Role of Neutrophil-to-lymphocyte ratio for monitoring stratification and prognosis of sepsis

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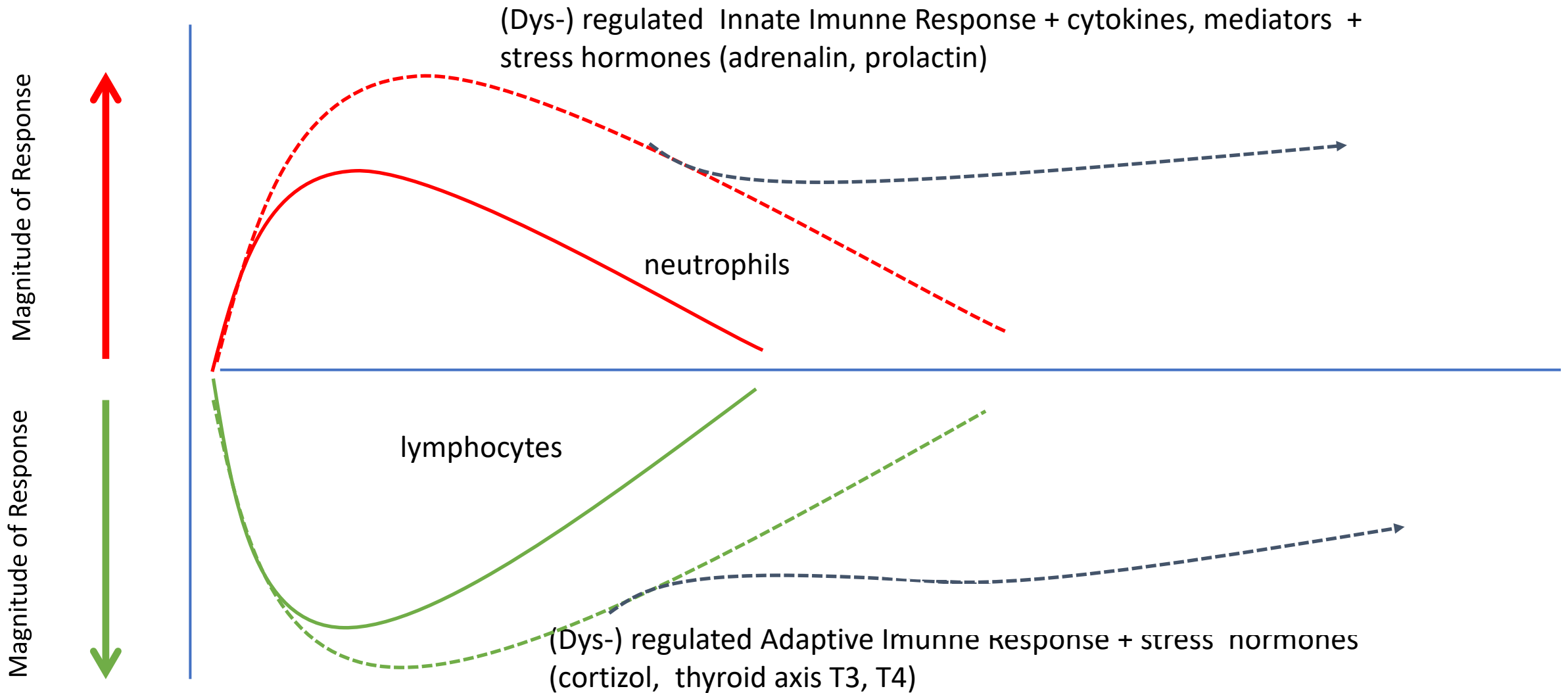St. Elizabeth s Cancer Institute , Bratislava, SVK

Neutrophil – to-lymphocyte ratio (NLR) , biomarker of **stress and immune-inflammatory** response , infection and severity of disease

- Parameter of systemic inflammation, activation of immune system leading to immune-inflammatory response (SIRS)

- Relation bw. Cellular innate (Neutrophils) and adaptive immunity (Lymphocytes)

- Reflects endocrinne stress (catecholamines and cortisol, prolactin, thyroid hormones T3,T4)

- Increased values of NLR are associated with the **severity** of the disease : bacterial and viral infection, inflammation, **sepsis** , stroke, acute myocardial infarction, cancer , sclerosis multiplex, autoimmune diseases, schizophrenia, acute pancreatitis, acute appnedicitis, surgical complications ..

Zahorec R, Bratisl Lek listy, 2021, 122:474-478

Neutrophil-to-lymphocyte ratio, past, present and future
Záhorec R, Bratisl Med J., 2021, 122 (7): 474 – 478 .

Neutrophil – to-lymphocyte ratio , cheap, easy available, reliable, „on-line" parameter of immune-inflammatory response , infection and severity of disease .

Ratio of neutrophil to lymphocyte counts — rapid and simple parameter of systemic inflammation and stress in critically ill

Zahorec R

Pomer neutrofilov a lymfocytov — rýchly a jednoduchý ukazovateľ systémového zápalu a stresu v kritických stavoch

Tab. 6. Inflammatory/immune response of circulating white blood cells, expressed as a Neutrophil-lymphocyte stress factor (NLSF), which is neutrophil-lymphocyte ratio.

Tab. 6. Návrh miery intenzity zápalu a stresu na relatívny počet neutrofilov a lymfocytov. NLSF — neutrofil-lymfocytový stresový faktor je pomer neutrofilov k lymfocytom vyjadrených v % z počtu leukocytov.
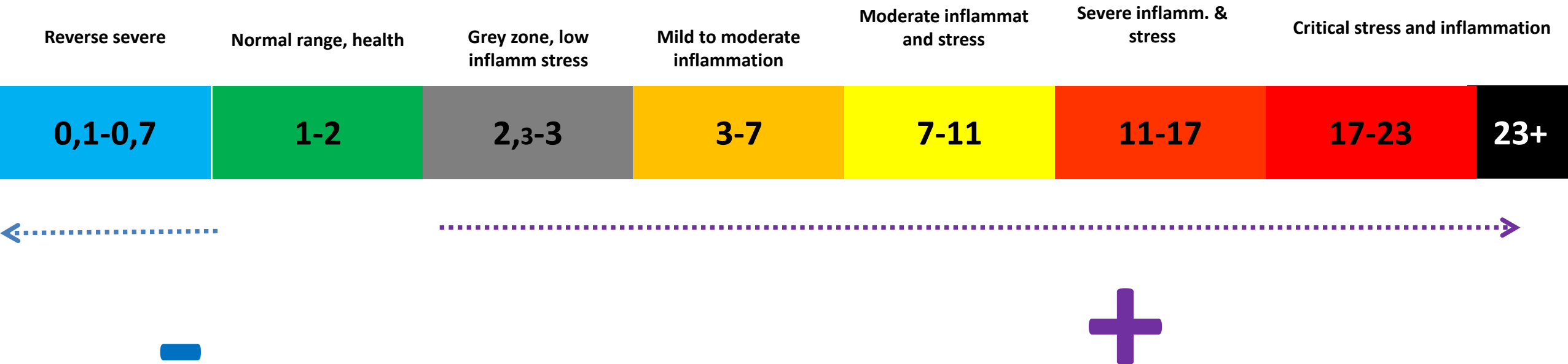
Differential white blood cell count (% relation of neutrophil/lymphocyte count), measured on blood cell counter SYSMEX SF 3000

Inflam/stress	Physiologic	Stress	Supraphysiolog.	Stress
Parameter	1-mild	2-moderate	3-severe	4-critical
Neutrophil %	78-84,9%	85-89,9%	90-94,9%	95 and higher %
Lymphoc. %	10,1-15%	5,1-10,0%	2,6-5,0%	2,5 and less %
NLSF	5,5-8,4	8,5-17,9	18-36	36 and higher

Neutrophil-to-lymphocyte ratio, past, present and future

Záhorec Roman, Bratisl Med J., 2021, 122 (7): 474 – 478 .

NLR Meter

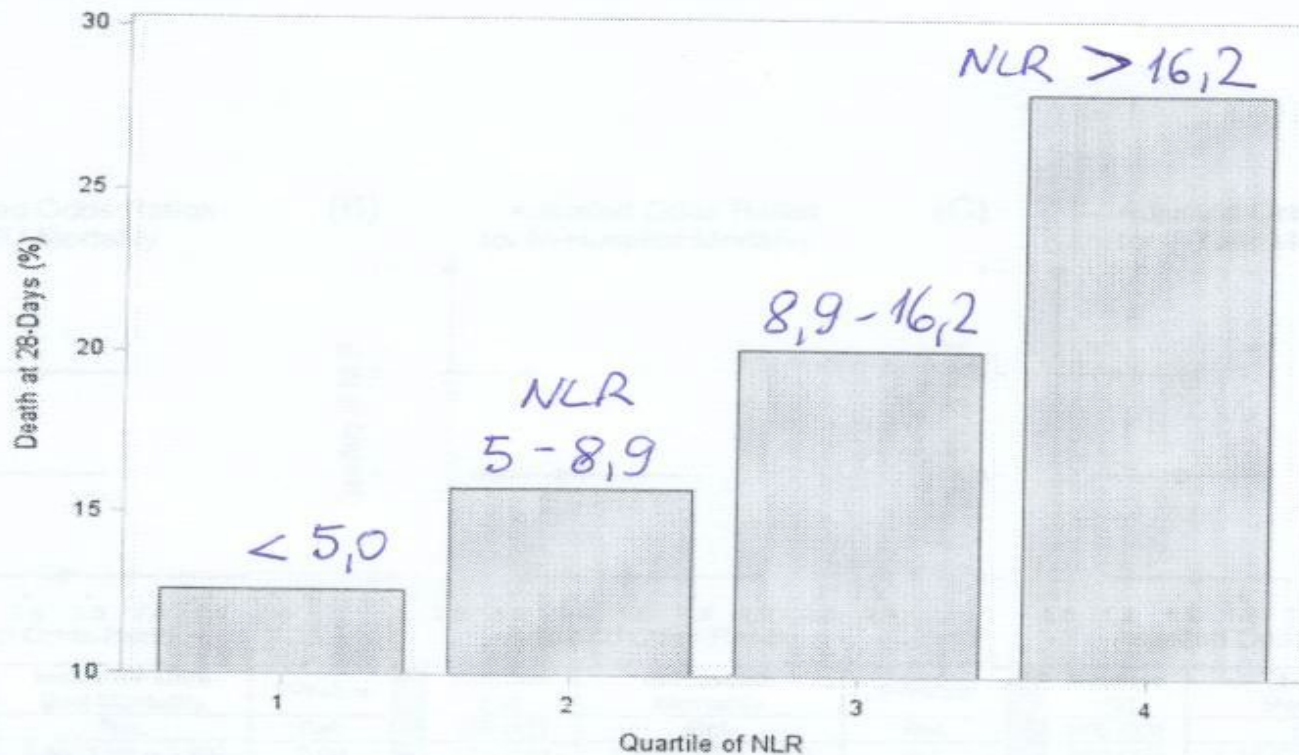| Reverse severe	Normal range, health	Grey zone, low inflamm stress	Mild to moderate inflammation	Moderate inflammat and stress	Severe inflamm. & stress	Critical stress and inflammation
0,1-0,7	1-2	2,3-3	3-7	7-11	11-17	17-23	23+

The association between the neutrophil-to-lymphocyte ratio and mortality in critical illness: an observational cohort study

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Marco AF Pimentel (marco.pimentel@eng.ox.ac.uk)

Quartile	Number Dead at 28-Days (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	P-Value
1	159 (13)	Ref.	Ref.	Ref.
2	199 (16)	1.30 (1.03 – 1.62)	1.32 (1.03 – 1.71)	0.03
3	254 (20)	1.75 (1.41 – 2.16)	1.43 (1.12 – 1.83)	0.004
4	354 (28)	2.70 (2.19 – 3.31)	1.71 (1.35 – 2.16)	< 0.001

CI, confidence interval; OR, odds ratio

Handwritten annotations:

NLR > 16,2

8,9 - 16,2

NLR 5 - 8,9

< 5,0

NLR
< 5,0
5,0 - 8,9
8,9 - 16,21
> 16,21

Reversal of neutrophil-to-lymphocyte count ratio in early versus late death from septic shock

Florence Riché et al. 2015

- Florence Riché **Affiliated with**Département d'Anesthésie – Réanimation – SMUR, Hôpitaux Universitaires Saint Louis — LariboisièreUFR de Médecine, Université Paris

Key messages

- In patients admitted to the ICU for septic shock, a low NLCR at admission is associated with a risk of early death.
- In the same population, an increase in the NLCR during the first 5 days is associated with a risk of late death.
- Early and late death should be distinguished because they may involve different underlying mechanisms.

Lymphocytopenia and neutrophil-lymphocyte count ratio predict bacteremia better than conventional infection markers in an emergency care unit

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Diagnostic accuracy of procalcitonin, neutrophil-lymphocyte count ratio, C-reactive protein, and lactate in patients with suspected bacterial sepsis.

- Utility and validity of four biomarkers of sepsis (Procalcitonin -PCT, NLR, C-Reactive protein CRP, Lactate) in early diagnosis of sepsis

- Pilot observational study on the cohort of 1572 adult patients approved validity , accuracy and reliability of laboratory parameters for diagnosis of Sepsis

- Optimal combination (panel) and cut-off values for sepsis:

NLR > 3,5 , PCT > 2,0 ng/ml, CRP > 100 mg/L, lactate > 2,0 mmol/l

The complete blood count to diagnose septic shock

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Table 1 Correlation between procalcitonin and other measurements among 1,468 patients with suspected infection
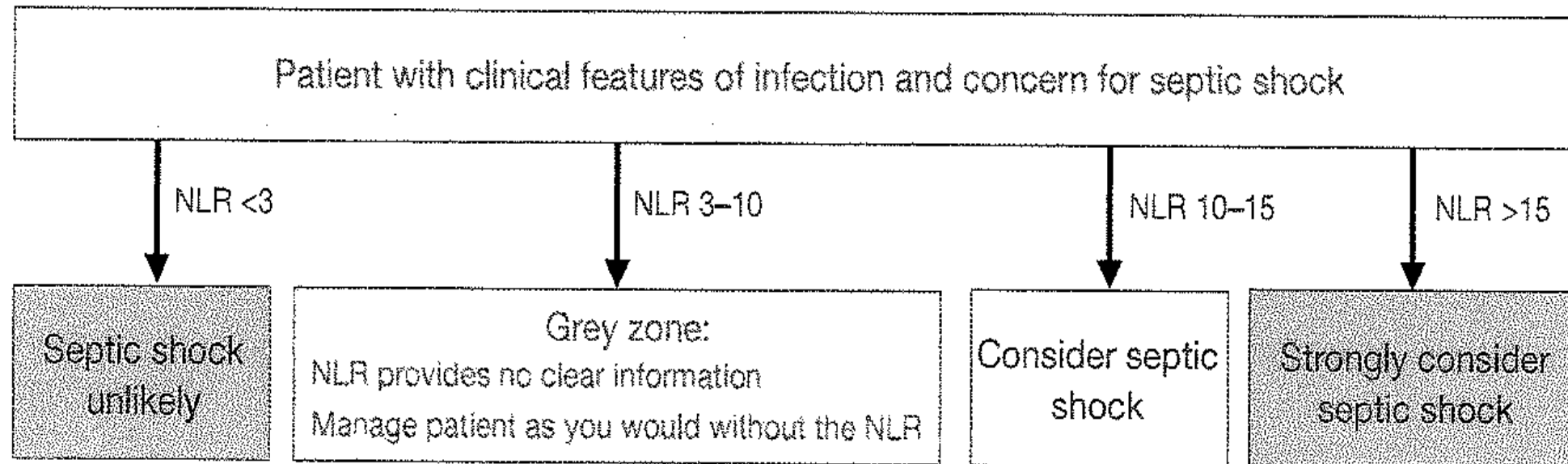
Patient group (ng/mL)	C reactive protein (mg/L)	WBC	NLR	NLR cutoff suggested by Gürol et al.
Procalcitonin <0.05	29±42	9±3	4±4	<5
Procalcitonin 0.05–0.5	70±67	11±5	6±9	5–10
Procalcitonin 0.5–2	121±102	14±11	12±14	10–13
Procalcitonin 2–10	138±114	13±8	13±7	13–15
Procalcitonin >10	161±146	16±12	17±10	>15

WBC, white blood count; NLR, neutrophil to lymphocyte ratio.

The complete blood count to diagnose septic shock ,

Hynek numb. < 2,4 , Neutr. bands > 10%, Immature Granul. >5%, erytroblasts, N-RBCs, signif. Increased values of **NLR >11**, trombocyty, MPV, RDW % , MDW %,

Patient with clinical features of infection and concern for septic shock

NLR <3

NLR 3–10

NLR 10–15

NLR >15

Septic shock unlikely

Grey zone:
NLR provides no clear information
Manage patient as you would without the NLR

Consider septic shock

Strongly consider septic shock

l approach to interpretation of the NLR in evaluation of septic shock. Note, however, that values m
ext and other sources of physiologic stress. The NLR reflects physiologic stress, rather than being a s

The utility of peripheral blood leucocyte ratios as biomarkers in infectious disea review and meta-analysis

Clark D. Russell,[a,b,1,*] Arun Parajuli,[c,1] Hugo J. Gale,[d] Naomi S. Bulteel,[b] Philipp Schuetz,[e] Cornelis P.C. de Jager,[f] Anne Merekoulias,[h] and J. Kenneth Baillie[i,j]

Results

Forty studies were included, reporting on bacterial and viral infections, malaria, and critical illness due to s an association of higher NLR with bacteraemia, supported by meta-analysis of patient-level data (five stud $p<0.0001$) identifying a cut-off of >12.65. Two studies reported an association with lower LMR and diagn infection in patients with respiratory tract infection. Meta-analysis of patient-level data ($n = 85$; AUC 0.66, off of ≤2.06. The directionality of associations between NLR and outcomes in heterogeneous cohorts of cri varied. Potential clinical utility was also demonstrated in pneumonia (NLR), pertussis (NLR), urinary tract foot infections (NLR) and Crimean Congo Haemorrhagic Fever (PLR). Longitudinal measurement of LMF infection reflected symptoms and NLR during sepsis and bacteraemia predicted mortality.

Conclusions

Peripheral blood leukocyte ratios are useful infection biomarkers, with the most evidence related to diagno influenza virus infection. In critical illness due to sepsis, a signal towards an association with NLR and out should be evaluated in future stratification models. Longitudinal measurement of ratios during infection co Overall, these biomarkers warrant further recognition and study in infectious diseases.

Keywords: Neutrophils, Lymphocytes, Monocytes, Blood platelets, Sepsis, Bacteremia, Influenza, Pneumonia, Strat

Introduction

Infection biomarkers can be used as adjuncts to inform differential diagnosis (e.g. distinguishing bacterial i prognostic markers to stratify patients into sub-groups and endotypes,[1] and to monitor the response to anti duration. Canonical biomarkers include the total white cell count (WCC) and C-reactive protein (CRP). Fo been increasing interest in the use of procalcitonin as a biomarker for discrimination of bacterial from viral response to antimicrobial therapy. Meta-analyses of clinical trials indicate that procalcitonin results can rec and improve outcomes in respiratory tract infections with similar findings in critically ill patients with pres intensive care unit (ICU).[2, 3, 4] However, procalcitonin measurement is currently expensive and is not uni contrast, the full blood count is a cheap, fast and ubiquitous laboratory investigation. Automated counters f enumerating circulating leucocytes including neutrophils, lymphocytes and monocytes, but these paramete isolation.

During sepsis, apoptosis of B-cells and T-cells causes lymphocyte depletion, and peripheral blood lymphoj
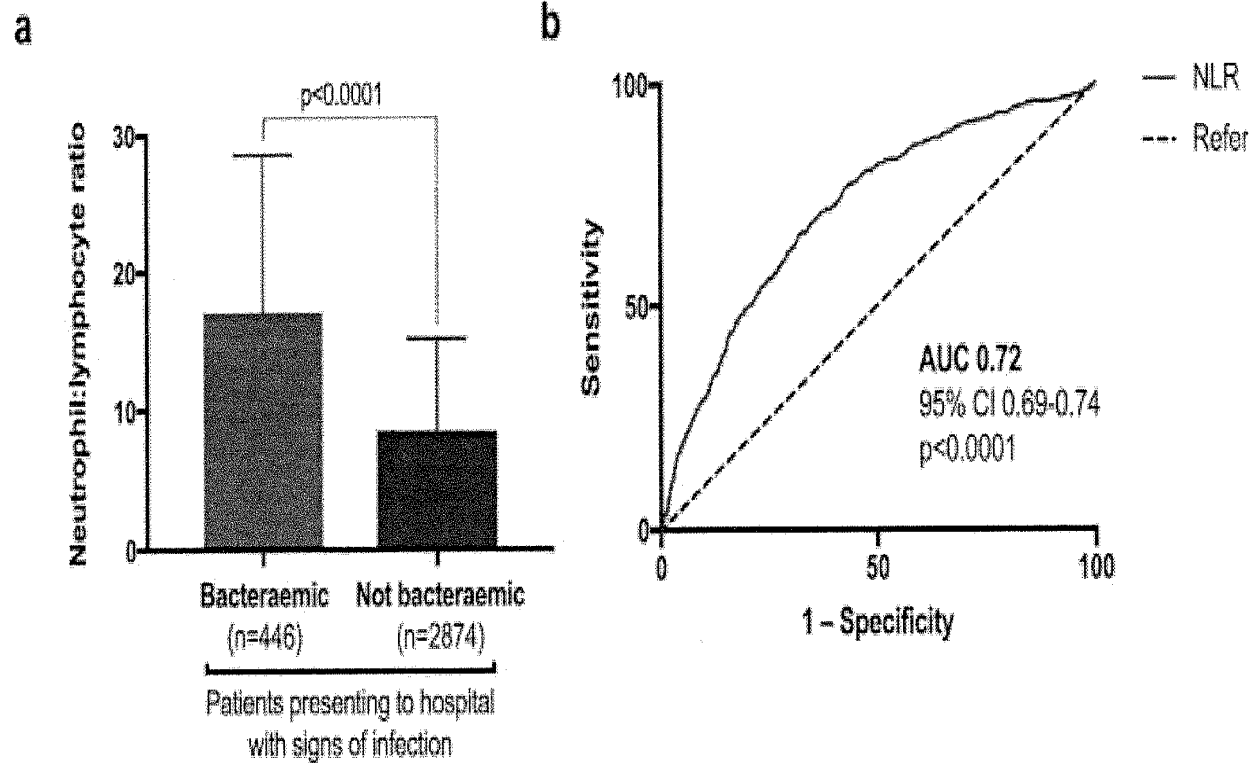
NLR > 12,65 , LMR < 2,06

Fig. 3

Meta-analysis results for NLR and bacteraemia. **a** NLR median and interquartile range derived from meta-data for 3320 patients. **b** Receiver operator characteristic analysis for NLR in predicting presence of bacter

Eosinophil Count and Neutrophil-Lymphocyte Count Ratio as Prognostic Markers in Patients with Bacteremia: A Retrospective Cohort Study

Roser Terradas[1,2]*, Santiago Grau[3,4], Jordi Blanch[1,5], Marta Riu[1,4,5], Pere Saballs[4,6], Xavier Castells[1,5], Juan Pablo Horcajada[4,6], Hernando Knobel[4,6]

NLR > 7

Bacteremia. Eosinophil Neutrophil-Lymphocyte Ratio

Table 2. Hazard ratios for the association between patient characteristics and mortality.

Variable	Categories	Univariate HR (95% CI)	Multivariate HR (95% CI)
Eosinophil count	$0.0000-0.0453 \cdot 10^3$/uL	4.77 (3.15–7.23)	4,20 (2,66–6,62)
	$0.0454-0.1510 \cdot 10^3$/uL	1.55 (0.97–2.47)	1,53 (0,92–2,52)
	$0.1511-1.4415 \cdot 10^3$/uL	Ref	Ref
NLCR	NLCR ≤7	Ref	Ref
	NLCR >7	2.74 (2.01–3.74)	1,72 (1,24–2,39)
Age	Increase 1 year	1.02 (1.01–1.03)	1,02 (1,01–1,03)
Sex	Women	Ref	Ref
	Men	1.50 (1.16–1.95)	1,21 (0,90–1,64)
Place of acquisition	Community-acquired	Ref	Ref
	Healthcare-related	2.54 (1.98–3.27)	1,64 (1,16–2,32)
Charlson Index	0	Ref	Ref
	1	0.77 (0.48–1.22)	1,02 (0,60–1,72)

Improved Early Detection of Sepsis in the ED With a Novel Monocyte Distribution Width Biomarker

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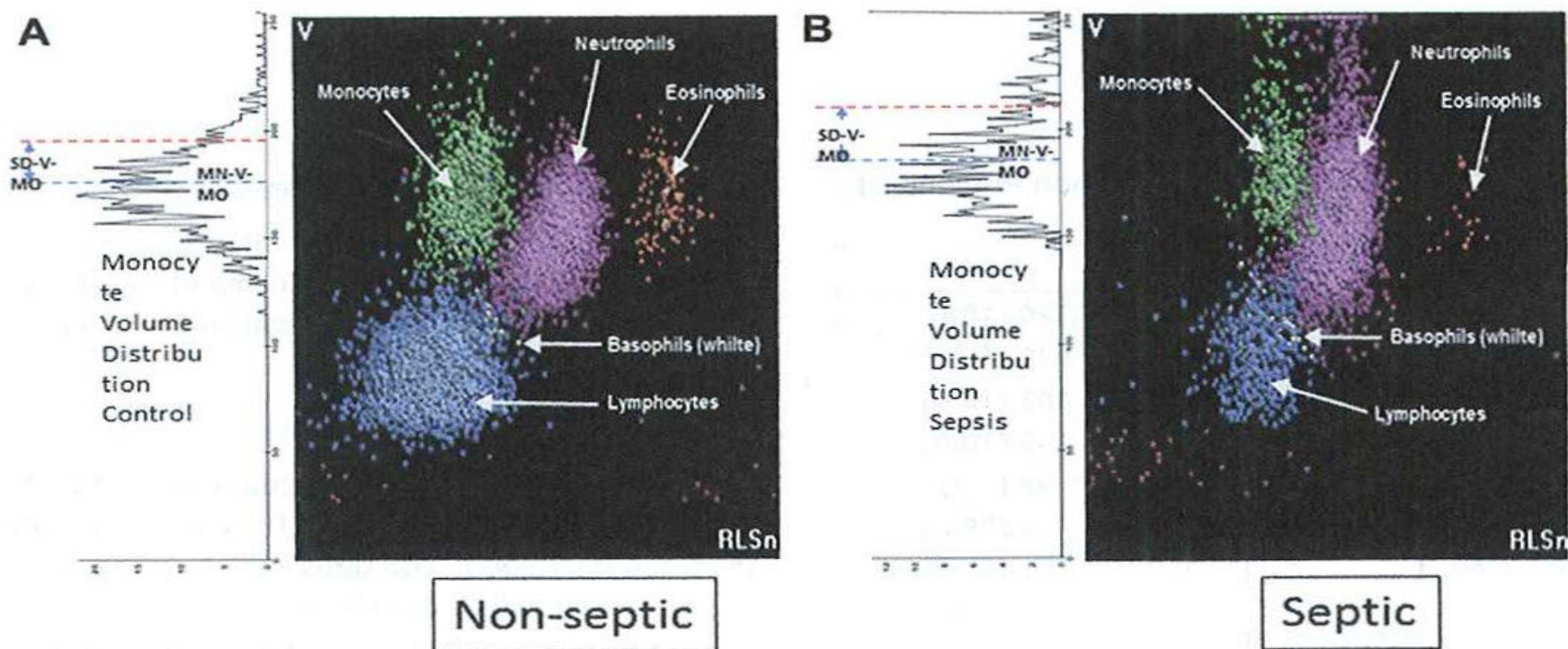
Figure 1 – A, B, Cell population distribution analysis. Representative histograms of WBC populations derived from the Beckman Coulter DxH 800 analyzer. (A) Example of a nonseptic donor. (B) Two-dimensional histogram corresponds to an example of a patient with septic shock. (A) The rotated one-dimensional histogram represents the distribution of the monocyte population volumes. The dotted blue line on top of the distribution represents the mean monocyte volume. The dotted red line represents 1 SD from the mean of the distribution (ie, monocyte distribution width), which is shown to be increased in the patient with sepsis.

Sensitive lab. Prameters able to discriminate viral and bacterial infection (NLR > 6,1),

Holub M. et al. 2012 , Naess et al. 2017.

Parameter zápalu (norma)	Vírusové infekcie	Bakteriálne infekcie
Pomer NLR (1,0 – 2,0)	0,3 – 5,9	≥ 5,0 – 7,0 – 11,0 – a viac
Pomer LMR (vyše 2,2)	Menej < 2,0	
C- reaktívny proteín (< 5,0 mg/l	5 – 20 mg/l, < 30 mg/l	≥ 40-50 mg/l, ≥ 100- 150 mg/l.
Prokalcitonín (0,01– 0,1 ng/ml)	0,05 – 0,1 ng/ml	≥ 0,25 ng/ml, ≥ 0,4 – 1,0 ng/ml
IL – 6 (1- 8 pg/ml)	8 – 20 – 30 pg/ml	≥ 100 pg/ml, ≥ 200 – 400 pg/ml
Neopterín (2 – 10 nmol/l)	15 – 50 nmol/l	< 15 nmol/l.

Time course of risk factors associated with mortality of 1260 critically ill patients with COVID-19 admitted to 24 Italian intensive care units

Alberto Zanella[1,2], Gaetano Florio[1], Mass
Luca Cabrini[10], Eleonora Carlesso[1], Gian
Irene Coloretti[12], Daniele Corti[13], France
Roberto Fumagalli[6,15], Massimo Girardis

- NLR dynamic changes the course of Neutr/lymph. ratio
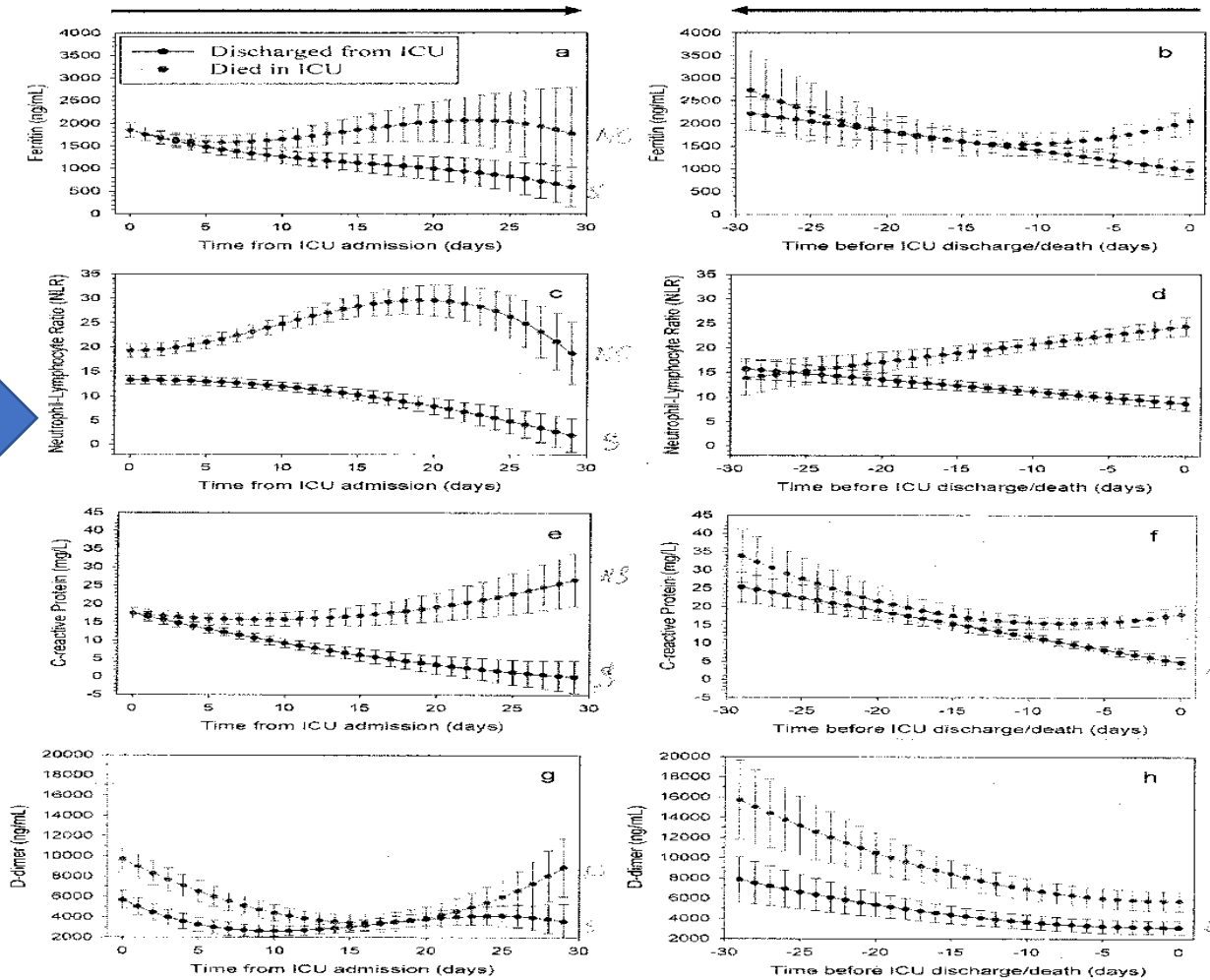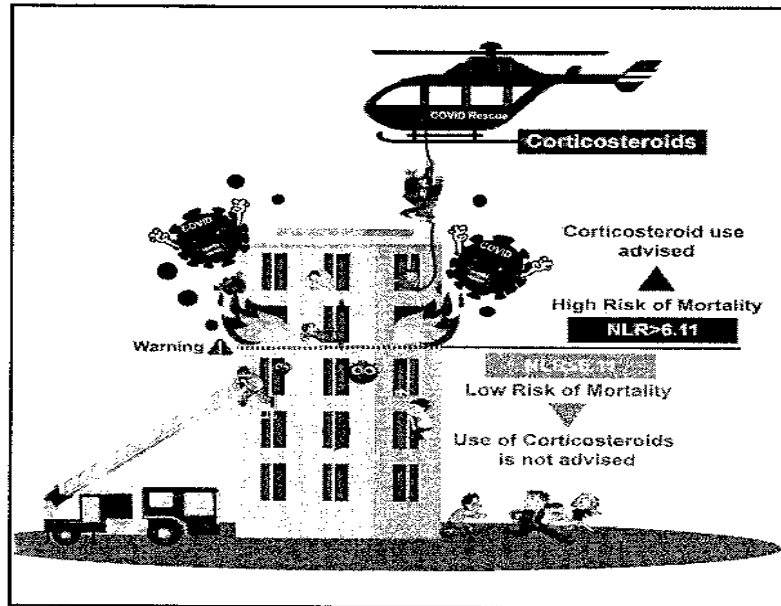
- CRP values and dynamics of COVID-19 inf. on ICU

g. 3 (See legend on previous page.)

Cell Metabolism

The Neutrophil-to-Lymphocyte Ratio Determines Clinical Efficacy of Corticosteroid Therapy in Patients with COVID-19

Graphical Abstract

Authors

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In Brief

While corticosteroid therapy is effective in the treatment of patients with severe COVID-19, a quantitative clinical parameter to identify such severity and which patients would respond well to corticosteroids has not been developed. Here, Cai et al. find that a simple blood test that measures the neutrophil-to-leukocyte ratio at admission discriminates high versus low mortality risk and a better response to corticosteroid therapy.

Highlights

- 12,862 COVID-19 cases on corticosteroid therapy or not were retrospectively studied

- NLR at admission is a key factor for patients with high or low risk of death

- An NLR > 6.11 was associated with lower mortality in patients on corticosteroids

SepsEast Registry indicates high mortality associated with COVID-19 caused acute respiratory failure in Central-Eastern European ICUs

Jan Benes , Miłosz Jankowski , Konstanty Szułdrzynski , Roman Zahorec , Mitja Lainscak , Zoltán Ruszkai , Matej Podbregar , Jan Zatloukal, Jakub Kletecka, Krzysztof Kusza , Jakub Szrama , Estera Ramic, Katarina Galkova, Stefan Krbila, Josef Valky, Jaka Ivanic, Marko Kurnik, Angéla Mikó , Tamás Kiss, Barbara Hetényi, Peter Hegyi , Alan Sustic * & Zsolt Molnar

	Overall		Survivors		Non-survivors		
	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)	p-value
SOFA	515	7 (4–10)	156	4 (2–8)	359	8 (5–11)	<0.0001
APACHE II	551	17 (12–25)	187	13 (10–19)	364	21 (14–27)	<0.0001
PaO₂/FiO₂ (mmHg)	1352	97 (66–150)	527	123 (80–200)	825	84 (62–124)	<0.0001
Lymphocyte count (10^9/L)	1286	0.46 (0.16–0.95)	424	0.70 (0.46–1.86)	862	0.32 (0.07–0.75)	<0.0001
CRP (mg/L)	1711	118 (62–190)	706	104 (54–173)	1005	128 (70–205)	<0.0001
PCT (ng/mL)	1490	0.39 (0.18–1.14)	501	0.30 (0.12–1.00)	989	0.41 (0.20–1.31)	<0.0001
IL-6 (pg/mL)	448	68 (23–144)	155	45 (15–106)	293	88 (28–191)	<0.0001
Ferritin (µg/L)	939	1081 (580–2000)	351	797 (418–1542)	588	1311 (741–2030)	<0.0001
D-dimers (mg/L)	1226	2.65 (1.22–9.00)	373	2.12 (1.13–7.32)	853	3.06 (1.26–10.19)	0.0083
Serum lactate (mmol/L)	1308	1.8 (1.3–2.9)	400	1.3 (1.0–1.8)	908	2.2 (1.5–3.5)	<0.0001

Country—Centre	No of ICU patients	Percentage of the dataset (%)
CROATIA	286	13
University Hospital Rijeka	286	13
CZECHIA	583	27
University Hospital Plzen	583	27
HUNGARY	269	13
Flór Ferenc Hospital County Pest	112	5
University of Pécs, School of Medicine	157	7
POLAND	115	5
Poznań Medical University Hospital	66	3
Central Clinical Hospital of the Ministry of Interior and Administration, Warsaw	49	2
SLOVAKIA	491	23
University Hospital Nitra	178	8
University Hospital Nové Zámky	166	8
University Hospital Banska Bystrica	147	7
SLOVENIA	395	18
General Hospital Celje	226	11
General Hospital Murska Sobota	169	8
Overall	2139	100

Table 1. Participating centres.

ORIGINAL RESEARCH

Value of Neutrophil:Lymphocyte Ratio Combined with Sequential Organ Failure Assessment Score in Assessing the Prognosis of Sepsis Patients

302 Patients with sepsis
NLR > 11,6
SOFA > 5,5
Prognosis : SOFA + NLRx0,15
bad prognosis : > 7,1

Yixuan Li, Junyu Wang, Bing Wei, Xiangqun Zhang, Le Hu, Xinghua Ye

Emergency Medicine Clinical Research Center, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, People's Republic of China

Table I Demographic and clinical data

	Survival group (n=238)	Death group (n=64)	P
Age (years)	72±14	78±10	<0.001
Sex (male)	133(55.9%)	42(65.6%)	0.161
Pulse (beats/minute)	94±24	101±28	0.113
Systolic pressure (mmHg)	138±27	118±35	<0.001
Diastolic pressure (mmHg)	74±17	63±20	<0.001
Consciousness disorder (%)	17.0%	50.8%	<0.001
Pct (ng/mL)	0.05(0.5, 0.27)	1.00(0.09, 5.95)	<0.001
CRP (mg/L)	14.0(8.0, 65.8)	93.0(43.3, 120.0)	<0.001
WBCs (×10⁹/L)	8.90(6.48, 11.70)	11.25(8.03, 16.60)	<0.001
Neutrophils (×10⁹/L)	6.86(4.70, 9.48)	9.69(6.43, 14.58)	<0.001
Lymphocytes (×10⁹/L)	1.16(0.73, 1.70)	0.96(0.58, 1.37)	0.042
Platelets (×10⁹/L)	185(142, 256)	203(129, 282)	0.409
Creatinine (μmol/L)	81 (62, 119)	127(86, 253)	<0.001
Urea nitrogen (mmol/L)	7.17(5.05, 10.87)	15.09(8.70, 23.75)	<0.001
Lac (mmol/L)	1.20(0.80, 1.80)	2.20(1.50, 4.35)	<0.001
NLR	6.25(3.18, 11.33)	12.41 (6.45, 28.32)	<0.001
SOFA score	4.0(2.8, 6.0)	7.0(5.3, 10.8)	<0.001
APACHE II score	11.0(8.0, 15.3)	20.5(16.0, 25.0)	<0.001

Table 5 Predictive value of risk factors of 28-day mortality in patients with sepsis

Predictor	AUC	95% CI	P	SE	Cutoff	Sensitivity (%)	Specificity (%)	
Age	0.645	0.573–0.717	<0.001	0.037	74.5	73.4	50.0	
Pct	0.761	0.691–0.831	<0.001	0.036	0.405	67.2	78.6	
CRP	0.746	0.677–0.816	<0.001	0.036	55.5	75.0	73.5	
Lac	0.767	0.700–0.834	<0.001	0.034	2.05	56.3	80.3	
NLR	0.721	0.651–0.790	<0.001	0.036	11.65	59.4	77.3	
SOFA	0.791	0.729–0.853	<0.001	0.032	5.5	75.0	72.7	
APACHE II	0.853	0.807–0.899	<0.001	0.023	14.5	84.4	73.1	
NLR combined with SOFA	0.868	0.824–0.911	<0.001	0.022	7.11	84.4	73.9	

Tips and tricks how to use NLR parameter - objective hematologic parameter for diagnosis/severity /intensity of inflammation and sepsis

- NLR easy available, valid and reliable laborartory parameter of stress/ inflammation, follow-up in hospitalized ICU patient on the routine use

- Interpretation of NLR values only with anamnesis, clinical course and clinical status

- In acute illness follow up NLR on the daily basis (WBCs count differential) day of admission 0., day 1st., 2nd., 3rd. and 5th. *event.* 7th. day

- Dynamics of NLR during illness is crucial for prediction and prognosis (compare values on the first 1st day, 3., 5., 7.Days)!

- Cooperation with dpt. Hematology implement automatic calculation of NLR = absol. Neutrophil count : absol. Lymphoc count = relat.Neu %/ realtiv Lymf % .

- Use combination of biomarkers for infection: NLR , CRP, IG %, PCT,

- Efective panel of biomarkers for Sepsis: NLR + CRP + PCT + IL6 +SOFA

- Prognostic value for severity of sepsis SOFA/NLR= SOFA + 0,15xNLR

Thank You for Your attention !

The association between the neutrophil to lymphocyte ratio and in-hospital mortality among sepsis patients
A prospective study

Ralph Bou Chebl, MD[a], Mohamad Assaf, MD[a], Nadim Kattouf, MD[a], Saadeddine Haidar, MD[a], Mohamed Khamis, MD[a], Karim Abdeldaem, MD[a], Maha Makki, MSc[b], Hani Tamim, PhD[b], Gilbert Abou Dagher, MD[a],*

Vital signs and lab parameters of patients presenting to the Emergency Department with neutrophil to lymphocyte ratio above vs below the cutoff.

| | < 14,2 Neutrophil to lymphocyte ratio > 14,2 | | |
	Below the cutoff N = 545 Mean ± SD	Above the cutoff N = 320 Mean ± SD	P value
Systolic blood pressure upon presentation (mmHg)	121.96 ± 26.03	118.90 ± 27.56	.10
Diastolic blood pressure upon presentation (mmHg)	68.60 ± 15.49	66.62 ± 15.93	.07
Heart rate upon presentation (beats/min)	98.44 ± 25.37	100.10 ± 25.21	.35
O_2 saturation upon presentation (%)	93.48 ± 9.59	93.64 ± 9.52	.08
Temperature upon presentation (C)	37.39 ± 1.78	37.39 ± 1.58	.97
Respiratory rate upon presentation (Breaths/min)	21.71 ± 8.24	21.64 ± 7.15	.90
White blood cell count (cu.mm)	10801.62 ± 7651.71	14877.80 ± 8492.98	
Neutrophil count (cu.mm)	8026.47 ± 4479.79	13514.00 ± 7530.05	
Lymphocyte count (cu.mm)	1661.41 ± 3417.68	520.08 ± 323.66	
Neutrophil to lymphocyte ratio	6.95 ± 3.60	33.68 ± 25.31	
Hematocrit (%)	35.15 ± 7.61	35.76 ± 5.99	.22
Hemoglobin (g/dL)	11.45 ± 2.30	11.68 ± 2.06	.15
Platelets (cu.mm)	228970.64 ± 129269.39	237883.64 ± 140994.58	.34
Lactate (mmol/L)	2.80 ± 2.00	3.21 ± 2.69	.01
C-reactive protein(mg/L)	119.33 ± 100.81	146.37 ± 103.80	.004
Albumin (g/L)	33.95 ± 6.52	31.92 ± 7.05	
Procalcitonin (ng/L)	5.05 ± 16.76	6.19 ± 15.16	.45
Glucose (mg/dL)	159.52 ± 83.90	177.13 ± 106.65	.02
BUN (mg/dL)	31.48 ± 22.93	38.54 ± 27.85	
Creatinine (mg/dL)	1.52 ± 1.34	1.64 ± 1.37	.21
Bicarbonate (mmol/L)	24.48 ± 10.33	22.64 ± 8.09	.007
Ph_arterial	7.39 ± 0.10	7.39 ± 0.10	.92

Pilot prospective study 865 patients with sepsis. NLR cut of value for severe sepsis > 14,2
NLR values signif. correlate with Lactate, C-reactive protein, hyperglycemia , bicarbonate (BE)