės prognostinės IL-6 reikšmės turi pasikeisti.

Ginamieji teiginiai:

1. Didesnis KMI ir peripankreatinės nekrozės tūris gali būti siejami su sunkesne ŪP eiga.
2. IL-6 ir resistinas yra potencialūs ankstyvi ŪP eigos žymenys.

3. Adipokinai, IL-6 ir CRB neprilygsta BISAP prognozinei sistemai universalumu, prognozuojant ūmaus pankreatito eigą, kasos ir peripankreatinės nekrozės išsivystymą, intervencijas bei mirštamumą.

Darbo metodologija

Sisteminės literatūros apžvalgos metodika

Sisteminė literatūros apžvalga parengta laikantis PRISMA pareiškime pateiktų rekomendacijų. Buvo atlikta paieška PubMed duomenų bazėje, apimanti dešimties metų laikotarpį (2002-2012). Norint įvertinti įtrauktų į apžvalgą studijų kokybę buvo naudojamas QUADAS pasiūlytas instrumentas. Dėl didelio į apžvalgą įtrauktų studijų heterogeniškumo, nevienodų diagnostikos kriterijų bei skirtingų vertinimų teko atsisakyti statistinio duomenų apdorojimo ir metaanalizės.

Perspektyvinio daugiacentrio kohortinio tyrimo metodika

Tyrimui atlikti 2012 m. kovo 26 d. gautas Lietuvos bioetikos komiteto leidimas Nr. L-12-02/1/2/3/4.

Įtraukimo į tyrimą kriterijai:

- Skubios pagalbos skyriuje patvirtinta ūminio pankreatito diagnozė (tipiniai skausmai viršutinėje pilvo dalyje, bei α-amilazės kiekis kraujyje tris kartus viršijantis normą).
- Sergantys ne ilgiau kaip 72 val.
- Amžius nemažiau kaip 18 metų.

Atmetimo kriterijai:

- Nėštumas
- Patvirtintas lėtinis pankreatitas
- Anamnezėje persirgtas ūminis nekrozinis pankreatitas

Į tyrimą įtraukti ir sąlyginai sveiki savanoriai (kontrolinė grupė), anamnezėje nesirgę ūminiu pankreatitu, neturintys sunkios lydinčios patologijos ir ne jaunesni nei 18 metų.

Tyrimai ir diagnostika:

Hospitalizavus sutinkantį dalyvauti tyrime pacientą, per pirmas 24 val. nuo hospitalizavimo buvo paimtas tyrimas adiponektino, leptino, resistino, visfatino ir IL-6 koncentracijoms kraujo serume nustatyti. Remiantis anamneze, objektyvaus ištyrimo duomenimis bei rutininiais tyrimais, paciento būklė įvertinta pagal SOFA, HAPS ir BISAP skales, apskaičiuojant surinktus balus. Praėjus 48-72 val. po hospitalizavimo (3-ią parą), ūminiu pankreatitu sergantiems pacientams buvo kartojami kraujo tyrimai adiponektino, leptino, resistino, visfatino ir IL-6 koncentracijoms nustatyti. Paciento būklė dar kartą įvertinta remiantis SOFA skale. 3-7-ą susirgimo parą visiems pacientams buvo atliekama pilvo organų kompiuterinė tomografija su i/v kontrastavimu. Jei pacientui buvo atliktas perkutaninis drenažas ar kita chirurginė intervencija – fiksuota data, intervencijos tipas bei pašalintų nekrozių masė. Fiksuota ir ligos baigtis – išgyveno ar mirė.

Remiantis surinktais klinikiniais duomenimis - t.y. organų nepakankamumo trukme, lokalių ir sisteminių komplikacijų buvimu – visi į tyrimą įtraukti pacientai retrospektyviai buvo suskirstyti į tris grupes – lengvos, vidutinio sunkumo bei sunkios eigos ŪP.

Laboratorinė dalis

VUL“SK“ Laboratorinės medicinos centre pacientų kraujo serumo mėginiai adipokinams buvo saugojami šaldiklyje, išlaikant pastovų -20^{0}C režimą. Tyrimai buvo atliekami etapais, t.y. surinkus pakankamą jų kiekį imunofermentiniam metodui (ELISA - Enzyme-Linked ImmunoSorbent Assay).

Radiologija

Kompiuterinės tomografijos tyrimai ŪP sergantiems pacientams buvo atlikti 3-7-ą susirgimo parą, ir, jei reikėjo, 2-3-ią ligos savaitę. Skaitmeninės laikmenos su pacientų KT vaizdais buvo perduotos dviem, vienas nuo kito nepriklausomiems, skirtingose įstaigose dirbantiems gydytojams radiologams. Radiologai vertino galimas nekrozes kasoje, peripankreatines skysčio sankaupas, ekstrapankreatines komplikacijas. Po to buvo apskaičiuoti CTSI ir MCTSI skalių balai bei pamatuoti peripankreatinių skysčio sankaupų matmenys.

Rezultatų vertinimas, statistika

Statistinė analizė atlikta naudojant statistikos R v. 3.2.0 paketą. ROC kreivių, ploto po ROC kreivėmis (AUC) ir optimalių kritinių reikšmių apskaičiavimui naudotas R paketo įskiepis pROC. Disertacijoje skirtumai tarp rodiklių duomenų skirstinių ar parametrų nagrinėjami kaip reikšmingi, jeigu p reikšmė buvo mažesnė už reikšmingumo lygmenį 0,05.

Tyrimo rezultatai:

Sisteminės literatūros apžvalgos rezultatai

Buvo analizuotos devynios studijos su žmonėmis ir trys eksperimentinės studijos su gyvūnais. Visos eksperimentinės studijos nustatė statistiškai reikšmingus leptino koncentracijos skirtumus tarp kontrolinės ir ŪP grupių. Viena studija ŪP grupę skirstė į ūmaus edeminio ir ūmaus nekrozinio pankreatito pogrupius. Po 12 valandų leptino koncentracijos statistiškai reikšmingai skyrėsi tarp kontrolės ir nekroziniu ŪP sirgusių žiurkių. Po 24 ir 48 valandų statistiškai reikšmingi skirtumai išryškėjo tarp kontrolinės grupės ir edeminiu bei nekroziniu ŪP sirgusių žiurkių. Dėl didelio klinikinių studijų heterogeniškumo, skirtingos metodologijos bei naudojamų terminų juos apibendrinti sunku, tačiau galima pasakyti, kad leptino ir resistino koncentracijos statistiškai reikšmingai skyrėsi kontrolinėje ir ŪP grupėse. Adiponektino, resistino ir visfatino koncentracijos statistiškai reikšmingai skyrėsi LŪP ir SŪP grupėse. Resistino ir visfatino koncentracijos teigiamai koreliavo su poreikiu intervencijoms, mirštamumu, taip pat buvo statistiškai patikimi peripankreatinės ir kasos nekrozės prognoziniai žymenys.

Perspektyvinio daugiacentrio kohortinio tyrimo rezultatai

Tiriamųjų charakteristika

Tyrime dalyvavo 102 asmenys, sirgę ūminiu pankreatitu ir atitikę įtraukimo į tyrimą kriterijus. Pagal atnaujintą Atlantos klasifikaciją LŪP sirgo 27 (26,5%), VSŪP – 55 (53,9%) ir SŪP – 20 (19,6%) pacientų.

Vilniaus miesto klinikinėje ligoninėje buvo įtraukti 54 (52,9%), Vilniaus Universiteto ligoninėje „Santariškių klinikos“ – 21 (20,6%), Respublikinėje Vilniaus

universitetinėje ligoninėje – 15 (14,7%), Lietuvos Sveikatos Mokslų Universiteto ligoninėje „Kauno klinikos“ – 12 (11,8%) pacientų. Iš jų 50 (49,0%) buvo vyrai, 52 (51,0%) – moterys. Vidutinis pacientų amžius – 55,7±18,1 metai, o KMI – 28,6±5,7 kg/m^2.Vidutinė ligos trukmė iki atvykstant į priėmimo skyrių – 20,3±13,8 valandos. 36 (35,3%) sirgo alkoholio sukeltu, 43 (42,2%) – biliariniu, o 23 (22,5%) – kitos etiologijos ŪP.

Detalesnis pacientų pasiskirstymas pagal lytį, etiologiją bei ligos eigą pateiktas 1-oje lentelėje.

1 lentelė. Pacientų pasiskirstymas pagal lytį, etiologiją bei ligos eigą.

	Visi ŪP	**LŪP**	**VSŪP**	**SŪP**
Alkoholinis, n (%) **vyrai/moterys,** **(%)**	36 (100,0) 31/5 (86,1/13,9)	8 (22,2) 7/1 (87,5/12,5)	18 (50,0) 15/3 (83,3/16,7)	10 (27,8) 10/0 (100,0/0,0)
Biliarinis, n (%) **vyrai/moterys,** **(%)**	43 (100,0) 10/33 (23,3/76,7)	13 (30,2) 1/12 (7,7/92,3)	24 (55,8) 7/17 (29,2/70,8)	6 (14,0) 2/4 (33,3/66,7)
Kita, n (%) **vyrai/moterys,** **(%)**	23 (100,0) 9/14 (39,1/60,9)	6 (26,1) 3/3 (50,0/50,0)	13 (56,5) 5/8 (38,5/61,5)	4 (17,4) 1/3 (25,0/75,0)
Viso, n (%) **vyrai/moterys,** **(%)**	102 (100,0) 50/52 (49,0/51,0)	27 (26,5) 11/16 (40,7/59,3)	55 (53,9) 27/28 (49,1/50,9)	20 (19,6) 13/7 (65,0/35,0)

ŪP – ūminis pankreatitas; LŪP – lengvas ūminis pankreatitas; VSŪP – vidutinio sunkumo ūminis pankreatitas; SŪP – sunkus ūminis pankreatitas

ŪP be kasos nekrozės sirgo 42 (41,2%), o nekroziniu ŪP – 60 (58,8%) tiriamųjų. Peripankreatinė nekrozė neišsivystė 35 (34,3%), ji nustatyta 67 (65,7%) pacientų.

Konservatyviai gydyti 92 (90,2%) pacientai, o intervencijos dėl ŪP atliktos – 10 (9,8%) pacientų. Iš jų 3 (30%) operuoti vieną kartą, 1 (10%) – du kartus, 4 (40%) – keturis kartus, 1 (10%) – penkis kartus ir 1 (10%) – šešis kartus. Vien drenažo kontroliuojant echoskopu užteko 1 (10%) pacientui, 5 (50%) pacientai buvo operuoti atviru būdu, likę 4 (40%) – operuoti po kelis kartus – drenuojant echoskopiškai, laparoskopiškai ir atviru būdu. Vidutinė gydymo trukmė ligoninėje – 20,8±28,3 paros. Išgyveno 97 (95,1%) pacientai, mirė – 5 (4,9%).

Nuo 2015 metų sausio 1d. iki 2015 metų kovo 31 d. į biomedicininį tyrimą buvo įtraukta 40 asmenų, kurie atstojo kontrolinę grupę. Kontrolinė grupė buvo sudaryta iš pacientų, kurie tuo metu buvo hospitalizuoti į Vilniaus miesto klinikinės ligoninės dienos chirurgijos ir abdominalinės chirurgijos skyrius planinėms operacijoms ir, atitiko įtraukimo kriterijus. Iš jų 17 (42,5%) buvo vyrai, 23 (57,5%) – moterys. Vidutinis šių asmenų amžius buvo 54,3±16,1 metai, o KMI 27,9±4,7 kg/m^2.

Ligoniai ir kontrolinės grupės asmenys buvo homogeniški pagal lytį, amžių ir KMI.

KMI ir peripankreatinės nekrozės prognozinė vertė

Buvo lygintos KMI medianos tarp ŪP grupės ir kontrolės, LŪP ir VSŪP, LŪP ir SŪP, VSŪP ir SŪP, LŪP+VSŪP ir SŪP grupių, pacientų su ir be kasos nekrozės, su ir be peripankreatinės nekrozės, su abiejų tipų nekroze ir be jos, operuotų ir neoperuotų, mirusių ir išgyvenusių. Statistiškai patikimi skirtumai buvo gauti tarp LŪP ir SŪP (24,8 ir 31,1 kg/m^2, $p<0,05$) bei LŪP+VSŪP ir SŪP (28,0 ir 31,1 kg/m^2, $p<0,05$) grupių.

Patikrinus hipotezę apie ligos eigos bei kasos ir peripankreatinės nekrozės nepriklausomumą, gauta, kad sunkesnė ligos eiga siejasi su kasos ir peripankreatinės nekrozės nustatymu (Fišerio tikslaus kriterijaus p reikšmė $7,40 \cdot 10^{-18}$). Dėl kai kurių kategorijų itin mažo dažnio detalesnė statistinė analizė neatlikta

Nustatyti statistiškai reikšmingi peripankreatinių nekrozių tūrio medianų skirtumai tarp LŪP, VSŪP ir SŪP grupių. Dėl rodiklių reikšmių išsibarstymo, apskaičiuota koreliacija tarp KMI ir peripankreatinių nekrozių tūrio yra silpna ($r=0,14$, $p>0,05$).

Analizuojant ROC kreives, buvo nustatytos kritinės peripankreatinių nekrozių tūrio reikšmės prognozuojant SŪP, intervencijas ir mirštamumą. Statistiškai patikimi rezultatai gauti prognozuojant SŪP (112,5 ml, jautrumas 61,0%, specifiškumas 95,0%, AUC 0,80) bei poreikį intervencijoms (433,0 ml, jautrumas 68,5%, specifiškumas 100%, AUC 0,87).

Tiriamųjų žymenų galimybės, prognozuojant ŪP eigą

Braižant ROC kreives nustatyta, jog LŪP+VSŪP nuo SŪP statistiškai patikimai atskiria 1-os (473,4 pg/ml, jautrumas 82,9%, specifiškumas 75,0%, AUC 0,80) ir 3-ios paros (119,9 pg/ml, jautrumas 54,9%, specifiškumas 100%, AUC 0,82) IL-6; 1-os

(13,7 ng/ml, jautrumas 63,4%, specifiškumas 80,0%, AUC 0,76) ir 3-ios paros (23,9 ng/ml, jautrumas 79,3%, specifiškumas 85,0%, AUC 0,89) resistinas; 3-ios paros CRB (301,1 mg/ml, jautrumas 70,7%, specifiškumas 80,0%, AUC 0,79).

Tiriamųjų žymenų galimybės prognozuojant kasos bei peripankreatinę nekrozę

Braižant ROC kreives nustatyta, jog pacientus su kasos ir peripankretine nekroze nuo pacientų be nekrozės statistiškai patikimai atskiria 1-os (157,0 pg/ml, jautrumas 75,0%, specifiškumas 67,1%, AUC 0,72) ir 3-ios paros (164,2 pg/ml, jautrumas 90,6%, specifiškumas 70,0%, AUC 0,88) IL-6; 3-ios paros resistinas (11,7 ng/ml, jautrumas 87,5%, specifiškumas 81,4%, AUC 0,90); 3-ios paros CRB (143,4 mg/ml, jautrumas 81,3%, specifiškumas 88,6%, AUC 0,92).

Tiriamųjų medžiagų galimybės, prognozuojant intervencijas

Braižant ROC kreives nustatyta, jog prie tam tikrų kritinių verčių 3-ios paros IL-6 (697,1 pg/ml, jautrumas 94,6%, specifiškumas 70,0%, AUC 0,87), resistinas (24,8 ng/ml, jautrumas 76,1%, specifiškumas 100%, AUC 0,92) ir CRB (327,3 mg/ml, jautrumas 72,8%, specifiškumas 90,0%, AUC 0,80) statistiškai patikimai atskiria operuotus ir neoperuotus pacientus.

Tiriamųjų medžiagų galimybės prognozuojant mirštamumą

Braižant ROC kreives nustatyta, jog prie tam tikrų kritinių verčių 3-ios paros IL-6 (458,8 pg/ml, jautrumas 80,4%, specifiškumas 80,0%, AUC 0,84), resistinas (25,9 ng/ml, jautrumas 75,3%, specifiškumas 100%, AUC 0,92) ir CRB (320,0 mg/ml, jautrumas 69,1%, specifiškumas 100%, AUC 0,80) statistiškai patikimai atskiria mirusius pacientus nuo išgyvenusių.

Klinikinių ir radiologinių skalių galimybės, prognozuojant ŪP eigą.

Analizuojant ROC kreives nustatyta, jog BISAP (≥2, jautrumas 64,6%, specifiškumas 100%, AUC 0,91), CTSI (≥6, jautrumas 67,1%, specifiškumas 90%, AUC 0,86) ir MCTSI (≥8, jautrumas 54,9%, specifiškumas 100%, AUC 0,84) skalės yra tinkamos ŪP eigos prognozei ir prie tam tikrų kritinių verčių statistiškai patikimai atskiria SŪP.

Klinikinių ir radiologinių skalių galimybės, prognozuojant kasos bei peripankreatinę nekrozę, intervencijas ir mirštamumą

Analizuojant ROC kreives nustatyta, jog nekrozei prognozuoti yra tinkamos BISAP (≥2, jautrumas 84,4%, specifiškumas 62,9%, AUC 0,76), CTSI (≥3, jautrumas

96,9%, specifiškumas 100%, AUC 1,00) ir MCTSI (≥5, jautrumas 96,9%, specifiškumas 100%, AUC 1,00) skalės. Intervencijoms prognozuoti galima naudoti BISAP (≥3, jautrumas 84,8%, specifiškumas 70,0%, AUC 0,85), CTSI (≥5, jautrumas 46,7%, specifiškumas 100%, AUC 0,80) ir MCTSI (≥8, jautrumas 48,9%, specifiškumas 100%, AUC 0,82) skalės. Mirštamumui prognozuoti tinka BISAP (≥4, jautrumas 99,0%, specifiškumas 60,0%, AUC 0,87), CTSI (≥6, jautrumas 58,8%, specifiškumas 100%, AUC 0,83) ir MCTSI (≥8, jautrumas 46,4%, specifiškumas 100%, AUC 0,77) skalės.

Išvados:

1. Sisteminė literatūros apžvalga parodė, jog adipokinai yra potencialūs ŪP eigos ir komplikacijų žymenys, tačiau jų prognozinės galimybės ištirtos nepakankamai.
2. Didesnis KMI ir peripankreatinė nekrozė (kritinė vertė 112,5 ml) gali būti siejama su sunkesne ŪP eiga.
3. Adiponketinas ir leptinas yra netinkami prognoziniai žymenys ŪP eigai, kasos ir peripankreatinei nekrozei, intervencijoms bei mirštamumui prognozuoti.
4. IL-6 (kritinė vertė 473,4 pg/l) ir resistinas (kritinė vertė 13,7 ng/l) yra potencialūs ankstyvi SŪP, o IL-6 (kritinė vertė 157,0 pg/ml) dar ir nekrozės (kasos ir peripankreatinės) žymenys. Nei vienas tirtas žymuo netinkamas ankstyvam intervencijų ir mirštamumo prognozavimui.
5. Adipokinai, IL-6 ir CRB neprilygsta BISAP prognozinei sistemai, kuri yra universalesnė ir ankstyvesnė prognozuojant ūmaus pankreatito eigą, kasos ir peripankreatinės nekrozės išsivystymą, intervencijas bei mirštamumą.

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