

The role of Neutrophil-Reactive Intensity (NEUT-RI) in ICU diagnosis of sepsis: a retrospective critical illness cohort study

E.M.A. Mantovani¹, S. Pastori², V. Roccaforte², R. Panella², P. Formenti¹, M. Gotti¹, A. Pezzi¹, G. Sabbatini^{1*}

¹ S.C. Anestesia Rianimazione e Terapia Intensiva, ASST Nord Milano, Ospedale Bassini, Cinisello Balsamo (MI)

² S.C. Analisi Chimico Cliniche e Microbiologiche, ASST Nord Milano, Ospedale Bassini, Cinisello Balsamo (MI)

* giovanni.sabbatini@asst-nordmilano.it

Background: The diagnosis of sepsis is often difficult and belated, substantially increasing the mortality in affected patients. Its early identification allows to choose the most appropriate therapies in the shortest time, improving patients' outcome and eventually their survival. Since neutrophil activation is an indicator of early innate immune response, the aim of the study was to evaluate the role of Neutrophil-Reactive Intensity (NEUT-RI), which is an indicator of their metabolic activity, in the diagnosis of sepsis.

Materials and Methods: Data from 96 patients consecutively admitted to the ICU were retrospectively analyzed (46 septic and 50 non-septic patients). Septic patients were further divided between sepsis and septic shock according to the severity of the illness. Patients were subsequently classified according to renal function.

Results: For the diagnosis of sepsis, NEUT-RI showed an AUC > of 0,80 and a better negative predictive value than Procalcitonin (PCT) and C-reactive protein (CRP) (87,4% vs 83,9% and 86,6%, p=0.038). Unlike PCT and CRP, NEUT-RI did not show significant difference within the "septic" group between patients with normal renal function and those with renal failure (p=0.182). Similar results were observed among the "non-septic" group (p=0.739). No significant difference in NEUT-RI values was observed according to the severity of sepsis (p=0.075).

Table 1. Baseline characteristics of the study population, divided by diagnosis of sepsis at ICU admission.

| | Septic (n 46) | Non septic (n 50) | P |
|---------------------------------------|-----------------|-------------------|--------|
| Age (years) | 70 [46; 87] | 68 [29; 90] | 0.172 |
| Male sex, N (%) | 24 (56) | 28 (58) | 0.992 |
| Complicated sepsis N (%) | 25 (54.3%) | | |
| Diagnosis: | | | |
| Pneumonia, N (%) | 23 (50) | | |
| Peritonitis, N (%) | 12 (26) | | |
| Urinary tract infection, N (%) | 11 (23) | | |
| Coma | | 11 (22) | |
| Other neurologic disorders | | 14 (28) | |
| Acute pulmonary edema | | 7 (14) | |
| Post-surgery monitoring | | 18 (36) | |
| SOFA score at ICU admission (points) | 7 [4; 8] | 6 [4; 8] | 0.951 |
| Renal Failure at ICU admission, n (%) | 28 (60.1) | 21 (42) | 0.245 |
| Serum creatinine (mg/dl) | 3.51 (2.35) | 2.04 (2.25) | <0.001 |
| NEUT-RI (FI) | 57 [52.8;62.7] | 48.7 [47.1;51.7] | <0.001 |
| PCT (ng/ml) | 17.7 [7.8;74.5] | 0.48 [0.9;1.27] | <0.001 |
| CRP (mg/dl) | 18.1 [8.3;25.3] | 3.3 [1.43;11.2] | <0.001 |

SOFA= Sequential Organ Failure Assessment; ICU= Intensive Care Unit; AKI= Acute kidney Injury as defined by KDIGO guidelines; PCT= Procalcitonin; CRP= C-Reactive Protein

Table 2. Inflammatory parameters in septic vs non-septic patients, and in patients diagnosed with or without renal failure.

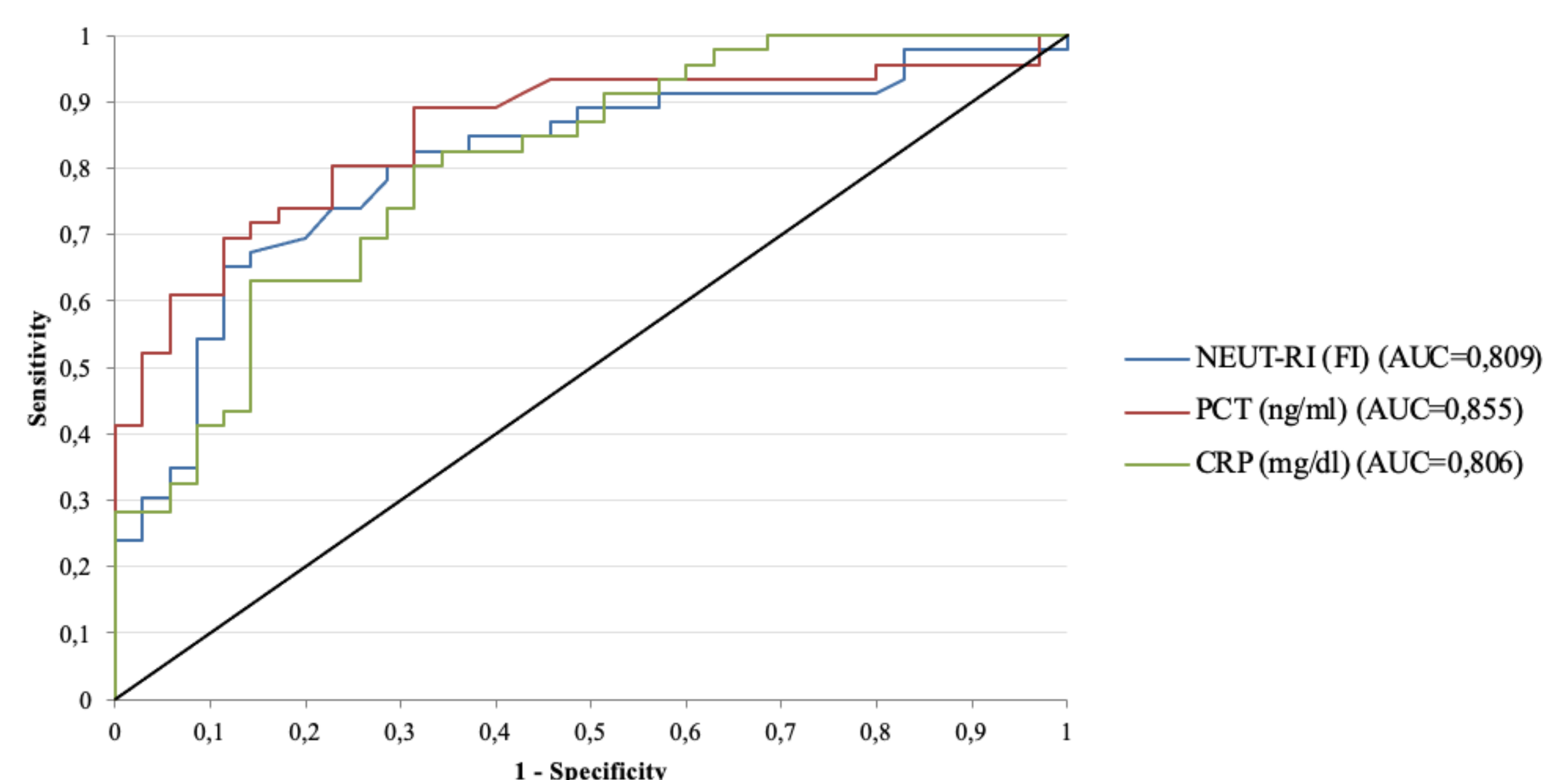
| | Normal Renal Function | n | Renal Failure | n | p |
|----------------------|-----------------------|----|-------------------------|----|-------|
| NEUT-RI (septic) | 52.3 [49.5;58.3] FI | 18 | 57.5 [55.1;63.9]FI | 28 | 0.182 |
| NEUT-RI (non-septic) | 49.3 [47;52.7]FI | 29 | 48.4 [47.6;50.7] FI | 21 | 0.739 |
| PCT (septic) | 1.7 [0.79;5.3] ng/mL | 18 | 57.9 [14.3;107.3] ng/mL | 28 | 0.002 |
| PCT (non-septic) | 0.43 [0.3;0.7] ng/mL | 20 | 1.23 [0.5;6.8] ng/mL | 15 | 0.016 |
| CRP (septic) | 9.13 [4.9;17.2] mg/dL | 18 | 18.7 [15.7;27.7] mg/dL | 28 | 0.005 |
| CRP (non-septic) | 2.7 [1.2;4.7] mg/dL | 24 | 6.9 [2.5;11.6] mg/dL | 17 | 0.162 |

Table 3. Accuracy, cut-off, sensitivity and specificity of inflammatory parameters for detection of sepsis.

| | AUROC (95% CI) | Cut-off | Youden's index | Sens (95% CI) | Spec (95% CI) | PPV | NPV |
|---------|---------------------|-------------|----------------|-------------------|-------------------|-------|-------|
| NEUT-RI | 0,80 [0,741-0,912] | ≥51,9 FI | 0,56 | 80,4% [68,9-91,8] | 76% [64,2-87,8] | 65,2% | 87,4% |
| PCT | 0,855 [0,771-0,938] | ≥2,16 ng/mL | 0,58 | 69,6% [56,3-82,9] | 88,6% [78-99,1] | 77,3% | 83,9% |
| CRP | 0,801 [0,736-0,908] | ≥6,91 mg/dL | 0,51 | 80,4% [68,9-91,9] | 70,7% [56,8-84,7] | 60,6% | 86,6% |

AUROC= Area Under the ROC curve; Sens= Sensitivity; Spec= Specificity; PPV= Positive Predictive Value; NPV= Negative Predictive Value

Figure 1. Performance evaluation of inflammatory parameters



The figure shows the area under the Receiver-operating characteristic (ROC) curve for the distinction of inflammatory parameters for detection of sepsis. The areas under the ROC curves are as follows: NEUT-RI (blue line): 0.80 [95%CI 0.74-0.91]; PCT (red line): 0.85 [95%CI 0.77-0.93]; CRP (green line): 0.80 [95%CI 0.77-0.93]; p<0.001; AUC= Area Under the Curve.

Conclusions: The increase in NEUT-RI values could be useful in the early ruling out of sepsis, and it does not appear to be influenced by renal failure. However, NEUT-RI has not proved efficient in discriminating the severity of sepsis at the time of admission. Larger, prospective studies are needed to confirm these results.

References:

- Zhang, W.; Zhang, Z.; Pan, S.; Li, J.; Yang, Y.; Qi, H.; Xie, J.; Qu, J. The Clinical Value of Hematological Neutrophil and Monocyte Parameters in the Diagnosis and Identification of Sepsis. *Ann Transl Med* 2021, 9, 1680, doi:10.21037/atm-21-5639.
- Cornet, E.; Boubaya, M.; Troussard, X. Contribution of the New XN-1000 Parameters NEUT-RI and NEUT-WY for Managing Patients with Immature Granulocytes. *Int J Lab Hematol* 2015, 37, e123-126, doi:10.1111/ijlh.12372.
- Kwiecień, I.; Rutkowska, E.; Kulik, K.; Kłos, K.; Plewka, K.; Raniszewska, A.; Rzepecki, P.; Chciałowski, A. Neutrophil Maturation, Reactivity and Granularity Research Parameters to Characterize and Differentiate Convalescent Patients from Active SARS-CoV-2 Infection. *Cells* 2021, 10, 2332, doi:10.3390/cells10092332.
- Lee, J.; Gu, J.; Seo, J.E.; Kim, J.W.; Kim, H.K. Diagnostic and Prognostic Values of Neutrophil Reactivity Intensity (NEUT-RI) in Pediatric Systemic Inflammatory Response Syndrome and Sepsis. *Ann Clin Lab Sci* 2023, 53, 173–180.