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Clinical paper

Mortality in patients resuscitated from out-of-hospital cardiac arrest based on automated blood cell count and neutrophil lymphocyte ratio at admission

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ABSTRACT

Introduction: The neutrophil lymphocyte ratio(NLR) is a marker of systemic inflammation. We hypothesized that admission NLR is related to mortality and that epinephrine application during resuscitation influences NLR in patients after successful resuscitation from out of hospital cardiac arrest (OHCA).
Methods: This retrospective cohort study is based on a registry including all OHCA patients who had a presumed cardiac cause of cardiac arrest and achieved sustained ROSC prior to admission between 2005 and 2014. Patients were categorized into three groups according to the calculated NLR at admission (NLR <6, ≥6, and 'abnormal differential' indicating no differential blood cell count on patients report due to exceedance of machine predefined parameter limits). The primary outcome measure was long-term mortality after OHCA. Cox proportional hazards models were used for multivariable analysis.
Results: Out of 2273 OHCA patients during the study period a total of 1188(52%) patients were eligible for analysis, of those 274(23%) were female and mean age was 64 (25–75 IQR:52-72). Compared to a NLR < 6 (n = 442), adjusted hazard ratio for long-term mortality was significantly higher in patients with a NLR ≥ 6 (n = 447; 1.52 (95%CI 1.03–2.24)) and in patients with abnormal differential (n = 299; 3.16 (95%CI 2.02-4.97)). Epinephrine application during resuscitation did not explain the effect of NLR on mortality.
Conclusion: In this large retrospective cohort study of altogether >1000 OHCA patients, hospital admission NLR < 6 compared to abnormal differential or NLR ≥ 6 was associated with mortality independently from epinephrine application.

Introduction

Patients surviving out of hospital cardiac arrest (OHCA) to hospital admission still carry a poor prognosis with high risk of subsequent mortality and morbidity even after induction of standardized post resuscitation care [1,2]. Whole-body ischemia leads to systemic inflammation response damage in active metabolic tissues and reperfusion to this tissue triggers even more tissue injury, a phenomenon called ischemic reperfusion injury, similar to severe sepsis [3,4]. One marker of systemic inflammation is the neutrophil lymphocyte ratio (NLR), which is believed to reflect the balance between innate (neutrophils) and adaptive (lymphocytes) immune responses. NLR and especially neutrophils play an important role in the mechanism of injuries caused by ischemia and reperfusion and have been linked to adverse outcomes in patients with cardiovascular disease [5–10,11]. Catecholaminergic activity like endogenous or exogenous epinephrine is one possibility to stimulate neutrophils, that express predominantly high-affinity b2-adrenoceptors, to immediate demarginate from vascular endothelial cells (marginating pool) into the circulation [12–16]. These stimulated neutrophils infiltrate remote organs contributing to multiple organ failure, as areas of brain ischemia and are the primary source of enhanced matrix metalloproteinase 9 activity in the ischemic brain, which is a critical mechanism underlying the breakdown of the blood brain barriere and the exacerbation of neurological injury [17,18]. Precisely this paradoxical pattern of neutrophil mobilization is not completely understood.

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Considering these data, we investigated if there is a relation between admission NLR, as part of differential blood count, and mortality in resuscitated patients, assuming that a raised admission NLR predicts worse outcome. Secondary, we estimated a difference in mortality in patients who had epinephrine application during cardiac arrest and those who had not which can already been detected in NLR at admission.

Methods

This retrospective cohort study was based on a prospectively designed registry of OHCA patients who were admitted to the emergency department of a tertiary-care hospital. The study was done in accordance with the ethical standards under exception from informed consent for emergency research and approved by the Ethics Committee of the Medical University of Vienna and Vienna General Hospital (reference number EK-456/2005, extended by EK-1814/2012–Cardiac Arrest Registry of the Department of Emergency Medicine). Acquisition and documentation of all cardiac arrest patients admitted to the Department of Emergency Medicine were performed according to the 'Utstein Style Criteria'- and data are stored in a local database (Microsoft Access 2010®, Redmond, California, USA) [19]. We matched all OHCA data sets with the database of the local Department of Laboratory Medicine at the Medical University of Vienna. Telephone follow up was done for one year and additional data for long-term outcome were captured due to a data reconciliation with Austrias official national register of death. Time intervals like no-flow time are collected by our study fellows through immediate structured telephone interview with the bystander who performed the emergency call during emergency medical service (EMS) is at scene. At hospital admission EMS personal is questioned about the observed quality of basic life support. EMS defibrillator protocol and EMS event documentation is stored for analyzing quality of advanced life support.

Study population

Datasets of the cardiac arrest registry were required to meet all of the following criteria: OHCA patients with presumed cardiac etiology, 18 years of age or older, who have achieved sustained ROSC (spontaneous circulation is restored and sustained for 20 min or longer), OHCA between January 1st, 2005 to December 31 st 2014 [20].

Laboratory values

Blood samples collected routinely and immediately after hospital admission were forwarded to the local Department of Laboratory Medicine of the Medical University of Vienna as emergency test panel. Complete blood cell (CBC) counts were measured on a Sysmex XE-5000 hematology analyzer (Sysmex Corporation, Kobe, Japan) within one hour after collection. Automated 5-part differential counts are only released by the machine onto patient reports if results have no suspect flags (means the presence of abnormal cells like blast cells, abnormal lymphocytes or lymphoblasts, and atypical lymphocytes) and do not exceed predefined limits. (Table 1) Differential blood cell count results that exceeded these limits or have suspect flags are not released on patient reports and are classified as 'abnormal' in this study.

Statistical methods

Continuous data are presented as mean ± standard deviation or median and 25–75% interquartile range, as appropriate. Categorized data are presented as absolute number and relative frequency. We used a convenience sample of available cases. Owing to the fact that this was an observational non-randomized trial we did not perform a formal sample size calculation for a confirmatory hypothesis testing procedure. Nonetheless, we expected that we would be able to simultaneously handle 11 parameters in a multivariable model given the available sample size of 1100+ patients. Furthermore, we expected to be able to detect a significant relative risk of at least 1.41 at a 5% type I error rate with a power of 80% given a baseline risk of 20% and balanced group sizes. Data for NLR calculation were available in 889 (75%) of our patients. The average value of NLR was 6. In 299 (25%) patients the blood cell counter flagged the results because of exceeding test limits, withholding categorical information. To analyze these data for the whole dataset we decided to create a common variable with three categories: 1. 'abnormal differential' 2. NLR >6 and 3. NLR ≤ 6.

Noteworthy, the NLR cut off value of 6 found in our study is in good agreement with predictive NLR cut-offs determined in patients with hemodynamically stable myocardial infarction (Sawant et al NLR 7.4; Hartopo et al. NLR 6.2; Ayca et al NLR 4.9) [8,6,9].

Accordingly, we compared three prognostic categories: NLR ≥ 6, NLR < 6, or 'abnormal differential'. To compare baseline variables between the exposure groups we used a chi-squared test for categorized variables, and the Mann-Whitney *U* test for continuous variables. To investigate the effect of NLR on survival, we used the Kaplan Meier method with the follow up time until failure (death from any cause) or to the end of study follow up in December 2014. We used the log rank test to test the equality of survivor functions and to test for a trend across NLR categories. We used Cox proportional hazards models to estimate the effect on survival of several covariables including age, female sex, witnessed cardiac arrest, Basic life support (external cardiac massage performed), no-flow time (interval from event onset to start of cardio-pulmonary-resuscitation (CPR)), low-flow time (interval of CPR), body mass index, duration of cardiac arrest onset to hospital admission, C-reactive protein (indicator variable of quartiles), shockable, body temperature on hospital admission (<33, 33–36, >36 °C); Glasgow coma scale after ROSC (<11 versus 11+); smoking history, diabetes history, high blood pressure and pH, lactate, leukocytes, pro-BNP at hospital admission. These variables were chosen conceptually if they were potential confounders and were different between the prognostic groups (Table 2). Assuming a causal relationship between epinephrine administration during resuscitation, neutrophils and outcome, we developed models with and without epinephrine as dichotomized covariable (any epinephrine during CPR: yes or no) [21,13]. We tested for linear effects and for first order interactions using the likelihood ratio test, and tested for proportionality of the final models. We also tested for interactions for the main effects by post-exposure variables target temperature management (TTM) (during the observation period 33 °C for 24 h) and percutaneous coronary intervention (PCI). We developed logistic regression models as described above for sensitivity analysis

Table 1
Cut off values for automatic release on patient reports of the Kobe Sysmex 5000 blood cell counter.

Blood cell/measurements	limits
white blood cells (WBC)	>3 × 10⁹ G/l and <15 × 10⁹ G/l
neutrophils	<95%
lymphocytes	<60% and/or <4 × 10⁹G/l
monocytes	<20%
eosinophils	<10%
basophils	<2.5%
immature granulocytes	<2%
nucleated red blood cells	<1/100 WBC
platelets	>100 × 10⁹/l and <500 × 10⁹/l
mean corpuscular volume	>73.0 fl and <105.0 fl