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A meta-analysis of critically ill patients reveals several potential risk factors for delirium☆

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ABSTRACT

Objective: To investigate potential risk factors for delirium in critically ill patients through a meta-analysis of clinical observational studies.
Method: A literature search was conducted of MEDLINE and Embase databases. Studies that reported risk factors for delirium in a critical care setting were included. Data were independently extracted by two reviewers and pooled using a fixed-effect or random effects model according to the result of a heterogeneity test.
Results: Twenty-five studies were included. The combined odds ratio (95% confidence interval) for each potential risk factor estimated by meta-analysis was as follows (univariate/multivariate): alcohol use, 1.47 (0.79–2.72)/2.34 (1.56–3.49); smoking, 1.01 (0.81–1.25)/1.61 (0.83–3.10); hypertension, 1.64 (1.30–2.06)/1.98 (1.44–2.72); age (per year), 1.03 (1.001–1.05)/1.04 (1.02–1.05); age >65 years, 2.52 (1.55–4.10)/2.59 (1.93–3.47); mechanical ventilation, 3.09 (1.43–6.66)/4.51 (1.41–14.39); and Acute Physiology and Chronic Health Evaluation (APACHE) II score (per point), 1.13 (1.06–1.21) (multivariate only). There was no evidence of publication bias except for APACHE II score.
Conclusion: Age, history of hypertension, clinical use of mechanical ventilation and higher APACHE II score are associated with increased risk of delirium in critically ill patients.

1. Introduction

Delirium is a frequently encountered clinical syndrome characterized by an acute alteration in attention and cognition. The incidence of delirium in intensive care units (ICUs) varies enormously across study populations and institutions, ranging from 20% to 80% [1–3]. In analogy to other end-organ injuries, delirium is now regarded as an "organ failure" of the brain [4]. Evidence indicates that the development of delirium is associated with numerous noxious outcomes in ICU patients. A study by Ely et al. found that delirious patients had higher 6-month mortality rate than patients without delirium (34% vs. 15%), a 10-day longer hospital stay, a longer post-ICU hospital stay and a higher incidence of cognitive impairment at the time of discharge [5]. Girard et al. provided further evidence that the incidence of delirium was associated with long-term cognitive impairment a full year after the critical illness [6]. Consequences such as these are detrimental to the health and overall quality of life for patients who survive critical illness. Delirium screening instruments such as the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) [7], the Intensive Care Delirium Screening Checklist (ICDSC) [8], the Neelon and Champagne (NEECHAM) confusion scale [9] and the Nursing Delirium Screening Scale (Nu-DESC) [10] have proven to be well-validated for use in ICU settings assessing delirious patients. The CAM-ICU is based on the *Diagnostic and Statistical Manual for Mental Disorders* (*DSM-IV*) definition of delirium and is used to assess nonverbal critically ill patients in ICU settings. The ICDSC is an eight-item questionnaire that uses the *DSM-IV* criteria for delirium combined with key features of delirium to detect its presence. The NEECHAM confusion scale is a nine-item scale that was originally created to detect delirium in acutely ill hospitalized patients and has been recently adopted for use in ICU settings. Finally, the Nu-DESC is a fast and simple screening instrument comprising five items that was designed to be administered by nurses based on clinical observation in routine practice [11,12].

Despite its profound impact on patients, the mechanisms underlying delirium in critically ill patients are not fully understood. The postulated mechanisms involve neurotransmitters, inflammation, physiological stressors, metabolic derangements and electrolyte disorders [13]. Many factors including medication use, sudden withdrawal of alcohol or drugs and metabolic disturbance can interfere with neurotransmission or cellular metabolism and become direct causes of delirium [13]. Other causal mechanisms may interfere with neurotransmission indirectly. Inflammation caused by sepsis or

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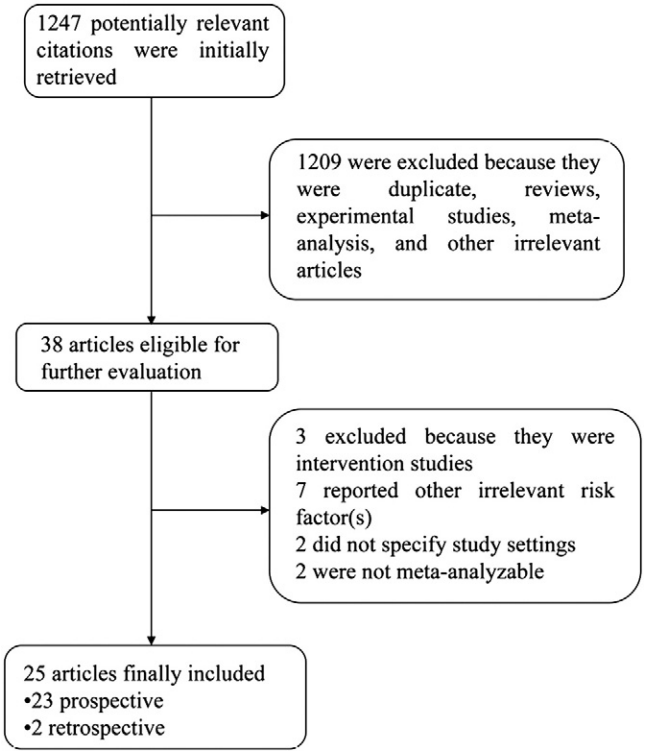

Fig. 1. Flow chart of the study selection.

multiorgan dysfunction may reduce cerebral blood flow and result in constriction of cerebral vasculature [13]. Although a single factor can lead to delirium, delirium is usually the consequence of multiple factors [13]. To date, many studies have investigated the risk factors for delirium, and preexisting cognitive impairment, acute illness and medication use have been consistently identified as significant risk factors [11,14]. However, results are conflicting for several commonly studied factors, including alcohol use, smoking, age, history of hypertension, mechanical ventilation and Acute Physiology and Chronic Health Evaluation (APACHE) II score. Discrepancies regarding the relevance of these risk factors, either predisposing or precipitating, may be explained by variations in sample size, study design, critical care setting and delirium assessment tools. One study indicated that patients with three or more risk factors have a 60% chance of developing delirium [15]. Knowledge of the risk factors for delirium would allow early identification of ICU patients with a high risk of developing delirium and would be helpful for positive prevention and developing intervention strategies for vulnerability factors. The aim of this study was to identify the risk factors for delirium in critically ill patients by systematically examining results of studies from diverse areas and pooling data where possible. In addition, we performed subgroup analysis stratified according to prespecified criteria that may have a significant impact on the influence of potential risk factors.

2. Methods

2.1. Search strategy and data extraction

Two investigators (Huai JP and Ye XH) independently performed a computerized search of MEDLINE (from 1 January 1966 to 5 January 2014) and Embase (from 1 January 1974 to 5 January 2014) databases to identify potentially relevant articles. The search was carried out using the following keywords: *delirium* ("delirium," "delirious," "intensive care unit syndrome," "delusion*"), *ICU* ("intensive care," "critically ill," "icu," "critical care"), and *risk factor**. The reference lists of all relevant articles were manually screened to identify additional studies relevant to the review. Citations were restricted to those published in the English language. Studies were included if they met the following inclusion criteria: (1) case–control or cohort design and published in manuscript form; (2) minimum of one risk factor associated with delirium; (3) used a validated delirium assessment tool. Studies were excluded if they investigated the impact of delirium on clinical outcome, compared interventions or were conducted in a non-ICU setting.

The following data were independently extracted from each study by two investigators (Ye XH and Huai JP): first author's last name, publication year, geographic location of the study population, study design, sample size, delirium assessment tool and univariate or multivariate odds ratio (OR) with corresponding 95% confidence interval (CI). If OR was not reported, it was calculated using the original data (number of case and control subjects exposed to the risk factor) from the study. Any disagreement was resolved by consensus.

2.2. Assessment of study quality

The quality of the included studies was assessed using the well-established, validated Newcastle-Ottawa Scale (NOS) [16]. The criteria included three categories: (1) patient selection (three items); (2) comparability of the two study arms (two items); and (3) assessment of outcome (two items). Studies were awarded a maximum of one star per item in the patient selection and assessment of outcome categories and a maximum of two stars per item in the comparability of the two study arms category. Studies were graded on an ordinal star scoring scale. Studies with 7–9 points were considered of high quality, studies with 5–6 points were considered of moderate quality, and studies with 0–4 points were considered of poor quality. Quality of studies was assessed independently by two reviewers. Discrepancies were settled by discussion and consensus.

2.3. Statistical analysis

The association between the putative risk factor and delirium was reported as either multivariate or univariate OR. Because multivariate OR is adjusted for potential confounders and univariate OR is not, we reported the results separately. Summary OR estimates with their corresponding 95% CIs were calculated for each risk factor using either a fixed-effect or random effects model according to the results of a heterogeneity test [17]. For studies that reported OR separately for males and females or different levels, we calculated the pooled OR and its corresponding 95% CI. Heterogeneity was evaluated using the Q-statistic and quantified using I^2 [18]. For the Q test, $P<0.10$ was considered to imply statistical heterogeneity. I^2 is the proportion of total variation contributed by between-study variation, and values of 25%, 50% and 75% were considered as low, moderate, and high respectively. To further test the robustness of the results, sensitivity analysis was performed according to the type of diagnostic tool used to screen delirium. Moreover, subgroup analysis was performed according to prespecified criteria including geographical regions (Asia vs. non-Asia) and types of diagnostic tools (CAM-ICU vs. non-CAM-ICU). Publication bias was evaluated using Begg's funnel plot and Egger's test [19,20]. All statistical analyses were performed using STATA software (Version 12.0; College Station, TX, USA).

3. Results

3.1. Search results and study characteristics

The initial literature search retrieved 1247 citations, and 1208 were excluded on the basis of title and/or abstract because they were duplicates, reviews, experimental studies, meta-analyses and other irrelevant articles. Full texts of the remaining 39 articles were