ORIGINAL ARTICLE

UDC: 616.37-002.1-036
https://doi.org/10.2298/ VSP160227100S

Clinical and laboratory parameters associated with death in acute pancreatitis

Klinički i laboratorijski parametri povezani sa smrtnim ishodom kod akutnog pankreatitisa

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Abstract

Background/Aim. Acute pancreatitis is an inflammatory condition having the significant mortality rate in the case of severe forms of the disease. The aim of this study was to investigate putative factors of increased mortality in patients with acute pancreatitis with contradictory prior evidence, and to reveal factors that were insufficiently explored previously. **Methods.** This prospective cohort study with nested case/control design included all adult patients treated for acute pancreatitis in the Clinical Center of Kragujevac, Serbia, during the 3-year period (from October 2011 to December 2014). The cases (n = 19) were patients who died, while the controls (n = 113) were patients who survived. The associations between putative risk factors and the study outcomes were tested by univariate and multivariate logistic regressions, and expressed as crude and adjusted odds ratios (OR) with corresponding 95% confidence intervals (CI). **Results.** Significant association with the lethal outcome in acute pancreatitis was found for advanced age (adjusted OR 1.12, 95%CI 1.02–1.23), presence of significant comorbidities (adjusted OR 10.62, 95%CI 1.01–111.39), higher interleukin-8 (IL-8) value on third day from onset of symptoms (adjusted OR 1.05, 95%CI 1.02–1.08), use of tramadol and/or morphine (adjusted OR 47.34, 95%CI 3.21–699.08), the Bedside index for severity in acute pancreatitis (BISAP) score ≥ 3 in the first 24 hours (adjusted OR 48.11, 95%CI 3.14–736.29), and prophylactic use of antibiotics (adjusted OR 0.07, 95%CI 0.01–0.85). **Conclusion.** Advanced age, significant comorbidities, use of tramadol and/or morphine and more severe disease as assessed by BISAP score can increase the risk of death in acute pancreatitis, while prophylactic use of antibiotics may have a protective role.

Key words:
pancreatitis; mortality; age factors; comorbidity; analgetics, opioid; severity of illness index; antibiotic prophylaxis.

Apstrakt

Uvod/Cilj. Akutni pankreatitis je zapaljenska bolest koja je u slučaju ispoljavanja teških oblika bolesti povezana sa visokom stopom smrtnosti. Cilj ove studije bio je da ispita faktore za koje postoje oprečni literaturni podaci o povezanosti sa povećanom smrtnošću kod bolelsnika sa akutnim pankreatitisom, kao i one faktore koji prethodno nisu dovoljno ispitivani. **Metode.** Ova prospektivna kohortna studija sa usađenom studijom tipa slučaj/kontrola, obuhvatila je sve bolesnike lečene zbog akutnog pankreatitisa u Kliničkom centru Kragujevac, Srbija, tokom trogodišnjeg perioda (od oktobra 2011. do decembra 2014. godine). Slučajevi (n = 19) bili su bolesnici koji su umrli, dok su kontrolnu grupu (n = 113) činili bolesnici kod kojih nije zabeležen smrtni ishod. Povezanost između pretpostavljenih faktora rizika i opserviranog ishoda ispitivana je pomoću univarijante i multivarijantne logističke regresione analize, a rezultati su prikazani vrednostima sirovog i korigovanog unakrsnog odnosa šansi (*odds ratio* – OR) sa pripadajućim 95% intervalom poverenja (*confidence interval* – CI). **Rezultati.** Značajna povezanost sa smrtnim ishodom kod akutnog pankreatitisa nađena je za starije životno doba bolesnika (korigovani OR 1,12, 95%CI 1,02–1,23), prisustvo značajnog komorbiditeta (korigovani OR 10,62, 95%CI

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1,01–111,39), povišene vrednosti interleukina (IL)-8 trećeg dana od početka bolesti (korigovani OR 1,05 95%CI 1,02, 1,08), primenu tramadola i/ili morfina (korigovani OR 47,34, 95%CI 3,21–699,08), *Bedside index for severity in acute pancreatitis* (BISAP) skor ≥ 3 u prvih 24 sata (korigovani OR 48,11, 95%CI 3,14–736,29), kao i za profilaktičku primenu antibiotika (korigovani OR 0,07, 95%CI 0,01–0,85). **Zaključak.** Starije životno doba, značajan komorbiditet, primena tramadola i/ili morfina i teži oblik bolesti procenjen BISAP skorom mogu povećati rizik od nastanka smrtnog ishoda kod bolesnika sa akutnim pankreatitisom, dok profilaktička primena antibiotika može imati zaštitnu ulogu.

Ključne reči:
pankreatitis; mortalitet; životno doba, faktori; komorbiditet; analgetici, opioidni; bolest, indeks težine; antaibiotici, profilaksa.

Introduction

Acute pancreatitis (AP) is an inflammatory condition with various clinical presentations ranging from mild to severe forms of the disease. The dominant pathological substrate of this disease is an acute inflammation which is usually not followed by fibrosis [1]. The incidence of AP all over the world ranges from 5 to 80 cases *per* 100,000 [2] and it is growing, e.g. in the United Kingdom with 2.7% yearly rate. The largest increase in incidence was noted in women younger than 35, and in men between 35 and 44 years of age [3].

Mortality in acute pancreatitis depends on the severity of the disease, being less than 1% in a mild form and 10–30% in severe forms [4]. Factors previously associated with greater severity of the disease and/or higher mortality rate are: levels of C-reactive protein (CRP), procalcitonin (PCT) and cytokines [interleukin (IL)-8, tumor necrosis factor-alpha (TNF-α), IL-6], acute phase proteins [5], and acute kidney injury [6]. Among the 27 possible risk factors investigated in one study, arterial pH, acute physiology and chronic health evaluation II (APACHE II) [7] scores, early shock, and multiple organ failures were associated with mortality [8]. Patients with the bedside index of severity in acute pancreatitis (BISAP) [9] and Ranson's [10] scores equal or higher than 3 had a significantly higher likelihood of mortality [11], as well as early surgery, advanced age, and sterility of tissue cultures [12]. On the other side, lower mortality was observed in patients with: higher values of serum calcium [13], in those who received fewer antibiotics and less amount of parenteral fluid [14], then in patients who started early enteral nutrition within the first 72 hours of the onset of symptoms [15].

Despite relatively large number of studies that have examined risk factors for mortality in AP, there are still disagreements in terms of the following factors: use of antibiotic prophylaxis [16–18], type of nutritional support and beginning of nutritional support since the onset of symptoms [15], amount and type of fluids administered for resuscitation [14], serum level of IL-8 and IL-6 during the first day after onset of symptoms [19–21], the accuracy of prognostic scores in predicting severity and/or death in patients with AP [22, 23], as well as age of a patient [24]. These controversies arise from the heterogeneity of methodological approaches in prior studies that consequently led to inconsistent results [14–24].

The aim of our study was to investigate putative factors of increased mortality in patients with AP contradictory prior evidence and to reveal factors that were insufficiently explored previously.

Methods

This study was of prospective cohort type, with nested case/control design. The cohort was composed of all patients with acute pancreatitis who were admitted to the Intensive Care Unit (ICU) of the Clinical Center Kragujevac Serbia from October 2011 to December 2014, providing that they fulfilled inclusion criteria: all patients with diagnosis of AP based on two of the three following criteria: abdominal pain characteristic of AP, serum amylase and/or lipase ≥ 3 times the upper limit of normal, and characteristic findings of AP on Computed tomography (CT) scan. The exclusion criteria were: patients with acute postoperative pancreatitis, pregnant women with AP, patients transferred from other hospitals or other wards to the ICU of the Clinical Center Kragujevac more than 48 hours after the admission, as well as those under 18 years of age. The cases were patients who died and controls all the other patients who were enrolled in the study.

After admission, the patients signed an informed consent and then were treated according to preferences of the responsible physician. Blood samples for measurements of laboratory parameters were taken within the first 24 hours of admission at our department and on the 3rd day of hospitalization, and then according to the requests of responsible physicians. There were no patients who were diagnosed with AP between 24 and 48 hours after the admission. The following laboratory parameters were measured: glucose, urea, creatinine, bilirubin, aminotransferase, alkaline phosphatase, amylase, lipase, lactate dehydrogenase, total protein, albumin, sodium, potassium, calcium, chloride, CRP, PCT, fibrinogen, bicarbonates, pH levels, base excess, the partial pressure of oxygen and carbon dioxide in the arterial blood, erythrocyte sedimentation rate, hematocrit, erythrocyte, leukocyte and platelet counts, leukocyte formula, triglycerides and cholesterol levels. All measurements except that of cytokines were made in the Central Laboratory of the Clinical Center Kragujevac, by competent specialists of biochemistry, independent from the study investigators. Serum levels of cytokines were measured in the following way: blood was collected following patient enrollment in the study within 24 hours from the onset of pain (1st day of admission) and on the third day of the disease course.

The blood clot was centrifuged for separating the serum and then all serum samples were kept at -20°C before measurement. Serum levels of cytokines TNF-alfa, epidermal growth factor (EGF), IL-6, IL-8, and IL-10 were measured using sensitive enzyme-linked immunosorbent assay (ELISA) kits specific for humans (R&D Systems, Minneapolis, MN) in the Center for Molecular Medicine and Stem Cell Research, the Faculty of Medical Sciences, the University of Kragujevac. We determined serum levels of cytokines using appropriate DuoSets (R&D Systems, Minneapolis, MN, USA): TNF-alfa (TNF-alfa: catalog number DY210; range of detection 15.6–1.000 pg/mL), EGF (EGF: catalog number DY236; range of detection 3.91–250 pg/mL), IL-6 (IL-6: catalog number DY206; range of detection 9.38–600 pg/mL, IL-8 (IL-8: catalog number DY208; range of detection 31.2–2,000 pg/mL) and IL-10 (IL-10: catalog number DY217B; range of detection 31.2–2,000 pg/mL). All samples with the cytokine levels above the range of detection of the assay used were diluted five times by adding phosphate buffer saline (PBS). Any of invasive diagnostic or therapeutic procedure which could affect the serum levels of these cytokines was not performed during the period when they had been measured. These cytokines were chosen given that they were strong mediators of a complex immune response having the crucial role in the pathophysiology of systemic pro- and anti-inflammatory response in AP.

The following demographic and clinical characteristics of the study patients were recorded: age and gender of the patient, body mass index, etiology of AP, alcohol consumption, smoking, prophylactic use of antibiotics, use of nonsteroidal anti-inflammatory drugs, use of other drugs, nutrition, artificial ventilation, severity of AP, systemic inflammatory response syndrome (SIRS), multiorgan dysfunction, the values of the vital parameters (blood pressure, heart and respiratory rate, blood oxygen saturation, body temperature), the values of Sepsis-related Organ Failure Assessment (SOFA) [25] score, APACHE II score, Ranson's score, modified Glasgow score, and BISAP score, evaluation of disease severity based on the findings of computed tomography – Balthazar's [26] score, radiological examinations of the chest, and comorbidities.

In order to define the severity of the disease course in this study, the original 1992 Atlanta classification of AP was used since the study started before the revision of these criteria in 2012 [27]. The severity of AP was defined according to criteria referring to the development of organ failure and/or local complications such as acute fluid collections, pancreatic necrosis, or pancreatic abscess, as well as initial Ranson's score 3 or higher or an APACHE II score 8 or higher. Organ failure and systemic complications were diagnosed if they occurred during the first 7 days from the onset of abdominal pain, lasted for more than 48 hours and included at least one of the following: hypovolemic shock (systolic blood pressure < 90 mmHg after fluid replacement), respiratory insufficiency (PaO_2 < 8 kPa), renal failure [blood creatinine level > 177 μmol/mL (2 mg/dL)], disseminated intravascular coagulation, or gastrointestinal bleeding (> 500 mL/24 hours). We used organ failure lasting for more than 48 hours as a strong confounding variable in order to assess the influence of other factors on the observed outcome.

The study was approved by the Ethics Committee of the Clinical Center Kragujevac, on September 1, 2011, (No 01-9024).

Statistics

The data were at first described by descriptive statistics, using measures of central tendency (median), variability (interquartile range, minimum and maximum values) and relative numbers. The significance of differences in values of continuous variables between the study groups was tested by Mann-Whitney test. The significance of difference in categorical variables between the study groups was tested by χ^2 test or Fisher's test (when values in some cells of contingency tables were lower than 5 or zero). The differences were considered significant if the probability of null hypothesis was below 0.05. Associations between putative risk factors and the study outcomes were tested by univariate and multivariate logistic regressions (using the stepwise approach with backward deletion, with removing all variables with $p \geq 0.1$), and expressed as crude and adjusted odds ratios. As we focused on various factors with inconsistent relevance according to prior studies or which were insufficiently examined previously, in multivariate logistic regression we also included those which had been found to have an insignificant association with death from AP in univariate analysis. All calculations were performed by the SPSS (Statistical Package for Social Science for Windows) software, version 20.

Results

A total of 132 patients with AP were enrolled in the study, of whom 19 (14.4%) died. Eight (42.1%) of them died within the first two weeks of admission to the ICU. From a total number of patients, 41 (31.1%) developed pancreatic necrosis, and in ten (7.6%) the necrosis was infected. In 22 (16.7%) patients the pancreatic pseudocyst was formed spontaneously. Regarding etiology of AP gallstone was found in 51.4%, alcohol consumption in 25.0%, and other causes in 23.6% of patients. The youngest patient was 23, and the oldest was 86 years old (59.61 ± 14.83). There were 84 (63.6%) men and 48 (36.4%) women. Average body mass index was 27.5 ± 4.5 kg/m^2 which puts our patients in a category of pre-obese.

Tables 1 and 2 show baseline characteristics of patients according to demographic and the majority of the examined clinical characteristics and the majority of the examined laboratory parameters. The differences between the cases and controls were significant in terms of age, severity of AP, organ failure, significant comorbidity, pleural effusion or consolidation of lung parenchyma, cardiovascular disease, blood glucose, urea, creatinine, alkaline phosphatase, LDL cholesterol, total proteins, potassium and albumins, as well as in all scores for predicting severity (SOFA, APACHE II, BISAP, Ranson's, Modified Glasgow and Balthazar's) (Table 3).

Table 1

Demographic characteristics and comorbidities in cases (deceased) and controls (surviving) patients with acute pancreatitis

Variable	Patients		Test value	Crude odds ratios
	cases (n = 19)	controls (n = 113)	*p*	(95%CI)
Age (years), median (IQR), range	75 (67–77) 41–84	60 (48.5–66) 23–86	U = 474.0[1] *p* < 0.001	1.07 (1.01, 1.12)
Body mass index (kg/m^2), median (IQR), range	26.17 (24.6–31) 21.6–35	27.21 (23.9–30) 19.16–42.50	U = 531.5[1] *p* = 0.878	1.02 (0.88, 1.17)
Gender, n (%)				
male	12 (63.2)	72 (63.7)	χ^2 = 0.002	0.96
female	7 (36.8)	41 (36.3)	*p* = 0.963	(0.35, 2.67)
Significant comorbidity, n (%)				
without	3 (15.8)	57 (51.4)*	χ^2 = 8.255	5.63
with	16 (84.2)	54 (48.6)*	*p* = 0.004	(1.55, 20.41)

[1]Mann-Whitney test; χ^2 – Chi-Square test; IQR – interquartile range; CI – confidence interval.
***the number is smaller than 113 for this calculation, since data for some patients were missing.**

Table 2

Clinical and laboratory parameters on admission in cases (deceased) and controls (surviving) patients with acute pancreatitis (AP)

Clinical parameters	Patients		Test value	Crude odds ratios
	cases (n = 19)	controls (n = 113)	*p*	(95%CI)
Severity of AP, n (%)				
mild form	2 (10.5)	76 (67.3)	χ^2 = 21.66	17.46
severe form	17 (89.5)	37 (32.7)	*p* < 0.001	(3.83, 79.58)
Cardiovascular disease, n (%)				
no	7 (36.8)	70 (61.9)		
yes, mild form	9 (47.4)	39 (34.5)	χ^2 = 7.10 *p* = 0.029	2.30 (0.80, 6.68)
yes, severe form	3 (15.8)	4 (3.5)		7.5 (1.39, 40.51)
Pulmonary disease, n (%)				
no	15 (78.9)	106 (93.8)	χ^2 = 4.70	4.03
yes	4 (21.1)	7 (6.2)	*p* = 0.300	(1.05, 15.45)
Pleural effusion or consolidation of lung parenchyma, n (%)				
no	6 (35.3)	67 (70.5)*	χ^2 = 7.89	4.38
yes	11 (64.7)	28 (29.5)*	*p* = 0.005	(1.47, 13.02)
Organ failure, n (%)				
without failure	3 (15.8)	101 (89.4)		
one organ/organ system	8 (42.1)	11 (9.7)	χ^2 = 63.55 *p* < 0.001	24.48 (5.65, 106.02)
more organ/organ system	8 (42.1)	1 (0.9)		269.33 (25.05, 2,895.34)
Laboratory parameters, median (IQR) range				
blood glucose (mmol/L)	9.1 (7.7–11.1) 5.8–17.7	7.4 (6.3–9.6) 3.2–33.6	U = 761.0[1] *p* = 0.043	1.07 (0.96–1.19)
urea (mmol/L)	9.9 (6.8–17.1) 5.6–91.2	5.3 (4.1–7.7) 5–70	U = 368.5[1] *p* < 0.001	1.07 (1.01, 1.13)
creatinine (umol/L)	116 (85–180) 73–1607	83 (70–100) 33–523	U = 499.5[1] *p* < 0.001	1.01 (1.00, 1.02)
alkaline phosphatase (U/L)	61.5 (35.25–87.75) 23–101	77 (56.63–146.13) 26–520	U = 380.5[1] *p* = 0.039	0.97 (0.95, 1.00)
LDL cholesterol (mmol/L)	2.29 (1.62–2.72) 1.33–3.68	2.92 (2.26–3.69) 0.74–6.61	U = 369.0[1] *p* = 0.018	0.51 (0.27, 0.94)
albumines (g/L)	29 (26–36.25) 21–41	35 (31–39) 18–52	U = 537.0[1] *p* = 0.002	0.88 (0.80, 0.96)
potassium (mmol/L)	4.0 (3.67–4.92) 3.3–6.1	3.8 (3.6–4.1) 2.8–5.0	U = 701.5[1] *p* = 0.038	4.42 (1.75, 11.16)
C - reactive protein (mg/L)	220.6 (54.5–310.1) 0.8–460	124.9 (50.1–213.7) 4.6–488	U = 723.0[1] *p* = 0.101	1.00 (1.00, 1.01)
procalcitonin (mg/L)	0.58(0.13–2.43) 0.12–118	0.25(0.12–0.73) 0.05–17.98	U = 588.0[1] *p* = 0.090	1.07 (0.99, 1.11)
hematocrit (%)	40.7 (37–47) 26–51	42.7 (38.1–45.5) 16.9–92.2	U = 975.5[1] *p* = 0.525	0.97 (0.89, 1.04)

[1]Mann-Whitney test; χ^2 – Chi-Square test; IQR – interquartile range; CI – confidence interval; LDL – low-density lipoprotein.
***the number is smaller than 113 for this calculation, since data for some patients were missing.**

Measured levels of cytokines were also associated with fatal outcome (Table 4). The greatest differences between the groups were observed in IL-6 value on the first and third day, IL-8 value on the first and third day, and IL-10 value on the first and third day. Values of TNF-α and EGF were not significantly different among those who died and survived.

Table 3

Scores used to predict the outcome in cases (deceased) and controls (surviving) patients with acute pancreatitis

Score	Patients		Test value	Crude odds ratios
	cases (n = 19)	controls (n = 113)	*p*	(95%CI)
SOFA, median (IQR), range	10.5 (8.75–13) 4–15	8 (7–9) 3–13	U = 469.0[1] *p* = 0.001	1.55 (1.20, 1.99)
SIRS, n (%)	14 (73.7)	27 (23.9)	χ^2 = 18.83 *p* < 0.001	8.92 (2.94, 27.03)
APACHE II, n (%)				
< 8	5 (26.3)	65 (62.5)*	χ^2 = 8.577	4.67
≥ 8	14 (73.7)	39 (37.5)*	*p* = 0.003	(1.56, 13.96)
BISAP, n (%)				
< 3	10 (55.6)	100 (90.9)*	χ^2 = 15.99	8.00
≥ 3	9 (44.4)	10 (9.1)*	*p* < 0.001	(2.57, 24.87)
Ranson's, n (%)				
< 3	7 (36.8)	80 (74.1)*	χ^2 = 10.38	4.89
≥ 3	12 (63.2)	28 (25.9)*	*p* = 0.001	(1.75, 13.67)
Modified Glasgow, n (%)				
< 3	2 (11.8)	65 (60.7)*	χ^2 = 14.17	11.60
≥ 3	15 (88.2)	42 (39.3)*	*p* < 0.001	(2.52, 53.37)
Balthazar's, n (%)				
< 3	5 (27.8)	57 (54.8)*	χ^2 = 4.49	3.15
≥ 3	14 (72.2)	47 (45.2)*	*p* = 0.034	(1.05, 9.48)

[1] Mann-Whitney test; χ^2 – Chi-Square test; CI – confidence interval; LDL – low-density lipoprotein; SOFA – sepsis ffelated organ failure assessment; SIRS – systemic inflammatory response syndrome; APACHE – acute physiology and chronic health evaluation; BISAP – bedside index of severity in acute pancreatitis.

***the number is smaller than 113 for this calculation, since data for some patients were missing.**

Table 4

Serum cytokines concentrations in cases (deceased) and controls (surviving) patients with acute pancreatitis

Cytokines (pg/mL)	Patients		Test value	Crude odds ratios
	cases (n = 19)	controls (n = 113)	*p*	(95%CI)
IL-6, median (IQR), range				
1 day	105.3 (37.5–164.3) 2.1–300	36.9 (13.4–87.9) 0–300	U = 605.0[1] *p* = 0.003	1.01 (1.00, 1.02)
3 day	68.7 (28.8–128.9) 1.3–203.0	26.29 (7.34–64.0) 0–221.2	U = 572.0[1] *p* = 0.003	1.01 (1.00, 1.02)
IL-8, median (IQR), range				
1 day	38.5 (22.1–75.5) 0–380.65	15.98 (0.4–38.4) 0–167.22	U = 607.0[1] *p* = 0.003	1.02 (1.01, 1.03)
3 day	36.0 (0.8–60.8) 0–287.2	0.17 (0–16.3) 0–120.7	U = 490.0[1] *p* < 0.001	1.03 (1.01, 1.04)
IL-10, median (IQR), range				
1 day	32.3 (15.3–76.5) 0–220.50	11.6 (0–2.6) 0–515.7	U = 661.0[1] *p* = 0.008	1.01 (0.99, 1.02)
3 day	17.2 (0–43.10) 0–116.45	0 (0–11.5) 0–258.11	U = 671.0[1] *p* = 0.016	1.01 (0.99, 1.02)
TNF-α, median (IQR), range				
1 day	0.3 (0–6.24) 0–28.0	0 (0–1.2) 0–250	U = 845.0[1] *p* = 0.093	0.99 (0.97, 1.02)
3 day	0 (0–6.4) 0–42.7	0 (0–0) 0–116.7	U = 847.0[1] *p* = 0.156	1.00 (0.97, 1.03)
EGF, median (IQR), range				
1 day	76.1 (52.2–105.7) 14.3–164.1	68.8 (35.7–107.8) 0–550.7	U = 997.5[1] *p* = 0.664	0.99 (0.99, 1.01)
3 day	51.9 (22.6–70.0) 0–104.7	64.8 (29.5–101.4) 0–467.4	U = 775.0[1] *p* = 0.116	0.99 (0.98, 1.00)

[1] Mann-Whitney test; CI – confidence interval; IQR – interquartile range; IL – interleukin; TNF-α – tumor necrosis factor alpha; EGF – epidermal growth factor.

Regarding parameters related to the treatment of patients with AP, Table 5 shows baseline characteristics of cases and controls. It could be seen from Table 5 that there was a significant correlation of certain parameters with the occurrence of fatal outcome, such as: type of solution used for intravenous fluid replacement, type of nutritional support, use of blood and blood derivatives, use of 20% albumin, use of opioid drugs, especially tramadol and/or morphine, and other invasive treatments (drainage, thoracocentesis), as well as the surgical procedure in AP.

Table 5

Treatment options used in cases (deceased) and controls (surviving) patients with acute pancreatitis

Treatment	Patients, n (%)		Test value	Crude odds ratios
	cases (n = 19)	controls (n = 113)	*p*	(95%CI)
Solution used for IV fluid replacement				
crystalloids	6 (31.6)	95 (84.1)	$\chi^2 = 24.94$	11.44
crystalloids and colloids	13 (68.4)	18 (15.9)	$p < 0.001$	(3.84, 34.03)
Amount of solution used for IV fluid replacement				
> 2,000 mL	18 (94.7)	102 (90.3)	$\chi^2 = 0.39$	0.51
< 2,000 mL	1 (5.3)	11 (9.7)	$p = 0.53$	(0.06, 4.24)
Nutritional support				
not required (regular oral food intake restored)	1 (5.3)	40 (35.4)		
total enteral nutrition through nasojejunal tube	1 (5.3)	9 (8.0)		4.45 (0.25, 77.96)
total enteral nutrition through nasogastric tube	5 (26.3)	8 (7.1)	$\chi^2 = 20.40$	25.00 (2.56, 243.75)
combined enteral and parenteral nutrition	6 (31.6)	17 (15.0)	$p = 0.001$	14.12 (1.58, 126.36)
total parenteral nutrition	6 (31.6)	16 (14.2)		15.00 (1.67, 134.70)
without nutritional support although it was indicated	0 (0)	23 (20.4)		0
Use of opioid drugs				
no	2 (10.5)	64 (56.6)		
yes, meperidin	1 (5.3)	8 (7.1)	$\chi^2 = 15.65$	4.00 (0.33, 49.24)
yes, other (tramadol and/or morphine)	16 (84.2)	41 (36.3)	$p < 0.001$	12.49 (2.73, 57.18)
Use of heparine				
no	6 (31.6)	77 (68.1)		
yes, LMWH	12 (63.2)	35 (31.0)	$\chi^2 = 10.25$ $p = 0.006$	4.40 (1.53, 12.68)
yes, standard	1 (5.3)	1 (0.9)		12.83 (0.71, 231.75)
Use of blood and blood derivatives	12 (63.2)	27 (23.9)	$\chi^2 = 12.05$ $p = 0.001$	0.18 (0.06, 0.51)
Use of 20% albumine	16 (84.2)	32 (28.3)	$\chi^2 = 21.96$ $p < 0.001$	0.07 (0.02, 0.27)
Other invasive treatment (drainage, thoracocenthesis)	6 (31.6)	8 (7.1)	$\chi^2 = 10.30$ $p = 0.001$	6.06 (1.81, 20.21)
Use of NSAID	12 (63.2)	91 (80.5)	$\chi^2 = 2.86$ $p = 0.090$	0.41 (0.14, 1.17)
Prophylactic use of antibiotics	11 (57.9)	66 (58.4)	$\chi^2 = 0.002$ $p = 0.967$	0.98 (0.37, 2.62)
Surgical treatment (operation)	7 (36.8)	6 (5.4)	$\chi^2 = 18.02$ $p < 0.001$	3.21 (1.72, 5.98)

χ^2 – Chi-Square test; CI – confidence interval; iv – intravenous; LMWH – low moleuclar weight heparin; NSAID – nonsteroidal anti-inflamatory drugs.

Baseline characteristics of the study patients (cases and controls) according to the occurrence of complications are shown in Table 6. One can see that the occurrence of any of local or systemic complication (such as necrosis of the pancreas and infection of necrosis) was associated with the fatal outcome ($p < 0.001$). The occurrence of pseudocyst of the pancreas was not higher in patients who died ($p = 0.912$).

The results of both univariate and multivariate logistic regression analysis (Cox and Snell R^2 0.401, Nagelkerke R^2 0.714, Hosmer-Lemeshow χ^2 1.836, df = 8, $p = 0.986$, overall model accuracy of 93.7%) presented in Table 7 suggest that the age, use of tramadol and/or morphine, BISAP score, comorbidity and IL-8 values on the third day were significantly associated with the occurrence of death in patients with AP. On the other hand, prophylactic use of antibiotics could have a protective role since it reduces the odds of the fatal outcome for slightly more than 93%. On the contrary, prophylactic use of antibiotics reduced the risk of death in our study.

The advanced age of a patient with AP can be a significant risk factor for adverse outcomes including death. Murata et al. [28], showed that patients with the advanced age (≥ 70 years) accompanied with severe comorbidities had an approximately double risk of death [23]. In the study of Kong et al. [29] there were significant differences in age between survivors and deceased patients with the severe AP (49.7 *vs* 62.8 years of age, respectively). The age difference between survivors and deceased in our study was even greater (60 *vs* 75 years, respectively). The advanced age is associated with fibrotic changes within the pancreatic tissue, which cause strictures and consequent dilatations of main pancreatic duct [30]; such abnormalities may contribute to the more severe course of the disease, and ultimately to death.

There is a variety of scoring systems for early detection of the severity of AP. The most commonly used in a daily practice are Ranson's score, APACHE II score, Balthasar CT score [26] and BISAP score [9, 31, 32]. BISAP scoring system in a simple manner can predict the clinical severity of AP within the first 24 hours after admission taking into account the following criteria: blood urea nitrogen > 8.92 mmol/L, impaired mental status, age > 60, ≥ 2 SIRS criteria, the presence of pleural effusion. In a recent study, Yang et al. [33] concluded that BISAP score was not an ideal single method for assessing the severity of AP, because the sensitivity was low. In another study BISAP score was a reliable tool for identification of pa-

Table 6

Occurrence of complications in cases (deceased) and controls (surviving) patients with acute pancreatitis

Complications	Patients, n (%)		Test value
	cases (n = 19)	controls (n = 113)	*p*
Any of local or systemic complications	19 (100)	42 (37.2)	$\chi^2 = 25.84$ $p < 0.001$
Necrosis of pancreas	12 (63.2)	29 (25.7)	$\chi^2 = 10.68$ $p = 0.001$
Infection of necrosis of pancreas	5 (26.3)	5 (4.4)	$\chi^2 = 11.13$ $p = 0.001$
Presence of pseudocyst of pancreas	3 (15.8)	19 (16.8)	$\chi^2 = 0.012$ $p = 0.912$
Presence of systemic complications	17 (89.5)	13 (13.5)	$\chi^2 = 47.43$ $p < 0.001$

χ^2 – Chi-Square test.

Table 7

Crude and adjusted odds ratios of factors associated with death in patients with acute pancreatitis

Risk factors	Crude OR (95% CI)	Adjusted OR (95%CI)
Age	1.07 (1.01, 1.12)	1.12 (1.02, 1.23)
IL-8 value on third day	1.03 (1.01, 1.04)	1.05 (1.02, 1.08)
EGF value on third day	0.99 (0.98, 1.001)	0.98 (0.95, 1.01)
TNF-α value on third day	1.00 (0.98, 1.03)	0.93 (0.85, 1.02)
Use of tramadol and/or morphine	12.49 (2.73, 57.18)	47.34 (3.21, 699.08)
Comorbidity	5.63 (1.55, 20.41)	10.62 (1.01, 111.39)
BISAP score	8.0 (2.57, 24.87)	48.11 (3.14, 736.29)
Prophylactic use of antibiotics	0.98 (0.37, 2.62)	0.07 (0.01, 0.85)

OR – odds ratio.
For other abbreviations see under previous tables.

Discussion

The mortality rate of AP in our cohort was 14.4% which is mostly in agreement with previously established rates. Some factors that we investigated may have an impact on the disease course or be associated with a fatal outcome such as: advanced age, presence of significant comorbidities, elevated IL-8 values on the third day from onset of symptoms, use of tramadol and/or morphine for pain relief and BISAP score equal or higher than 3 in the first 24 hours.

tients with high risk for adverse outcomes, although sensitivity for mortality was suboptimal [11]. However, both, our study and several other studies showed a strong relation between BISAP ≥ 3 and death of patients with AP [34–37]. Besides, BISAP score had better predictive power in comparison to Ranson's [10] score in our study, perhaps because it uses higher cut-off value for the age of patients (60 *vs* 55), as our patients who died were much older than those who survived.

There is widespread controversy about the effects of prophylactic antibiotics in AP. Although some studies did not show beneficial effects of antibiotic prophylaxis [38], the majority of published data favors the prophylactic use of antibiotics in patients with AP who develop necrosis [39], since necrotic tissue greatly increases the risk of infection [40]. In our study, even 64% of patients who died had necrosis of pancreatic tissue, while only 63% of patients in this group received antibiotic prophylaxis. Therefore, one of the reasons why some of the patients within this group died could have been a lack of necrotic tissue protection from infection. On the other hand, among the survivors, even 58% of patients received antibiotic prophylaxis, which surely helped to almost 26% of patients with necrosis to avoid infection and death. Rada and Pena [41] confirmed our results showing that prophylactic antibiotics may reduce mortality and length of hospitalization in patients with AP [42]. Surely routine antibiotic prophylaxis in all patients with AP is not justified [43], but physicians should be alert not to miss cases with necrosis, who definitely will benefit from antibiotic prophylaxis.

Since AP is an inflammatory disease, pro-inflammatory mediators are being released from leukocytes and the neutrophils in the beginning, but also during the disease course. IL-6 is being released from macrophage as a reaction to tissue injury and is responsible for the synthesis of the proteins in the acute phase of the inflammation. In the first 24 hours from the admission, it significantly correlates with the severity of the clinical picture and fatal outcome. Combined with lipase, IL-6 is a good diagnostic marker, and it may predict the outcome of AP. In our study, the most pronounced increase of IL-6 was registered in the first 24 hours from the admission, unlike CRP whose concentration increased later on, between 24 and 48 hours. IL-8, a chemokine which attracts neutrophils to the point of inflammation increases when the patients have a severe form of pancreatitis. When measured in the first 24 hours, IL-8, is a better predictor of the severity and adverse outcomes of AP [19–21], as it was shown in our study. Serum concentrations of IL-10, the cytokine which inhibits the release of the pro-inflammatory interleukins from macrophages, were much higher in our patients with AP who died. Pezzilli et al. [44] showed something in the opposite direction: plasma levels of IL-10 were lower in patients with more severe forms of pancreatitis. However, several previous studies in patients with other diseases showed that IL-10 reached higher

levels in those who died (e.g. in abdominal sepsis or brain injury) [45, 46]. So far investigations of IL-10 roles in immune response gave diverse results, and effective therapeutic strategies which target this cytokine were not developed in the area of inflammatory diseases [47]. The role of the EFG was so far mostly investigated in animal models in relation to its role in the prevention of intestinal permeability and bacteria translocation [48], as well as in prevention of septic complications in patients with AP [49]. However, in our study, we did not find a correlation between serum levels of EGF and fatal outcome. Likewise, levels of TNF-alpha, pro-inflammatory cytokine with multitudes of actions (activation of prostaglandin and leukotriene pathways, induction of apoptosis, expression of integrins, promotion of platelet aggregation, etc.) were not different among our patients with AP who died or survived. We are still far away from a complete understanding of immune and inflammatory responses in AP, and further studies focused on causal relationships and mechanisms of action of numerous mediators are necessary [50].

Comorbidity has been recognized as an important factor in patients with AP. In our study from 19 deceased patients, there were 3 (15.8%) without and 16 (84.2%) with comorbidities. Our study showed that patients with significant comorbidities have an increased risk from death compared to patients without. Several recently published studies came to the same conclusion [28, 51, 52]. Comorbidities decrease the capacity of vital organs to compensate for increased needs of tissues induced by inflammation and infection, resulting in lower chances of survival. However, there are some dissonant voices: in a study of Uomo et al. [53] the comorbidity had only the limited influence on the course and outcome of AP and did not correlate with mortality.

Pain is one of the major symptoms of AP. It spreads in a belt-like fashion and patients may experience it as very intensive. In the treatment of AP analgesics have an important role in mitigating stress and decreasing chances of shock. However, choice of analgesics is extremely important. In our study, the patients who received the opioid analgesics for pain relief, especially tramadol and/or morphine, had increased risk of death in comparison to the patients who received some other analgesics. Opioids may lead to spasm of the sphincter of Oddi and decrease the outflow of bile and pancreatic juice, aggravating the course of AP. Not all studies found the harmful effect of opioids in patients with AP, which could be explained by high variability of dosing regimens of opioids among the studies [54, 55].

Our study has several limitations which should be taken into account when interpreting its results. First, the study was uni-centric, which increased the possibility of study site personnel bias. Second, we were not able to measure cytokine levels beyond the third post-admission day, so full profiles of secretion could not have been established. And finally, our study had sufficient, yet modest statistical power, due to relatively small number of available patients with AP. Having regarded the aforementioned, and also the fact that we have only identified the significant association between some factors and mortality, but not independent risk factors for such outcome, this study should be considered as hypothesis-generating for further interventional investigations dealing with the causality of fatal outcome in AP.

Conclusion

Results of this study suggest that advanced age, the presence of significant comorbidities, the higher IL-8 value on

the third day from the onset of symptoms, use of tramadol and/or morphine, and BISAP score ≥ 3 in the first 24 hours are associated with lethal outcome in acute pancreatitis. On the other hand, prophylactic use of antibiotics may have the protective role and can reduce mortality in patients with severe acute pancreatitis.

Acknowledgements

This study was partially financed by grant No 175007, given by the Serbian Ministry of Education, Science and Technical Development, and also by the Macro project (No JP 13-11) entitled "The analysis of factors that contribute to complications and/or death of acute pancreatitis in patients treated in intensive care unit", that was implemented in cooperation between the Faculty of Medical Sciences, University of Kragujevac, and Clinical Center of Kragujevac.

We also wish to thank Dr. Bojan Stojanović, Dr. Jelena Miljković, Dr. Zorica Savović, Dr. Radiša Vojinović, Dr. Živan Babić, MPH Stefan Stojanović, MPH Milena Jurišević and MPH Viktorija Artinović, who kindly helped with gathering relevant data for this study.

Conflict of interests

The authors declare that have no conflict of interest in this study.

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Received on February 27, 2016.
Revised on April 01, 2016.
Revised on April 30, 2016.
Aceepted on May 10, 2016.
Online First May, 2016.