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CORRESPONDENCE

Lung–kidney cross-talk in the critically ill: insights from the Lung Safe study

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Dear Editor,

We read with interest the consensus report on lung–kidney 'cross-talk' in the critically ill by Joannidis and colleagues arising from the 2018 Acute Disease Quality Initiative (ADQI 21) workshop [1]. The report identified key knowledge gaps in our understanding of the mechanisms underlying lung–kidney cross-talk and prioritised research initiatives to address these gaps [1].

Since the AQDI conference, we published a secondary analysis of the LUNG SAFE study [2], which found that even mild-moderate AKI was associated with a substantial increase in mortality, highlighting the importance of these issues [3]. We wish to highlight some insights from that analysis, and provide additional analyses regarding the role of lung–kidney cross-talk as an injury mechanism [3].

In the LUNG SAFE Cohort, AKI and ARDS generally developed contemporaneously rather than sequentially. AKI occurred at or within 48 h of ARDS development in 765 (39%) of 1974 ARDS patients, with a further 4.3% developing AKI on days 3–7 of ARDS. Of the 228 AKI patients (30%) that received RRT, 62% commenced within 48 h, 29% between days 3 and 7, and 9% between days 8 and 28 following ARDS development. Reassuringly, the impact of AKI on the ventilatory management of patients with ARDS appeared limited. Specifically, despite the presence of acidosis in patients with AKI, there were no differences in arterial CO_2 tension, or in tidal or minute ventilation between the groups. While our data do not exclude the potential for an impact of AKI on lung function, it does appear that 'protective' ventilatory strategies were prioritized over attempts to compensate for pH status.

A multivariate analysis of risk factors for early AKI (i.e. in the two first days of ARDS) in patients with ARDS suggests that the impact of ARDS on the development of AKI was limited (Table 1). Specifically, no association was found between ventilatory variables (i.e. tidal volume, total respiratory rate, FIO_2, PEEP,) or indices of lung injury severity (i.e. peak inspiratory pressure and PaO_2/FiO_2) and the presence of AKI. Of importance, this analysis identified known 'ARDS risk factors' such as sepsis [4], non-cardiogenic shock, TRALI and pancreatitis, as independent risk factors for AKI. The presence of shock was also associated with AKI development. This analysis suggests that these factors constitute common underlying injury mechanisms that drive the concomitant development of organ failures, including AKI and ARDS, in the critically ill.

In conclusion, the spatio-temporal relationships regarding acute lung and kidney failure in the critically ill remain poorly understood [5]. In the LUNG SAFE cohort, AKI and ARDS frequently evolved contemporaneously and early in the course of critical illness, likely driven by common underlying pathophysiologic processes. Our findings did not support a central role for lung–kidney 'cross talk' in mediating early AKI in patients with ARDS, with no evidence that the presence of AKI impacted ARDS management, or that the ventilatory management or ARDS severity was associated with risk of AKI development. These findings do not preclude a role for lung–kidney cross-talk in the development of AKI later in the course of ARDS, or for ARDS to negatively impact the resolution of AKI. A better understanding of the roles of shared underlying risk factors such as sepsis, the overall severity of critical illness, hemodynamic instability and

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Table 1 Multivariate analysis of factors associated with early AKI in our ARDS population

Variable	OR	95% CI	*P* value
Baseline characteristics			
Age (years)	1.02	1.01–1.03	< 0.001
Male (Ref. female)	1.53	1.21–1.93	< 0.001
BMI (kg/m^2)	1.03	1.01–1.04	0.001
Illness severity (day 1 of ARDS)			
SOFA score—Cardiovascular	1.28	1.20–1.37	< 0.001
Risk factors of ARDS			
Sepsis (Ref. No)	1.96	1.46–2.64	< 0.001
Non-cardiogenic shock (Ref. No)	1.82	1.23–2.69	0.003
TRALI (Ref. No)	2.42	1.43–4.09	0.001
Pancreatitis (Ref. No)	2.46	1.17–5.20	0.018
Comorbidities			
Diabetes (Ref. No)	1.43	1.08–1.90	0.013
Chronic liver failure (Ref. No)	1.93	1.12–3.33	0.018
COPD (Ref. No)	0.54	0.40–0.72	< 0.001
Metabolic variables (day 1 of ARDS)			
pH (per 0.01 increase)	0.94	0.93–0.95	< 0.001
Other			
Medical admission (Ref. No)	1.58	1.21–2.07	0.001

Variables with a *P* value < 0.20 at the univariate analysis were included into a multivariable logistic regression model using a stepwise selection approach. Statistical significance was considered with a *P* value < 0.05 (two-tailed). No ventilator variables (i.e. tidal volume per predicted body weight, total respiratory rate, peak inspiratory pressure, PEEP, PaO_2/FiO_2 and FIO_2) selected at the univariate analysis was significant in the multivariate model $n = 1765$

BMI body mass index, *SOFA* sequential organ failure assessment, *TRALI* transfusion related acute lung injury, *COPD* chronic obstructive pulmonary disease

of Lung-Kidney 'cross-talk' is essential to improving outcomes in these patients.

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Compliance with ethical standards

Conflicts of interest

The authors attest that they have no conflicts of interest in regard to the subject of this manuscript.

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