Prediction of long-term outcome subtypes in ARDS: first steps towards personalised medicine in critical care

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In *Thorax*, Samuel Brown and colleagues present their result on early identification of physical, cognitive and mental health outcome subtypes in patients who survived acute respiratory distress syndrome (ARDS).[1] Using data from the ARDSNet Long-Term Outcomes Study, the authors identified a group of 645 patients who had been studied with a comprehensive battery of validated health outcome instruments, which included measures of physical, cognitive and mental health (anxiety, depression and post-traumatic stress disorder), as well as quality of life status, obtained at 6-month follow-up. After splitting the data into derivation and validation datasets, the authors used a data mining approach, weighted network analysis, to identify and validate four outcome subphenotypes. They identified four subtypes: (1) mildly impaired physical and mental health status; (2) moderately impaired physical and mental health status; (3) severely impaired physical and moderately impaired mental health status; and (4) severely impaired physical and mental health status. In each of the four subtypes, one-third of patients suffered a significant decrease from baseline in their health state measured with the EQ-5D or SF36. Separation of outcome subtypes in relation to various instruments of physical and mental health assessment was good, while cognitive function evaluated with Mini-Mental State Examination did not differ significantly across subtypes. Cognitive outcomes remained unrelated to the subtypes defined by physical and mental health outcomes also when using a battery of more detailed cognitive tests available for a subset of patients. This multicentre study confirms that ARDS is associated with long-lasting disability after the resolution of the acute condition: fewer than half of patients were living at home independently at 6 months compared with 91% at baseline. Physical and mental impairments were both severe in one quarter of them, who were mainly female, current smokers and of Latino ethnicity.

Among 144 variables available at baseline, a previous study by the same authors had identified nine predictors associated with health status at 6-month follow-up[2]: age, female sex, Latino ethnicity, current smoking, body mass index, pulmonary comorbidity, AIDS comorbidity, nadir respiratory rate and residential independence. In this paper, five of these nine variables independently predicted physical and mental outcome subtypes in ARDS survivors: female sex, Latino ethnicity, pulmonary comorbidity, current smoker and residential independence. Of note, variables related to acute illness severity and measured at the time of enrolment (APACHE 3 scores, shock at enrolment, sepsis as primary cause of ARDS, PaO_2/FIO_2 ratio, PEEP, Glasgow Coma Scale score) as well as age and intensive care unit (ICU) length of stay did not predict long-term functional outcome subtypes in ARDS survivors. A first message of this study is that the predictors of acute mortality and those of long-term disability can be different. If this is confirmed in future studies, we would be encouraged to do absolutely everything we can to make patients with ARDS survive the acute illness, knowing that a good long-term functional outcome may still be possible even in older individuals with high disease severity.

A second message is that early prediction of long-term outcome subtypes in patients with ARDS is feasible. Subtyping, defined as recognition of aggregated patterns of observable clinical, radiological, biochemical and physiological characteristics within a heterogeneous cohort of patients, is an integral part of clinical practice, and has always been used by physicians to select those patients that are more likely to respond to treatment in case of protean disease. In the historical trial on streptomycin treatment of pulmonary tuberculosis, 'a first prerequisite [required by investigators] was that all patients in the trial should have a similar type of disease'.[3] After having defined disease features, they commented: 'Such closely defined features were considered indispensable, for it was realized that no two patients have an identical form of the disease, and it was desired to eliminate as many of the obvious variations as possible'.[3] This perfectly expresses the reason why such operational subtyping is on the way of personalised medicine, which starts at the population level and uses 'various approaches and disciplines to characterize subsets on subsets of such patients, ending with the individual patient'.[4] With the availability of large datasets and powerful statistical analysis tools of modern times, this medical art of clinical pattern recognition has become science and is currently applied in many fields of medicine. The importance of ARDS subtyping has been demonstrated in some recent studies showing for example the selective effect of prone positioning in severe ARDS: a reduction in mortality could be demonstrated only when this treatment was targeted at patients with ARDS with a PaO_2/FiO_2 ratio ≤ 150 rather than all patients with ARDS.[5] Another example is the selective response to positive end expiratory pressure (PEEP) in patients with ARDS with hyperinflammatory profile, characterised by high plasma levels of inflammatory biomarkers, profound shock, low serum bicarbonate and a high prevalence of sepsis as the cause of ARDS.[6] ARDS subtypes have also been shown to have a differential response to randomly assigned fluid management strategy, with patients with hyperinflammatory profile showing reduced mortality with a conservative strategy.[7] However, the main scope of these studies was to identify subtypes of patients with ARDS with different hospital mortality, and not with different long-term disability as in the current study.

Identifying outcome subtypes does not necessarily imply the identification of their underlying pathogenetic mechanisms. When this happens, people refer to 'endotypes', that is, subtypes of a disease with distinct pathophysiological mechanisms that can be targeted by selective treatment.[4] Brown's study did not assess pathophysiological mechanisms, and hence it should be considered a preliminary step towards full characterisation of ARDS long-term outcomes with potentially distinct response to treatment, as the authors acknowledge. However, the fact that predictors of physical and mental impairment did not predict cognitive impairment strongly suggests different pathophysiological mechanisms underlying cognitive and non-cognitive

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outcomes. This is in line with findings from a recent Canadian study,[8] and represents a further important result of the study by Brown and colleagues.

Possible explanations for this difference in pathophysiological mechanisms remain speculative. In critically ill patients, delirium is a strong predictor of cognitive impairment that persists for months to years after ICU discharge.[9] Moreover, delirium is associated with brain atrophy[10] and, in postoperative patients, with brain microstructural abnormalities reflecting diffuse cerebral white matter damage.[11] Early ICU physical rehabilitation is associated with reduced incidence and shorter duration of delirium,[12 13] and hence, it is tempting to speculate that rehabilitation may also be beneficial in reducing post-ICU cognitive impairment. Delirium and immobility potentiate each other,[14] and therefore, early mobilisation in the ICU may exert its beneficial effect by interrupting this vicious circle. However, rehabilitation may be ineffective in patients with severe ischaemic brain disease or, at the other end of severity spectrum, in those with transient delirium associated with sedation. Future studies in patients with ARDS should consider the assessment of delirium during the ICU stay as a high priority in order to identify the mechanisms underlying its effect on long-term cognitive impairment and to evaluate the impact of early ICU mobilisation on delirium and long-term cognition.

ARDS is a potentially lethal, inflammatory lung disease, with hospital mortality varying between 35% in milder forms and 46% in severe forms.[15] It is therefore reasonable that researchers prioritise their efforts on developing strategies to reduce mortality. However, survivors of ARDS may suffer from long-term physical impairments, exercise limitations, profound neuromuscular weakness, pain and fatigue,[14] cognitive and psychiatric morbidity,[16] decreased physical quality of life, a negative impact on employment and family income,[17] and increased costs and use of healthcare services.[18] Care is often provided by family members, for many of whom the occurrence of depressive symptoms is high[19] and the impact on employment is negative.[17]

The 'A' of the acronym ARDS has changed over time from indicating 'adult' to indicating 'acute'. After 50 years since the first description of this syndrome,[20] the time has come that we start considering the 'A' as also indicating 'after'. This would emphasise the need to address early survivorship care aimed at preventing disability after ICU[20] with the same high priority that is given to the treatment of the acute lung injury to reduce mortality. By identifying baseline characteristics that can predict at the time of ICU admission the risk of developing long-term physical and mental impairment if the patient survives the acute phase, the study by Brown and colleagues represents an important step towards this end.

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