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João Luís da Rocha Miranda

Avaliação do prognóstico da pancreatite aguda
através do rácio neutrófilos-linfócitos /
Assessment of acute pancreatitis prognosis
using neutrophil-lymphocyte ratio

março, 2018

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Mestrado Integrado em Medicina

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Trabalho efetuado sob a Orientação de:
Doutor Rui Jorge Ferreira Mendes da Costa

Trabalho organizado de acordo com as normas da revista:
Pancreatology

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Eu, João Luis da Rocha Miranda, abaixo assinado, nº mecanográfico 201204440, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter atuado com absoluta integridade na elaboração deste projeto de opção.

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Faculdade de Medicina da Universidade do Porto, 19/03/2018

Assinatura conforme cartão de identificação:

João Luís da Rocha Miranda

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NOME

João Luís da Rocha Miranda

NÚMERO DE ESTUDANTE	E-MAIL
201204440	joaoluisrm@gmail.com

DESIGNAÇÃO DA ÁREA DO PROJECTO

Cirurgia Geral

TÍTULO DISSERTAÇÃO/MONOGRAFIA (riscar o que não interessa)

Assessment of acute pancreatitis prognosis using neutrophil-lymphocyte ratio

ORIENTADOR

Dr. Rui Jorge Ferreira Mendes da Costa

COORIENTADOR (se aplicável)

-

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Faculdade de Medicina da Universidade do Porto, 19/03/2018

Assinatura conforme cartão de identificação: *João Luís da Rocha Miranda*

Title: Assessment of acute pancreatitis prognosis using neutrophil-lymphocyte ratio

Short Title: NLR as a predictor of prognosis in pancreatitis

Authors: João Miranda[1], Telma Vale-Fonseca[1,2], Rui Mendes Costa[1,2]

[1] Faculty of Medicine. University of Porto. Porto. Portugal.

[2] Department of General Surgery. Hospital of São João. Porto. Portugal

Corresponding author:

João Miranda

Adress: Alameda Professor Hernâni Monteiro

4200 Porto, Portugal

Telephone: 00351 913383065

E-mail: joaoluisrm@gmail.com

ABSTRACT

Background/Objectives: Acute pancreatitis (AP) is one of the most common causes of hospitalization and severe cases are usually associated with a poor prognosis. Neutrophil to lymphocyte ratio (NLR) has been pointed as an indicator of systemic inflammation in several disorders. The aim of this study was to assess whether NLR at admission is able to predict severity of AP and some associated outcomes (need for ICU admission, in-hospital mortality, length of hospital stay > 7 days and organ failure development), while trying to establish the best cut-off value for outcomes.

Materials and methods: This was a single-center retrospective study carried with clinical data from AP patients between January 2014 and December 2015. Four hundred and forty five patients were eligible for the study and NLR was calculated based on admission laboratory data. Patients were stratified according to severity, based on the Atlanta Classification, and comparative analysis was carried between groups.

Results: A total of 391 patients presented with mild AP and 54 with moderate or severe AP. NLR for the severe group was significantly higher than for the mild group (13,9±13,6 versus 10,1±9,4, respectively). There were also statistical differences in NLRs between all groups of analyzed outcomes except for in-hospital mortality. The best predictive NLR value for the stratification of AP severity was 9,2.

Conclusions: This study shows a significant correlation between NLR at admission and the severity of AP. Higher NLR values also predicted the development of organ failure, ICU admission and longer hospitalizations.

Key words: acute pancreatitis, neutrophil, lymphocyte, prognosis, severity

INTRODUCTION

Acute pancreatitis (AP) is an inflammatory disorder of the pancreas caused by an impairment in the secretion of pancreatic enzymes, usually due to an obstruction of the pancreatic ducts[1]. This leads to the accumulation of digestive enzymes in the acinar cells and interstitial space, which can be activated and cause acinar cell injury and a subsequent inflammation of the pancreatic parenchyma[2]. The most common cause of AP is widely recognized to be gallstones (almost half of all cases) followed by alcohol consumption, while other causes (such as hypertriglyceridemia, medications or iatrogenic) usually account for less than 10% of all episodes[3]. In about one third of all patients, a cause is not found[4].

AP still remains one of the most common causes of hospitalization due to gastrointestinal disease, with a reported increase in its incidence worldwide[3, 5]. In fact, global epidemiological studies have found incidence rates for AP ranging from 13 to 45 cases per 100000 persons every year in occidental countries[5]. Mild cases of AP (MAP, approximately 80% of all episodes[1]) are usually characterized by edema and inflammation restrict to the pancreas, with no other complications. These are usually self-limited and carry very low morbidity and mortality rates[6, 7]. On the other hand, patients presenting with moderate or severe AP (SAP) can develop multiple complications, such as organ failure and/or pancreatic necrosis, with mortality rates as high as 30% in the most complicated groups[6, 8].

Therefore, a prompt identification of the severe cases should occur in order to prevent worst outcomes, which seem to be related to an uncontrolled systemic inflammatory response with multiorgan failure[8, 9]. For that reason, several scoring systems have been developed to help predict the severity of AP, including Ranson's criteria, Glasgow score, APACHE-II score, BISAP and imaging scores (like Balthazar score and CTSI score)[2, 10]. However, these all have some major flaws that limit their use in the emergency department. For instance, both Ranson's and Glasgow criteria need a 48h blood work-up (with some variables not routinely assessed) to be fully calculated, therefore missing the purpose of early identifying some severe cases; APACHE-II (Acute Physiology and Chronic Health Evaluation II) is a complex scoring system (not specific for acute pancreatitis) that requires more than 14 different variables; and BISAP (Bedside Index of Severity in Acute Pancreatitis), even though it is a simple score easily calculated in the emergency room, requires the realization of a chest x-ray. On the other hand, the imaging scoring systems (namely Balthazar and CT Severity Index) demand performing a CT at admission on all patients with suspected AP and did not exhibit better accuracy at predicting severe cases

of AP[11]. Furthermore, studies confirm that all described criteria have a relative low sensitivity in the early phases of the disease[10, 12, 13], probably because they weight all the variables equally, not accounting for deleterious synergistic effects[13]. For all the listed reasons, new ways of quickly, easily and accurately evaluate the severity of new cases of AP are needed.

The neutrophil-lymphocyte ratio (NLR) is an easily obtained parameter from routine white blood cell counts, which are performed in almost all emergency admissions. For that reason, this parameter has been presented over the last decade as a predictor of poor outcomes in several gastrointestinal disorders (such as acute appendicitis, acute cholecystitis and some malignant neoplasms, like hepatocellular, esophageal and colorectal carcinomas), often being considered a more reliable tool than the total white blood cell count for that purpose[14-18]. Regarding AP, some studies have shown a correlation between this ratio and the severity, mortality of AP, the length of hospitalization and need for ICU admission, demonstrating a prognostic value for the NLR with higher reliability than other common tools[19-21]. On the other hand, there have been some conflicting results too, and there are some concerns regarding the real usefulness of this marker in this context[22-24]. For instance, Gulen *et al*. proposed NLR was not effective at predicting AP mortality in the first 48 hours[22].

In this study, we aimed to assess whether NLR at admission correlates with AP severity and its adverse outcomes, namely need for ICU admission, longer length of stay (>7 days), presence of organ failure and in hospital mortality. We also studied the best NLR cut-off value to predict said outcomes.

METHODS

Study design and patients

We performed a retrospective cohort study including all patients with the diagnosis of AP between 1st January 2014 and 31th December 2015 at Centro Hospitalar São João, a tertiary care center in Oporto, Portugal. During this period, from 504 patients presenting with AP, 59 were excluded from data analysis for the following reasons: pediatric age (n=10), HIV infection (n=1), lymphoproliferative disorders (n=4), immunosuppressive drugs (n=5), iatrogenic etiology (n=31) and missing clinical data (n=8). A total of 445 patients was included.

Data collection and definitions

The study was approved by the Ethical Committee "Comissão de Ética para a Saúde do Centro Hospitalar São João". The confidentiality and privacy of the data were guaranteed according to the Declaration of Helsinki.

Data was obtained from electronic medical records and included demographic information (age, sex), laboratory data at admission, clinical data regarding the episode evolution (AP etiology, presence of pain, length of hospital stay, ICU admission, organ failure and in-hospital mortality) and radiologic findings (CT at admission or during hospitalization, if performed).

AP diagnosis was confirmed for each patient if at least two of the following three criteria were present:

    (1) abdominal pain suggestive of AP;

    (2) serum amylase or lipase greater than three times the normal upper limit;

    (3) typical radiological findings.

AP severity was defined based on the Revised Atlanta Classification[6], meaning patients were considered to have mild AP if there were no complications or presence of organ failure, moderately severe acute pancreatitis if there was presence of transient organ failure (duration < 48h) and/or local or systemic complications, and severe acute pancreatitis if there was persistent organ failure (duration ≥ 48h). The modified Marshall scoring system[25] was used to determine the presence of organ failure, with a score of 2 or higher in each measurement indicating loss of organ function. For the purpose of statistical analysis, patients were grouped in two groups: MAP (mild acute pancreatitis, with no complications nor organ failure) and SAP (moderately severe and severe acute pancreatitis, with local or systemic complications and/or organ failure).

NLR was calculated dividing the neutrophil count by the lymphocyte count for each patient at admission.

Statistical analysis

Statistical analysis was performed using *IBM SPSS Statistics 25*, and a *p* value < 0,05 was accepted as statistically significant. Unless noted otherwise, categorical data was described using frequencies with proportions and continuous data using means with standard deviations. Comparison between groups was carried using the Fisher's exact or Chi-square tests for categorical data and Mann-Whitney U or Student's t-test for continuous data, as appropriate. Correlation between NLR at admission and AP severity was determined based on Spearman's Rank coefficient. ROC (receiver operating characteristic) curve analysis was performed for the studied outcomes with significant differences in NLR between groups in order to determine the best discriminating NLR cut-off value for each outcome. The optimal cut-off value for each ROC curve was computed based on the higher possible sensitivity and specificity values. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for the results, and accuracy of prediction was estimated using the area under the curve (AUC) for each ROC curve.

RESULTS

A total of 445 patients were included in the study, of which 391 presented with MAP (87,9%) and 54 with SAP (12.1%). The most common etiology for AP cases was biliary lithiasic ductal obstruction (n=279, 62,7%), followed by alcohol abuse (n=73, 16,4%). In 72 cases (16,2%), no cause for AP was found either during the episode or the follow-up. Patient demographics and laboratory data at admission are presented in Table 1. Patients in the SAP group were significantly older, but no differences between groups were found regarding gender or etiology of pancreatitis. Need for ICU admission, prolonged hospital stay (> 7 days), organ failure and death were lower in the MAP group (Table 1).

No differences were found in white blood cell counts (WBC) at presentation; on the other hand, the calculated mean NLR was significantly higher in MAP group (10,1±9,4 vs. 13,9±13,6 for SAP, p=0.003). The distribution of NLRs by severity of AP cases can be seen in Figure 1.

Regarding the occurrence of adverse outcomes, we found a statistical difference between NLR in patients admitted to the ICU (16,6 vs 9,7 in the other group; p<0,001), in patients with a LOS > 7 days (12,5 vs 9,3 in the group with LOS < 7 days; p<0,001) and whenever organ failure was present (12,6 vs 10,1 if no organ failure occurred; p=0,045). There were no statistical differences in NLR between groups according to in-hospital mortality (12,6 vs 10,4, if death occurred or not, respectively; p=0,099). A positive correlation between higher NLR values and severe cases was found using Spearman's correlation test (r=0.130, p=0,003). A ROC curve for the prediction of AP severity using NLR was performed and the AUC for that curve was 0,623 (95% CI: 0,549-0,698); the NLR cut-off value determined for maximum accuracy was 9,2 (53,7% sensitivity, 65,5% specificity, 17,8% positive predictive value and 91,1% negative predictive value). ROC analysis for NLR and secondary outcomes also pointed 9,2 as the most accurate cut-off value at predicting organ failure and need for ICU admission; meanwhile, LOS>7 days was better predicted with a cut-off point of 7,9. AUC for all ROC curves and respective optimal cut-off points are presented in Table 2. Sensitivity, specificity and predictive values for the chosen cut-off (NLR = 9,2) at predicting the evaluated outcomes are presented in Table 3.

DISCUSSION

Multiple studies have shown in the past the usefulness of NLR at predicting disease severity, recurrence and prognosis in several disorders[14-18]. In particular, the NLR has been studied before as a predictor of AP severity and unfavorable prognosis, being often proposed as an effective tool for that purpose[19-21]. Neutrophils have been shown to play a pivotal role in the propagation of the inflammation pathways in AP through cytokine and chemokine cascades, trypsin production[26]. Regarding lymphocyte counts, lymphocyte depletion was demonstrated in severe cases of AP, mainly because of premature apoptotic death of these cells (especially T CD8 subpopulations)[27]. For these reasons, it is expected that AP cases associated with necrosis or organ failure (i.e., SAP cases) develop higher levels of neutrophilia and lymphopenia, translating into higher NLR values[28]. As mentioned before, the most practical advantage of this parameter is the fact that it is readily obtained from a routine hemogram with leucocyte count in the emergency department, not needing further workups.

In this study, we focused on assessing whether higher values of NLR calculated at admission correlate with worse outcomes. Our results show that SAP cases were generally associated with higher values of NLR than those of the MAP cases, therefore being an useful tool for stratification of AP severity. We also found NLR to be significantly higher in patients admitted to the ICU, with longer lengths of stay and with presence of organ failure (one of the most important factors at defining AP severity, as indicated by the Atlanta Classification of Acute Pancreatitis[6]).

The biggest differences between studies regarding NLR in AP concern the optimal cut-off value for the severity stratification. Azab et al.[19] and Jeon and Park[20] suggested that the optimal NLR cut-off value at admission should be 5 or 4,76, respectively, while Suppiah et al.[21] proposed it to be 10,6. We found higher sensitivity and specificity at predicting SAP cases with a cut-off point of 9,2 (62,3% accuracy, as determined by the AUC of the ROC curve), which is way closer to what Suppiah et al. found. We also could confirm the superiority of NLR over WBC count at distinguishing between MAP and SAP cases, as proposed by Azab et al., considering we found no statistical differences between WBC in both groups.

Our study also showed that the NLR also has a decent accuracy at predicting the need for ICU admission (AUC 0,684), presence of organ failure (AUC 0,614) and length of stay > 7 days (AUC 0,605), but not at predicting in-hospital mortality (unlike previous studies), possibly because of the insufficient sample size. From the presented data, we can determine NLR at admission performs better at predicting need for ICU

admission comparing to the other examined outcomes, but its low positive predictive value possibly presents itself as an obstacle for that purpose, considering the high rate of false positives.

Even though the accuracy of NLR at predicting AP severity may be lower than the reported accuracy of other currently used scoring systems[29], the present study (and any other else, to our knowledge) directly compared these, and for that reason further research on the subject should be conducted. On the other hand, instead of considering the NLR an independent tool to predict AP severity, maybe it should be taken in account in association to other laboratory markers (and/or possibly already existing scoring systems) in order to improve its accuracy and diagnostic performance. Prospective research should be conducted for that matter.

Some limitations can be evident in our study, mainly concerting the investigation design. As a retrospective study; a selection bias, inherent to this type of studies, is often present; and the outcomes assessment heavily depended on the medical records provided by others. A bigger sample size would also benefit the study, especially considering one of the outcomes (in-hospital mortality) that could not be correctly evaluated because of lack of cases.

In conclusion, this study shows evidence that the NLR at admission of patients presenting with AP should be considered as an effective, easy and rapid tool of assessing AP severity and adverse outcomes (namely, development of organ failure, need for ICU admission and longer hospitalizations). A cut-off point of 9,2 seems to be the most accurate at predicting all the referred outcomes in this sample.

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REFERENCES

1.   Forsmark, C.E., S.S. Vege, and C.M. Wilcox, *Acute Pancreatitis.* N Engl J Med, 2016. **375**(20): p. 1972-1981.

2.   Lankisch, P.G., M. Apte, and P.A. Banks, *Acute pancreatitis.* The Lancet, 2015. **386**(9988): p. 85-96.

3.   Yadav D, L.A., *Trends in epidemiology of the first attack of acute pancreatitis.* Pancreas, 2006. **33**(4): p. 8.

4.   Yijun Chen, Y.Z., Tina Hernandez-Boussard, Walter Park and Brendan C. Visser, *The Epidemiology of Idiopathic Acute Pancreatitis, Analysis of the Nationwide Inpatient Sample From 1998 to 2007.* Pancreas, 2015. **42**(1): p. 5.

5.   Yadav, D. and A.B. Lowenfels, *The epidemiology of pancreatitis and pancreatic cancer.* Gastroenterology, 2013. **144**(6): p. 1252-61.

6.   Banks, P.A., et al., *Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus.* Gut, 2013. **62**(1): p. 102-11.

7.   Singh, V.K., et al., *An assessment of the severity of interstitial pancreatitis.* Clin Gastroenterol Hepatol, 2011. **9**(12): p. 1098-103.

8.   Mofidi, R., et al., *Association between early systemic inflammatory response, severity of multiorgan dysfunction and death in acute pancreatitis.* Br J Surg, 2006. **93**(6): p. 738-44.

9.   Petrov, M.S., et al., *Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis.* Gastroenterology, 2010. **139**(3): p. 813-20.

10.   Kuo, D.C., et al., *Acute Pancreatitis: What's the Score?* J Emerg Med, 2015. **48**(6): p. 762-70.

11.   Bollen, T.L., et al., *A comparative evaluation of radiologic and clinical scoring systems in the early prediction of severity in acute pancreatitis.* Am J Gastroenterol, 2012. **107**(4): p. 612-9.

12.   Harshit Kumar, A. and M. Singh Griwan, *A comparison of APACHE II, BISAP, Ranson's score and modified CTSI in predicting the severity of acute pancreatitis based on the 2012 revised Atlanta Classification.* Gastroenterology Report, 2017.

13.   Papachristou, G.I., et al., *Comparison of BISAP, Ranson's, APACHE-II, and CTSI scores in predicting organ failure, complications, and mortality in acute pancreatitis.* Am J Gastroenterol, 2010. **105**(2): p. 435-41; quiz 442.

14.   Hao Duan, X.Z., Fei-Xiang Wang, Mu-Yan Cai, Guo-Wei Ma, Hong Yang, Jian-Hua Fu, Zi-Hui Tan, and X.-Y.F. Yu-Qi Meng, Qi-Long Ma, Peng Lin, *Prognostic role of neutrophil-lymphocyte ratio in operable esophageal squamous cell carcinoma.* World J Gastroenterol, 2015. **21**(18): p. 7.

15.   Kahramanca, S., et al., *Neutrophil-to-lymphocyte ratio as a predictor of acute appendicitis.* Ulus Travma Acil Cerrahi Derg, 2014. **20**(1): p. 19-22.

16.   Kayadibi, H., et al., *Neutrophil-lymphocyte ratio is useful for the prognosis of patients with hepatocellular carcinoma.* World J Gastroenterol, 2014. **20**(28): p. 9631-2.

17.   Li, M.X., et al., *Prognostic role of neutrophil-to-lymphocyte ratio in colorectal cancer: a systematic review and meta-analysis.* Int J Cancer, 2014. **134**(10): p. 2403-13.

18. Sato, N., et al., *Inflammation-based prognostic scores predict disease severity in patients with acute cholecystitis.* Eur J Gastroenterol Hepatol, 2018. **30**(4): p. 484-489.

19. Azab, B., et al., *Neutrophil-lymphocyte ratio as a predictor of adverse outcomes of acute pancreatitis.* Pancreatology, 2011. **11**(4): p. 445-52.

20. Jeon, T.J. and J.Y. Park, *Clinical significance of the neutrophil-lymphocyte ratio as an early predictive marker for adverse outcomes in patients with acute pancreatitis.* World J Gastroenterol, 2017. **23**(21): p. 3883-3889.

21. Suppiah, A., et al., *The prognostic value of the neutrophil-lymphocyte ratio (NLR) in acute pancreatitis: identification of an optimal NLR.* J Gastrointest Surg, 2013. **17**(4): p. 675-81.

22. Gulen, B., et al., *Effect of harmless acute pancreatitis score, red cell distribution width and neutrophil/lymphocyte ratio on the mortality of patients with nontraumatic acute pancreatitis at the emergency department.* World J Emerg Med, 2015. **6**(1): p. 29-33.

23. Binnetoglu, E., et al., *The prognostic value of neutrophil-lymphocyte ratio in acute pancreatitis is controversial.* J Gastrointest Surg, 2014. **18**(4): p. 885.

24. Li, Y., et al., *Comparison of the prognostic values of inflammation markers in patients with acute pancreatitis: a retrospective cohort study.* BMJ Open, 2017. **7**(3): p. e013206.

25. Marshall JC, C.D., Christou NV, Bernard GR, Sprung CL, Sibbald WJ, *Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. .* Crit Care Med, 1995. **23**(10): p. 14.

26. Yang, Z.W., X.X. Meng, and P. Xu, *Central role of neutrophil in the pathogenesis of severe acute pancreatitis.* J Cell Mol Med, 2015. **19**(11): p. 2513-20.

27. Takeyama Y, T.K., Ueda T, Hori Y, Goshima M, Kuroda Y, *Peripheral lymphocyte reduction in severe acute pancreatitis is caused by apoptotic cell death.* J Gastrointest Surg, 2000. **4**(4): p. 8.

28. R, Z., *Ratio of neutrophil to lymphocyte counts--rapid and simple parameter of systemic inflammation and stress in critically ill.* Bratisl Lek Listy, 2001. **102**(1): p. 9.

29. Cho, J.H., et al., *Comparison of scoring systems in predicting the severity of acute pancreatitis.* World J Gastroenterol, 2015. **21**(8): p. 2387-94.

Table 1. Sample descriptive statistics (n = 445)

		All	MAP	SAP
	n	**445**	**391**	**54**
Demographics	Age (years)	62,3 ± 18,4	61,1 ± 18,1	70,9 ± 18,4
	Gender, male (%)	250 (56,2%)	222 (56,8%)	28 (51,9%)
Etiology, n (%)	Biliary	279 (62,7%)	245 (62,7%)	34 (63,0%)
	Alcoholic	73 (16,4%)	66 (16,9%)	7 (13,0%)
	Idiopathic	72 (16,2%)	60 (15,3%)	12 (22,2%)
	Others	21 (4,6%)	20 (5,1%)	1 (1,9%)
Laboratory data (at admission)	Hemoglobin (g/dL)	13,7 ± 1,9	13,9 ± 1,8	12,2 ± 2,4
	White Blood Cells ($\times 10^9$/L)	12,5 ± 5,4	12,5 ± 5,3	12,8 ± 6,2
	Neutrophils ($\times 10^9$/L)	10,2 ± 5,6	10,1 ± 5,6	10,6 ± 5,6
	Lymphocytes ($\times 10^9$/L)	1,6 ± 2,2	1,7 ± 2,3	1,1 ± 0,9
	Glucose (mg/dL)	142,7 ± 60,7	140,0 ± 54,1	163,3 ± 95,8
	C-Reactive Protein (mg/dL)	48,4 ± 69,9	42,7 ± 65,8	88,6 ± 84,1
	Total bilirrubin (mg/dL)	2,0 ± 2,1	2,0 ± 2,1	2,2 ± 2,4
	Direct bilirrubin (mg/dL)	1,1 ± 1,6	1,0 ± 1,6	1,2 ± 1,6
	Urea (mg/dL)	41,7 ± 26,0	37,3 ± 16,4	74,1 ± 50,1
	Creatinin (mg/dL)	1,0 ± 0,83	0,8 ± 0,3	2,2 ± 1,9
	LDH (U/L)	381,2 ± 427,6	374,0 ± 391,2	423,4 ± 603,8
	AST (U/L)	250,7 ± 497,4	249,6 ± 433,0	258,5 ± 823,8
Clinical data	Abdominal pain, n (%)	428 (96,2%)	377 (96,4%)	51 (94,4%)
	Death, n (%)	18 (4,0%)	6 (1,5%)	12 (22,2%)
	ICU admission, n (%)	51 (11,5%)	29 (7,4%)	22 (40,7%)
	LOS (days)	9,0 ± 12,9	8,0 ± 11,1	15,8 ± 20,6
	LOS > 7 days, n (%)	171 (38,5%)	139 (35,6%)	32 (59,3%)
	Organ Failure, n (%)	46 (10,3%)	0 (0%)	46 (85,1%)
	NLR	**10,1 ± 9,4**	**10,1 ± 9,4**	**13,9 ± 13,6**

Data is presented as mean ± standard deviation, unless noted otherwise.

MAP = mild acute pancreatitis, SAP = severe acute pancreatitis, LDH = Lactate dehydrogenase, AST = Aspartate transaminase, ICU = intensive care unit, LOS = length of stay, NLR = neutrophil-lymphocyte ratio.

Table 2. AUC of ROC curves for each studied outcome and their respective cut-off value with better performance (higher sensitivity and specificity).

| Outcome	AUC (95% CI)	Optimal NLR cut-off
Severity	0,623 (0,549-0,698)	9,21
Organ failure	0,614 (0,530-0,698)	9,20
LOS > 7 days	0,605 (0,551-0,659)	7,89
ICU admission	0,684 (0,600-0,768)	9,17

Table 3. Sensitivity, specificity, PPV and NPV of cut-off point NLR = 9,2 at predicting AP severity, occurrence of organ failure, need for ICU admission and length of stay > 7 days.

	Sensitivity	Specificity	PPV	NPV
Severity	53,7%	65,5%	17,8%	91,1%
Organ Failure	54,3%	65,3%	15,2%	92,5%
ICU admission	68,6%	57,0%	20,7%	94,5%
LOS > 7 days	47,6%	69,2%	50,6%	66,7%

**Figure 1.** NLR cases distribution by acute pancreatitis severity. Measures of position are as follows:

MAP – 25th percentile = 4,0; Median/50th percentile = 7,0; 75th percentile = 12,9.

SAP – 25th percentile = 6,1; Median/50th percentile = 9,3; 75th percentile = 16,8.
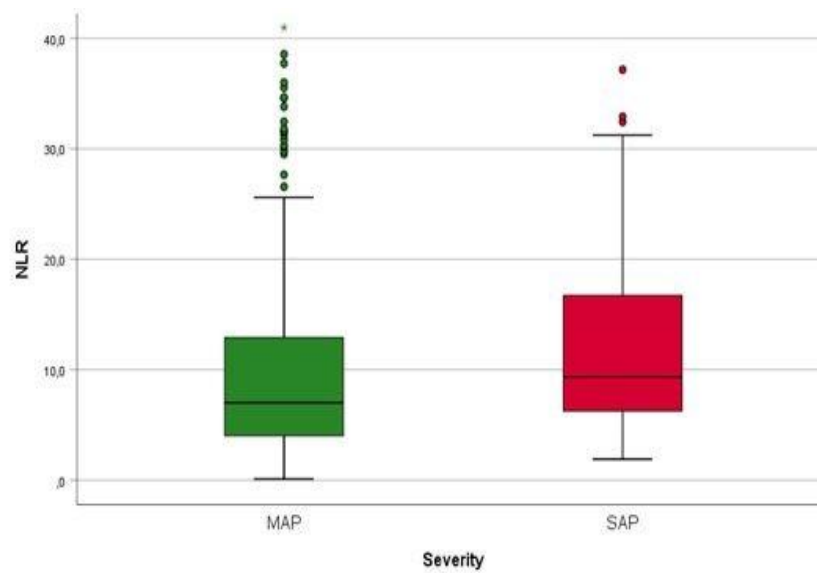
MAP = mild acute pancreatitis; SAP = severe acute pancreatitis.

Figure 2. ROC curve for NLR at admission predicting AP severity.
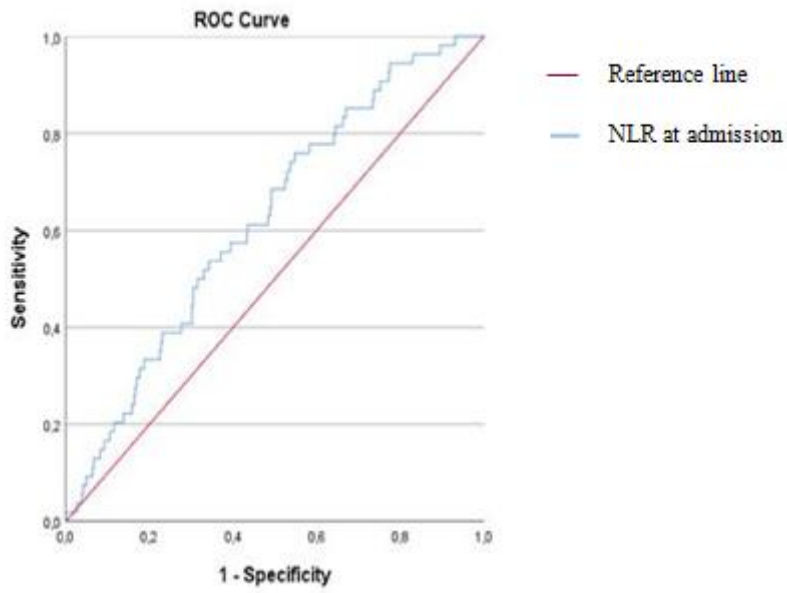
ANEXOS

ANEXO 1. Normas da Revista para Publicação

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Editor-in-chief Professor Minoti Apte
Contact Information:
Professor Minoti Apte MBBS MMedSci PhD
Presiding Member, Faculty of Medicine
Director, Pancreatic Research Group
The University of New South Wales
Level 3, Samuels Building,
UNSW Sydney, NSW 2052 Australia
Ph : 61-2-93858273
Fax : 61-2-93136185
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4. Once published, the copyright of the manuscript(s) shall stand transferred to the Journal.
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papers, including an abstract not exceeding 150 words. Rapid communications should not be more than four printed pages in length (including figures, tables and references). Rapid communications will only be accepted as they are or with minor modifications. Rejected manuscripts can only be reconsidered as regular papers. Review will be rapid, and once accepted, the paper will be included in the next planned issue.

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Case report: As for Rapid Communication

Editorial

Virtual Microscope The journal encourages authors to supplement in-article microscopic images with corresponding high resolution versions for use with the Virtual Microscope viewer. The Virtual Microscope is a web based viewer that enables users to view microscopic images at the highest level of detail and provides features such as zoom and pan. This feature for the first time gives authors the opportunity to share true high resolution microscopic images with their readers. More information and examples. Authors of this journal will receive an invitation e-mail to create microscope images for use with the Virtual Microscope when their manuscript is first reviewed. If you opt to use the feature, please contact virtualmicroscope@elsevier.com for instructions on how to prepare and upload the required high resolution images.

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General: Type the manuscript (using 'Times New Roman' font, size 10) with double spaces. Please arrange the manuscript as follows: Title page, Abstract, Introduction, Methods, Results, Discussion, and References. Number all pages consecutively, beginning with the title page. Figures and Tables must be referred to in the manuscript. If necessary, consult a recent issue of the Journal for details. Only the Title page should bear the names and addresses of the author(s). Editorials are mostly accepted by invitation only.
Title page: The first page of each paper should indicate the title, the authors' names, the institute where the work was conducted, and a short title to use as the running head.
Full address: The exact postal address of the corresponding author, complete with postal code must be provided at the bottom of the title page. Also, please provide phone, fax as well as e-mail details.
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Abstract: Original articles should include a structured abstract of about 250 words under the following headings:
Background/Objectives: What is the major problem that prompted the study?
Methods: How was the study performed?
Results: Most important findings?
Conclusions: Most important conclusion?

[See Ann Intern Med 1990; 113: 69-76]. References should not be included. Up to 5 key words, not present in the title, to assist indexing, should be typed in alphabetical order below the Abstract; and these may be obtained from the Medical Subject Headings (MeSH) database of 'Pubmed'.

Acknowledgements: These should appear at the end of the manuscript. The *source of funding* as well as a *disclosure statement* mentioning *conflict of interest*, if any, should appear under this heading.

References: References must be numbered in the order, in which they first appear in the text and identify the same in the text in superscript. References may be placed at the end of the manuscript. Publications as abstract and letters should be identified in parentheses. The responsibility for accuracy of references lies with the respective authors. The Journal is in agreement with the International Committee of Medical Journal Editors (www.icmje.org). The general arrangement, abbreviations of the Journal names and punctuations followed are as per the Uniform Requirements for Manuscripts submitted to Biomedical Journals (www.icmje.org). Please pay attention to the style of references and punctuations as follows:

Journal article

List all authors when six or less as shown in the example below: Tallon D, Chard J, Dieppe P. Exploring the priorities of patients with osteoarthritis of the knee. Arthritis Care and Res 2000; 13: 312-9. In the case of seven or more authors, list only the first six and add et al.

Book or monograph

Following is an example: Cassidy JT. Juvenile rheumatoid arthritis. In: Textbook of Rheumatology 6th ed, Kelly et al (eds) Philadelphia Saunders 2000; pp. 1297-313.

Papers published only with DOI numbers:

Theoharides TC, Boucher W, Spear K: Serum interleukin-6 reflects disease severity and osteoporosis in mastocytosis patients. Int Arch Allergy Immunol DOI: 10.1159/000063858.

Data references

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Tables: Each Table should be typed on a separate page and numbered consecutively in Arabic numerals. Necessary explanatory notes, if any, may be given below the Table.

Figures/Illustrations/Photographs: Photographs may be submitted as 'jpg', or 'tiff ' files in a zipped folder. In clinical photographs, identity of the subjects should be suitably masked; in case this is not possible, a written permission from the concerned person must accompany the manuscript. Only high-resolution photographs of figures (300 DPI JPG/ TIF scanned image of the figures; low resolution files of figures i.e. less than 300 DPI are not appropriate for printing) are accepted to be included along with each manuscript.

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Units: All measurements must be in metric units, preferably with corresponding SI units in parentheses.

REVISED SUBMISSIONS:

Please submit a detailed, point-by-point response to the reviewers' comments. Please ensure that you include the text of the specific comment to which you are responding

Special Requirement:

1. 'Pancreatology' requires the authors to confirm that they **qualify for (co-)authorship**, according to the 'Uniform Requirements for Manuscripts' published in the guidelines of the 'International Committee of Medical Journal Editors' in 1988 as follows:

Authorship credit should be based only on substantial contributions to:

(a) Conception and design, or analysis and interpretation of data; (b) Drafting the article or revising it critically for important intellectual content; (c) Final approval of the version to be published.

Conditions (a), (b), and (c) must all be met. Participation solely in the acquisition of funding or the collection of data does not justify authorship. General supervision of the research group is also not sufficient for authorship. Any part of an article critical to its main conclusions must be the responsibility of at least one author. Persons who have contributed intellectually to the article but whose contributions do not justify authorship may be named and their particular contribution described in the 'Acknowledgements'. Importantly, it must be noted that such person(s) must have extended their permission to be named.

ANEXO 2. Aprovação Comissão de Ética

n.º 228/17

SÃO JOÃO

PEDIDO DE AUTORIZAÇÃO

Realização de Investigação

AUTORIZADO

CONSELHO DE ADMINISTRAÇÃO ⦿ REUNIÃO DE 09 NOV 2017

Presidente do Conselho de Administração

(Dr. António Oliveira e Silva)

Diretor Clínico | Enfermeira Diretora | Vogal Executivo | Vogal Executivo

(Prof. Dr. José Artur Paiva) (Enf.ª Margarida Cardoso) (Dr. Luís Porto Gomes) (Dr. Renato G. Matos)

*Exmo. Senhor Presidente do Conselho de Administração
do Centro Hospitalar de São João*

Nome do Investigador Principal: João Luís da Rocha Miranda

Título da Investigação: Pancreatite aguda - avaliação de critérios de gravidade

Pretendendo realizar no(s) Serviço(s) de: Cirurgia Geral

a investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efetivação.

Para o efeito, anexo toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar de São João/ Faculdade de Medicina da Universidade do Porto respeitante à investigação, à qual enderecei pedido de apreciação e parecer.

Com os melhores cumprimentos.

O Investigador/ Promotor

Porto, 25 de setembro de 2017.

João Luís da Rocha Miranda
assinatura

CES-IM005-0

<u>Parecer da Comissão de Ética para a Saúde do</u>
<u>Centro Hospitalar de São João / Faculdade de Medicina da Universidade do Porto</u>

Título do Projeto: Pancreatite aguda - avaliação de critérios de gravidade

Nome do Investigador Principal: João Luís da Rocha Miranda, aluno do Mestrado Integrado em Medicina da FMUP

Onde decorre o Estudo: No Serviço de Cirurgia Geral do CHSJ. Dispõe de autorização do Dr. José Costa Maia.

Objectivos do Estudo:
Avaliação da adequabilidade da razão neutrófilos/linfócitos (à admissão do doente, às 24h e às 48h) como preditor da gravidade de um episódio de pancreatite aguda.
Insere-se no âmbito do Mestrado Integrado em Medicina da FMUP, sob orientação do Dr. Rui Jorge Ferreira Mendes da Costa, que será o profissional de ligação.

Benefício/risco: N/A

Confidencialidade dos dados: Está garantida a confidencialidade dos dados e esta informação será restrita aos investigadores. Será eliminada qualquer informação que permita ligação aos doentes.

Respeito pela liberdade e autonomia do sujeito de ensaio: N/A

Curriculum **do investigador**: Adequado à investigação.

Data previsível da conclusão do estudo: Janeiro de 2018

Conclusão: Proponho um parecer favorável à realização deste projecto de investigação.

Porto, 13 de Outubro de 2017

O Relator da CES, Dr. John Preto

U.PORTO

FMUP **FACULDADE DE MEDICINA**
UNIVERSIDADE DO PORTO

SÃO JOÃO

Questionário para submissão de Investigação

Exmo. Sr. Presidente da Comissão de Ética do Centro Hospitalar de São João/
Faculdade de Medicina da Universidade do Porto,

Pretendendo realizar a investigação infracitada, solicito a V. Exa., na qualidade de Investigador, a sua apreciação e a
elaboração do respetivo parecer. Para o efeito, anexo toda a documentação requerida.

IDENTIFICAÇÃO DO ESTUDO

Título da investigação: Pancreatite aguda - avaliação de critérios de gravidade

Nome do investigador: João Luís da Rocha Miranda

Endereço eletrónico: joaoluisrm@gmail.com   **Contacto telefónico:** 913383065

Caracterização da investigação:

☒ Estudo retrospetivo   ☐ Estudo observacional   ☐ Estudo prospetivo

☐ Inquérito   ☐ Outro. Qual? _____

Tipo de investigação:

☐ Com intervenção   ☒ Sem intervenção

Formação do investigador em boas práticas clínicas (GCP): ☐ Sim   ☒ Não

Promotor *(se aplicável):* _____

Nome do orientador de dissertação/tese *(se aplicável):* Rui Jorge Ferreira Mendes da Costa

Endereço eletrónico: rjmcosta@gmail.com

Local/locais onde se realiza a investigação: Serviço de Cirurgia Geral do Hospital São João

Data prevista para início: 1 / 10 / 2017   Data prevista para o término: 31 / 1 / 2018

PROTOCOLO DO ESTUDO

Síntese dos objetivos:

Avaliação da adequabilidade da razão neutrófilos/linfócitos (à admissão do doente, às 24h e às 48h) como preditor da gravidade de um
episódio de pancreatite aguda.

Fundamentação ética (ganhos em conhecimento/inovação; ponderação benefícios/riscos):

Estabelecimento de um protocolo de orientação clínica dos doentes admitidos com pancreatite aguda, de forma a que precocemente
sejam identificados fatores prognósticos, estratificando assim a gravidade da doença e o respetivo tratamento adequado.

CES-IM007-0

CONFIDENCIALIDADE

De que forma é garantida a anonimização dos dados recolhidos de toda a informação?

Será eliminada qualquer informação que permita ligação aos doentes.

O investigador necessita ter acesso a dados do processo clínico? ☒ Sim ☐ Não

Está previsto o registo de imagem ou som dos participantes? ☐ Sim ☒ Não

Se sim, está prevista a destruição deste registo após o sua utilização? ☐ Sim ☐ Não

CONSENTIMENTO

O estudo implica recrutamento de:

Doentes: ☐ Sim ☒ Não   Voluntários saudáveis: ☐ Sim ☒ Não

Menores de 18 anos: ☐ Sim ☒ Não

Outras pessoas sem capacidade do exercício de autonomia: ☐ Sim ☒ Não

A investigação prevê a obtenção de Consentimento Informado: ☐ Sim ☒ Não

Se não, referir qual o fundamento para a isenção:

Estudo é retrospetivo e apenas requer acesso a registos clínicos para a sua realização.

Existe informação escrita aos participantes: ☐ Sim ☒ Não

PROPRIEDADE DOS DADOS

A investigação e os seus resultados são propriedade intelectual de:

☒ Investigador   ☐ Promotor   ☐ Ambos   ☒ Serviço onde é realizado

☐ Não aplicável   Outro: _____

BENEFÍCIOS, RISCOS E CONTRAPARTIDAS PARA OS PARTICIPANTES

Benefícios previsíveis:

Nenhum

Riscos/incómodos previsíveis:

Nenhum

São dadas contrapartidas aos participantes:

· *pela participação*   ☐ Sim ☐ Não ☒ Não aplicável

· *pelas deslocações*   ☐ Sim ☐ Não ☒ Não aplicável

· *pelas faltas ao emprego*   ☐ Sim ☐ Não ☒ Não aplicável

· *por outras perdas e danos*   ☐ Sim ☐ Não ☒ Não aplicável

CUSTOS / PLANO FINANCEIRO

Os custos da investigação são suportados por:

☒ Investigador   ☐ Promotor   ☐ Serviço onde é realizado

☐ Não aplicável   Outro: _____

Existe protocolo financeiro? ☐ Sim ☒ Não
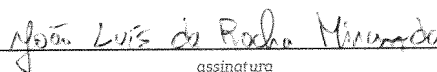
LISTA DE DOCUMENTOS ANEXOS

- ☒ Pedido de autorização ao Presidente do Conselho de Administração do Centro Hospitalar de São João *(se aplicável)*
- ☐ Pedido de autorização à Diretora da Faculdade de Medicina da Universidade do Porto *(se aplicável)*
- ☒ Protocolo do estudo
- ☒ Declaração do Diretor de Serviço onde decorre o estudo
  (sendo um estudo na área de enfermagem deve anexar também a concordância da chefia de enfermagem)
- ☐ Profissional de ligação
- ☒ Informação dos orientadores
- ☐ Informação ao participante
- ☐ Modelo de consentimento
- ☐ Instrumentos a utilizar *(inquéritos, questionários,escalas, p.ex.):* _____
- ☒ Curriculum Vitae abreviado *(máx. 3 páginas)*
- ☐ Protocolo financeiro
- ☐ Outros:

COMPROMISSO DE HONRA E DECLARAÇÃO DE INTERESSES

Declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (1960 e respetivas emendas), e da Organização Mundial da Saúde, Convenção de Oviedo e das "Boas Práticas Clínicas" (GCP/ICH) no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo, nos últimos três meses. Comprometo-me a entregar à CES o relatório final da investigação, assim que concluído.

Porto, __25__ de ____setembro____ de __2017__

Nome legível: João Luís da Rocha Miranda

João Luís da Rocha Miranda
assinatura

Parecer da Comissão de Ética do Centro Hospitalar de São João/ FMUP　　　Emitido na reunião plenária da CE de __13__ / __10__ / __17__

> A Comissão de Ética para a Saúde
> APROVA por unanimidade o parecer do
> Relator, pelo que nada tem a opor à
> realização deste projecto de investigação.