Kidney Diseases

Research Article

Kidney Dis 2024;10:262–273
DOI: 10.1159/000539139

Received: November 14, 2023
Accepted: April 23, 2024
Published online: May 7, 2024

Clinical Characteristics and the Prognostic Impact of Acute Kidney Injury in Critically Ill Patients with Invasive Pulmonary Aspergillosis in the Intensive Care Unit: A Retrospective, Single-Center Study

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Keywords
Invasive pulmonary aspergillosis · Acute kidney injury · Acute kidney injury management

Abstract

Introduction: The incidence and impact of acute kidney injury (AKI) in patients with invasive pulmonary aspergillosis (IPA) admitted to the intensive care unit (ICU) are unknown. ***Methods:*** This retrospective study included 140 patients who were diagnosed with IPA and admitted to the medical ICU of China-Japan Friendship Hospital in Beijing, China. AKI was defined according to the Kidney Disease: Improving Global Outcomes guidelines. Data on demographic characteristics, comorbidities, laboratory tests, treatments, and prognosis at ICU admission were collected. ***Results:*** The rate of AKI was 71.4% ($n = 100$), and approximately 30% of the patients had preadmission acute kidney dysfunction. Of the 100 patients with AKI, 19, 8, and 73 patients had stage I, II, and III AKI, respectively, and 64 (87.6%) patients required continuous renal replacement therapy. Overall ICU mortality rate was 52.1%. Irreversible AKI was a strong independent risk factor for ICU mortality (odds ratio 13.36, 95% confidence interval 4.52–39.48, $p < 0.001$), followed by chronic lung disease, use of intermittent positive-pressure ventilation, and long-term corticosteroid treatment within 1 year prior to ICU admission. Higher cardiac troponin I levels at admission and worse volume control during the first 7 days of ICU stay were potential predictive factors of irreversible kidney dysfunction. Patients with irreversible AKI and those who died during the ICU stay had greater volume overload during the first 14 days of ICU stay. Patients who survived received earlier renal replacement therapy support after ICU admission compared to those who died (median, 2 vs. 5 days; $p = 0.026$). ***Conclusion:*** Compared to the patients with IPA in the absence of AKI, those with AKI presented with more volume overload, worse disease burden, and required stronger respiratory support, while experiencing worse prognosis. Irreversible AKI was a strong predictor of mortality in patients with critical IPA. Better volume control and earlier CRRT initiation should be considered key points in AKI management and prognostic improvement.

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Introduction

Invasive pulmonary aspergillosis (IPA) is a life-threatening putative infection in immunocompromised patients [1] and those who lack classic immunosuppressive factors [2] admitted to the intensive care unit (ICU). Severe invasive aspergillosis can lead to the sudden loss of excretory kidney function, resulting in persistent kidney dysfunction associated with irreversible loss of nephrons and kidney cells in some patients [3]. Acute kidney injury (AKI) is a common complication of critical infections and independently associated with mortality [4, 5]. However, information on the incidence and impact of AKI in patients with IPA is limited. Previous studies suggested that patients with putative IPA developed acute kidney impairment [6], and severe kidney injury requiring continuous renal replacement therapy (CRRT) was an independent risk factor for ICU mortality [7]. AKI management in critical pulmonary aspergillosis is challenging, and details on volume control and the timing of kidney support have not been established. The present study aimed to evaluate whether the presence of AKI was associated with worse outcomes in critically ill patients with IPA admitted to the ICU.

Methods

Study Patients and Data Collection

This retrospective study included critically ill adult patients diagnosed with IPA who were admitted to the medical ICU of China-Japan Friendship Hospital in Beijing, China, between February 2015 and May 2022. The diagnoses of proven, probable, and possible IPA were based on the European Organization for Research and Treatment definitions [8], which ranged from the definitive histopathologic evidence of fungal invasion (proven) to a set of host risk factors and clinical features related (probable) or unrelated (possible) to positive mycologic criteria. Data on baseline demographic and clinical characteristics and laboratory data at ICU admission were collected using medical records. Baseline prednisolone-equivalent cumulative corticosteroid doses during the year and the 7 days prior to ICU admission were calculated. Additionally, information on medical treatment, volume management, oxygen support, and prognosis, among others, during hospitalization were collected for all patients. Patients remained anonymous, and the requirement for informed consent was waived because of the retrospective, observational study design. The study protocol was approved by the Ethics Committee of the China-Japan Friendship hospital and was conducted in full accordance with the principles of the Declaration of Helsinki. All tests and procedures were ordered by the attending physicians in the study institution.

Definitions of AKI, Subtypes of AKI, and Indications for CRRT

AKI was defined according to the following Kidney Disease: Improving Global Outcomes guidelines [9]: increase in serum creatinine (Scr) by ≥0.3 mg/dL (≥26.5 mmol/L) within 48 h or increase in Scr to ≥1.5 times the baseline, which was known or presumed to have occurred within 7 days prior to admission, or urine volume of <0.5 mL/kg/h for 6 h. The following criteria were used to define specific AKI stages: stage I, increase in Scr by ≥0.3 mg/dL (≥26.5 mmol/L) or to 1.5–1.9 times the baseline or urine volume reduction to <0.5 mL/kg/h for 6–12 h; stage II, increase in Scr to 2.0–2.9 times the baseline or urine volume reduction to <0.5 ML/kg/h for more than 12 h; and stage III, increase in Scr by ≥4.0 mg/dL (≥353.6 mmol/L) or to 3.0 times the baseline, urine volume reduction to <0.3 mL/kg/h for >24 h, anuria for >12 h, or the initiation of renal replacement therapy (RRT) [10].

In the present study, AKI onset within and after 72 h of ICU admission was defined as early and late AKI, respectively. Acute kidney disease (AKD) was defined as the presence of clinical signs of AKI, subacute decrease in estimated glomerular filtration rate (eGFR) to <60 mL/min/1.73 m^2 or by >35%, or increase in Scr by >50% for less than 3 months after ICU admission [9]. Irreversible AKI was defined as the diagnosis of AKI during hospitalization accompanied with the deterioration of kidney function despite active treatment for at least 1 week. In this context, deterioration of kidney function was defined as a significant decline in eGFR, which could not be restored to a normal level or a continuously insufficient daily urine volume despite treatment with cautious fluid management, nutritional and glycemic control, avoidance of nephrotoxins, and the use of diuretics or RRT. Therefore, the present study included patients without comorbid chronic kidney disease (CKD) who developed persistent kidney hypofunction (AKD or CKD), which could not be resolved after treatment, and those diagnosed with CKD before IPA onset and progressed to CKD despite treatment. In the present study, CRRT included (a) RRT in patients with hyperkalemia (K^+ >6.5 mmol/L), metabolic acidosis ($HCO3^-$ <15 mmol/L), symptomatic uremia leading to acute brain injury, cerebral edema, or pericarditis, and severe liquid overload causing cardiovascular instability or acute cardiac pulmonary edema and (b) renal support for volume management, nutritional support, medication use, adjustment of acid base balance, and clearance of inflammatory factors.

Statistical Analysis

Continuous variables were presented as means ± standard deviation or medians with interquartile range, in terms of the obedience of normal distribution or not. Categorical variables were presented as absolute numbers and percentages. Continuous variables were compared using Student's *t* test or one-way analysis of variance, and categorical variables were compared using the χ^2 or Fisher's exact test, as appropriate.

Multicollinearity was determined by calculating variance inflation factor for all predictors. Variables with a variance inflation factor of ≥2.0 were not included in multivariate analysis. Continuous variables were categorized and retained for multivariate testing. Cutoff values were identified using the Youden index with receiver operator characteristic curve analysis or were based on clinically relevant cutoff values. Matrix correlation coefficient analysis was performed to determine the degree of correlation between risk factors.

Variables with a p value of <0.05 were included in univariate logistic regression. All univariate predictors with a p value of <0.10 were considered potential risk factors and included in multivariate logistic regression analysis for overall mortality using backward elimination of variables with a p value of ≥0.05 based on the conditional likelihood ratio test. Survival of specific study groups was compared using the univariate approach with the Kaplan-Meier method.

Table 1. Baseline prehospital clinical information of patients with IPA

	All patients (n = 140)	AKI group (n = 100)	Non-AKI group (n = 40)	p value
Baseline characteristics				
Age, years	61.53±15.12	61.28±15.58	62.15±14.06	0.76
Male	95 (67.9)	71 (71.0)	24 (60.0)	0.290
BMI, kg/m^2	23.30±4.17	23.23±4.12	23.48±4.35	0.756
Pre-ICU in-hospital days	6 (2–14)	10 (3–17)	8 (2–21)	0.427
Smoking history	69 (49.3)	48 (48.0)	21 (52.5)	0.769
Alcohol history	46 (32.9)	31 (31.0)	15 (37.5)	0.589
APACHE II	21.12±7.78	22.63±7.80	17.35±6.37	<**0.001**
SOFA	8.30±4.19	9.20±4.26	6.05±3.01	<**0.001**
Background diseases				
DM	38 (27.1)	31 (31.0)	7 (17.5)	0.158
HbA1c	7.00±1.50	7.11±1.41	6.73±1.70	0.304
Hypertension	57 (40.7)	43 (43.0)	14 (35.0)	0.449
Chronic lung disease	63 (45.0)	45 (45.0)	18 (45.0)	1.000
COPD	22 (15.7)	14 (14.0)	8 (20.0)	0.532
Asthma	2 (1.4)	1 (1.0)	1 (2.5)	0.999
ILD	25 (17.9)	21 (21.0)	4 (10.0)	0.197
Bronchiectasis	7 (5.0)	4 (4.0)	3 (7.5)	0.668
Chronic heart disease	47 (33.6)	34 (34.0)	13 (32.5)	0.999
Chronic renal disease	15 (10.7)	13 (13.0)	2 (5.0)	0.232
Tumor	23 (16.4)	13 (13.0)	10 (25.0)	0.139
Connective tissue diseases	25 (17.9)	19 (19.0)	6 (15.0)	0.754
Pre-hospital treatment				
Corticosteroid in 1 year	84 (60.0)	60 (60.0)	24 (60.0)	1.000
Immunosuppressor in 1 year	36 (25.7)	30 (30.0)	6 (15.0)	0.105
Corticosteroid in 7 days	68 (48.6)	46 (46.0)	22 (55.0)	0.438
Corticosteroid dose in 7 days, mg	200 (77–475)	200 (70–430)	201 (50–475)	0.899
Antibiotics	123 (87.9)	87 (87.0)	36 (90.0)	0.838
Cephalosporins	71 (50.7)	51 (51.0)	20 (50.0)	0.998
Beta-lactamase inhibitor	59 (42.1)	42 (42.0)	17 (42.5)	0.999
Quinolones	73 (52.1)	55 (55.0)	18 (45.0)	0.377
Carbapenems	49 (35.0)	34 (34.0)	15 (37.5)	0.845
>2 types of antibiotics	83 (59.3)	63 (63.0)	20 (50.0)	0.221
>3 types of antibiotics	42 (30.0)	31 (31.0)	11 (27.5)	0.838
Antifungal	36 (25.7)	25 (25.0)	11 (27.5)	0.927
Voriconazole	24 (17.1)	17 (17.0)	7 (17.5)	0.999

BMI, body mass index; SOFA, sequential organ failure assessment score; APACHE-II, Acute Physiology and Chronic Health Evaluation II score; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease. *Use of corticosteroid and the dose within 7 days before admission of ICU.

All statistical analyses were performed using R version 4.3.0. All tests were two sided, and a p value of <0.05 was considered significant.

Results

Clinical Features and Prevalence of IPA in Patients Admitted to the ICU

The study cohort included 140 patients with IPA, including 95 male and 45 female patients, who were admitted to the ICU. The baseline patient characteristics are summarized in Table 1. Briefly, the median age at diagnosis was 61.53 years. Chronic lung disease was the most common comorbidity, with interstitial lung disease and chronic obstructive pulmonary disease as the most frequent lung diseases. The other less frequent comorbidities were chronic heart disease, diabetes, connective tissue diseases, and cancer, in descending order. Fifteen patients who were diagnosed with CKD before IPA onset had already been hospitalized for an average of 10.1 days before ICU admission. The rates of patients with long-term corticosteroid and immunosuppressor

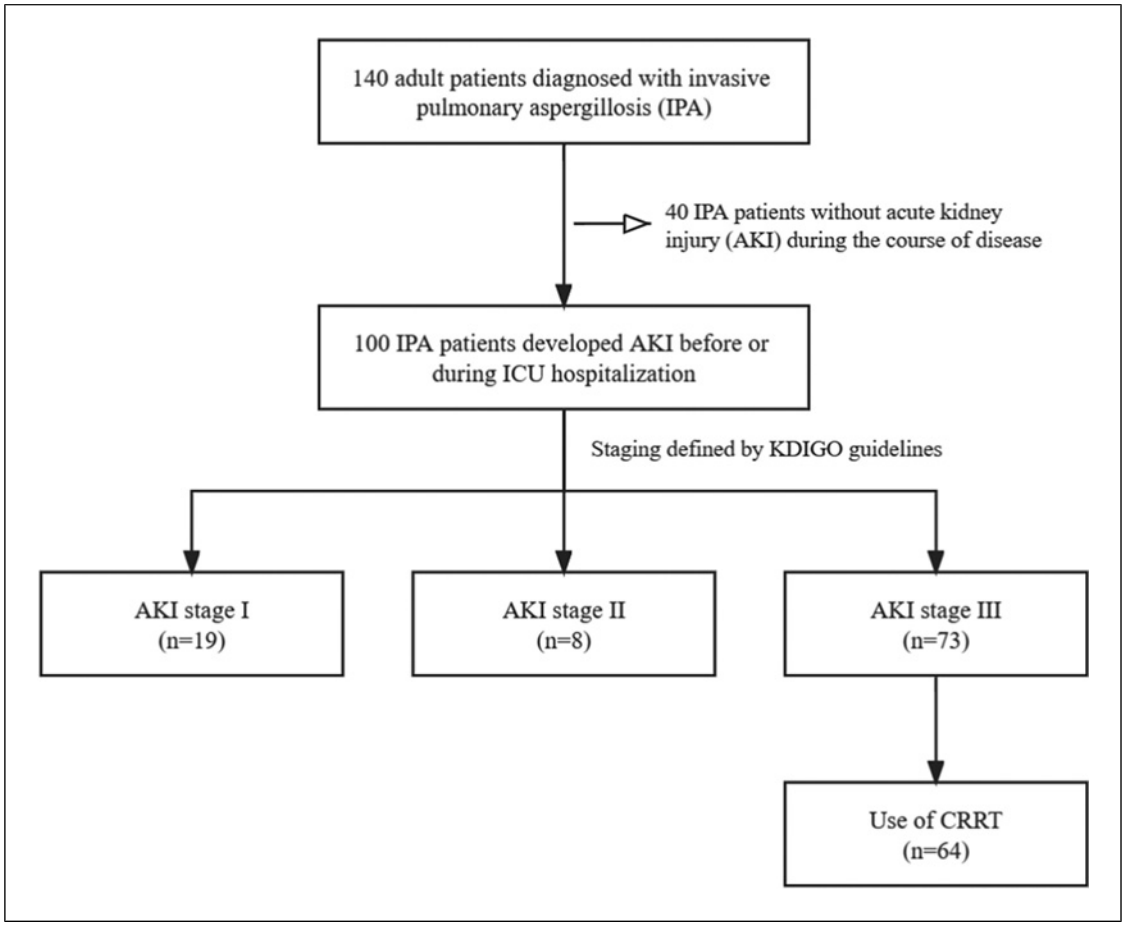


Fig. 1. Flowchart of the study.

use within 1 year before ICU admission for IPA were 60% and 25.7%, respectively. The cumulative corticosteroid dose within 7 days before ICU admission was high, with an average dose of 311.9 mg. Multiple antibiotics were administered before ICU admission in 83 (59.3%) patients, whereas prior voriconazole treatment was used in 24 (17.1%) patients before disease progression.

According to the 2021 European Organization for Research and Treatment of Cancer criteria [1], 4 patients were diagnosed with IPA based on histopathology whereas the remaining 136 patients were diagnosed with probable IPA. Among the patients with probable IPA, 60 patients (42.8%) had lower respiratory tract cultures positive for *Aspergillus* spp., including *A. fumigatus*, *A. flavus*, *A. niger*, *A. terreus*, *A. nigulans*, and *A. tubinen* in 37 (26.4%), 25 (17.9%), 6 (4.3%), 1, 1, and 1 patients, respectively. No patient was diagnosed with IPA in the present study.

Incidence of AKI in Patients with IPA

In the study cohort, 100 (71.4%) patients developed AKI (Fig. 1); approximately 30% of the patients had AKI prior to ICU admission. Of the 100 patients with AKI, 19, 8, and 73 patients had stage I, II, and III AKI, respectively, and 64 (87.6%) patients required CRRT. Moreover, 51 patients exhibited early signs of AKI within 72 h after ICU admission, whereas the remaining 49 patients developed AKI later during their ICU stay.

The comparison of the baseline characteristics, ICU laboratory results, and details of treatment, comorbidities, and complications between the patients with and without AKI are presented in Tables 1–3. Compared to the patients without AKI, those with AKI had several distinguishing features. First, the patients with AKI had relatively higher volume overload with higher systolic blood pressure, higher levels of β-nitropropionic acid, and more volume input on the first day of ICU admission. Additionally, the patients with AKI had worse disease

Table 2. Baseline in-hospital clinical and laboratory information of patients with IPA

	All patients (n = 140)	AKI group (n = 100)	Non-AKI group (n = 40)	p value
Symptoms				
Fever (>38°C)	107 (76.4)	83 (83.0)	24 (60.0)	**0.007**
Cough	129 (92.1)	95 (95.0)	34 (85.0)	0.101
Hemoptysis	16 (11.4)	13 (13.0)	3 (7.5)	0.529
Chest pain	15 (10.7)	7 (7.0)	8 (20.0)	**0.052**
Dyspnea	129 (92.1)	93 (93.0)	36 (90.0)	0.586
Nausea or vomiting	19 (13.8)	12 (12.2)	7 (17.5)	0.589
Dysuria	30 (21.7)	24 (24.5)	6 (15.0)	0.318
Edema	35 (25.4)	25 (25.5)	10 (25.0)	0.999
Heart rate, bpm	101.74±23.53	104.09±24.30	95.88±20.63	0.062
Respiratory rate, n/min	24.74±6.80	25.16±6.75	23.70±6.90	0.253
SBP, mm Hg	127.28±27.04	130.31±27.52	119.78±24.57	**0.037**
In-hospital MAP, mm Hg	98.81±18.97	100.44±18.82	94.78±18.97	0.111
In-ICU MAP, mm Hg	99.58±21.19	99.73±20.83	99.20±22.31	0.895
Moist crackles	93 (66.4)	69 (69.0)	24 (60.0)	0.412
Laboratory information				
WBC, $\times 10^9$/L	12.26±9.62	12.67±9.13	11.24±10.78	0.427
Neutrophils, $\times 10^9$/L	17.18±80.32	20.58±94.57	8.49±4.79	0.427
Lymphocytes, $\times 10^9$/L	0.68 (0.38–1.10)	0.56(0.39–1.68)	0.58 (0.37–0.98)	0.331
CD3+ CD4+ T-cell counts	251 (141–425)	255 (147–421)	225 (138–432)	0.924
Platelets, $\times 10^9$/L	176.59±94.27	179.97±93.69	168.13±96.39	0.504
hsCRP, mg/L	14.61±15.51	16.00±17.40	11.92±10.71	0.229
CRP, mg/L	114.98±71.76	113.31±71.77	118.95±72.73	0.711
PCT, ng/mL	0.72 (0.23–2.53)	0.56 (0.24–1.98)	0.31 (0.18–1.42)	0.138
ESR, mm/h	51.76±32.93	54.07±34.15	45.84±29.23	0.232
pH	7.39±0.24	7.37±0.28	7.44±0.09	0.173
$PaCO_2$, mm Hg	41.32±16.41	41.90±16.38	39.89±16.59	0.515
PaO_2/FiO_2, mm Hg	172 (119–221)	186 (130–224)	176 (121–215)	0.306
Lactate, mmol/L	2.02±1.52	2.11±1.71	1.78±0.85	0.243
Albumin, g/L	31.99±6.41	31.94±6.52	32.12±6.22	0.883
ALT, U/L	29 (18–49)	32 (16–50)	28 (19–48)	0.164
AST, U/L	35 (21–59)	35 (19–59)	39 (18–87)	0.279
TBil, μmol/L	12.1 (8.8–20.0)	10.9 (7.6–24.0)	9.3 (7.5–15.6)	0.254
APTT, s	44.05±10.38	44.79±11.10	42.23±8.15	0.188
D-dimer, mg/L	5.39±5.77	5.77±5.90	4.46±5.39	0.228
cTnI, ng/mL	0.29±0.98	0.38±1.15	0.08±0.13	0.102
BNP, pg/mL	230 (75–410)	239 (51–462)	96 (57–230)	**0.039**
BUN, mmol/L	8.4 (5.9–15.3)	10.4 (7.2–20.3)	6.4 (4.4–8.2)	**0.004**
Creatinine, μmol/L	71.8 (53.6–109.4)	90.7 (56.2–176.6)	56.3 (45.8–70.0)	**0.006**
eGFR, mL/min/1.73 m^2	87.9 (59.5–101.4)	77.9 (31.7–100.9)	97.9 (83.8–117.2)	<**0.001**
Proteinuria, g/L	0.43±0.47	0.47±0.49	0.34±0.40	0.165
Hematuresis, n/μL	116.72±674.40	151.40±800.94	35.48±115.71	0.377

SBP, systolic blood pressure; MAP, mean arterial pressure; WBC, white blood cell; CRP: C-reactive protein; PCT, procalcitonin; ESR, erythrocyte sedimentation rate; ALT, alanine aminotransferase; AST, aspartic transaminase; TBil, total bilirubin; APTT, activated partial thromboplastin time; cTnI, cardiac troponin I; BNP, β-nitropropionic acid; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.

burden at ICU admission based on higher sequential organ failure assessment (SOFA) and acute physiology and chronic health enquiry-II scores and had more frequent complications associated with higher risk of mortality, such as shock, bacterial coinfections, and hospital-acquired pneumonia. Furthermore, the patients with AKI required stronger respiratory support, as reflected in the higher rate of intermittent positive-pressure ventilation (IPPV) or tracheotomy, and had worse prognosis with longer ICU stay and higher ICU mortality rate.

Table 3. In-hospital treatment, comorbidities, and complications of patients with IPA

	All patients (n = 140)	AKI group (n = 100)	Non-AKI group (n = 40)	p value
Aspergillus diagnosis				
Proven diagnosis	60 (42.9)	40 (40.0)	20 (50.0)	0.373
Possible diagnosis	80 (57.1)	60 (60.0)	20 (50.0)	0.373
BALF GM of diagnosis	1.11±2.02	1.20±2.12	0.88±1.75	0.404
Blood GM of diagnosis	4.17±3.57	4.21±3.65	4.08±3.37	0.858
Symptom to IPA days	20.28±18.00	19.37±16.34	22.59±21.73	0.347
In-ICU to IPA days	2 (1–5)	3 (1–7)	3 (2–5)	0.076
Antibiotics in ICU				
Voriconazole	117 (83.6)	83 (83.0)	34 (85.0)	0.971
Amphotericin B aerosol	47 (33.6)	41 (41.0)	6 (15.0)	**0.006**
Caspofungin	23 (16.4)	22 (22.0)	1 (2.5)	**0.010**
Posaconazole	5 (3.6)	5 (5.0)	0	0.349
Co-bacteria infection	110 (78.6)	88 (88.0)	22 (55.0)	<**0.001**
Use of antibiotics in ICU	140 (100.0)	100 (100.0)	40 (100.0)	
Cephalosporins	112 (80.0)	81 (81.0)	31 (77.5)	0.815
Beta-lactamase inhibitor	121 (86.4)	86 (86.0)	35 (87.5)	0.998
Quinolones	114 (81.4)	83 (83.0)	31 (77.5)	0.606
Carbapenems	86 (61.4)	64 (64.0)	22 (55.0)	0.426
Sulfonamides	46 (32.9)	32 (32.0)	14 (35.0)	0.887
Co-viral infection in ICU	111 (79.3)	82 (82.0)	29 (72.5)	0.307
Use of antiviral therapy	98 (70.0)	69 (69.0)	29 (72.5)	0.838
Ganciclovir	53 (37.9)	38 (38.0)	15 (37.5)	0.999
Oseltamivir	60 (43.2)	43 (43.0)	17 (43.6)	0.997
Organ support				
HFNC	80 (57.1)	54 (54.0)	26 (65.0)	0.318
NPPV	104 (74.3)	73 (73.0)	31 (77.5)	0.737
IPPV	31 (22.1)	14 (14.0)	17 (42.5)	**0.001**
Early ICU IPPV in 3 days	66 (47.1)	55 (55.0)	11 (27.5)	**0.006**
Early ICU IPPV in 7 days	81 (57.9)	64 (64.0)	17 (42.5)	**0.033**
IPPV days	20.45±39.49	22.89±43.60	11.31±14.21	0.213
Tracheotomy	48 (34.3)	42 (42.0)	6 (15.0)	**0.004**
ECMO	24 (17.3)	21 (21.0)	3 (7.7)	0.106
ECMO days	9.88±7.15	8.52±6.00	19.33±8.62	**0.011**
Vasoactive treatment	109 (77.9)	86 (86.0)	23 (57.5)	**0.001**
Prognosis				
In-ICU days	11 (7–22)	12 (7–21)	8 (5–11)	0.084
In-ICU mortality	73 (52.1)	59 (59.0)	14 (35.0)	**0.017**
Shock	109 (77.9)	86 (86.0)	23 (57.5)	**0.001**
Barotrauma	26 (18.6)	23 (23.0)	3 (7.5)	0.059
HAP	90 (64.3)	72 (72.0)	18 (45.0)	**0.005**
Urinary tract infection	20 (14.3)	15 (15.0)	5 (12.5)	0.909
Abdominal infection	4 (2.9)	4 (4.0)	0	0.470
Blood stream infection	28 (20.0)	21 (21.0)	7 (17.5)	0.815
CRBSI	0.071	15 (15.0)	1 (2.5)	0.071

BALF, bronchoalveolar lavage fluid; IPA, invasive pulmonary aspergillosis; ICU, intensive care unit; HFNC, high-flow nasal cannula; NPPV, non-invasive positive-pressure ventilation; IPPV, intermittent positive-pressure ventilation; ECMO, extracorporeal membrane oxygenation; HAP, hospital-acquired pneumonia; CRBSI, catheter-related bloodstream infection.

Online supplementary Table 1 (for all online suppl. material, see https://doi.org/10.1159/000539139) shows the clinical characteristics of patients categorized according to the AKI stage. The rates of intubation, tracheotomy, vasoactive treatment, and shock or mortality during the ICU stay increased in parallel with the AKI

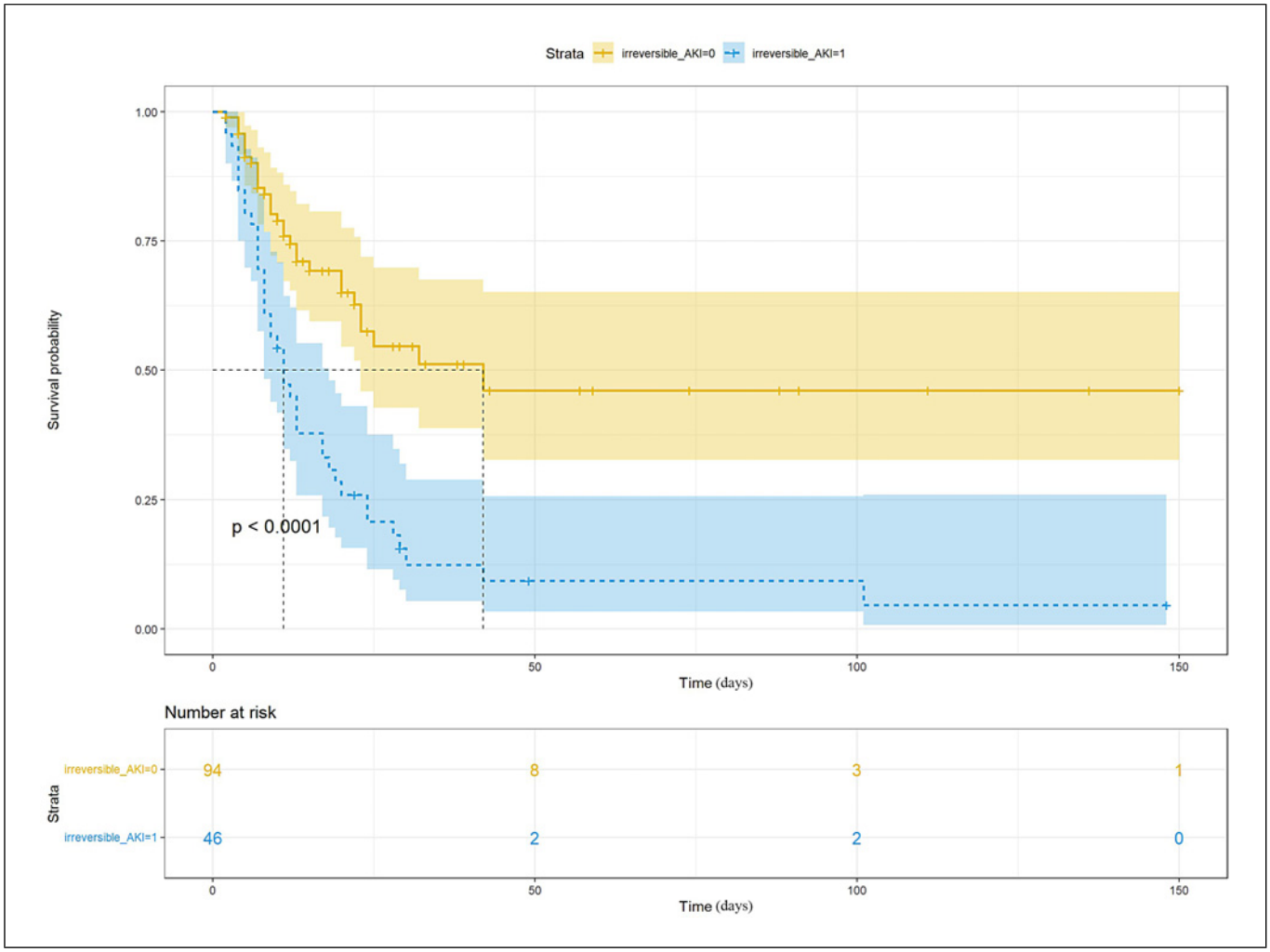


Fig. 2. KM curve between IPA patients who developed irreversible AKI and IPA patients without irreversible AKI.

Table 4. Factors available at ICU admission independently associated with death of IPA patients

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age	1.024	1.001–1.048	0.040			
SOFA	1.098	1.010–1.193	0.027			
Chronic lung disease	4.375	2.136–8.963	<0.001	4.122	1.724–9.844	0.001
IPPV	5.262	2.086–13.277	<0.001	3.153	1.096–9.076	0.033
Irreversible AKI	12.323	4.733–32.085	<0.001	13.364	4.524–39.481	<0.001
Corticosteroid within 1 year	2.708	1.348–5.441	0.005	2.890	1.201–6.954	0.018

SOFA, sequential organ failure assessment score; IPPV, intermittent positive-pressure ventilation.

Table 5. Factors available at ICU admission independently associated with the onset of irreversible AKI among IPA patients

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Volume of first 7 days in ICU, mL	1.016	1.001–1.032	0.009	1.020	1.001–1.066	0.008
cTnI, ng/mL	1.738	1.063–3.139	0.047	1.845	1.038–3.279	0.037
SOFA	1.132	1.038–1.236	0.005			
IPPV	4.231	1.382–12.951	0.011			

cTnI, cardiac troponin I; SOFA, sequential organ failure assessment score; IPPV, intermittent positive-pressure ventilation.

stage, indicating worsening prognosis with more advanced AKI. Among the 100 patients with AKI, the diagnosis was reached at the time of ICU admission in 29 (29%) patients whereas the remaining 71 (71%) patients developed acute kidney dysfunction during the ICU stay. The comparisons of these two groups, presented in online supplemental Table 2, revealed no statistical differences in the rates of mortality and irreversible AKI [11–13].

Characteristics and Risk Factors of ICU Mortality in Patients with IPA

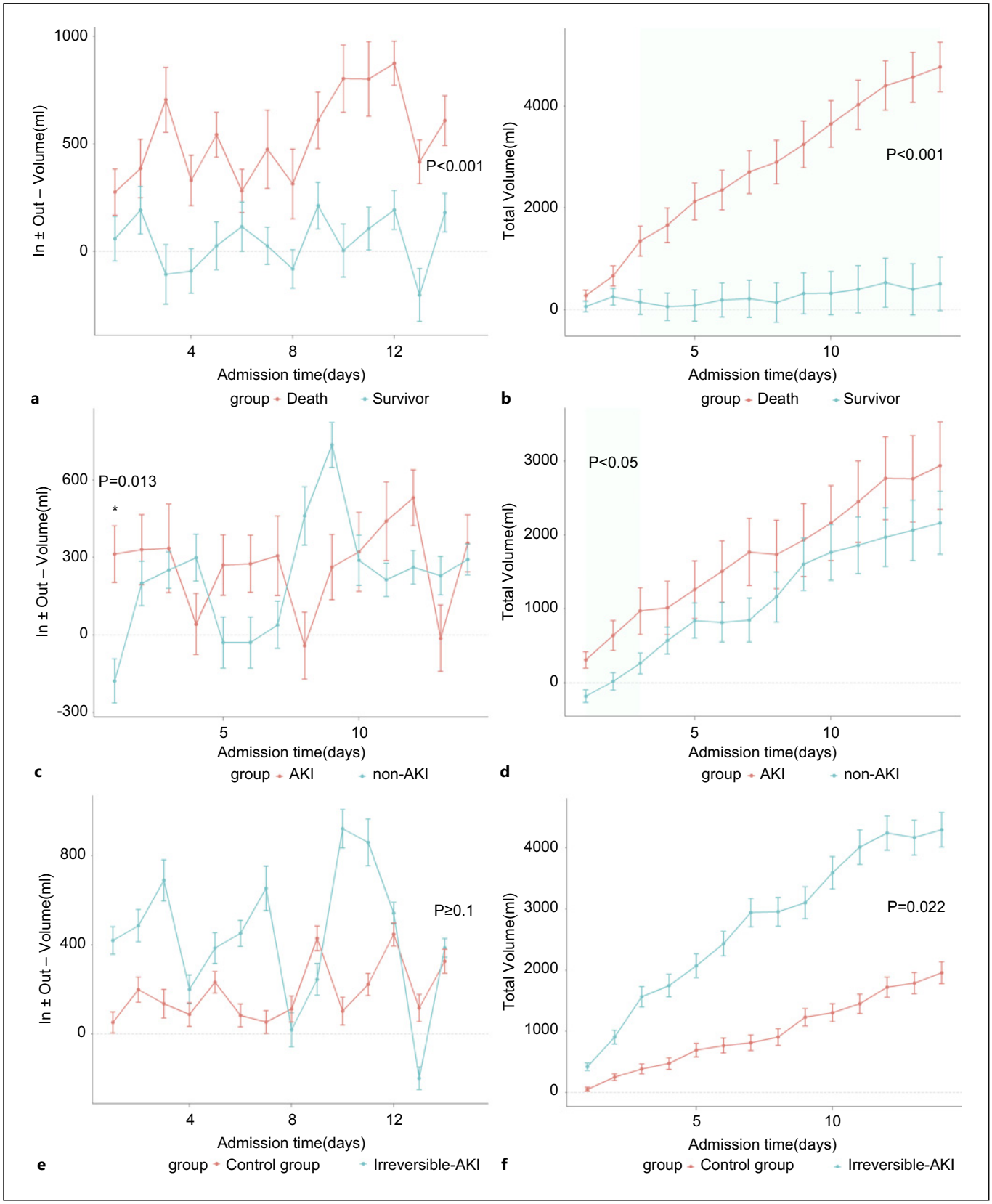
Online supplemental Table 3 shows the comparison of baseline characteristics and prognosis between the patients with IPA who died during the ICU stay (non-survivors) and those who survived the ICU stay (survivors). The overall ICU mortality rate was 52.1%. By univariate analysis, the mortality rate was significantly higher in patients with AKI than in those without AKI (59.0% vs. 35.0%, $p = 0.017$; odds ratio 2.672, 95% confidence interval 1.247–5.727), although the relationship between AKI and mortality was not significant according to the Kaplan-Meier survival analysis ($p > 0.05$). The ICU mortality rate was significantly higher in patients with irreversible AKI than in those without irreversible AKI (54.8% vs. 9.0%, $p < 0.001$) by univariate analysis; the difference was significant by the Kaplan-Meier survival analysis (Fig. 2).

Compared with the patients who survived the ICU stay, those who did not survive the ICU were older with higher SOFA and acute physiology and chronic health enquiry-II scores, more frequently required vasoactive support and tracheotomy, required earlier IPPV implementation, and experienced higher rates of shock, bacterial infections, and hospital-acquired pneumonia. By multivariate correlation analysis, irreversible AKI was the strongest independent risk factor for ICU mortality, followed by chronic lung disease, recent corticosteroid use within the previous year, and IPPV use (Table 4).

Irreversible AKI in Patients with IPA

Among the 46 patients with irreversible AKI, 7 patients with comorbid CKD experienced disease progression and 5 of the 7 patients died during the ICU stay. Thirty-seven of the remaining 39 patients without kidney injury at the time of ICU admission fulfilled the AKD criteria. Of these, 35 patients died within 90 days of hospitalization whereas the remaining 2 patients developed CKD.

The patients with and without irreversible AKI were compared to evaluate the potential ability of irreversible AKI in predicting ICU mortality in patients with IPA and to determine larvate factors associated with the onset of irreversible AKI. As shown in online supplementary Table 4, AKI stage, the interval between ICU admission and AKI diagnosis, baseline Scr levels at ICU admission, and maximum Scr levels during hospitalization did not significantly differ between the two groups. Volume control was comparatively better in patients without irreversible AKI than in those with irreversible AKI. The patients with irreversible AKI had more severe organ involvement and worse function, based on higher SOFA scores, lower PaO_2/FiO_2 ratio, and higher cardiac troponin I (cTnI) at ICU admission, as well as higher rates of IPPV and extracorporeal membrane oxygenation for oxygen support during the ICU stay. By multivariate logistic regression analysis, cTnI levels at ICU admission and excessive volume overload during the first 7 days of the ICU stay were significantly associated with the onset of irreversible AKI (Table 5).



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(For legend see next page.)

AKI Management in Patients with IPA: Daily Volume Control and Timing of CRRT

Study patients with IPA categorized according to the survival and AKI statuses were compared to determine the role of the extent of daily volume control and the timing of CRRT implementation on ICU mortality risk. Figure 3 shows the comparison of fluid balance and volume management among specific groups. The daily in-and-out volume as well as the cumulative volume since the third day of the ICU stay was significantly higher in the non-survivor group than in the survivor group (Fig. 3a, b). As shown in Figures 3c and d, except for the first day, the daily in-and-out volume did not significantly differ between the AKI and non-AKI groups. Moreover, the cumulative total volume curves were essentially parallel. The volume loads on days 1 and 3 after ICU admission were higher in patients with AKI than in those without AKI, indicating that the difference in volume control between the two groups occurred within the first 3 days. As shown in Figures 3e and f, the comparison of patients with irreversible AKI and the group without irreversible AKI revealed significant differences in cumulative volume curves between the two groups, despite crossovers observed in the curves of daily in-and-out volume. The volume load was also higher in patients with irreversible AKI than in those without irreversible AKI, consistent with that observed between the survivor and non-survivor groups.

Finally, the timing of kidney support was compared between the survivor and non-survivor groups, with a focus on two timepoints: the interval between ICU admission and CRRT initiation and the interval between AKI diagnosis and CRRT initiation. As shown in online supplementary Figure 1, RRT support was initiated earlier after ICU admission in survivors than in non-survivors (median, 2 vs. 5 days; $p = 0.026$). Additionally, the interval between AKI diagnosis and CRRT initiation was shorter in the survivor group than in the non-survivor group, albeit without statistical significance (median, 1 vs. 3 days; $p = 0.061$).

Discussion

In this largest study to date focusing on AKI in patients with IPA requiring intensive care, irreversible AKI was associated with increased mortality in patients with severe IPA. Additionally, initiation of accurate volume management starting at the time of ICU admission and earlier CRRT initiation when needed may improve prognosis.

In patients with AKI developing in response to severe infection, the affected excretory function of kidneys leads to altered fluid homeostasis, resulting in eGFR decline and the activation of the renin-angiotensin system [3]. Additionally, AKI is strongly associated with injurious inflammatory response in patients with critical infections and is usually followed by sepsis and death [14]. Nevertheless, the role of AKI in putative IPA remains unclear. Except for the pathogenesis of AKI during critical aspergillosis, antifungal therapeutics, including azoles, are also a significant cause of acute kidney dysfunction, with these most common drug-related adverse events reported in approximately one-fifth of the patients treated with antifungals [15]. Novel drugs without nephrotoxicity, including the Gwt1 inhibitor fosmanogepix, remain out of reach to most patients [16, 17]. Although few studies have elucidated the role of AKI in survival in patients with IPA, numerous studies have demonstrated the ability of CRRT in predicting mortality in patients with IPA in ICU settings [6, 7], indicating that severe kidney injury requiring RRT might be closely associated with death. Indeed, our analyses revealed higher mortality rates in patients with stage III AKI. However, the onset of AKI itself was not strongly associated with mortality in patients with IPA.

Although AKI was previously considered a short-term and fully reversible complication of severe infection, the persistence of impaired kidney function despite the resolution of infection is garnering increasing attention [18]. Previous studies reported that incomplete recovery of AKI was closely associated with more rapid and subsequent loss of kidney function, resulting in accelerated progressive CKD [19–21]. Moreover, compared to patients without CKD, those with CKD are more prone to AKI [22] and require less severe insult that necessitates CRRT [23]. In the present study, incomplete AKI recovery was defined as irreversible AKI. Our analyses indicated that irreversible AKI was an independent risk factor for mortality in patients with IPA in the ICU, suggesting its potential role as a major contributor to the loss of kidney function over the long term [24]. Therefore, in patients with IPA who develop AKI, therapeutic management aimed to reverse kidney injury should be the most important strategy to improve prognosis.

Fig. 3. Fluid balance and volume management between different groups of IPA patients. The left column represents the daily in-and-out volume control during the first 14 days of ICU stay, and the right column represents the cumulative daily volume change since ICU admission. **a** and **b** show the comparison between the survivor and non-survivor groups. **c** and **d** compare the AKI and non-AKI groups. **e** and **f** show the differences between the irreversible AKI group and the control group.

AKI management is critical to prevent irreversible kidney dysfunction, and better volume control and the early CRRT initiation were effective interventions in the present study. The daily in-out volume curves of survivors fluctuated around the equilibrium point throughout the ICU stay, indicating better control of daily liquid volume. This balance could be achieved by the rational use of diuretics or the timely initiation of CRRT. The widespread implementation of RRT in ICUs has led to a decline in mortality in patients who develop AKI due to various etiologies, including severe infection and sepsis [25]. CRRT can remove inflammatory cytokines and circulating toxins during infections, including IPA [26]. However, whether the timing of CRRT initiation can improve prognosis has remained a controversy until recently. The randomized-controlled ELAIN trial demonstrated that early CRRT initiation led to significant improvement in survival and kidney recovery in comparison with the delayed delivery of kidney replacement support [27], advocating that early CRRT initiation can facilitate homeostasis and reduce fluid overload. Meanwhile, another viewpoint emphasized that CRRT could not reduce the risk of insertion complications or catheter-related bloodstream infections and thus could be associated with increased bedside workload. In such cases, the renal replacement capacity was comparable between timely and delayed CRRT initiation and the rate of catheter-related bloodstream infections was lower in association with lower catheter days in patients undergoing delayed CRRT initiation [12]. Therefore, the hypothetical effect of early CRRT should be carefully considered based on reliable quality benchmarks, which should be extensively explored in future studies.

The present study has several limitations that should be acknowledged. First, this was an observational, single-center study and potential bias cannot be denied due to the small number of cases. Second, as reported by others [28], some patients receiving CRRT would have been classified as AKI stage I or II, which might have altered their outcome and clinical strategies. Additionally, the evidence regarding the high mortality rate associated with AKI might be weakened due to the lack of histologic confirmation by post-mortem autopsy or kidney biopsy. Another potential bias is related to the lack of serum concentrations of antifungal drugs, especially voriconazole, which are related to acute kidney failure.

Conclusion

In patients with putative IPA requiring intensive care, those diagnosed with AKI presented with more volume overload, worse disease burden, dependency on stronger respiratory support, and worse prognosis compared to those without AKI. Irreversible AKI was a strong predictor of mortality in critically ill patients with IPA. Higher cTnI levels at ICU admission and worse volume control during the first 7 days of ICU stay were predictors that could cause irreversible kidney dysfunction. Better volume control and earlier CRRT initiation should be considered key points in AKI management and prognostic improvement.

Statement of Ethics

The study protocol was approved by the Ethics Committee of the China-Japan Friendship Hospital, approval number 2019-79-K51. The requirement for informed consent was waived because of the retrospective, observational study design according to local guideline. This research was conducted in full accordance with the principles of the Declaration of Helsinki.

Conflict of Interest Statement

The authors declare that they have no competing interests.

Funding Sources

The funding source of the study [horizontal subject (2021-HX-74)] is an academic non-profit organization that played no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. This work was also supported by the National Natural Science Foundation of China (No. 82203375).

Author Contributions

All authors made a significant contribution to the work. L.G. wrote the main manuscript text revised by Q.Z. and L.H. X.W. and X.C. prepared tables. M.L. and L.Y. collected the dataset. Y.F. and L.H. prepared the figures. All authors reviewed the manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from Dr. Linna Huang upon reasonable request.

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