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Original Article

Establishment and application of severity assessment system for patients with delayed encephalopathy caused by carbon monoxide poisoning

Yan Zhang*, Yanyan Bai*, Ting Feng, Yang Li, Hong Zhang, Ting Wang

*Department of Neurology, The First Hospital of Yulin, Yulin 719000, Shaanxi, China. *Equal contributors.*

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Abstract: Objective: To identify the factors related to the severity of delayed encephalopathy after acute carbon monoxide poisoning (DEACMP) and establishment of a clinical nomogram assessment model. Methods: Clinical data of 200 patients with DEACMP admitted to the First Hospital of Yulin from January 2019 to December 2022 were retrospectively analyzed. The patients were classified into severe and non-severe groups according to the severity of the disease. Clinical data was collected from both groups. Logistic regression was applied to analyze the risk factors for disease severity of DEACMP patients. The risk prediction model of the nomogram was constructed by incorporating risk factors, and its effectiveness was verified. Model differentiation performance was evaluated using the Respondent Operating Characteristic (ROC) Curve. Model calibration curve was adopted for fitting the situation of evaluation. The consistency of the model was evaluated by Hosmer-Lemeshow (H-L) analysis. Result: Age, coma time out of exposure, creatine kinase (CK), caspase, and red blood cell distribution width (RDW) were the risk factors for the severe DEACMP. A nomogram prediction model was built based on the above indicators. The area under the curve (AUC) of the model in predicting severe DEACMP was 0.961 (95% CI: 0.934-0.988) and 0.929 (95% CI: 0.841-1) in the training and test sets, respectively. The H-L test showed good goodness of fit (χ^2 = 4.468, P = 0.813). The calibration curve showed a good agreement between the predicted values of the nomogram and the actual observed values. Conclusion: Age, coma time out of exposure, CK, caspase, and RDW were significantly correlated with the severity of DEACMP patients. The nomogram prediction model incorporating the five indicators has certain clinical reference value for predicting the severe DEACMP and could be used as an accurate and rapid clinical assessment tool.

Keywords: DEACMP, the severity of the illness, nomograph

Introduction

Carbon monoxide (CO) poisoning is one of the most common fatal poisoning accidents and causes serious damage to people's health and life safety [1]. DEACMP is one of the complications after CO poisoning with diverse symptoms, including slow response, memory impairment, inattention, hemiplegia aphasia, and motor coordination disorder [2, 3]. At present, DEACMP is primarily treated by hyperbaric oxygen and other comprehensive treatment methods [4]. However, it is important to note that not all patients with DEACMP respond well to hyperbaric oxygen therapy. For some patients, after receiving a series of treatments, the prognosis is still poor, especially in elderly patients. There is still a lack of reliable detection methods for predicting the severity and prognosis of patients, and the evaluation of the severity should take into account factors such as the degree of intoxication, symptom manifestations, and medical examination results such as brain magnetic resonance diffusion weighted imaging (DWI). However, this method has shortcomings such as individual differences and subjective symptom assessment [5]. Many clinical teams have studied the clinical characteristics of DEACMP [6]. In this study, we established a nomogram for predicting the severity of patients with DEACMP and provide a reference for individualized monitoring and treatment.

Material and methods

Research subjects

In this retrospective study, 200 patients with DEACMP admitted to the First Hospital of Yulin from January 2019 to December 2022 were selected as the study subjects. Inclusion criteria: (1) Patients who met the criteria for CO poisoning and were diagnosed with DEACMP by imaging examination [7, 8]; (2) Patients with complete clinical data, laboratory test data and other information. Exclusion criteria: (1) Patients with severe cardiac and cerebral diseases; (2) Patients with abnormal liver and kidney function; (3) Pregnant and lactating women. This study was approved by the Ethics Committee of the First Hospital of Yulin.

General data collection

By consulting hospital electronic medical records, we collected patient clinical data, including gender, age, history of hypertension, history of stroke, coma time out of exposure, hemoglobin (Hb), CK, Serum creatinine (Scr), caspase, RDW, Glasgow Coma Scale (GCS) score.

Prognostic grouping

The GCS score consists of three parts: eye opening response, verbal response and motor response, with a total score of 15 points. A full score indicates clear awareness, a score of 12-14 indicates mild consciousness disorder, a score of 9-11 indicates moderate consciousness disorder, and a score below 8 is considered coma. In this study, according to the state of consciousness and Glasgow Coma Scale (GCS) score at admission, the severity was classified into three categories: 13 to 15 as mild, 9 to 12 as moderate, and 3 to 8 as severe. In this study, 200 patients were classified into two groups: severe and non-severe groups (including mild and moderate).

Statistical analysis

SPSS 23.0 and RStudio software were employed for data analyses. Measurement data were expressed as $\bar{x} \pm s$, and t-test were performed for between-group comparisons. Counting data were expressed as cases (%), and compared by chi-square test. Logistic regression was employed to analyze the risk factors of severe DEACMP. The influence factors are introduced into R software, and the nomogram risk prediction model is built with R software. The discrimination performance of the model was evaluated by ROC curve and calibration curve. The Hosmer-Lemeshow test was applied to evaluate the consistency of the model, with $P>0.05$ representing good consistency. $P<0.05$ was considered with statistical significance.

Results

Comparison of general data

Comparison of general information between the two groups showed no significant differences in terms of age, coma time out of exposure, CK, caspase, and RDW (all $P<0.05$) (**Table 1**).

Analysis of risk factors for severe DEACMP

The severity of the disease was taken as the dependent variables (0 = non-severe, 1 = severe), and age, coma time out of exposure, CK, caspase, RDW were taken as the independent variables. Logistic regression analysis was performed, and the assignment was input as the original value. The results showed that age, coma time out of exposure, CK, caspase and RDW were risk factors for severe DEACMP (**Table 2**).

Construct a nomogram risk prediction model

Based on the results of the multi-factor analysis, the above 5 risk factors affecting the severity of DEACMP patients were included in the risk assessment, and a nomogram risk model was established (**Figure 1**), the calculation formula is: logit (P) = -28.251 + 0.11 × Age + 0.551 × Coma time out of exposure + 0.053 × CK + 1.008 × Caspase + 0.388 × RDW. To further validate the predictive efficacy of the model, the ROC curves were plotted for the training and test sets, respectively (**Figure 2**). The findings indicated that the model showed a high prediction accuracy. The AUCs for predicting severe DEACMP in the training set and testing set were 0.961 (95% CI: 0.934-0.988) and 0.929 (95% CI: 0.841-1), respectively. The Hosmer-Lemeshow test indicated high goodness of fit ($\chi^2 = 4.468$, $P = 0.813$). The calibration curve (**Figure 3**) indicated that the model

Table 1. Comparison of general information between the two groups [x±s, n (%)]

Influencing factors	Non-severe group (n = 137)	Severe group (n = 63)	χ^2/t	*P*
Gender				
Male	68	32	0.023	0.879
Female	69	31		
Hypertension history				
Yes	58	33	1.756	0.185
No	79	30		
Stroke history				
Yes	69	34	0.224	0.636
No	68	29		
Age (years)	53.28±6.76	57.57±6.11	-4.301	<0.001
Coma time out of exposure (h)	10.12±2.06	14.94±4.08	-8.859	<0.001
Hb (g/L)	105.69±19.85	111.68±23.01	-1.885	0.061
CK (U/L)	99.42±24.36	124.62±20.79	-7.107	<0.001
Scr (μmol/L)	63.30±5.87	64.13±6.21	-0.910	0.364
Caspase (mg/L)	3.19±1.01	4.25±1.12	-6.686	<0.001
RDW (%)	12.53±1.87	14.22±2.31	-5.072	<0.001

Note: Hb: hemoglobin; CK: Creatine Kinase; Scr: Serum creatinine; RDW: red blood cell distribution width.

Table 2. Analysis of multiple factors affecting the severity of DEACMP

Factors	*B*	*SE*	*Wald*	*P*	*OR (95% CI)*
Age	0.11	0.044	6.207	0.013	1.116 (1.024-1.216)
Coma time out of exposure	0.551	0.111	24.591	<0.001	1.735 (1.396-2.158)
CK	0.053	0.013	17.103	<0.001	1.055 (1.028-1.082)
Caspase	1.008	0.286	12.454	<0.001	2.739 (1.565-4.793)
RDW	0.388	0.133	8.579	0.003	1.474 (1.137-1.911)
Constant	-28.251	4.694	36.216	<0.001	-

Note: CK: Creatine Kinase; Scr: Serum creatinine; RDW: red blood cell distribution width.

showed good agreement between the training and test sets.

Discussion

According to relevant reports, the incidence and mortality of CO poisoning are 137 and 4.6 per million people, respectively [9]. Patients with CO poisoning can be cured if treated in time, but some patients may have a false recovery period after treatment. At the end of the pseudo recovery period, patients will again develop delayed disturbances of consciousness, mental disorders, and nervous system damage, known as DEACMP. The incidence of DEACMP has been reported to be high in severe CO poisoning patients, approximately 13%-50% [10]. While a small number of patients can regain brain function after months of treatment or even longer, the majority of patients typically experience long-term neurocognitive sequelae associated with brain injury. The disability rate of DEACMP is high [11]. Therefore, how to effectively predict the occurrence of severe DEACMP is the focus of research.

In this study, logistic regression was employed to analyze the risk factors for severe DEACMP, and a nomogram prediction model was constructed. The results indicate that nomogram has good predictive efficacy with a sensitivity of 93.8% and a specificity of 83.7%.

The findings suggest that age is a risk factor for severe DEACMP. This is in agreement with the findings of Zhang [12]. This may be related to the weakened tolerance of nerve tissue to hypoxia in the elderly population. Cerebral vascular function and central nervous system function in elderly patients are gradually

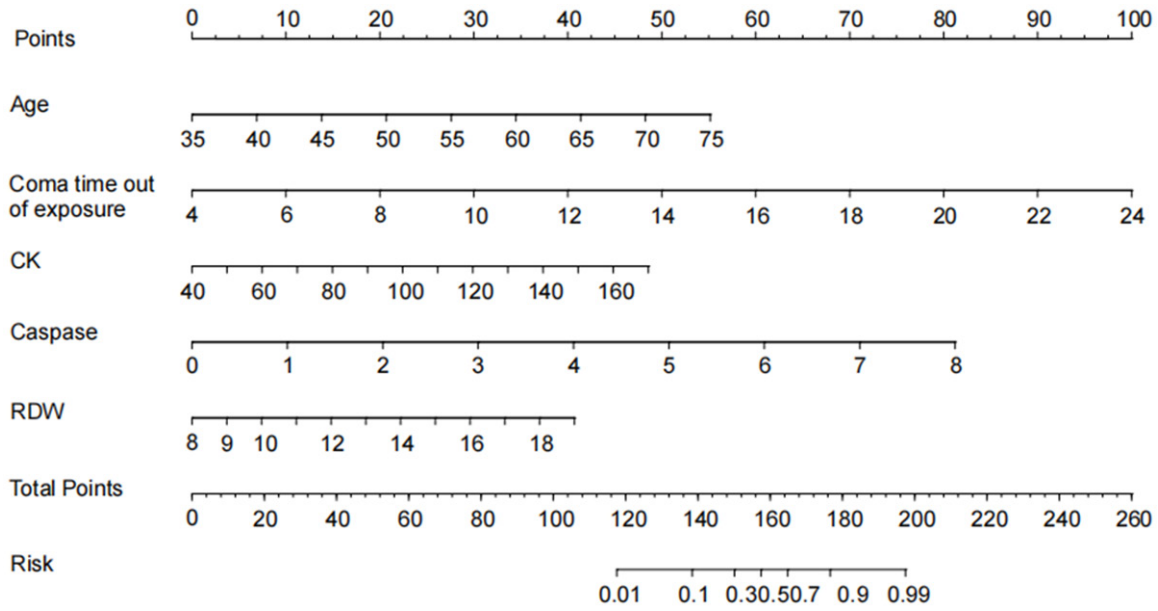

Figure 1. A nomogram predicting the severity of DEACMP patients. Note: DEACMP: delayed encephalopathy after acute carbon monoxide poisoning.

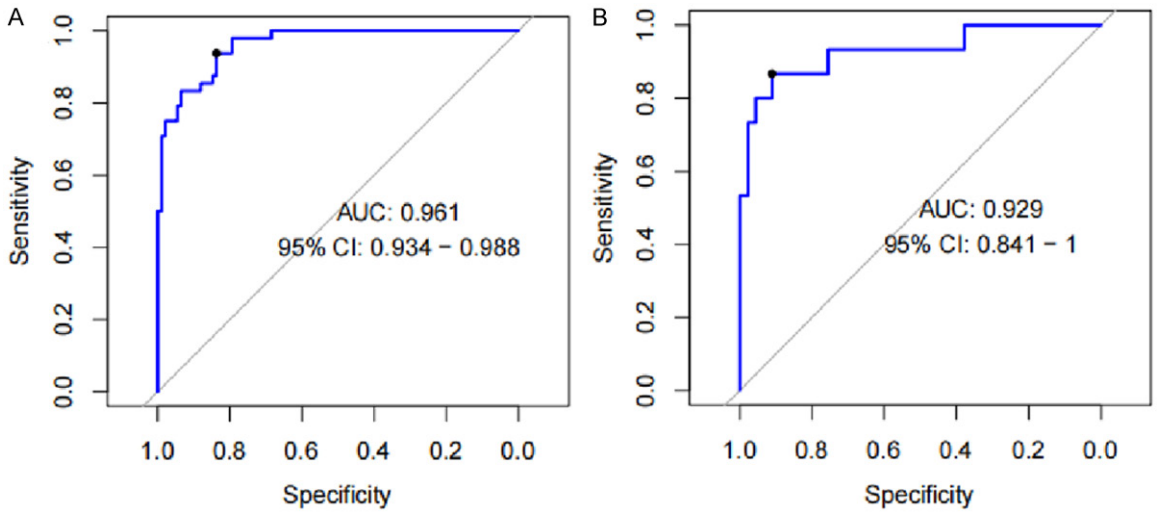

Figure 2. ROC curve. Note: (A) ROC curve of the training set; (B) ROC curve of the test set.

degraded. Meanwhile, factors such as cerebral arteriosclerosis, abnormal cerebral metabolism, and poor vascular regulation ability will aggravate the condition of DEACMP patients, increase the difficulty of treatment, affect the therapeutic effect, and lead to poor prognosis.

In addition, the duration of coma is also a risk factor for severe DEACMP. Gao et al. [13] studied 13 patients who were in a coma for more than 7 hours after acute CO poisoning, and the results showed that patients with longer coma period had worse prognosis and a higher incidence of DEACMP. Wang et al. [14] showed that a longer duration of disturbance of consciousness (OR = 4.268, P<0.05) was a risk factor for delayed brain encephalopathy, implying that for every 1-hour increase in coma duration, the incidence of DEACMP increased by 4.268 times. The possible mechanism is that since brain tissue has high oxygen consumption, it is particularly sensitive to the effects of tissue hypoxia caused by CO poisoning. Coma is one of the common symptoms after CO expo-

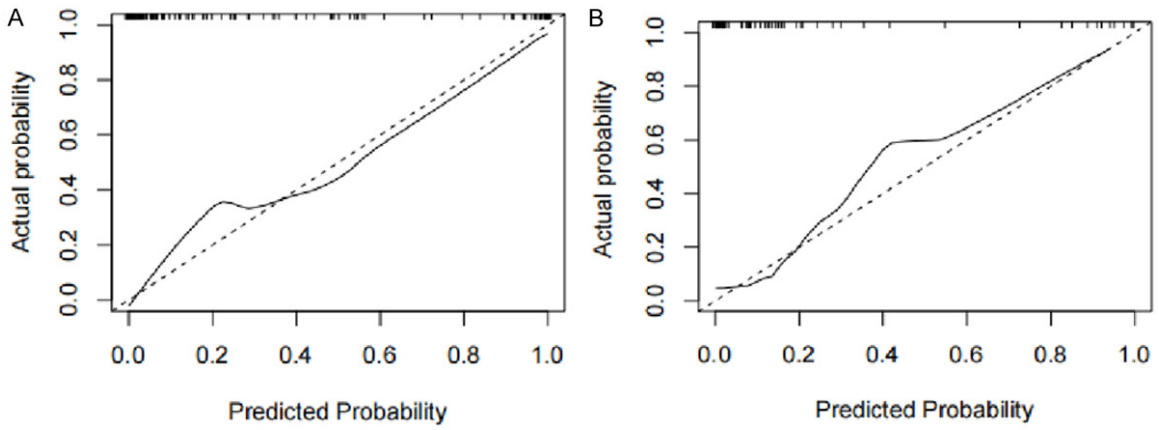

Figure 3. Calibration curve analysis. Note: (A) Training set calibration curve; (B) Test set calibration curve.

sure. After poisoning, 20% of the patients are still in unconsciousness while arriving at the hospital, more than 90% of comatose patients regain consciousness within 24 hours of onset, and a small number of patients remain unconscious for a long time after initial treatment [15].

Creatine kinase (CK) is an enzymatic protein that mainly functions to participate in the creatine phosphorylation process in muscle cells and generate creatine phosphate [16]. Lee et al. [17] showed that the severity of poisoning was positively correlated with the level of CK, which is consistent with the results of this study. Elevated CK level is a sign of severe CO poisoning and indicates a higher severity of late-onset encephalopathy. The release of CK into blood is caused by brain tissue damage, and the increase of CK levels in patients is related to the severity of disease. The more serious the damage to the brain, the more the release of creatine kinase [18]. In addition, relevant studies have pointed out that high CK levels can affect the severity of DEACMP, and the increase in CK concentration indicates myocardial damage and brain damage, resulting in aggravated disease [19].

Red blood cell distribution width (RDW) is a parameter that reflects the heterogeneity of peripheral red blood cell volume and is often used in the differential diagnosis of various types of anemia. Study has shown that this indicator is related to the prognosis of cardiovascular and cerebrovascular diseases [20]. The results of this study suggest that RDW is a risk factor for severe DEACMP, which is consistent with the findings of Sunman et al. [21]. They conducted a study on 571 patients with CO poisoning, and the results pointed out that a high RDW level (OR = 1.221, $P<0.05$) was a risk factor for long-term mortality in patients with CO poisoning. The mechanism of RDW in the severity of delayed encephalopathy is not clear. The possible reason is that RDW is a marker of inflammatory factors, and severe patients with high levels of RDW have high levels of inflammation.

The findings of this research indicate that the serum caspase and RDW levels were higher in the severe group than in the non-severe group, suggesting their potential in preliminarily predicting the severity of the disease. The results were consistent with those of Zhou et al. [22], who indicated that serum caspase and RDW levels were positively correlated with the severity of DEACMP. The reason may be that cysteine is a vascular-damaging amino acid and can produce oxygen-free radicals, which can promote the oxidative stress response, constantly damaging vascular endothelial cells, which will deteriorate endothelial function, and then cause atherosclerosis in the body, which is an important independent risk factor for cerebrovascular diseases [23].

The clinical symptoms of acute CO poisoning and their severity are not always correlated with hemoglobin concentration on admission. This difference may be due to two reasons: (1) Haemoglobin saturation in the blood is influenced by some factors, for example, the concentration of CO inhaled, the duration of exposure, and the time interval between CO expo-

sure and blood sampling; (2) Because CO has a high affinity for hemoglobin, there may be certain amount of CO diffused into tissues. Therefore, even after being removed from the environment or taking oxygen, the body may still have a large amount of CO. Studies have demonstrated that hemoglobin concentration is not a risk factor for DEACMP [24, 25], which is consistent with ours.

There are some limitations to this research. First, this is a retrospective analysis, so selection bias is inevitable. Second, this is a single-center study, and the applicability of the findings needs to be further confirmed in different centers and populations in different regions. Finally, this research had a small sample size, which may have had some impact on the results. Larger samples are needed for further confirmation in the future.

In summary, age, coma time out of exposure, CK, caspase, and RDW were risk factors for severe DEACMP. The nomogram model constructed by incorporating these five risk factors displayed good predicting performance and can be used as an indicator for clinical evaluation of the severity of DEACMP.

Disclosure of conflict of interest

None.

Address correspondence to: Ting Wang, Department of Neurology, The First Hospital of Yulin, No. 93, Yuxi Road, Kaifa District, Yulin 719000, Shaanxi, China. Tel: +86-0912-3865639; E-mail: wtingdo@126.com

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