Red cell distribution width and Glasgow coma scale score as predictors of in-hospital mortality in maintenance hemodialysis patients diagnosed with spontaneous intracerebral hemorrhage

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Abstract
Glasgow Coma Scale (GCS) score is being widely used as a useful predictor to investigate patients with head injury. High red cell distribution width (RDW) values have been independently associated with mortality and poor neurological outcome. However, there are few data available for Spontaneous Intracerebral Hemorrhage (SIH) in maintenance hemodialysis (MHD) patients. This study aimed to evaluate the prognostic value of the combined measurement of RDW and GCS score in MHD patients with SIH. We retrospectively studied 46 MHD patients who was admitted to our hospital for nontraumatic SIH from October 2014 to May 2020. Data including demographic information, cause of renal failure, comorbidities at ESRD, clinical and laboratory parameters at admission were collected from medical records. Univariate and multivariate Logistic regression analysis were performed to identify independent risk factors of the in-hospital Mortality in Hemodialysis Patients with SIH. The receiver operating characteristic curve (ROC) and areas under the curve (AUCs) were determined. The sensitivity and specificity of independent risk factors were calculated for a range of different cutoff points. A total of 46 patients were enrolled in the study. The in-hospital mortality rate was 69.57%. We divided subjects into 2 groups based on the clinical outcomes. Compared with survivors (n = 14), non-survivors (n = 32) had longer hemodialysis vintage (P = .017), lower GCS score (P < .001), higher hemoglobin (Hb) (P = .032) and RDW (P = .009). In multivariate logistic regression analysis, GCS score (OR 0.719, 95% CI 0.546-0.946; P = .018) and RDW (OR 4.549, 95% CI 1.243-0.946; P = .017) were independent risk factors of in-hospital mortality in MHD patients with SIH. The area under the ROC curve (AUC) for GCS score was 0.849 (95% CI 0.729-0.970) while that for RDW was 0.743 (95% CI 0.596-0.891). The AUC for the combined prediction was 0.916 (95% CI 0.828-1.000), with a sensitivity of 90.63% and a specificity of 88.46%. In conclusion, high RDW and low GCS score were useful and independent poor prognostic markers for in-hospital mortality of MHD patients with SIH.

Abbreviations: ALB = albumin, AUC = areas under the curve, Ca = calcium, CKD = chronic kidney disease, CR = creatinine, ESRD = end-stage renal disease, GCS = Glasgow coma scale, Hb = hemoglobin, iPTH = intact parathyroid hormone, MHD = maintenance hemodialysis, NLR = neutrophil to lymphocyte ratio, P = phosphorus, PLT = platelet, RDW = red cell distribution width, ROC = receiver operating characteristic curve, SIH = spontaneous intracerebral hemorrhage, UREA = urea nitrogen, WBC = white blood cell.

Keywords: GCS score, hemodialysis, prognosis, red blood cell distribution width, spontaneous intracerebral hemorrhage

1. Introduction
Nowadays, cerebrovascular events are major causes of morbidity and mortality worldwide. [1–4] Spontaneous intracerebral hemorrhage (SIH) is one of the most lethal complications that can occur in maintenance hemodialysis (MHD) patients, which leads to a mortality rate that is approximately 3.8 times higher than that in the general population. [5] Uremia, the pathophysiological state and the routine use of heparin during hemodialysis can increase the risk of SIH. [6] Moreover, the fluctuations of cerebral hemodynamics such as hypertension or hypotension during the process of dialysis as well as repeated swings of...
blood pressure occurred frequently in hemodialysis patients can also result in a higher risk for SIH.\(^{7,8}\) It is well documented that inflammation plays a critical role in brain injury after intracerebral hemorrhage onset.\(^{9,10}\)

Red cell distribution width (RDW) is a marker of variation of the size of the circulating red blood cells, which may reflect an underlying inflammatory state.\(^{11}\) Previous studies\(^{11}\) had shown that high RDW values were independently associated with mortality and poor neurological outcome. For ease of application, simplicity and quickness, Glasgow Coma Scale (GCS) score is being widely used as a useful predictor to investigate patients with head injury.\(^{13–15}\) Previous researches\(^{16}\) had demonstrated that lower GCS score is an independent risk factor for 30-day mortality in hemodialysis patients with SIH. The RDW and GCS score had been proven to be associated with adverse outcomes in patients with SIH. However, the impact of the combined assessment of the RDW and GCS score levels as a prognostic marker of in-hospital mortality in hemodialysis with SIH is unknown. The aim of the study was to identify the GCS and RDW as predictors of the in-hospital mortality in hemodialysis patients with SIH.

2. Methods

2.1. Patients and study design

This study was a single-center, retrospective cohort study. We enrolled 46 end-stage renal disease (ESRD) patients treated with MHD for at least 3 months (3 times per week for 4 h sessions), who were admitted to the people’s hospital of Deyang City with a diagnosis of SIH by clinical examinations and cranial computed tomography from October 2014 to May 2020. The patients were followed up for 30 days from the onset of SIH. Patients with previous neurological disease including trauma, ischemic or hemorrhagic stroke, a history of blood transfusion within 3 months, pregnancy, age <18 years, malignant disease, hematological disease, inflammatory disease were excluded.

2.2. Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of People’s hospital of Deyang City (no. 2021-04-144-K01). Data were collected from electronic patient records. Obtaining informed consent was waived by the Medical Ethics Committee since data were collected and processed anonymously. If patients objected against use of their medical record for research purposes they were not included in the database. We confirm that the study methods were in accordance with the standards formulated by the Declaration of Helsinki and relevant guidelines and regulations.

2.3. Clinical assessments

Demographic information, clinical characteristics and laboratory test results were routinely collected on admission including sex, age, hemodialysis vintage, cause of renal failure, comorbidities at ESRD, systemic blood pressure, diastolic blood pressure, mean arterial pressure, GCS score, white blood cell (WBC), neutrophils, lymphocyte, neutrophil to lymphocyte ratio (NLR), hemoglobin (Hb), RDW, platelet (PLT), urea nitrogen (UREA), creatinine (CR), albumin (ALB), calcium (Ca), phosphorus (P), intact parathyroid hormone (iPTH), international normalized ratio, prothrombin time, activated partial thromboplastin time, ferritin, transferrin saturation.

2.4. Statistical analysis

SPSS 22.0 statistical software (IBM, Armonk, NY) was used for data analysis. Normally distributed variables including age, systemic blood pressure, diastolic blood pressure, mean arterial pressure, lymphocyte, NLR, Hb, PLT, UREA, CR, ALB, Ca, P, international normalized ratio, prothrombin time, activated partial thromboplastin time, ferritin, transferrin saturation are expressed as mean ± standard deviation. Nonnormally distributed variables including hemodialysis vintage, GCS score, WBC, neutrophils, RDW, iPTH are expressed as median (25%-75% interquartile range). Student t test or the Mann–Whitney U test was used for comparisons between 2 groups. Categorical variables including sex, cause of renal failure and comorbidities are expressed as number and proportions (percentage), and the Chi-squared test was used for comparisons between 2 groups. Univariate and multivariate Logistic regression analysis were performed to identify independent risk factors of the in-hospital Mortality in Hemodialysis Patients with SIH. The receiver operating characteristic curve (ROC) and areas under the curve (AUCs) were determined. The sensitivity and specificity of independent risk factors were calculated for a range of different cutoff points. \(P\) values of <.05 was regarded as statistically significant.

3. Results

3.1. Baseline characteristics

A total of 46 patients were enrolled in the study. There were 33 (71.74%) male patients and 13 (28.26%) female patients, who had a mean age of 60.04 ± 10.70 (range, 39–84) years. 32 patients (69.57%) died during hospitalization. Baseline clinical and laboratory characteristics of the patients were presented in Table 1. Compared with survivors (n = 14), non-survivors (n = 32) had longer hemodialysis vintage (\(P = .017\)), lower GCS score (\(P < .001\)), higher Hb (\(P = .032\)) and RDW (\(P = .009\)). However, there were no significant differences in sex, cause of renal failure, comorbidities at ESRD, clinical and laboratory parameters including blood pressure, WBC, NLR, PLT, UREA, CR, ALB, Ca, P, iPTH, indices of coagulation and iron metabolism between survivors and non-survivors group (\(P > .05\)).

3.2. Risk factors for in-hospital mortality of MHD patients with SIH

Logistic regression was used to analyses the independent risk factors for in-hospital mortality of MHD patients with SIH. Significant factors from the univariate logistic regression analysis were included in the multivariable logistic regression analysis (Table 2). GCS score (OR 0.719, 95% CI 0.546-0.946; \(P = .018\)) and RDW (OR 4.549, 95% CI 1.243-9.46; \(P = .022\)) remained statistically significant after adjusting for confounding factors.

3.3. The combined predictive value of GCS score and RDW

The AUC was used to estimate the predictability of in-hospital mortality of MHD patients with SIH. The AUC for GCS score was 0.849 (95% CI 0.729-0.970) while that for RDW was 0.743 (95% CI 0.596-0.891). In order to get a further understanding whether GCS score and RDW in combination could improve the prognostic performance of MHD patients with SIH, we combined the 2 biomarkers to construct a new ROC curve. The AUC for the combined prediction was 0.916 (95% CI 0.828-1.000), with a sensitivity of 90.63% and a specificity of 88.46% (Table 3 and Fig. 1).

4. Discussion

RDW is a marker of variation of the size of the circulating red blood cells. Higher RDW had been proven to be associated with higher mortality in patients suffering from different diseases.
### Table 1
Baseline clinical and laboratory characteristic of subjects at admission.

|                        | Total (n = 46) | Survivors (n = 14) | Non-survivors (n = 32) | P value |
|------------------------|---------------|---------------------|------------------------|---------|
| Male, n                | 33(71.74)     | 10(71.43)           | 23(71.88)              | .745    |
| Age, yrs               | 60.04 ± 10.67 | 64.00 ± 11.08       | 58.31 ± 9.86           | .090    |
| Hemodialysis vintage, months | 31.5(15.8,62.3) | 26.0(10.0,49.0) | 43.0(20.0,83.0) | .017    |
| **Cause of renal failure** |              |                     |                        |         |
| Glomerular nephritis   | 17(36.96)     | 3(21.43)            | 14(43.75)              | .149    |
| Diabetes               | 18(39.13)     | 6(42.86)            | 13(40.63)              | .887    |
| Polycystic kidney disease | 7(15.22)    | 3(21.43)            | 4(12.5)                | .742    |
| Hypertension           | 3(6.52)       | 2(14.29)            | 1(3.13)                | .580    |
| **Comorbidities at ESRD** |          |                     |                        |         |
| Diabetes               | 19(41.30)     | 6(42.86)            | 13(40.63)              | .887    |
| Hypertension           | 43(93.48)     | 13(92.86)           | 30(93.75)              | .592    |
| Cardiovascular disease | 16(34.78)     | 5(35.71)            | 11(34.38)              | .858    |
| **Clinical and laboratory parameters** | |                     |                        |         |
| SBP, mm Hg             | 187.20 ± 38.04| 190.07 ± 29.26      | 185.94 ± 40.68         | .734    |
| DBP, mm Hg             | 97.89 ± 20.347| 98.21 ± 16.58       | 97.75 ± 21.49          | .944    |
| MAP, mm Hg             | 127.66 ± 24.07| 128.83 ± 17.75      | 127.15 ± 26.00         | .826    |
| GCS score              | 9(5,14.25)    | 15(13,15)           | 7(4,13)                | .000    |
| WBC, 10^9/L            | 7.15(5.05,9.49)| 5.35(4.93,7.12)      | 7.20(5.82,11.79)       | .181    |
| Neutrophils, 10^9/L    | 5.41(3.95,7.96)| 3.97(3.85,5.48)      | 5.33(3.89,8.99)        | .152    |
| Lymphocyte, 10^9/L     | 0.87 ± 0.46   | 0.87 ± 0.54         | 0.87 ± 0.42            | .963    |
| NLR                    | 9.49 ± 6.96   | 7.34 ± 4.40         | 10.42 ± 7.70           | .170    |
| Hb, g/L                | 107.04 ± 22.96| 96.36 ± 19.93       | 111.72 ± 22.26         | .002    |
| RDW, %                 | 14.6(13.8,15.4)| 13.8(13.2,14.6)     | 15.1(14.4,16.5)        | .009    |
| PLT, 10^9/L            | 121.00 ± 46.69| 127.50 ± 37.79      | 118.16 ± 49.14         | .538    |
| UREA, mmol/L           | 18.00 ± 6.72  | 18.17 ± 6.21        | 17.93 ± 6.82           | .924    |
| CR, μmol/L             | 722.12 ± 224.78| 754.92 ± 207.52     | 707.99 ± 227.09        | .511    |
| ALB, g/L               | 43.09 ± 4.90  | 41.68 ± 4.61        | 43.70 ± 4.82           | .191    |
| Ca, mmol/L             | 2.11 ± 0.28   | 2.09 ± 0.21         | 2.14 ± 0.29            | .592    |
| P, mmol/L              | 1.35 ± 0.47   | 1.31 ± 0.35         | 1.37 ± 0.51            | .699    |
| iPTH, pg/ml            | 323.6(235.5574.5)| 352.3(320.8371.5)  | 364.5(275.6,1094.6)    | .496    |
| INR                    | 1.06 ± 0.08   | 1.03 ± 0.07         | 1.07 ± 0.08            | .230    |
| PT, s                  | 12.09 ± 0.90  | 11.86 ± 0.80        | 12.19 ± 0.91           | .254    |
| APTT, s                | 27.24 ± 4.16  | 26.09 ± 2.82        | 27.75 ± 4.47           | .207    |
| FER, μg/L              | 318.81 ± 359.61| 305.85 ± 186.41     | 357.60 ± 410.53        | .655    |
| TSAT, %                | 28.95 ± 11.78| 24.04 ± 10.90       | 28.26 ± 11.72          | .257    |

ALB = albumin, APTT = activated partial thromboplastin time, Ca = calcium, CR = creatinine, DBP = diastolic blood pressure, FER = ferritin, GCS score = Glasgow Coma Scale score, Hb = hemoglobin, INR = international normalized ratio, iPTH = intact parathyroid hormone, MAP = mean arterial pressure, NLR = neutrophil to lymphocyte ratio, P = phosphorus, PLT = platelet, PT = prothrombin time, RDW = red cell distribution width, SBP = systemic blood pressure, TSAT = transferrin saturation, UREA = urea nitrogen, WBC = white blood cell.

### Table 2
Logistic regression analysis of independent risk factors related to in-hospital mortality of hemodialysis patients with spontaneous cerebral hemorrhage.

|                        | Univariate | Multivariate |
|------------------------|------------|--------------|
|                        | OR         | 95%CI        | P value | OR         | 95%CI        | P value |
| Hemodialysis vintage   | 1.030      | 1.001–1.060  | .045    | 1.014      | 0.975–1.054  | .497    |
| GCS score              | 0.720      | 0.595–0.892  | .002    | 0.719      | 0.546–0.946  | .018    |
| Hb                     | 1.036      | 1.001–1.072  | .044    | 1.041      | 0.991–1.095  | .110    |
| RDW                    | 2.525      | 1.218–5.237  | .013    | 4.549      | 1.243–16.646 | .022    |

GCS score = Glasgow Coma Scale score, Hb = hemoglobin, RDW = red cell distribution width.

### Table 3
Diagnostic performance of the GCS score, RDW and the combined marker.

| Variables           | AUC (95%CI) | Cutoff point | Sensitivity (%) | Specificity (%) | Youden's index | P value |
|---------------------|-------------|--------------|-----------------|-----------------|----------------|---------|
| GCS score           | 0.849(0.729–0.970)| 13            | 81.25           | 71.43           | 0.53           | <.001   |
| RDW                 | 0.743(0.596–0.891)| 14.9          | 53.13           | 85.71           | 0.41           | .009    |
| Combined marker     | 0.916(0.828–1.000)| -             | 90.63           | 88.46           | 0.79           | <.001   |

AUC = area under the curve, GCS score = Glasgow Coma Scale score, RDW = red cell distribution width.
also suggested that RDW has a better predictive value for mortality than other traditional anemia laboratory markers in HD patients with CKD, and may also reflect recent hemorrhage. [33] Elkhatib et al [34] conducted a prospective observational study had shown that the combination of GCS score and RDW represented a better biomarker for hemodialysis patients with SAH than RDW and GCS score separately.

There were several limitations of our investigation which should be discussed. Firstly, it was a single-center and retrospective study with a relatively small number of patients so that our population may not reflect the whole cohort. Secondly, the follow-up was limited to the period of hospital stay and the patients were not followed for long-term outcomes after their discharge. Thirdly, since ours was not a randomized trial, the inherent bias was inevitable. It is necessary for further prospective studies with larger patient groups to investigate the combination prognostic value of the 2 parameters.

In conclusion, this study suggested that high RDW and low GCS score were useful and independent poor prognostic markers for in-hospital mortality of hemodialysis patients with SIH.

**Authors’ contributions**

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**References**

[1] Kochanek KD, Murphy SL, Xu J, Arias E. Mortality in the United States, 2013. NCHS Data Brief. 2014:1–8.

[2] Koton S, Schneider AL, Rosamond WD, et al. Stroke incidence and mortality trends in US communities, 1987 to 2011. JAMA. 2014;312:2359–68.
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[26] Ujszaszi A, Molnar MZ, Czira ME, Novak M, Mucsi I. Renal function of kidney transplant recipients: a potential new auxiliary parameter for the clinical evaluation of patients with chronic kidney disease. Br J Haematol. 2013;161:713–23.

[27] Doci D, Delvecchio C, Gollini C, Turi E, Baldrati L, Gilli P. Red blood cell volume distribution width (RDW) in uraemic patients on chronic haemodialysis. Int J Artif Organs. 1989;12:170–4.

[28] Liu H, Awad H, Hu ZD. Prognostic value of admission red blood cell distribution width in acute pancreatitis: a systematic review. Ann Transl Med. 2017;5:5342.

[29] Afonso L, Zalawadiya SK, Veeranna V, Panaich SS, Niraj A, Jacob S. Relationship between red cell distribution width and microalbuminuria: a population-based study of multietnic representative US adults. Nephron Clin Pract. 2011;119:277–82.

[30] Peng F, Li Z, Zhong Z, et al. An increasing of red blood cell distribution width was associated with cardiovascular mortality in patients on peritoneal dialysis. Int J Cardiol. 2014;176:379–81.

[31] Zhang T, Li J, Lin Y, Yang H, Cao S. Association between red blood cell distribution width and all-cause mortality in chronic kidney disease patients: a systematic review and meta-analysis. Arch Med Res. 2017;48:378–85.

[32] Vashista T, Streja E, Molnar MZ, et al. Red cell distribution width and mortality in hemodialysis patients. Am J Kidney Dis. 2016;68:10–21.

[33] Paulus EM, Weinberg JA, Magnottl LJ, et al. Admission red cell distribution width: a novel predictor of massive transfusion after injury. Am Surg. 2014;80:685–9.

[34] ElKhathib THM, Shehta N, Bessar AA. hemotamia expansion predictors: laboratory and radiological risk factors in patients with acute intracerebral hemorrhage: a prospective observational study. J Stroke Cerebrovasc Dis. 2019;28:2177–86.

[35] Altintas O, Durusu H, Baran G, et al. The relationship of hematoma growth to red blood cell distribution width in patients with hypertensive intracerebral hemorrhage. Turk Neurosurg. 2017;27:368–73.

[36] Garcia JH, Ho KL, Caccamo DV. Intracerebral hemorrhage: Pathology of selected topics. In: Kase CS, Caplan LR, eds. Intracerebral Hemorrhage. Boston: Butterworth-Heinemann, 1994; 45–72.

[37] Kase CS, Mohr JP, Caplan LR. Intracerebral hemorrhage. Stroke. 2004;327:376.

[38] Pierce CN, Larson DF. Inflammatory cytokine inhibition of erythropoiesis in patients implanted with a mechanical circulatory assist device. Perfusion. 2005;20:83–90.

[39] Laftah AH, Sharma N, Brookes MJ, et al. Tumour necrosis factor alpha causes hypoferraemia and reduced intestinal iron absorption in mice. J Biol Chem. 2006;281:7096–7107.

[40] Tekce H, Kin Tekce B, Aktas G, Tanrisev M, Sit M. The evaluation of the Glasgow Coma Scale in intubated patients: a linear conundrum of the Glasgow Coma Scale in intubated patients: a linear - level analysis of 100 trauma patients. Can J Surg. 2005;48:378–83.

[41] Gali J. Anemia and heart failure. Curr Opin Cardiol. 2009;24:172–8.

[42] Arbós KA, Claro LM, Borges L, Santos CA, Wefort-Santos AM. Human erythrocytes as a system for evaluating the antioxidant capacity of vegetable extracts. Nutr Res. 2008;28:457–63.

[43] Niki E, Komuro E, Takahashi M, Urano S, Ito E, Terao K. Oxidative hemolysis of erythrocytes and its inhibition by free radical scavengers. J Biol Chem. 1988;263:19089–14.

[44] Tekce H, Kin Tekce B, Aktas G, Tanrisev M, Sit M. The evaluation of the Glasgow Coma Scale in intubated patients: a linear conundrum of the Glasgow Coma Scale in intubated patients: a linear - level analysis of 100 trauma patients. Can J Surg. 2005;48:378–83.

[45] Niki E, Komuro E, Takahashi M, Urano S, Ito E, Terao K. Oxidative hemolysis of erythrocytes and its inhibition by free radical scavengers. J Biol Chem. 1988;263:19089–14.

[46] Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet. 1974;2:81–4.

[47] Gennarelli TA, Champion HR, Copes WS, Sacco WJ. Comparison of mortality, morbidity, and severity of 59,713 head injured patients with 114,447 patients with extracranial injuries. J Trauma. 1994;37:962–8.

[48] Huang BR, Liao CC, Huang WH, et al. Prognostic factors of spontaneous intracerebral haemorrhage in haemodialysis patients and predictors of 30-day mortality. Intern Med. 2008;38568–74.

[49] Oishi T, Takehara S, Yamamura Y, et al. Hemodialysis increases the incidence of post-traumatic seizure in hemodialysis patients with traumatic intracranial hemorrhage. No Shinkei Geka. 2017;45:303–9.

[50] Meredith W, Rutledge R, Fakhry SM, Emery S, Kroumohout-Schiro S. The conundrum of the Glasgow Coma Scale in intubated patients: a linear regression prediction of the Glasgow verbal score from the Glasgow eye and motor scores. J Trauma. 1998;44:839–45.