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Urine NGAL is useful in the clinical evaluation of renal function in the early course of acute pancreatitis

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Abstract: I n t r o d u c t i o n: Acute Kidney Injury (AKI) is a serious early complications in patients with acute pancreatitis (AP) that significantly increases mortality rates compared to patients without AKI. The early diagnosis of AKI during its treatable phases and implementation of appropriate treatment protocols can improve outcomes for this group of patients. A promising biomarker for AKI is neutrophil gelatinase-associated lipocalin (NGAL).
A i m: This study evaluated the diagnostic value of NGAL concentrations in serum and in urine for patients developing AKI as an early complication of AP compared to AP patients without AKI. Material and methods: The study group composed of 65 patients (34 men and 31 women) with a mean age of 62.2 ± 16 years with AP and hospitalized in the Surgery Department of the Direct Hospital in Sucha Beskidzka, Poland

between January and December 2014. Serum NGAL (sNGAL) levels were measured with the BioVendor ELISA kit, and urine NGAL (uNGAL) with the Abbott ARCHITECT Analyzer.
R e s u l t s: In the early phase of AP, 11 patients (17%) developed AKI, including 10 patients with stage 1 and one with stage 2. AKI was associated with more severe AP, higher BISAP scores, the need for more intensive treatment, longer hospital stays and higher mortality. Both serum and urine NGAL concentrations were significantly higher in patients with AKI throughout the study and significantly predicted AKI in simple and multiple logistic regression adjusted for age, sex and comorbidities. Serum and urine NGAL concentrations were significantly correlated with levels of serum urea, creatinine, urine albumin, and the maximum change in serum creatinine. Serum and urine NGAL levels also correlated positively with direct neutrophil counts and CRP concentrations throughout the study.
C o n c l u s i o n s: The measurement of NGAL levels, particularly in urine, is simple, easy to interpret, routinely available, and clinically useful in the assessment of dynamic changes in kidney function for patients with AP.

Key words: urine NGAL, severe of acute pancreatitis, acute kidney injury.

Introduction

Acute pancreatitis (AP) in the most of patients have mild course of the disease (MAP — *mild acute pancreatitis*). Laboratory tests and imaging studies performed in the early stages of the disease may not give any warning signs of eventual organ failure. But, timely recognition of the severity of AP and monitoring of organ function is the only way to survive this condition [1–4]. It should be noted that more than half of patients with severe acute pancreatitis (SAP) die within the first week of the illness, and that the most common causes of death (70–80%) are acute renal injury (AKI) and acute lung injury (ALI) due to acute respiratory distress syndrome (ARDS) [2, 5–9]. The established criteria for measuring AKI, the 2004 RIFLE classification and 2012 KDIGO guidelines, are both based on estimated increase in creatinine and decrease in urine output over time [8, 10]. These biomarker measurements for AKI were proposed for use internationally due to their general availability in clinical settings across the world. Unfortunately, serum creatinine level has limited value as an indicator of renal impairment as it varies with factors such as muscle mass, age, sex, and diet of the patient [5, 11]. More importantly, the increase in serum creatinine usually occurs 24–48 hours after kidney damage [10]. As such, monitoring serum creatinine does not meet the diagnostic needs of clinicians treating patients with SAP whose condition may change from hour to hour. Similarly, the hourly measurement of urine output commonly used in most surgery departments is also not an ideal benchmark for estimating renal function. Limitations include general variability, invasiveness and laboriousness of acquiring measurements and difficulty of interpreting the results. Instead, clinicians need a fast and simple diagnostic tool that provides reliable assessment of a patient's risk for AKI. There is a pressing need for new markers of kidney damage that allow for quick diagnosis and appropriate treatment. One such promising marker is neutrophil gelatinase-associated lipocalin (NGAL). This

protein's increased concentration in blood serum and urine is observed as early as 4–6 hours after kidney ischemia or exposure to nephrotoxic agents in both the preclinical and reversible phases of AKI [8, 10, 12]. NGAL, also known as gelatinase siderocalin or lipocalin 2, is a secretory protein in the lipocalin family present in the granules of neutrophils and macrophages [11]. NGAL was first described as a marker for acute kidney injury in 2003 when it was found in patients having undergone cardiac surgery [13]. Under normal physiological conditions, NGAL is freely filtered by the kidney glomerulus and is mostly resorbed at the proximal convoluted tubule. It begins to be secreted in response to kidney ischemia as soon as 2 hours after the injury and may be considered as a sort of "renal troponin." The concentration of NGAL in blood serum is considered to be a "morphological" indicator of damage to the renal tubules (as opposed to serum creatinine, which is only a marker of kidney activity) [11, 13]. Increased concentration of NGAL in urine indicates damage to the proximal convoluted tubule of the nephron and lack of resorption. However, the majority of urine NGAL is synthesized in the distal part of the nephron in response to ischemia or exposure to nephrotoxic agents [10]. A clinically negligible expression of NGAL has also been shown in numerous other human tissues but only significantly increasing serum NGAL levels in response to inflammatory agents. The increase in concentration of urine NGAL during AKI is significantly larger than the increase in the serum NGAL.

The aim of the study was to compare the concentrations of NGAL in serum and urine for AP patients with AKI and AP patients without AKI at 24, 48 and 72 hours after the onset of acute pancreatitis.

Materials and methods

This prospective observational study included 65 adult patients with a diagnosis of AP, treated in the Department of Surgery, District Hospital in Sucha Beskidzka, Poland between January and December 2014. AP was diagnosed based on the revised Atlanta Classification 2012 [14]. The patients with symptoms of AP lasting longer than 24 hours and those who have not signed an informed consent form were excluded from the study. The severity of AP was stratified according to the revised Atlanta Classification into mild (MAP), moderately severe (MSAP) or severe AP (SAP), based on the presence of transient or persistent organ failure, exacerbation of comorbidities and/or local complications. AKI was diagnosed according to KDIGO guideline, i.e. when serum creatinine increased ≥26.5 μmol/L within 48 hours, or ≥1.5-times within 7 days or urine volume was <0.5 ml/kg/h for 6 hours [15]. All laboratory tests conducted for the routine assessment of patients were performed in the Department of Laboratory Diagnostics Health Care Centre in Sucha Beskidzka on the date of the order. Measured parameters included amylase activity, concentration of total calcium, serum albumin, blood urea nitrogen (BUN), serum creatinine, C-reactive protein (CRP) and complete blood counts. Complete

blood counts were performed on whole blood in K_2EDTA using an automated hematology counter type 5-diff Sysmex XE 2100 (Sysmex Corp., Japan). Urine NGAL (uNGAL) concentration was measured in individual urine samples with an ARCHITECT Analyzer Abbott Diagnostics (Abbott Park, USA) using chemiluminescent microparticle immunoassays (CMIA). Concentration of NGAL in blood serum (sNGAL) was measured using Human Lipocalin-2/NGAL ELISA kits from BioVendor (Brno. Czech Republic) on the Automatic Micro ELISA Reader ELX 808 (BIO-Tek® Instruments Inc., Winooski, VT, USA).

The study design was approved by the Bioethics Committee of the Jagiellonian University (Decision No. KBET/247/B/2013).

Statistical analysis

Categorical data were reported as numbers of patients (percentage of the appropriate group) and compared with the chi-squared test. Median (lower-upper quartile) or mean ± standard deviation were reported for continuous variables. The variables' distributions were checked for normality using the Shapiro–Wilk's test. The differences between groups were tested with the t-test or Mann–Whitney's test. Simple correlations between NGAL and the selected variables were assessed with the Spearman's rank coefficient as both sNGAL and uNGAL were characterized by non-normal distributions. Odds ratios (OR) of 95% with confidence intervals (CI) of 95% were reported in case of the simple and multiple logistic regression; multiple models were adjusted for a-priori chosen confounders. The results were considered significant at $p < 0.05$. The Statistica 12.5 software package (StatSoft, Tulsa, USA) was used for computations.

Results

AP was classified as mild in 46 (71%), moderately-severe in 14 (22%), and severe in 5 (8%). At the early phase of AP, 11 patients (17%) developed AKI according to the KDIGO criteria. AKI stage 1 was diagnosed in 10 patients and stage 2 in one patient. The clinical and laboratory characteristics of patients with and without AKI are reported in Table 1. The diagnosis of AKI was associated with more severe AP, higher BISAP scores, the necessity for more intensive treatment and longer hospital stay, as well as with higher mortality (although there were only 3 deaths, all in late phase of the disease) (Table 1). Patients with and without AKI did not differ in overall prevalence of comorbidities, however, chronic kidney disease and diabetes were significantly associated with AKI (Table 1). The comorbidities were observed in nearly 80% of patients, most commonly hypertension (22 patients, 34%), ischemic heart disease (18 patients, 28%), and diabetes (10 patients, 15%); 7 patients (11%) were diagnosed with lung diseases and 3 (5%) with kidney diseases (chronic kidney disease stage G3 in 2 patients and G4 in 4 patients).

Table 1. Clinical characteristics of patients with acute pancreatitis (N = 65) and the results of laboratory tests at 24 hours.

Variable	Patients without AKI (N = 54)	Patients with AKI (N = 11)	p
Male sex, N (%)	27 (50)	7 (63)	NS
Age, years	59 ± 18	69 ± 17	NS
Duration of pain until admission, hours	12 (6–24)	16 (8–24)	NS
Duration of hospital stay, days	6 (5–8)	14 (10–27)	<0.001
Mild acute pancreatitis, N (%)	45 (83)	1 (9)	
Moderately severe acute pancreatitis, N (%)	8 (19)	6 (55)	<0.001
Severe acute pancreatitis, N (%)	1 (2)	4 (36)	
BISAP score ≥3 in the first 24 hours, N (%)	0	6 (55)	<0.001
Co-morbidities, N (%)	40 (74)	10 (91)	NS
Renal disease diagnosed before AP, N (%)	1 (2)	2 (18)	0.020
Diabetes, N (%)	6 (11)	4 (36)	0.034
SIRS, N (%)	2 (4)	6 (55)	<0.001
Pancreatic or peripancreatic necrosis, N (%)	1 (2)	2 (18)	0.020
Peripancreatic fluid collections, N (%)	5 (9)	0	NS
Transient organ failure, N (%)*	2 (4)	4 (36)	<0.001
Persistent organ failure, N (%)*	1 (2)	4 (36)	<0.001
Pleural effusion, N (%)	7 (13)	6 (55)	0.002
Antibiotic prophylaxis, N (%)	21 (40)	10 (91)	0.002
Parenteral nutrition, N (%)	0	3 (27)	0.003
Surgery, N (%)	1 (2)	2 (18)	0.020
Early mortality / late mortality, N (%)	0 / 1 (2)	0 / 2 (18)	– / 0.019
Leukocytes, $x10^3/\mu l$	11.2 (9.3–14.6)	13.6 (10.4–18.4)	NS
Neutrophils, $x10^3/\mu l$	9.1 (7.4–11.0)	10.7 (6.6–15.6)	NS
Hematocrit, %	43.1 ± 4.6	39.4 ± 6.3	NS
Platelets, $x10^3/\mu l$	240 (201–266)	130 (116–230)	0.001
Amylase, U/l	1217 (631–1873)	733 (432–1046)	NS
Glucose, mmol/l	7.8 (6.4–10.1)	9.6 (6.6–12.6)	NS
Serum albumin, g/l	40.6 (37.7–44.1)	37.6 (29.0–40.0)	0.015
CRP, mg/l	12.2 (2.5–76.8)	128.0 (74.6–225.7)	<0.001
Calcium, mmol/l	2.35 (2.21–2.43)	2.18 (1.80–2.39)	NS

Variable	Patients without AKI (N = 54)	Patients with AKI (N = 11)	p
Urea, mmol/l	5.9 (4.3–6.9)	11.7 (6.7–15.2)	0.003
Creatinine, µmol/l	73 (63–92)	157 (104–211)	<0.001
Urine albumin, mg/dl	340 (150–990)	2300 (560–4650)	0.024
sNGAL, ng/ml	105 (68–137)	276 (229–427)	<0.001
uNGAL, ng/ml	26.3 (14.9–43.7)	550.6 (72.6–856.2)	<0.001

N — number of patients; BISAP — bedside index for severity in acute pancreatitis; SIRS — systemic inflammatory response syndrome; NGAL — neutrophil gelatinase-associated lipocalin; s — serum; u — urine; CRP — C-reactive protein
* according to modified Marshall scoring system.

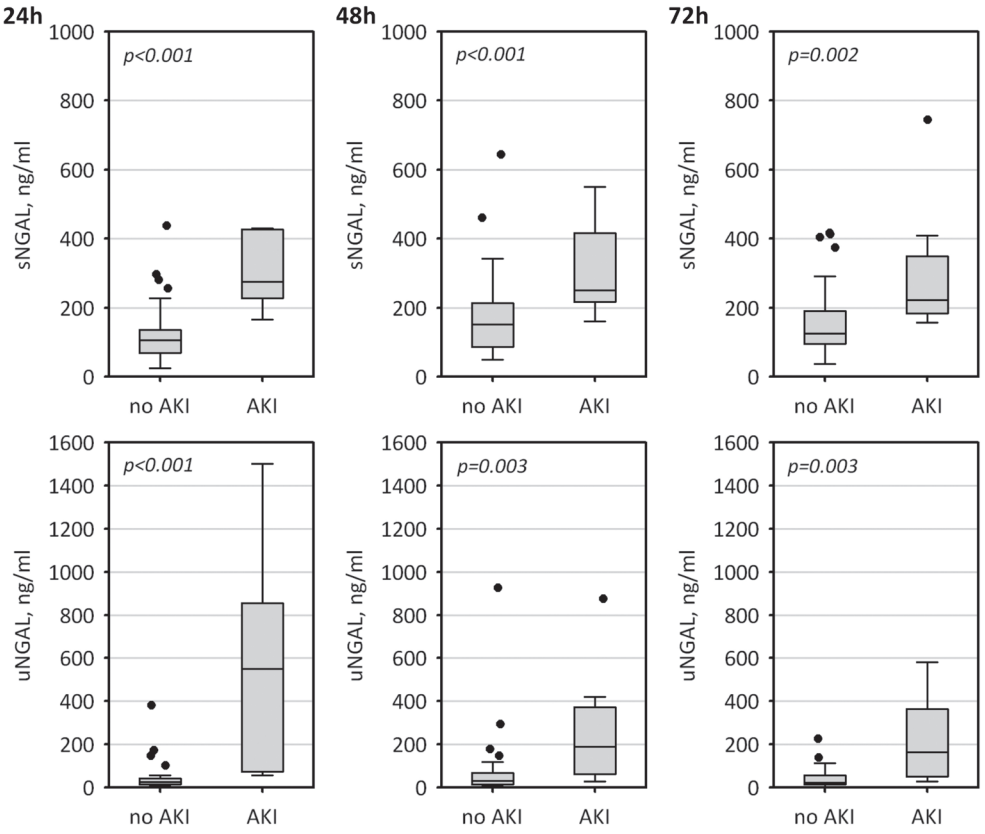

Fig. 1. NGAL concentrations in serum (sNGAL) and urine (uNGAL) of patients with and without AKI at 24, 48 and 72 hours after onset of symptoms of AP. Data are shown as median, 25–75 percentile (boxes) and non-outlier range (whiskers), points represent the outliers.

At 24 hours after the onset of AP, the patients who do not developed AKI were characterized by higher platelets, decreased in serum albumin, and increased in CRP, urea, creatinine as well as higher urine albumin concentrations (Table 1). Serum and urine NGAL concentrations were significantly higher in AKI patients throughout the study (Table 1, Fig. 1).

In logistic regression analysis, both serum and urine NGAL concentrations significantly predicted AKI (Table 2). The association between sNGAL and uNGAL with AKI was independent of age, sex and comorbidities. The odds ratios for AKI estimated for sNGAL and uNGAL were of similar magnitude.

Table 2. Serum and urine NGAL concentrations as predictors of acute kidney injury in patients with acute pancreatitis.

Time*	Independent variable	Simple OR (95% CI)	Adjusted** OR (95% CI)
24 hours	sNGAL, per 10 ng/ml	1.20 (1.08–1.33)	1.09 (1.02–1.18)
	uNGAL, per 10 ng/ml	1.20 (1.08–1.35)	1.11 (1.01–1.21)
48 hours	sNGAL, per 10 ng/ml	1.08 (1.02–1.14)	1.07 (1.01–1.14)
	uNGAL, per 10 ng/ml	1.08 (1.01–1.15)	1.08 (1.01–1.16)
72 hours	sNGAL, per 10 ng/ml	1.09 (1.02–1.17)	1.19 (1.03–1.38)
	uNGAL, per 10 ng/ml	1.10 (1.02–1.18)	1.20 (1.02–1.41)

* Time between the onset of AP symptoms and blood/urine collection for NGAL determination.
** The models were adjusted for age, sex and comorbidities.

Table 3. Simple correlations between serum and urine NGAL concentrations and the selected variables during the first 72 hours of acute pancreatitis.

Variable	24 h		48 h		72 h	
	sNGAL	uNGAL	sNGAL	uNGAL	sNGAL	uNGAL
Urea	R = 0.34 p = 0.007	R = 0.21 p = 0.1^{NS}	R = 0.25 p = 0.042	R = 0.34 p = 0.008	R = 0.34 p = 0.005	R = 0.35 p = 0.005
Creatinine	R = 0.40 p <0.001	R = 0.16 p = 0.2^{NS}	R = 0.33 p = 0.009	R = 0.32 p = 0.011	R = 0.22 p = 0.08^{NS}	R = 0.11 p = 0.4^{NS}
Creatinine max. change*	R = 0.43 p <0.001	R = 0.45 p <0.001	R = 0.39 p = 0.001	R = 0.38 p = 0.002	R = 0.46 p <0.001	R = 0.39 p = 0.001
Urine albumin	R = 0.31 p = 0.013	R = 0.51 p <0.001	R = 0.52 p <0.001	R = 0.58 p <0.001	R = 0.11 p = 0.4^{NS}	R = 0.21 p = 0.1^{NS}
CRP	R = 0.66 p <0.001	R = 0.58 p <0.001	R = 0.70 p <0.001	R = 0.41 p <0.001	R = 0.60 p <0.001	R = 0.53 p <0.001
Neutrophils	R = 0.49 p <0.001	R = 0.31 p = 0.014	R = 0.71 p <0.001	R = 0.42 p <0.001	R = 0.67 p <0.001	R = 0.57 p <0.001

NGAL — neutrophil gelatinase-associated lipocalin; s — serum; u — urine; CRP — C-reactive protein
* Maximum change in serum creatinine concentrations during the first 72 hours after the onset of symptoms of AP

Moreover, both serum and urine NGAL concentrations were significantly correlated with other laboratory markers of kidney function, i.e. serum urea, serum creatinine and urine albumin (Table 3). Of note, the correlations between NGAL and creatinine concentrations were relatively weak or even non-significant in some time-points, however, there were significant correlations between both serum and urine NGAL and maximum change in serum creatinine, throughout the study (Table 3). Also, both serum and urine NGAL were positively correlated with the direct neutrophil counts as well as with CRP concentrations (Table 3).

Discussion

The clinical diagnosis of acute pancreatitis requires at least two of the three diagnostic criteria: abdominal pain typical to AP, at least a threefold increase of lipase or amylase in serum and CT imaging consistent with AP [16]. However, these criteria indicate neither the severity nor prognosis of the disease. For these, the clinician needs to conduct an experienced analysis of a multitude of additional studies. This requires careful clinical observation and continuous monitoring of many parameters such as heart and respiratory rates, arterial blood gases, body temperature, pulse oximetry, serum creatinine, blood urea nitrogen, level of consciousness on the Glasgow Coma Scale, the presence of pleural effusion and the presence and extent of pancreatic necrosis as measured by Balthazar scoring [3, 17–18]. It should be emphasized that in the case of a patient with AP lasting more than 48 hours, organ failure is the major predictor of morbidity and mortality regardless of the assessment method of the severity of AP (Ranson Scale, APACHE II, BISAP score) [3, 9, 19–21]. The assessment of multiple organ dysfunction (Marshall score) is essential for the formulation of a personalized patient treatment plan including indications for intravenous fluid administration, enteral and parenteral nutrition, pain management, decompressive nasogastric tube, antibiotics, percutaneous drainage, endoscopic treatment or laparotomy [8, 14, 16, 22]. The Marshall score assumes a loss of kidney function when serum creatinine is between 168 and 318 mmol/L (1.9–3.6 mg/dL), while levels below 124 mmol/L (1.4 mg/dL) indicate normal kidney function [23]. This classification is not consistent with the definition of AKI currently used by nephrologist. Notably, KDIGO guidelines are based on the change of serum creatinine concentration over time as well as hourly urine output [15]. These guidelines specify treatment protocols for patients depending on the severity of AKI and can be useful in speeding up decision making in time-sensitive cases [15]. In the present study, the severity of AKI as defined by KDIGO correlated with a longer hospital stay, severity of AP, severity of disease as assessed with the BISAP score upon admission, the advent of systemic inflammatory response syndrome (SIRS), persistent organ failure and the presence of pleural effusion. Patients with diagnosed AKI had more frequent need for antibiotic administration and surgical intervention. These results are confirmed by

the observations of other authors, for whom the presence of AKI indicated a poor prognosis for AP patients [24–25]. But, since evaluating AKI based on serum creatinine and urine output can be inadequate, the clinician is in need of a simple biomarker for the assessment of patients with AP with special consideration of renal function. The ideal biomarker, to be useful clinically, should be easy to measure and interpret, dynamically responsive to the patient's condition and reliable in informing therapeutic decisions. Based on previous studies, NGAL concentrations in the serum and urine are excellent candidates as clinically useful biomarkers in the evaluation of patients with AP. Patients with AKI had significantly higher concentrations of sNGAL and uNGAL compared to those that did not develop this complication. Additionally, this study's results demonstrate that significantly higher levels of NGAL in serum and urine also correlate with a more severe clinical state (e.g. higher BISAP scores in the first 24 hours, greater organ dysfunction assessed via Marshall score, accompanying pancreatic necrosis or presence of pleural effusion) and higher parameters of inflammation (CRP and direct neutrophil count) [Table 1]. Lipinski *et al.* [2] observed that urine NGAL levels in AP patients, particularly when collected in the first 24 hours, is a reliable predictor of more severe disease and mortality. In the cited work uNGAL levels above 68.9 ng/mL were predictive of SAP [2]. Our clinical observations support this interpretation of uNGAL levels to rapidly identify AP patients at risk for AKI, when the samples are taken during the first day of hospitalization. The vast majority of patients our study group that developed AKI had concentration uNGAL was higher than 100 ng/mL. It can be concluded that these patients would benefit from immediate and aggressive prevention of AKI. This should primarily include intensive rehydration precisely regulated by the daily urine output, blood pressure and blood volume based on daily measurements of body weight. It should also include the elimination of potentially nephrotoxic drugs and avoiding the use of imaging studies with potentially nephrotoxic contrast agents, at least until the decrease in the concentration of uNGAL. These patients also require careful dosage of drugs metabolized by the kidney, depending on their degree of function. Measuring uNGAL again after 48 hours allows for the evaluation of the effects of treatment of AKI in AP patients. A significant decrease in concentration of uNGAL infers a reduction or avoidance of AKI and should be considered as an effective treatment of this complication. As such, in the case of avoiding AKI in AP, uNGAL can be thought of as a "renal troponin" similarly predictive as its cardiac counterpart. Other studies have also shown that uNGAL levels change dynamically over time (in as little as four hours), after the activation of a nephrotoxic contrast agent. The measurement of urine NGAL levels is simple, fast, responsive to change, easily added to routine laboratory protocols and provides the clinician with diagnostically and therapeutically relevant information. This marker has significant potential for practical application in monitoring the kidney function of patients with AP. Neyra *et al.* [26] found that in patients with AKI in intensive care units, albuminuria greater than 30 mg/dL on the dipstick test correlates with a potentially

worse prognosis in their AKI recovery compared to similar patients with lower albuminuria. Those results correspond well with our study's significant correlations of high uNGAL and sNGAL levels with high albuminuria urine samples (all above 150 mg/dL). This correspondence indicates that the levels of these biomarkers in patients 24 and 48 hours after the onset of abdominal pain have predictive value for AKI. Monitoring serum NGAL during the subsequent days of AP allows the clinician to expect either improvement or systemic inflammation and the development of SIRS (*Systemic Inflammatory Response Systems*). Lipinski *et al.* [2] observed that the initial phase of SAP is marked by the release of NGAL from ischemic cells and organs (particularly the kidney), which is typical of the pathophysiology of acute systemic diseases. In our study, measurement of sNGAL at 24, 48 and 72 hours after admission yielded comparably increasing concentrations. This increase should be treated like other acute phase proteins, such as increasing CRP or declining serum albumin, that signal a systemic inflammatory process developing as part of AP. Although the authors observed a statistically significant correlation between the increase of sNGAL in AP patients with AKI compared to AP patients without AKI (229–427 ng/mL vs 68–137 ng/mL), it is the levels of uNGAL that showed the more remarkable correlations for these two groups of patients (72.6–856.2 ng/mL vs. 14.9–43.7 ng/mL) [Table 1]. This conclusion is supported by the study authored by Soto *et al.* [27] based on prospective observation of 616 ICU patients, confirming the usefulness of sNGAL levels in the monitoring of renal function in patients with AKI [27]. Measurements of NGAL in the urine and serum, however, have its limitations. Because it is a protein associated with neutrophil gelatinase, the increase in NGAL levels can be a consequence of the presence of an infection in the body which may not necessarily be associated with AP (eg. bacterial pneumonia or pyelonephritis) [28]. There is also evidence that sNGAL levels increase in patients with pancreatic cancer, and although it is not a very specific marker for this disease, this protein may be present in the early stages of tumor development [29]. It is also reported that concentration of sNGAL may increase in cancers of other organs including the ovaries, lungs and stomach [30–32]. Increases in uNGAL are in turn observed in patients with chronic renal failure even in the very early stages [33], and in patients with leukocyturia, which may limit the predictive quality of the biomarker in the assessment of renal failure in patients with AP. These limitations require further study to validate.

Conclusions

Acute pancreatitis is a complex disease that if accompanied by organ failure can cause serious complications and death. Measuring NGAL levels, particularly in urine, in patients with AP is simple, easy to interpret, routinely available and above all clinically useful in the diagnosis and evaluation of dynamic changes in renal function. NGAL levels in

these patients is correlated with other parameters of inflammation and is most useful as an additional test in the assessment of ongoing systemic inflammation. These results need further research on larger groups of patients to be fully validated.

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Conflict of interest

No declared.

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