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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The role of interleukin-4 and interleukin-5 Th2 cytokines in assessing severity and prognosis of acute pancreatitis

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SUMMARY

Introduction/Objective Acute pancreatitis (AP) is a relatively common disease which in most patients has favorable course. However, in approximately 20% patients, the course of the disease is more severe with high mortality (40–50%). The evaluation of disease severity is now primarily based on protocols that includes clinical, laboratory, and radiographic diagnostic procedures, APACHE II score, Ranson score, CT index, and CT necrosis score. Key cells in the immunopathogenesis of AP are T-lymphocytes, and recent studies indicate the role of Th2 and their effector cytokines: interleukin (IL) -4 and interleukin (IL) -5. The purpose of our study was to determine the potential clinical value of IL-4 and IL-5 as biochemical markers for predicting development of severe, necrotizing form of acute pancreatitis with systemic complication such as systemic inflammatory response syndrome (SIRS).

Methods This prospective study included 240 patients hospitalized at The Clinic for Emergency Surgery of Clinical Center of Serbia as AP. Levels of IL-4 and IL-5 in serum were detected using commercial Bender Med Systems (BMS716FF) kits.

Results IL-4 and IL-5 were statistically significant increased on the second day of hospitalization with maximum values on the third day. In patients with severe AP complicated with necrosis and/or sepsis values were rising all through the seventh day.

Conclusion Levels of IL-4 and IL-5 in peripheral blood correlate with SIRS, Ranson score and clinical outcome in AP patients, therefore these cytokines are potential early biomarkers of disease progression and related complications.

Keywords: acute pancreatitis; interleukin-4; interleukin-5; biomarker

INTRODUCTION

Acute pancreatitis (AP) is a common inflammatory condition with a highly variable clinical course that can cause severe local and extra-pancreatic organ dysfunction and failure. The most common causes are gallstones and alcohol, accounting for up to 80% of cases [1]. The diagnosis of AP requires the patient to present with abdominal pain consistent with AP and the elevation of serum amylase or lipase (> 3 times upper limit of normal). Although advancement in diagnosis and treatment of AP has been made, this disease is still serious and potentially lethal [2]. The clinical course of AP can show minimal organ dysfunction with recovery in several days, but patients may experience a severe attack involving organ failure and severe complications as well as a high mortality rate. Severe acute pancreatitis (SAP) is defined as an episode of pancreatitis with persistent organ failure [3]. SAP is associated with high morbidity and mortality due to the development of pancreatic and extra-pancreatic necrosis, their subsequent infection and multisystem organ failure (MOF). In the case of SAP with sterile necrosis mortality rate can be as low as 12%, but in those with multiple organ failure mortality rate could be as high as 85% [4]. Thus, early assessment of the severity and initial aggressive fluid resuscitation decreases morbidity and mortality [5]. Patients with SAP benefit considerably from early management in an intensive care unit [5, 6]. Therefore, esearches focus on possibilities of an early assessment of the severity of an attack. Development of an Early severe acute pancreatitis (ESAP), in first week, accounts for 37.5–44% mortality among patients with AP [7]. During the second week AP progresses to Infected pancreatic necrosis (IPN), which results in Systemic inflammatory response syndrome(SIRS), Multiple organ dysfunction syndrome MODS, sepsis and a second wave of mortality [8]. Nevertheless, not all patients with acute necrotizing pancreatitis (ANP) develop IPN, suggesting that certain susceptibility factors make the patients with ANP prone to IPN. In AP innate immunity recognize damage-associated molecular patterns released from necrotizing pancreatic cells and stimulate adaptive immune response [9]. Cytokines play an important role in etiopathogenesis of AP by causing an inflammatory response that leads to tissue damage and organ dysfunction or failure in patients with SAP. The inflammatory response trigger both

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recruitment and activation of inflammatory cells that can progress to pancreatic necrosis [10]. Local recruitment and activation of inflammatory cells in acute pancreatitis induce the production of pro-inflammatory (IL-1β, IL-6, and IL-8as well as tumor necrosis factor-alpha [11]) and anti-inflammatory cytokines (IL-4, IL-10, IL-13, and TGFβ) [9]. Previous studies have shown increased production of IFN-γ, typical Th1 cytokine in patients with AP [12]. On the other hand, role of Th2 cells and their cytokines (IL-4 and IL-5) in development of acute and chronic pancreatitis is still controversial. In Th2-mediated response IL-4 stimulates B-cells to produce IgE and induce alternative activation of macrophages resulting in M2 phenotype, while IL-5 is important in eosinophil recruitment and activation [13].

Therefore, the purpose of our study was to determine the potential clinical value of IL-4 and IL-5 as biochemical marker for predicting development of severe, necrotizing form of acute pancreatitis with systemic complications (SIRS, ARDS, MODS, POF).

METHODS

Patients

A total of 240 patients at the Clinic for emergency surgery, Emergency center, Clinical center of Serbia, aged 18–75 years, with no history of malignancy and/or systemic diseases, were included in our study. Study was conducted multidisciplinary. Informed consent was obtained from all cases before enrollment into the study. The protocol of this study was approved by the Ethics Committee of the Clinical Center of Serbia. The diagnosis of AP was established based on the following 3 criteria: 1) abdominal pain or signs of AP; 2) serum amylase and/or lipase 5 times the upper limit of normal, and 3) characteristic findings for AP on computed tomography scan. We monitored 75 parameters divided in 7 groups: demographic, clinical, radiographic, operations, laboratory, systemic complications and scores (SIRS, APACHE II, Ranson, CT index, necrosis score) [14, 15].

Radiographic method: native RTG, abdominal US, CT and/or MR.

Three group of laboratory analysis were followed:

1. standard and specific biochemical analysis: D-dimer, CRP, INR and plasminogen;
2. microbiological findings for diagnosis of infection in necrotic pancreatitis;
3. serum levels of IL-4 and IL-5.

Monitoring levels of cytokines and laboratory findings

Daily samples of blood were routinely tested for standard, specific biochemical analysis and for determining the levels of serum cytokines from day 1 to day 7. Blood samples were centrifuged with the speed of 3000 rpm for 10 minutes and prior to the analysis the serum was kept at -20^0 C. The cutoff of 6 pg/ml was taken as a minimal concentration of IL-4 and IL-5.

Cytokines were quantified according to the manufacturer's instructions using Bender Med Systems GmbH (BMS716FF). The samples were run on Beckman Coulter system. CRP was quantified according to the manufacturer's instructions with commercial Olympus test using Olympus analyzer AU400. Standard laboratory methods were used for hemostatic, blood and enzyme activity.

Statistical analysis

Continuous variables are reported as mean ± standard deviation (SD), and categorical variables are expressed as N (%) of study participants. The student t-test was used to compare continuous variables between the two groups, and ANOVA for comparing continuous variables between three or more groups. The Pearson's correlation analysis was used for determining the correlation between the biochemical parameters and scores. ROC (receiver operative characteristics) curves were used to assess the predictive power of v methods were used. The most predictive parameters were approximately under 1 of the ROC curve. On the other hand, 0.5 parameters proved to be with no significance. All p values were two-sided, and $p \leq 0.05$ was considered to be statistically significant. All statistical analyses were conducted using SPSS for Windows, Version 11.1 (SPSS Inc., Chicago, IL, USA).

The study was done in compliance with the institutional standards on ethics.

RESULTS

There was a total of 240 patients with AP that fulfilled inclusion criteria, 144 subjects (53.3%) were male and 96 (41.7%) were female. Forty-five percent had SIRS score 3 and 4 at the time of admission and 95% had SIRS score two or more. Ranson score was 3–6 in 65% of patients and 16% of patients had maximal values (6 and 7) of Ranson score.

Overall, 78 (32.5%) patients died during hospitalization.

We quantified the circulating cytokines IL-4 and IL-5 on the first day (day of admission into hospital) and after 24, 48, 72, and 168 hours. We evaluated these cytokines in

Table 1. Measurement time IL-4 and IL-5

Measurement time (h)	Mean (pg/ml)	Standard deviation	95% confidence interval	
			Lower limit	Upper limit
IL-4				
0	1920.67	3323.52	1423.37	2417.97
24	2305.84	6261.21	1441.49	3170.19
48	7184.94	15536.24	5007.54	9362.33
72	3040.39	5627.20	2239.36	3841.43
168	2175.86	4640.94	1504.51	2847.21
IL-5				
0	325.50	631.18	231.05	419.94
24	262.11	538.30	187.80	336.42
48	584.32	1509.28	369.47	799.17
72	319.77	443.65	256.61	382.92
168	236.52	405.06	176.94	296.09

Table 2. Intragroup and intergroup dependence (concentration of IL-4 and IL-5)

Source of variation	Variance	F	p
IL-4			
Between groups	941061024.49	13.240	0.000
Within groups	71077579.37		
IL-5			
Between groups	3675826.141	5.469	0.000
Within groups	672141.520		

Table 3. Tukey HSD (parameter interdependence-dependent variable: IL-4 and IL-5)

(I) Measurement time (h)	(J) Measurement time (h)	Mean difference (I-J) (h)	Standard error	p	95% confidence interval	
					Lower limit	Upper limit
IL-4						
0	24	-385.17	870.00	0.992	-2762.92	1992.58
	48	-5264.26 (*)	876.05	0.000	-7658.54	-2869.98
	72	-1119.72	882.43	0.710	-3531.43	1291.99
	168	-255.18	889.17	0.999	-2685.32	2174.94
24	0	385.17	870.00	0.992	-1992.58	2762.92
	48	-4879.09 (*)	841.06	0.000	-7177.76	-2580.42
	72	-734.54	847.71	0.909	-3051.37	1582.27
	168	129.98	854.72	1.000	-2206.00	2465.97
48	0	5264.26(*)	876.05	0.000	2869.98	7658.54
	24	4879.09(*)	841.06	0.000	2580.42	7177.76
	72	4144.54(*)	853.91	0.000	1810.76	6478.32
	168	5009.07(*)	860.88	0.000	2656.26	7361.88
72	0	1119.72	882.43	0.710	-1291.99	3531.43
	24	734.54	847.71	0.909	-1582.27	3051.37
	48	-4144.54(*)	853.91	0.000	-6478.32	-1810.76
	168	864.53	867.37	0.857	-1506.01	3235.08
168	0	255.18	889.17	0.999	-2174.94	2685.32
	24	-129.98	854.72	1.000	-2465.97	2206.00
	48	-5009.07(*)	860.88	0.000	-7361.88	-2656.26
	72	-864.53	867.37	0.857	-3235.08	1506.01
IL-5						
0	24	63.38	84.60	0.945	-167.84	294.61
	48	-258.82 (*)	85.81	0.022	-493.35	-24.29
	72	5.72	85.81	1.000	-228.80	240.25
	168	88.98	87.16	0.846	-149.23	327.19
24	0	-63.38	84.60	0.945	-294.61	167.84
	48	-322.20 (*)	82.43	0.001	-547.51	-96.90
	72	-57.65	82.43	0.957	-282.95	167.64
	168	25.59	83.83	0.998	-203.54	254.73
48	0	258.82 (*)	85.81	0.022	24.29	493.35
	24	322.20 (*)	82.43	0.001	96.90	547.51
	72	264.55 (*)	83.67	0.014	35.86	493.24
	168	347.80 (*)	85.05	0.000	115.33	580.27
72	0	-5.72	85.81	1.000	-240.25	228.80
	24	57.65	82.43	0.957	-167.64	282.95
	48	-264.55 (*)	83.67	0.014	-493.24	-35.86
	168	83.25	85.05	0.865	-149.21	315.72
168	0	-88.98	87.16	0.846	-327.19	149.23
	24	-25.59	83.83	0.998	-254.73	203.54
	48	-347.80 (*)	85.05	0.000	-580.27	-115.33
	72	-83.25	85.05	0.865	-315.72	149.21

*The mean difference is statistically significant, p < 0.05.

patients with SAP and early mortality. There was statistically significant increase in the concentration of circulating IL-4 and IL-5 on the second day of hospitalization with maximum values on the third day (Table 1). In patients with SAP complicated with necrosis and/or sepsis values were rising all through the seventh day (Tables 1, 2, and 3).

There was highly statistically significant correlation between concentrations of IL-4, IL-5 and SIRS (Tables 4 and 5). Concentrations of these cytokines in serum of our patients did not corelate with CRP values and Apache II score (Tables 4 and 5). Levels of IL-5 were significantly higher in group of patients with negative outcome (Tables 5 and 6). Interleukin-4 was also higher in these patients, but correlation with outcome have not reached statistical significance (Tables 4 and 6). Correlation between Ranson score and measured levels of IL-5 was satistically highly significant (Table 5) in contrast to IL-4 (Table 4). Amylase levels, important for diagnosis of AP, were lower in patients with negtive outcome, and there is negative correlation with concetrations of both cytokines that we analyzed in this study (Tables 4, 5, and 6).

DISSCUSION

The aim of this study was to analyze serum levels of Th2 cytokines in AP patients and potential correlation with the severity of disease. Initial clinical response to pancreatitis is SIRS which can develop in sepsis with MODS. SIRS usually happen in the first week and its progression is a critical step in the prognosis of AP [16]. Most of our patients had SIRS score two or more (95%) and 45% had SIRS score 3 and 4 at the time of admission. This indicates that on admission most of our patient had complicated AP with highly developed inflammatory process, and almost 50% had developed septic syndrome. After initial injury of acinar cells progression of AP could be divided in three stages: local inflammation, generalized inflammatory response and final stage of sepsis with MODS. In our study group most of our patients were in stage of generalized inflammatory response. Ranson score was in 65% of patients 3–6, and 16% of patients had maximal values (6 and 7) of Ranson score. These values can explain, and certainly highly correlate with, the high SIRS scores on admission. Overall, in this study 78 (32.5%) patients died during hospitalization, while in literature mortality rates as high as 30% [17]. The main cause of early death in AP patients is ARDS, 60% of our

Table 4. Correlations of IL-4 concentration and protocol parameters

Parameters		Sex	SIRS	Outcome	Years	CRP	Amylase	Apache II	Ranson	IL-4
Sex	r	1	-0.139*	-0.194**	0.185**	-0.306**	-0.130	-0.062	-0.104	-0.083
	p		0.043	0.004	0.006	0.000	0.059	0.367	0.140	0.295
SIRS	r	-0.139*	1	0.677**	0.232**	0.274**	0.028	0.268**	0.331**	0.201**
	p	0.043		0.000	0.000	0.000	0.683	0.000	0.000	0.009
Outcome	r	-0.194**	0.677**	1	0.569**	0.502**	-0.110	0.481**	0.520**	0.099
	p	0.004	0.000		0.000	0.000	0.102	0.000	0.000	0.186
Years	r	0.185**	0.232**	0.569**	1	0.414**	0.146*	0.373**	0.334**	0.168*
	p	0.006	0.000	0.000		0.000	0.032	0.000	0.000	0.027
CRP	r	-0.306**	0.274**	0.502**	0.414**	1	-0.181**	0.274**	0.277**	-0.023
	p	0.000	0.000	0.000	0.000		0.000	0.000	0.000	0.469
Amylase	r	-0.130	0.028	-0.110	0.146*	-0.181**	1	0.066*	-0.202**	-0.079*
	p	0.059	0.683	0.102	0.032	0.000		0.041	0.003	0.025
Apache II	r	-0.062	0.268**	0.481**	0.373**	0.274**	0.066*	1	0.327**	0.013
	p	0.367	0.000	0.000	0.000	0.000	0.041		0.000	0.686
Ranson	r	-0.104	0.331**	0.520**	0.334**	0.277**	-0.202**	0.327**	1	0.069
	p	0.140	0.000	0.000	0.000	0.000	0.003	0.000		0.390
IL-4	r	-0.083	0.201**	0.099	0.168*	-0.023	-0.079*	0.013	0.069	1
	p	0.295	0.009	0.186	0.027	0.469	0.025	0.686	0.390	

*The correlation is statistically significant, $p < 0.05$;
**the correlation is statistically significant, $p < 0.01$;
r – Pearson correlation coefficient

Table 5. Correlations of IL-5 concentration and protocol parameters

Parameters		Sex	SIRS	Outcome	Years	CRP	Amylase	Apache II	Ranson	IL-5
Sex	r	1	-0.139*	-0.194**	0.185**	-0.306**	-0.130	-0.062	-0.104	-0.087
	p		0.043	0.004	0.006	0.000	0.059	0.367	0.140	0.269
SIRS	r	-0.139*	1	0.677**	0.232**	0.274**	0.028	0.268**	0.331**	0.332**
	p	0.043		0.000	0.000	0.000	0.683	0.000	0.000	0.000
Outcome	r	-0.194**	0.677**	1	0.569**	0.502**	-0.110	0.481**	0.520**	0.254**
	p	0.004	0.000		0.000	0.000	0.102	0.000	0.000	0.001
Years	r	0.185**	0.232**	0.569**	1	0.414**	0.146*	0.373**	0.334**	0.082
	p	0.006	0.000	0.000		0.000	0.032	0.000	0.000	0.284
CRP	r	-0.306**	0.274**	0.502**	0.414**	1	-0.181**	0.274**	0.277**	0.001
	p	0.000	0.000	0.000	0.000		0.000	0.000	0.000	0.966
Amylase	r	-0.130	0.028	-0.110	0.146*	-0.181**	1	0.066*	-0.202**	-0.059
	p	0.059	0.683	0.102	0.032	0.000		0.041	0.003	0.094
Apache II	r	-0.062	0.268**	0.481**	0.373**	0.274**	0.066*	1	0.327**	-0.007
	p	0.367	0.000	0.000	0.000	0.000	0.041		0.000	0.828
Ranson	r	-0.104	0.331**	0.520**	0.334**	0.277**	-0.202**	0.327**	1	0.280**
	p	0.140	0.000	0.000	0.000	0.000	0.003	0.000		0.000
IL-5	r	-0.087	0.332**	0.254**	0.082	0.001	-0.059	-0.007	0.280**	1
	p	0.269	0.000	0.001	0.284	0.966	0.094	0.828	0.000	

*The correlation is statistically significant, $p < 0.05$;
**the correlation is statistically significant, $p < 0.01$;
r – Pearson correlation coefficient

Table 6. Values of IL-4, IL-5, and other parameters relating to outcome

Parameters	Outcome	Mean	Standard deviation
Years	alive	46.38	12.08
	dead	62.30	8.02
CRP	alive	104.60	113.98
	dead	251.28	128.51
Amylase	alive	1383.62	1257.38
	dead	1094.20	867.69
Apache II	alive	12.44	3.75
	dead	17.84	6.04
IL-5	alive	214.27	452.21
	dead	557.57	860.65
IL-4	alive	1653.14	3550.45
	dead	2360.03	2504.26

Table 7. Results of comparison of two patient groups in respect of outcome (Student's t-test)

Parameters	t	p
Years	-10.529	0.000
CRP	-8.953	0.000
Apache II	-8.475	0.000
IL-4	-1.327	0.186
IL-5	-3.498	0.001

Grouping variable: OUTCOME

patients died in the first six days of hospitalization mostly because of pulmonary complication [18].

Wide spectrum of inflammatory mediators are included in inflammatory process which consequently modulates migration of leukocytes, increases vascular permeability, damages local tissue and can cause generalized inflammation with damages to the kidneys, lungs and other organs [19]. T-helper cells are grouped with varieties of cytokines they produce. Th1 cells are involved in defense mechanisms against intracellular pathogens and produce TNF-α and interferon-γ [9]. Various factors can influence the polarization of Th cells, including the cytokine profile of the environment in which Th cells undergo the process of transdifferentiation. Th1 and Th2 cytokine products reciprocally reduce each other's activity [9].

In our study, according to the similarities between these two interleukins, their behavior in severe forms of acute pancreatitis is practically identical. The values of their concentrations increase significantly on the second day of the disease, reaching the highest values on the third day, and in severe forms of infected necrosis and sepsis, these values increase until the seventh day, when the last measurements were made (Tables 1, 2, and 3). Table 6 shows the values of IL-4 and IL-5 in correlation to the outcome. In our study the survivors, both IL-4 and IL-5, had lower values than non-survivors but only IL-5 was statistically significant (Table 7). Rogriguez et al. [20] reported lower levels of IL-4 but significantly higher IL-5 in serum of patients with severe AP and non-survivors. Similarly, our results showed that IL-5 highly significantly correlates with the outcome of acute pancreatitis (Table 5). Intracellular labeling of IL-4 and IL-10 showed that Th2 and regulatory T cells were induced in a mouse model of severe acute pancreatitis. These findings suggest that anti- inflammatory response develops not only after but also during tissue damage in AP. Sendler et al. [21] also found higher IL-4 analyzing human samples, but levels of this cytokine were not in correlation with disease severity. Alternative macrophage activation induced by IL-4 and IL-13 is responsible not only for anti-inflammatory response in AP but also for fibrosis in chronic pancreatitis which can be reduced by blocking these cytokines [22].

IL-4 and IL-5 correlate with SIRS (Tables 4 and 5), as reported in the literature [23], although more attention is paid to the values of these interleukins in some other conditions (asthma) [24, 25].

CONCLUSION

Values of IL-4 and IL-5 can potentially be used as an early marker of severity of AP, early marker of sepsis and outcome because of a significant statistical correlation with outcome, SIRS and Ranson score.

Conflict of interest: None declared.

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Улога *Th2* цитокинâ интерлеукина-4 и интерлеукина-5 у процени тежине и прогнозе акутног панкреатитиса

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САЖЕТАК

Увод/Циљ Акутни панкреатитис (АП) релативно је често обољење које у већини случајева има бениган ток. Међутим, код око 20% болесника ток болести је много тежи, а смртност и даље врло висока (40–50%). Процена тежине болести сада се превасходно заснива на протоколима који укључују клиничке, лабораторијске и радиографске дијагностичке поступке, скор *APACHE* II, Рансонов скор, индекс компјутеризоване томографије и скор некрозе мерен компјутеризованом томографијом. У имунопатогенези АП кључне ћелије су Т-лимфоцити, а новија истраживања указују на улогу *Th*2 и њихових ефекторских цитокина: интерлеукина (ИЛ)-4 и ИЛ-5. Циљ ове студије био је да се испита клинички значај серумских нивоа ИЛ-4 и ИЛ-5 као потенцијалних биомаркера тешке форме АП са системским компликацијама, као што је синдром системског инфламаторног одговора.

Методе Ова проспективна студија укључила је 240 болесника са АП хоспитализованих на Клиници за ургентну хирургију Универзитетског клиничког центра Србије. Серумски нивои ИЛ-4 и ИЛ-5 свакодневно су детектовани употребом комерцијално доступних китова *Bender Med Systems* (*BMS716FF*).

Резултати Нивои ИЛ-4 и ИЛ-5 у серуму били су статистички значајно повишени другог дана, док су максималне вредности достигли трећег дана хоспитализације. Код оболелих од тешке форме АП са системским компликацијама (синдром системског инфламаторног одговора) нивои поменутих цитокина били су повишени до седмог дана.

Закључак Вредности концентрација ИЛ-4 и ИЛ-5 показују високо значајну корелацију са синдромом системског инфламаторног одговора и Рансоновим скором и исходом, те наша студија показује да ови цитокини могу бити рани биомаркер тежине АП, појаве системских компликација и исхода болести.

Кључне речи: акутни панкреатитис; интерлеукин-4; интерлеукин-5; биомаркер