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Making advances in delirium research: coupling delirium outcomes research and data sharing

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Understanding and improving the current management of delirium in critically ill patients has become a major challenge for clinicians at the bedside and researchers. In the past decade significant advances have been made increasing our knowledge on the epidemiology, clinical phenotype, diagnosis, prevention, treatment, and risk assessment of delirium [1]. As clinicians in the intensive care unit (ICU), being able to predict the occurrence of delirium early in the course of critical illness may be extremely useful for the implementation of preventive measures or to design interventions for preemptive treatment of high-risk individuals. In a recent study Wassenaar et al. [2] demonstrated the ability to predict

delirium with a relatively straightforward model for implementation at ICU admission.

Before publishing the E-PRE-DELIRIC, the authors planned and realized a series of rigorous studies. In their first study, the authors developed the PREdiction of DELIRium for Intensive Care patients (PRE-DELIRIC) model for prediction of delirium based on variables readily available in the first 24 h after ICU admission. The authors then temporally validated it in a second prospective cohort in the same hospital and finally validated it externally in four other Dutch hospitals. Prevalence of delirium varied between 25.5 and 36.8 %. Risk factors were selected on the basis of a systematic review [3]. Of the 25 potential risk factors, ten were retained (Table 1). The area under receiver operating characteristics curve (AUROC) of pooled data varied for development (AUROC = 0.86), temporal validation (AUROC = 0.89), and external validation (AUROC = 0.84), resulting in an AUROC of 0.85.

In a second study [4], the PRE-DELIRIC was re-calibrated in eight ICUs from six countries; the median delirium incidence was 22.5 % (IQR 12.8–36.6 %). The incidence of the ten predictors differed significantly between centers, but the AUROC of the eight participating centers remained good at 0.77 [95 % confidence interval (CI) 0.74–0.79].

In this third prospective cohort study in 13 ICUs from seven countries [2], the authors enrolled 2914 patients to develop and validate a predictive model for ICU delirium based on data available at ICU admission. Multiple logistic regression analysis was used to develop the model on data of the first two-thirds and validated on data of the last one-third of the patients from every participating ICU. The incidence of delirium was 24.5 % in the development cohort (1962 patients), 21.8 % in the validation cohort (952 patients), and 23.6 % in the entire study population. The AUROC was 0.76 (95 % CI

Table 1 Risk factors for delirium from validated predictive models

PRE-DELIRIC	E-PRE-DELIRIC	Other settings ^a
Age (years)	Age (years)	Older age (≥ 75 years)
APACHE II score (per point)		Comorbidity or disease severity ^b
Coma (drugs/miscellaneous/combinations)		
Admission category (surg/med/trauma/neurol)	Admission category (surg/med/trauma/neurol)	
Infection (yes)		
Metabolic acidosis (yes)		
Morphine use		
Sedation (yes) ^b		
Urea (mmol/L)	BUN at time of ICU admission	
Urgent admission (%)	Urgent admission	Cognitive impairment and dementia
	History of cognitive impairment	Alcohol abuse
	History of alcohol abuse	
	MAP at the time of ICU admission	
	Corticosteroids use	
	Respiratory failure	
		History of delirium ^b
		Functional, visual, or hearing impairment ^b
		Depression ^b
		History of transient ischemia or stroke ^b
		Several drugs used ^b
		Physical restraints ^b
		Bladder catheter ^b
		Abnormal albumin, sodium, potassium, glucose ^b

BUN blood urea nitrogen, *MAP* mean arterial blood pressure

^a From Inouye et al. [12]

^b Variables that would be worth considering in future studies aiming at predicting delirium early during ICU stay

0.73–0.77) in the development data set and 0.75 (95 % CI 0.71–0.79) in the validation data set.

Of 18 candidate risk factors for delirium selected from the PRE-DELIRIC model and systematic review, nine were excluded and nine were retained on the basis of consensus of the members of Postoperative Delirium and Cognitive Dysfunction (PoDeCoD) group of the European Society of Intensive Care Medicine working group (Table 1).

There is increasing benefit for the scientific community when more transparency is allowed in relation to trial designs [5] and also when patient data is shared for meta-analysis. For the purpose of individual patient data meta-analysis, it is crucial not only to make the data available but also for the main research groups to make efforts towards establishing more homogeneous core patient data. More open approaches are also desirable in the fields of outcomes research and predictive analysis. Predictive models can be used for planning therapeutic decisions or to risk-stratify participants in therapeutic clinical trials [6]. All the statistical methods used in the development of a prediction model should be reported, as the general principle is that enough detail should be given such that a knowledgeable reader with access to the original data could verify the reported results [7]. There is indeed no obligation for researchers to make their data publicly available. However, times are changing. The Institute of

Medicine explicitly recommends data sharing, although with adoption of specific rules to guarantee a fair opportunity for researchers to publish results before secondary investigators gain access to the data, to protect the commercial interests of sponsors and to avoid privacy concerns and inappropriate use [8]. Some large pharmaceutical companies are already sharing clinical trial data [9], and the European Medicines Agency has started doing so this year [8]. Making the analyzable data set available to researchers avoids unnecessarily duplicating trials and allows meta-analyses, applications of innovative statistical methods, novel new analyses, cross-study comparisons, sample size estimation for new studies, and replication of results. Ensuring the reproducibility of biomedical research is a fundamental assumption of science [10].

Should a similar framework apply to observational studies? Observational studies are mostly prevalent in our field, and they influence clinical practice as well. The National Heart, Lung, and Blood Institute (NHLBI) established a formal data sharing policy in 1989 and since 1999 has provided improved consistency owing to individual-level data on more than 560,000 participants from 100 NHLBI-supported clinical trials and observational studies [11].

Delirium is a common, serious, and often fatal disorder [12], and has become a first-line clinical and research

topic in critical care medicine. Dutch investigators have made enormous efforts to produce high-quality research on this topic. With a trilogy of studies and thousands of patients enrolled, the amount of data available is considerable. Recently, other groups have also made substantial advances in this field [13, 14]. Making them accessible for systematic reviews and individual patient-data meta-analyses and sharing them with the scientific community would be a welcome and pioneering initiative

in critical care medicine. Such an initiative, we think, will pay dividends [15].

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Conflicts of interest None.

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