UNIVERSITY OF MEDICINE AND PHARMACY,
„CAROL DAVILA", BUCHAREST
DOCTORAL SCHOOL
FIELD OF MEDICINE

THE INFLUENCE OF ORGAN DYSFUNCTIONS ON THE PRESEPSIN USEFULNESS AS AN INDICATOR OF SEPSIS

SUMMARY OF THE DOCTORAL THESIS

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Content

1. The fundamental problem

On the one hand, sepsis is a major cause of mortality, accounting for 20% of all global deaths, so prompt recognition and administration of specific therapy, antibiotics, is essential. (1). On the other hand, antibiotic abuse leads to increased bacterial resistance with the increasing narrowing of the classes of antibiotics to which bacterial strains are sensitive, ultimately causing infections that are difficult to treat and which lead to the death of patients.(2)

Sepsis is a critical condition resulting from excessive activation of the immune system in response to an infection.(3). Presepsin is a biomarker of sepsis and acts as a receptor for lipopolysaccharide-lipopolysaccharide carrier protein complexes.(4) LPS (also known as endotoxins) are components of the membrane of gram-negative bacteria that bind to CD14 and initiate a systemic inflammatory response.(4,5) CD14 is a glycoprotein receptor and is found in two forms: mCD14 – bound to the cell membrane and sCD14 – soluble.(4,6). First, mCD14 is attached to the membrane of monocytes, macrophages, and neutrophils via a glycophosphatidylinositol (GPI) structure. LPS binds to mCD14 and leads to activation of TLR4 and then activation of protein kinases, (e.g., mitogen-activated protein kinase and tyrosine kinases), leading to cytokine production.(4) sCD14 in plasma can have two origins: by cleavage of the GPI structure on the membrane of monocytes, macrophages and neutrophils (sCD14α) or by secretion by the same cells (sCD14β).(6) These soluble forms can bind to LPS and form complexes that lead to cellular activation via TLR4,(6,7) resulting in an immune response in both CD14 negative cells (endothelial or epithelial cells) and CD14 positive cells.(4) Various proteases cleave the N-terminal portion of sCD14 resulting in a 13-kilodalton fragment, called presepsin, which is closely correlated with bacterial infection.(4,8)

Numerous studies have shown that sepsis leads to multiple events such as activation of biological pathways, stimulation or inhibition of various enzymes and transport systems, organ dysfunctions, including liver and kidney, resulting in higher levels of both conjugated bilirubin (and cholestasis enzymes), creatinine and presepsin. Establishing the relationship between bilio-hepatic parameters, renal function, reflected by creatinine and the infectious state having presepsin as a marker, is important both for the correct diagnosis of sepsis and for prognosis. Studies in the specialized literature have demonstrated not only the association between sepsis and cholestasis, but also the role of cholestasis as a prognostic factor for sepsis-induced

mortality.(9–11). Presepsin allows differentiation between sepsis and non-infectious systemic inflammatory response syndrome, but this can be difficult when renal failure is associated.(12) The level of presepsin increases with the degree of renal failure (presepsin being metabolized in the proximal convoluted tubule), without signifying sepsis..(13) (Fig. 1.1.)

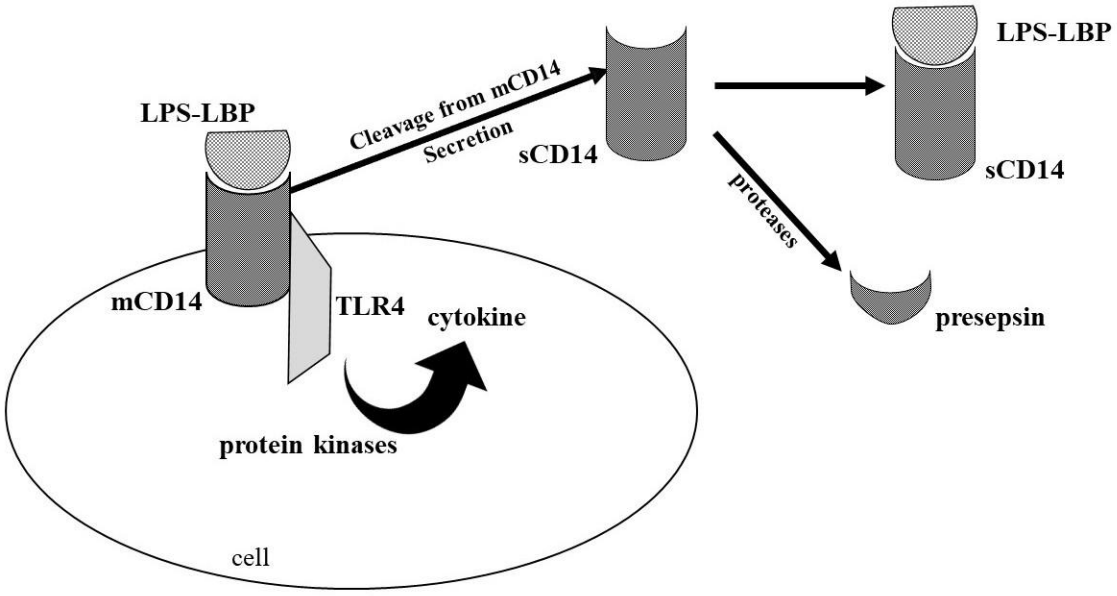

Fig. 1. Bacterial lipopolysaccharides binding to mCD14 activates TLR4, thus switching on protein-kinases and cytokine synthesis. The sCD14 in plasma either originates from mCD14 cleavage or is secreted by various cells. Binding of sCD14 to lipopolysaccharides generates a complex that activates various cells, triggering immune responses. Cleavage of sCD14 by proteases produces presepsin. CD14: cluster of differentiation 14, LBP: lipopolysaccharides binding protein, LPS: lipopolysaccharides, mCD14: membrane-bound CD14, sCD14: soluble CD14, TLR 4: Toll like receptor 4.

2. Hypothesis, objectives and research methodology

The present study aims to determine, first, whether the alteration of cholestasis-related parameters observed in septic states is primarily caused by the infection itself or by the inflammation it triggers. Our working hypothesis is that infection, which is reflected by presepsin levels, is the main determinant of the increase in biliary parameters in sepsis. Recognition of this strong cholestasis-intrasepsis relationship may help to avoid unnecessary imaging procedures, especially in critically ill patients, allowing physicians to focus their efforts on treating the underlying infectious process. Two other objectives are to assess the impact of the septic state on hepatobiliary function and to evaluate the correlation between hepatobiliary markers (especially those of cholestasis) with various parameters in the context of sepsis.

A second aim of the work was to evaluate the impact of renal dysfunction on presepsin levels by establishing presepsin thresholds based on serum creatinine levels in order to avoid overdiagnosis of bacterial infection, abusive prescription of antibiotics and the risk of bacterial resistance.

Both studies were retrospective and included patients admitted to the emergency department of the Internal Medicine I and Nephrology departments of the Bucharest University Emergency Hospital, regardless of age or diagnosis, whose presepsin levels were determined in the emergency room before admission. The statistical analysis included descriptive and inferential statistics. Statistical calculations were performed primarily using the R programming language and environment for statistical computing and graphics (version 4.2.3.) and Microsoft Excel.

In the first part of the work, it was demonstrated that parameters related to cholestasis are associated with presepsin, with a higher probability than with hemodynamic, inflammatory or coagulation-related variables in the septic state. Presepsin emerged as the most likely variable correlated with all cholestasis markers: alkaline phosphatase ($p = 7 \times 10^{-8}$), gamma-glutamyl transferase ($p = 5 \times 10^{-10}$) and conjugated bilirubin ($p = 4 \times 10^{-15}$). Platelet count, C-reactive protein, age, creatinine, urea, lactate and blood pressure were associated with only one or two of these markers.(14)

In the second part of the paper, it was highlighted that the level of presepsin is higher the more severe the renal dysfunction, and the thresholds obtained for presepsin are 600, 1000 and 1300 pg/mL in patients with serum creatinine ≤ 1.5 mg/dl, between 1.5 and 2 mg/dl and between 2 and 4 mg/dl, respectively. In patients with serum creatinine at presentation > 4 mg/dL, presepsin is not a reliable marker for sepsis and should not be used as an argument for this condition. (15)

3. Chapter summary

The general part is divided into two chapters. The first chapter addresses the pathophysiology of sepsis-induced cholestasis. Cholestasis occurs in up to 40% of critically ill patients, sepsis being one of the multiple causes.(16) Sepsis-associated liver dysfunction includes: hypoxic hepatitis, sepsis-induced cholestasis, and decreased protein synthesis leading to coagulopathy.(17) Sepsis-induced cholestasis results from: impaired uptake and transport of bile acids and bilirubin secondary to hypoxia and hypoperfusion, but also from the detrimental effect of endotoxins and inflammatory cytokines on the gene expression of proteins involved in the transport of bile acids and bilirubin, on the architecture of the cytoskeleton around the bile ducts, and on the tight junctions between hepatocytes.(18). Numerous studies have shown that LPS-induced sepsis can lead to cholestasis through multiple mechanisms: 1. interference with: a. the activity of membrane pumps (Fig. 3.1.), b. aquaporins, c. nuclear receptors involved in inflammatory responses (Fig 3.2.); 2. activation of the LPS/TLR4 and PI3K signaling pathways; 3. generation of a proinflammatory state. A review was conducted on this topic that included relevant articles regarding the pathophysiology of sepsis-associated liver dysfunction.(19)

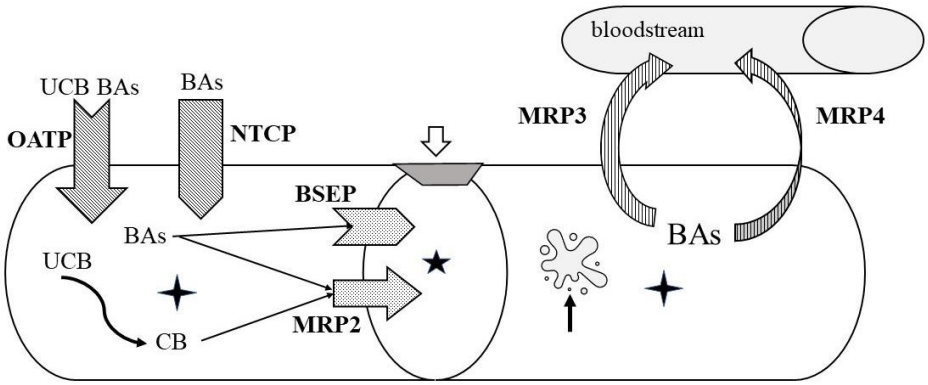

Fig. 3.1. Sepsis induced disruption of the: 1. cytoskeletal architecture (black arrow) in the liver cells (four points star) lining the bile canaliculi (five points star), 2. tight junctions (open arrow) between hepatocytes, and 3. transporter proteins' activity in liver cell membrane: NTCP (which transports bile acids from plasma into hepatocytes), OATP (which transports conjugated and unconjugated bile acids and unconjugated bilirubin into hepatocytes), BSEP (which transports bile salts into bile ducts), MRP 2 (which transports conjugated bile acids and conjugated bilirubin from hepatocytes into bile ducts). MRP 3 and MRP 4 mediate the

expulsion of bile acids from hepatocyte into the blood stream, acting as a protective mechanism activated in cholestatic conditions. BAs: bile acids, BSEP: bile salt export pump, CB: conjugated bilirubin, MRP: multidrug resistance protein, NTCP: sodium taurocholate cotransporting polypeptide, OATP: organic anions transporting polypeptides, UCB: unconjugated bilirubin.

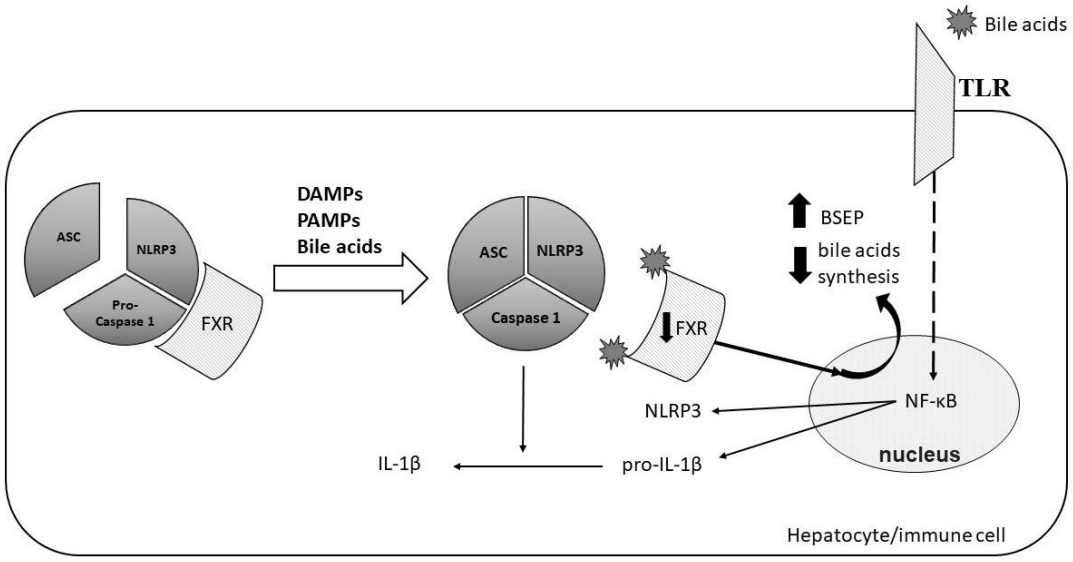

Fig. 3.2. A brief representation of FXR role in sepsis-induced cholestasis. **A**: inflammation driving NLRP3 inflammasome consists of intracellular proteins NLRP3, ASC, and pro-caspase 1. FXR, a nuclear receptor, blocks mitochondrial NLRP3 inflammasome assembly by interfering with NLRP3 and pro-caspase 1. **B**: High bile acids level in the bloodstream leads to: 1. TLR-NFκB pathway activation followed by NLRP3 and pro-IL-1β synthesis; 2. FXR downregulation, which promotes NLRP3 inflammasome assembly with consequent caspase-1 activation engendering IL-1β from pro-IL-1β. FXR activation by bile acids depresses bile acids synthesis and induces BSEP expression. ASC: Apoptosis-associated Speck-like protein containing a CARD, BSEP: bile salt export pump, DAMPs: danger-associated molecular patterns, FXR: farnesoid X receptor, IL: Interleukin, Leucine-Rich-containing family, Pyrin domain-containing-3, NLRP3: Nucleotide-binding domain, PAMPs: pathogen-associated molecular patterns, TLR-NF-κB: Toll-like receptor- nuclear factor-kappaB.

The second chapter included data on the influence of renal dysfunction on presepsin levels. Metabolism of presepsin by proximal tubular cells explains the increase in presepsin with decreased renal function.(13) Presepsin is a specific marker for bacterial infection but, unfortunately, the lower the level of renal function, the higher the normal level of presepsin,

therefore the reference values of presepsin in patients with normal renal function are not applicable to those with renal dysfunction.(20)

The personal contributions section was also divided into two chapters according to the topics addressed in the general section. The first study was conducted on 396 patients (after applying the exclusion criteria). Patients were divided into two groups according to the conjugated bilirubin level: normal level (≤0.3 mg/dl) comprising 253 patients (64%) and increased (>0.3 mg/dl) comprising 143 patients (36%). Comparisons of relevant demographic, biological and clinical parameters (numerical and categorical variables) were made for patients with normal conjugated bilirubin (n = 253) compared to those with increased conjugated bilirubin (n = 143). The most important results were: when applying the Mann-Whitney test, the group with increased conjugated bilirubin compared to the one with normal conjugated bilirubin was statistically significantly correlated with a higher value of presepsin ($p=6\times10^{-7}$), a higher score of the SOFA score ($p=4\times10^{-4}$), and of SOFA-CV ($p=4\times10^{-4}$), a higher level of serum lactate ($p=5\times10^{-5}$) and higher values of ALT ($p=8\times10^{-7}$) and AST ($p=2\times10^{-10}$). (Table 3.1.)

Table 3.1. Comparison between the numerical variables, in two groups of patients: those with normal conjugated bilirubin (n = 253) vs those with increased conjugated bilirubin (n = 143). The Mann-Whitney test was used to calculate W statistics and p-values. According to Bonferroni's correction, the threshold for the p-value should be set at 0.05/20 (as 20 comparisons were conducted), resulting in a threshold of 0.0025. Statistically significant results are represented. ALT: alanine aminotransferase; AST: aspartate aminotransferase; IQR: interquartile range; SOFA: Sequential Organ Failure Assessment; SOFA_hmd = the fourth parameter in SOFA score reflecting the hemodynamic status ("Mean arterial pressure OR administration of vasoactive agents required)

Numerical parameter	**median [IQR] for patients with increased ConjBil**	**median [IQR] for patients with normal ConjBil**	**W statistics**	**p-value**
Presepsin (pg/ml)	1340 [618.5-3220.5]	789 [318-1700]	12633.5	6×10^{-7}
SOFA score	5 [2-8]	4 [2-6]	14210	4×10^{-4}
SOFA_hmd	0 [0-2]	0 [0-0]	15112	4×10^{-4}
Lactate (mmol/L)	2.18 [1.215-4.005]	1.27 [0.8-2.23]	6794.5	5×10^{-5}
ALT (U/L)	41 [25-78.5]	28 [17-45]	12695	8×10^{-7}
AST (U/L)	49 [28-102]	28 [20-43]	11134	2×10^{-10}

Comparisons of categorical parameters were then made between the group of patients with increased conjugated bilirubin and normal conjugated bilirubin. Of all the comparisons made, the only one that remained statistically significant was for the male gender, which suggested that men are more prone to increased conjugated bilirubin than women. Comparisons were made between hepatobiliary function parameters (ALT, AST, total bilirubin, conjugated bilirubin, GGT and alkaline phosphatase) and categorical/numeric parameters. The Mann Whitney test showed that: for all categorical parameters (except urinary infection) the association with conjugated bilirubin was statistically more significant than with total bilirubin, the level of conjugated and total bilirubin was statistically (but not clinically) significantly higher in males and in patients with skin and urinary infection, deceased patients had higher levels of conjugated bilirubin (but not total bilirubin) and AST. After applying the Bonferroni correction, the only comparison that remained statistically significant was between conjugated bilirubin and skin infection.

Simple regression (by Spearman method) demonstrated multiple associations between hepatobiliary parameters and other numerical parameters. A direct, highly statistically significant, but low to mild correlation was noted between presepsin and alkaline phosphatase, GGT, ALT, AST, conjugated bilirubin, total bilirubin. (Table 3.2.)

Table 3.2. Correlations between liver-biliary parameters (considered dependent variables) and the other numerical parameters by simple regression. Given the probable non-linear relationship between these numerical parameters, Spearman method was employed for performing the calculations; as this method correlates ranks, and not actual numbers, no confidence limits could be calculated for the correlation coefficient. Given the large number of comparisons (96), the threshold for statistical significance was lowered to $0.05/96 \approx 0.0005$. The results observing this threshold are represented. (~ = correlated with; SOFA hmd stands for the fourth parameter in SOFA score ("Mean arterial pressure OR administration of vasoactive agents required") and may have discrete (integer) values 1 to 4.) AlkPh: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ConjBil: conjugated bilirubin; CRP: C reactive protein; GGT: Gamma-glutamyl transferase; GCS: Glasgow coma scale; IL: interleukin; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; SOFA: Sequential Organ Failure Assessment; TotBil: total bilirubin

Dependent parameter ~ independent parameter	**Correlation coefficient**	**Statistic**	**p-value**
AlkPh ~ Presepsin	0.41	1519505.514	1.70×10^{-11}
ALT ~ Presepsin	0.22	8045542.415	7.70×10^{-6}
AST ~ Presepsin	0.34	6836703.192	3.90×10^{-12}

AST ~ SOFA_score	0.28	7493080.88	2.30×10^{-8}
AST ~ Lactate	0.29	2816683.155	4.30×10^{-7}
AST ~ Urea	0.21	8212445.52	3.50×10^{-5}
AST ~ Creatinine	0.18	8501298.197	0.00035
AST ~ GCS at admission	-0.18	12171483.73	0.00043
ConjBil ~ Presepsin	0.33	6977716.014	3.00×10^{-11}
ConjBil ~ SOFA_hmd	0.22	8065443.121	9.30×10^{-6}
ConjBil ~ SOFA_score	0.21	8160413.815	2.20×10^{-5}
ConjBil ~ Lactate	0.22	3107592.858	0.00017
ConjBil ~ Urea	0.18	8497828.022	0.00035
TotBil ~ Thrombocyte count	-0.22	12630166.97	9.60×10^{-6}
TotBil ~ Presepsin	0.19	8377724.454	0.00014
TotBil ~ pH	0.2	6415689.375	0.00018
TotBil ~ Lactate	0.21	3157448.397	0.00041
GGT ~ Presepsin	0.34	1872381.002	2.70×10^{-8}
GGT ~ Age	-0.24	3495443.038	0.00014

Subsequently, multivariate analysis was performed to determine factors independently associated with parameters related to cholestasis in the context of sepsis, which could suggest possible explanations for biliary tract damage induced by systemic infection. Multivariate analysis showed presepsin to be the parameter with the highest probability of being associated with all parameters related to cholestasis and the only one correlated with all these parameters. (Table 3.3.)

Table 3.3. Multivariate analysis (MVA). In the second column there are the factors independently associated with the liver-biliary parameters in the first column. The third column contains the estimate, which is the average change in the log odds of the dependent variable associated with a one unit increase in each independent variable. SOFA_hmd stands for the fourth parameter in SOFA score ("Mean arterial pressure OR administration of vasoactive agents required") and may have discrete (integer) values 1 to 4. For each parameter in the first two columns (with the exception of SOFA_hmd, thrombocyte count, and age) the name of the parameter should be understood as the serum level of the respective parameter. AlkPh: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ConjBil: conjugated bilirubin; GGT: gamma-glutamyl transferase; SOFA: Sequential Organ Failure Assessment.

Dependent variable	Independent variable	Estimate	95% confidence interval	t-statistic	p-value
AlkPh	Presepsin	0.019	[0.012, 0.024]	5.649	7×10^{-8}
AlkPh	Creatinine	-7.58	[-12.98, -2.18]	-2.752	0.007
AlkPh	CRP	1.34	[0.2, 2.48]	2.300	0.02
ALT	Lactate	8.97	[4.65, 13.28]	4.074	6×10^{-5}

ALT	Presepsin	0.0095	[0.0048, 0.014]	3.957	1×10^{-4}
AST	Lactate	13.6	[6.26, 20.93]	3.631	0.0003
AST	Presepsin	0.013	[0.0055, 0.021]	3.331	0.001
AST	SOFA_hmd	26.95	[6.28, 47.61]	2.555	0.01
ConjBil	Presepsin	0.00011	[0.000080, 0.00013]	8.185	4×10^{-15}
ConjBil	Creatinine	-0.077	[-0.11, -0.044]	-4.665	4×10^{-6}
ConjBil	Urea	0.0014	[0.00040, 0.0024]	2.767	0.006
ConjBil	Thrombocyte count	0.00043	[-0.00082, -0.000032]	-2.117	0.035
GGT	Presepsin	0.019	[0.013, 0.024]	6.480	5×10^{-10}
GGT	Age	-1.76	[-2.90, -0.61]	-3.004	0.003

The second study was conducted on 510 patients (after applying the exclusion criteria) and demonstrated that there is an exponential relationship between presepsin and serum creatinine. (Fig. 3.3.)

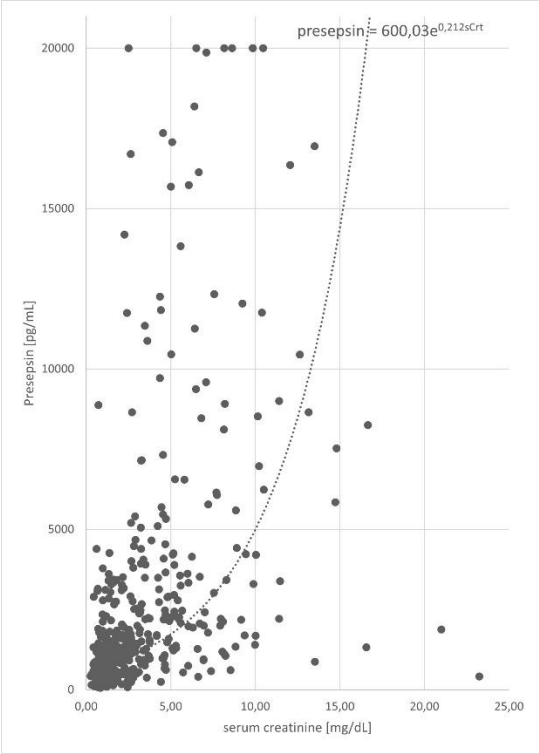

Fig .3.3. The exponential relationship between presepsin and serum creatinine at presentation.

Other factors that may influence the relationship between presepsin levels and kidney function were also taken into account: gender, age and patient evolution. Gender did not influence presepsin levels. There was a statistically significant correlation between age and presepsin, but

a negative one, although weak. There was no correlation between age and serum creatinine, probably because in most patients with renal dysfunction, if present, it was mainly or exclusively acute. Taking into account the sum of sensitivity and specificity, the product of sensitivity and specificity, and the Youden index, the optimal thresholds of presepsin reported to the level of renal dysfunction were determined. (Table 3.4., Table 3.5.)

Table 3.4. Optimal cutpoints for presepsin (in pg/mL) on the receiver operating characteristic (ROC) curves corresponding to the 4 degrees of severity of kidney dysfunction (KD) [evaluated by means of serum creatinine (sCrt)] as calculated by the various methods: sum of sensitivity and specificity (sum_sens_spec), product of sensitivity and specificity (prod_sens_spec), Youden index. Optimal cutpoints are highlighted by bold typing. For reasons explained in the text, for KD_3 patients several other cutpoints (beside the optimal one) are listed for prod_sens_spec. AUC = area under the curve.

sCrt [mg/dL]	Method	Cutpoint	accuracy	sensitivity	specificity	AUC
≤1.5 (KD_1)	sum_sens_spec	**982**	0.77	0.53	0.91	0.78
	prod_sens_spec	**700**	0.73	0.64	0.78	0.78
	Youden index	**982**	0.77	0.53	0.91	0.78
>1.5 and ≤2 (KD_2)	sum_sens_spec	**588**	0.72	1	0.53	0.78
	prod_sens_spec	**1125**	0.76	0.68	0.81	0.78
	Youden index	**588**	0.72	1	0.53	0.78
>2 and ≤4 (KD_3)	sum_sens_spec	**1065**	0.79	0.82	0.7	0.82
	prod_sens_spec	**1065**	0.79	0.82	0.7	0.82
	prod_sens_spec	1200	0.75	0.76	0.73	0.82
	prod_sens_spec	1300	0.72	0.71	0.73	0.82
	prod_sens_spec	1400	0.69	0.67	0.73	0.82
	prod_sens_spec	1500	0.68	0.64	0.8	0.82
	prod_sens_spec	1600	0.66	0.61	0.8	0.82
	Youden index	**1065**	0.79	0.82	0.7	0.82
>4 (KD_4)	sum_sens_spec	**2260**	0.61	0.7	0.47	0.59
	prod_sens_spec	**2260**	0.61	0.7	0.47	0.59
	Youden index	**2260**	0.61	0.7	0.47	0.59

Table 3.5. Presepsin thresholds (in pg/mL) for the 4 degrees of severity of kidney dysfunction evaluated by means of serum creatinine. sCrt = serum creatinine

sCrt [mg/dL]	Normal	Slightly increased	Definitely increased	Much increased
≤1.5	≤300	300 to 500	**500** to 1000	>1000
>1.5 and ≤2	≤500	500 to 950	**950** to 1400	>1400
>2 and ≤4	≤950	950 to 1600	**1600** to 3000	>3000
>4	≤1800	1800 to 3500	**3500** to 8000	>8000

The best cutoffs for presepsin were set at 600, 1000, and 1300 pg/mL for patients with sCrt ≤1.5 mg/dL, between 1.5 and 2 mg/dL, and between 2 and 4 mg/dL, respectively. Unfortunately, in patients with sCrt at presentation >4 mg/dL, presepsin is not a reliable marker for sepsis and should not be used as an argument for infection.

5. Conclusions and personal contributions

From the literature search, this was the first attempt to perform multivariate analysis to determine factors independently associated with cholestasis-related parameters in the context of sepsis, which could suggest possible explanations for biliary tract damage induced by systemic infection. Cholestasis-related parameters are associated with presepsin, with a higher probability than hemodynamic, inflammatory, or coagulation-related variables in the septic state. Presepsin emerged as the most likely variable correlated with all cholestasis markers: alkaline phosphatase ($p = 7 \times 10^{-8}$), gamma-glutamyl transferase ($p = 5 \times 10^{-10}$) and conjugated bilirubin ($p = 4 \times 10^{-15}$).

To our knowledge, this was the first study to attempt to establish thresholds for presepsin tailored to different degrees of renal dysfunction. The greater the severity of renal dysfunction, as reflected by serum creatinine at presentation, the higher the expected presepsin level, and therefore the higher the threshold for significant presepsin elevation.

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