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Association of imipenem/cilastatin with development of acute kidney injury in critically ill patients requiring carbapenem treatment

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Article

Keywords: Acute kidney injury, Carbapenems, Cilastatin, Imipenem Drug Com bination, Intensive Care Units

Posted Date: July 16th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10145500/v1

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Additional Declarations: Competing interest reported. This material is the result of work which was supported with resources and the use of facilities at the Portland Veterans Affairs Medical Center. The opinions and assertions expressed herein are those of the author(s) and do not necessarily reflect the official policy or position of the Uniformed Services University, the Department of War, or the Department of Veterans Affairs. A.L. is the coinventor of cilastatin patents as a renal protector against toxic injuries ('Use of cilastatin to reduce nephrotoxicity of various compounds', patent numbers: EP 2143429 B1; US 9,216,185 B2;

US 9,522,128 B2; US-9,757,349 B2) and for the treatment of sepsis and sepsis-associated AKI (“Cilastatin for use in the treatment of sepsis”. Number of patents granted: EP3474897A1; US 11185522; 7109791; CN109843330B; 20177281744 and CA3028846A1). These were assigned to the Fundación para la Investigación Biomédica del Hospital Gregorio Marañón (FIBHGM), licensed to Telara Pharma S.L., and transferred to Arch Biopartners. A.L. is a co-founder of Telara Pharma S.L. For the remaining authors, none were declared.

Version of Record: A version of this preprint was published at Scientific Reports on November 5th, 2026. See the published version at https://doi.org/10.1038/s41598-026-76428-6.

Abstract

Cilastatin is an inhibitor of drug metabolism in the kidney which is only available for human use in combination with imipenem, a carbapenem antibiotic, as imipenem/cilastatin (I/C). Animal studies demonstrate cilastatin protects against acute kidney injury (AKI) and clinical studies suggest I/C may reduce the risk of AKI. However, the effective dose of cilastatin in animal studies is higher than that approved with imipenem, and rigorous assessment of the effect of I/C on AKI in patients with high risk of AKI, such as those in the intensive care unit (ICU), is indicated. To address this issue, we conducted a retrospective cohort study using 3 large ICU databases, including Medical Information Mart for Intensive Care III (MIMIC-III), MIMIC-IV, and the Amsterdam University Medical Center database (AUMC). Total 3916 patients were included and patients treated with I/C or non-cilastatin carbapenems (NCC) were compared using propensity score-based overlap weighting analysis. AKI development or progression was less commonly observed in I/C-treated patients than in NCC-treated patients in MIMIC-III (odds ratio [OR] and 95% confidence interval of I/C group: 0.51 [0.30–0.85]) while the outcome was similar between the groups in MIMIC-IV (OR: 1.22 [0.80–1.86]) and in AUMC (OR: 1.07 [0.77–1.48]). The outcome development was also similar between the groups with the overall analysis across all datasets by random effect model meta-analysis (OR: 0.89 [0.54–1.48]). In conclusion, I/C and other carbapenems do not differentially associate with AKI risks in ICU, and its putative effects may depend on patient characteristics and clinical settings.

Introduction

Acute kidney injury (AKI) is a frequent complication in hospitalized patients, especially in intensive care units (ICU) where incidence is often higher than 50%[1–3]. Sepsis, cardiac surgery, medication with nephrotoxic drugs, and profound hypotension are the major causes of AKI in intensive care patients[4,5]. Development of AKI independently increases mortality, length of stay in ICU, and treatment costs including those for subsequent chronic complications of AKI[6]. Therefore, interventions which reduce the incidence or severity of AKI have high importance.

Cilastatin was developed in the 1980s to reduce the renal metabolism of imipenem, a broad-spectrum carbapenem antibiotic, through inhibition of renal dipeptidase (DHP-1)[7,8]. Cilastatin also inhibits megalin, an endocytic transporter, reducing reabsorption of more than 60 filtered proteins, peptides, and small molecules in the proximal tubule [9,10]. Literature suggests that cilastatin has a renoprotective effect in diverse animal AKI models through its inhibitory effects on DHP-1 and megalin[11–20]. Cilastatin is currently US Food and Drug Administration-approved only in combination with imipenem[21] (imipenem/cilastatin; I/C) and several studies have reported renoprotective effects of this combination on patients with infection, organ transplant, and cancer[21,22]. However, comparisons in high-risk patients and direct comparison with non-cilastatin containing carbapenem antibiotics (NCC) are lacking.

To clarify this issue, we assessed whether intensive care patients treated with I/C were less likely to develop AKI relative to those treated with NCC in large ICU patient datasets.

Methods

Selection of databases

We considered 6 large ICU patient datasets for inclusion in the study, including the Medical Information Mart for Intensive Care III (MIMIC-III)[23], MIMIC-IV[24], Amsterdam University Medical Center database (AUMC)[25], high time-resolution ICU dataset (HiRID)[26], eICU Collaborative Research Database (eICU)[27], and Salzburg ICU database (SICdb)[28]. HiRID had no subjects treated with I/C. Only 4 subjects in eICU received I/C. Despite multiple attempts it proved impossible to access SICdb. Therefore, we performed a retrospective cohort study using MIMIC-III, MIMIC-IV, and AUMC data. This study was determined to not be human subjects research by the Oregon Health & Science University Institutional Review Board, and was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines[29] and the Helsinki Declaration. Given that all data were anonymized to protect patient privacy, the requirement for written informed consent was waived. MIMIC-III is a large database comprising de-identified data of over 40,000 ICU patients at the Beth Israel Deaconess Medical Center between 2001 and 2012[23]. MIMIC-IV is an updated version of MIMIC-III, covering patients admitted to the same center between 2008-2019[24]. Since patients who stayed in the center between 2008 and 2012 may be duplicated in those two datasets, the MIMIC-III Clinical Database CareVue subset Version 1.4 (https://doi.org/10.13026/8a4q-w170), which only contains data between 2001–2008, was used instead of the full MIMIC-III dataset. AUMC is a deidentified critical care database from Amsterdam University Medical Centers in the Netherlands, containing data from over 23,000 ICU admissions between 2003 and 2016[25]. We obtained permission for access to those databases through Physionet, a public ICU database portal[30]. Data were collected from the selected databases using the R language package “ricu”[31] .

Study design

Prescription records were extracted from the datasets, and subjects who were treated with carbapenem drugs during their ICU stay were included in this study. We included I/C and I/C-relbactam under the rubric I/C. NCC were meropenem, meropenem/vaborbactam, doripenem, and ertapenem. Subjects were assigned to the I/C or the NCC group based on the first carbapenem drug they received in ICU. Since prescription data from MIMIC-III does not contain the time of the treatment, we imputed MIMIC-III treatment time as 1:00 PM, which was the median time of carbapenem treatment in MIMIC-IV. We excluded patients who: 1) were already being treated with carbapenem drugs prior to transfer to ICU, 2) receiving both types of carbapenems within 24 hours after the first carbapenem treatment (“treatment start”), 3) received carbapenems for anaphylaxis desensitization, 4) had no recorded serum creatinine (sCr) levels before or after treatment, or 5) were suffering AKI stage 3 or were receiving renal replacement therapy (RRT) at treatment start.

Data collection

Data including age, sex, type of ICU (whether surgical unit or not), sCr levels, scores of Sequential Organ Failure Assessment (SOFA)[32], quick SOFA (qSOFA)[33], and Systemic Inflammatory Response Syndrome (SIRS)[34,35], blood cultures, treatment with vancomycin and vasopressors, and mechanical ventilation during

168 hours prior to or after treatment start were collected. If a subject received carbapenems of the other group, the observation was censored at that point. The lowest sCr level during 168 hours prior to treatment was defined as the baseline sCr level. sCr levels measured temporally closest to and before treatment start were defined as the sCr level at treatment start. AKI stage at treatment start was estimated with baseline sCr levels and sCr levels at treatment start according to definition of AKI by Kidney Disease Improving Global Outcomes (KDIGO) guideline[36]. Because many subjects lacked or had extensive spurious urine output data, AKI stage was assessed only using sCr levels. Detailed method for AKI staging is described in Supplementary Fig. 1. Subjects treated with vasopressors during 24 hours prior to treatment start were assessed as receiving vasopressors at treatment start. Whether the subjects were tested for blood culture during 72 hours prior to treatment start or within 24 hours after treatment start was assessed to infer the purpose of carbapenem usage (for treatment of infection *vs.* possibly empiric or prophylactic purpose) and severity of infection[37].

Outcomes

The primary outcome of this study was development of AKI or progression of AKI stage (AKI development/progression) within 168 hours after treatment start. AKI stage after treatment start was assessed with sCr levels and RRT data after treatment start compared with the baseline sCr levels. Subjects who newly developed AKI after treatment or subjects with AKI at treatment start but who developed more severe AKI after treatment were judged as having AKI development/progression. The combined outcome of AKI development/progression or death was assessed in a sensitivity analysis, considering the competing outcome risks. Receiving RRT (RRT-intervention), death, and RRT-intervention or death were assessed as secondary outcomes.

Statistical analysis

The demographic factors of the I/C group and the NCC group were compared in each dataset. Continuous variables were compared using the Wilcoxon–Mann–Whitney test. Categorical variables were assessed by means of the chi-square test or Fisher's exact test. To adjust subject backgrounds of the I/C and the NCC groups in each dataset, we conducted overlap weighting analysis[38] based on scores underlying the propensity to receive I/C drugs. Propensity scores were calculated with potential confounders including age, sex, type of ICU, baseline sCr levels, and SIRS score, treatment with vancomycin, treatment with vasopressors, testing for blood culture, sCr levels, and AKI stage at treatment start. SOFA score was not used as a predictor for propensity scores since the score was missing in 104 of 692 subjects (15.0%) in AUMC. The outcome development in the I/C group and the NCC group were assessed and odds ratio (OR) of I/C group was calculated in each dataset. The results of each dataset were combined using random effect model meta-analysis with the "metafor" R package[39] to combine results across datasets. When an outcome developed only in the I/C group or only in the NCC group, the effect size was estimated using Firth's penalized logistic regression model[40,41]. Stratified analysis was performed and subjects in each dataset were stratified based on the predictors for calculating the propensity scores. After stratification, propensity scores for receiving I/C drugs were calculated and the outcomes were assessed using overlap weighting. All

statistical analyses were performed on the R software (version 4.5.3, R Foundation for Statistical Computing, Vienna, Austria). Values of $p < 0.05$ were considered statistically significant.

Results

Patient characteristics

After exclusion, 77 and 332 in MIMIC-III, 88 and 2727 in MIMIC-IV, and 480 and 212 subjects in AUMC receiving I/C and NCC respectively were analyzed in this study (Fig. 1). Demographics of the subjects in each dataset are shown in Supplementary table 1. In all datasets, 98% or more subjects in I/C group were treated with I/C. More than 99% of subjects in NCC group were treated with meropenem. Although baseline sCr levels and sCr levels at treatment start were similar between the groups in MIMIC-III and MIMIC-IV, those levels were higher in the I/C group compared to the NCC group in AUMC. Propensity scores to receive I/C drugs were calculated in each dataset (Supplementary Fig. 2). After overlap weighting, 121.0, 170.2, and 288.6 weighted subjects were analyzed in MIMIC-III, MIMIC-IV, and AUMC, respectively. Subject characteristics in each dataset were well adjusted between the groups with overlap weighting (Table 1 and Supplementary Fig. 3).

Table 1
Study characteristics after overlap weighting

	MIMIC-III			MIMIC-IV			AUMC		
	I/C N = 60.5	NCC N = 60.5	p-value	I/C n = 85.1	NCC N = 85.1	p-value	I/C n = 144.3	NCC N = 144.3	p-value
Age (years)			0.87			0.63			0.56
18–39	3.4 (5.6%)	4.5 (7.5%)		7.8 (9.2%)	6.8 (8.0%)		16.0 (11.1%)	20.1 (14.0%)	
40–49	6.3 (10.4%)	5.2 (8.6%)		9.7 (11.4%)	7.7 (9.1%)		15.6 (10.8%)	15.1 (10.4%)	
50–59	10.8 (17.8%)	9.5 (15.8%)		10.7 (12.5%)	16.7 (19.6%)		31.9 (22.1%)	25.5 (17.7%)	
60–69	13.5 (22.3%)	12.6 (20.8%)		24.2 (28.4%)	22.2 (26.1%)		44.9 (31.1%)	41.2 (28.6%)	
70–79	13.8 (22.9%)	17.5 (28.9%)		18.3 (21.5%)	17.4 (20.5%)		29.9 (20.7%)	36.2 (25.1%)	
80+	12.7 (21.0%)	11.2 (18.5%)		14.4 (16.9%)	14.2 (16.7%)		5.9 (4.1%)	6.2 (4.3%)	
Sex			> 0.99			> 0.99			> 0.99
Female	29.2 (48.3%)	29.2 (48.3%)		36.7 (43.2%)	36.7 (43.2%)		52.7 (36.5%)	52.7 (36.5%)	
Male	31.3 (51.7%)	31.3 (51.7%)		48.3 (56.8%)	48.3 (56.8%)		91.6 (63.5%)	91.6 (63.5%)	
ICU type			> 0.99			> 0.99			> 0.99
Non-surgery	36.7 (60.7%)	36.7 (60.7%)		70.4 (82.8%)	70.4 (82.8%)		85.5 (59.3%)	85.5 (59.3%)	
Surgery	23.8 (39.3%)	23.8 (39.3%)		14.7 (17.2%)	14.7 (17.2%)		58.8 (40.7%)	58.8 (40.7%)	
qSOFA score	1.0 (0.0, 1.0)	1.0 (0.0, 1.0)	> 0.99	1.0 (0.0, 1.0)	1.0 (0.0, 1.0)	0.67	1.0 (0.0, 1.0)	1.0 (0.0, 1.0)	0.90
SIRS	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	0.84	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	0.95	2.0 (2.0, 3.0)	2.0 (1.0, 3.0)	0.95
Blood culture	48.4 (80.1%)	48.4 (80.1%)	> 0.99	65.7 (77.3%)	65.7 (77.3%)	> 0.99	21.3 (14.8%)	21.3 (14.8%)	> 0.99

	MIMIC-III			MIMIC-IV			AUMC		
	I/C N = 60.5	NCC N = 60.5	p-value	I/C n = 85.1	NCC N = 85.1	p-value	I/C n = 144.3	NCC N = 144.3	p-value
Vancomycin usage	19.5 (32.3%)	19.5 (32.3%)	> 0.99	52.4 (61.6%)	52.4 (61.6%)	> 0.99	72.0 (49.9%)	72.0 (49.9%)	> 0.99
Vasopressor usage	24.9 (41.2%)	24.9 (41.2%)	> 0.99	7.7 (9.0%)	7.7 (9.0%)	> 0.99	91.4 (63.3%)	91.4 (63.3%)	> 0.99
Ventilation	40.9 (67.7%)	41.1 (67.9%)	0.97	11.6 (13.6%)	7.4 (8.7%)	0.11	96.3 (66.7%)	85.8 (59.4%)	0.07
Baseline sCr (mg/dL)	0.9 (0.6, 1.4)	0.9 (0.6, 1.4)	0.89	1.0 (0.6, 1.5)	1.0 (0.6, 1.5)	> 0.99	0.8 (0.6, 1.2)	0.7 (0.6, 1.1)	0.21
sCr at treatment start (mg/dL)	1.1 (0.8, 1.7)	1.1 (0.7, 1.7)	0.78	1.1 (0.7, 2.0)	1.1 (0.7, 1.8)	0.92	1.0 (0.7, 1.5)	0.9 (0.6, 1.5)	0.26
AKI stage at treatment start			> 0.99			0.97			0.90
0	45.2 (74.7%)	45.2 (74.7%)		64.7 (76.0%)	64.3 (75.6%)		105.2 (72.9%)	106.2 (73.6%)	
1	13.7 (22.7%)	13.7 (22.7%)		15.5 (18.3%)	16.2 (19.0%)		30.6 (21.2%)	28.7 (19.9%)	
2	1.6 (2.6%)	1.6 (2.6%)		4.9 (5.7%)	4.5 (5.3%)		8.5 (5.9%)	9.4 (6.5%)	

AKI development or progression was not attenuated by I/C compared to other carbapenems

The number of subjects who received carbapenems of the other group and total observed time of the subjects were similar between the groups in all datasets (Supplementary table 2 and 3). After overlap weighting, the outcome was observed at 31.9% in MIMIC-III, 34.0% in MIMIC-IV, and 29.6% in AUMC. Although AKI development/progression developed less frequently in the I/C group compared to the NCC group in MIMIC-III (OR and 95% confidence interval of I/C group: 0.51 [0.30, 0.85], p = 0.01), the outcome was similarly observed between groups in MIMIC-IV (OR: 1.22 [0.80, 1.86], p = 0.35) and in AUMC (OR: 1.07 [0.77, 1.48], p = 0.69) (Fig. 2). Random effect model meta-analysis revealed that the overall OR across all datasets was 0.89 [0.54, 1.48] (p = 0.66, heterogeneity among datasets: p = 0.02). In sensitivity analyses, AKI development/progression or death, a composite outcome, developed less frequently in the I/C group compared to the NCC group in MIMIC-III while the outcome was similarly observed between the groups in MIMIC-IV and in AUMC and at overall analysis across the datasets (Supplementary Fig. 4). The development

of RRT-intervention, death, and RRT-intervention or death were also similar between the groups in each dataset, and the overall OR of the I/C group across all datasets was assessed as 0.74 [0.49, 1.11] (p = 0.15, heterogeneity: p = 0.53), 1.03 [0.78, 1.36] (p = 0.81, heterogeneity: p = 0.76), and 0.91 [0.71, 1.16] (p = 0.44, heterogeneity: p = 0.58), respectively (Fig. 3). These results suggest that AKI or other outcomes was not altered by I/C drugs compared to NCC drugs except for AKI development/progression in MIMIC-III.

AKI development or progression developed similarly between the groups in both subgroups stratified based on whether having AKI at treatment start

Next, we stratified the subjects by whether they had AKI at treatment start. Backgrounds of the subjects after overlap weighting are shown in Supplementary table 4 and 5. Among subjects without AKI at treatment start, development of AKI less frequently developed in the I/C group compared to the NCC group in MIMIC-III (OR: 0.51 [0.27, 0.94], p = 0.03), it was similarly observed between I/C and NCC groups in MIMIC-IV (OR: 1.45 [0.86, 2.42], p = 0.16) and in AUMC (OR: 1.23 [0.78, 1.95], p = 0.37) (Fig. 4a). Overall OR for the I/C group across all datasets was 0.99 [0.54, 1.83] (p = 0.98, heterogeneity: p = 0.03). Secondary outcomes including RRT-intervention, death, RRT-intervention or death also developed similarly between the groups in each dataset and at overall analysis (Supplementary Fig. 5). Among subjects with AKI at treatment start, progression of AKI similarly developed between the groups in each dataset (OR: 0.17 [0.00, 7.43], p = 0.17 in MIMIC-III, 1.00 [0.49, 2.05], p > 0.99 in MIMIC-IV, and 0.70 [0.39, 1.25], p = 0.23 in AUMC) and at overall analysis across all datasets (OR: 0.79 [0.50, 1.24], p = 0.57, heterogeneity: p = 0.57) (Fig. 4b). Secondary outcomes also developed similarly between the groups in each dataset and at overall analysis across all datasets (Supplementary Fig. 6).

Subgroup analysis was also conducted with the stratified groups based on age, sex, type of ICU, SIRS score, testing for blood culture, treatment with vancomycin, or treatment with vasopressors. At the overall analysis across all datasets, AKI development/progression similarly developed between the groups in all subgroups (Supplementary Fig. 7). In MIMIC-III, the outcome was less common in the I/C group of certain subgroups (Age < 60 years, female, non-surgical unit, SIRS score ≥ 2, with testing for blood culture, without vancomycin treatment, and treated with vasopressor). However, the outcome similarly developed between the groups in all subgroups in MIMIC-IV and AUMC.

These results suggest that I/C drugs do not attenuate AKI and other outcomes regardless patient characteristics and clinical settings except for in MIMIC-III.

Discussion

The most important finding of this investigation is that I/C, compared to NCC, does not suppress development or progression of AKI among patients in ICU. Although MIMIC-III subjects treated with I/C developed less AKI, AKI development was similar between the groups in MIMIC-IV and AUMC. Acharya, et al. conducted a meta-analysis testing the renoprotective effect of I/C, assessing 10 studies including 5 randomized controlled trials and 5 retrospective observational studies[21]. They reported that overall risk ratio for AKI across the datasets was decreased by 48% in patients treated with I/C. Among the 10 studies included in meta-analysis, 2 observational studies (research by King Faisal Specialist Hospital and Research

Centre [KFSH&RC] group[42] and by Pediatrix Medical Group[43]) compared I/C to meropenem, similar to the present study, reporting that I/C decreased the risk ratio of AKI by 48% and 52% relative to meropenem, respectively. However, the Pediatrix Medical Group excluded adults, and the KFSH&RC study did not focus on patients in ICU and excluded patients with chronic kidney disease or those treated with vancomycin. These differences in research settings and subject inclusion might explain the contradictory results in our study. A strength of our study is the use of propensity-matched analysis, which was necessitated by the observation that carbapenem choice is associated with preexisting renal function. Additionally, variables chosen for propensity analysis were limited to variables tracked in all three datasets. Therefore, it is possible unmeasured confounding could also be a source of our discrepant result. I/C reduces seizure threshold, particularly in patients with kidney dysfunction[43–46]. Therefore, patients with medical history of seizure or with kidney dysfunction may be more likely to receive NCC, which could bias results. Although medical history could not be assessed in this study, we adjusted for pre-treatment kidney function and other potential confounders with propensity score-based overlap weighting to avoid biased patient-assignment between the groups. Prior studies did not employ propensity matching for the assessment of AKI. To the best of our knowledge, no studies have compared the renoprotective effect of I/C in ICU patients to that of other carbapenems, the most similar possible comparator. The present result is discordant with multiple studies conducted in rodents and large animals, in which cilastatin administration robustly reduces kidney injury[11–20]. An important difference between I/C administratation in humans and cilastatin administration in preclinical studies is that the approved dosing of cilastatin in humans is ~ 15–20 mg/kg/24h, while preclinical dosing for AKI is 100–200 mg/kg/24h. This 5-10-fold difference in dose is possible explanation for the discordance. A phase I trial of cilastatin at the higher dose was completed in 2018 (NCT03595189), and 2 phase II trials for cilastatin in nephrotoxic AKI are currently underway (NCT06886464 and EU ID:2024-518854-18-00). Our result provides important additional context for further studies, especially in ICU patients.

Subjects treated with I/C were less likely to experience AKI development/progression relative to those treated with NCC in the MIMIC-III cohort but the outcomes were similar between the groups in MIMIC-IV and AUMC. Additionally, in subgroup analysis, the outcome was less common in I/C-treated patients in some subgroups of MIMIC-III while it was similar between the groups in subgroups of MIMIC-IV and AUMC. Together these imply that the effect of I/C was associated with dataset itself rather than with patient characteristics assessed in this study. Notably, results were discordant between MIMIC-III and MIMIC-IV, datasets from the same medical center and group. The MIMIC-III Care Vue subset data (2001–2008) is older than MIMIC-IV (2009–2017), and the medical practice environment and data collection likely differed. For example, we note that the percentage of vancomycin-treated patients and patients with mechanical ventilation were different between the datasets as shown in Supplementary table 1. During the period 2001–2017 there were several practice-altering changes in critical care of patients with sepsis and AKI which might explain differences in outcomes between MIMIC-III and MIMIC-IV. For example, the first Surviving Sepsis guidelines, published in 2004 and updated in 2008, included was a guideline requiring administration of antibiotics within 1 h of ICU admission[47]. Within a few years, studies demonstrated that adherence to Surviving Sepsis guidelines associated with significant reductions in mortality[48,49]. Additionally, shifts in recognition and care for AKI in the ICU have also occurred, with the KDIGO Clinical Practice Guideline for AKI,

published in 2012[36]. Therefore, the renoprotective effect of I/C observed in MIMIC-III might be masked in patients treated with more recent treatment strategies available to patients represented in MIMIC-IV. This hypothesis is supported by AUMC, which includes data from 2003–2016, temporally between that of MIMIC-III and MIMIC-IV. The estimated OR for AKI development/progression in the I/C group in AUMC was also between the estimated OR in MIMIC-III and MIMIC-IV. Although AUMC is the dataset from Netherlands and environments of patients, data collection, and treatment might be different from the other datasets, those results imply the importance of the potential relationship between time difference in datasets and renoprotective effect of I/C. Unfortunately, because dates of treatment are patient identifiers, they are obfuscated in our datasets and we cannot test this hypothesis.

This study had several limitations. First, it was conducted retrospectively, and the patients were not allocated randomly to I/C or NCC groups. Although we adjusted the patient characteristics using propensity score-based overlap weighting, several potential confounders including race, medical history of seizure, consciousness level, comorbidities, and whether the patients received cardiac surgery could not be abstracted and not adjusted. Additionally, dose and duration of the carbapenem treatment are unknown, possibly affecting the results. Second, the AKI development/progression was assessed without reference to urine volume because these data are frequently missing or inaccurate. Third, the effects of I/C for other outcomes such as persistence of AKI, cardiovascular events, middle or long-term survival prognosis, and AKI-induced chronic kidney disease are still unknown. Our recent preclinical study documented earlier recovery in crush syndrome-exposed swine treated with cilastatin [18], indicating an effect on persistent AKI. Lastly, we assessed datasets from large medical centers in United States and the Netherlands. Therefore, results in other countries or smaller medical centers may be different from the results in this study. Studies with prospective research design and in other hospitals and countries will help further clarifying the effect of I/C or cilastatin alone in AKI.

Conclusions

In critically ill patients, I/C and NCC are associated with similar risk of development or progression of AKI. Relative effects of cilastatin within carbapenem antibiotic therapy on AKI may depend on timing of drug administration, dose, patient characteristics, and clinical settings.

Declarations

Author contributions: D.A. collected and analyzed data and drafted the manuscript. T.G. administered the project. A.L., D.J.M., I.J.S., and J.T.H. edited and revised the manuscript. M.P.H. conceived and designed the study, edited the manuscript, and led the research team. All authors approved final version of manuscript.

Data availability statement : All code used to perform analyses in this manuscript is available on https://doi.org/10.5281/zenodo.20561181.

Competing interests: This material is the result of work which was supported with resources and the use of facilities at the Portland Veterans Affairs Medical Center. The opinions and assertions expressed herein are those of the author(s) and do not necessarily reflect the official policy or position of the Uniformed Services

University, the Department of War, or the Department of Veterans Affairs. A.L. is the coinventor of cilastatin patents as a renal protector against toxic injuries ('Use of cilastatin to reduce nephrotoxicity of various compounds', patent numbers: EP 2143429 B1; US 9,216,185 B2; US 9,522,128 B2; US-9,757,349 B2) and for the treatment of sepsis and sepsis-associated AKI ("Cilastatin for use in the treatment of sepsis". Number of patents granted: EP3474897A1; US 11185522; 7109791; CN109843330B; 20177281744 and CA3028846A1). These were assigned to the Fundación para la Investigación Biomédica del Hospital Gregorio Marañón (FIBHGM), licensed to Telara Pharma S.L., and transferred to Arch Biopartners. A.L. is a co-founder of Telara Pharma S.L. For the remaining authors, none were declared.

Funding: This work was supported by the US Department of Veterans Affairs Merit Review Award# I01BX04288 (to M.P.H).

Ethics approval and consent to participate: This study was determined to not be human subjects research by the Oregon Health & Science University Institutional Review Board and was conducted in accordance with the Helsinki Declaration. Given that all data in the databases were anonymized to protect patient privacy, the requirement for written informed consent was waived.

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Figures

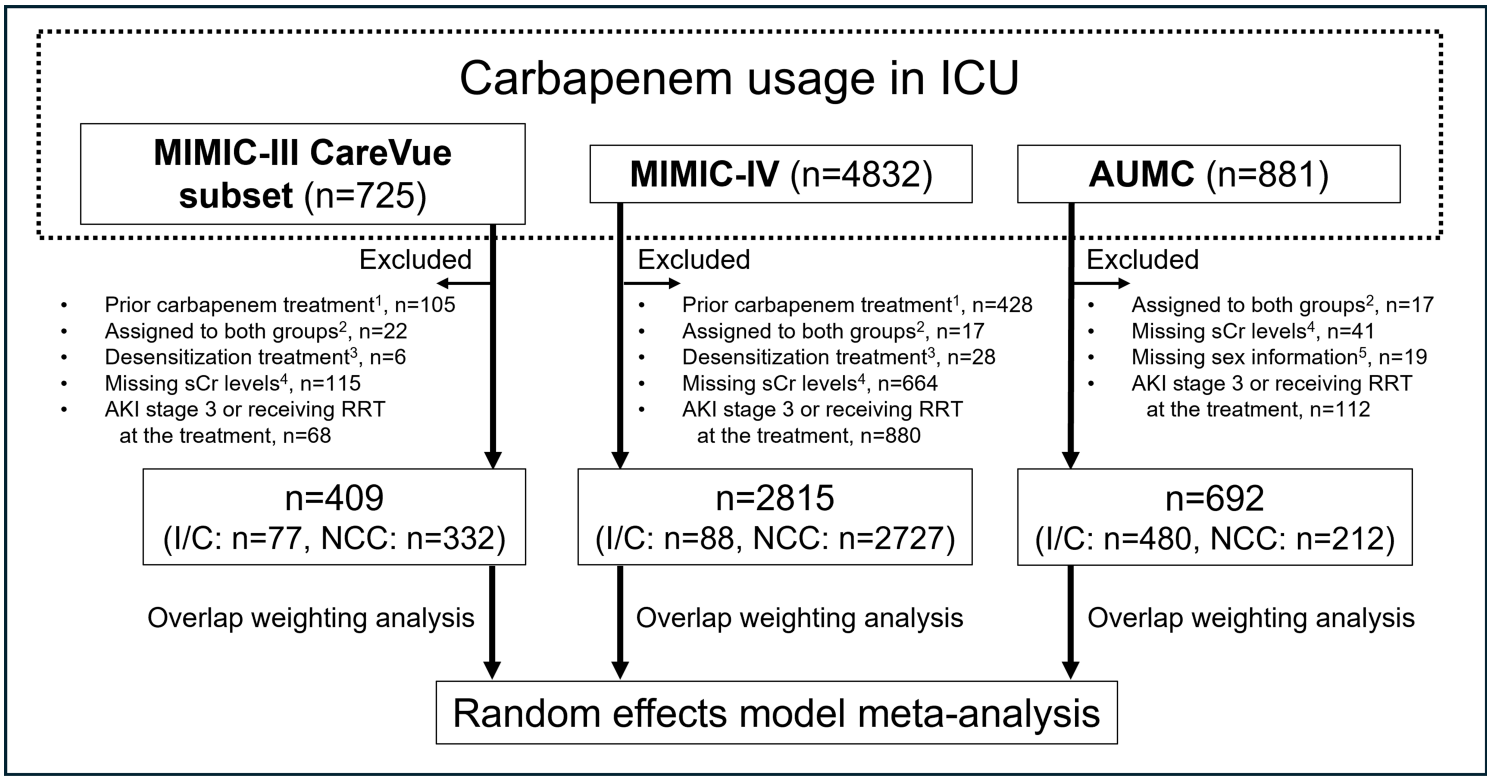


Figure 1

Flow chart

Flow chart of this study. Subjects treated with carbapenem drugs in intensive care unit (ICU) of MIMIC-III CareVue subset, MIMIC-IV, and AUMC datasets were included. Exclusion criteria are 1receiving carbapenems prior to ICU admission, 2receiving both imipenem/cilastatin (I/C) drugs and non-cilastatin containing carbapenems (NCC) during first 24 hours, 3initiation of carbapenem treatment with a dose for desensitization, 4serum creatinine (sCr) levels before the treatment or after the treatment were not available, missing of information about sex, and having stage 3 acute kidney injury (AKI) or receiving renal replacement therapy (RRT) at treatment start. I/C and NCC groups were compared in each dataset using propensity score-based overlap weighting. Results of each dataset were combined using random effect model meta-analysis.

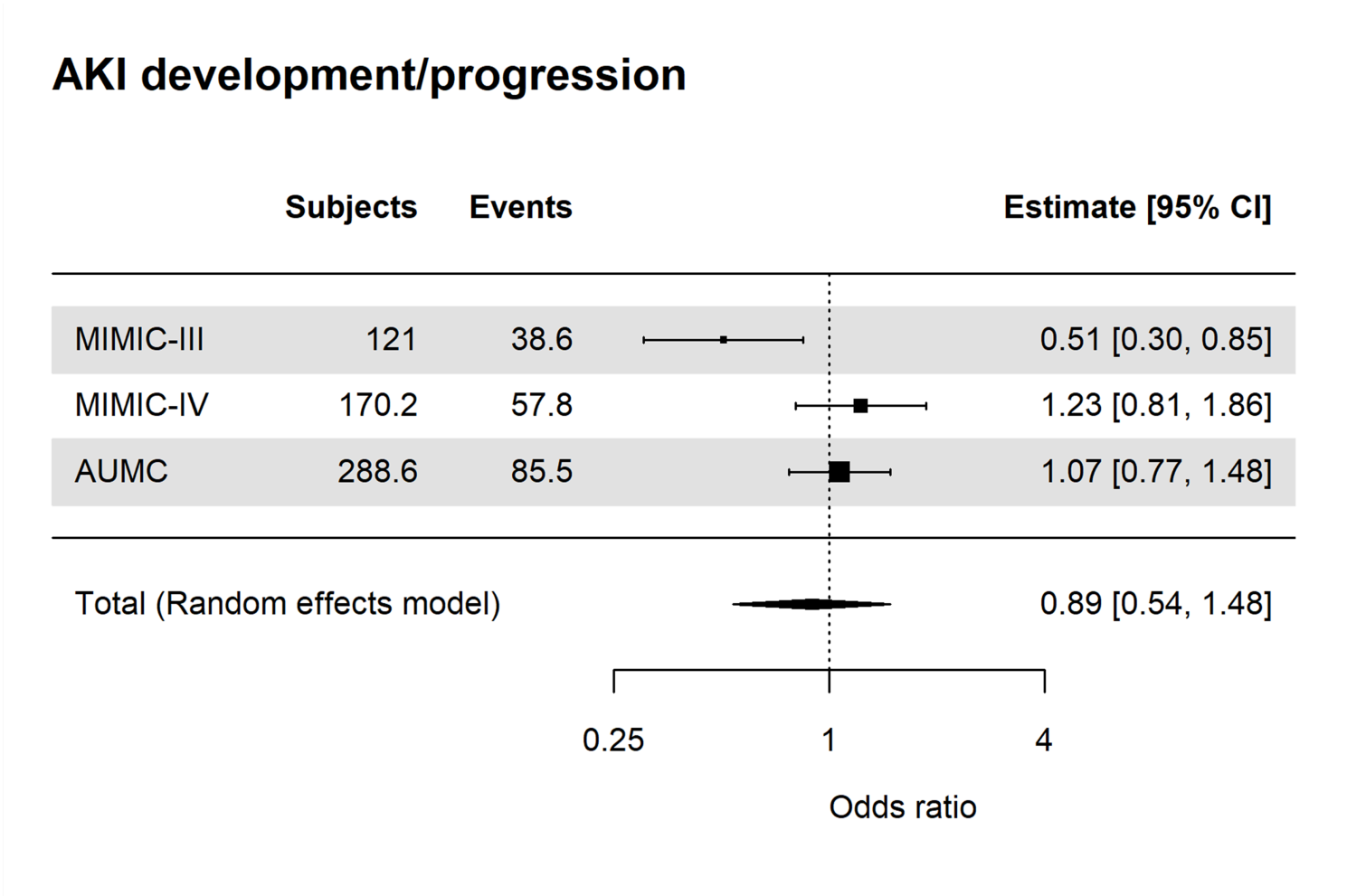


Figure 2

Development or progression of AKI

Forrest plot for odds ratio (OR) and 95% confidence interval of the I/C group for development or progression of AKI (AKI development/progression). Although AKI development/progression was less developed in I/C treated-subjects relative to NCC treated-subjects in MIMIC-III, the outcome development was similarly observed between the groups in MIMIC-IV and AUMC. Random effect model meta-analysis indicated that AKI development/progression similarly developed between the I/C and NCC group as the overall results across all datasets.

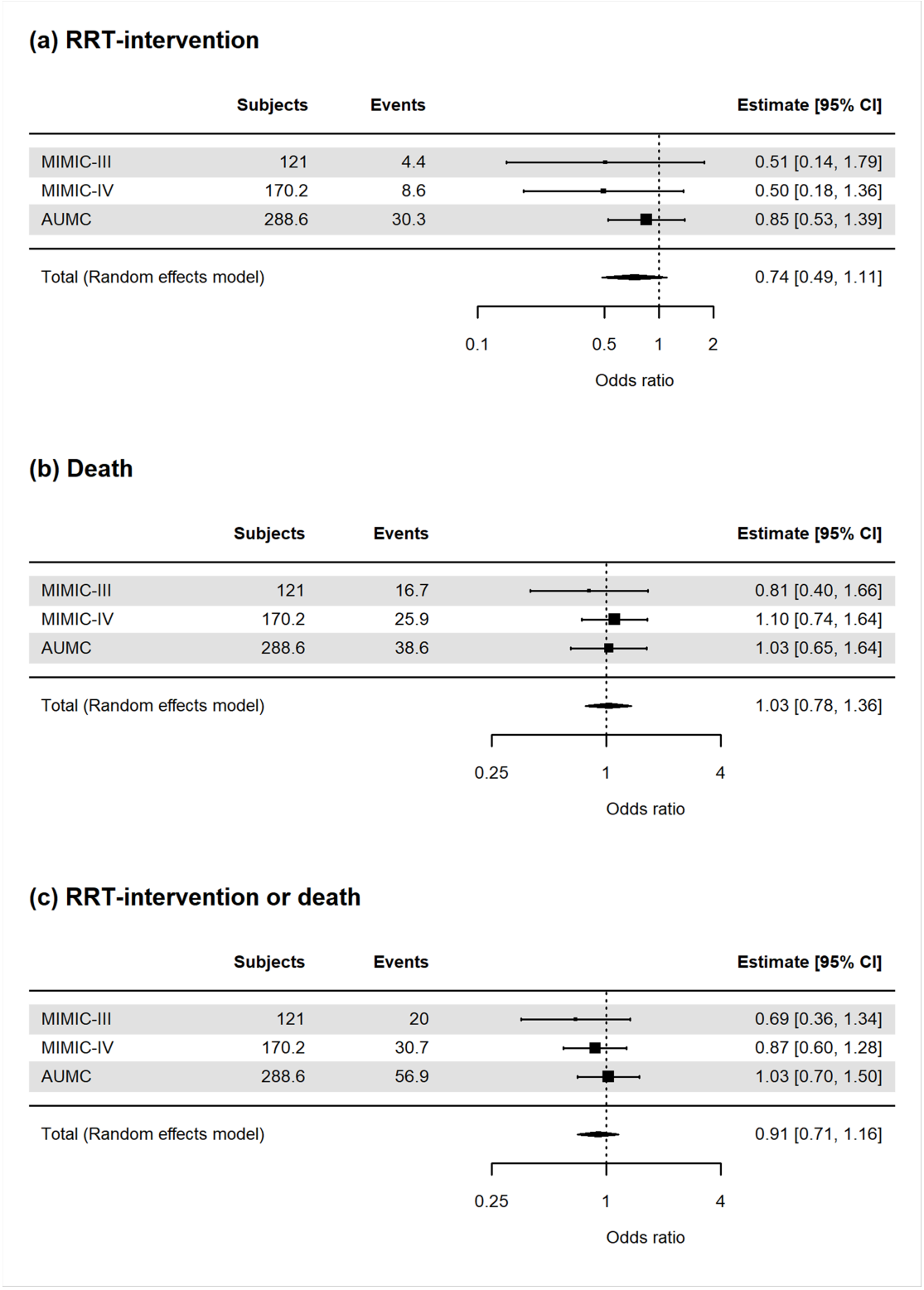


Figure 3

Development of secondary outcomes

Forrest plot for OR of the I/C group for (a) intervention with renal replacement therapy (RRT-intervention), (b) death, or (c) RRT-intervention or death. The outcomes similarly developed between the I/C and the NCC groups.

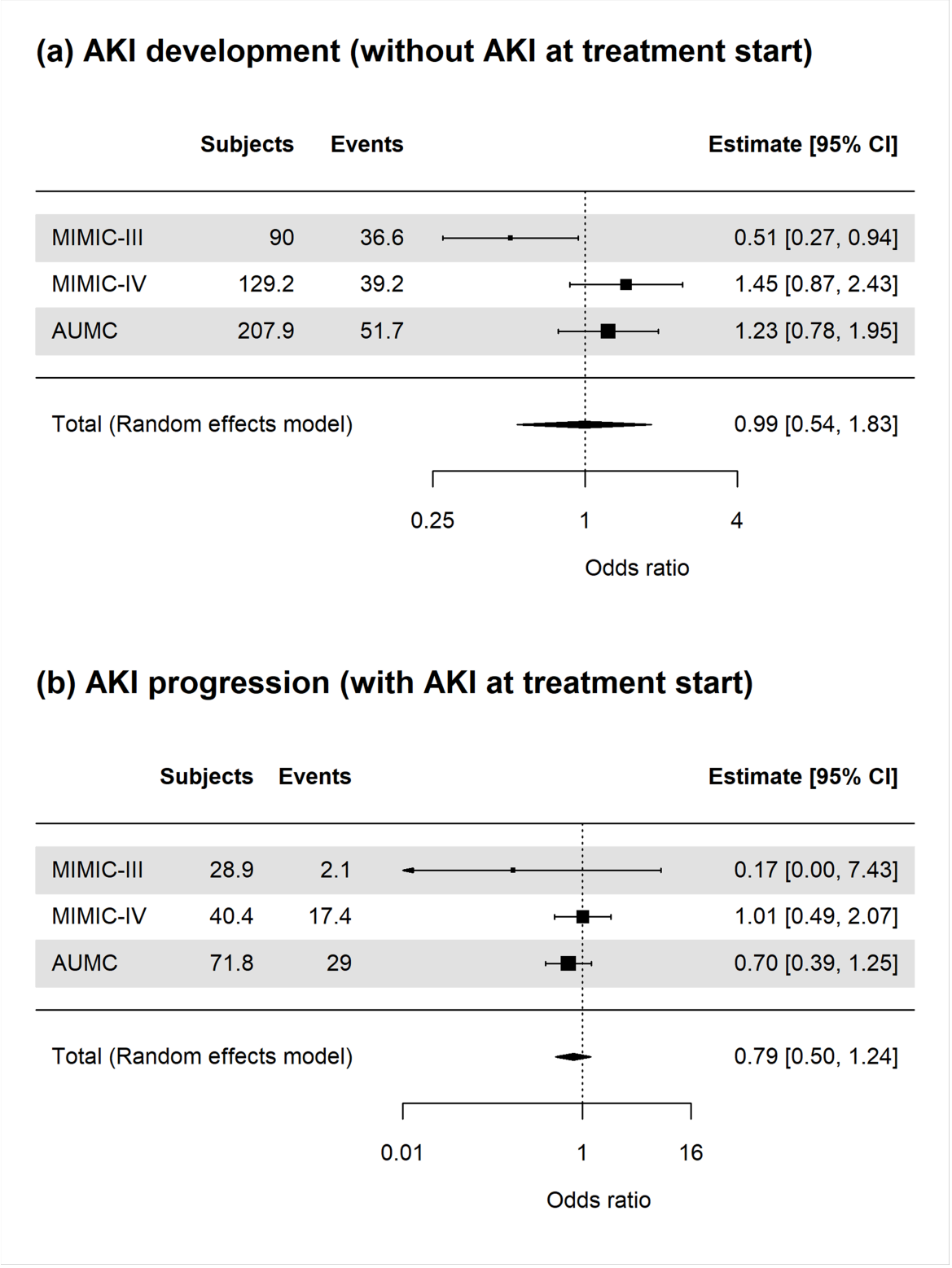


Figure 4

Subgroup analysis based on whether the subjects had AKI at treatment start

Forrest plot for OR of the I/C group for AKI development or progression among subjects (a) without AKI at treatment start and (b) with AKI at treatment start. The outcomes similarly developed between the groups

except for among subjects having AKI at treatment start in MIMIC-III, in which AKI developed less commonly in the I/C group relative to the NCC group.

Supplementary Files

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- 20260624Supplementaryfiles.pdf