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Estimated Effects of Early Diuretic Use in Critical Illness

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Objectives: To estimate the effects of diuretic use during the first 24 hours of an ICU stay on in-hospital mortality and other clinical outcomes including acute kidney injury and duration of mechanical ventilation.

Design: Retrospective cohort study.

Setting: Urban, academic medical center.

Patients: Adult patients admitted to medical or cardiac ICUs between 2001 and 2012, excluding those on maintenance dialysis or with ICU length of stay less than 24 hours.

Interventions: None.

Measurements and Main Results: We included 13,589 patients: 2,606 with and 10,983 without early diuretic use (loop diuretic exposure during the first 24 hr of an ICU stay). Propensity score matching generated 2,523 pairs with well-balanced baseline characteristics. Early diuretic use was unassociated with in-hospital mortality (risk ratio, 1.01; 99.5% CI, 0.83–1.22). We found no evidence of associations with ICU or hospital length of stay, or duration or provision of mechanical ventilation. Early diuretic use was associated with higher rates of subsequent acute kidney injury (risk ratio, 1.41; 99.5% CI, 1.25–1.59) and electrolyte abnormalities. Results were not materially different in subgroups of patients with heart failure, chronic kidney disease, or acute lung injury.

Conclusions: Early diuretic use in critical illness was unassociated with in-hospital mortality, ICU or hospital length of stay, or duration of mechanical ventilation, but risks of acute kidney injury and electrolyte abnormalities were higher.

Key Words: acute kidney injury; critical care; diuretics; hospital mortality; mechanical ventilators; ventilator weaning

Diuretics have been commonly used in the care of critically ill patients for decades, but there remains little evidence to guide their use, especially early in the ICU course. The first 24 hours after ICU admission is often the most unstable time in a patient's ICU course, and diuretic use is most controversial during this early period (1). Clinicians may be more inclined to use diuretics early given recent observational trials associating fluid overload—which may be treated with diuretics—with ICU mortality (2–5). A recent analysis of early diuretic use in patients on vasopressors reported a greater than 25% decrease in the odds of mortality (6). Other observational studies have suggested an adverse effect of diuretics on mortality (7, 8).

Randomized controlled trial evidence for the benefits of diuretics in and of themselves is lacking. Although the Acute Respiratory Distress Network Fluid and Catheter Treatment Trial (FACTT) showed a shorter duration of mechanical ventilation with a fluid-conservative strategy including diuretics in patients with acute lung injury (ALI) (9), the trial intervention began more than 40 hours after ICU admission and was not limited to diuretics by themselves. Because of the lack of consensus surrounding diuretic use, practice patterns vary widely (2, 10).

The disparate results of studies on ICU mortality may be due to confounding by indication (i.e., that the group receiving diuretics may be fundamentally different, in ways that are not measured, from the group not receiving diuretics, and/or attempts to adjust for measured characteristics fail to adequately account for differences between groups). Another, perhaps even larger, reason for the differing results may be the distinct and often broadly defined exposure periods for diuretic use. Risks and benefits of a diuretic may be different on the first ICU day when the patient may be more hemodynamically unstable, as compared to on the next ICU day when the patient may have stabilized. If this scenario was true, one might expect widely varying results from trials evaluating "exposure to a diuretic at any point during the ICU admission."

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In this study, we used a large, clinically detailed dataset and propensity-score matching, a method that mitigates confounding by indication in observational data (11), to estimate the effects of early diuretic use on in-hospital mortality and other key clinical outcomes in critically ill patients.

MATERIALS AND METHODS

Data Source (MIMIC-III)

We analyzed de-identified, date-shifted data from the publicly available Medical Information Mart for Intensive Care (MIMIC)–III database v1.4. MIMIC-III is managed by the Massachusetts Institute of Technology (MIT) Laboratory for Computational Physiology and contains data on over 40,000 ICU patients at the Beth Israel Deaconess Medical Center (BIDMC) between 2001 and 2012 (12). The database was approved for research by the Institutional Review Boards of MIT and BIDMC and studies of the database are granted a waiver of informed consent.

We included the first ICU admission for each patient who was at least 18 years old at hospital admission (**Fig. 1**). Given the marked heterogeneity in diuretic use among ICU types that we found on previous descriptive analysis (13), we restricted the cohort to patients admitted to either the medical or cardiac ICUs. We excluded patients with ICU length of stay less than 24 hours, end-stage renal disease, or missing data on medication orders, fluid balance, or serum creatinine concentration.

Baseline Characteristics

We defined admission serum creatinine concentration as the first serum creatinine measured during the hospital admission. We captured comorbidities from *International Classification of Diseases*, 9th Edition (ICD-9) codes billed for each hospital admission according to version 3.7 of the Elixhauser comorbidities defined by the Agency for Healthcare Research and Quality (14). We categorized admission type based on the primary ICD-9 code for each admission (15). Markers of illness severity included mechanical ventilation and Sequential Organ Failure Assessment (SOFA) score, both assessed in the first 24 hours of ICU admission. The SOFA score is a composite of six organ failure domains including hypotension/vasopressor use (16).

Exposure Classification and Outcomes

Our studied exposure was early diuretic use, which we defined as any loop diuretic use (bumetanide, etacrynic acid/ethacrynate sodium, furosemide, torsemide) during the first 24 hours of ICU admission. Our primary outcome was in-hospital mortality. We also analyzed other outcomes including provision of any mechanical ventilation, duration of mechanical ventilation, ICU length of stay, hospital length of stay, net fluid balance, acute kidney injury (AKI), provision of renal replacement therapy, and electrolyte abnormalities. Our follow-up period for ascertaining outcomes began after the exposure period and continued through the 7th day after ICU admission (further details available as **supplementary material**, Supplemental Digital Content 1, http://links.lww.com/CCX/A60).

We defined AKI as an increase in serum creatinine of greater than or equal to 0.3 mg/dL within 48 hours from the Kidney Disease: Improving Global Outcomes criteria (17). We employed a rolling 48-hour window to compare all serum creatinine values during the follow-up period (17, 18). We defined hyponatremia and severe hyponatremia as serum sodium concentrations less than 135 mEq/L and less than 130 mEq/L, respectively, hypokalemia and severe hypokalemia as serum potassium concentrations less than 3.5 mEq/L and less than 3.0 mEq/L, respectively, and metabolic alkalosis and severe metabolic alkalosis as serum bicarbonate concentrations greater than 30 mEq/L and greater than 40 mEq/L, respectively.

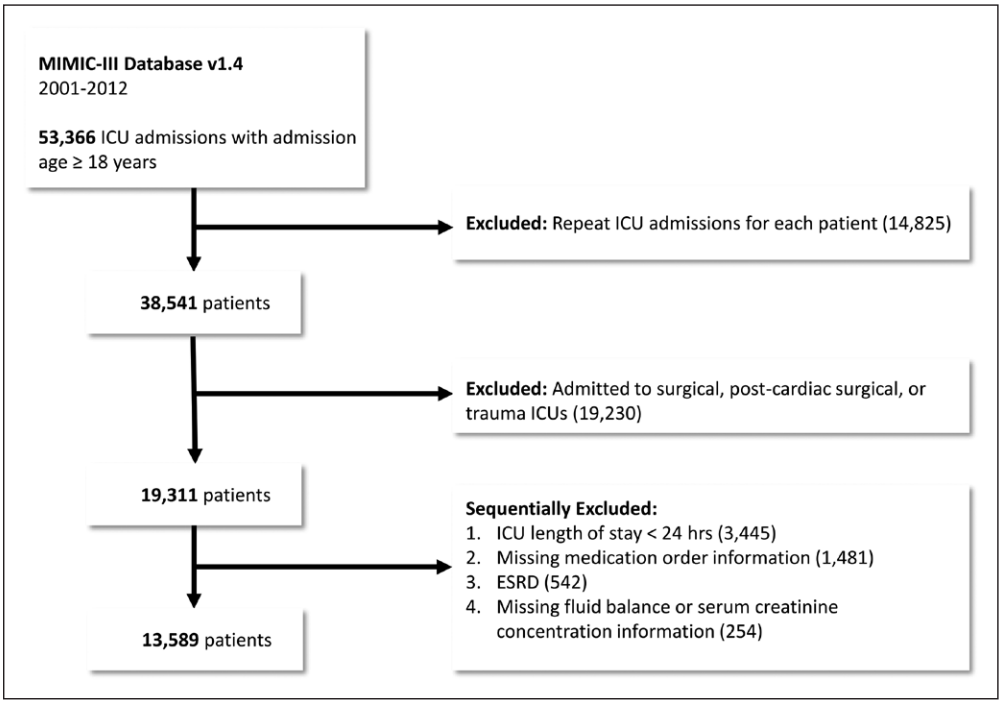

Figure 1. Cohort assembly. ESRD = end-stage renal disease, MIMIC-III = Medical Information Mart for Intensive Care III.

Propensity Score Models

To estimate each patient's propensity to receive a diuretic (vs no diuretic) during the exposure period, we fitted multivariable logistic regression models in which the predictor variables were age, sex, race, comorbidities, admission type, ICU type, admission serum creatinine, mechanical ventilation, and each component of the six-component ICU admission SOFA score. After propensity-score estimation, we matched patients with and without diuretic exposure in a 1:1 ratio using a greedy-matching algorithm (19). We set the maximum allowable difference in propensity scores between members of a

matched pair at 0.1. The quality of matching was assessed by both visual comparison of propensity-score histograms for each exposure group and calculation of absolute standardized differences. An absolute standardized difference less than 0.1 was considered to represent well-balanced matching (20).

Subgroup Analyses

We chose to perform subgroup analyses on three nonmutually exclusive patient subgroups in which we hypothesized a priori that the effects of diuretics might differ from those in the overall cohort: 1) patients with a history of heart failure (defined by ICD-9 codes as above), 2) patients with a history of chronic kidney disease (CKD; defined by ICD-9 codes as above), and 3) patients with ALI (using as a proxy a ratio of arterial oxygen partial pressure to fractional inspired oxygen less than 300 torr at any time during the first 24 hr of ICU admission). We fitted a separate propensity-score model for each subgroup and performed 1:1 matching within each subgroup.

Statistical Analysis

Using the matched cohorts, we fit generalized linear models (gamma distribution with log link for continuous outcomes; binomial distribution with log link for binary outcomes) with robust SEs (21) accounting for propensity-score matched pairs. Because baseline characteristics were well balanced after matching, no additional adjustments were made to the models. Given the multiple outcomes studied, we considered two-sided p values of less than 0.005 as statistically significant. We report risk ratios (RRs) for the binary outcomes and mean differences for the continuous outcomes together with 99.5% CIs, the latter corresponding to the more stringent significance criterion. We performed all statistical analyses using SAS software, Version 9.4 (SAS Institute, Cary, NC) and StataMP Version 15.1 (StataCorp, College Station, TX).

RESULTS

We identified 13,589 adult ICU patients admitted to either medical or cardiac ICUs (Fig. 1), including 4,430 with heart failure, 1,881 with CKD, and 3,062 with ALI. Early diuretic use (within the first 24 hr in the ICU) was present in 20% of the entire cohort, in 40% of patients with heart failure, in 29% of patients with CKD, and in 27% of patients with ALI.

Before propensity score matching, the diuretic and no-diuretic groups had distinctly different baseline characteristics (**Table 1**). The diuretic group was significantly older, with higher rates of heart failure, hypertension, and CKD. The diuretic group was also more commonly admitted for a cardiovascular diagnosis and more commonly admitted to the cardiac unit. Interestingly, the prevalence of vasopressor use was similar in both groups.

Of the 2,606 patients receiving early diuretics, we matched 2,523 with patients (97%) who did not receive early diuretics (propensity-score model *C*-statistic 0.78, Hosmer-Lemeshow $p = 0.15$). Ninety percent had IV furosemide exposure, 8% had oral furosemide exposure, and fewer than 2% had exposure to torsemide, bumetanide, or ethacrynic acid. After dose conversion to IV furosemide equivalents, the median cumulative dose received during the first 24 hours of ICU admission was 40 mg (25–75th percentiles: 20–80 mg). After propensity-score matching, the cohorts were well balanced on all characteristics (Table 1; and **Tables S1–S4**, Supplemental Digital Content 1, http://links.lww.com/CCX/A60). Patients in the matched cohort had a mean age of 71 years, had high rates of hypertension and heart failure (68% and 60%, respectively), had a mean serum creatinine of 1.4 mg/dL, and 39% were mechanically ventilated during the first 24 hours in the ICU.

There was no difference in the primary outcome of in-hospital mortality among patients who received early diuretics and patients who did not receive early diuretics (15% in both groups) (**Table 2**). The percent of patients who received any mechanical ventilation after the 24 hour exposure period was also no different (33% of those who received diuretics versus 34% of those who did not; $p = 0.76$) (**Fig. 2**). The mean duration of mechanical ventilation was 1.6 hours shorter in the early diuretics group (19.5 ± 38.8 hr vs 21.1 ± 40.5 hr), but this difference was not statistically significant ($p = 0.15$). Mean ICU length of stay and hospital length of stay were similar (0.23 d longer in the early diuretics group; $p = 0.70$ and 0.46 d longer in the early diuretics group; $p = 0.55$, respectively).

AKI developed more often in the group that received early diuretics (36% vs 25%; $p < 0.001$; RR 1.41 [99.5% CI, 1.25–1.59]), as did electrolyte abnormalities including hypokalemia (43% vs 37%; $p < 0.001$; RR 1.17 [99.5% CI, 1.06–1.29]) and severe metabolic alkalosis (4% vs 1%; $p \leq 0.001$; RR 2.47 [99.5% CI, 1.43–4.27]). The use of renal replacement therapy was infrequent and similar in both groups (2%; $p = 0.46$; RR 1.17 [99.5% CI, 0.65–2.11]). The mean net fluid balance was 1.09 L (99.5% CI, 0.67–1.52 L) lower in the group that received early diuretics (+ 0.4 L) compared with the group that did not receive early diuretics (+ 1.5 L).

Overall, the RRs and differences in means among patients who received early diuretics and patients who did not receive early diuretics were similar to those from the primary analysis (**Tables S5–S7**, Supplemental Digital Content 1, http://links.lww.com/CCX/A60). For all the subgroups and for the primary analysis, the RRs for AKI were between 1.23 and 1.41 with overlapping CIs. There were no statistically significant benefits on survival, length of stay, duration of mechanical ventilation, or proportion mechanically ventilated in any of the three subgroups.

DISCUSSION

In this large propensity score-matched study of early diuretic use in the ICU, we found no association between early diuretic use and in-hospital mortality. We also found no evidence of associations with ICU or hospital length of stay, or duration or provision of mechanical ventilation. Early diuretic use was associated with subsequent AKI and with several electrolyte abnormalities.

Previous studies that found an association between early diuretic use and mortality used different patient populations (7) or used different analytic methods without or with less complete adjustment for baseline characteristics (8). For example, in an analysis of the Program to Improve Care in Acute Renal Disease (7), diuretic use on the day of nephrology consultation was associated with a 1.68 (95% CI, 1.06–2.64) higher odds of in-hospital mortality; however, that study cohort was restricted

TABLE 1. Baseline Characteristics in the Unmatched and Propensity Score-Matched Cohorts

Characteristics	Unmatched Cohort			Propensity Score-Matched Cohort		
	Diuretics (*n* = 2,606)	No Diuretics (*n* = 10,983)	Standardized Difference	Diuretics (*n* = 2,523)	No Diuretics (*n* = 2,523)	Standardized Difference
Age (yr)	71 ± 15	64 ± 18	0.45	71 ± 15	71 ± 15	0.01
	74 (62–83)	65 (52–79)		74 (61–83)	74 (61–83)	
Female sex	49%	46%	0.06	48%	48%	0.00
White race	73%	71%	0.04	73%	73%	0.01
Comorbidities						
Diabetes mellitus	35%	26%	0.20	34%	34%	0.00
Heart failure	69%	24%	1.00	68%	68%	0.01
Hypertension	61%	51%	0.20	60%	59%	0.01
Chronic kidney disease	21%	12%	0.25	20%	20%	0.00
Liver disease	7%	10%	0.10	7%	7%	0.00
Admit type						
Cardiovascular	48%	27%	0.44	47%	45%	0.03
Gastrointestinal	9%	14%	0.15	9%	9%	0.00
Infectious	9%	14%	0.15	10%	10%	0.03
Respiratory	15%	12%	0.07	15%	15%	0.01
Neoplasm	6%	7%	0.04	6%	6%	0.02
Injuries/poisonings	5%	11%	0.20	6%	6%	0.00
Other	7%	15%	0.24	8%	9%	0.03
ICU type						
Cardiac unit	44%	26%	0.40	43%	42%	0.03
Medical unit	56%	74%	0.40	57%	58%	0.03
Vasopressor use	18%	18%	0.01	19%	19%	0.01
Admission serum creatinine (mg/dL)	1.4 ± 1.0	1.4 ± 1.2	0.05	1.4 ± 1.0	1.4 ± 1.0	0.02
	1.2 (0.9–1.7)	1.0 (0.8–1.5)		1.2 (0.9–1.6)	1.1 (0.8–1.6)	
ICU admission Sequential Organ Failure Assessment	5.2 ± 3.6	4.9 ± 3.8	0.08	5.2 ± 3.6	5.1 ± 3.8	0.00
	4 (2–7)	4 (2–7)		4 (2–7)	4 (2–7)	
Mechanically ventilated on first ICU day	39%	33%	0.13	39%	38%	0.01

Categorical variables are given as percentages. Continuous variables are given as both mean ± SD and median (25–75th percentiles).

to patients with AKI. In contrast, Shen et al (6) recently published an analysis that also used the MIMIC dataset but found a significant survival benefit to early diuretic use (odds ratio, 0.69; 95% CI, 0.57–0.84). However, diuretic use in the MIMIC dataset is independently associated with admission to the postcardiac surgical ICU (13), and admission to the postcardiac surgical ICU, in turn, is associated with a three-fold higher survival rate compared with the other ICUs. The study by Shen et al (6) did not account for ICU type in the analysis and included all ICU types, including postcardiac surgical ICU admissions, whereas we a priori restricted our analysis to medical and cardiac ICU admissions for this reason.

Early Diuretics and Duration of Mechanical Ventilation

We found no statistically significant association between early diuretic use and duration of mechanical ventilation. We also found no evidence that early diuretic use prevents subsequent intubation or increases extubation during the exposure period since there was no difference in the proportion mechanically ventilated after the exposure period. In contrast to the FACTT trial, which showed a 2.5-day increase in ventilator-free days ($p < 0.0001$) using a fluid-conservative strategy including diuretics compared with a fluid-liberal strategy (9), we saw no significant difference in the duration of mechanical ventilation in our analysis. Reasons for this difference may include the more delayed

TABLE 2. Outcomes From Propensity-Matched Cohort

Outcomes	Diuretics ($n = 2,523$)	No Diuretics ($n = 2,523$)	Risk Ratio or Difference in Mean (99.5% CI)	p
In-hospital mortality	15%	15%	1.01 (0.83–1.22)	0.91
Any mechanical ventilation	33%	34%	0.99 (0.89–1.10)	0.76
Acute kidney injury	36%	25%	1.41 (1.25–1.59)	< 0.001
Renal replacement therapy	2%	2%	1.17 (0.65–2.11)	0.46
Hyponatremia	31%	29%	1.07 (0.95–1.21)	0.12
Severe hyponatremia	10%	10%	0.93 (0.73–1.19)	0.43
Hypokalemia	43%	37%	1.17 (1.06–1.29)	< 0.001
Severe hypokalemia	8%	9%	0.83 (0.64–1.09)	0.05
Metabolic alkalosis	37%	25%	1.51 (1.33–1.70)	< 0.001
Severe metabolic alkalosis	4%	1%	2.47 (1.43–4.27)	< 0.001
Duration of mechanical ventilation, hr	19.5 ± 38.8 0.0 (0.0–16.0)	21.1 ± 40.5 0.0 (0.0–18.1)	−1.58 (−4.68 to 1.53)	0.15
ICU length of stay, d	5.1 ± 6.0 3.1 (2.0–5.7)	4.8 ± 6.1 2.9 (1.8–5.1)	0.23 (−0.24 to 0.70)	0.17
Total length of stay, d	10.9 ± 10.2 8.0 (5.0–12.9)	10.5 ± 10.4 7.5 (4.5–12.8)	0.46 (−0.34 to 1.27)	0.11
Fluid balance, L	0.4 ± 5.5 −0.2 (−1.7 to 0.9)	1.5 ± 5.1 0.1 (−0.6 to 2.2)	−1.09 (−1.52 to −0.67)	< 0.001

Binary outcomes are given as percentages and risk ratios. Continuous variables are expressed as mean ± SD, median (25–75th percentiles), and differences in mean.

diuretic exposure period (> 40 hr after ICU admission), the different cohort definition of ALI, the effects of fluid restriction and differential dosing of vasopressors and inotropes included in the "fluid-conservative strategy" protocol, and the larger separation in net fluid balance seen in FACTT (> 6 L higher in the fluid-liberal strategy). Although there may be select patients in whom the duration of mechanical ventilation may be shortened with early use of diuretics, we found no aggregate effect in propensity-matched cohorts, even when restricting analyses to patients with heart failure or ALI.

Early Diuretics and AKI

Early diuretic use was associated with about a 40% higher relative risk (and 11% higher absolute risk) of AKI in our analysis. This finding was consistent across subgroup analyses of heart failure, CKD, and ALI, despite different prevalences of AKI in these groups (34%, 45%, 37%, respectively). Our results are consistent with previous work by Kane-Gill et al (22), who found odds ratios for AKI in the ICU with diuretic use of 1.5–2.1 in a multivariable logistic regression analysis, and by Grams et al (3) who reanalyzed data from the FACTT trial using a similar AKI definition and found a RR of 1.23 (95% CI, 1.02–1.49) for a fluid-conservative strategy including diuretics. Although AKI is associated with in-hospital mortality (23), the risk of in-hospital mortality in the current study was not significantly higher in the early diuretics group (RR, 1.01; 99.5% CI, 0.83–1.22), although the width of our CI suggests that we may have missed a modest increase in mortality risk. Furthermore, the risk of requiring renal replacement therapy was similar in both groups, suggesting that the excessive AKI with early diuretic use was not severe enough to require dialysis.

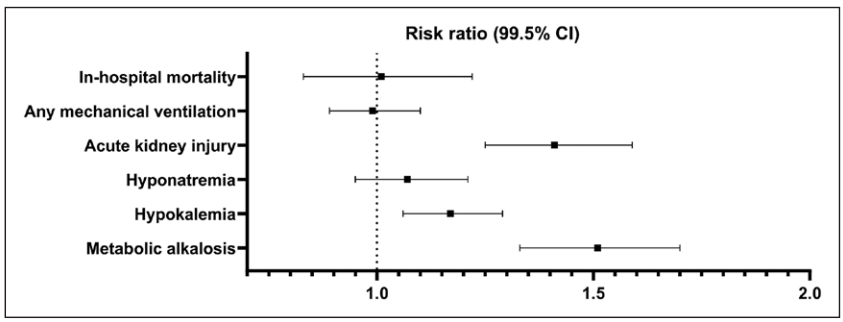

Figure 2. Outcomes from propensity-matched cohort.

Early Diuretics and Electrolyte Abnormalities

The increased risks of hypokalemia and metabolic alkalosis in patients who received early diuretics were consistent across all subgroup analyses, except in the CKD subgroup where there was no increased risk of hypokalemia. These effects were seen despite ICU-level monitoring and likely repletion of

potassium by the ICU teams. The increased risks of hypokalemia and metabolic alkalosis were also seen in FACTT (9), although the authors note that none were associated with arrhythmias. We were unable to assess for the presence of arrhythmias in this study.

Strengths and Limitations

Strengths of our study include the large cohort size, with over 5,000 patients in our propensity-matched cohort. The high number of available controls allowed us to use propensity-score matching, which has been shown to reduce residual confounding compared with alternative methods such as propensity-score adjustment (24). Also, the MIMIC data are extremely detailed, allowing outcome variables like fluid balance and duration of mechanical ventilation to be calculated using only inputs recorded after the exposure period, which further reduces confounding by indication.

Our study has several important limitations. These data are all observational and thus subject to unmeasured and residual confounding. The lack of outpatient baseline creatinine data prevents determination of true baseline kidney function, and therefore, some patients may have already been developing AKI prior to admission. Patients with prehospitalization AKI may have also been more likely to have oliguria and therefore to require diuretics, although we did include oliguria as part of the renal component of the SOFA score in our models. The lack of outpatient medication information precludes determination of whether diuretic exposure was new or a continuation of a home medication. Our data source was from a single center, and we relied on ICD-9 codes to ascertain comorbidities and admission types. The binary nature of our exposure (early diuretic use vs nonuse) does not explore the effects of dose amount or repeated diuretic dosing using a time-varying exposure approach. Finally, we were unable to ascertain the specific clinical indications for each diuretic prescribed (e.g., pulmonary edema, elevated central venous pressures). Although our results were materially unchanged in the subgroups we evaluated, the heterogeneity of patients included raises the possibility that certain subgroups of patients might have different results.

CONCLUSIONS

In summary, early diuretic use in the ICU is common (20% in our study). We found no evidence of benefit to diuretic use in the first 24 hours after ICU admission, whether examined in the cohort overall or in subgroups with heart failure, CKD, or ALI that might be expected to derive greater benefit from early diuretic use. We found consistent and highly statistically significant adverse effects—AKI and electrolyte abnormalities—of early diuretic use. Our results suggest that diuretics may not have a net benefit on the first day of ICU admission.

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