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ORIGINAL ARTICLE

Pathophysiological factors of delirium among critically ill elders after non-cardiac surgery based on artificial neural networks: a pilot study

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ABSTRACT

Objectives: To utilize artificial neural networks (ANN) for early identification of pathophysiological risk factors of delirium among elders in surgical intensive care unit (SICU) after non-cardiac surgery.

Methodology: This prospective, single-center observational study was conducted at an SICU with 19 beds. Patients aged 65 and over were included. Delirium was screened by the Richmond Agitation-Sedation Scale and Confusion Assessment Method for the ICU. Factors analyzed were age, gender, disease, symptoms, sedatives and analgesics used, and biochemical parameters. Mean impact value (MIV) of each variable was calculated by MATLAB. Then, ANN was established based on the SPSS 20.0.

Results: Data from 134 patients were analyzed. The mean age was 77.045 ± 7.375 years (65-94), 50.7% were male and 11.94% had delirium. There were 13 important risk factors based on MIV, which were included to build ANN. The important pathophysiological risk factors were age, the use of sedatives, dose of propofol, dose of remifentanil, acidosis, fever, hyponatremia, hyperkalemia, albumin level, pre-albumin level and Child-Pugh score, and anemia. The area under ROC curve was 0.893.

Conclusion: Application and significance of artificial neural networks mainly lies on mean impact value, which can be used as a relative stable reference for early screening of pathophysiological risk factors of delirium among critically ill elders.

Key word: Artificial Neural Networks; Critically ill; Elders; Delirium; Surgical intensive care unit; Risk factors

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INTRODUCTION

Delirium is an acute organic brain dysfunction with fluctuating course of attention and cognition.[1] It is an unpleasant experience for all involved, including patients, caregivers, and nursing staff.[2] Patients describe their delirium experience as frightening, life-threatening, fearful, panic, or unsafe. Patients' relatives are distressed by delirium and nurses report a higher burden when caring for delirious patients.[3] The incidences of delirium in the surgical intensive care units (SICU) vary from 2.48 to 79 %,[4,5] depending on the types of surgical procedures, patient settings, and screening tools for diagnosis of delirium. Although delirium can be experienced in all age groups, it has an increased frequency in elders.[6] As reported that prevalence of delirium among older intensive care unit (ICU) patients ranges from 78% to 87%.[5] Generally, delirium is a serious problem because of its negative clinical outcomes, such as prolonged intensive care unit (ICU) stay and hospitalization, decreased cognitive functioning, higher mortality rate, and increased odds of re-admission.[7,8] Data from previous researches indicated that the median ICU, postoperative hospital, and hospital length of

stay were approximately 2.5, 2, and 4 days longer for patients with delirium respectively.[7] The duration of delirium in the ICU predicts long-term cognitive impairment, physical disability and death up to a year after discharge.[9] Once delirium develops in patients, pharmacotherapy options are limited.[10]

For all that, diagnosis of delirium is not sufficiently made. Delirium is not noticed in 64–84% and not diagnosed in 33–66% [11,12] for it is "expected" to happen in patients with severe illness, and medical resources are dedicated to those who are more immediate "life-threatening" patients preferentially. Besides, clinicians generally give less attention to acute brain syndrome as a predictor of poorer overall outcome than acute dysfunction of other organ systems and regard delirium as transitory with no long-term adverse effect.[13] A delay in delirium therapy is associated with higher mortality.[14] Fortunately, delirium can be prevented. Evaluation of patients at risk may lead to better recognition, earlier intervention and decreasing delirium prevalence. Possible risk factors include medication, acute illness, environmental and patient characteristics, and underlying chronic pathology.[15] However, some of these factors are not modifiable, and some are unavailable for assessment for ICU patients. Data of pathophysiological factors are convenient to acquired, especially at the first 24 hours in the ICU settings, so that clinicians and nurses are allowed to pay key attention and deliver adequate care to patients at risk at an early stage.

With regard to risk factors identification, bivariate logistic regression was most widely used before. Recently, artificial neural networks (ANN) has been viewed as a robust technique with higher accuracy than logistic regression analyses.[16,17] The architecture for ANN employed a systematic method where the number of neurons is changed incrementally.[16] It has no limitation on the form of relationship between response and predictor variables. Also, ANN finds the form of relationship which is not necessarily linear. Furthermore, the data are implicitly analyzed in ANN, so it has a high probability of finding the correct solution even if a part of the network layers is deleted or works incorrectly.[18] This study was aimed to utilize ANN for early identification of pathophysiological risk factors of delirium in critically ill elders in SICU after non-cardiac surgery.

METHODOLOGY

This was a prospective single-center observational study in a 19-bed surgical ICU of our Hospital from March 2016 to April 2017. The study was approved by hospital ethical committee (No. 2014[012]). Informed consent was obtained as patient privacy rights must always be observed.

Inclusion criteria were patients aged 65 years or more who stayed in surgical ICU for at least 24 hours. Following patients were excluded: (1) with cognitive impairment before operation, (2) with history of delirium, (3) with visual and (or) hearing impairment , (4) taking antipsychotic drugs in recent six months, (5) received cerebral operations, (6) operation time less than one hour, (7) ICU stay less than 24 hours, (8) refused to participated in the study.

Delirium assessment:

Delirium was screened by ten-point rating scale for assessing sedation status based on the Richmond Agitation-Sedation Scale (RASS) and Confusion Assessment Method for the ICU (CAM-ICU) criteria. Trained nurses applied the CAM for delirium evaluation during three shifts a day at 0600, 1400, 2200 hours during the SICU stay. The training program for nurses consisted of three parts, namely information about delirium, one-to-one instruction and evaluations at the patients' bedside completed by a delirium expert compared with the evaluations completed by the nurses.

Factors analyzed:

Factors analyzed were age, gender, disease (stroke, diabetes, hypertension, coronary heart disease, arrhythmia, hyperlipidemia, asthma and COPD), symptoms (fever, hypertension and hypotension), sedatives and analgesics (propofol, midazolam, dexmedetomidine, fentanyl and remifentanil) and biochemical parameters (white blood cell (WBC), red blood cell (RBC), hemoglobin (Hb), Hematocrit (Hct), platelet count (PLT), total protein (TP), albumin (Alb), pre-albumin (PA), alanine aminotransferase (ALT), aspartate transaminase (AST), total bilirubin (TBIL), direct bilirubin (DBIL), creatinine (Cr), blood urea nitrogen (BUN), blood sodium (Na^+), blood potassium (K^+), blood calcium (Ca^{++}), alkalinity (pH), arterial blood gas-carbon dioxide partial pressure ($PaCO_2$), oxygen partial pressure (PaO_2), and blood lactate (Lac)) during first 24-hour stay in ICU . We did not include morphine and pethidine because they are not used at our center. Child-Pugh score was calculated. Data of these factors were observed once during the first 24 h in the ICU setting.

Statistical analysis:

Statistical analyses were performed by MATLAB software and SPSS 20.0. Mean impact value (MIV) of each variable was calculated by MATLAB. First, the MIV was used to calculate the influence of factors to the dependent variable, for positive or negative impact. The second step was ANN establishment based on the SPSS 20.0 software. Furthermore, a 70% sample for the learning and a 30% sample for the test

and prediction of the topology of the final network were used. Finally, the area under ROC curve (AUC) was used to interpret predictive accuracy.

RESULTS

From the 174 patients screened during the study period, 134 were eligible and were analyzed (Figure 1). The mean age of participants was 77.045 ± 7.375 years (65-94), 50.7% were male and 16 (11.940%) had delirium during their ICU stay. The sequence of the factors according to their absolute MIVs was sorted.

There were 13 important risk factors, whose absolute value of MIV was greater than 0.05, were included to build ANN (Table I). The SPSS Neural Network software automatically re-scales the negative pseudo-probabilities (less than 0) and pseudo-probability more than 1 irrespective of the value of the dependent variable in this case. According to the absolute value of MIV, the rank of the 13 factors was as follows: alkalinity (pH), body temperature, blood sodium (Na^+), albumin (Alb), Child-Pugh score, use of sedatives, arterial carbon dioxide partial pressure ($PaCO_2$), hemoglobin (Hb), remifentanil, propofol, age, pre-albumin (PA), and blood potassium (K^+).

There were 93 cases originally assigned to the training sample, and 41 to the testing sample. According to data from the classification table (Table 2), the correct percentage was 93.5% in the learning set, and 75.6% in the testing set.

Table 1: Rank of 13 important pathophysiological risk factors based on MIV

Factors X / n		Delirium		Non-Delirium		MIV
		SD / (%)	X / n	SD / (%)		
pH	7.35	3	18.750	18	15.254	5.834
	≥7.35	13	81.250	100	84.746	
Body Temperature		36.625	0.949	36.181	0.986	-0.335
Na^+ (mmol/L)		141.000	3.596	140.305	4.359	-0.283
Alb (g/L)		27.187	6.299	30.362	4.678	0.142
Child-Pugh Score		6.438	0.629	6.305	0.965	0.120
Sedatives	Yes	14	87.500%	98	83.051%	0.118
	No	2	12.500%	20	16.949%	
$PaCO_2$ (mmHg)		38.750	10.260	40.851	7.027	0.109
Hb (g/L)		99.313	19.815	105.779	20.012	0.107
Remifentanil (mg)		0.544	0.731	0.437	0.875	-0.088
Propofol (g)		0.440	0.899	0.218	0.321	0.071
Age		82.375	7.108	76.322	7.137	0.071
PA (g/L)		95.750	50.316	131.183	57.088	-0.070
K^+ (mmol/L)		3.888	0.503	3.800	0.506	0.067

Note: MIV= mean impact value, ANN= artificial neural net work, SD= standard deviation

Table 2: Classification table of training and testing cases

Sample	Observed	Predicted		Percent Correct
		0	1	
Training	0	76	5	93.8%
	1	1	11	91.7%
	Overall Percent	82.8%	17.2%	93.5%
Testing	0	29	8	78.4%
	1	2	2	50%
	Overall Percent	75.6%	24.4%	75.6%

The network performance was in a good pattern when the network contained 13 risk factors. The ROC curve (Figure 2) described the sensitivity and specificity for all possible cutoffs in a single plot. The chart shown here displayed two curves, one for the category "Delirium" and one for the category "Non-Delirium". The curves were sharply upward to the upper left corner of the chart and followed with a stability to the upper right corner. The area under ROC curve (AUC) was 0.893, which was used to interpret predictive accuracy.

DISCUSSION

The CAM-ICU adapted from the CAM, is an excellent bedside tool[19] for non-psychiatrists to evaluate patients in the ICU setting for delirium even if mechanically ventilated (MV), who is frequently under-diagnosed if monitoring instruments are not used.[20] The CAM-ICU evaluates: (1) acute onset and fluctuating course; (2) inattention; (3) disorganized thinking; and (4) altered level of consciousness. Delirium is considered in presence of 1 and 2 and additional either 3 or 4.[21,22] Factors included in this study were based on literatures review, including cohort studies,[6,23-34] systematic reviews,[35,36] and meta-analysis.

In this study, the rate of delirium among elderly aged 65 years and above admitted in ICU after non-

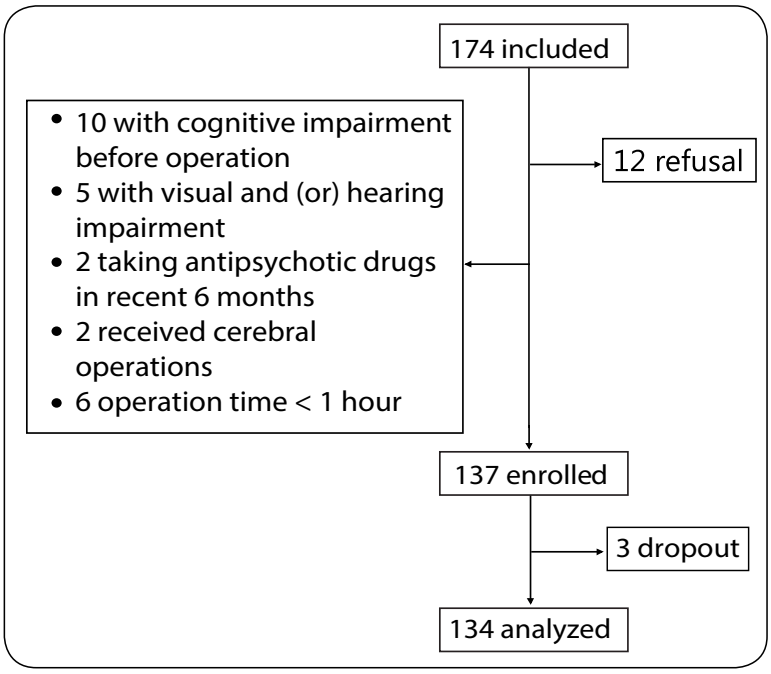

Figure 1: Flow diagram

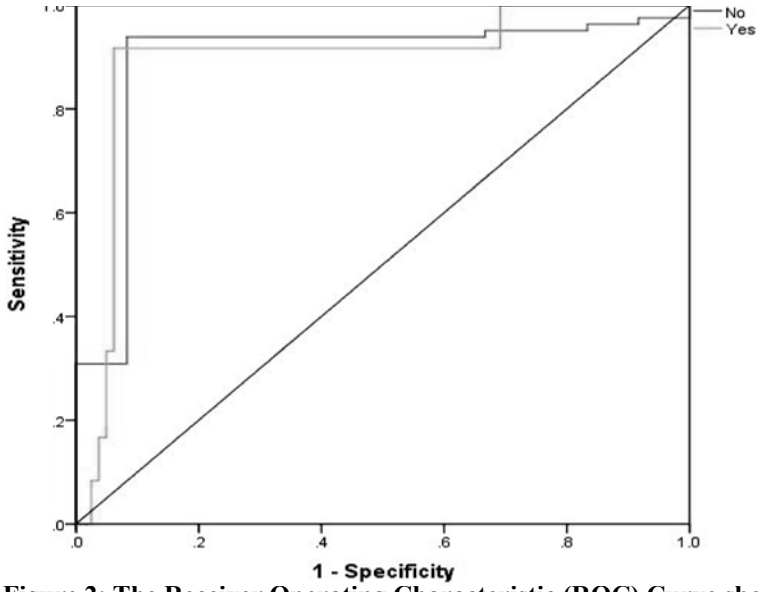

Figure 2: The Receiver Operating Characteristic (ROC) Curve shows good network performance 13 risk factors for delirium in critically ill elders in surgical ICU after non-cardiac surgery

cardiac surgery was 11.94%, similar with Ranhoff *et al*[23] report of delirium in 13.73% among elders (aged 60 and over) during their stay in the SICU.

Delirium is a temporary mental disorder that is characterized by abnormal arousal, language and cognition, perception, orientation, mood, sleeping patterns, and neurologic functioning in the context of a medical etiology.[7] The incidences of delirium reported in previous studies various according to the research population, types of settings, and evaluation tools for diagnosis. The prevalence rate was 100% among 107 survivors treated with therapeutic hypothermia after cardiac arrest.[37] Similarly, patients suffering from open heart surgery,[38] liver transplantation,[39] esophageal cancer,[40] major trauma,[26] or burn[20] in ICU settings are also reported to have a high incidence of delirium, 41.7%, 47.4%, 50%, 59% and 77% respectively.

Numerous studies have found ICU delirium to be associated with many negative outcomes such as: increased time on the mechanical ventilation, longer ICU and hospital lengths of stay, increased costs, higher mortality –both in-hospital and after discharge, and greater long-term cognitive dysfunction.[4,41,42] Recognition of risk factors, therefore, is a key component for the prevention and early identification of delirium.

The ANN is a nonlinear dynamic system, an information-deal-with system invoked by biology neural network for its structure, function and some basic characters, but being abstracted and simplified. It has distributed storage form and parallel disposing form of information.[43] The ANN with self-study ability did not require the distribution form and independence of variables and also could handle the problem of collinearity better.[18] The MIV was an important index of calculating influence of factors to the dependent variable, whose absolute data in rank can be used to select factors before ANN analysis.[44]

In this study, we preliminarily screened pathophysiological factors, using MIV and examined reliability of results through ANN analysis. According to the absolute values of MIV, we could determine the ranking of importance of each factor and provide the basis for further analysis. Results of this study indicated that pathophysiological factors of delirium among elders after non-cardiac surgery in the SICU contains: age, use of sedatives, dose of remifentanil, dose of propofol,

body temperature, alkalinity (pH), arterial carbon dioxide partial pressure ($PaCO_2$), albumin (Alb), pre-albumin (PA), Child-Pugh score, hemoglobin (Hb), blood sodium (Na^+), and blood potassium (K^+). Factors above could be collected at the first 24 hours in the ICU setting.

Increased age has been universally identified as a risk factor of delirium,[28] especially for those who are admitted for surgery.[45] Delirium in elderly (> 65 years) patients was associated with an increased risk of death.[46] Increasing age is a universally identified risk factor of delirium, suggesting that the naturally aged brain might be the basis of the occurrence of delirium.[47] Sedatives and analgesics factors contributing to delirium are controversial in previous studies. In this study, the use of sedatives and higher dose of propofol both had impact on delirium. But midazolam or dexmedetomidine did not. Since excessive sedation can prolong length of stay, it may lead to increased risk of delirium. However, some but not all clinical studies demonstrated that propofol led to delirium.[48] Midazolam, as one of benzodiazepines, is an independent predictor of transitioning to delirium ($p < 0.01$),[26] and even associated with longer duration of delirium.[5] But, Zaal *et al*[49] confirmed that benzodiazepines increases the risk for delirium in critically ill adults seems to be limited to continuous infusion only. Similarly, dexmedetomidine may indirectly decrease the incidence of delirium as reported in some researches. However, its direct effect on the prevention of delirium remains theoretical and unproven.[50]

With regard to association between analgesics and delirium, result of this study demonstrated that higher dose of remifentanil was considered as a protective factor of delirium. In a prospective randomized controlled trial from China reports that, patients receiving midazolam had lower incidence ($p < 0.01$) and shorter duration of delirium ($p < 0.001$). The reported no impact of fentanyl to delirium. But, Pandharipande et al reported that fentanyl was a risk factor for delirium in the SICU ($p < 0.01$) but not in the TICU ($p > 0.05$).[26] Therefore, future prospective study is needed to investigate the use of sedatives and (or) analgesics and occurrence of delirium.

Acidosis was viewed as an important risk factor leading to delirium, which was matched with data from several studies before.[6,30,51] There's still no consensus on types of acidosis, metabolic, respiratory, or both leads to delirium. Fever was always deemed as a sign of infections which leads to mental changes because of cytokines and/or bacterial toxins and cerebral metabolic changes.[6] However, WBC as a laboratory index of infection had little impact on delirium in this study. As a result, fever associated with delirium may result from other reasons except from infections. Among value of blood electrolytes, hyponatremia and hyperkalemia were found to be important risk factors contributing to delirium in present study. While, hypocalcemia was not. Low Alb, PA and high Child-Pugh score, index of renal function, were important predictors of delirium in present study. The ALT, AST, TBIL, and DBIL were not. Anemia was also a predictor of delirium in previous researches.[4,6]

There were 174 patients screened during the study period, 12 refused to participated in the study, 25 were excluded because of cognitive impairment before operation, visual and (or) hearing impairment, taking antipsychotic drugs in recent six months, cerebral operations, or operation time less than one hour. As a result, 137 patients enrolled and 3 dropout. In the end, 134 patients were eligible and were analyzed.

One of the limitations in the study is that not all risk factors, including medication, acute illness, environmental and patient characteristics, and underlying chronic pathology, were considered in the analysis, and some of information may be lost. Besides, this is a pilot study based on single center. Therefore, it is promising for the application of ANN based on the MIV into a large scale, longitudinal study to determine the association between delirium and modifiable risk factors for timely and optimal intervention to reduce the burden resulting from delirium in critically ill elder patients.

CONCLUSION

Delirium was found to occur in nearly 12% of critically ill elders in SICU after non-cardiac surgery. The important pathophysiological risk factors associated with delirium were age, the use of sedatives, dose of propofol, dose of remifentanil, acidosis, fever, hyponatremia, hyperkalemia, albumin level, pre-albumin level and Child-Pugh score, and anemia. Furthermore, this study suggests that application and significance of artificial neural networks (ANN) mainly lies on mean impact value (MIV), which can be used as a relative stable reference for early screening of variables.

The chart shown here displays two curves, one for the category No (Non-Delirium) and one for the category Yes (Delirium). The curves are symmetrical about a 45-degree line from the upper left corner of the chart to the lower right.

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Authors' contribution:

MJ: Conduction of the work and manuscript writing
SX: Data collection
YY: Study design and manuscript editing

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