The First national survey on Practices of Neurological Prognostication after Cardiac Arrest in China, still a lot to do

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Abstract

Aims: To investigate current practices and problems of neurological prognostication in comatose cardiac arrest (CA) patients. Methods: An anonymous questionnaire was distributed to 1600 emergency physicians in 75 hospitals which were selected randomly from China between January and July 2018. Results: 92.1% respondents fulfilled the survey. The details of the neurological prognosis were not well understood. The predictive value of brain stem reflex, motor response and myoclonus was confirmed by 63.5%, 44.6% and 31.7% respondents respectively. Only 30.7% knew that GWR value <1.1 indicated poor prognosis and only 8.1% know the most commonly used SSEP N20. Epileptiform, burst suppression, and isoelectric was considered to predict poor outcome by 35.0%, 27.4% and 45.7% respondents. 46.7% knew NSE, and only 24.7% knew S-100β. Only a few respondents knew that neurological prognostication should be performed later than 72h from CA either in TTM or non-TTM patients. In practice, the most commonly used method was clinical examination (85.4%). 67.9% had used brain CT for prognosis, and 18.4% for MRI. NSE (39.6%) was a little more widely used than S-100β (18.0%). However, SSEP (4.4%) and EEG (11.4%) were occasionally performed. The survey may have been subject to bias ascertainment as only university affiliated hospitals and university teaching hospitals were selected, making it likely that the degree of neuroprognostication awareness and practice reflected in our survey is an optimistic perspective. Conclusions: Neurological prognostication in CA survivors had not been well understood and performed by emergency physicians in China. They were more likely to use clinical examination rather than objective tools, especially SSEP and EEG, which also illustrated that multimodal approach was not well performed in practice.

What's known?

The neurological prognostication has become a very important part of post-CA care. Early and accurate prediction of neurological outcome should allow optimizing identification of those individuals with no chance

of recovery and avoid making inappropriate decisions to withdrawal of life support in patients who had the potential for recovery. The practice of neurological prognostication in CA patients had never been assessed before.

What's new?

Neurological prognostication in CA survivors had not been well understood and performed by emergency physicians who were more likely to take care of such patients in China. A certain percentage of respondents did not know what methods should be used to predict outcome. In practice, they were more likely to use clinical examination rather than objective tools, especially SSEP and EEG.

Main text

IntroductionCardiac arrest (CA) is a major healthy concern worldwide.[1] Most patients who survive to hospital after return of spontaneous circulation (ROSC) are still comatose in the first few days or weeks.[2] Therefore, neurological prognostication has become a very important part of post-CA care. Early and accurate prediction of neurological outcome should allow optimizing identification of those individuals with no chance of a good recovery and avoid making inappropriate decisions to withdrawal of life support in patients who had the potential for recovery which is a frequent cause of death in the ICU.[3,4]

It remains challenging to differentiate patients who may recover from those who cannot, despite the emerging of numerous ancillary tests. The prognostic tools that are commonly used in practice include clinical examination, electrophysiological measurements, biomarkers and neuroimaging.[5,6] There is no single test to reliably predict outcome. A multimodal diagnostic algorithm was currently recommended to minimize prognostic uncertainty. [5,6]The best time point for initiating the process of neurological evaluation was unknown. Current guidelines recommend it should not be performed before 72h from ROSC, especially in the ear of target temperature management (TTM).[6] Both TTM itself and sedatives or muscle relaxant agents used to maintain it may weaken predictive value of prognostic indexes. So prolonging examination was suggested in cooling patients, ensuring the clearance of confounders.

For providing guidance for future work, it would be very important to understand the current problems of neurological prognostication for CA survivors in China. However, to our best knowledge, no study has to date evaluated this situation. The national survey was therefore conducted to give an overview of current awareness and practice of post CA neurological evaluation in China focusing on large university affiliated hospitals or university teaching hospitals which are key opinion leaders in this field.

Methods

Geographical background

China is divided into 6 administrative regions according to geographical distribution, including east region, north region, east and north region, west and south region, central south region, west and north region. Those regions differ in medical development.

Study design

This was a cross-sectional multicenter study. Hospitals were selected by random sampling in 6 administrative regions separately. In China, Hospitals are classified by the National Health and Family Planning Commission of the People's Republic of China as follows: Level III hospitals refer to medical centers or tertiary hospitals that have independent emergency departments (EDs) and are also teaching hospitals; Level II hospitals are regional hospitals which have independent EDs but are not teaching hospitals; and Level I hospitals, also called community hospitals, do not have EDs. Only level III hospitals were selected in an attempt to target providers likely to care for CA patients. First of all we screened all level III hospitals in one administrative region. The hospitals were coded randomly by SPSS and then were arranged in ascending order in each administrative region. Top 20% hospitals were enrolled in the study. The alternative hospitals were considered if the hospital was inaccessible or refused to participate (in ascending order). Finally 75 hospitals were included. The distribution of hospitals was shown in figure 1. Then we conducted a

questionnaire survey for all emergency physicians of selected hospitals. Informed consent was obtained from all participants.

The questionnaire was developed by a senior emergency physician and discussed 3 times by an expert team which consists of emergency specialists experienced in the management of resuscitated patients, neurologists, and epidemiologist, working on rephrasing and improvement. Briefly, the questionnaire includes three parts: (1) Background data of the respondent; (2) The awareness of neurological prognosis (3) The practice of neurological evaluation. The questionnaires were distributed to the respondents from January to March 2018. Data collection ended in July 2018. The study protocol was approved by Peking university third hospital.

Statistical methods

The data were analyzed by SPSS 20.0. Quantitative variables were expressed as mean (standard deviation) when following a Gaussian distribution or median (interquartile range 25 75%) otherwise. Qualitative variables were expressed as frequencies. Data was tested for normality using the Shapiro-Wilk Normality Test.

Results

A total of 1473 replies (92.1%) were analyzed. General characteristics of respondents and their emergency departments are described in table 1. The admissions for CA patients between 11-30 cases per year were reported by 38.4% respondents. But less than 5% CA survivors with good neurological outcome at discharge was reported by 40.3% respondents.

The awareness of neurological prognostication in comatose CA patients

97.8% reported awareness of one or more prognostic tools. As shown in table 2, the details of neurological prognostication were not well understood. Brain stem reflex, motor response and myoclonus were considered to be related with prognosis by 63.5%, 44.6% and 31.7% respondents respectively. Only 30.7% knew that GWR value <1.1 indicated a poor prognosis and only 8.1% know the most commonly used SSEP N20. Epileptiform, burst suppression, low voltage and isoelectric was considered to predict poor neurological outcome by 35.0%, 27.4%, 33.3% and 45.7% respondents respectively. 46.7% confirmed the prognostic value of NSE, and only 24.7% for S-100β.

The optimal timing of neurological prognostication considered by respondents was shown in figure 2 and figure 3. Nearly 1/4 did not know the best time point of prognostic tools. As indicated in figure 2, 26.1% respondents considered the best time of clinical evaluation was within 24h from ROSC, 28.8% between 24h-72h and 19% later than 72h for non TTM-patients. The corresponding number for TTM-patients was 13.5%, 31.1% and 28.2% respectively. As shown in figure 3, that the optimal time of EEG, SSEP and NSE for neuroprognosticaion was later than 72h after ROSC was reported by only 27.6%, 16.2% and 10.5% respondents respectively.

The practice of neurological prognostication in comatose CA patients

As shown in table 3, a formalized prognostic protocol is only available in 6.8% respondents. Compared with clinical examination (85.4%), neuroimaging (65.6%) and biomarkers (30.1%), electrophysiological measurement (21.9%) is less used. Among stem reflexes, pupillary reflex (91.9%) and corneal reflex (68.1%) was used by most respondents. 67.9% respondents had used brain CT for predicting outcome, but 18.4% for MRI. Among biomarkers, NSE was a little more widely used than S-100β. However, only 4.4% respondents had performed SSEP and 11.4% had performed EEG for prognostication in CA patients.

Disscussion

This survey serves as the first nation-wide analysis of neurological prognostication in survivors after CA in China and can serve as a baseline for future work. The main finding is that post CA neurological assessment has not been well understood and performed by emergency physicians who are more likely to take care

of such patients in China. In practice, they were more likely to use clinical evaluation rather than other objective prognostic tools.

Clinical examination is the most commonly used method to predict outcome after CA in our study. However, the details were not well understood. Assessment of brainstem reflexes, motor responses to pain, and myoclonus represent the standard test in clinical examination.[5,6] But in our survey, only 50% recognized that brainstem reflexes and motor responses to pain correlated with outcome. Corneal reflex was significantly less performed than pupillary reflex despite of its easy use. 62.7% confirmed the progGnostic value of myoclonus. In fact, myoclonus is variably associated with outcome. Myoclonic jerk is not consistently associated with poor outcome and status myoclonus starting within 48h from ROSC is highly predictive of poor outcome.[7,8] This was partly explained by the lack of developed post-CA care centers in China. Moreover, the lack of special training in neurological prognostication, together with limited attendance of emergency physicians contributed to the insufficient understanding of clinical evaluation.

Guidelines suggest EEG for prognostication after CA. Certain EEG patterns such as electrocerebral silence, burst suppression, absence of reactivity and status epilepticus, was associated with a high rate of poor outcome, though not uniformly.[9-11] The other patterns (including low-voltage, seizures alone and discontinuous background) were less reliable because of limited evidence.[12] But epileptiform, burst suppression, isoelectric was considered to predict poor outcome by only 35.0%, 27.4%, 33.3% respondents respectively in our survey. Only 11.4% had performed EEG in routine practice in this study. However, recent surveys showed that EEG was widely used.[13,14] Friberg et al reported that 74% of members from European Society of Emergency Medicine had used intermittent EEG or continuous EEG for CA patients in practice.[14] The low level utility of EEG in China is likely due to several causes. One primary reason is lack of national recommendations and formalized SOP for neurological prognosis in CA patients which can improve the practice and makes the assessment less physician and/or hospital-dependent. However, national recommendation was not available until 2018 one year after our study.[15] A written SOP is only available in 6.8% respondents in present study, which is far behind that of European countries. [3] In addition, there also exist barriers to access EEG services in timely manner even at developed university-affiliated hospitals in China.

Among evoked potentials, somatosensory evoked potentials (SSEP) are best studied after CA. Bilateral absence of SSEP N20 response is strongly associated with poor outcomes.[5,6] Surprisingly, the present study showed that only 7.3% respondents knew the predictive value of SSEP N20 and only 4.4% had performed SSEP for CA patients in practice. There was still a huge gap with that in European countries. It was reported that more than half of respondents or ICUs had used SSEP in post CA patients.[3,14] In addition to the lack of national guidelines and local protocols, the need for special skill and experience is one of the main reasons why SSEP is less used.

Despite the evidences of neuroimaging for prognostication were limited and its use only in combination with other predictors was recommended in guidelines, our survey showed that next to clinical examination, brain CT was the most widely used methods to predict outcome after CA which is in line with previous studies.[14-16] This was likely related to the extensive use of brain CT to exclude brain hemorrhage or infarction after CA and to the fact that this technique is easily available. When it comes to details, however, only 30% of respondents know that a marked reduction of the grey matter/white matter ratio was associated with poor outcome.[17,18] MRI has a high sensitivity for identifying ischemic brain injury and was considered to be an even more accurate tool for prognostication, however, its use can be problematic in the most clinically unstable patients.[19] This partly explained the finding that the use of brain MRI for predicting outcome was reported by only 18.8% respondents in our survey.

Biomarkers were more commonly used than EEG and SSEP in present study, mainly because of their simplicity, independence from sedation and low cost. Although a wide range of proteins have been identified as indicators of brain injury, only NSE and S-100β have been extensively studied.[20,21] S-100β is less well documented than NSE. However, there is a great variability in thresholds due to heterogeneity. The cut off levels varied in different studies and at different time point.[20-22] Furthermore, the threshold of NSE in TTM-patients might be higher than in those without cooling as hypothermia may significantly reduce NSE

levels.[23] So no optimal threshold of NSE or S-100βwas established to predict poor neurological outcome with a false positive rate of 0%.

No single test can accurately predict the prognosis of patients following CA. A multimodal approach combining clinical examination, EEG, biomarkers and brain imaging was recommended to increase the certainty of prognostication. Combining any of two or more tools improved prognostic performance compared to either each individual method.[24,25] Ji Hoon Kim and his college reported a stepwise model combining brain CT and MRI, NSE, EEG, SSEPs and pupil light reflex predicted poor outcomes with a 0% false positive rate.[25] But in our study, the low utility of EEG, SSEP and biomarkers illustrated that multimodal approach was not well performed in practice.

The optimal time of neurological evaluation is under discussion. The current advisory suggests that multimodal modalities should not be performed before 72h from ROSC, especially in the ear of TTM.[6,26] Previous studies had shown that TTM and the related pharmacological sedation may influence the neurological examination and also modify the predictive value of NSE or the accuracy of SSEPs.[27] So prolonging clinical observation after rewarming, usually beyond 72h from ROSC, may be suggested when interference from residual effects of drugs is suspected.[28] But our survey reported only a few respondents knew that neurological prognostication should be performed later than 72h from CA either in TTM or non-TTM patients. This misunderstanding may cause premature decisions to withdrawal of life support in practice.

Limitations

Several limitations of this study should be noted. First, it is very difficult to conduct a rigorous randomized observational survey. There is unavoidable selection bias in this study. Second, the survey may have been subject to bias ascertainment as only university affiliated hospitals and university teaching hospitals were selected, making it likely that the degree of neuroprognostication awareness and practice reflected in our survey is an optimistic perspective. The true proportion may be lower than that reported in this study.

Conclusions

Neurological prognostication in comatose survivors after CA had not been well understood and performed by emergency physicians in China. They were more likely to use clinical examination rather than objective prognostic tools, including EEG, SSEP, neuroimaging and biomarkers. This also illustrated that multimodal approach was not well performed in practice. Only a few respondents knew that neurological prognostication should be performed later than 72h from CA either in TTM or non-TTM patients. This misunderstanding may cause premature decisions to withdrawal of life support in practice.

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Author contribution

All authors have made substantial contributions to the work. Lanfang Du, Kang Zheng, Lu Feng, Qingbian Ma and Guoqiang Zhang have made contributions to the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article and final approval of the version. The other authors have made important contributions to the conception and design of the study and acquisition of data.

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Figure legendsFig.1 Geographic distribution of surveyed hospitalsFig.2 The best time of clinical evaluation for neurological prognosis considered by respondentsTTM: target temperature management; ROSC: return of spontaneous circulation**Fig.3 The best time of EEG, SSEP and NSE for neurological prognosis considered by respondents**EEG: electroencephalogram; SSEP: Somatosensory evoked potential; NSE: neuro-specific enolase

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