Association of Increase of NETosis and Nucleosome Biomarkers measured by Nu.Q® NETs assay with Mortality in Septic Shock

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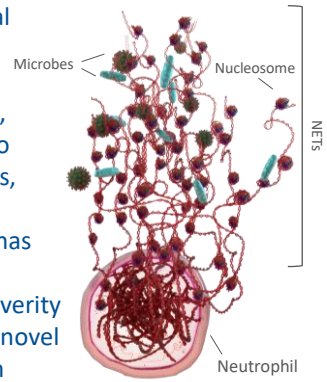
INTRODUCTION

Neutrophils, release extracellular traps (NETs) as part of the antimicrobial response, which can neutralize and kill microorganisms. However, excessive NETosis may also contribute to pathogenesis, tissue damage and organ dysfunction. This process has been hypothesized to be associated with disease severity and mortality. Recently, a novel automated assay has been proposed for the routine measurement of nucleosomes, which are fundamental units of chromatin that are released during NETosis.



OBJECTIVES

To measure nucleosome levels using the Nu.Q® NETs assay in septic shock patients and to determine association with mortality.

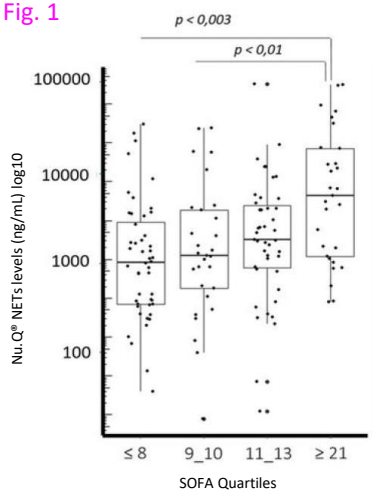
METHODS

151 septic shock patients (SEPSIS-3 definition, IMMUNOSEPSIS cohort). Plasma samples obtained at day (D) 1-2, D 3-4, D 6-8 after admission). Nucleosome measurements : chemiluminescent Nu.Q® NETs immunoassay, CE-IVD (Belgian Volition SRL, Belgium); IL-6 : Ella automated immunoassay system (Bio-Techne); Immunological cellular parameters : flow cytometry (BeckmanCoulter).

RESULTS

- Main patients' characteristics (median) were age (69), SAPS II (65), SOFA (10), 28-day mortality 45 %.
- Immunological parameters indicated early inflammation (IL-6 = 1335 pg/mL at D 1-2) along with marked immunosuppression (e.g., mHLA-DR = 3853 AB/C and CD4 lymphocytes = 338 /µL at D 3-4).
- The nucleosome levels were markedly and significantly elevated (median) at all-time points: D1-2 (1515 ng/ml); D3-4 (919 ng/mL); D6-8 (546 ng/mL) compared to the control group (15.4 ng/ml).
- We found **significant positive correlation between D1-2 nucleosome levels and SOFA score (Fig. 1),** SAPS II score, IL-6 concentrations and neutrophil count.
- **Significantly higher nucleosome levels (D 1-2; 3-4) were measured in non-survivor patients (28-day mortality, D1-2, Fig. 2A).**
- **This association was still significant after multivariate analysis and was more pronounced with highest concentration (upper quartile D1-2, Fig. 2B-C).**
- Early (D 1-2) increased nucleosome levels were also independently associated with 5-day mortality.
- At D 6-8, persistent elevated nucleosome levels were negatively correlated to mHLA-DR values.

Fig. 1



Box represent 25th-75th percentile with median and individual values.

Fig. 2A

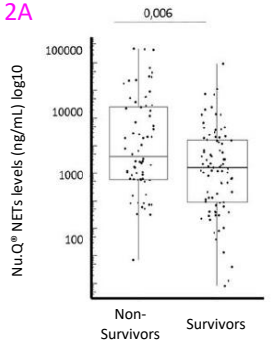


Fig. 2B

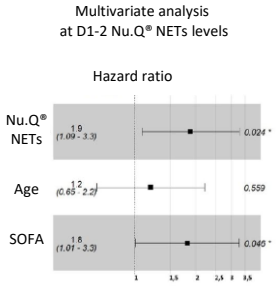
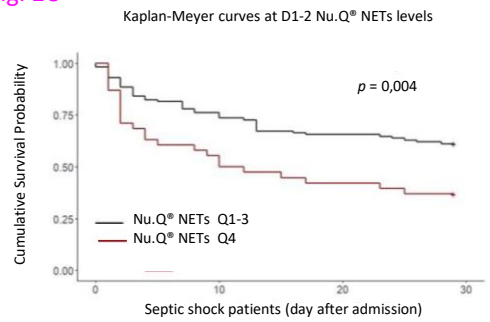


Fig. 2C



CONCLUSIONS

- First study to investigate both nucleosomes and immunological parameters in septic shock.
- Significant elevation of nucleosome in patients during a one-week follow-up.
- Association of increased circulating nucleosome (H3.1) with mortality in septic shock.
- The nucleosome levels showed correlation with neutrophil count and IL-6 and association with SOFA score.
- The nucleosome levels were independently associated with 5-day and 28-day mortality.

In summary, nucleosomes measured by Nu.Q® NETs seem to be a promising biomarker for the evaluation of disease severity and could help in sepsis prognosis.

**Additional investigations are required to confirm clinical interests.*

CONTACT INFORMATION

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