JACOBS PUBLISHERS

OPEN ACCESS

Jacobs Journal of Emergency Medicine

Research Article

New Biomarkers in the Management of Sepsis in the Emergency Department: Role of Galectin-3

Claudia Galluzzo[*1], Elisa Pizzolato[2,3], Marilena Rende[4,5], Manuela Lucchiari[4,6], Samuele Raso[4,6], Anna Rita Vitale[4,6], Monica Masoero[1,3], Marco Ulla[1], Letizia Barutta[2,3], Elena Maggio[2], Bruno Tartaglino[2], Enrico Lupia[1], Giulio Mengozzi[4], Stefania Battista[1]

[1]*Emergency Medicine Department, "Città della Salute e della Scienza" University Hospital, Turin, Italy*

[2]*Emergency Medicine Department, Santa Croce and Carle Hospital, Cuneo, Italy*

[3]*School of Emergency Medicine, University of Turin, Italy*

[4]*Clinical Biochemistry Laboratory "Città della Salute e della Scienza" University Hospital Turin, Italy*

[5]*School of Clinical Biochemistry, University of Turin*

[6]*School of Clinical Pathology, University of Turin*

**Corresponding author: Dr. Claudia Galluzzo, Emergency Medicine Department, Corso Bramante, 88 - 10126 Turin, Italy, Tel : 39011633564; E-mail: claudia88.galluzzo@gmail.com*

Received: 05-27-2015

Accepted: 06-09-2015

Published: 07-23-2015

Copyright: © 2015 Claudia

Abstract

Purpose

To evaluate the diagnostic and prognostic role of Galectin-3 as compared to Procalcitonin in patients presenting to the Emergency Department with SIRS and either suspected infection or not.

Methods

Multicenter observational study including 163 patients (final diagnosis was sepsis in 37, severe sepsis/septic shock in 94 and SIRS in 32 who served as the control group). Blood samples were collected at the first medical assessment and analyzed using the Galectin-3 Vidas® assay. Definitive diagnosis and 30 days in-hospital mortality were obtained from the analysis of digital medical records.

Results

Galectin-3 distinguished the population with severe sepsis/septic shock (median plasma concentration 31.3 ng/mL, 95% CI 25.5-37.4) from patients with sepsis (20.2 ng/mL, 15.1-25.5)(p=0.007) but not from patients with SIRS (25.4 ng/mL, 17.4-41.8). The Area under the ROC curve of Galectin-3 was 0.70 (95% CI 0.61-0.77) and the best combination of sensitivity (79.6%, 95% CI 69.9-87.2) and specificity (55.6%, 38.1-72.1) was detected at Galectin-3 threshold of 20.7 ng/mL. Galectin-3 concentrations were correlated with leukocytes (p=0.0003), lactate (p=0.026) and PCT (p=0.0003). In patients with poor prognosis Galectin-3 values were higher and Galectin-3 was the only statistically significant prognostic factor according to Cox regression analysis, when combined with other clinical and laboratory parameters.

Conclusions

Galectin-3 is a promising marker of disease severity in the clinical management of sepsis and could play a role as an independent prognostic factor, any increase in its concentrations being associated with poor outcome.

Keywords: Sepsis; Biomarkers; Galectin-3; Procalcitonin; Emergency Department

Introduction

Sepsis is among the most frequent clinical condition handled in the Emergency Department (ED). Its incidence and mortality remains high despite the improvement in the antibiotic therapy associated with cardiovascular and respiratory supports.

In the United States, there are about 750.000 cases of severe sepsis and septic shock each year and short term mortality is 20% or more [1]. Even if two recent randomized trials (ProCESS and ARISE trials) questioned the EGDT (Early Goal-Directed Therapy) efficacy as a key strategy to decrease mortality, the most recent sepsis guidelines published in 2013 by the Surviving Sepsis Campaign, suggest an early diagnosis and a prompt administration of the appropriate therapy as strong recommendations [1-3].

Blood cultures, which can support physicians in the right antibiotic choice, are diagnostic in only 25% of subjects with clinical signs of sepsis [4]. Biomarkers may provide an important contribution in detecting the infections. Inthe last years, new molecules have been tested for this purpose, but very few of them are currently used in the clinical practice [5].

In the recent past, C-Reactive Protein (PCR) and Procalcitonin (PCT) have been widely used in this setting. Nowadays PCR and PCT plasma levels more than two standard deviations (SD) above the normal value are part of the sepsis definition [4,6]. In addition, it was observed that a reduction in PCT concentrations is associated with the improvement in the clinical conditions and may guide the physician judgment in the eventual discontinuation of antibiotic therapy in those patients who appeared septic but have no subsequent evidence of infection [7].

However, the diagnostic accuracy of both these biomarkers is limited by the findings of increased levels in non-infectious inflammatory conditions (e.g. surgery, burns, trauma).

Presepsin, the soluble subtype of cluster of differentiation 14 (sCD14-ST), expressed on macrophage surface, takes part of the inflammatory cascade, contributing to the interaction between lipopolysaccharides (LPSs) and LPS-binding proteins. Several studies demonstrated that it has high sensitivity and good specificity for sepsis [8, 9]. However, the interpretation of its concentrations could be altered in the elderly and/or in renal failure [10].

Galectin-3 is an approximately 30 kDa lectin, encoded by a single gene, LGALSS3, located on chromosome 14. It belongs to the family of galectins, a group of proteins that bind carbohydrates, equipped with a specific sequence that recognizes the β-galactose [11]. In this family of proteins, Galectin-3 is unique for its chimeric structure consisting of a C-terminal domain for carbohydrate recognition (CRD, Single Carbohydrate Recognition Domain) which allows specific binding of the fragments of β-galactose, and a N-terminal domain which takes part in protein oligomerization [12,13]. Galectin-3 has a broad tissue distribution and is mainly expressed on the innate immunity cell membrane surface, in particular in macrophages. It plays both intra-and extracellular functions and can be passively released by damaged cells or secreted through an active way; when it loses its leader sequence, it localizes in the cytosol and participates in many cellular events, including apoptosis. In the extra-cellular environment, it interacts with extracellular matrix proteins (ECM) in order to promote cellular adhesion or to act as soluble ligand, reacting with many different molecules, such as CD66a and CD66b leading to the activation and degranulation of neutrophils and eosinophils via the MAP kinases [12,13] .

It is directly implicated in inflammatory and fibrotic processes and it also exerts a role in the modulation of immune response to various stimuli [14-16].

A preliminary study showed that Galectin-3 significantly differs in patients with SIRS and sepsis and may improve the diagnostic power of CRP, when combined [17]. Furthermore, a study carried out on the general population found that high concentrations of this lectin are predictors of mortality from any cause [18].

The availability of rapid and automated methods for the measurement of Galectin-3, based on chemiluminescent enzyme immunoassay, may allow its use in the clinical practice and also in the emergency setting [19].

Based on these premises, we compared Galectin-3 with PCT in terms of diagnostic and prognostic efficacy in an adult population admitted to the Emergency Department with SIRS (control group), suspected sepsis, severe sepsis and septic shock (study group).

Materials and Methods

Study Design and Setting

We conducted a multicenter and an observational study of patients presenting to the ED with a diagnosis of SIRS and either confirmed or suspected sepsis, severe sepsis and septic shock at the first medical evaluation.

Selection of Participants

Patient enrollment was conducted in a six-month period. An informed consent to participate in the study, in accordance with the principles of the Ethics Committee of Turin University Hospital and Santa Croce and Carle Hospital of Cuneo

based on the Declaration of Helsinki (1964), was obtained from each patient or one of his relatives.

One hundred and sixty-three patients (48 females, 83 males) referred to the ED of Città della Salute e della Scienza University Hospital of Turin and Santa Croce and Carle Hospital (Cuneo) with the suspicion of sepsis, severe sepsis or septic shock and thirty-two subjects (12 females, 20 males) affected by SIRS were enrolled as controls. In Table 1 demographic and clinical characteristics of the patients recruited in the study are shown.

Table 1. Demographic and clinical characteristics of subjects in the study.

	SIRS (n=32)	SEPSIS (n=37)	SEVERE SEPSIS /SEPTIC SHOCK (n=94)	ANOVA p-value <0.05
MALE	20	25	58	/
FEMALE	12	12	36	/
AGE	46 (18-92)	78 (27-99)	72 (28-98)	< 0.001 Controls vs Sepsis and Septic Shock
SOFA SCORE	3 (0-6)	4 (0-11)	7 (0-17)	< 0.001 Septic Shock vs Sepsis and Controls
APACHE II SCORE	10 (0-18)	15 (2-29)	16 (4-38)	<0.001 Controls vs Sepsis and Septic Shock

Values are described as medians and (range: minimum and maximum). SOFA and APACHE II scores are calculated at the first evaluation in the Emergency Department.

The inclusion criteria were: patients who could undergo a blood test, presence of at least two clinical criteria for SIRS, suspected diagnosis of sepsis, severe sepsis and septic shock (according to the American College of Chest Physicians/Society of Critical Care Medicine and the International Surviving Sepsis Campaign Guidelines Committee) [19,20]. Exclusion criteria were: patients unable to provide informed legal consent, age less than 18 years, the presence of a valid different diagnosis.

Data Collection and Processing

On admission in the ED, clinical and biochemical data were collected before any medical treatment; using clinical parameters and blood test results, Acute Physiology and Chronic Health Evaluation II (APACHE II) score [21] and Sequential Organ Failure Assessment (SOFA) score [22] were calculated. After the appropriate treatment in the ED, patients were admitted to intensive care areas to continue the diagnostic and therapeutic process.

Collected samples were stored at -70° C and were subsequently analyzed for Procalcitonin and Galectin-3 in the Clinical Chemistry Laboratory of Turin University Hospital.

The analysis of digital medical records and the criteria of the International Guidelines for Management of Severe Sepsis and Septic Shock [2] were used to obtain a definitive diagnosis (SIRS, sepsis, severe sepsis, septic shock); the prognostic role of biomarkers was assessed by correlating their values to the in-hospital mortality at 30 days.

Methods of Measurement

Endotoxin-free tubes containing ethylenediaminetetraacetate (EDTA) were used to collect blood samples, which were then centrifuged al 3000g for ten minutes and then stored at -70° C until they were assayed blindly for PCT and Galectin-3 measurements.

Galectin-3 was determined using the VIDAS® (bioMérieux, Bagno a Ripoli, Florence, Italy) automated method which requires about twenty minutes to be completed. It is a quantitative test which allows the assessment of Galectin-3 concentrations in human serum or plasma by means of Enzyme-Linked Fluorescent Assay (ELFA) technique. The volume of sample to be used is 200 µL. The VIDAS kit includes cartridges consisting of 10 wells and a disposable cone, sensitized with mouse monoclonal antibodies against Galectin-3. Samples are transferred into the well containing anti-Galectin-3 antibodies labeled with alkaline phosphatase (ALP). The mixture sample/conjugate is drawn and released several times from the cone. In this way, Galectin-3 binds both to immunoglobulins and to labeled antibody. In the detection step, the substrate (4-Methyl-umbelliferil phosphate) is aspirated/released from the cone. The enzyme, linked to the conjugate, catalyzes its hydrolysis in a fluorescent product (4-methyl-umbelliferone). The intensity of the emitted fluorescence is measured at 450 nm and the signal value of the fluorescence is proportional to the concentration of Galectin-3 in the sample. The clinical performance of VIDAS analyzer has been evaluated by a group of 1387 patients suffering from chronic heart failure with left ventricular dysfunction and symptoms of NYHA class II, III or IV. The values of the molecule obtained were classified according to the following three categories of mortality and hospitalization risk: “Low-risk” (64.5% of the total number of enrolled patients) ≤17.8 ng/mL; “Moderate risk” (27%): >17.8 and ≤25.9 ng/mL; “Strong risk” (8.5%): >25.9 ng/mL.

Procalcitonin concentrations were measured by the method Elecsys® BRAHMS PCT (Roche Diagnostics). It is an electrochemiluminescence immunoassay (ECLIA) for the in vitro quantitative determination of the concentration of Procalcitonin (PCT) in serum or plasma. The test took about 18 minutes and the assays were performed automatically on the analyzer e601® Cobas (Roche Diagnostics, Mannheim, Germany).

Statistical Analysis

The One-way Analysis of Variance (ANOVA), followed by the test of correction according to the Student-Newman-Keuls, was used to evaluate differences among the three patient populations and to compare the diagnostic efficacy of biomarkers in the study. The correlation of biomarker values with clinical and laboratory data was obtained using Spearman’s rank correlation test.

The Kaplan-Meier curve was built to estimate the prognostic

role of Galectin-3.-

In order to estimate how changes in Galectin-3 concentrations, taken as an independent variable, affect survival, the semiparametric Cox regression model was applied. The same model was used to evaluate the combination of Galectin-3 results with laboratory tests and clinical scores. Statistical analysis and graphing were performed using the software MedCalc® (MedCalc Software, Belgium).

A P-value <0.05 was considered to be significant.

Results

Characteristics of Study Subjects

The study was carried out on a total of 163 patients: 32 were suffering from a condition of SIRS without evidence of an infectious outbreak, 37 were diagnosed with sepsis and 94 had severe sepsis/septic shock. Table 1 shows some demographic and clinical scores of the study population.

Diagnostic Role

The median Galectin-3 concentrations in the three study groups are 25.4 ng/mL (range: 6.6-100.0; 95% confidence interval: 17.4-41.8) in the control group, 20.2 ng/mL (6.0-63.5; 15.1-25.5) in sepsis, and 31.3 ng/mL (6.0-100.0; 25.5-37.4) in severe sepsis/septic shock (Figure1).

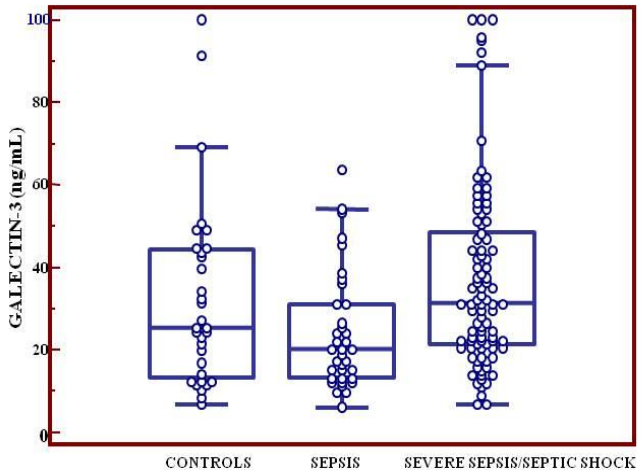

Figure 1. Galectin-3 concentrations in the study populations.

Upon arrival to the Emergency Department, Galectin-3 concentrations were significantly higher in patients with severe sepsis/septic shock than in those with sepsis (p=0.007), whereas there was no statistically significant difference between patients with SIRS and those with sepsis/severe sepsis/septic shock (p>0.05).

PCT median concentrations in controls, sepsis and severe sepsis/septic shock groups were 0,030 ng/mL (range: 0,02-12,3; 95% confidence intervals: 0.02-0.13), 1,1 ng/mL (0,05-61,2; 0.50-2.15), and 6.85 ng/mL (0,07-100.0; 3.33-11.9),respectively. The biomarker showed to be higher in severe sepsis/septic shock than in sepsis and in SIRS (both p<0.001) (Figure 2).

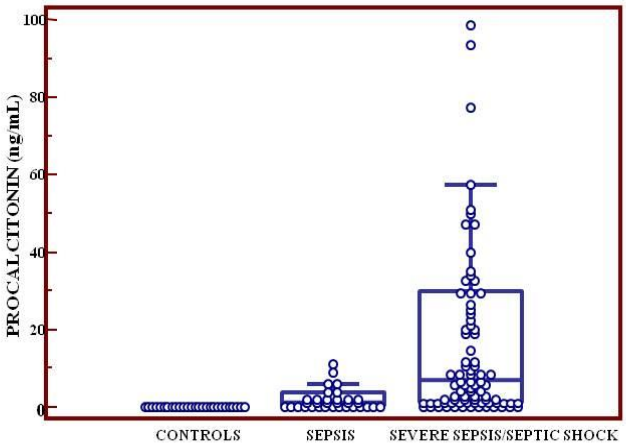

Figure 2. Procalcitonin concentrations in the study populations.

Galectin-3 values significantly correlated with the count of leukocytes (p=0.0003, ρS=0.29), blood lactate levels (p=0.026, ρS=0.20) as well as with PCT concentrations (p=0.0003, ρS=0.28) (Figure3). The correlation with clinical scores (APACHE II and SOFA) didn't result statistically significant (p>0.05).

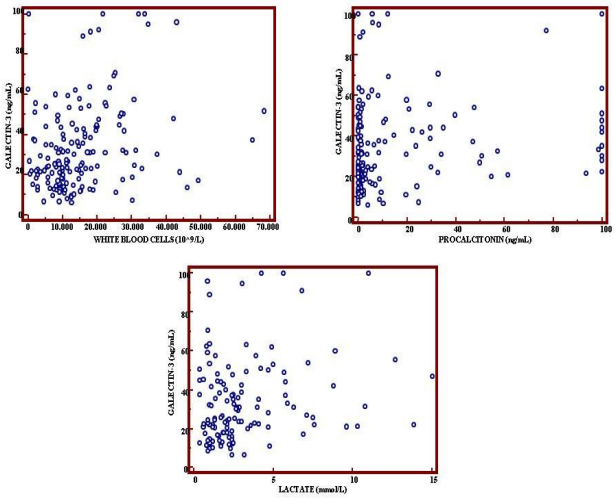

Figure 3. Correlation between Galectin-3 concentrations and White Blood Cells, Procalcitonin and lactate levels.

Diagnostic Accuracy

The ROC curve of Galectin-3 distinguishing patients with severe sepsis/septic shock from those with sepsis was significant with an AUC of 0.70 (p=0.0001).

The best cut-off in terms of diagnostic accuracy was found at a Galectin-3 concentration of 20.7 ng/mL, with 69.6% sensitivity (95% CI: 69.9-87.2) and 55.6% specificity (95% CI: 38.1-72.1).

The AUC for PCT ROC curve distinguishing cases from controls was 0.73 (p=0.0001) and the best cut-off in terms of diagnostic accuracy was found at a PCT levels of 5.82 ng/mL, with 54.3% sensitivity (95% CI: 43.7-64.6) and 83.8% specificity (95% CI: 68.0-93.8).

It was not observed a statistically significant difference between the ROC curves of Galectin-3 and PCT (p=0,63, 95% IC: 0.089-0.147) (Figure4).

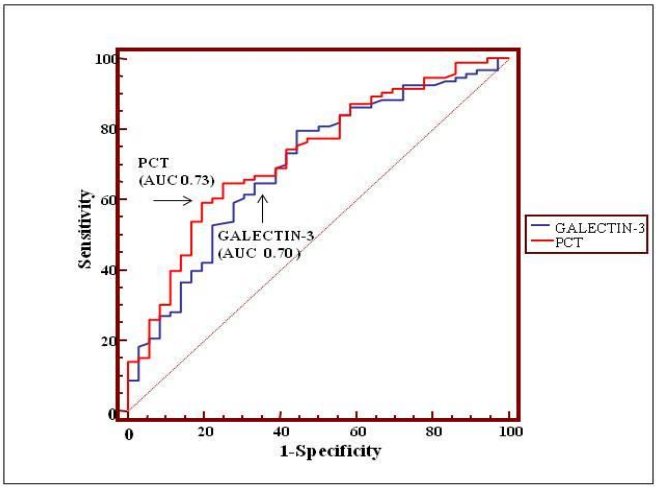

Figure 4. The ROC curves of the study biomarkers.

Prognostic Role

According to Kaplan-Meier curve analysis, Galectin-3 values at first evaluation in the ED were able to significantly predict 30-day mortality in our study population, higher concentrations been associated with poor outcome (p=0.03) (Figure5).

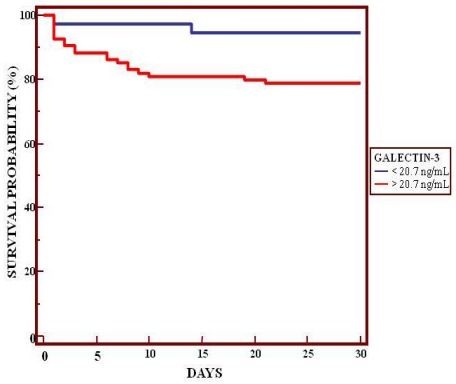

Figure5. Kaplan-Meier curve showing correlation between Galectin-3 values at first evaluation in the ED and 30-day mortality in the study population: concentrations higher than 20.7 ng/mL were associated with poor outcome (p=0.003).

Furthermore, Galectin-3 was the only variable that allows to estimate the survival rate in the study patients (p=0.0002) when the Cox regression model was applied, including laboratory parameters (leukocytes, lactate, bicarbonate) and changes in the concentrations of PCT.

Limitations

The limited size of the population included in this study does not allow to better clarify possible implications of Galectin-3 as a diagnostic tool in the septic population. When tested on a larger cohort of patients, we cannot exclude that a subpopulation analysis, e.g. differentiating patients with severe sepsis from those with septic shock, would reveal a lower concentration of Galectin-3 in more compromised patients, thus demonstrating its potential protective role. The strong prognostic power of Galectin-3 tested on admission should be further investigated by assessing whether serial measurements could help monitoring the patient response to treatment. This may be applied also in an in-depth analysis of cost-benefit effectiveness taking into account the introduction of this new biomarker in combination with those actually used in the management of sepsis patients.

Discussion

Sepsis, severe sepsis and septic shock are frequently handled in the Emergency Department and represent one of the major causes of mortality in critically ill patients. Despite the progress of current antibiotic therapy and cardiovascular and respiratory supports, reported mortality in these clinical conditions is still between 30% and 50% [1]. Recent studies also suggest that the septic state, in addition to the worsening of pre-existing pathological conditions, promotes the onset of chronic diseases that reduce life expectancy of those who have survived to an acute previous event [3].

Therefore the interest of the scientific community in identifying new strategies in order to early identify these clinical conditions and quickly administer the most appropriate therapy (specific antibiotic therapy, fluid management, vasopressor and respiratory supports, inotropes and blood transfusions) is growing. Nowadays, because of the heterogeneity of population presenting at the ED and the large amount of comorbidities in elderly people, clinical features and laboratory tests are not always able to identify infectious diseases. In this regard, it should be noted that blood cultures performed in ED are diagnostic in only 25% of patients with sepsis [4]. Recent researches focused on the identification of new biomarkers potentially useful for sepsis diagnosis have provided encouraging results, i.e. the availability of biomarkers which closely correlate with the onset and evolution of the continuum of sepsis.

Several studies have identified more than 170 different molecules which can play an important role in the identification of sepsis. The ideal biomarker is a molecule 1) which is able to reflect the alteration of the normal physiological state during the disease and in response to therapy, 2) with a known kinetic, 3) which can be measured using objectively tests, easily reproducible and cost-effective 4) and which results can be related to the standard of reference [23]. Unfortunately, no molecule presents all these requirements at the same time.

C-reactive protein (CRP) has been used for years in the clinical practice to identify inflammatory and/or infectious conditions, but its low specificity limits the diagnostic efficacy [23]. Procalcitonin (PCT) has a good diagnostic accuracy in terms of sensitivity and specificity; high levels suggest a poor prognosis, whereas decreasing plasma concentrations are associated with a good response to therapy [24]. However, PCT presents some limitations, since it transiently increases in non-infectious inflammatory conditions [23]. sCD14-ST, also called Presepsin, increases in several pathological conditions, including infectious diseases, acute inflammatory states, autoimmune diseases. Moreover the combined use with other biomarkers, especially with PCT, allows for a more accurate diagnosis of sepsis [8,9].

The pathophysiological mechanisms of sepsis are complex and involve both the infecting pathogen and the host [25]. In particular, the systemic inflammatory response that should help the host against the infectious stimulus represents the main factor in determining the onset of organ damage, which is normally observed in septic patients. This mechanism is supported by the up-regulation of genes that code for inflammatory mediators, including tumor necrosis factor (TNF), interleukins (IL-1, IL-12, IL-18), Ƴ-interferon (IFNγ) and Galectin-3 [26, 27].

This lectin, primarily expressed by macrophages, has a wide tissue distribution; it normally takes part to intra- and extracellular functions. In the extracellular environment, it acts as a signalling molecule participating in different transduction signal pathways involved in the inflammatory response, and supporting cell interactions in the extracellular matrix [11]. The role of Galectin-3 as a marker of heart failure is well known and ascertained: it stratifies patients relying on the risk of re-hospitalization at 30 days and short term-mortality [14, 19].

We designed a multicenter prospective study in which we evaluated the diagnostic efficacy and the prognostic role (in term of survival rates) of Galectin-3 compared to PCT in a group of patients presenting to the Emergency Department of *Città della Salute e della Scienza* University Hospital of Turin and *Santa Croce and Carle Hospital* of Cuneo, with two or more diagnostic criteria of SIRS, with or without a suspicion of sepsis, severe sepsis or septic shock. Overall, we evaluated 163 patients who were divided into three groups according to the definition criteria of SIRS, sepsis, severe sepsis and septic shock validated by the most recent International Guidelines. Severe sepsis and septic shock have been considered as a unique group because they present similar clinical and prognostic features. The control population included subjects with SIRS, mainly secondary to trauma, and other medical conditions. The obtained results show that Galectin-3 can distinguish sepsis conditions from severe sepsis/septic shock, being significantly higher in patients whose septic state is associated with acute organ damage and/or hypotension refractory to fluid administration. However, there is no significant difference in plasma Galectin-3 values between cases and controls. This is probably due to the fact that the mechanisms of Galectin-3 synthesis primarily depend on the inflammatory response entity more than on the nature of the stimuli (inflammatory/infectious). Galectin-3 takes part to many biological activities: in addition to the great number of works highlighting its key-role in the pathogenesis of inflammation, several studies show its protective role [13, 27]. Data currently available to explain these controversial functions are weak.

Our research shows that, in patients affected by sepsis, the increased expression of Galectin-3 is associated with an intense inflammatory stimulation that leads to a worsening of the clinical conditions and, in such cases, to a fatal outcome. Although no significant differences were found between the ROC curves of the two biomarkers included in this study, PCT is significantly higher in cases with severe sepsis/septic shock in comparison with both subjects with sepsis and controls, thus confirming the better diagnostic accuracy of PCT. The best combination of sensitivity and specificity is observed for Galectin-3 plasma concentrations of 20.7 ng/mL. Our results are similar to those presented in Ten Over study indicating Galectin-3 diagnostic cut-off of 20.6 ng/mL [17].

Galectin-3 is significantly correlated with leukocytes, lactate and PCT, confirming its role as a biomarker of inflammation.

Analysis of 30-day mortality reveals that the levels of Galectin-3 are significantly higher in patients with a poor prognosis. This result confirms the role of this lectin as a marker of severity of sepsis. The most relevant information on Galectin-3 prognostic significance has been obtained by Cox regression analysis. It assesses patients survival considering the increase of Galectin-3 and PCT, as well as laboratory tests and clinical scores: Galectin-3 is the only statistically significant independent predictor.

The spread tissue distribution and its many cellular interactions support the hypothesis that Galectin-3 may represent one of the most important factors in the clinical development that lead to organ and system dysfunction during infectious stimuli.

Conclusion

In conclusion, our findings suggest that-Galectin-3 is a new promising biomarker, readily available, cost-effective and able to identify with the population of septic patients presenting to the ED, those with the worst clinical conditions and with a very poor outcome. The close correlation between Galectin-3 initial levels and in-hospital mortality suggests that this biomarker could be used to obtain an early and reliable risk stratification in order to identify patients who could benefit of a quick and aggressive approach starting from the ED.

It is noteworthy that the ability of Galectin-3 to stratify the population of septic subjects on the basis of the severity of

their condition is not related only to a fixed cut-off threshold, but mainly to any increase in its concentrations associated with a higher probability of a poor outcome.

Competing of interests

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Galectin-3 commercial kits were partially provided by bio-Mérieux Italia S.p.A. PCT was tested as part of a routine assay performed in the EDs, with no financial support.

The authors declare that they have not competing interests.

Authors' Contribution

CG, EP, MM and MU enrolled patients, acquired, analyzed and interpreted data and wrote the manuscript. MRe and MLu managed plasma samples and performed biochemical assays. SB and GM designed and coordinated the research, analyzed and interpreted data and reviewed the manuscript. All authors have read and approved the manuscript for publication. CG and EP contributed equally to the paper.

Acknowledgements

We would like to thank all the staff of the Emergency Department and the Clinical Biochemistry Laboratory of "Città della Salute e della Scienza" University Hospital of Turin, the Emergency Department and Dr. C. Ginardi with all the staff of the Clinical Biochemistry Laboratory of Santa Croce and Carle Hospital of Cuneo for their kind collaboration. Many thanks also to Dr. Maurizio Berardino and the staff of the Major Trauma Center for their valuable help.

References

1. The ProCESS Investigators. A randomized trial of protocol-based care for early septic shock. N Engl J Med. 2014, 370(18):1683-1693.

2. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013, 41(2): 580-637.

3. Peake SL, Delaney A, Bailey M, Bellomo R, Cameron PA et al. Goal-directed resuscitation for patients with early septic shock. N Engl J Med. 2014, 371(16): 1496-1506.

4. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001, 29(7): 1303-1310.

5. Dupuy AM, Philippart F, Péan Y, Lasocki S, Charles PE et al. Role of biomarkers in the management of antibiotic therapy: an expert panel review: I - currently available biomarkers for clinical use in acute infections. Ann Intensive Care. 2013, 3(1): 22.

6. Tang BM, Eslick GD, Craig JC, McLean AS. Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis. Lancet Infect Dis. 2007, 7(3): 210-217.

7. Bouadma L, Luyt CE, Tubach F, Cracco CH, Alvarez A et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet. 2010, 375(9713): p463-474.

8. Ulla M, Pizzolato E, Lucchiari M, Loiacono M, Soardo F et al. Diagnostic and prognostic value of presepsin in the management of sepsis in the emergency department: a multicenter prospective study. Crit Care. 2013, 17(4): R168.

9. Bo Liu, Yun-Xia Chen, Qin Yin, Yun-Zhou Zhao, Chun-Sheng Li. corresponding author. Diagnostic value and prognostic evaluation of Presepsin for sepsis in an emergency department. Critical Care. 2013, 17(5): R244.

10. Giavarina D, Carta M. Determination of reference interval for presepsin, an early marker for sepsis. Biochem Med (Zagreb). 2015, 25(1): 64-68.

11. Li Y, Komai-Koma M, Gilchrist DS, Hsu DK, Liu FT et al. Galectin-3 is a negative regulator of lipopolysaccharide-mediated inflammation. J Immunol. 2008, 181(4): 2781-2789.

12. Elola MT, Wolfenstein-Todel C, Troncoso MF, Vasta GR, Rabinovich GA. Galectins: matricellular glycan-binding proteins linking cell adhesion, migration, and survival. Cell Mol Life Sci. 2007, 64(13):1679-1700.

13. Gao P, Simpson JL, Zhang J, Gibson PG. Galectin-3: its role in asthma and potential as an anti-inflammatory target. Respir Res. 2013,14: 136.

14. de Boer RA, Edelmann F, Cohen-Solal A, Mamas MA, Maisel A et al. Galectin-3 in heart failure with preserved ejection fraction. Eur J Heart Fail. 2013, 15(10): 1095-1101.

15. Schmidt T, Zündorf J, Grüger T, Brandenburg K, Reiners AL et al. CD66b overexpression and homotypic aggregation of human peripheral blood neutrophils after activation by a gram-positive stimulus. J Leukoc Biol. 2012, 91(5): 791-802.

16. Fermino ML, Polli CD, Toledo KA, Fu-Tong Liu, Dan K. Hsu et al. LPS-induced galectin-3 oligomerization results in enhancement of neutrophil activation. PLoS One. 2011, 6(10).

17. ten Oever J, Giamarellos-Bourboulis EJ, van de Veerdonk FL, Stelma FF, Simon A et al. Circulating galectin-3 in infections and non-infectious inflammatory diseases. Eur

J Clin Microbiol Infect Dis. 2013, 32(12):1605-1610.

18. de Boer RA, van Veldhuisen DJ, Gansevoort RT, Gansevoort RT, Muller Kobold AC et al. The fibrosis marker galectin-3 and outcome in the general population. J Intern Med. 2012, 272(1): 55-64.

19. Peacock WF. How galectin-3 changes acute heart failure decision making in the emergency department. Clin Chem Lab Med. 2014, 52(10): 1409-12.

20. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992, 101(6): 1644-1655.

21. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985, 13(10): 818-829.

22. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med. 1996, 22(7): 707-710.

23. Sung-Yeon C, Jung-Hyun C. Biomarkers of sepsis. Infect Chemother. 2014, 46(1): 1-12.

24. Poddar B, Gurjar M, Singh S, Amita Aggarwal,1 Ratender Singh et al. Procalcitonin kinetics as a prognostic marker in severe sepsis/septic shock. Indian J Crit Care Med. 2015, 19(3): 140-146.

25. Angus DC, Van der Poll T. Severe sepsis and septic Shock. N Engl J Med. 2013, 369: 840-851.

26. Ruf W. New players in the sepsis-protective activated protein C pathway. J Clin Invest. 2010, 120(9): 3084-3087.

27. Li Y, Komai-Koma M, Gilchrist DS, Hsu DK, Liu FT et al. Galectin-3 is a negative regulator of lipopolysaccharide-mediated inflammation. J Immunol. 2008, 181(4): 2781-2789.