ORIGINAL ARTICLE

Incidence, Outcomes, and Predictors of Subphenotypes of Acute Kidney Injury among Acute Respiratory Distress Syndrome Patients: A Prospective Observational Study

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Abstract

Background: Acute kidney injury (AKI) is a heterogeneous syndrome with subphenotypes. Acute kidney injury is one of the most common complications in acute respiratory distress syndrome (ARDS) patients, which influences mortality.

Material and methods: It was a single-center observational study on 266 ARDS patients on invasive mechanical ventilation (IMV) to determine the subphenotypes of AKI associated with ARDS. Subphenotyping was done based on the serum creatinine (SCr) trajectories from day 1 to day 5 of IMV into resolving (subphenotype 1) or non-resolving (subphenotype 2) AKI.

Results: Out of 266 ARDS patients, 222 patients were included for data analysis. 141 patients (63.51%) had AKI. The incidence of subphenotype 2 AKI among the ARDS cohort was 78/222 (35.13%). Subphenotype 2 AKI was significantly more among the non-survivors (87.7% vs 36.2 %, $p < 0.001$). Subphenotype 2 AKI was an independent predictor of mortality among ARDS patients ($p < 0.001$, adjusted odds ratio 8.978, 95% CI [2.790–28.89]. AKI subphenotype 1 had higher median day 1 SCr than subphenotype 2 but lower levels by day 3 and day 5 of IMV. The median time of survival was 8 days in AKI subphenotype 2 vs 45 days in AKI with subphenotype 1 [Log-Rank (Mantel-Cox) $p < 0.001$]. The novel DRONE score (Driving pressure, Oxygenation, and Nutritional Evaluation) ≥ 4 predicted subphenotype 2 AKI.

Conclusion: The incidence of subphenotype 2 (non-resolving) AKI among ARDS patients on IMV was about 35% (vs 20% subphenotype 1 AKI), and it was an independent predictor of mortality. The DRONE score ≥ 4 can predict the AKI subphenotype 2.

Highlights: The serum creatinine trajectory-based subphenotype of AKI (resolving vs non-resolving) determines survival in ARDS patients. Non-resolving AKI subphenotype 2 is an independent predictor of mortality in ARDS. The novel DRONE score (driving pressure, oxygenation, and nutritional evaluation) ≥ 4 within 48 hours of IMV predicted the AKI subphenotype 2 among ventilated ARDS patients.

Keywords: Acute respiratory distress syndrome, Acute kidney injury, DRONE score (driving pressure, oxygenation, and nutritional evaluation), Mortality, Non-resolving, Subphenotypes, Serum creatinine trajectory.

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Introduction

Extrapulmonary organ dysfunction is present in >80% patients of with acute respiratory distress syndrome (ARDS) even at the time of onset.[1] The severity of extrapulmonary organ dysfunction correlates with the ARDS severity.[1] Acute kidney injury (AKI) is the most common extrapulmonary organ dysfunction in ARDS patients in up to 50% of subjects.[2] The fact that AKI is an independent risk factor of mortality in ARDS is known.[3,4] However, the mere diagnosis of AKI with ARDS may not portend a worse outcome. AKI is just a syndromic diagnosis or broader phenotype, with the specific subphenotypes within it having different outcomes.[5] Subphenotyping aids in prognostic enrichment (different outcomes based on a particular subphenotype) and predictive enrichment (different responses to treatment subphenotype).[5] There are different ways of subphenotyping in AKI, like clinical subphenotypes based on serum creatinine (SCr) trajectory or biomarker-based subphenotypes.[5–8] Till date, the outcomes of patients with ARDS along with AKI based on the different subphenotypes of AKI have not been studied. Secondly, there is also a paucity of data regarding the early identification of AKI subphenotypes in a particular ARDS patient within 48 hours of IMV, rather than over 5 days, with the help of SCr trajectories.[9,10]

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In a recent study, the DRONE score [Driving pressure (>15 cm H_2O), Oxygenation (ratio of partial pressure of oxygen in arterial blood to the fraction of inspired oxygen (PaO_2/FiO_2) ratio <208 mmHg, and Nutritional Evaluation (modified Nutritional Risk in Critically ill score ≥4)] has been proven to be an independent predictor of mortality in ARDS patients.[11]

Since the DRONE score included factors such as respiratory system compliance (driving pressure), oxygenation (PaO_2/FiO_2 ratio), and multiorgan dysfunction variables (the Acute Physiology and Chronic Health Evaluation [APACHE II] score and the Sequential Organ Failure Assessment [SOFA] score in the calculation of modified NUTRIC (mNUTRIC) score), it may serve as an early indicator of subphenotype of AKI in ARDS patients on invasive mechanical ventilation (IMV).

Aim: To study the incidence and predictive factors of AKI subphenotypes and evaluation of their outcomes in mechanically ventilated ARDS patients with AKI.

Objectives

- The incidence of non-resolving AKI subphenotype (subphenotype 2) among ARDS patients on IMV.
- To determine if AKI subphenotype 2 is an independent predictor of mortality in ARDS patients.
- To determine the utility of the novel driving pressure, oxygenation, and nutritional evaluation (DRONE) score within 48 hours of IMV for early identification of AKI subphenotype 2 in ARDS patients on IMV.

Primary outcome: Mortality of ICU stay.

Materials and Methods

It was a single-center prospective observational study. A total of 266 patients of ARDS were enrolled in the study. After obtaining the Institutional Ethical Committee clearance (IEC 765/2019), the study was registered in Clinical Trial Registry of India (CTRI)-CTRI/2020/04/024940. The study was conducted from September 2020 to February 2023. Written informed consent was obtained from legally authorized representatives prior to recruitment for the study.

Inclusion Criteria

- All adult patients aged 18–80 years with ARDS as defined by Berlin definition.
- ARDS patients on invasive mechanical ventilation (IMV).
- Within 48 hours of ARDS diagnosis.

Exclusion Criteria

- ARDS due to proven coronavirus disease of 2019 (COVID-19).
- Documented air-leak syndromes.
- Penetrating chest injuries.
- Pregnant patients
- Patients referred for palliative care or discharged against medical advice.
- Patients diagnosed with chronic kidney disease (CKD)

Data collection: All consecutive patients admitted with ARDS were screened for the inclusion and exclusion criteria of the study. After obtaining informed consent, the participants were enrolled into the study. Data collected on the day of admission were demographics, such as age, gender, APACHE II, SOFA score, cause of ARDS (pulmonary or extrapulmonary cause), the admitting diagnosis of patient with any comorbidities, the days from hospital to ICU admission was noted. The blood values of procalcitonin, SCr values at different timepoints (day 1, 3, and 5) presence of AKI, presence of chronic kidney disease (CKD), the requirement of renal replacement therapy (RRT) in ICU were noted.

Mechanical ventilation parameters, such as fraction of inspired oxygen (FiO_2), positive end expiratory pressure (PEEP), plateau pressure (Pplat) and driving pressure (DP) were collected and partial pressure of oxygen in arterial blood gas (PaO_2) was used to calculate the oxygenation as calculated by PaO_2/FiO_2. Measurement of Pplat was done by applying an inspiratory pause of 5 seconds to the mandatory ventilated breath (when the patient is sedated and paralyzed with no spontaneous breaths). The Pplat is displayed digitally on the ventilator and DP was calculated by subtracting PEEP from Pplat.

DRONE score calculation was done within the first 48 hours of IMV in ARDS patients: the calculation of DRONE score was done by following:[11]

DR = Driving pressure = Pplat- PEEP (Highest value in 48 hours of IMV initiation)

O= Oxygenation = PaO_2/FiO_2 (Lowest value in 48 hours of IMV initiation)

NE-nutritional evaluation = mNUTRIC score on admission to intensive care[12]

The DRONE score calculation and point assignment was performed as follows:

The highest DP ≥15 cm H_2O – 2 points were assigned, and the lowest or worst oxygenation (PaO_2/FiO_2) < 208, 4 points were assigned and for nutritional evaluation score (mNUTRIC score) >4, then 3 points were assigned. The sum of all three components gives the total DRONE score. The total score ranged from a minimum of 0 to a maximum of 9 points.

Acute Kidney Injury was defined as: An increase in SCr by ≥0.3 mg/dL within 48 hours; or increase in SCr to 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or Urine volume of 0.5 mL/kg/h for 6 hours.[13]

The trajectories of SCr of patients was noted from day 1, day 3, and day 5 of IMV. The classification for AKI was done into subphenotype 1 (resolving type) and subphenotype 2 (non-resolving type), as follows:

Subphenotype 1 (resolving AKI): Patients fitting into AKI definition on day 1 of IMV, with a decrease in SCr levels by at least ≥ 0.3 mg/dL from day 1 over the next 48 hours to day 3, or a decrease in SCr at least ≥ 0.3 mg/dL between day 3 and day 5. The day 5 SCr value must be lesser than day 1 SCr by at least ≥ 0.3 mg/dL.

Subphenotype 2 (non-resolving AKI): Patients of AKI not meeting the criteria for subphenotype 1 were considered as non-resolving AKI.

The classification was similar to that done by Bhatraju et al. except that we followed the SCr trajectories for 5 days rather than 72 hours.[6]

Sample size: Sample size was calculated as follows:

The prevalence of AKI following ARDS onset in a recent study is about 69.4%.[2]

The prevalence of non-resolving AKI patterns, among AKI patients is about 33%.[10]

Therefore, prevalence *p* was taken as 0.33*0.69 = 0.22.

Therefore, sample size for evaluating the prevalence of AKI subphenotype 2 patients among ARDS patients is calculated using the formula:

$$N = \frac{z^2 p\,(1-p)}{e^2}$$

$z = 1.96$ at 5% level of significance

e = estimated precision of 5%

$$= \frac{1.96 \times 1.96 \times 0.222 \times 0.778}{0.0025}$$

$= 266$ patients

Statistical Analysis

The analysis was done using the Statistical Software for the Social Sciences (SPSS) version 29.0 (IBM SPSS Statistics for Windows version 6.0 Armonk, NY: IBM). For variables with parametric distribution, mean ± standard deviation (SD) was calculated, whereas for the non-parametrically distributed variables, median and interquartile range (IQR) was calculated. Independent Student *t*-test was used to compare the means between two groups, and Mann–Whitney *U* test was used to compare the medians between the two groups. Chi-square test was used to determine the association between categorical variables.

For determination of predictors of outcomes, the variables that were found to be significant after the Independent Student *t*-test or the Mann–Whitney U test between the two respective groups (p-value ≤ 0.05) were taken for univariate analysis and odds ratio (OR) was calculated. For multivariable logistic regression for determining the independent predictors, the variables with p-value ≤ 0.1 in univariate analysis were selected and the adjusted OR was calculated. Only variables such as AKI and AKI subphenotypes which are part of same group were not selected for multivariable logistic regression analysis to avoid the problem of collinearity. The variables which were found to be significant after multivariable regression (p-value ≤ 0.05) were considered independent predictors of a particular outcome. Such variables were selected for plotting the receiver operating characteristic curve (ROC), and the area under the curve (AUC), p-value, cut-off value, sensitivity, specificity, and 95% confidence interval (CI) was determined for predicting the outcomes of interest. Bootstrapping multivariable logistic regression was done with 1000 samples to determine the independent predictor of mortality for additional internal validation. Kaplan–Meier survival plots were plotted to compare AKI subphenotype 1 vs 2 and the Log-Rank (Mantel-Cox) p-value was determined, along with the median survival times in both groups.

Results

The demographic data and variables of interest in the study is depicted in Table 1. Among the ARDS patients, 141 (64.1%) had AKI, and subphenotyping was possible in 123 patients. The overall incidence of AKI subphenotype 1 among the ARDS patients was 45/222 (20.27%), whereas that of AKI subphenotype 2 was 78/222 (35.13%) (Table 1). Among those with subphenotype classification, 63.4% belonged to the non-resolving (subphenotype 2) of AKI. (Table 1). Mean ± SD or median (IQR) of the physiological variables among the ARDS patients is depicted (Table 2).

A comparison of the survivors and non-survivors of ARDS revealed that the APACHE II score, SOFA score, DRONE score, and SCr levels on day 3 and day 5 of IMV were significantly higher (Table 3).

Table 1: Demographics and frequencies of variables of interest among the ARDS patients ($n = 222$)

Variables	*Number (%)*
Gender (males)	140/222 (64%)
ARDS source (Pulmonary)	74/222 (33.3%)
Serum creatinine levels available	220/222 (99.1%)
AKI	141/222 (63.51%)
AKI subphenotype classified among those with AKI	123/141 (87.94%)
AKI subphenotype 1 (resolving AKI) among the AKI patients	45/123 (36.6%)
AKI subphenotype 2 (non-resolving AKI) among the AKI patients	78/123 (63.4%)
AKI subphenotype 1 (resolving AKI) among the ARDS patients	45/222 (20.27%)
AKI subphenotype 2 (non-resolving AKI) among the ARDS patients	78/222 (35.13%)
Renal replacement therapy (HD) among patients	72/222 (32.43%)
HD among AKI patients	72/220 (32.72%)
Mortality	103/222 (46.39%)
DRONE score high (≥ 4)	110/222 (35.9%)

ARDS, acute respiratory distress syndrome; AKI, acute kidney injury; HD, hemodialysis; DRONE score, driving pressure, oxygenation and nutritional evaluation score

Table 2: The study variables with their mean ± SD or median (IQR)

Variables	*Mean ± SD/Median (IQR)*
Age ($n = 222$) years	52.27 ± 15.33
APACHE II score ($n = 222$)	16 (12–21.5)
SOFA score ($n = 222$)	8 (6–12)
Serum procalcitonin level (µg/dL) ($n = 196$)	3.07 (0.59–10.04)
Neutrophil-lymphocyte ratio (NLR) ($n = 221$)	10 (6–17)
DRONE score ($n = 222$)	4 (2–7)
MV days ($n = 213$)	5 (3–9)
LOS ICU, days ($n = 222$)	7 (4–11)
LOS hospital, days ($n = 229$)	12 (5–18)
SCr day 1 (mg/dL) ($n = 218$)	1.52 (0.92–3.04)
SCr day 3 (mg/dL) ($n = 197$)	1.68 (0.84–3.64)
SCr day 5 (mg/dL) ($n = 162$)	1.08 (0.64–3.34)

APACHE II, Acute Physiology and Chronic Health Evaluation; DRONE score, driving pressure, oxygenation and nutritional evaluation score, ICU, intensive care unit; LOS, length of stay; MV, mechanical ventilation; NLR, Neutrophil-lymphocyte ratio; SOFA score, Sequential organ failure assessment; SCr, serum creatinine

Out of the 123 patients with AKI-subphenotyping done, there were 65 non-survivors (52.84%). The Table 4 shows that among these 65 non-survivors, 87.7% belonged to AKI subphenotype 2, whereas only 12.3% belonged to AKI subphenotype 1 ($p < 0.001$ Chi-square test, Phi and Cramer's V strength of association 0.534, depicting moderately strong association between mortality and AKI subphenotype 2).

Table 3: Differences in the variables between survival and mortality groups of ARDS patients

Variables	*Survival (n = 119)*	*Non-survivors (n = 103)*	*p-value*
Age (years), mean ± SD	53.10 ± 14.09	51.75 ± 16.41	0.514*
APACHE II score, Median (IQR)	14 (10–19)	19 (15–24)	<0.001**
SOFA score, Median (IQR)	7 (5–9)	10 (8–15)	<0.001**
Procalcitonin, (ng/mL) Median (IQR)	3.17 (0.56–9.20)	2.43 (0.61–11.10)	0.861**
NLR, Median (IQR)	10 (6–15)	11 (6–23)	0.164**
DRONE score, Median (IQR)	2(0–3)	6(5–9)	<0.001**
MV days, Median (IQR)	6 (4–10)	4 (3–8)	<0.001**
SCr (day 1), (mg/dL) Median (IQR)	1.38 (0.87–3.02)	1.99 (1.03–3.08)	0.081**
SCr (day 3), (mg/dL) Median (IQR)	1.09 (0.72–2.95)	2.25 (2.56–3.79)	<0.001**
SCr (day 5), (mg/dL) Median (IQR)	0.84 (0.6–2.11)	2.57 (1.33–5.16)	<0.001**
AKI incidence, N (%)	58/119 (48.73%)	83/101 (82.17%)	<0.001**
AKI subphenotype 1 (resolving), N (%)	37 (63.8%)	8 (12.3%)	<0.001#
AKI subphenotype 2 (non-resolving), N (%)	21(36.2%)	57 (87.7%)	<0.001#
ARDS source pulmonary, N (%)	80 (67.2%)	68 (66%)	0.887#
Renal replacement therapy, N (%)	24 (20.2%)	48 (46.6%)	<0.001#
LOS (ICU), Median (IQR)	8 (6–12.25)	4 (3–9)	<0.001#

*Independent Student's *t*-test. **Man–Whitney *U*-test. #Pearson Chi-square test. AKI, acute kidney injury; APACHE II, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; DRONE score, driving pressure, oxygenation and nutritional evaluation score, ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; MV, mechanical ventilation; NLR, Neutrophil-lymphocyte ratio; SD, standard deviation; SOFA score, Sequential organ failure assessment

Table 4: Difference in the distribution of the AKI subphenotypes between the mortality and survival groups of ARDS

Variables	*Survival*	*Non-survivors*
AKI subphenotype 1, N (%)	37 (63.8%)	8 (12.3%)
AKI subphenotype 2, N (%)	21 (36.2%)	57 (87.7%)
Total	58 (100%)	65 (100%)
Pearson Chi-Square test *p*-value <0.001 Phi and Cramer V 0.534 (Moderately strong association)		

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome

Table 5: The difference between the serum creatinine values among the ARDS patients with AKI subphenotype 1 vs AKI subphenotype 2

Serum creatinine (mg/dL)	*AKI subphenotype 1 (Resolving type)*	*AKI subphenotype 2 (Non-resolving type)*	*p-value*
Day 1, Median (IQR)	2.71 (1.87–4.02)	2.15 (1.20–3.45)	0.017*
Day 3, Median (IQR)	2.04 (1.15–3.85)	3.40 (2.06–4.64)	0.001*
Day 5, Median (IQR)	1.37 (0.68–3.06)	3.92 (2.29–5.45)	<0.001*

*Mann–Whitney *U*-test. AKI, acute Kidney injury; IQR, interquartile range

The AKI subphenotype 1 had a significantly higher median SCr level on day 1 of IMV as compared with the subphenotype 2 (2.71 mg/dL vs 2.15 mg/dL), whereas it was reversed in day 3 (2.04 vs 3.40 mg/dL) and 5 (1.97 vs 3.92mg/dL) of IMV (Table 5). The median SCr in AKI subphenotype 1 was higher on day 1 as compared with the SCr in AKI subphenotype 2, with a decrease on day 3 and day 5 of IMV (Figs 1 and 2). A persistent decrease in SCr in AKI subphenotype 1 is seen as compared with the persistent rise in AKI subphenotype 2 (Fig. 2).

Univariate and multivariable logistic regression was done to predict non-survivors of ARDS, and the AKI subphenotype 2 was an independent predictor (adjusted OR 8.978, 95% CI [2.790–28.897], $p < 0.0010$) as shown in Table 6. However, when the same variables were selected for the regression analysis and AKI subphenotype 2 was replaced with the mere presence of AKI only on either day 1,3, or 5 of IMV, then, the mere presence of AKI on days 1,3 or 5 was not an independent predictor of mortality among the ARDS patients (Table 7). Bootstrap multivariable logistic regression with 1000 samples for internal validation showed that the AKI subphenotype 2 was an independent predictor of mortality among ARDS patients ($p = 0.002$. 95% CI [1.147–5.364]).

Regarding the association of a high DRONE score (≥4) and AKI subphenotype, 71.1% of the patients with AKI subphenotype 1 had a low DRONE score < 4, whereas 68% of the patients with AKI subphenotype 2 had a high DRONE score (≥ 4) ($p < 0.001$, Chi-square test) (Table 8). The Phi and Cramer V value was 0.377 (comparatively low strength of association). The ROC plotted for the DRONE score to predict AKI subphenotype 2 depicted that the DRONE score was a reliable predictor of AKI subphenotype 2 among ARDS patients (AUC 0.706, *p*-value <0.001, 95% CI [0.613–0.800], cut-off score ≥ 4, 69% sensitivity, 68% specificity) (Fig. 3). The relationship between the DRONE score and AKI subphenotypes 1 and 2 are depicted which shows that there is a strong association between the AKI subphenotype 1 and the lower DRONE scores (score 1–3), and the AKI subphenotype 2 is strongly associated with higher DRONE scores (score 5–9) (Fig. 4).

Survival analysis with the Kaplan–Meier survival plot displayed a significant difference in survival between the ARDS patients

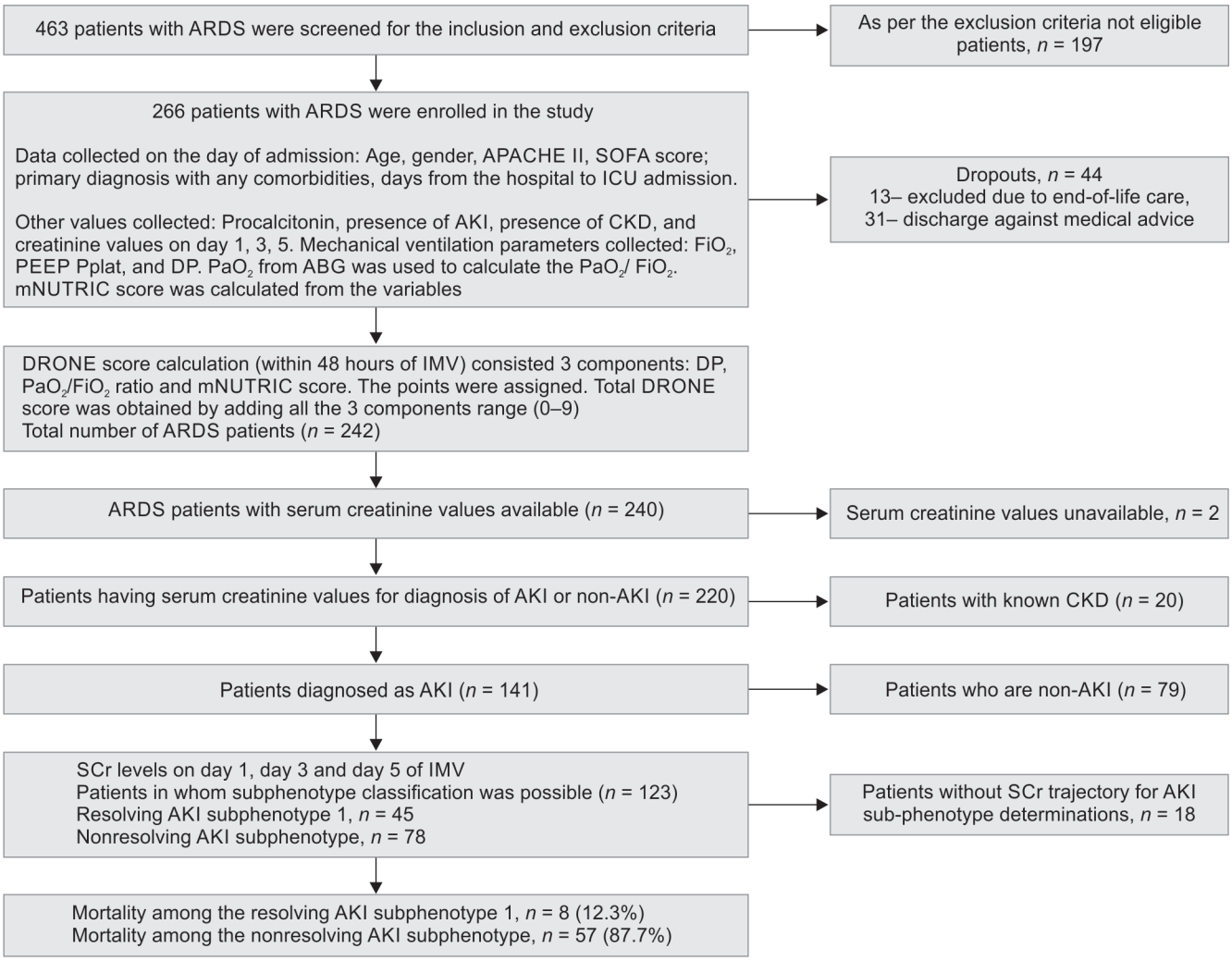

Fig. 1: Flow diagram of the methodology

ABG, arterial blood gas; AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; APACHE II, Acute Physiology and Chronic Health Evaluation; CKD, chronic kidney disease; DP, driving pressure; DRONE score, driving pressure, oxygenation and nutritional evaluation score; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; IMV, invasive mechanical ventilation; NLR, Neutrophil-lymphocyte ratio; SCr, serum creatinine; SOFA score, Sequential Organ Failure Assessment; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure; Plat, plateau pressure

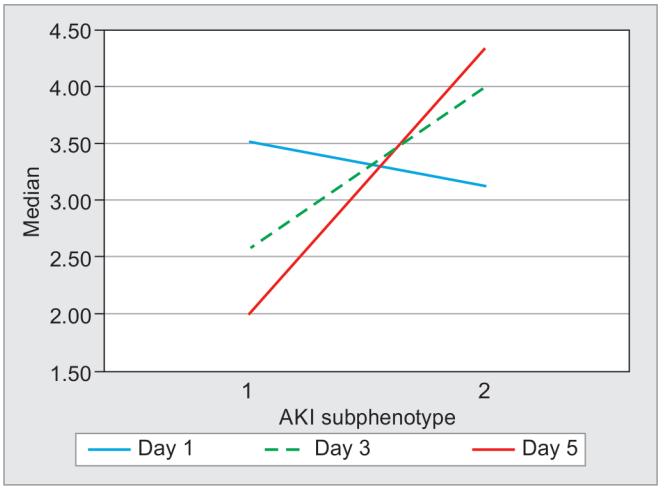

Fig. 2: The median SCr trend change from day 1, day 3 to day 5 of IMV in both the AKI subphenotypes 1 and 2

AKI, acute kidney injury; SCr, serum creatinine

with subphenotype 1 of AKI and AKI subphenotype 2 [Log-Rank (Mantel–Cox) p-value < 0.001] (Fig. 5). The median time of survival was 8 days in ARDS patients having AKI with subphenotype 2 vs 45 days in ARDS patients having AKI with subphenotype 1. There was a significant difference between the requirement for RRT among patients of AKI subphenotype 1 (35.6%) and subphenotype 2 (57.7%) ($p = 0.018$, Pearson Chi-square test).

Discussion

We found that among the ARDS patients with AKI, a majority (63.4%) had AKI subphenotype 2. In ARDS patients, the influence of positive pressure ventilation and reduced renal perfusion, reduced glomerular filtration rate, and alterations in the neurohormonal axis in the kidney are present.[14,15] About 50% of the patients with ARDS develop AKI, and out of those, 90% of them develop AKI within 48 hours of IMV.[2,16] Respiratory compliance, PEEP, and driving pressure are all factors associated with severe AKI.[17,18] However, AKI may also be due to factors such as hypotension, hypovolemia, persistent shock, and hospital-acquired causes.[5]

Table 6: Univariate and multivariable logistic regression for mortality prediction in ARDS patients with the novel DRONE score and AKI subphenotypes 1 and 2

	Univariate analysis			*Multivariable logistic regression*		
Variables	*p-value*	*OR*	*95%CI*	*p-value*	*Adjusted OR*	*95% CI*
APACHE II score	<0.001	1.126	1.074–1.181	0.334	0.948	0.852–1.056
SOFA score	<0.001	1.259	1.166–1.360	0.534	1.049	0.901–1.222
DRONE score	<0.001	1.895	1.620–2.217	<0.001	1.906	1.458–2.492
MV days	0.056	0.955	0.911–1.001	0.316	0.959	0.884–1.041
AKI subphenotype 2	<0.001	10.263	4.394–23.973	<0.001	8.978	2.790–28.897
HD required	<0.001	23.455	1.911–6.244	0.764	1.199	0.367–3.913

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; APACHE II, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; DRONE score, driving pressure, oxygenation and nutritional evaluation score; HD, hemodialysis; MV, mechanical ventilation; OR, odds ratio; SOFA score, Sequential Organ Failure Assessment

Table 7: Univariate and multivariable logistic regression for mortality prediction in ARDS patients with the novel DRONE score and the presence of AKI only without classifying for AKI subphenotypes 1 and 2

	Univariate analysis			*Multivariable logistic regression*		
Variables	*p-value*	*OR*	*95%CI*	*p-value*	*Adjusted OR*	*95% CI*
APACHE II score	<0.001	1.126	1.074–1.181	0.284	0.961	0.974–6.865
SOFA score	<0.001	1.259	1.166–1.360	0.118	1.094	0.977–1.226
DRONE score	<0.001	1.895	1.620–2.217	<0.001	1.869	1.547–2.257
MV days	0.056	0.955	0.911–1.001	0.279	0.968	0.884–1.041
AKI present	<0.001	4.850	2.599–9.048	0.057	2.586	0.912–7.779
HD required	<0.001	23.455	1.911–6.244	0.015	3.112	1.245–7.779

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; APACHE II, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; DRONE score, driving pressure, oxygenation and nutritional evaluation score; HD, hemodialysis; MV, mechanical ventilation; NLR, Neutrophil-lymphocyte ratio; OR, odds ratio; SOFA score, Sequential Organ Failure Assessment

Table 8: Relation between high DRONE score and AKI subphenotypes 1 and 2

Variable	*Low DRONE score (<4) N (%)*	*High DRONE score (≥4) N (%)*
AKI subphenotype 1	32(71.1%)	13 (28.9%)
AKI subphenotype 2	25 (32.1%)	53 (67.9%)
Pearson Chi-square *p*-value <0.001 Phi and Cramer's V strength of association 0.377		

AKI, acute kidney injury; DRONE score, driving pressure, oxygenation and nutritional evaluation score

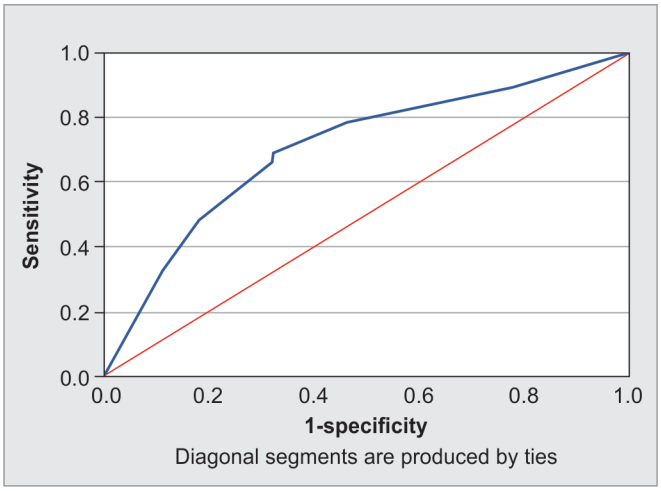

Fig. 3: ROC of the DRONE score predicting the subphenotype 2 of AKI in ARDS patients (AUC 0.706, *p*-value <0.001, 95% CI [0.613-0.800], cut-off score ≥ 4, 69% sensitivity, 68% specificity)

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; AUC, area under the curve; CI, confidence interval; DRONE score, driving pressure, oxygenation and nutritional evaluation score; ROC, receiver operating characteristic curve

The AKI due to these various causes has different outcomes and responses to treatment.[5] Thus, subphenotypes of AKI are essential to understand their role as mortality predictors.[5]

Just like AKI may be due to various factors, and can be classified into subphenotypes, the AKI in patients with ARDS can lead to varying complications which may or may not be responsive to renal replacement therapy (RRT).[14] The "traditional complications" of AKI are electrolyte derangements, uremia, and fluid overload, with poor oxygenation.[14] These complications are amenable to RRT.[14] However, the "non-traditional" complications of AKI are often not correctable by RRT and lead to a mortality of up to 60%.[15,19,20] These "non-traditional" complications include inflammatory lung injury, cardiac dysfunction, and immune paralysis.[14]

We found that even though the incidence of AKI was significantly higher in the non-survivors of ARDS, the mere presence of AKI was not an independent predictor of mortality. Rather, the non-resolving (subphenotype 2) of AKI is an independent predictor of mortality after regression analysis, which was validated even after the bootstrapping method. We found that even though patients with resolving AKI (subphenotype 1) had significantly higher SCr levels on day 1 (median 2.71 mg/dL) as compared

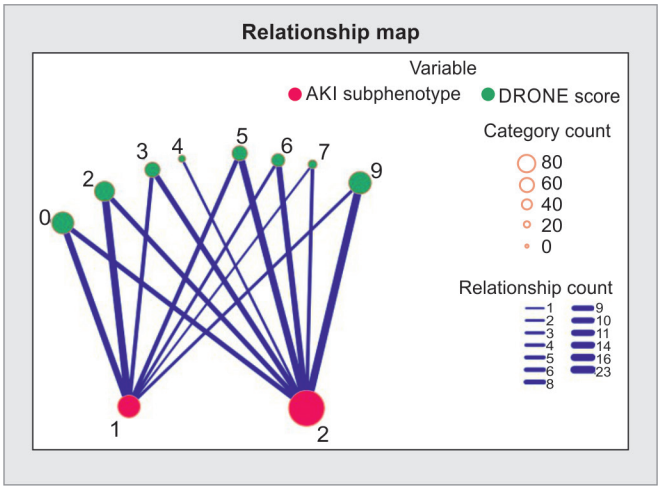

Fig. 4: The relationship map of the DRONE score to the AKI subphenotypes 1 and 2

AKI, acute kidney injury; DRONE score, driving pressure, oxygenation and nutritional evaluation score

The red circles mentioned 1 and 2 represent the AKI subphenotypes 1 and 2 respectively, and the green circles represent the DRONE scores (Range of 0-9). Blue lines represent the strength of the relationship, with thicker lines representing a stronger association. There is a strong association between the AKI subphenotype 1 and the lower DRONE scores (score 1-3), whereas the AKI subphenotype 2 is strongly associated with higher DRONE scores (score 5-9)

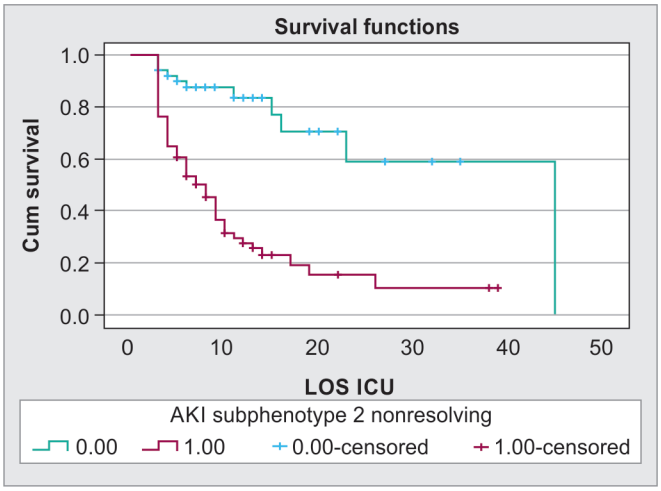

Fig. 5: Kaplan–Meier survival analysis plot showing the difference in survival between the ARDS patients with subphenotype 1 of AKI and subphenotype 2 of AKI. The green line depicts AKI subphenotype 1. The red line depicts AKI subphenotype 2

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome

with AKI subphenotype 2 (median 2.15 mg/dL), eventually by day 3 and day 5 of IMV, the SCr levels were significantly lower in the AKI subphenotype 1. This supports the fact that single-point classification of patients into AKI or non-AKI categories in ARDS patients based on the severity may not predict outcomes, rather subphenotyping based on serum creatinine trajectories is the reliable predictor. Our results are similar to that of Bhatraju et al. where the authors found that the creatinine trajectory classifies AKI subphenotypes with different risks for mortality, even within AKI cases of similar severity.[6] However, in contrast to the aforementioned study where the creatinine trajectory was followed for 72 hours, we followed the trajectory for up to 5 days.[6] We also found that the need for RRT was significantly different among the AKI patients in the two subphenotypes. (RRT in 36% of patients of AKI subphenotype 1 vs 58% of patients in AKI subphenotype 2 (Pearson Chi-square *p*-value = 0.018). However, the mortality was higher in AKI subphenotype 2 though more underwent RRT. This shows that AKI patients with subphenotype 2 showed poorer response to therapy or they have a difference in predictive enrichment as compared with patients with subphenotype 1. However, we did not investigate whether this differential response to RRT could possibly be due to the aforementioned "non-traditional" complications of AKI on lung and heart in patients with subphenotype 2.[14]

We found that the novel DRONE score (comprising of DP, PaO_2/FiO_2 ratio, and the mNUTRIC score) ≥ 4 predicted the AKI subphenotype 2 in ARDS. Our results may be due to three facts, also corroborated in recent literature. Firstly, DP has been shown to be the best ventilator parameter for predicting mortality in ARDS, and higher DP has also been associated with AKI.[21,22] Secondly, in a recent study, patients with non-recovery of AKI were associated with severe ARDS, which explains that the DRONE score encompassing poorer oxygenation can predict AKI subphenotype 2.[23]

Thirdly, poor nutritional status worsens outcomes of AKI in critically ill, which is again incorporated in the DRONE score.[24]

Apart from these, literature shows that shock and comorbid illnesses like hypertension and malignancy are associated with non-recovery of AKI in ARDS patients.[22] It is notable, that co-morbid illnesses are part of the calculation of DRONE score as well since it incorporates APACHE II and mNUTRIC score. Likewise, the presence of shock is incorporated in the SOFA score used for calculation of the DRONE score.[11]

There were certain strengths of the study. It proved that ARDS patients with AKI having initial higher creatinine levels need not necessarily have a poorer outcome. Outcomes are based on the recovery versus non-recovery subphenotypes from the initial AKI. We used a creatinine trajectory (day 1–day 5)-based AKI subphenotype, which can be used in resource-limited settings as well. It is the first study of its kind that could devise an objective score that can be used within 48 hours of IMV in ARDS patients with AKI to predict possible subphenotype outcomes on day 5 of IMV. However, there were certain limitations, being a single-center study, with small sample size. Also, apart from procalcitonin, no other renal or inflammatory biomarkers were evaluated as to its possible role in AKI subphenotype 2. We did not determine the cause of AKI based on pre-renal (hypovolemic shock), intrinsic renal (nephrotoxic medications) or post-renal causes.

Conclusion

The incidence of subphenotype 2 (non-resolving) AKI among ARDS patients on IMV was about 35% as compared with about 20% of subphenotype 1 (resolving) AKI. The subphenotype 2 AKI was an independent predictor of mortality. The DRONE score ≥ 4 within 48 hours of IMV in ARDS patients can predict the subphenotype 2 (non-resolving) AKI. The findings need to be validated in future.

Clinical Significance

Even though ARDS patients with AKI may have higher baseline creatinine levels, it is the creatinine trajectory-based subphenotype of AKI (resolving vs non-resolving) that determines the survival outcomes in ARDS patients, and not the mere presence of AKI. Non-resolving subphenotype 2 AKI with ARDS is an independent predictor of mortality. The novel DRONE score (driving pressure, oxygenation, and nutritional evaluation) ≥ 4 within 48 hours of IMV predicted the subphenotype 2 AKI among ventilated ARDS patients.

Data Availability

The data will be provided by the first or corresponding author upon email request. This is due to the reason of patient data confidentiality.

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