The Chinese Expert Consensus on Evaluation of Coma after Cardiopulmonary Resuscitation

Neurocritical Care Committee of the Chinese Society of Neurology (NCC/CSN)

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Introduction

The prognosis of patients who suffer from coma after cardiopulmonary resuscitation (CPR) may be poor (defined as cerebral performance categories scores from 3 to 5).[1,2] Thus, an accurate prediction of their neurological outcomes is an essential component of post-cardiac arrest evaluation, especially for decisions to limit or withdraw life-sustaining care. Since the 1960s, a series of domestic and foreign studies began to focus on the evaluation of coma patients after CPR, and considerable progress has been achieved in this field.

To more appropriately apply these research results to decision-making for clinicians and patients' family numbers, a Chinese expert consensus on the evaluation of coma after CPR has been written by the Neurocritical Care Committee of the Chinese Society of Neurology from four features: Clinical examination, electrophysiological examination, neurological biomarkers, and neuroimaging. To achieve our objective, the following three steps were followed. First, we searched and selected literature from the MEDLINE and the China National Knowledge Infrastructure (1988–2014) databases. Second, we rated the quality of the resulting evidence according to the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence.[3] Third, we graded the recommendations according to the Oxford Centre Levels of Evidence and expert discussion. For recommendations with insufficient evidence, the grade for the recommendation received a positive rating (Recommendation Level A) only after expert discussions reached a high degree of consensus. For Class I evidence with a high false positive rate (FPR), the grade for the recommendation received a negative rating (Recommendation Level B) only after expert discussions reached a high degree of consensus.

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Evaluations of Patients without Hypothermia Treatment

Clinical examinations

Evidence

The motor component of the Glasgow Coma Scale (GCS) score is useful and accurate for predicting the outcomes of comatose patients after CPR. A 2006 meta-analysis (10 studies, 1303 patients) showed that there were no false predictions of poor outcome for a GCS motor score ≤2 (i.e., extensor or absent motor responses) 72 h after CPR (FPR = 0, 95% confidence interval [*CI*]: 0.00–0.06)[4] (Evidence Class I). Moreover, the absence of brainstem reflexes was an important predictor of poor outcomes. A 2013 meta-analysis (13 studies, 1188 patients) showed that there were no false predictions of poor outcome for absent oculovestibular reflexes 24 h after CPR (FPR = 0, 95% *CI*: 0.00–0.35), absent corneal reflexes 48 h after CPR (FPR = 0, 95% *CI*: 0.00–0.22), and absent pupillary light reflexes 72 h after CPR (FPR = 0, 95% *CI*: 0.00–0.08)[5] (Evidence Class I). The predictive value for poor outcome of the presence of myoclonic status epilepticus,

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which was defined as spontaneous, repetitive, unrelenting, generalized multifocal myoclonus involving the face, limbs, and axial musculature in comatose patients,[4] was reaffirmed in a 2013 meta-analysis (6 studies, 764 patients), and at 24 h after CPR, the presence of myoclonic status epilepticus had an FPR of 0 (95% *CI*: 0.00–0.03)[5] (Evidence Class I).

Recommendations

For the prediction of poor prognosis in comatose patients, appropriate predictors for clinical examination include the presence of myoclonic status epilepticus 24 h after CPR, absent pupillary light reflexes 72 h after CPR, and a GCS motor ≤2 score 72 h after CPR (Recommendation Level A, Evidence Class I). These criteria can also be used as predictive indicators of poor prognosis in comatose patients such as absent oculovestibular reflexes 24 h after CPR and absent corneal reflexes 48 h after CPR (Recommendation Level B, Evidence Class I). Assessments for clinical examinations must be evaluated repeatedly when there is any doubt (Recommendation Level A, expert opinions).

Electroencephalography

Evidence

Three meta-analyses, which were published in 2006 (5 studies, 237 patients), 2010 (25 studies, 2395 patients), and 2013 (12 studies, 778 patients),[4-6] showed that there were no false predictions of poor outcomes for generalized suppression or burst suppression on electroencephalograph (EEG) within 72 h (FPR = 0, 95% *CI*: 0.00–0.24)[5] (Evidence Class I). At 24–48 h after CPR, the FPR was 0.02 for poor outcomes associated with generalized epileptiform activity or generalized periodic epileptiform complexes[7,8] (Evidence Class III). In addition, at 72 h after CPR, the FPR was 0.07 (95% *CI*: 0.01–0.24) for poor outcomes associated with the EEG status epilepticus[9] (Evidence Class II). At 24 h after CPR, the positive predictive value (PPV) was 100% (95% *CI*: 37–100) for poor outcomes associated with the alpha coma pattern[5,10] (Evidence Class I and II). However, a few retrospective cohort studies with small sample sizes have shown that the presence of an alpha coma pattern is not consistently associated with poor outcomes. Some patients with alpha coma on EEG have revealed long-term survival and eventually regained consciousness. Within 1–7 days after CPR, the FPR was 0.45 (95% *CI*: 0.17–0.77) for poor outcomes associated with the absence of EEG reactivity[11] (Evidence Class II). Moreover, within 1–7 days after CPR, the FPR was 0.27 for poor outcomes associated with the burst suppression ratio (BSR) of the quantitative electroencephalograph (QEEG) >0.239, which was superior to other quantitative parameters[12] (Evidence Class II).

Recommendations

The presence of generalized suppression or burst suppression on EEG, within 72 h after CPR, can be used to predict poor outcomes in comatose patients (Recommendation Level B, Evidence Class I). To predict poor prognosis in comatose patients, other predictors for EEG include the presence of an alpha coma pattern 24 h after CPR, EEG status epilepticus 72 h after CPR, the absence of EEG reactivity within 1–7 days after CPR, and an increased BSR within 1–7 days after CPR (Recommendation Level B, Evidence Class II). The presence of generalized epileptiform activity or generalized periodic epileptiform complexes 24–48 h after CPR may be predictors of poor outcomes in comatose patients (Recommendation Level B, Evidence Class III). Because the findings of EEG can be affected easily by drugs, greater attention should be focused on the identification of false positive reports (Recommendation Level A, expert opinions).

Evoked potential

Evidence

A 2010 meta-analysis (25 studies, 2395 patients) showed that the bilateral absence of the N20 component of the short-latency somatosensory evoked potential (SLSEP) with median nerve stimulation had a good predictive value for poor outcomes. The area under the receiver operating characteristic curve was 0.891 within the first 24 h after CPR, and it was 0.912 at 48–72 h after CPR[6] (Evidence Class I). However, the presence of the N20 response of SLSEP was not helpful for predicting good outcomes. Two studies indicated that approximately 40% of comatose patients with the bilateral presence of the N20 response failed to regain consciousness[13,14] (Evidence Class I and III). Research investigating middle-latency somatosensory evoked potential (MLSEP) revealed that predictive value of MLSEP for indicating favorable outcomes was better than that of SLSEP at 24 and 72 h after CPR. If only the short-latency component N20 had been evaluated, then the PPV of SLSEP for the prediction of recovery would have been 70%. Adding the assessment of the middle-latency and long-latency components, the PPV for the prognosis of recovery increased to 82%. When all of the SLSEP components are detectable, a good outcome can be predicted with 66% accuracy, and the presence of P45 and N60 (or N70) was consistently associated with the recovery of conscious awareness[15] (Evidence Class II). A prospective cohort study of event-related potential showed that within 1–56 days (the average time 8 days) after cardiac arrest, all patients with the presence of the mismatch negativity (MMN) ultimately awakened (100% specificity)[16] (Evidence Class II).

Recommendations

Within 24–72 h after CPR, the bilateral absence of the N20 component of SLSEP can be used to predict poor outcomes in comatose patients. However, the bilateral presence of the N20 response of the SLSEP does not guarantee a favorable outcome (Recommendation Level A, Evidence Class I). The bilateral presence of the N60 (or N70) component or the presence of the MMN 7 days after CPR can be used to predict the recovery of conscious awareness (Recommendation Level B, Evidence Class II).

Neurological biomarkers

Evidence

A 2013 meta-analysis (10 studies, 935 patients) showed that the highest threshold of neuron-specific enolase (NSE) or S-100B protein serum concentration associated with a 0%

FPR varied with timing. There were no false predictions of poor outcome for serum NSE, which correlated with neuron damage, at concentrations >33 μg/L 24 h after CPR (FPR = 0, 95% *CI*: 0.00–0.08), >65 μg/L 48 h after CPR (FPR = 0, 95% *CI*: 0.00–0.03), and >80 μg/L 72 h after CPR (FPR = 0, 95% *CI*: 0.00–0.03), or for serum S-100B protein, which correlated with glial cell damage, at concentrations >0.7 μg/L 72 h after CPR (FPR = 0, 95% *CI*: 0.00–0.08)[5] (Evidence Class I).

Recommendations

To predict a poor prognosis in comatose patients, increased serum levels of NSE (>33 μg/L at 24 h, >65 μg/L at 48 h, and >80 μg/L at 72 h, respectively) and increased serum level of S-100B protein (>0.7 μg/L at 72 h) are good prognostic indicators (Recommendation Level A, Evidence Class I).

Neuroimaging

Evidence

A 2013 meta-analysis (3 studies, 113 patients) showed that diffuse brain swelling on brain computed tomography (CT) scan, which was quantified as a reduction of the density ratio (measured in Hounsfield units) between the gray matter (GM) of the caudate and the white matter (WM) of the posterior internal capsule (GM/WM), predicted an almost invariably poor outcome. Within 72 h after CPR, the FPR was 0.05 (95% *CI*: 0.00–0.25) for poor outcomes associated with a GM/WM density ratio <1.22 on brain CT scan[5] (Evidence Class I). Moreover, a cohort study showed that the FPR was 0.00 (95% *CI*: 0.00–0.78)[5] for poor outcomes associated with the reduction of the apparent diffusion coefficient (ADC), which was below 650×10^{-6} mm^2/s at 49–108 h after CPR, in more than 10% of the total brain volume on diffusion-weighted magnetic resonance imaging (DWI)[17] (Evidence Class II).

Recommendations

Diffuse brain swelling on brain CT scan, a GM/WM density ratio <1.22 on basal ganglia within 72 h after CPR, can be used to predict poor outcomes in comatose patients (Recommendation Level B, Evidence Class I). A reduction of ADC (<650×10^{-6} mm^2/s) in more than 10% of the brain volume on brain DWI 2–5 days after CPR can also be used to predict poor outcomes in comatose patients (Recommendation Level B, Evidence Class II).

Evaluation of Patients With Hypothermia Treatment

Hypothermia is a helpful therapy for comatose patients after CPR, and it is defined as the induction of a low body core temperature that is monitored using, for example, an esophageal thermometer, bladder catheter or pulmonary artery catheter, etc. During this procedure, the body is cooled to 32–34°C.[1] Hypothermia therapy has been validated in reliable randomized controlled clinical trials, and mild therapeutic hypothermia has been associated with neuroprotection in comatose patients after cardiac arrest.[18] However, nervous system activities can be affected by hypothermia therapy, as well as by antishivering drugs, such as analgesics, sedatives, and muscle relaxants. Therefore, the prediction of neurological outcomes in patients undergoing hypothermia treatment requires further confirmation.

Evidence

Two meta-analyses, published in 2013 (10 studies, 1153 patients) and 2014 (10 studies, 1250 patients),[19,20] analyzed the predictive value of brainstem reflexes, motor responses, and myoclonus in patients undergoing hypothermia treatment after CPR. During or after rewarming from hypothermia, the FPR was 0.05 (95% *CI*: 0.03–0.09) and 0.02 (95% *CI*: 0.01–0.07), respectively, for poor outcomes associated with the presence of myoclonic status epilepticus. After rewarming from hypothermia, the FPR was 0.21 (95% *CI*: 0.08–0.43) and 0.04 (95% *CI*: 0.01–0.10), respectively, for poor outcomes associated with a GCS motor ≤2 (i.e., extensor or absent motor responses). After rewarming from hypothermia, the predictive value of absent pupillary light reflexes or absent corneal reflexes was not significantly different in patients with hypothermia compared with patients without hypothermia (Evidence Class I).

Two studies of the bispectral index (BIS) in QEEG revealed that the BIS value could help predicting poor neurological outcomes in patients undergoing hypothermia therapy after CPR. During or after rewarming from hypothermia, there were no false predictions of poor outcomes associated with the BIS values of 0[21,22] (Evidence Class II). A 2014 meta-analysis (11 studies, 552 patients) showed that the predictive value of generalized suppression, burst suppression, or status epilepticus on EEG, or the absence of EEG reactivity, after rewarming from hypothermia, showed no significant changes in patients with hypothermia when compared with patients without hypothermia[20] (Evidence Class I).

In a 2013 meta-analysis (12 studies, 1058 patients), during or after rewarming from hypothermia, the FPR was 0 (95% *CI*: 0.00–0.02, 95% *CI*: 0.00–0.04, respectively) for poor outcomes associated with the bilateral absence of the N20 response of SLSEP[23] (Evidence Class I).

A 2013 meta-analysis (12 studies, 976 patients) showed that the highest threshold of the NSE or S-100B protein serum concentration associated with a poor prognosis changed in response to hypothermia therapy. There were no false predictions of poor outcomes for serum NSE ≥52.4 μg/L 24 h (during hypothermia) after CPR (FPR = 0, 95% *CI*: 0.00–0.14), serum NSE ≥ 81.8 μg/L 48 h (after rewarming from hypothermia) after CPR (FPR = 0, 95% *CI*: 0.00–0.02), serum NSE ≥78.9 μg/L 72 h (after rewarming from hypothermia) after CPR (FPR = 0, 95% *CI*: 0.00–0.06), serum S-100B protein ≥ 0.18–0.21 μg/L 24 h (during hypothermia) after CPR (FPR = 0, 95% *CI*: 0.00–0.07), or serum S-100B protein ≥0.3 μg/L 48 h (after rewarming from hypothermia) after CPR (FPR = 0, 95% *CI*: 0.00–0.07)[23] (Evidence Class I).

Recommendations

During hypothermia (32–34°C), predictors of poor

prognosis in comatose patients with hypothermia treatment include the bilateral absence of the N20 response of SLSEP (Recommendation Level A, Evidence Class I), the highest threshold of the NSE (24 h ≥52.4 μg/L) or S-100B (24 h ≥0.18–0.21 μg/L) protein serum concentration (Recommendation Level A, Evidence Class I), and a BIS value of 0 in QEEG (Recommendation Level B, Evidence Class II).

After rewarming from hypothermia only, predictors of poor prognosis in comatose patients with hypothermia treatment include the clinical examination (absent pupillary light reflexes, absent corneal reflexes, or presence of myoclonic status epilepticus), EEG (generalized suppression, burst suppression, status epilepticus on EEG, or the absence of EEG reactivity), and neurological biomarkers (48 h NSE ≥81.8 μg/L, 72 h NSE ≥78.9 μg/L, or 48 h S-100B ≥0.3 μg/L) (Recommendation Level A, Evidence Class I). In addition, a GCS motor score ≤2, only after rewarming from hypothermia, could be used to predict poor outcomes in comatose patients with hypothermia therapy (Recommendation Level B, Evidence Class I).

However, after rewarming from hypothermia, a GCS motor score ≤2 and the presence of myoclonic status epilepticus were not associated with invariably poor outcomes (without a 0% FPR). More attention should be focused on identifying the false positive results (Recommendation Level A, Evidence Class I).

In conclusion, coma is a very common occurrence in patients subsequent to CPR. Because early prognostication of neurological outcomes becomes an essential element in post-cardiac arrest evaluations, medical decision-making must be accurate and easy to follow. At present, all of the tools used to predict outcomes still have limitations. With the development and improvement of additional and more refined techniques and methods, these tools will afford higher sensitivity and specificity, and the resulting predictive information will provide more reliable evidence for medical decision-making and tailoring of the treatment program.

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Conflicts of interest

There are no conflicts of interest.

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