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Red blood cell distribution width is an independent predictor of mortality in patients with aneurysmal subarachnoid hemorrhage

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ABSTRACT

Objectives: This study was performed to evaluate the association between red blood cell distribution width (RDW) and 3-month mortality in patients with aneurysmal subarachnoid hemorrhage.

Patients and methods: This observational study was performed from March 2007 to May 2017 in an emergency department. The baseline characteristics and clinical and laboratory data were collected prospectively and analyzed. Clinical outcomes included 3-month mortality and poor functional outcome referred to as modified Rankin scale 3–6.

Results: A total 364 patients were included, and the overall 3-month mortality was 8.5%. The median RDW increased with disease severity classified according to the Hunt and Hess scale. RDW was significantly higher in patients with poor functional outcome than in patients with good functional outcome. The optimal RDW cutoff for predicting 3-month mortality was 13.9%.

Cox regression analysis showed that higher RDW was independently associated with 3-month mortality (hazard ration 17.187, 95% CI 4.474–66.022). The area under the receiver-operating curve for RDW was 0.917 (95% CI 0.883–0.943).

Conclusion: An elevated RDW is associated with poor functional outcome and 3-month mortality in patients with aneurysmal subarachnoid hemorrhage.

1. Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a major health problem that is characterized by bleeding of blood into the subarachnoid spaces. Despite significant improvements in early diagnostic modality such as computed tomography (CT) angiography, the use of nimodipine, and advances in radiologically guided intervention or neurosurgery, the mortality from aSAH remains high [1]. aSAH accounts for about 5% of all acute strokes, but is responsible for 27% of acute stroke-related annual mortality [2].

Prediction of the disease severity and prognosis is recommended for the proper management of aSAH. The Hunt and Hess (HH) scale and the World Federation of Neurological Surgeons (WFNS) scale are used widely for assessing the severity and clinical outcomes in patients with aSAH. Although the WFNS scale has a better interobserver correlation on admission, more clinical research is needed [3]. Regardless of the high mortality, the means to estimate prognosis are still limited in patients with aSAH.

Red blood cell distribution width (RDW) indicates the variability in size of circulating erythrocytes and is reported as part of the routine complete blood count (CBC). In conjunction with mean corpuscular volume (MCV), RDW is commonly used in the diagnosis of different types of anemias. Recent studies have found that an increased RDW is significantly associated with thrombotic and inflammatory conditions, including ischemic stroke, heart failure, myocardial infarction, and trauma [4–7]. Other recent studies have reported an associated between RDW and higher 3-month and 1-year mortality rates in intensive care unit (ICU) patients with aSAH [8,9].

However, few studies have focused on RDW as a prognostic marker of neurological outcome and mortality, and no study has suggested a cutoff RDW for predicting mortality in patients with aSAH. Therefore, the aim of this study was to establish a cutoff RDW value as a prognostic marker for assessing disease severity, functional outcome, and mortality risk in aSAH patients.

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2. Material and methods

2.1. Study population

The overall study protocol was reviewed and approved by the Institutional Review Board of the Konkuk University Medical Center (IRB No: KUH1260034). Individual informed consent was not required by the review board because the laboratory data were measured routinely during the course of management in the emergency department (ED).

This observational study was performed from March 2007 to May 2017 in the ED of Konkuk University Medical Center, an 870-bed teaching hospital with about 53,000 annual ED visits. The inclusion criteria for this study were age ≥19 years, SAH from a nontraumatic spontaneously ruptured cerebral artery aneurysm confirmed by either CT or digital subtraction angiography, arrival at the ED within 24 h after the onset of symptoms. The exclusion criteria were previous neurological disease including trauma, ischemic or hemorrhagic stroke, recent infection (within 1 month), prior use of anticoagulant medication, or concurrent systemic comorbidities including liver cirrhosis, uremia, or malignancy. The healthy control group consisted of the age and sex matched individuals who came to our hospital for healthy examination between January 2015 and May 2017.

All patients were treated according to institutional treatment protocol that included prevention and management of rebleeding, vasospasm, and other complications. Determination of aneurysm treatment, as judged by both experienced neurosurgeons and endovascular specialists, should be a multidisciplinary decision on characteristics of the patient and the aneurysm. All patients received oral nimodipine. Euvolemia was maintained for all patients. Transcranial Doppler was performed daily for the diagnosis of vasospasm-induced delayed cerebral ischemia. Patients experiencing delayed cerebral ischemia received induced hypertension therapy in accordance with the patient's neurological status. Intracranial hypertension was treated by head elevation, a bolus of mannitol, and cerebrospinal fluid drainage such as extraventricular or lumbar drainage.

The baseline characteristics and clinical and laboratory data were collected prospectively and analyzed after the study period. All records of enrolled patients were anonymized before the analysis.

2.2. Data collection and assessment

Blood samples were obtained from a peripheral vein within 30 min of arrival at the ED. The CBC with differential blood count was obtained using a Sysmex automated hematology analyzer (Sysmex, Kobe, Japan). The reference range of RDW in our institution is 11.5–14.5%. The diagnostic automated hematology system (Sysmex XE-2100) was replaced with new system (Sysmex XN-9000) in March 2014. However, there was no change in the reference range due to system replacement because the correlation between the results of the two systems was very high.

Clinical severity was assessed in all aSAH patients at the time of ED admission using the HH grade. We defined nonsevere aSAH as HH grade I–III and severe aSAH as HH grade IV or V. The primary outcome of interest was mortality within 3 months following ED admission. The secondary outcome was functional outcome as defined by the modified Rankin scale (mRS) at 3 months after aSAH onset. Poor functional outcome was defined as a mRS score of 3–6.

2.3. Statistical analysis

All aggregated data were processed using Microsoft Excel 2016 (Microsoft, Redmond, WA, USA), and all statistical analyses were performed using IBM SPSS Statistics 22 (IBM, Armonk, NY, USA) and R version 3.5.0 (The R foundation, Vienna, Austria). Normally distributed variables including age, hemoglobin (Hb), MCV, mean corpuscular hemoglobin (MCH), and platelet (PLT) count are expressed as mean ± standard deviation. Nonnormally distributed variables including white blood cell (WBC) count, RDW, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and albumin are expressed as median (25–75% interquartile range). Student's *t*-test or the Mann–Whitney *U* test was used for 2-group comparisons. Categorical variables are expressed as number and percentage, and the χ^2 test was used for comparisons.

To compare the prognostic value of laboratory markers for predicting 3-month mortality, receiver operating-characteristic (ROC) curves were generated, and the areas under the curve (AUC) were determined. The patients with aSAH were classified into 2 groups according to their RDW, and Kaplan–Meier survival curves were produced. A multivariable Cox regression analysis was used to evaluate the independent prognostic factors for 3-month mortality, and the hazard ratio (HR) and 95% confidence interval (CI) were calculated. All statistical analyses were 2-sided, and $p < 0.05$ was interpreted as statistically significant.

3. Results

3.1. Clinical characteristics and RDW level

Between March 2007 and May 2017, 364 patients were enrolled in this study and observed for 3 months. Additionally, 364 age and sex matched healthy control were enrolled. The baseline characteristics, clinical presentation, and outcomes of the participating patients are summarized in Table 1. The mean age was 54.2 ± 12.8 years and 216 (59.3%) patients were females. The admission median modified Fisher scale was 3 (2–4). A total of 209 (57.4%) patients treated by aneurysmal endovascular coiling, others underwent neurosurgical clipping. Overall, 81 (22.3%) patients were transfused packed RBCs. The admission RDW levels were slightly elevated in patients compared with healthy controls (12.7 (12.2–13.4)% vs. 12.5 (11.9–12.9)% ($p = 0.001$)

All patients were classified into 2 subgroups according to their HH

Table 1
Baseline characteristics of enrolled subjects.

Characteristics	Total number of patients (n = 364)
Female (no.)	216 (59.3)
Age (years)	54.2 ± 12.8
Hunt and Hess grade	292 (80.2)
Nonsevere (I–III)	72 (19.8)
Severe (IV–V)	3 (2–4)
Modified Fisher scale	155 (42.6)
Treatment modality	209 (57.4)
Neurosurgical clipping	10.5 (8.2–14.3)
Endovascular coiling	12.7 (12.2–13.4)
Laboratory results	13.5 ± 1.8
WBC ($\times 10^3/\mu L$)	89.2 ± 5.4
RDW (%)	30.9 ± 2.3
Hb (g/dL)	234.6 ± 63.0
MCV (fL)	4 (2–11)
MCH (pg)	0.09 (0.04–0.25)
PLT ($\times 10^3/\mu L$)	4.1 (3.8–4.3)
ESR (mm/h)	81 (22.3)
CRP (mg/dL)	278 (76.4)
Albumin (g/dL)	86 (23.6)
RBC transfusion (no.)	31 (8.5)
Functional outcome	
Good (mRS 0–2)	
Poor (mRS 3–6)	
3-month mortality	

Abbreviations: WBC, white blood cells; RDW, red blood cell distribution width; Hb, hemoglobin; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; PLT, platelet count; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RBC, red blood cell; mRS, modified Rankin scale.