Editorial

ARDS onset time and prognosis: is it a turtle and rabbit race?

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According to the last Berlin definition, ARDS is a form of acute diffuse lung injury occurring in patients with predisposing risk factors, onset within one week of a known clinical insult or new/worsening respiratory symptoms, presence of bilateral opacities on the chest radiographs not fully explained by effusions, lobar/lung collapse, or nodules, respiratory failure not fully explained by cardiac failure or fluid overload, and hypoxemia. It can be classified as mild (200 mmHg < PaO_2/FiO_2 ≤300 mmHg or 27 kPa < PaO_2/FiO_2 ≤40 kPa), moderate (100 mmHg < PaO_2/FiO_2 ≤200 mmHg or 13 kPa < PaO_2/FiO_2 ≤27 kPa) or severe (PaO_2/FiO_2 ≤100 mmHg or PaO_2/FiO_2 ≤13 kPa) (1).

ARDS represents one of the most common reasons for admission to the intensive care unit (ICU) and it is still a major cause of mortality and morbidity in critically ill patients despite the application of lung protective strategies (2,3).

ARDS can be already present at ICU admission (early ARDS) or it can have a later onset during ICU stay (late ARDS). Several studies try to investigate if early- and late-onset ARDS are different clinical entities, have different characteristics, clinical course and outcomes with conflicting results: Croce and colleagues in 1999 retrospectively studied post-traumatic ARDS patients (defined according to AECC definition) (4) and found that incidence and mortality were similar between early- and late-onset, while aetiology and cause of death were different. In particular, early-onset ARDS was mainly associated with haemorrhagic shock and pulmonary contusion and the most common cause of death was profound shock; while late-onset ARDS was associated to pulmonary contusion complications, pneumonia or haemorrhage's and resuscitation's sequelae and death was mainly due to progressive multiple organ failure (5). In the same time, Rady and colleagues studied post-cardiovascular surgery patients and found that early-onset ARDS patients had higher mortality than late-onset, besides higher creatinine increase, more neurologic complications and nosocomial infection rates (6). On the other hand, Liao and colleagues found opposite results in medical ICU patients: timing of ARDS onset was associated with the severity of initial illness, underlying comorbidity and response to initial therapy. Late-onset ARDS had higher mortality, SOFA score, length of ventilation and hospital stay than early-onset patients (7). In an observational study in ICU patient, Lobo and colleagues found similar mortality between early- and late-onset, while both groups have higher SOFA and APACHE scores, infections and length of ventilation and hospital stay than patients without acute respiratory failure. Moreover, early-onset ARDS had worse respiratory function (lower PaO_2/FiO_2) and more cardiovascular impairment (higher cardiovascular SOFA) at admission than late-onset ARDS, while a lower GCS at admission was associated with late-onset ARDS and death if it last more than 48 hours from admission.

In this issue, Zhang and colleagues present an elegant two-stage study to determine the cut-off point between early- and late-onset ARDS and then test the association between ARDS onset time and prognosis. Enrolled patients

have moderate or severe ARDS, defined according to Berlin definition (8) and were randomly assigned into derivation and validation dataset. Authors estimated the hazards ratio of onset time with a multivariate Cox proportional hazards model of survival time and defined the best cut-off point as 48 hours from ICU admission. Interestingly, this cut off was concordant with that adopted in several other studies (5,7,9-11).

The recent multicenter prospective cohort study LUNG-SAFE defined ARDS onset from the first day the acute hypoxemic respiratory failure criteria were satisfied independently from ICU admission date (12). Zhang and colleagues inferred that as in LUNG-SAFE 70% of patients were moderate or severe ARDS and that as 93% of patients had ARDS onset within 2 days, thus early-onset moderate or severe ARDS could be 93%×70%=65% that correspond to Zhang's early-onset incidence.

Even if there were no significant differences in demographic data, chronic diseases or severity scores between early- and late-onset ARDS patients at admission time, from their analysis resulted that late-onset ARDS was associated with shorter 28-day and 60-day survival time and with faster death rate than early-onset ARDS. This strong association was present both in derivation and validation dataset and was confirmed in 5 different randomly generated derivation and validation datasets, as well as, in a subgroup analysis by different ARDS risk factors. Here, the association between ARDS onset and survival time remained significant for the main ARDS risk factors: sepsis, septic shock and pneumonia.

Considering clinical characteristics at ICU admission, early-onset ARDS had higher lung injury scores with more pneumonia and lower PaO_2/FiO_2 ratio, more septic shock and thus lower blood pressure and more vasopressor use than late-onset ARDS, while multiple fracture rate was lower. However, at ARDS onset time, late-onset ARDS had lower PaO_2/FiO_2, and thus a greater decline from time of admission to time of ARDS onset, and more thrombocytopenia than early-onset.

Authors suggest that early-onset patients may have an acute loss of function during their critical illness, from which they could gradually recover (Big Hit hypothesis); while late-onset patients may have slight loss of function in the beginning, but keep more rapid function decline persistently later, resulting in worse prognosis (Slow Burn hypothesis). More research is still needed to understand and confirm these mechanisms.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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