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Fluid management in patients with acute kidney injury – A post-hoc analysis of the FINNAKI study

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ABSTRACT

Purpose: Whether positive fluid balance among patients with acute kidney injury (AKI) stems from decreased urine output, overzealous fluid administration, or both is poorly characterized.
Materials and methods: This was a post hoc analysis of the prospective multicenter observational Finnish Acute Kidney Injury study including 824 AKI and 1162 non-AKI critically ill patients.
Results: We matched 616 AKI (diagnosed during the three first intensive care unit (ICU) days) and non-AKI patients using propensity score. During the three first ICU days, AKI patients received median [IQR] of 11.4 L [8.0–15.2]L fluids and non-AKI patients 10.2 L [7.5–13.7]L, $p < 0.001$ while the fluid output among AKI patients was 4.7 L [3.0–7.2]L and among non-AKI patients 5.8 L [4.1–8.0]L, $p < 0.001$. In AKI patients, the median [IQR] cumulative fluid balance was 2.5 L [−0.2–6.0]L compared to 0.9 L [−1.4–3.6]L among non-AKI patients, $p < 0.001$. Among the 824 AKI patients, smaller volumes of fluid input with a multivariable OR of 0.90 (0.88–0.93) and better fluid output (multivariable OR 1.12 (1.07–1.18)) associated with enhanced change of resolution of AKI.
Conclusions: AKI patients received more fluids albeit having lower fluid output compared to matched critically ill non-AKI patients. Smaller volumes of fluid input and higher fluid output were associated with better AKI recovery.

1. Introduction

Fluid therapy is one of the most common interventions in intensive care units (ICUs) all over the world. Intravenous resuscitation fluid is given to critically ill patients mainly to restore intravascular volume [1], but considerable amounts of administered fluid are maintenance fluids and carrier fluids for drugs and nutrition [2]. Acute kidney injury (AKI) is one of the most significant disorders worsening the outcome of critically ill patients. It increases morbidity, mortality and costs [3-8]. Ensuring sufficient renal perfusion by preventing fluid deficit has conventionally been one of the cornerstones of AKI treatment [9-11]. Additionally, fluids are given to in response to oliguria [12], typically occurring in patients with early AKI [10].

Fluid therapy may lead to fluid accumulation, known to associate with the impaired outcome of critically ill patients with AKI [7,8, 13-19]. Moreover, AKI patients are particularly prone to develop fluid accumulation [8,20-25] and more susceptible to harms of fluid accumulation compared to non-AKI patients [7]. However, only few studies have addressed whether fluid accumulation in AKI stems from overzealous fluid administration, reduced fluid output due to oliguria, or both. High fluid intake, but not reduced urine output, has been associated in a single-center analysis with further worsening of pre-existing AKI suggesting that worsening of AKI could potentially be preventable by limiting fluid input [26]. On the contrary, in septic patients regardless of AKI status, reduced fluid output (not fluid input) was found to mainly account for fluid accumulation [27]. Although some studies report the amount of received fluid and/or fluid balance between AKI and critically ill non-AKI patients [23-25,28], none describes if more positive fluid balance is due to higher fluid intake or reduced fluid output between AKI and non-AKI patients.

We hypothesized that AKI patients receive more fluids than non-AKI patients despite of impaired fluid output. In this analysis, we aimed to

Abbreviations: AKI, acute kidney injury; ICU, intensive care unit; GFR, glomerular filtration rate; IQR, interquartile range; KDIGO, Kidney Disease Improving Global Outcomes; MDRD, modification of diet in renal diseases; OR, odds ratio; RRT, renal replacement therapy; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment.

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evaluate the amount of administered fluid, fluid output, and cumulative balance between propensity score -matched critically ill AKI and non-AKI patients during the first three days of ICU admission. Additionally, we studied the association of fluid input and output with recovery of AKI.

2. Material and methods

This study was a post-hoc analysis of the prospective multicenter observational Finnish Acute Kidney Injury (FINNAKI) cohort study conducted in 17 Finnish intensive care units in 2011–12 [3]. Nationwide approval for the study was given by The Ethics Committee of the Department of Surgery at the Helsinki University Hospital (reference number: 18/13/03/02/2010) and the use of deferred consent from the patient or next of kin with written informed consent obtained as soon as possible was accepted. The Finnish National Institute of Health and Welfare allowed data collection from medical records of deceased patients to avoid bias in the primary endpoint of the FINNAKI study (incidence and outcome of AKI).

The FINNAKI study enrolled all adult emergency ICU admissions to study ICUs of any length and elective post-operative patients with an expected ICU stay longer than 24 h [3]. Exclusion criteria were 1) age under 18, 2) chronic dialysis, 3) received renal replacement therapy (RRT) during previous ICU admission already included in the FINNAKI study, 4) organ donor, 5) admitted for intermediate care, 6) transfer from another study ICU with completed study observation period, and 7) no permanent residency in Finland or insufficient language skills for informed consent. The current analysis included all FINNAKI study patients whose 1) ICU length of stay was more than 24 h, 2) fluid therapy data were available for the 5-day study period or until ICU stay if less than 5 days, and 3) who had not commenced RRT before ICU admission.

2.1. Data collection

We collected information of patient characteristics, chronic illnesses, fluid administration and balance, physiological and laboratory data, diagnoses, severity scores including Simplified Acute Physiology Score II (SAPS II) and Sequential Organ Failure Assessment score (SOFA score) and given ICU treatment using case report forms. Data were recorded from admission to day 5 if patient was still located in the ICU. These data were supplemented by data from Finnish Intensive Care Consortium database including for example ICU diagnoses.

2.2. Definitions

We defined AKI (diagnosed during the first three ICU days) according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria [10] considering creatinine, urine output, and use of RRT. Baseline creatinine was estimated using the modification of diet in renal disease (MDRD) formula assuming a glomerular filtration rate (GFR) of 75 mL/min/1.73 m2 [29] if it was not available. Sepsis was defined according to the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) definition [30]. We defined ICU admission day as the first fluid day. To calculate total fluid input, we collected daily data of the amount of fluid input that included resuscitation and maintenance fluids, blood products, nutrition and drug infusions. In balance calculations, we considered the total fluid output that included urine output, bleeding, potential ultrafiltration, losses from gastrointestinal tract, drainage fluids and a surrogate for evaporation (generally 1000 mL daily for normothermic patients and additionally, an addition for each Celcius degree for fever per hour). We subtracted total fluid output from fluid input to calculate fluid balance. AKI recovery on day 5 was defined as survival to 5 days and the absence of AKI, i.e. no AKI according to KDIGO criteria [10] on day 5.

2.3. Outcomes

The primary outcomes were the amount of received fluid, fluid output (urine output and possible ultrafiltration), and fluid balance on day 3 (or until ICU discharge if earlier) in the propensity-matched cohort. Additionally, among all AKI patients, we studied the associations of these variables with AKI recovery on day 5.

2.4. Statistical analyses

We used one-to-one propensity score for AKI to match AKI and non-AKI patients to make them more comparable (e.g. regarding disease severity). A total of 1986 patients (824 with AKI onset during three first ICU days, 1162 without) were included in the matching process. Matching was performed sequentially (three separate matching procedures) by day of AKI onset as follows: Patients developing AKI on day 1 were matched with patients with no AKI on any day. Then, patients developing AKI on day 2 were matched with patients with no AKI on any day not previously matched. Finally, patients developing AKI on day 3 were matched with patients with no AKI on any day not previously matched. In total, 22 variables (e.g. age, sex, chronic kidney disease, SAPS score) were included in the propensity model by clinical judgement (see Additional file page two for details). Matching was performed using nearest neighbor matching with a caliper width of 0.2 SD. In total, 616 AKI patients were matched, leaving 208 (25.2%) unmatched and excluded from analyses. We proceed the outcome analysis using matched samples [31].

We report baseline characteristics using counts and percentages for categorical variables and medians with interquartile ranges (IQR) for continuous variables as data were non-normally distributed. We used the Fisher's exact or Chi-squared tests to compare categorical data and the Mann-Whitney *U* test to compare continuous data to assess possible differences between AKI patients classified with AKI recovery. We used logistic regression in AKI patients to study fluid input and output (cumulative diuresis and/or possible ultrafiltration) and those association with AKI recovery. Potential interaction between fluid input and output was assessed using the likelihood ratio test. We conducted analyses using SPSS statistics 24 and R 3.6.1.

3. Results

3.1. Patient characteristics and fluid management in propensity-matched cohort

Using propensity score, we sequentially matched 616 AKI patients to 616 non-AKI patients (Fig. 1). The groups were well balanced (Table 1). AKI patients left without a match had more severe acute illness and more often chronic comorbidities compared to matched AKI patients (Supplemental Table S1). By day 90, 166 (26.9%) of patients with AKI were deceased (Table 1).

Compared to non-AKI patients, AKI patients received more fluid during three first ICU days with median [IQR] of 11.4 L [8.0–15.2]L vs 10.2 L [7.5–13.7]L, $p < 0.001$, had lower fluid output with median [IQR] of 4.7 L [3.0–7.2]L vs 5.8 L [4.1–8.0]L, $p < 0.001$, and higher cumulative fluid balance with median [IQR] 2.5 L [−0.2–6.0]L vs 0.9 L [−1.4–3.6]L, $p < 0.001$. Daily fluid administration, fluid output and balance are presented in Fig. 2. The median follow-up time from ICU admission to the primary endpoint was 55 h (IQR [46–64] h). We found no association between cumulative fluid input, fluid output, and balance on day three and the day AKI developed (Supplemental Table S2).

3.2. AKI recovery

Of all 887 AKI patients, 531 (59.9%) patients had recovered their AKI by ICU day 5. Those in whom kidney function recovered were younger and had less often chronic heart failure and had less severe acute illness

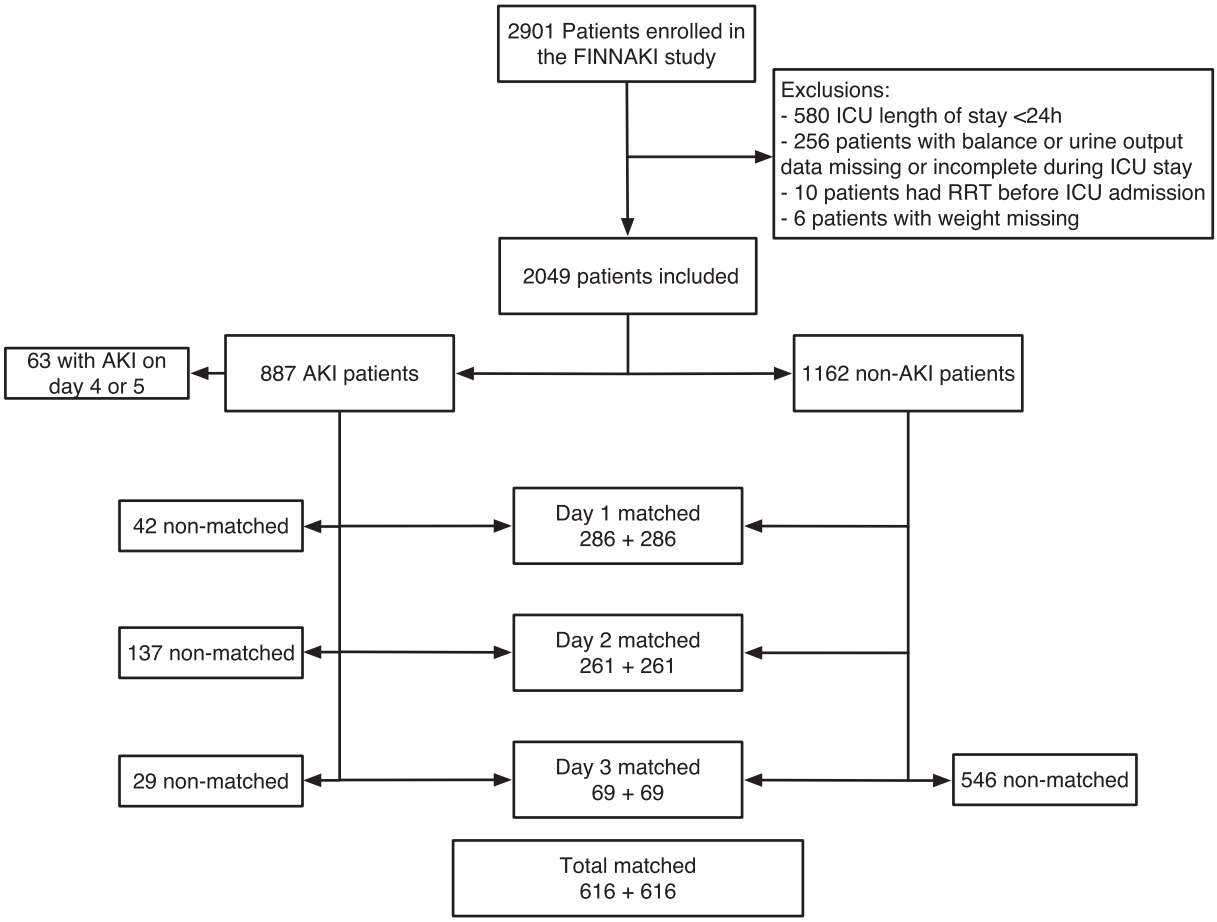

Fig. 1. Study flow chart with exclusions.

than those who did not (Supplemental Table S3). They also received less fluid by ICU day 3 with median [IQR] of 10.7 L [7.6–14.1]L vs 13.0 L [9.9–17.3]L and their cumulative fluid balance on ICU day 3 was lower with median [IQR] 1.6 L [−0.6–4.5]L vs 4.6 L [1.3–8.6]L compared to those who did not recover their AKI (Supplemental Table S3). Of all 887 AKI patients 144 (16.2%) had AKI diagnosis based merely on KDIGO diuresis criteria.

In an unadjusted logistic regression model, fluid input by ICU day 3 and the amount of diuresis and possible ultrafiltration by ICU day 3 associated with renal recovery at ICU day 5 and this association remained also in an adjusted model (Table 2). These results remained also in the analysis implemented in AKI patients without RRT (Supplemental Table S4). No interaction between fluid input and output was detected using the likelihood ratio test.

4. Discussion

In propensity score -matched, well-balanced cohort of 616 AKI and 616 non-AKI patients, we found AKI patients to both receive more fluids and have reduced fluid output, and consequently, have higher fluid balance compared to non-AKI patients on the third ICU day. Regarding recovery of AKI assessed on day 5, both lower fluid input and higher fluid output associated with higher renal recovery rate.

Prospective observational studies among the critically ill have reported higher cumulative fluid balance in critically ill AKI patients compared to non-AKI patients [7,8,23]. These studies did not investigate whether higher amount of received fluid or lower fluid output (or both) were responsible for fluid accumulation. We studied these fluid parameters between AKI and non-AKI patients in a propensity score -matched cohort to make these patient groups more comparable regarding several possible confounders, such as severity of illness. In our study, we observed both higher amount of received fluid and lower fluid output, and consequently, higher cumulative fluid balance in AKI patients compared to non-AKI patients.

Patients with more severe acute illness are at higher risk of also developing AKI [3]. One of the most common attempts to prevent AKI is ensure sufficient renal perfusion by ensuring adequate cardiac output and blood pressure level, although the relationship between cardiac output and AKI has been debated [32]. A conventional intervention to maintain sufficient cardiac output is administering intravenous fluids [12]. Thus, one could interpret that AKI patients receive higher amounts of fluid due to more severe acute illness state and impaired hemodynamics. Furthermore, oliguria is frequent in AKI patients and is likely responsible for impaired fluid output [10], but it is also a common trigger for fluid administration [12]. To neutralize the confounding effects of illness severity as a trigger for fluid administration, we performed sequential propensity matching [33] and found differences in received fluid, fluid output, and cumulative fluid balance to persist. These findings indicate that AKI patients with comparable severity of illness compared to non-AKI patients received more fluid possibly to due low urine output. Thus, the consequence was higher cumulative fluid balance with known associations with adverse outcomes.

We found that higher cumulative fluid balance due to both higher amount of received fluid and lower fluid output associated with AKI non-recovery. Similar results have been described in previous retrospective [14,26,34,35] and prospective [36] studies. Fluid overload presumably raises venous pressure [37] and renal volume leading to renal venous congestion and renal interstitial edema which may decelerate

Table 1
Characteristics of the propensity score -matched patients.

	Data available	All matched patients, n = 1232	AKI, n = 616	Non-AKI, n = 616	*p*-Value	SMD
Age (years)	1232	65 [54–75]	65 [55–75]	65 [54–75]	0.715	0.016
Sex; female	1232	422 (34.3%)	212 (34.4%)	210 (34.1%)	0.952	0.007
Weight (kg)	1232	80 [68–90]	80 [70–95]	75 [65–87]	<0.001	0.317
Comorbidities						
Hypertension	1224	632 (51.6%)	320 (52.2%)	312 (51.2%)	0.731	0.026
Coronary artery disease or ASO	1220	189 (15.5%)	95 (15.5%)	94 (15.5%)	>0.999	0.004
Chronic heart failure	1223	162 (13.2%)	80 (13.1%)	82 (13.4%)	0.933	−0.010
COPD	1224	125 (10.2%)	58 (9.5%)	67 (10.9%)	0.450	−0.050
Chronic kidney disease (GFR < 60 mL/min/1.73m^2)	1224	72 (5.9%)	33 (5.4%)	39 (6.4%)	0.544	−0.043
Diabetes	1232	268 (21.8%)	146 (23.7%)	122 (19.8%)	0.112	0.092
Chronic liver disease	1217	40 (3.3%)	22 (3.6%)	18 (3.0%)	0.630	0.035
Pre-ICU diuretics	1192	413 (34.6%)	210 (35.5%)	203 (33.8%)	0.584	0.024
Pre-ICU ACE or ATBR use	1205	331 (27.5%)	169 (28.2%)	162 (26.7%)	0.606	0.025
Pre-ICU NSAID use	1170	119 (10.2%)	59 (10.1%)	60 (10.3%)	0.923	−0.006
Received colloids before ICU admission	1232	422 34.2%)	217 (35.2%)	205 (33.3%)	0.509	0.041
Received radiocontrast before ICU admission	1226	275 (22.4%)	142 (23.2%)	133 (21.7%)	0.538	0.035
Received massive transfusion before ICU admission[a]	1232	49 (4.0%)	25 (4.1%)	24 (3.9%)	>0.999	0.008
Pre-ICU hypotension[b]	1212	314 (25.9%)	153 (25.4%)	161 (26.4%)	0.743	−0.030
Surgical admission	1231	493 (40.0%)	235 (38.2%)	258 (41.9%)	0.201	0.076
Sepsis on ICU admission	1232	323 (26.2%)	165 (26.8%)	158 (25.6%)	0.698	0.026
Septic shock 0–24 h from ICU admission	1232	297 (24.1%)	154 (25.0%)	143 (23.2%)	0.505	0.041
Septic shock 0–48 h from OCU admission	1232	309 (25.1%)	159 (25.8%)	150 (24.4%)	0.599	0.033
Septic shock 0–72 h from ICU admission	1232	321 (26.1%)	165 (26.8%)	156 (25.3%)	0.604	0.033
Highest Lactate on ICU admission day (mmol/L)	996	2.20 [1.20–3.70]	2.33 [1.50–4.30]	2.00 [1.30–3.20]	<0.001	0.084
Pre-ICU lactate or within 6 h from ICU admission	1112	2.00 [1.20–3.70]	2.20 [1.25–4.40]	1.90 [1.17–3.20]	0.001	0.003
SOFA score at day 1	1232	8 [6–10]	8 [6–11]	7 [5–9]	<0.001	0.363
Cardiovascular SOFA score at ICU day 1	1232	3 [1–4]	3 [2–4]	3 [1–4]	0.156	0.098
SAPS II score	1232	39 [30–51]	42 [32–54]	36 [28–46]	<0.001	0.312
SAPS II score without age and renal components	1228	22 [15–30]	23 [16–30]	22 [15–31]	0.515	0.006
Acute liver failure	1230	24 (2.0%)	13 (2.1%)	11 (1.8%)	0.687	0.023
Rhabdomyolysis	1227	36 (2.9%)	20 (3.3%)	16 (2.6%)	0.504	0.037
90-day mortality	1232	271 (22.0%)	166 (26.9%)	105 (17.0%)	<0.001	0.223

Categorical data reported as count (percentage) and continuous data as median [interquartile range, IQR].
AKI; acute kidney injury, SMD; standardized mean difference, ASO; arteriosclerosis obliterans, COPD; chronic obstructive pulmonal disease, ICU; intensive care unit, ACE; angiotensin convertase inhibitor, ATRB; angiotensin receptor blocker, NSAID; non-steroidal anti-inflammatory drug, SOFA; Sequential Organ Failure Assessment; considering all six organ systems, SAPSII; Simplified Acute Physiology Score II.
[a] Patient had received >10 units of red blood cells.
[b] Systolic blood pressure < 90 mmHg >1 h.

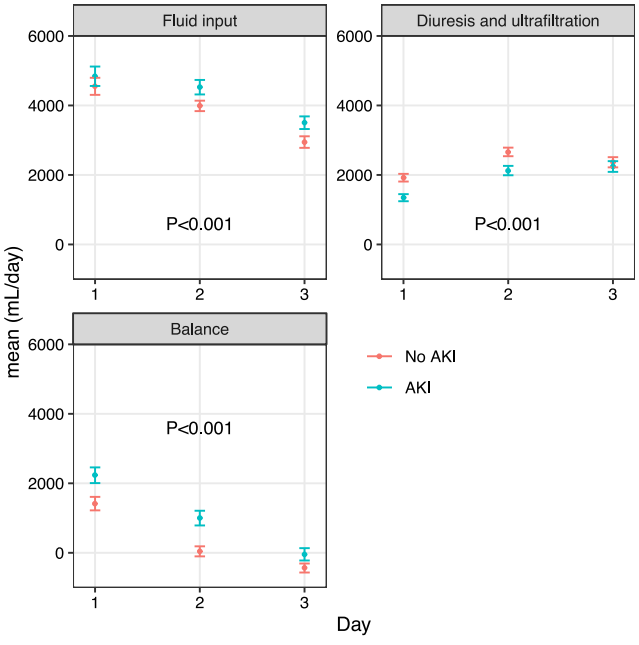

Fig. 2. Daily fluid administration, fluid output and balance in the propensity score matched cohort, n = 1232. *p*-Value from two-way repeated measures ANOVA.

AKI recovery [38]. Tissue edema in the kidney impairs perfusion pressure and worsens kidney function [39], thus may further delay the recovery of kidney function.

Our results build on the previous evidence about the harms of accumulated fluid among critically ill AKI patients. We showed that even in the setting of reduced fluid output, the received amount of fluids is not reduced, but actually increased thus leading to increasingly high cumulative fluid balance with known association with worse outcomes. Thus, strategies to reduce accumulation of fluid among these patients should be searched. One potential means being matching the prescribed fluid input to fluid output which is being tested in a pilot randomized trial [40]. A pilot trial among critically ill septic shock patients showed that restriction of resuscitation fluids is safe and moreover, the incidence of AKI worsening was lower among patients with smaller amounts of resuscitation fluid [28]. Additionally, albeit administering fluid bolus to reverse oliguria is a frequent intervention [12], the actual benefit of it in terms of reversal of oliguria remains unclear and is being investigated in randomized setting [41].

Some limitations to our study should be addressed. First, we cannot exclude the possible bias due to missing confounders. However, we performed a propensity score matching to reduce the possibility of bias of measured confounders. Second, due to the strict matching rules, one fourth of the AKI patients were discarded due to lack of a match, and, thus, the results are not fully representable of the AKI patients treated at study ICUs. Difficulties in finding a match for the most severely ill AKI patients have been reported earlier [33]. Third, data concerning administered fluids before ICU admission could not be obtained, and we

Table 2
Logistic regression models for renal recovery on day 5 among patients with acute kidney injury.

		Unadjusted OR (95% CI)	*p*-Value	Adjusted[a] OR (95% CI)	*p*-Value
5-day AKI recovery	3-day fluid input (liters)	0.90 (0.86–0.92)	<0.001	0.90 (0.88–0.93)	<0.001
	3-day diuresis and ultrafiltration (liters)	1.12 (1.09–1.19)	<0.001	1.12 (1.07–1.18)	<0.001

Unadjusted OR refers to the ORs from a model with 3-day fluid input and 3-day diuresis and ultrafiltration both as predictors. Number of patients in the model 887.
[a] Adjusted ORs refer to models adjusted for age, sex, weight, pre-existing heart failure, chronic liver disease, pre-ICU hypotension, the location from where admitted to ICU, pre-ICU lactate value or lactate value 6 h within ICU admission, cardiovascular SOFA points and SAPS II scores without age and renal components.

do not know if fluid balance was positive already at ICU admission. Fourth, because weighting of all study participants was not possible we calculated fluid balance using inputs and outputs. Nevertheless, this method may be delicate enough according to previous study [42]. Fifth, we studied AKI recovery in a quite early phase on the fifth ICU day and cannot comment on later recovery rates. Sixth, patients in the FINNAKI study were recruited during 2011–2012 and fluid management strategies have changed towards more moderate since then [43]. Seventh, we used a surrogate for evaporation (1000 mL daily for normothermic patients and additionally, an addition for each Celsius degree for fever per hour) which may overestimate fluid output in patients on mechanical ventilation using humidifiers. However, propensity matching strategy balanced the AKI and non-AKI patients well and we believe that the results are not affected by this. Eighth, to include all AKI patients and ensure generalizability, we included all patients fulfilling the KDIGO definition, also those who had AKI based only on the urine output criterion (16% in our cohort) [10]. Oliguria is one of the signs of AKI and thus presumably manifested significantly more in AKI patients than among those without AKI. We acknowledge that by definition, the inclusion of oliguric AKI patients will generate differences in fluid output between AKI and non-AKI patients. However, the aim in this study was exactly to discern whether decreased urine output among AKI patients would be considered also when prescribing administered fluids. Had we used only the creatinine criterion to define patients with AKI, those patients fulfilling only the urine output criterion would have been classified as non-AKI patients, and the results might have been biased.

As a strength, first, our study included a large and representative population of ICU patients and thus results are well generalizable to critically ill patient population. Second, we performed propensity score matching to decrease the bias due to confounding variables in well-balanced AKI and non-AKI patient cohort. Third, fluid-related data were comprehensively gathered.

5. Conclusions

We found AKI patients to receive more fluids and have reduced fluid output, and as a result, have higher fluid balance compared to matched non-AKI patients on the third ICU day. Concerning recovery of AKI assessed on day 5, both lower fluid input and higher fluid output associated with higher renal recovery rate.

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Ethics approval and consent to participate

The Ethics Committee of the Department of Surgery at the Helsinki University Hospital gave nationwide approval for the study (reference number: 18/13/03/02/2010) and accepted the use of deferred consent from the patient or next of kin with written informed consent obtained as soon as possible.

Consent for publication

Not applicable.

Availability of data and material

The datasets analyzed during this study are available from the corresponding author for a reasonable request.

Authors' contributions

STV and VP conceptualized the study. VP organized resources. NI analyzed the data with help from SJ, RW and MP and drafted the manuscript. SJ performed the propensity score matching and logistic regression analyses, created figures and helped writing the manuscript. STV helped to interpret the results and write the manuscript. SJ, RW and MP critically commented the manuscript. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2021.05.002.

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