

LETTER

Circulating neutrophil counts and mortality in septic shock

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Polynuclear neutrophils can play dual roles in sepsis: on the one hand they mediate major antimicrobial activities and on the other hand they can contribute to the development of multiple organ failure [1]. Nonetheless, in spite of the importance of these cells in sepsis, the influence of the circulating neutrophil count (CNC) on the prognosis of septic patients with this pathology has not been properly evaluated.

We analyzed the association between CNC and outcome in two cohorts of patients with diagnostic criteria of septic shock (SS) [2]: the first was recruited in the context of a single center study (EXPRESS study, discovery cohort, $n = 195$; Table 1), and the second in the context of a multi-centric study (GRECIA study, validation cohort, $n = 194$; Table 2). Written informed consent was obtained from each patient or their legal representative. The two studies were approved by the Research Ethics Committee of the Hospital Clínico Universitario, Valladolid, Spain (for the EXPRESS study) and Hospital Universitario Río Hortega, Valladolid, Spain (coordinating center for the GRECIA study).

When patients of the discovery cohort were split based on deciles for CNC at SS diagnosis, those with CNC $< 7,226$ cells/mm³ (decile 2) died earlier than the other non-survivors (Figure 1). Multivariate Cox regression analysis showed that patients with CNC below this cutoff value had an almost two-fold risk of death (Figure 1). The cutoff value was evaluated again in the validation cohort, with similar results (Figure 1). Counts of other leukocyte subtypes had no significant association with outcome.

Although normal reference values in blood vary depending on sex, race and age, available literature supports that 7,226 cells/mm³ is at the upper limit of normal CNC values [3]. Patients with insufficient numbers of circulating neutrophils during the early stages of SS could have difficulties mounting effective innate responses against the invading microbe(s). Increased neutrophil adhesion to the vascular endothelium in sepsis could contribute to lower CNC. Neutrophils adhered to the blood vessel wall seem to induce endothelial damage [4], forming leukocyte aggregates that could lead to microvascular thrombosis [1,5]. Host immunity compromise and/or increased endothelial damage could both impair outcome in these patients.

CNC at diagnosis is a major prognostic factor in SS. Our work provides a CNC cutoff that is potentially useful as a prognostic indicator.

Abbreviations

CNC: Circulating neutrophil count; SS: Septic shock.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JFBM, GR, DAO, and MFM designed the study, analyzed the data and participated in writing the article; ET, JB, and JIGH helped with the study design, provided a critical review of the results and participated in writing the article; RHM, AMB, MHR, and RC provided a critical review of the results and participated in writing the article. All authors have read and approved the final version for publication.

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Table 1 Clinical characteristics of the patients in the discovery study in survivors and non-survivors at 28 days

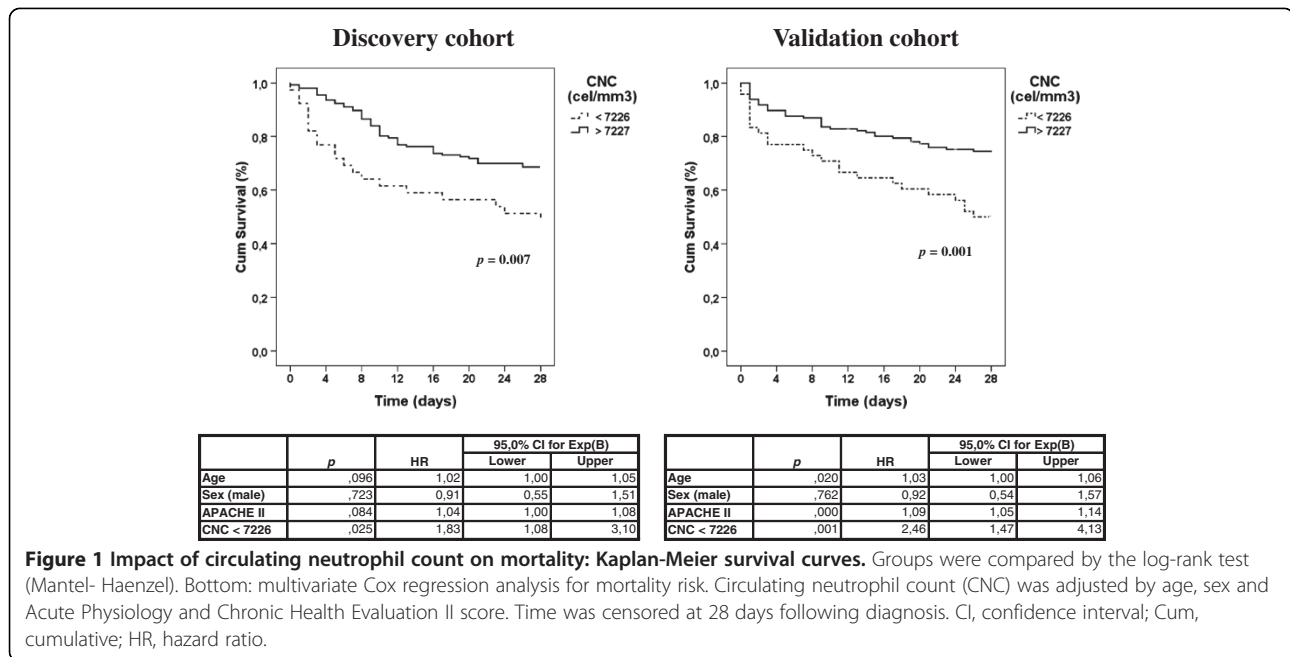
	Total (n = 195)	Survivors (n = 125)	Non-survivors (n = 70)	P
Patient details				
Gender (male)	125 (64.1%)	79 (63.2%)	46 (65.7%)	NS
Age (years)	71.6 ± 11.1	70.2 ± 11.1	74.2 ± 10.7	0.014
Hypertension	109 (55.9%)	71 (56.8%)	38 (54.3%)	NS
Cardiovascular disease	87 (44.6%)	54 (43.2%)	33 (47.1%)	NS
Cancer	44 (22.5%)	21 (16.8%)	23 (32.8%)	0.010
COPD	33 (16.9%)	24 (19.2%)	9 (12.8%)	NS
Diabetes	31 (15.9%)	24 (19.2%)	7 (10%)	NS
Obesity	32 (16.4%)	21 (16.8%)	11 (15.7%)	NS
Smoker	27 (13.8%)	17 (13.6%)	10 (14.2%)	NS
Chronic renal failure	26 (13.3%)	15 (12.0%)	11 (15.7%)	NS
Alcohol abuse	12 (6.1%)	8 (6.4%)	4 (5.7%)	NS
Inmunosuppression	9 (4.6%)	5 (4.0%)	4 (5.7%)	NS
Hepatic disease	6 (3.1%)	4 (3.2%)	2 (2.8%)	NS
Clinical status at admission				
APACHE II	14.7 ± 5.9	13.9 ± 5.8	16.2 ± 5.9	0.013
Mechanical ventilation	134 (68.7%)	83 (66.4%)	51 (72.9%)	NS
OARF	41 (21.0%)	19 (15.2%)	22 (31.4%)	0.008
Presumed source of infection				
Digestive system	115 (58.9%)	76 (60.8%)	39 (55.7%)	NS
Respiratory system	19 (9.7%)	14 (11.2%)	5 (7.1%)	NS
Central nervous system	20 (10.2%)	14 (11.2%)	6 (8.5%)	NS
Urinary system	10 (5.1%)	5 (4.0%)	5 (7.1%)	NS
Endocardium	7 (3.5%)	5 (4.0%)	2 (2.8%)	NS
Catheter	34 (17.4%)	26 (20.8%)	8 (11.4%)	NS
Wound/skin, soft tissue	28 (14.3%)	20 (16.0%)	8 (11.4%)	NS
Other/unknown	55 (28.2%)	35 (28.0%)	20 (28.5%)	NS
Type of surgery				
Abdominal	99 (50.7%)	56 (44.8%)	43 (61.4%)	0.030
Cardiac	71 (36.4%)	54 (43.2%)	17 (24.3%)	
Other	25 (12.8%)	15 (12.0%)	10 (14.3%)	
Urgent surgery				
Yes	130 (66.6%)	77 (61.6%)	53 (75.7%)	0.045
Documented microbial agent				
Gram-negative	67 (41.6%)	48 (44.4%)	19 (35.8%)	NS
Gram-positive	68 (42.2%)	47 (43.5%)	21 (39.6%)	NS
Fungi	24 (14.9%)	16 (14.8%)	8 (15.1%)	NS
Laboratory data				
Bilirubin (mg/dL)	1.4 ± 1.3	1.5 ± 1.4	1.2 ± 1.0	NS
Glycemia (mg/dL)	166.4 ± 65.1	165.4 ± 58.3	168.2 ± 76.0	NS
Procalcitonin (ng/mL)	19.3 ± 32.5	16.5 ± 28.6	24.3 ± 38.1	NS
CRP (mg/mL)	231.8 ± 119.2	221.9 ± 106.6	249.4 ± 138.1	NS
INR	1.7 ± 0.9	1.6 ± 0.9	1.7 ± 0.8	NS
Platelets (×10 ³ /μl)	190.2 ± 140.0	196.9 ± 143.5	178.2 ± 133.5	NS
Leukocytes (×10 ³ /μl)	16.3 ± 10.1	16.4 ± 9.0	16.2 ± 11.7	NS
Monocytes (×10 ³ /μl)	0.7 ± 0.4	0.7 ± 0.4	0.6 ± 0.5	NS
Lymphocyte (×10 ³ /μl)	1.1 ± 0.7	1.1 ± 0.8	1.0 ± 0.6	NS
Neutrophils (×10 ³ /μl)	14.4 ± 9.4	14.4 ± 8.4	14.3 ± 11.1	NS
Basophils (×10 ³ /μl)	0.1 ± 0.0	0.1 ± 0.1	0.1 ± 0.0	NS
Eosinophils (×10 ³ /μl)	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	NS

For the demographic characteristics of the patients, differences between groups were assessed using the χ^2 test for categorical variables and the Student's *t*-test for continuous variables when appropriate. Continuous variables are expressed as mean ± standard deviation. APACHE, Acute Physiology and Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; INR, international normalized ratio; NS, not significant; OARF, oliguric acute renal failure.

Table 2 Clinical characteristics of the patients in the validation study in survivors and non-survivors at 28 days

	Total (n = 194)	Survivors (n = 132)	Non-survivors (n = 62)	P
Patient details				
Gender (male)	126 (64.9%)	85 (64.3%)	41 (66.1%)	NS
Age (years)	67.1 ± 13.3	65.3 ± 14.3	71.1 ± 9.5	<0.001
Immunosuppression	35 (18.0%)	15 (11.3%)	20 (32.2%)	<0.001
Diabetes	32 (16.4%)	21 (15.9%)	11 (17.7%)	NS
Cardiovascular disease	24 (12.3%)	14 (10.6%)	10 (16.1%)	NS
Cancer	18 (9.2%)	10 (7.5%)	8 (12.9%)	NS
COPD	23 (11.8%)	12 (9.0%)	11 (17.7%)	NS
Chronic renal failure	15 (7.7%)	10 (7.5%)	5 (8.0%)	NS
Alcohol abuse	12 (6.1%)	7 (5.3%)	5 (8.0%)	NS
Hepatic disease	4 (2.0%)	1 (0.7%)	3 (4.8%)	NS
Clinical status at admission				
APACHE II score	22.6 ± 7.0	21.0 ± 6.5	25.9 ± 7.1	<0.001
Mechanical ventilation	150 (77.7%)	93 (70.9%)	57 (91.9%)	<0.001
OARF	39 (20.1%)	17 (12.8%)	22 (35.4%)	<0.001
Presumed source of infection				
Respiratory system	67 (34.5%)	45 (34.1%)	22 (35.5%)	NS
Digestive system	52 (26.8%)	32 (24.2%)	20 (32.3%)	NS
Urinary system	26 (13.4%)	21 (15.9%)	5 (8.1%)	NS
Catheter	16 (8.2%)	11 (8.3%)	5 (8.1%)	NS
Wound/skin, soft tissue	15 (7.7%)	11 (8.3%)	4 (6.5%)	NS
Other/unknown	18 (9.3%)	12 (9.1%)	6 (9.7%)	NS
Documented microbial agent				
Gram-negative	52 (26.8%)	36 (27.2%)	16 (25.8%)	NS
Gram-positive	33 (17.0%)	25 (18.9%)	8 (12.9%)	NS
Fungi	12 (6.1%)	4 (3.0%)	8 (12.9%)	0.020
Laboratory data				
Bilirubin (mg/dL)	1.4 ± 2.2	1.4 ± 2.1	1.6 ± 2.4	NS
Glycemia (mg/dL)	168 ± 64.0	167 ± 62.4	172.0 ± 67.6	NS
INR	1.8 ± 3.1	1.9 ± 3.8	1.6 ± 0.6	NS
Platelets (×10 ³ /μl)	177.4 ± 118.5	173.6 ± 105.2	186.4 ± 146.1	NS
Leukocytes (×10 ³ /μl)	18.0 ± 16.4	18.4 ± 17.0	17.3 ± 15.3	NS
Monocytes (×10 ³ /μl)	0.7 ± 1.7	0.8 ± 20.2	0.6 ± 0.9	NS
Lymphocyte (×10 ³ /μl)	1.8 ± 70.5	1.6 ± 73.5	2.3 ± 64.1	NS
Neutrophils (×10 ³ /μl)	14.9 ± 12.5	15.6 ± 12.9	13.6 ± 11.5	NS
Basophils (×10 ³ /μl)	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	NS
Eosinophils (×10 ³ /μl)	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	NS

For the demographic characteristics of the patients, differences between groups were assessed using the χ^2 test for categorical variables and the Student's *t*-test for continuous variables when appropriate. Continuous variables are expressed as mean ± standard deviation. APACHE, Acute Physiology and Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease; INR, international normalized ratio; NS, not significant; OARF, oliguric acute renal failure.



Acknowledgements

Discovery study (EXPRESS) was supported by ISCIII, 'Proyectos de Investigación Sanitaria, PI 10/01362. Validation study (GRECIA) was supported by Proyectos de investigación en Biomedicina, Health Council, Castilla y León Government, Spain (BOCYL-D-26072010). Investigators of the EXPRESS group: Esther Gómez-Sánchez, Sandra Gutiérrez, Felipe Bobillo, Francisco Gandía, Verónica Iglesias, Lucía Rico, Raquel Almansa, Raúl Ortiz de Lejarazu (Hospital Clínico Universitario, Valladolid, Spain). Investigators of the GRECIA group: Pedro Merino, Marta María García-García (Hospital Universitario Río Hortega, Valladolid, Spain); M^a Jesús López Pueyo, Jose Antonio Fernandez Ratero, Miguel Martínez Barrios, Fernando Callejo Torre, Sergio Ossa Echeverri (Hospital General Yagüe, Burgos, Spain); Demetrio Carriedo Ule, Ana M^a Domínguez Berrot, Fco Javier Díaz Domínguez (Complejo Hospitalario de León, Spain); Susana Moradillo (Hospital Río Carrión, Palencia, Spain); Braulio Alvarez Martínez (Hospital del Bierzo, Ponferrada, Spain); Noelia Albalá, Juan Carlos Ballesteros, Marta Paz Perez, Elena Perez Losada (Hospital Clínico Universitario de Salamanca, Spain); Santiago Macías, Rafael Pajares García, Noelia Recio García Cervigón (Hospital General de Segovia Spain); M^a Mar Gobernado Serrano, M^a José Fernández Calavia, Daniel Moreno Torres (Complejo Hospitalario de Soria, Spain); Concha Tarancón, Teresa Loreto, Priscila Carcelen (Hospital Virgen de la Concha, Spain).

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Published: 14 February 2014

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doi:10.1186/cc13728

Cite this article as: Bermejo-Martín *et al.*: Circulating neutrophil counts and mortality in septic shock. *Critical Care* 2014 **18**:407.