In-hospital Mortality of Critically Ill Patients with Interactions of Acute Kidney Injury and Acute Respiratory Failure in the Resource-limited Settings: Results from SEA-AKI Study

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Abstract

Background: While the theory of kidney-lung interorgan cross-talk has been postulated for several years, their clinical outcomes and causal relationship remained unclear. Thus, our goal was to describe clinical outcomes and explore the interactions between acute kidney injury (AKI) and acute respiratory failure (ARF) in critically ill patients.

Methods: Data were retrieved from the SEA-AKI study, a multinational multicenter database of adult ICUs from Thailand, Laos, and Indonesia. AKI was defined using KDIGO criteria stage 2-3. ARF was defined by being mechanically ventilated. Patients were assigned into 6 patterns based on AKI and ARF sequence: “no AKI/ARF”, “ARF alone”, “AKI alone”, “ARF first”, “AKI first”, and “Concurrent AKI-ARF”. The primary outcome was in-hospital mortality of each pattern.

Results: A final cohort of 5468 patients were eligible for the analysis. The “Concurrent AKI-ARF” had the highest in-hospital mortality of 69.6%. The “AKI first” and the “ARF first” had in-hospital mortality of 54.4% and 53%, respectively. Among patients with single organ failure, in-hospital mortality was 14.6% and 31.5% in the “AKI alone” and the “ARF alone”, accordingly. In-hospital mortality was 12.4% in patients without AKI and ARF.

Conclusion: Critically ill patients with ARF and AKI are at higher risk of in-hospital death. Further analysis and experiment is suggested to better understand the nature of this relationship.

Introduction

Acute kidney injury (AKI) and acute respiratory failure (ARF) are common associated complications which independently lead to higher mortality among critically ill patients.¹⁻⁴ When both conditions overlap, the incidence of in-hospital mortality is enhanced.

It has been demonstrated that AKI led to systemic fluid congestion, retention of uremic toxins, and metabolic acidosis. A subsequent increase in work of breathing would cause or worsen lung injuries.^{5,6} Conversely, ARF could affect gas exchange, and stimulate neurohormonal activities such as renin-angiotensin-aldosterone system, sympathetic activities, and release arginine vasopressin. These would result in salt and water retention, yet renal hypoxia and vasoconstriction.^{7,8} The use of mechanical ventilation could also cause right ventricular dysfunction from increased intrathoracic pressure and lead to impaired hemodynamic status, systemic and renal congestion. Moreover, the injury in either renal tubular, or alveolar cells, or biotrauma from mechanical ventilation would contribute to a release of systemic inflammatory mediators causing further injury in the other organ, as in vicious cycle.⁹⁻¹²

While the theory of kidney-lung interorgan cross-talk has been postulated for several years, the causal relationship remained unclear.¹³ During the pandemic of COVID-19 infection, more studies report strong relationship between AKI and ARF in critically ill patients with COVID-19 infection.¹⁴ However, the clinical outcomes from each patterns of simultaneous kidney and lung injuries has not been clearly demonstrated. Thus, we aimed to explore the interaction between AKI and ARF, and their clinical outcomes among critically ill patients.

Methods

Patients and study design

This was a subanalysis of the prospective, multicenter, multinational, observational study, Southeast Asia AKI (SEA-AKI) study.¹⁵ In brief, this study was conducted in 23 ICUs throughout 22 hospitals from various countries across SEA region including Thailand, Laos, and Indonesia. The study sites in this study included all level of hospitals ranging from

university hospitals, regional hospitals, and provincial hospitals. All available data from the cohort were retrieved to maximize the power and generalizability of the results. We excluded patients with prior history of end stage renal disease (ESRD) and patients who had missing important classification data i.e. daily ventilator status, daily urine output, and daily serum creatinine and hence their AKI-ARF pattern cannot be defined. The study protocol was reviewed by the Institutional Review Board at each participating site and the need for informed consent was waived. For this study, the Institutional Review Board of Faculty of Medicine, Chulalongkorn University approved the study (IRB 440/63). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.¹⁶

Study outcomes

Our primary outcome was in-hospital mortality of each AKI-ARF pattern. Secondary outcomes included ICU length of stay, hospital length of stay, total ventilator day, ventilator free day, renal recovery at discharge, the factors associated with in-hospital mortality and the factors associated with the development of AKI after ARF and ARF after AKI.

Study definitions

We defined AKI as stage 2-3 AKI using the Kidney Disease Improving Global Outcomes (KDIGO) classification.¹⁷ This definition of AKI aimed to avoid misclassification of minor changes in renal function or influences of fluid balance. KDIGO stage 2 AKI is defined as a 2.0–2.9 times baseline increase in serum creatinine (SCr). KDIGO stage 3 AKI is defined as an increase in SCr to ≥ 3.0 times baseline or an increase in SCr to ≥ 4 mg/dL. Stages were determined based on SCr and urine output (UO) data. ARF was defined based on the need for endotracheal intubation and mechanical ventilatory support for at least 24 hours.¹⁸⁻²⁰ For patients with known preadmission SCr, the most recent value in the last 12 months prior to hospitalization was used as baseline SCr. For patients without preadmission SCr, baseline SCr was estimated either using the Modification of Diet in Renal Disease (MDRD) equation back calculation or the lower SCr from hospital admission, as recommended by the Acute Disease Quality Initiative.²¹ Pattern of AKI and ARF of each patient were categorized based on the onset of development of AKI compared to ARF. The “Concurrent AKI-ARF” was defined by the development of AKI and ARF on the same day (within 24 hours apart). The “AKI first” was defined by the development of AKI before ARF (at least 24 hours apart). The “ARF first” was defined by the development of ARF before AKI (at least 24 hours apart). The “AKI alone” was defined by the development of AKI without ARF during ICU admission. The “ARF alone” was defined by the development of ARF without AKI during ICU admission. The “no AKI/ARF” was defined by neither AKI nor ARF was observed. Renal recovery at discharge was defined by the absence of AKI by either SCr or UO criteria.

Data collection

Data were collected prospectively by using preprinted case-record forms. Demographic data were collected on the first day of ICU admission. This included age, sex, body mass index, comorbidity diseases (hypertension, diabetes, coronary artery disease, cerebrovascular disease, malignancy, and chronic kidney disease), Acute Physiology and Chronic Health Evaluation (APACHE) II score²², Sequential Organ Failure Assessment (SOFA) score²³, and principle diagnosis of ICU admission which was classified by disease system according to Internal Classification of Diseases 10th revision coding²⁴. All clinical and laboratory data were collected every day for the first 7 days and then weekly until day 28. Clinical and laboratory data comprised of serum creatinine, blood urea nitrogen (BUN), urine output, fluid balance, status of vasopressor, status of mechanical ventilation.

Statistical analysis

Categorical data were presented as counts and percentages. Continuous data were presented as mean and standard deviation (SD) if normally distributed or median with inter-quartile range(IQR)if non-normally distributed. The Chi-square asymptotic test of independence was used to compare the proportions of different patterns of patients, whereas as Kruskal-Wallis one-way analysis of variance by ranks was used to compare continuous variables.

Kaplan-Meier survival curves were also generated stratified by AKI and ARF pattern. Log-rank test was used to compare survival of each pattern. Cox proportional hazards model was also done to graphically describe the covariate-adjusted survival at 14 day after ICU admission. The rationale of showing only Cox-adjusted survival curve of 14 days was to preserve constant proportional hazards assumption which was found to be violated beyond this time point.

As this was a multi-center study with centers representing clusters, multivariable logistic mixed effect regression was used to identify risk factors for in-hospital mortality, AKI development after ARF, ARF development after AKI. To determine the interactions of AKI-ARF pattern and considered risk factors on in-hospital mortality, we use AKI-ARF pattern as a main effect and accounting for interactions between AKI-ARF pattern and all other risk factors.

Mixed effect model allowed us to adjust for the site specific random effect. We investigated both the random intercept and random coefficients model. Choosing the random intercept model as it had a lower Akaike's Information Criteria and therefore a lower propensity to overfit to the sample. We also run multicollinearity diagnostics as part of our modeling process, variance inflation factor above 4 was of concern. Factors with p-value below 0.20 in univariable analysis were retained in the multivariable analysis. Regression coefficients of each factor were reported as odds ratios (OR). All analysis was conducted using the R statistical package (V4.0.3, R core team, 2020) and the mixed effect modeling using the R library, lme4. A P-value of less than 0.05 was considered to be statistically significant. To avoid false discovery of multiple pairwise comparison, Benjamini-Hochberg correction was also applied.

Results

ICU characteristics

This cohort included 6993 eligible patients from 23 centers. After excluding 270 records of ESRD patients and 1255 records of patients with missing classification data regarding mechanical ventilation status and AKI status, 5468 patients were available for the final analysis (Figure 1). The majority of the patients were from Thailand (59.4%) followed by Laos (26.5%), and Indonesia (14.1%). Mixed ICU and medical ICU were the most common type of ICU in this cohort (49.8% and 44.5% respectively). In terms of hospital types, there were 3207 patients from university hospital (58.7%), 1109 patients from regional hospital (20.3%), and 1152 patients from provincial hospital (21.1%). The definitions of each hospital type were provided in the previously published study.²⁵

Patient characteristics by pattern of AKI and ARF

Of the analyzable cases, 1392 patients had AKI (25.5%) and 2680 patients had ARF (49%). Of all included AKI cases, 562 had AKI stage 3 (40.4%) and 830 patients had stage 2 (59.6%) at the time of diagnosis. After categorizing patients into each pattern of AKI and ARF, the most common pattern observed was "No AKI/ARF" (N=2156, 39.4%), followed by "ARF alone" (N=1920 patients, 35.1%), "AKI alone" (N=632 patients, 11.6%), "ARF first" (N=658 patients, 12%), "AKI first" (N=79 patients, 1.4%), and "Concurrent AKI-ARF" (N=23 patients, 0.4%).

The average age of the entire cohort was 59.3 ± 8.7 years and 41.2% were female patients. The main primary diagnosis for ICU admission were cardiovascular disease, infectious disease, pulmonary disease, and surgical-related disease. All patient baseline characteristics stratified by pattern of AKI and ARF are provided in Table 1. Regarding the etiology of AKI, sepsis and renal hypoperfusion were the leading causes of AKI across all patterns of AKI and ARF (Table S1). As for ARF, hypoxemic ARF was the most predominant type in all patterns (Table S2).

Patient outcomes

Overall in-hospital mortality of this cohort was 25.1 percent. Based on AKI and ARF pattern, “No AKI/ARF” had in-hospital mortality of 12.4% similar to 14.6% of those in “AKI alone” while “ARF alone” had mortality of 31.5%. As expected, in-hospital mortality was higher in patients with dual organ failure (53% in “ARF first” and 54.4% in “AKI first”). Among those with dual organ failure, “Concurrent AKI-ARF” had higher in-hospital mortality of 69.6% than the other two groups. As shown in Figure 2, survival is also significantly different between AKI-ARF pattern with median survival time of 47 days for “ARF alone”, 59 days for “AKI alone”, 31 days for “ARF first”, 15 days for “AKI first”, and 21 days for “Concurrent AKI-ARF” ($P=0.001$; log-rank test). Median survival time was not reached in “No AKI/ARF”. The same trends observed in unadjusted analyses were also seen in the adjusted model, in that “No AKI/ARF” does best followed by “AKI alone”, “ARF alone”, “ARF first”, “AKI first”, and “Concurrent AKI-ARF”, accordingly (Figure 3).

For secondary outcomes, both ICU and hospital length of stay rose with the increasing number of organ failure, with the median of 2 days (IQR 2-3) and 9 days (IQR 5-15) for “No AKI/ARF”, 4 days (IQR 3-8) and 11 days (IQR 6-20) for “ARF alone”, 3 days (IQR 2-5) and 8 days (IQR 5-14) for “AKI alone”, 7 days (IQR 4-14) and 14 days (IQR 7-29) for “ARF first”, 5 days (IQR 4-8) and 10.5 days (IQR 5-18) for “AKI first”, and 5 days (IQR 4-7) and 9 days (IQR 5-17.5) for “Concurrent AKI-ARF”, respectively. There is no clinical significance in the difference of ventilator-free days between each group. Renal recovery rate was found to be lowest in “Concurrent AKI-ARF” compared to the other groups (Table 2).

Factors associated with in-hospital mortality

Multivariable binary logistic mixed effect modelling revealed AKI-ARF pattern as significant risk factors for in-hospital mortality compared to “No AKI/ARF” ($OR_{ARF\text{ alone}} 4.29$, 95% CI 2.76-3.81, $P<0.001$; $OR_{AKI\text{ alone}} 2.85$, 95% CI 1.86-4.39, $P<0.001$; $OR_{ARF\text{ first}} 13.45$, 95% CI 9-20.1, $P<0.001$; $OR_{AKI\text{ first}} 10.91$, 95% CI 5.43-21.9, $P<0.001$; $OR_{\text{Concurrent}} 16.1$, 95% CI 6.81-42.2, $P<0.001$). Other statistically significant risk factors associated with in-hospital mortality were non-surgical ICU admission, increasing APACHE II score, use of vasopressor, and fluid overload (Table 3).

To explore whether risk factors for in-hospital mortality would change between patterns of AKI and ARF, separate multivariable logistic regression models were built for each of the pattern of AKI and ARF pattern (Table S3). We also discovered significant interactions between patterns of AKI and ARF and the other risk factors on in-hospital mortality including hospital type and vasopressor use (Table 4).

Factors associated with the development of the secondary organ failure

Multivariable logistic regression models were also performed to explore the risk factors associated with the development of secondary organ failure i.e. secondary ARF (ARF after AKI) and secondary AKI (AKI after ARF). Table S4 compares patients with AKI alone versus those with AKI first. The risk factors for secondary ARF were fluid overload ($OR 5.72$, 95% CI 2.11-15.54, $P=0.001$) and maximum AKI stage 3 ($OR 1.93$, 95% CI 1.09-3.41, $P=0.023$), while protective factors for

secondary ARF were medical ICU admission (OR 0.07, 95% CI 0.01-0.5, $P=0.009$) and renal recovery (OR 0.08, 95% CI 0.01-0.41, $P=0.003$). Table S5 compares patients with ARF alone versus those with ARF first. The risk factors for secondary AKI were mixed ICU admission (OR 5.65, 95% CI 1.42-22.46, $P=0.014$), medical ICU admission (OR 4.91, 95% CI 1.3-18.52, $P=0.019$), overweight (OR 2.08, 95% CI 1.53-2.81, $P<0.001$), obese (OR 1.94, 95% CI 1.18-3.21, $P=0.009$), vasopressor use (OR 2.78, 95% CI 2.15-3.59, $P<0.001$), increase of APACHE II score by 1 (OR 1.06, 95% CI 1.04-1.08, $P<0.001$), and fluid overload (OR 4.01, 95% CI 3.04-5.29, $P<0.001$) while protective factors for secondary AKI were underweight (OR 0.63, 95% CI 0.44-0.89, $P=0.01$).

Discussion

We have displayed that the incidence of patients with either AKI or ARF in resource-limited settings were as high as 60.6% of the total ICU population, 22.9% of which had both AKI and ARF. The in-hospital mortality between different groups of patients varied from 12.4% to 69.6%. (Table 2) Patients with double organ failure had much poorer outcomes than those with single organ failure, especially those with “Concurrent AKI-ARF”. (Table 2, Figure 2) Our study also showed that the onset-based classification of AKI and ARF interplay has shown different risk profiles. (Table 3, 4)

In our study, the in-hospital mortality rates of patients in each group were higher than those previously reported in high-resource-settings.^{4, 26-29} For example, an observational cohort by Darmon et al. showed that the in-hospital mortality of AKI with acute respiratory distress syndrome (ARDS) were 42.3%. These distinct findings are probably due to the different risk associated with the resource-limited settings. One of the main factors is the delayed ICU admission which could be reflected by the earlier onset of AKI and ARF in the ICUs (median time to organ failure onset 1 day for ARF and 2 days for AKI). Among patients with single organ failure, we observed that the in-hospital mortality of “ARF alone” appeared to be higher than “AKI alone”. This may be due to the higher severity of acute illness which were reflected by higher APACHE II score and SOFA score in “ARF alone”. After adjusting severity scores as confounders, the adjusted odds ratio of “AKI alone” and “ARF alone” on in-hospital mortality were not statistically different (Table 3). This might imply that the definition of AKI by KDIGO stage 2 and the definition of ARF by mechanical ventilation status reflect similar mortality outcomes.

Another interesting result of our analysis is that the outcome of AKI-ARF interaction depends not only on the additive effect of the total number of organ failure but also the timing of organ failure which results in the highest in-hospital mortality among those with “Concurrent AKI-ARF”. Though the higher severity of concurrent occurrence of organ failure may be confounded by the shorter time of organ failure evolution, contradicting evidence were described by Sakr et al. that the time required for ICU patients to reach the highest degree of organ failure was shorter in survivors.²⁹ Thus, the different pattern of AKI and ARF interaction may be regarded as different clinical entity.

From our analysis, fluid overload, defined by positive fluid balance of more than 10% of the actual bodyweight, was a major independent risk factor for the development of secondary organ failure in both AKI after ARF and ARF after AKI. This finding was consistent with many studies in the past.³⁰⁻³² This signifies the importance of conservative fluid management to prevent further organ failure after an occurrence of either AKI or ARF as fluid overload is a modifiable risk factor.

While higher maximum AKI staging was a risk factor for ARF after AKI, renal recovery was an independent protective factor. These results suggest that the patients with severe and/or persistent AKI are at higher risk of subsequent development of ARF. The dose-response relationship further validates the causality between AKI and ARF. Therefore, providing proper AKI management may also improve pulmonary outcomes.¹³

Unsurprisingly, vasopressor use and higher APACHE II score were both independent risk factors for AKI after ARF. Though this may merely reflect the higher severity of illness, the independent relationship between vasopressor use and AKI development after ARF may also suggest unstable hemodynamics as a pathophysiological mechanism of AKI in patients with ARF. Moreover, obesity was also found to increase the risk of AKI development after ARF. This result was corroborated by the study by Soto et al. which observed obesity as an independent risk factor for development of AKI in 751 patients with acute respiratory distress syndrome.³³ However, the underlying mechanism is still yet to be elucidated.

To our knowledge, this is one of the first few studies that demonstrates the patterns of AKI and ARF and their relevance to the clinical outcomes. A key strength of our study is the large database of patients and its multicenter, including a wide coverage of population in Southeast Asia and a wide variety of ICUs. It also contains the data regarding the process of care i.e., reimbursement data and levels of hospital. This data are very important and highly relevant to the treatment decision especially in the limited-resource settings.³⁴ Another strong point is that our AKI definition and staging adhere to the KDIGO criteria which incorporates both serum creatinine and urine output data. Furthermore, the availability of data permitted the detailed analysis of risk factors of AKI after ARF and ARF after AKI, something that has previously received little attention.

We acknowledge a number of limitations of our study. First, because the parent study, the SEA-AKI study, mainly focused on risk factors for AKI, we lack some of the important ARF-related data including the etiology of ARF, blood gas, and mechanical ventilator settings. However, a large observational study by Panitchote et al. reported that ventilator-specific variables had no impact on the development of AKI in patients with ARDS.²⁷ Therefore, including those variables may not substantially alter the findings of our study. Second, our study covers only short-term outcomes, namely, the in-hospital mortality. The longer-term outcomes still needed to be further elucidated. Third, the number of patients in “Concurrent AKI-ARF” is relatively low because most patients who simultaneously met criteria of AKI and ARF on the day of ICU admission could not be determined whether AKI and/or ARF was developed prior to the ICU admission and, hence, need to be excluded from our analysis. In the resource-limited settings, large number of patients are mechanically ventilated outside the ICUs due to short supply of ICU beds.³⁵ Therefore, we could not determine the true onset of those who developed ARF since the first day of the ICU admission. Fourth, true prior baseline serum creatinine levels were determined only in 22% of patients and we chose the reference creatinine from the lowest value between the first serum creatinine on the day of admission and the MDRD formula assuming a GFR of at least 75 mL/min/1.73 m². If a patient had a history of CKD, then we used the first available serum creatinine as the baseline serum creatinine, as MDRD back calculation assumes that patients do not have CKD. Lastly, the amount of urine output was recorded on the 24-hour basis. Therefore, the modified urine output criteria were used for the diagnosis of AKI. This approach would have delayed the diagnosis in some of the patients with stage 2 AKI by urine output which may result in misclassification of AKI-ARF pattern. However, we allowed the time span of 24-48 hours between each pattern in order to compensate the risk of misclassification.

Conclusion

AKI and ARF are very prevalent in the ICU. The outcomes of the interaction of AKI and ARF are severe, especially in the resource-limited settings. Based on the sequence of organ failure occurrence, different patterns of AKI and ARF and their distinct clinical outcomes were identified. While the risk factors of in-hospital mortality of each pattern of AKI and ARF were almost similar, the risk factors for the development of secondary organ failure varied by the condition of the primary organ failure. Fluid optimization may be the key to prevent the development of secondary organ failure in the AKI and ARF interaction. The results of our study should foster further research into the clear understanding of lung-kidney interactions in critically ill patients.

Declarations

Ethical approval and consent to participate

The study protocol was reviewed by the Institutional Review Board at each participating site and the need for informed consent was waived. For this study, the Institutional Review Board of Faculty of Medicine, Chulalongkorn University approved the study (IRB 440/63).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

WK, SP, NL, and NS were responsible for the study concept and design. WK, SP, NL, and NS were responsible for the data acquisition. WK and KS were responsible for statistical analysis. WK, SP, ST, NL, JK and NS were responsible for data interpretation. WK, SP, ST, NL, and NS were responsible for drafting the main manuscript. WK prepared the figures. All authors reviewed the manuscript.

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Tables

Table 1

Baseline characteristics stratified by acute kidney injury and acute respiratory failure patterns

	Overall	No AKI/ARF	ARF alone	AKI alone	ARF first	AKI first	Concurrent AKI-ARF	P-value
N	5468	2156	1920	632	658	79	23	
Age, mean (SD), years	59.3 (18.7)	57.6 (17.9)	58.8 (19.6)	60.8 (18.1)	64.5 (18.0)	60.8 (17.4)	62.1 (20.5)	<0.001
Female, n (%)	2253 (41.2)	885 (41.0)	748 (39.0)	286 (45.3)	289 (43.9)	35 (44.3)	10 (43.5)	0.058
Country, n (%)								<0.001
Thailand	3247 (59.4)	856 (39.7)	1355 (70.6)	390 (61.7)	586 (89.1)	43 (54.4)	17 (73.9)	
Indonesia	772 (14.1)	446 (20.7)	166 (8.6)	86 (13.6)	42 (6.4)	27 (34.2)	5 (21.7)	
Laos	1449 (26.5)	854 (39.6)	399 (20.8)	156 (24.7)	30 (4.6)	9 (11.4)	1 (4.3)	
Hospital type, n (%)								<0.001
Provincial	1152 (21.1)	563 (26.1)	310 (16.1)	162 (25.6)	108 (16.4)	8 (10.1)	1 (4.3)	
Regional	1109 (20.3)	219 (10.2)	519 (27.0)	139 (22.0)	212 (32.2)	14 (17.7)	6 (26.1)	
University	3207 (58.7)	1374 (63.7)	1091 (56.8)	331 (52.4)	338 (51.4)	57 (72.2)	16 (69.6)	
ICU type, n (%)								<0.001
Surgical	313 (5.7)	148 (6.9)	119 (6.2)	27 (4.3)	11 (1.7)	8 (10.3)	0 (0.0)	
Mixed	2713 (49.8)	1409 (65.7)	772 (40.3)	332 (52.6)	148 (22.5)	43 (55.1)	9 (39.1)	
Medical	2425 (44.5)	588 (27.4)	1026 (53.5)	272 (43.1)	498 (75.8)	27 (34.6)	14 (60.9)	
Reimbursement (%)								<0.001
UC. SS	2547 (46.9)	773 (36.0)	1060 (55.6)	251 (39.9)	414 (63.5)	40 (50.6)	9 (42.9)	
Government	1367 (25.2)	589 (27.4)	367 (19.2)	199 (31.6)	173 (26.5)	28 (35.4)	11 (52.4)	
Self pay	1521 (28.0)	785 (36.6)	480 (25.2)	179 (28.5)	65 (10.0)	11 (13.9)	1 (4.8)	
BMI, n (%)								<0.001
Normal	3671 (67.4)	1549 (71.9)	1295 (67.9)	393 (62.3)	380 (57.9)	41 (53.2)	13 (56.5)	
Overweight	974 (17.9)	392 (18.2)	259 (13.6)	133 (21.1)	162 (24.7)	25 (32.5)	3 (13.0)	
Obese	215 (3.9)	53 (2.5)	66 (3.5)	47 (7.4)	44 (6.7)	3 (3.9)	2 (8.7)	

Underweight	589 (10.8)	161 (7.5)	287 (15.0)	58 (9.2)	70 (10.7)	8 (10.4)	5 (21.7)	
Comorbidity, n (%)								
Hypertension	2027 (37.1)	822 (38.1)	651 (33.9)	247 (39.1)	265 (40.3)	32 (40.5)	10 (43.5)	0.016
DM	1217 (22.3)	485 (22.5)	363 (18.9)	172 (27.3)	160 (24.4)	31 (39.2)	6 (26.1)	<0.001
CKD	356 (6.5)	127 (5.9)	75 (3.9)	97 (15.3)	46 (7.0)	9 (11.4)	2 (8.7)	<0.001
CAD	384 (7.0)	118 (5.5)	126 (6.6)	67 (10.7)	66 (10.1)	5 (6.3)	2 (8.7)	<0.001
CVD	215 (3.9)	58 (2.7)	84 (4.4)	25 (4.0)	46 (7.0)	2 (2.5)	0 (0.0)	<0.001
Malignancy	415 (7.6)	151 (7.0)	149 (7.8)	42 (6.6)	63 (9.6)	8 (10.1)	2 (8.7)	0.27
Primary diagnosis, n (%)								
Cardiovascular disease	1615 (29.6)	626 (29.0)	465 (24.2)	244 (38.7)	249 (37.8)	23 (29.5)	8 (34.8)	<0.001
Renal disease	327 (6.0)	114 (5.3)	111 (5.8)	50 (7.9)	40 (6.1)	11 (14.1)	1 (4.3)	0.009
Infectious disease	1332 (24.4)	309 (14.3)	581 (30.3)	127 (20.1)	284 (43.2)	28 (35.9)	3 (13.0)	<0.001
Gastrointestinal disease	639 (11.7)	270 (12.5)	209 (10.9)	82 (13.0)	70 (10.6)	8 (10.3)	0 (0.0)	0.18
Hematologic disease	188 (3.4)	52 (2.4)	62 (3.2)	24 (3.8)	40 (6.1)	9 (11.5)	1 (4.3)	<0.001
Pulmonary disease	1171 (21.4)	189 (8.8)	638 (33.2)	57 (9.0)	274 (41.6)	8 (10.3)	5 (21.7)	<0.001
Neurological disease	565 (10.3)	184 (8.5)	277 (14.4)	29 (4.6)	68 (10.3)	5 (6.4)	2 (8.7)	<0.001
Rheumatologic disease	94 (1.7)	25 (1.2)	32 (1.7)	11 (1.7)	23 (3.5)	2 (2.6)	1 (4.3)	0.004
Oncologic disease	388 (7.1)	139 (6.4)	157 (8.2)	31 (4.9)	54 (8.2)	4 (5.1)	3 (13.0)	0.031
Surgical-related disease	1006 (18.4)	494 (22.9)	363 (18.9)	92 (14.6)	42 (6.4)	10 (12.8)	5 (21.7)	<0.001
Metabolic disease	242 (4.4)	98 (4.5)	79 (4.1)	41 (6.5)	19 (2.9)	3 (3.8)	2 (8.7)	0.040
SOFA score, mean (SD)	5.2 (3.4)	3.7 (3.1)	6.3 (3.0)	4.6 (3.1)	7.1 (3.2)	7.3 (3.4)	5.4 (3.3)	<0.001
Non renal/respiratory SOFA score, mean (SD)	3.2 (2.8)	1.8 (2.3)	4.2 (2.5)	2.0 (2.3)	5.4 (3.0)	5.3 (3.1)	5.0 (3.2)	<0.001

APACHE II, mean (SD)	14.6 (7.3)	11.7 (7.2)	17.1 (6.5)	12.7 (6.0)	19.1 (6.3)	15.9 (5.4)	12.8 (4.6)	<0.001
Time to AKI, median (IQR), days	2 [1, 3]	-	-	1 [1, 2]	3 [2, 5]	1 [1, 1]	2 [2, 3]	<0.001
Time to ARF, median (IQR), days	1 [1, 1]	-	1 [1, 1]	-	1 [1, 1]	2 [2, 4]	2 [2, 3]	<0.001
Anemia, n (%)	1631 (29.8)	628 (29.1)	524 (27.3)	209 (33.1)	234 (35.6)	31 (39.2)	5 (21.7)	<0.001
Percent fluid overload, mean (SD)	12.4 (26.1)	6.8 (20.1)	15.6 (28.6)	10.1 (22.7)	17.8 (30.6)	15.4 (22.0)	12.3 (24.3)	<0.001
Vasopressor, n (%)	2433 (44.5)	948 (44.0)	811 (42.2)	255 (40.3)	362 (55.0)	46 (58.2)	11 (47.8)	<0.001

ICU, intensive care unit; UC, universal coverage; SS, social security; BMI, body mass index; DM, diabetes mellitus; CKD, chronic kidney disease; CAD, coronary artery disease; CVD, cerebrovascular disease; SOFA, sequential organ failure assessment; APACHE, Acute Physiology and Chronic Health Evaluation; AKI, acute kidney injury; ARF, acute respiratory failure.

Table 2

Clinical outcomes stratified by acute kidney injury and acute respiratory failure patterns

	Overall	No AKI/ARF	ARF alone	AKI alone	ARF first	AKI first	Concurrent AKI-ARF	P-value
N	5468	2156	1920	632	658	79	23	
Hospital death, n (%)	1373 (25.1)	268 (12.4)	605 (31.5)	92 (14.6)	349 (53.0)	43 (54.4)	16 (69.6)	<0.001
Length of ICU stay (day), median [IQR]	3 [2, 6]	2 [2, 3]	4 [3, 8]	3 [2, 5]	7 [4, 14]	5 [4, 8]	5 [4, 7]	<0.001
Length of hospital stay (day), median [IQR]	9 [5, 15]	7 [4, 11]	11 [6, 20]	8 [5, 14]	14 [7, 29]	10.5 [5, 18]	9 [5, 17.5]	<0.001
Total ventilator day, median [IQR]	0 [0, 3]	-	3 [1, 6]	-	5 [3, 12]	2 [1, 5]	3 [1.5, 4]	<0.001
Ventilator free day, median [IQR]	7 [3, 12]	7 [4, 11]	6 [2, 14]	8 [5, 14]	6 [1, 15.25]	6.5 [2, 13.75]	5 [2.5, 12.5]	<0.001
Renal recovery at discharge, n (%)	269 (19.3)	-	-	125 (19.8)	127 (19.3)	15 (19)	2 (8.7)	0.62

ICU, intensive care unit.

Table 3

Risk factors for in-hospital mortality

Variables	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
AKI-ARF pattern				
No AKI/ARF	Reference		Reference	
ARF alone	3.24 (2.76-3.81)	<0.001	4.29 (2.97-6.19)	<0.001
AKI alone	1.2 (0.93-1.54)	0.16	2.85 (1.86-4.39)	<0.001
ARF first	7.96 (6.52-9.72)	<0.001	13.45 (9-20.1)	<0.001
AKI first	8.41 (5.31-13.4)	<0.001	10.91 (5.43-21.9)	<0.001
Concurrent AKI-ARF	16.1 (6.81-42.22)	<0.001	52.01 (16.86-160.4)	<0.001
Age, 10 years	1.04 (1.01-1.08)	0.014	0.97 (0.92-1.04)	0.41
Female	1.01 (0.89-1.14)	0.89	-	-
Hospital type				
Provincial hospital	Reference		Reference	
Regional hospital	1.1 (0.89-1.35)	0.38	0.86 (0.35-2.16)	0.76
University hospital	1.63 (1.39-1.93)	<0.001	1.39 (0.6-3.21)	0.44
ICU type				
Surgical ICU	Reference		Reference	
Mixed ICU	11.54 (6.61-22.53)	<0.001	8.69 (1.81-41.63)	0.007
Medical ICU	8.13 (4.64-15.89)	<0.001	5.66 (1.26-25.48)	0.024
Reimbursement				
UC, SS	Reference		Reference	
Government	0.97 (0.82-1.13)	0.67	1.15 (0.92-1.46)	0.22
Self pay	1.79 (1.55-2.06)	<0.001	0.93 (0.6-1.44)	0.75
BMI				
Underweight	1.2 (0.99-1.46)	0.059	1.3 (0.98-1.74)	0.07
Normal	Reference		Reference	
Overweight	0.8 (0.67-0.95)	0.01	0.82 (0.63-1.08)	0.16
Obese	0.64 (0.44-0.9)	0.014	0.62 (0.38-1.03)	0.06
Comorbidity				
Hypertension	1.11 (0.98-1.26)	0.11	0.93 (0.75-1.16)	0.53
DM	1.59 (1.38-1.82)	<0.001	1.25 (0.98-1.58)	0.07
CKD	1.14 (0.89-1.45)	0.28	-	-
CAD	0.8 (0.62-1.02)	0.08	0.95 (0.68-1.35)	0.79

CVD	0.81 (0.57-1.11)	0.20	-	-
Malignancy	0.97 (0.77-1.22)	0.80	-	-
Anemia	1.88 (1.65-2.14)	<0.001	1.22 (0.98-1.51)	0.07
Vasopressor	3.38 (2.97-3.84)	<0.001	2.9 (2.31-3.63)	<0.001
APACHE II	1.15 (1.14-1.16)	<0.001	1.09 (1.07-1.11)	<0.001
Fluid overload	1.73 (1.48-2.01)	<0.001	1.43 (1.15-1.79)	0.002

AKI, acute kidney injury; ARF, acute respiratory failure; ICU, intensive care unit; UC, universal coverage; SS, social security; DM, diabetes mellitus; CKD, chronic kidney disease; CAD, coronary artery disease; CVD, cerebrovascular disease; APACHE, Acute Physiology and Chronic Health Evaluation.

Table 4

Multivariable analyses examining interactions between acute kidney injury and acute respiratory failure patterns and risk factors associated with in-hospital mortality

Interaction of AKI-ARF pattern with:	χ^2	df	P-value
Age, increase by 10 years	8.8	5	0.12
Gender	4.6	5	0.47
Hospital type	20.1	10	0.028
ICU type	15.1	9	0.09
Reimbursement	11.2	9	0.27
BMI	15.6	15	0.41
Hypertension	8.9	5	0.11
DM	0.9	5	0.97
CKD	4.9	5	0.43
CAD	0.5	4	0.97
CVD	8.1	5	0.15
Malignancy	3.6	5	0.61
Anemia	5.1	5	0.40
Vasopressor	12.0	5	0.035
APACHE II	10.1	5	0.07
Fluid overload	8.9	5	0.12

ICU, intensive care unit; DM, diabetes mellitus; CKD, chronic kidney disease; CAD, coronary artery disease; CVD, cerebrovascular disease; APACHE, Acute Physiology and Chronic Health Evaluation.

Figures

Figure 1

Figure 1

Study flow

Figure 2

Figure 2

Kaplan-Meier curve for survival after intensive care unit admission by acute kidney injury and acute respiratory failure patterns. ICU, intensive care unit; AKI, acute kidney injury; ARF, acute respiratory failure.

Figure 3

Figure 3

Adjusted survival by acute kidney injury and acute respiratory failure patterns. Survival differences are highly significant overall ($P < 0.001$). All pairwise comparisons are also significant except “No AKI/ARF” versus “AKI alone” ($P = 0.93$) and “AKI first” versus “ARF first” ($P = 0.22$). AKI, acute kidney injury; ARF, acute respiratory failure.

Supplementary Files

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