The Presence of Nucleated Red Cells in the Blood of Critical Care Patients is Associated with an Increased Mortality Risk

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Background: The occurrence of nucleated red blood cells (NRBCs) in critically ill patients is a consequence of either hypoxic or inflammatory injuries. Therefore erythroblasts' detection may be used as an early indicator of high mortality risk.
Material and methods: In a prospective study the detection of NRBCs was used for daily monitoring of 90 patients for a 3-months term. The prognostic significance of the NRBCs presence was compared with two risk scores: APACHE II and SAPS II.
Results: The incidence of erythroblasts' presence was 20% (18/90). The mortality of NRBC-positive patients was 88.8% (16/18) and was significantly higher ($p < 0.05$) than the mortality of NRBC-negative patients: 30.5% (22/72). The incidence of the erythroblasts in peripheral blood has increased simultaneously with APACHE II and SAPS II scores. On average, NRBCs were detected for the first time 6.5 days before death. The occurrence of NRBCs was not associated with a specific cause of death; however septic patients who died had the highest incidence of NRBCs' presence.
Conclusion: The daily screening of the presence of NRBCs seems to be a useful tool to estimate the mortality risk in critically ill patients, the parameter being of high prognostic strength regarding the mortality risk.

Keywords: nucleated red blood cells, mortality risk, prognostic strength

Introduction

The peripheral blood of healthy adult people is usually free of nucleated red blood cells (NRBCs), the occurrence of these cells in the bloodstream is associated with severe diseases [1] and indicates a relatively poor prognosis [2]. The mechanism of this phenomenon is still unknown, the hypothesis being either of bone marrow stimulation or of bone marrow insufficiency caused by the possible role that cytokines could play in the process [3]. Recent study revealed that the detection of NRBC in blood was associated with increased erythropoietin, IL-3 and IL-6 concentrations. Therefore, the detection of NRBC may be considered a parameter that sums up life-threatening hypoxic and inflammatory injuries [3]. However, since the reticulocyte concentration was increased both in NRBC-positive and NRBC-negative patients, the bone marrow function was obviously not disturbed in these conditions. Beyond the newborn period, the presence of nucleated red blood cells (NRBC) in the blood of adults is pathologic. If detectable, these patients have a relatively poor prognosis.

The concentration of the NRBCs can be determined either macroscopically by a stained peripheral blood smear, or using a more convenient and sensitive technique in the form of mechanized blood analyzers which can routinely measure concentrations of less than 100/µl [4].

Materials and methods

Ninety intensive care patients were included in the study, treated between January 1st and March 31, 2009 in the Intensive Care Department of Elias Emergency Hospital, Bucharest, Romania. Patients under 18 years of age and surgical patients were excluded from the study. Every morning we yielded a blood sample from every patient from the intensive care unit and we performed automatically blood elements count with Sysmex XE-2100 and a microscopically analyze of a stained peripheral blood smear. If the NRBCs were detected in the blood at least once the patient was defined as NRBC-positive. The in-hospital mortality was considered to be the patient's outcome.

The prognostic significance of NRBCs was evaluated taking in consideration established risk models: the Acute Physiology and Chronic Health Evaluation II (APACHE II) and the Simplified Acute Physiology Score II (SAPS II). The APACHE II severity index includes the following risk factors: body temperature, mean arterial pressure, heart rate, respiratory rate, blood oxygenation, arterial pH, sodium, potassium, creatinine, hematocrit, white blood cell count, Glasgow coma scale, age, and anamnestic data concerning severe organ insufficiency or immunocompromised condition. The SAPS II includes the following risk factors: age, heart rate, systolic blood pressure, body temperature, blood oxygenation, urinary output, urea, white blood cell count, potassium, sodium, bicarbonate, bilirubin, Glasgow coma scale, chronic diseases (that is, malignancies and acquired immunodeficiency syndrome), and type of admission (that is, medical and unscheduled surgical). Both the APACHE II score and the SAPS II are determined from the most altered (worst) physiologic value (for example, the lowest

Table I. The presence of NRBCs at medical intensive care patients who have died due to various causes

Pathology	No. of patients	Ńo. of deaths
Cardiovascular pathology	2	2
Pulmonary pathology	2	2
Neurological pathology	1	0
Sepsis	7	7
Trauma	5	4
Other	1	1

blood pressure or the highest white blood cell count) during the initial 24 hours after intensive care unit admission.

Data are presented as the mean ± standard error of mean. A p value of less than 0.05 was considered statistically significant.

Results

We included 90 medical intensive care patients, 58.7% male, 41.35% female. The mean age was 66.3±0.8 years (range 20 to 92 years). The length of stay in the ICU was on average 7.1±0.3 days. Overall mortality rate was 42.2%. The APACHE II score and the SAPS II amounted to 20.6±0.6 and 44.1±1.2, respectively. The incidence of NRBCs' presence in the blood was 20% (18/90). No significant difference was found between the incidences in male (18.9%) and female (21.5%) patients.

On average, NRBCs were detected for the first time on the third day of intensive care treatment (3.1±0.4); (Figure 1).

The mortality of NRBC-positive patients was 88.8% (16/18). In contrast, the mortality of NRBC-negative patients was significantly lower: 30.5% (22/72), (p <0.05).

The occurrence of NRBCs was not associated with a specific cause of death; however septic patients who died had the highest incidence of NRBCs' presence (Table I).

The incidence of NRBCs' presence increased with higher APACHE II and SAPS II scores (Tables II and III). Because the determination of the erythroblasts in the peripheral blood was not quantitative, we could not obtain a correlation with statistical value between the NRBCs concentration and APACHE II and SAPS II scores progression. However, we noticed that the doubling of the number of the erythroblasts per 100 leukocytes correlated with adding 6.8 points to the APACHE II score.

NRBCs were an early indicator of patients with increased mortality risk. In the group of NRBC positive patients who died, NRBCs were detected on average for the first time 6.5 days before death.

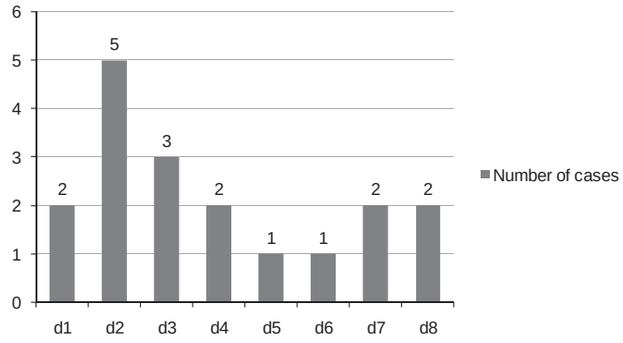

Fig. 1. Intensive care days when nucleated red blood cells were detected for the first time in the blood of medical intensive care patients

Discussions

In this study the NRBC detection and quantification were based on the microscopic analysis of stained blood smears. This technique is only to some extent suitable for the detection and quantification of NRBC concentrations of less than 200/µl. This is the reason why when comparing with literature's data the mortality of the NRBC-positive patients in our study was higher (88.8% versus 50.75%) [1].

The present study revealed that approximately 20% of all medical intensive care patients were NRBC-positive at least once and at two NRBC-positive patients, NRBCs were detected already on the admission day. Our data confirmed the high prognostic strength of the detection of NRBCs in blood regarding mortality. The total in-hospital mortality of NRBC-positive patients in this study was significantly higher than that of the negative patients.

The study revealed that the daily screening for NRBCs can be used to estimate the patients' mortality risk.

Analyzing the hospital stay at the patients who died showed that NRBCs in blood were found not just immediately before death. Moreover, our present study showed that the detection of NRBCs is often a relatively early phenomenon prior to death. In deceased patients, NRBCs were detected 6.5 days before death. Therefore, NRBCs seems to be an early indicator of increased risk.

There was not found an association with none of the various causes of patients' death in this study. NRBCs may thus be considered a marker that includes hypoxic and inflammatory injuries that occur at critical ill patients and influence the outcome. This could be the reason why the occurrence of NRBCs is a strong predictor of increased mortality.

Identical ages as the patients at the University Hospital Bochum in 2007, i.e. 66.3 +/- 0.8 years.

Identical statistical mean and std dev obtained in 2007 by Stachon et al, i.e. 3.1 +/- 0.4 days.

Table II. Correlation between the incidence of the NRBCs' presence and APACHE II score

APACHE II	NRBCs Incidence
<11	0% (0/20)
11–20	8% (2/25)
21–30	29% (7/24)
>31	42% (9/21)

Table III. Correlation between the incidence of the NRBCs' presence and SAPS II score

SAPS II	NRBCs Incidence
<21	0% (0/18)
21–40	11% (3/27)
41–60	28% (7/25)
>61	40% (8/20)

Due to the association between inflammation-SIRS, sepsis and NRBCs occurrence, we can speculate that maybe early onset or intensifying the anti-inflammatory therapy or antibiotic administration at NRBC-positive patients can improve their outcome.

Conclusion

NRBC detection in critically ill patients was associated with significantly increased in-hospital mortality. The presence of NRBCs correlates to other risk models like APACHE II and SAPS II. The detection of NRBCs in blood is a relatively early phenomenon prior to death, so screening for NRBCs may aid in the early identification of patients at high risk.

Acknowledgement

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