Predictive Values of Serum Biochemical Markers and Apparent Diffusion Coefficient on Delayed Encephalopathy After Acute Carbon Monoxide Poisoning

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ABSTRACT

AIM: To explore the predictive values of serum biochemical markers and apparent diffusion coefficient (ADC) on delayed encephalopathy after acute carbon monoxide poisoning (DEACMP).

MATERIAL and METHODS: Seventy-nine patients were divided into two groups based on the onset of DEACMP 60 days after with acute carbon monoxide poisoning. The baseline data of ACMP patients were collected. Serum levels of cardiac troponin I (cTNI), lactic acid (Lac), carboxyhemoglobin (COHb), creatine kinase (CK), creatine kinase isoenzyme (CK-MB), lactate dehydrogenase (LDH), C-reactive protein (CRP), and neuron-specific enolase (NSE) were measured within 24 hours of ACMP onset. The ADC of globus pallidum, centrum semiovale, and periventricular white matter were recorded by diffusion-weighted magnetic resonance imaging (DW-MRI) within 48 hours of admission. Logistic regression analysis was performed to determine the risk factors for DEACMP.

RESULTS: The incidence of coma and duration of poisoning in the DEACMP group were significantly higher than those in the non-DEACMP group. The levels of Lac, CK, CK-MB, LDH, CRP and NSE in the DEACMP group were higher than those in the non-DEACMP group. The ADC value of globus pallidus in the DEACMP group was significantly higher than that in non-DEACMP group. The duration of poisoning, coma degree, CK, LDH, NES, and CRP were closely associated with the occurrence of DEACMP.

CONCLUSION: The duration of poisoning, coma degree, and serum levels of CK, LDH, CRP, and NSE were independent risk factors for DEACMP.

KEYWORDS: Carbon monoxide poisoning, Coma, Creatine kinase, Neuron-specific enolase, Magnetic resonance imaging

ABBREVIATIONS: ADC: Apparent diffusion coefficient, cTNI: Cardiac troponin I, Lac: Lactic acid, COHb: Carboxyhemoglobin, CK: Creatine kinase, CK-MB: Creatine kinase isoenzyme, LDH: Lactate dehydrogenase, CRP: C-reactive protein, NSE: Neuron-specific enolase
**INTRODUCTION**

Acute carbon monoxide poisoning (ACMP) is the most common type of fatal air poisoning, causing dysfunction of the cardiovascular and central nervous system (26). Delayed encephalopathy after ACMP (DEACMP) is one of its most serious complications (11). DEACMP is characterized by a series of neuropsychiatric symptoms such as extrapyramidal symptoms, dementia, and mental disorders (9,33). Patients with DEACMP have varying degrees of hypoxia and nerve cell damage (35). Sex, age, and degree of intoxication are significantly different among patients with DEACMP (47), thereby warranting efforts to explore new diagnostic methods for DEACMP.

Numerous studies have investigated the relationship between the values of serum biochemical factors and the incidence of late-onset disorder after ACMP. Wang et al. have reported that blood lactic acid (Lac) clearance rate in ACMP patients is negatively related to the incidence of DEACMP (39). Zhang et al. have found that the serum levels of creatine kinase isoenzyme (CK-MB) and lactate dehydrogenase (LDH) are markedly increased in patients with ACMP (46). Cha et al. have shown that serum neuron-specific enolase (NES) serves as an early predictor of delayed neuropsychiatric sequelae (DNS) in patients with ACMP (5). The diagnostic roles of these serum biochemical indexes, including Lac, CK-MB, LDH, and NSE on DEACMP need to be further investigated.

**MATERIAL and METHODS**

**Patients**

A total of 79 ACMP patients were admitted at Zibo Municipal Hospital from June 2015 to March 2018. Based on DEACMP onset after 60 days, patients were divided into the DEACMP group and non-DEACMP group. The diagnostic criteria for DEACMP were in line with WHO recommendations. The clinical data of the ACMP patients were retrospectively analyzed, including their ages, genders, and whether they smoke and/or drink, previous coma cases, duration of poisoning, and the presence of other comorbidities such as hypertension, coronary heart disease, and diabetes. Informed consent was obtained from all patients before collection of samples. This study was approved by the Ethics Committee of Zibo Municipal Hospital in accordance with the Declaration of Helsinki.

**Serum Biochemical Indexes**

Blood samples from the vein were taken from the patients within 24 hours of DEACMP onset. White blood cell (WBC) count was measured using an automatic blood cell analyzer (Sysmex, Kobe, Japan). The serum was separated by centrifugation at 2500 g for 15 min. The serum level of COHb was measured using a pulse oximeter (Masimo Rad-7, Masimo, Irvine, CA, USA), cTnl using a chemiluminescent immunoassay on Access 2 analyzer (Beckman Counter, Brea, California, USA), Lac using a Cobas 6000 analyzer (Roche Diagnostics GmbH, Mannheim, Germany), CK by a colorimetric method using a creatine kinase activity assay kit (Abcam, Cambridge, MA, USA), CKMB isoenzyme using a Beckman CX3 automatic biochemistry analyzer (Hitachi, Tokyo, Japan), LDH using an AU 2700 automatic biochemistry analyzer (Olympus, Tokyo, Japan), NSE using a solid-phase immunoassay with double monoclonal antibodies with an Elecsys 2010 (Roche Diagnostics GmbH, Germany), and CRP using a turbidimetric method based on latex agglutination on a CRP-Latex II X2 reagent Hitachi 7020 analyzer (Hitachi, Tokyo, Japan).

**Brain DW-MRI Techniques**

A GE Signa HDxT 1.5T (MRI) (GE, Milwaukee, WI, USA) was used to examine craniocerebral MRI scans within 48 hours after onset of DEACMP. The radiographs were analyzed using an ADW4.4 workstation, and the apparent diffusion coefficient (ADC) values of the globus pallidum, centrum semiovale, and periventricular white matter were determined.

**Statistical Analysis**

Statistical analysis was performed with SPSS 23.0 (SPSS Inc., Chicago, IL, USA). Measurement data were presented as means ± standard deviations (SD) and assessed using a Student’s t-test. Enumeration data were presented as numbers (N) and assessed using a χ² test. Logistic regression analysis was performed to identify the independent risk factors for DEACMP. A p value<0.05 was considered statistically significant.
that serum levels of Lac, CK, CK-MB, LDH, CRP, and NSE were significantly higher in the DEACMP group than those in the non-DEACMP group (p<0.01). However, there was no difference in the serum levels of COHb and cTnI as well as WBC counts between the two groups (p>0.05) (Table II).

### ADC Values of Different Brain Tissues in DEACMP

The ADC values of the globus pallidum, centrum semiovale, and periventricular white matter were determined by DW-MRI. The results found the ADC value of globus pallidum in the DEACMP group to be lower than that in the non-DEACMP group (p<0.01). However, there was no statistical difference between these two groups in terms of ADC values of the centrum semiovale and periventricular white matter (p>0.05) (Table III).

### Logistic Regression Analysis of Risk Factors for DEACMP

Logistic regression analysis showed that there was a significant correlation between DEACMP and the duration of poisoning (p<0.05), coma degree (p<0.05), CK (p<0.001), LDH (p<0.05),

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### Table I: Baseline Data for DEACMP and no-DEACMP Groups

<table>
<thead>
<tr>
<th>Items</th>
<th>DEACMP group (n=34)</th>
<th>no-DEACMP group (n=45)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>21/13</td>
<td>26/19</td>
<td>0.721</td>
</tr>
<tr>
<td>Age (years old)</td>
<td>57.34 ± 17.34</td>
<td>52.43 ± 15.42</td>
<td>0.195</td>
</tr>
<tr>
<td>Smoke</td>
<td>14</td>
<td>24</td>
<td>0.284</td>
</tr>
<tr>
<td>Drink alcohol</td>
<td>16</td>
<td>24</td>
<td>0.581</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15</td>
<td>25</td>
<td>0.314</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>12</td>
<td>20</td>
<td>0.412</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13</td>
<td>21</td>
<td>0.454</td>
</tr>
<tr>
<td>Coma</td>
<td>27**</td>
<td>18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of poisoning (hour)</td>
<td>22.54 ± 10.25**</td>
<td>13.41 ± 16.78</td>
<td>0.006</td>
</tr>
</tbody>
</table>

**p<0.01 vs. no-DEACMP group.

### Table II: Biochemical Values Between DEACMP and no-DEACMP Groups

<table>
<thead>
<tr>
<th>Biochemical values</th>
<th>DEACMP group</th>
<th>No-DEACMP group</th>
<th>p</th>
<th>F value</th>
</tr>
</thead>
<tbody>
<tr>
<td>COHb (%)</td>
<td>21.24 ± 18.11</td>
<td>24.01 ± 13.89</td>
<td>0.444</td>
<td>0.588</td>
</tr>
<tr>
<td>cTnI (mg/L)</td>
<td>1.62 ± 3.33</td>
<td>0.48 ± 1.76</td>
<td>0.053</td>
<td>0.279</td>
</tr>
<tr>
<td>WBC (/μL)</td>
<td>14287.23 ± 3786.46</td>
<td>13784.24 ± 8946.13</td>
<td>0.759</td>
<td>5.582</td>
</tr>
<tr>
<td>Lac (U/L)</td>
<td>6.11 ± 2.54*</td>
<td>5.08 ± 1.63</td>
<td>0.032</td>
<td>0.412</td>
</tr>
<tr>
<td>CK (IU/L)</td>
<td>4231.18 ± 5346.17**</td>
<td>721.34 ± 2332.14</td>
<td>0.0002</td>
<td>0.190</td>
</tr>
<tr>
<td>CK-MB (IU/L)</td>
<td>51.32 ± 33.12*</td>
<td>36.72 ± 23.24</td>
<td>0.024</td>
<td>0.492</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>384.67 ± 276.45**</td>
<td>231.22 ± 108.64</td>
<td>0.001</td>
<td>0.154</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>30.34 ± 36.28*</td>
<td>4.12 ± 2.57</td>
<td>&lt;0.0001</td>
<td>0.005</td>
</tr>
<tr>
<td>NSE (U/mL)</td>
<td>18.73 ± 5.46*</td>
<td>11.98 ± 4.16</td>
<td>&lt;0.0001</td>
<td>0.580</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01 vs. no-DEACMP group.

### Table III: ADC Values of Different Brain Tissues Between DEACMP and no-DEACMP Groups

<table>
<thead>
<tr>
<th>Position (×10^{-3}mm^{2}/s)</th>
<th>DEACMP group</th>
<th>No-DEACMP group</th>
<th>p</th>
<th>F value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Globus pallidum</td>
<td>0.52 ± 0.07**</td>
<td>0.76 ± 0.04</td>
<td>&lt;0.0001</td>
<td>0.327</td>
</tr>
<tr>
<td>Semi-soft circle</td>
<td>0.67 ± 0.07</td>
<td>0.71 ± 0.16</td>
<td>0.177</td>
<td>5.224</td>
</tr>
<tr>
<td>Periventricular white matter</td>
<td>0.70 ± 0.06</td>
<td>0.72 ± 0.05</td>
<td>0.110</td>
<td>0.694</td>
</tr>
</tbody>
</table>

**p<0.01 vs. no-DEACMP group.
et al. have indicated that Lac is associated with short-term outcomes in patients with ACMP, as patients with high initial Lac level exhibit a high incidence of DEACMP (22). CK and CK-MB are intracellular enzymes predominantly located in skeletal muscle, myocardium, and the brain (3). High CK and CK-MB levels can be induced by CO-induced damage in multiple organs in patients with ACMP. Thus, serum CK and CK-MB levels can be used as predictors for ACMP-associated diseases (19,38). LDH is an important enzyme of the anaerobic metabolic pathway (10). Winburn et al. have found that exposure of human erythrocytes to exogenous CO moderately inhibited LDH activity (42). Kudo et al. have reported the levels of CK, CK-MB and LDH to be markedly increased in DEACMP patients (18). In this study, the serum levels of Lac, CK, CK-MB and LDH in the DEACMP group were significantly higher than those in the non-DEACMP group. Our results indicate that these serum biochemical markers are closely associated with the occurrence of DEACMP, which are consistent with previous studies. Furthermore, logistic regression analysis found increased serum levels of CK and LDH to be independent risk factors for DEACMP. These results indicate that CK and LDH may act as promising predictive factors of DEACMP in clinical practice.

CRP is a common acute phase protein that can be elevated by hypoxia, trauma and other stress states in human organisms (23,43). Sawiniec et al. have proved CRP levels to have diagnostic value for ACMP, with CRP levels in ACMP patients found to increase by over 33% (28). Song et al. have shown that serum CRP level is useful for the early diagnosis and prognostic assessment of DEACMP (32). NSE is a marker of the condition of the central nervous system, with elevations in its levels closely related to the degree of brain damage (4,44). Yildirim et al. have demonstrated that serum NSE level is an indicator for brain injury in CO poisoning patients (45). Cha et al. have also reported that serum NES acts as an early predictor of DNS in patients with ACMP (5). In this study, serum levels of CRP and NSE in the DEACMP group were significantly higher than those in the non-DEACMP group. In addition, logistic regression analysis showed that increased serum levels of CRP and NES were independent risk factors for DEACMP (p<0.05), and CRP (p<0.01) (Table IV). The above indices were possible independent risk factors for DEACMP with statistically significant differences.

## DISCUSSION

DEACMP is a CO poisoning-induced disease with poor prognosis (15). CO poisoning causes both tissue hypoxia and direct cellular changes causing inflammatory or immunological injury (36,41). Prolonged exposure to CO leads to the development of neurologic sequelae, especially delayed encephalopathy (25,29). Song et al. have presented that approximately 10% to 30% patients who had CO poisoning develop DEACMP (32). Du et al. have shown that patients with DEACMP have a longer exposure to CO compared with those without DEACMP (9). In this study, the duration of exposure to CO in the DEACMP group was significantly higher than that in the non-DEACMP group. Our results are consistent with previous studies and illustrate that CO poisoning can cause DEACMP. Coma is one of the most obvious clinical manifestations of CO poisoning (27). Prolonged duration of coma after ACMP is also a risk factor for DEACMP (14,34). Pan et al. have shown that prolonged duration of coma for 11 hours may result in a markedly increased incidence rate of DEACMP (14). Taki and Nakajima have found that ACMP patients with coma have a higher incidence of DEACMP than ACMP patients without coma (34). In this study, the number of coma cases in the DEACMP group was also significantly higher than those in the non-DEACMP group, indicating that coma is closely related to the onset of DEACMP. Furthermore, upon logistic regression analysis, the duration of poisoning and coma degree were found to be independent risk factors for DEACMP. Therefore, special attention should be paid to the occurrence of DEACMP in ACMP patients with long duration of poisoning and high degree of coma.

Many serum biochemical markers which may be able to determine the degree of DEACMP have been studies, which include Lac (22), CK, CK-MB (20,31), and LDH (18). Lac is a product of anaerobic glycolysis under low oxygen supply that can act as an indicator for early CO poisoning (7).出会い

<table>
<thead>
<tr>
<th>Items</th>
<th>β</th>
<th>SE</th>
<th>Wald</th>
<th>P value</th>
<th>Exp (β)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coma degree</td>
<td>-0.096</td>
<td>0.057</td>
<td>0.624</td>
<td>0.008</td>
<td>0.872</td>
</tr>
<tr>
<td>Duration of poisoning</td>
<td>0.014</td>
<td>0.008</td>
<td>5.624</td>
<td>0.019</td>
<td>1.048</td>
</tr>
<tr>
<td>Lac</td>
<td>-0.412</td>
<td>0.204</td>
<td>3.683</td>
<td>0.056</td>
<td>0.672</td>
</tr>
<tr>
<td>NSE</td>
<td>-0.654</td>
<td>0.326</td>
<td>5.118</td>
<td>0.027</td>
<td>0.514</td>
</tr>
<tr>
<td>CK</td>
<td>0.064</td>
<td>0.026</td>
<td>12.859</td>
<td>&lt; 0.001</td>
<td>1.099</td>
</tr>
<tr>
<td>CK-MB</td>
<td>0.285</td>
<td>0.231</td>
<td>1.695</td>
<td>0.181</td>
<td>1.302</td>
</tr>
<tr>
<td>CRP</td>
<td>-0.145</td>
<td>0.057</td>
<td>9.215</td>
<td>0.002</td>
<td>0.826</td>
</tr>
<tr>
<td>LDH</td>
<td>1.313</td>
<td>0.564</td>
<td>4.625</td>
<td>0.026</td>
<td>3.263</td>
</tr>
<tr>
<td>ADC value of Globus pallidum</td>
<td>0.354</td>
<td>0.386</td>
<td>0.849</td>
<td>0.361</td>
<td>1.462</td>
</tr>
</tbody>
</table>
for DEACMP. Our results illustrate that CK and LDH may be promising predictive factors of DEACMP.

MRI is an important diagnostic tool to identify ACMP patients who have developed chronic neurological symptoms (16). It can reveal neurological lesions resulting from DEACMP that are mainly located in the globus pallidus, subcortical white matter, and basal ganglia (40). The globus pallidus is a vulnerable structure in patients who had CO poisoning, including ACMP (6). Ischemic lesions in patients with ACMP are easily reflected in globus pallidus (24). Bleecker have reported that the globus pallidus was the most commonly affected area of the brain following CO poisoning (2). Hopkins et al. have observed bilateral lesions in the globus pallidus after CO exposure (13). ADC values measured by DWI is an effective indicator of brain dysfunction (17,37). Bang and Kim have reported the ADC values of the globus pallidus in DNS patients to be lower than that in non-DNS patients (1). Moon et al. have shown the ADC value of globus pallidus to be decreased in patients with ACMP (21). In this study, the ADC value of globus pallidus in the non-DEACMP group was significantly higher than that in the DEACMP group. This result is consistent with previous studies and indicates that the ADC value of globus pallidus can reflect the onset of DEACMP to some extent. However, logistic regression analysis showed that a decreased ADC value of the globus pallidus was not an independent risk factor for DEACMP, indicating that the predictive value of the ADC value of the globus pallidus for DEACMP is limited. Further studies on the predictive value of DW-MRI on DEACMP therefore need to be further investigated.

**CONCLUSION**

In conclusion, the serum levels of Lac, CK, CK-MB, LDH, CRP, and NSE in ACMP patients were positively related to DEACMP, while ADC value of the globus pallidus in ACMP patients was negatively related to DEACMP. Additionally, the duration of poisoning, coma degree, CK, LDH, NSE, and CRP were independent risk factors for DEACMP.

**REFERENCES**


