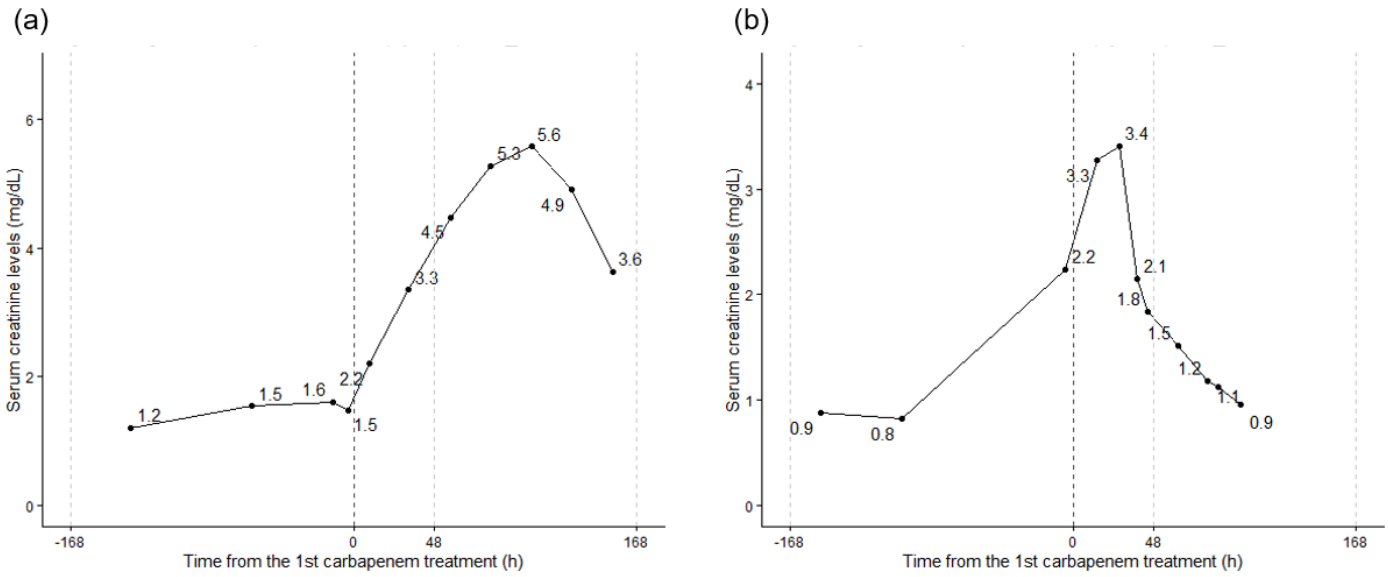
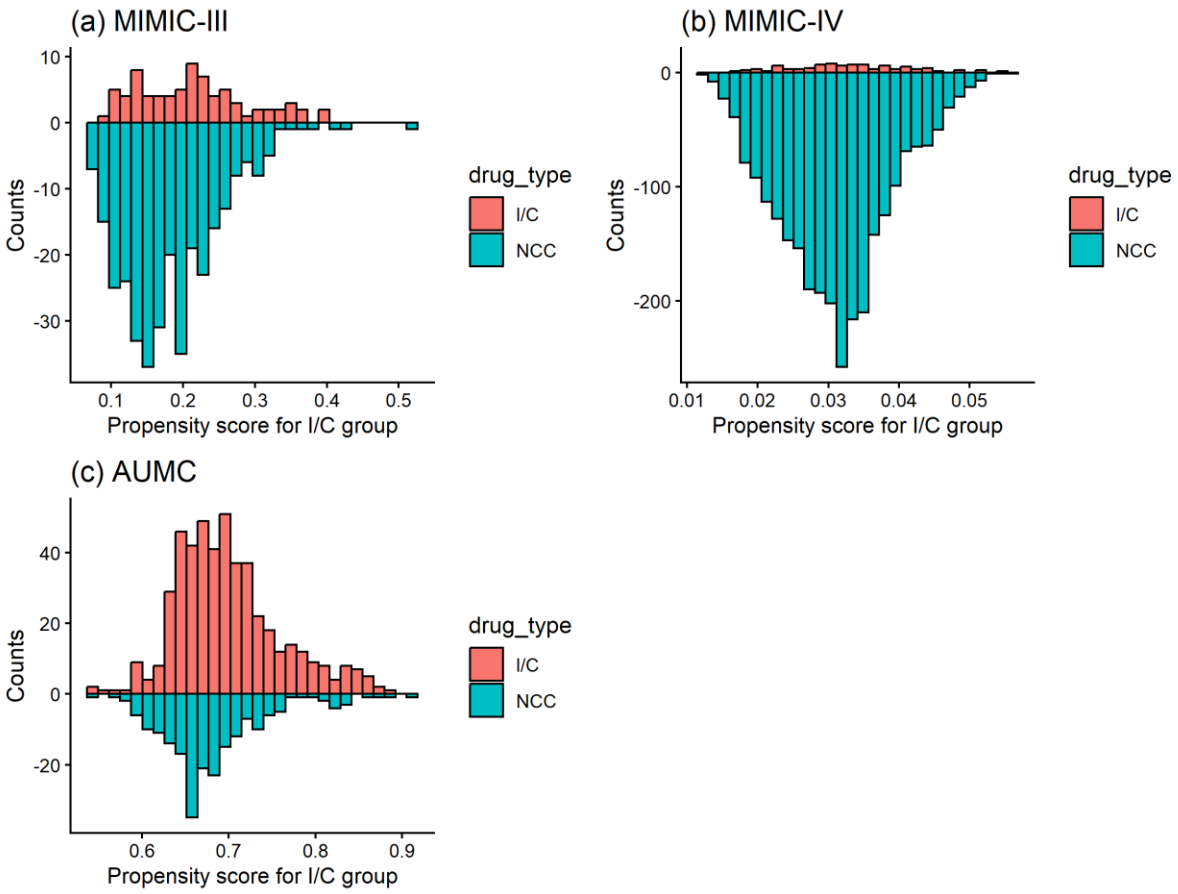
Supplementary figure 1: Assessment of AKI stage and development or progression of AKI.



AKI stage was assessed according to the criteria by Kidney Disease Improving Global Outcomes (KDIGO) guideline. The lowest serum creatinine (sCr) level during 168 hours prior to the treatment start with carbapenems was defined as baseline sCr level. AKI stage 1 was identified when sCr levels at treatment start with carbapenems increased by at least 0.3 mg/dL from baseline sCr levels and time difference of those 2 measurements was shorter than 48 hours or when sCr levels at treatment start rose to 1.5 to 1.9 times the baseline sCr levels. Stage 2 was defined by sCr levels at treatment start increased to 2.0 to 2.9 times the baseline sCr level. Stage 3 was identified when sCr levels at treatment start increased to 3.0 times or more compared to the baseline sCr levels, when the absolute sCr levels at treatment start reached 4.0 mg/dL or higher, or when the subjects receive renal replacement therapy (RRT). Urine volume was not considered for the assessment. As examples, changes in sCr levels of 2 subjects are depicted in the figure. Both subjects did not receive RRT during the observation period. (a) Baseline sCr level, defined as the lowest sCr level prior to the treatment start, was 1.2 mg /dL. sCr level at treatment start, assessed prior to and most nearly to treatment start, was 1.5 mg/dL. Time difference in those 2 measurements was over 48 hours and sCr levels at treatment start was less than 1.5 times to baseline sCr levels. Therefore, their AKI stage at treatment start was assessed as stage 0. The highest sCr level after treatment start was 5.6 mg /dL, which is higher than 3 times to baseline sCr levels. AKI after treatment start was stage 3, and this subject was assessed as developing AKI after the treatment. (b) With baseline sCr levels as 0.8 mg /dL and sCr levels at treatment start as 2.2 mg /dL, their AKI stage at treatment start was assessed as stage 2. The highest sCr levels after treatment start was 3.4 mg /dL, which is higher than 3 times to baseline sCr levels. AKI stage after treatment start was stage 3 and this subject developed AKI progression after the treatment.

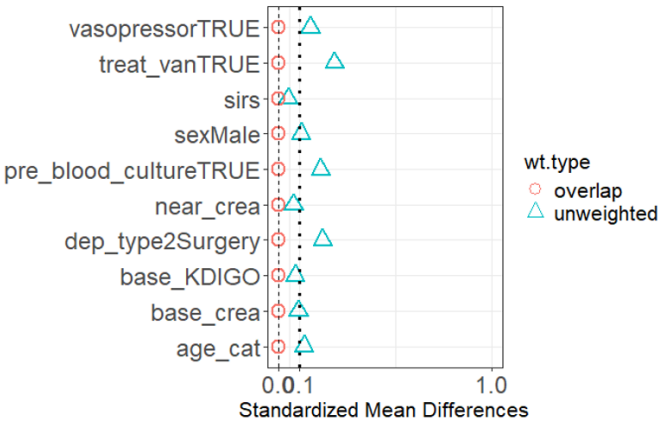
Supplementary figure 2: Distribution of propensity scores



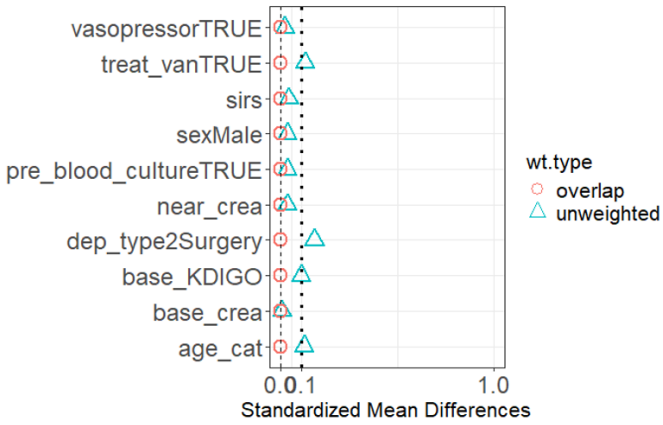
Histograms of propensity scores for receiving I/C drugs in each dataset.

Supplementary figure 3: Difference of subject characteristics between the I/C and the NCC groups before and after propensity score-based overlap weighting

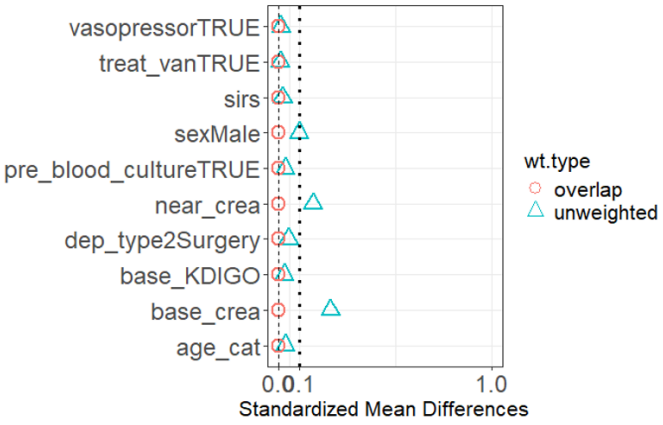
(a) MIMIC-III



(b) MIMIC-IV

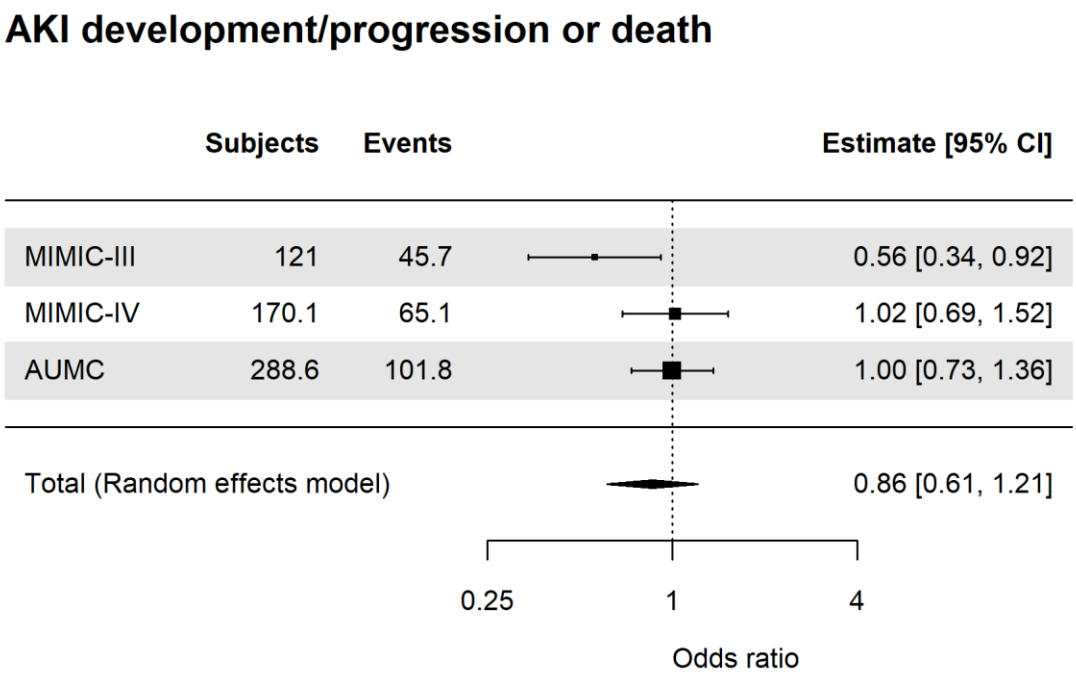


(c) AUMC



Standardized mean differences (SMD) of subject backgrounds between the I/C and the NCC groups in each dataset. The backgrounds of the subjects were adjusted with overlap weighting based on propensity scores to receive I/C drugs. SMD of propensity score-predictors are depicted as blue triangles (before overlap weighting) or red circles (after overlap weighting). The subject backgrounds were well adjusted with overlap weighting.

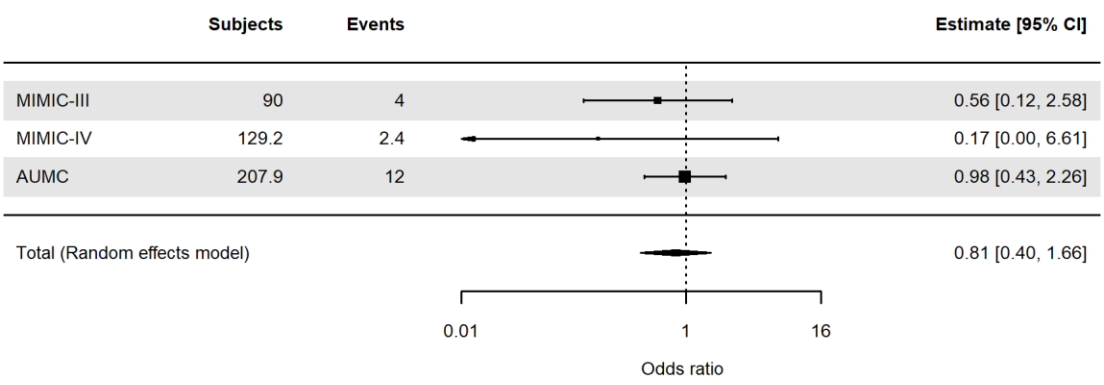
Supplementary figure 4: Sensitivity analysis against competing risks of the outcomes



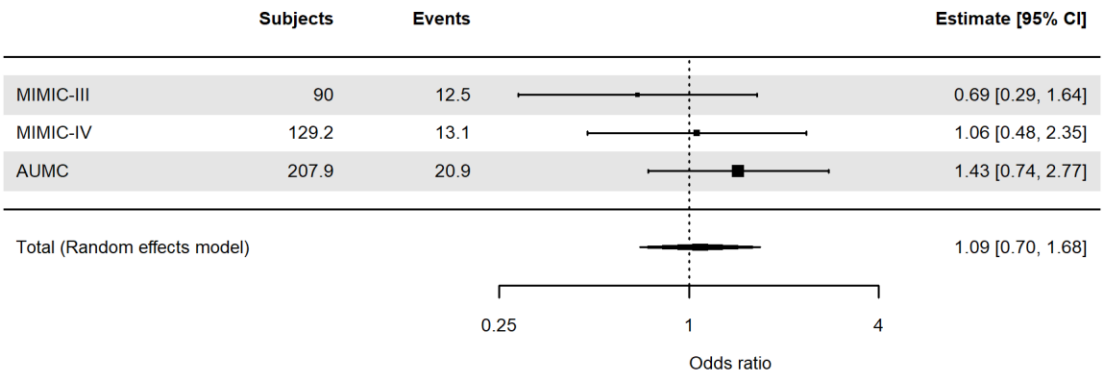
Forrest plot for OR of the I/C group for AKI development/progression or death. The combined outcome was assessed considering the competing risks of AKI development/progression with death. The outcome less developed in the I/C group relative to the NCC group in MIMIC-III but similarly developed between the groups in MIMIC-IV and AUMC and at overall analysis across all datasets.

Supplementary figure 5: Development of secondary outcomes among subjects without AKI at treatment start

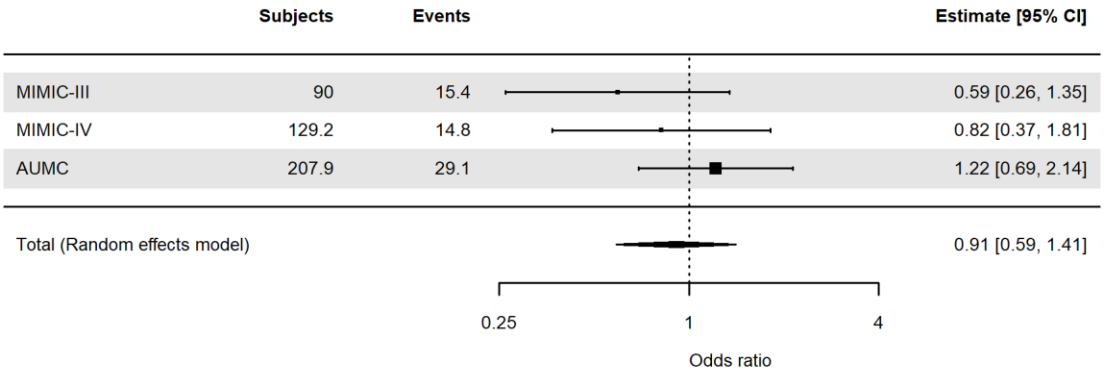
(a) RRT-intervention (without AKI at treatment start)



(b) Death (without AKI at treatment start)



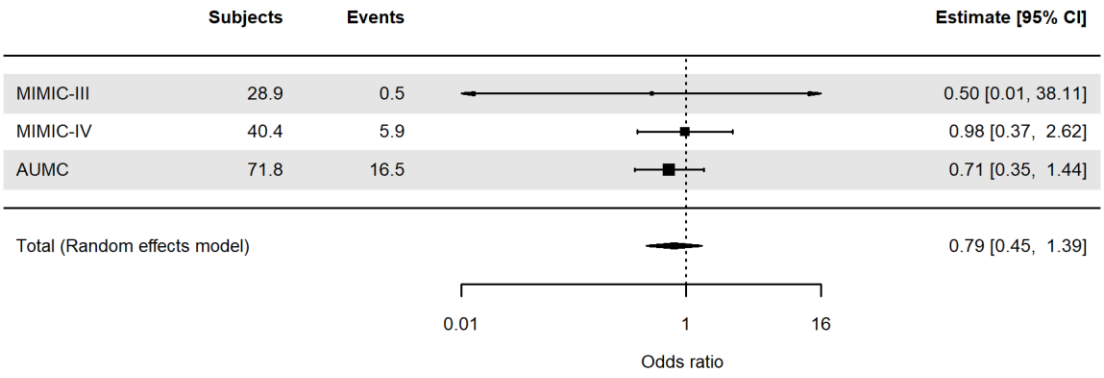
(c) RRT-intervention or death (without AKI at treatment start)



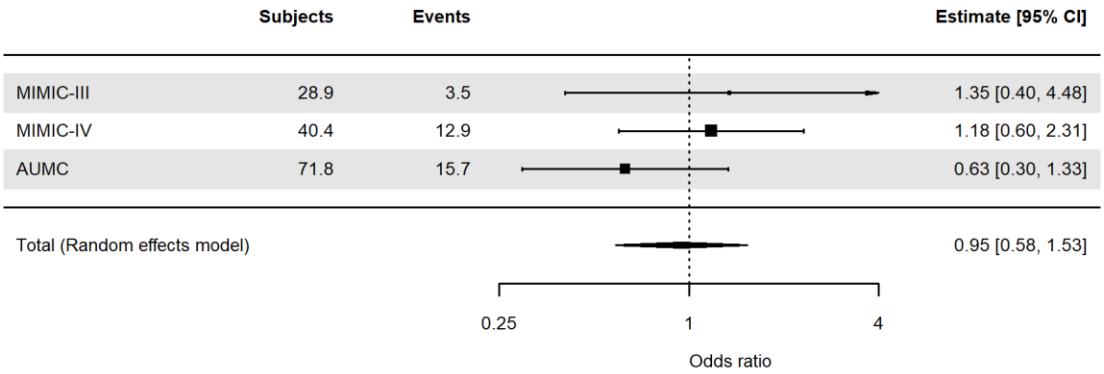
Forrest plot for OR of the I/C group for secondary outcomes among subjects without AKI at treatment start. The outcomes similarly developed between the I/C and the NCC groups.

Supplementary figure 6: Development of secondary outcomes among subjects with AKI at treatment start

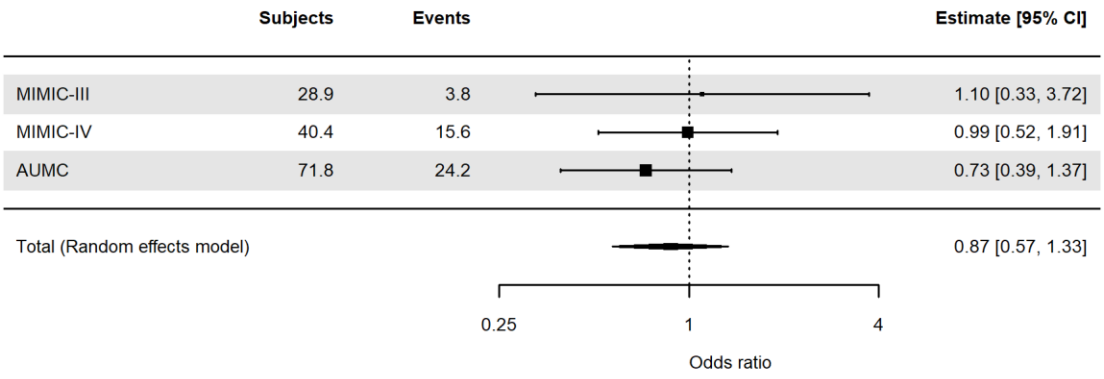
(a) RRT-intervention (with AKI at treatment start)



(b) Death (with AKI at treatment start)

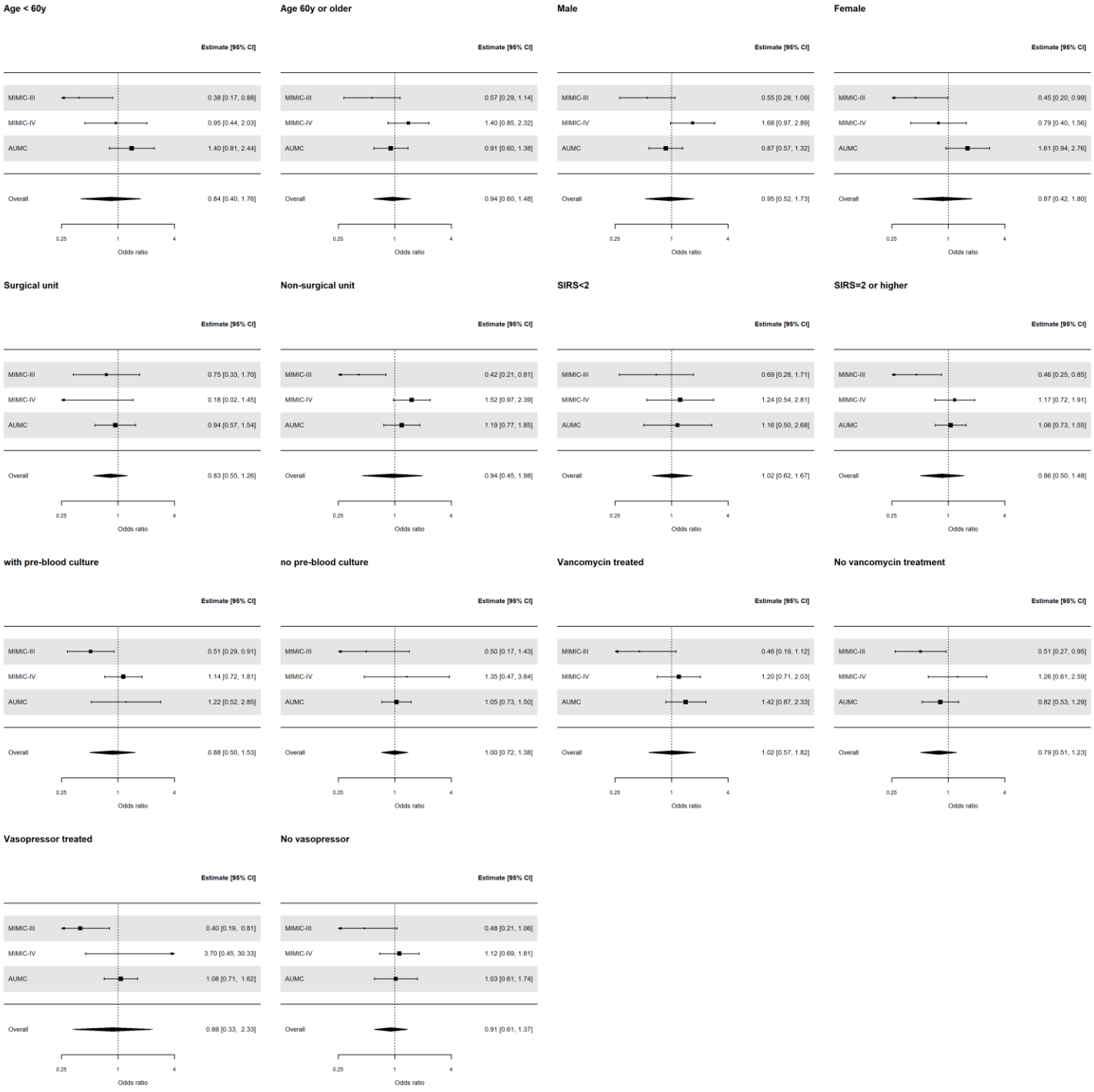


(c) RRT-intervention or death (with AKI at treatment start)



Forrest plot for OR of I/C group secondary outcomes among subjects with AKI at treatment start. The outcomes similarly developed between the I/C and the NCC groups.

Supplementary figure 7: Subgroup analysis for development or progression of AKI.



Forrest plot for OR of the I/C group for AKI development/progression among subgroups stratified based on age, sex, type of ICU, SIRS score, pre-testing for blood culture, treatment with vancomycin, and treatment with vasopressor at treatment start. AKI development/progression similarly developed between the I/C and NCC groups except for in certain subgroups of MIMIC-III, where the outcome less commonly developed in the I/C group.

Supplementary table 1: Study characteristics

	MIMIC-III			MIMIC-IV			AUMC		
	I/C N = 77	NCC N = 332	p-value	I/C N=88	NCC N=2727	p-value	I/C N=480	NCC N=212	p-value
Age (years)			0.77			0.57			0.58
18-39	4 (5.2%)	29 (8.7%)		8 (9.1%)	274 (10.0%)		51 (10.6%)	30 (14.2%)	
40-49	8 (10.4%)	32 (9.6%)		10 (11.4%)	282 (10.3%)		51 (10.6%)	22 (10.4%)	
50-59	13 (16.9%)	59 (17.8%)		11 (12.5%)	560 (20.5%)		104 (21.7%)	38 (17.9%)	
60-69	17 (22.1%)	67 (20.2%)		25 (28.4%)	708 (26.0%)		152 (31.7%)	61 (28.8%)	
70-79	18 (23.4%)	90 (27.1%)		19 (21.6%)	517 (19.0%)		101 (21.0%)	52 (24.5%)	
80+	17 (22.1%)	55 (16.6%)		15 (17.0%)	386 (14.2%)		21 (4.4%)	9 (4.2%)	
Sex			0.39			0.76			0.24
Female	38 (49.4%)	146 (44.0%)		38 (43.2%)	1,222 (44.8%)		161 (33.5%)	81 (38.2%)	
Male	39 (50.6%)	186 (56.0%)		50 (56.8%)	1,505 (55.2%)		319 (66.5%)	131 (61.8%)	
ICU type			0.10			0.16			0.56
Non-surgery	45 (58.4%)	227 (68.4%)		73 (83.0%)	2,088 (76.6%)		292 (60.8%)	124 (58.5%)	
Surgery	32 (41.6%)	105 (31.6%)		15 (17.0%)	639 (23.4%)		188 (39.2%)	88 (41.5%)	
Type of carbapenem			<0.001			<0.001			<0.001
Imipenem/cilastatin	77 (100%)	0 (0.0%)		87 (98.9%)	0 (0.0%)		480 (100%)	0 (0.0%)	
Imipenem/cilastatin/relebactam	0 (0.0%)	0 (0.0%)		1.0 (1.1%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Meropenem	0 (0.0%)	332 (100%)		0 (0.0%)	2,710 (99.4%)		0 (0.0%)	212 (100%)	
Doripenem	0 (0.0%)	0 (0.0%)		0 (0.0%)	5 (0.2%)		0 (0.0%)	0 (0.0%)	
Ertapenem	0 (0.0%)	0 (0.0%)		0 (0.0%)	12 (0.4%)		0 (0.0%)	0 (0.0%)	
SOFA score	5 (3, 8)	4 (3, 7)	0.87	4.5 (3, 8)	5 (3, 8)	0.15	7 (5, 10)	7 (4, 9)	0.36
Missing							67	37	
qSOFA score	1 (0, 1)	1 (0, 1)	0.52	1 (0, 1)	1 (0, 1)	0.66	1 (0, 1)	1 (0, 1)	0.98
Missing	0	8		0	8		1	0	
SIRS score	2 (1, 3)	2 (1, 3)	0.86	2 (1, 3)	2 (1, 3)	0.76	2 (1, 3)	2 (1, 3)	0.75
Blood culture	60 (77.9%)	284 (85.5%)	0.10	68 (77.3%)	2,143 (78.6%)	0.77	67 (14.0%)	32 (15.1%)	0.69
Vancomycin usage	23 (29.9%)	141 (42.5%)	0.04	54 (61.4%)	1,826 (67.0%)	0.27	240 (50.0%)	107 (50.5%)	0.91
Vasopressor usage	30 (39.0%)	154 (46.4%)	0.24	8 (9.1%)	232 (8.5%)	0.85	303 (63.1%)	135 (63.7%)	0.89
Ventilation	52 (67.5%)	229 (69.0%)	0.81	12 (13.6%)	227 (8.3%)	0.078	321 (66.9%)	126 (59.4%)	0.06
Baseline sCr (mg/dL)	0.9 (0.6, 1.4)	0.9 (0.6, 1.4)	0.43	1.0 (0.6, 1.5)	1.0 (0.6, 1.5)	0.98	0.9 (0.6, 1.3)	0.7 (0.6, 1.1)	<0.001
sCr at treatment start (mg/dL)	1.1 (0.8, 1.7)	1.0 (0.7, 1.7)	0.50	1.1 (0.7, 2.0)	1.1 (0.7, 1.8)	0.71	1.1 (0.8, 1.6)	0.9 (0.6, 1.5)	0.001
AKI stage at treatment start			0.91			0.65			0.45
0	58 (75.3%)	240 (72.3%)		67 (76.1%)	1,954 (71.7%)		351 (73.1%)	156 (73.6%)	
1	17 (22.1%)	80 (24.1%)		16 (18.2%)	583 (21.4%)		105 (21.9%)	41 (19.3%)	
2	2 (2.6%)	12 (3.6%)		5 (5.7%)	190 (7.0%)		24 (5.0%)	15 (7.1%)	

Supplementary table 2: Number of subjects receiving carbapenems of the other group

Before overlap weighting	I/C	NCC	p-value
MIMIC-III	3 (3.9%)	1 (0.3%)	0.02
MIMIC-IV	4 (4.5%)	0 (0%)	<0.001
AUMC	15 (3.1%)	2 (0.9%)	0.09
After overlap weighting	I/C	NCC	p-value
MIMIC-III	2.4 (3.9%)	0.2 (0.3%)	0.01
MIMIC-IV	3.9 (4.5%)	0 (0%)	0.04
AUMC	4.5 (3.1%)	1.4 (1.0%)	0.10

The number of subjects who were censored due to receiving carbapenems of the other group during the observation period.

Supplementary table 3: Total observation time of the subjects

Before overlap weighting	I/C	NCC	p-value
MIMIC-III	168.0 [168.0, 168.0]	168.0 [168.0, 168.0]	0.34
MIMIC-IV	168.0 [125.4, 168.0]	168.0 [159.0, 168.0]	0.19
AUMC	168.0 [64.6, 168.0]	165.6 [62.1, 168.0]	0.71
After overlap weighting	I/C	NCC	p-value
MIMIC-III	168.0 [168.0, 168.0]	168.0 [168.0, 168.0]	0.49
MIMIC-IV	168.0 [128.4, 168.0]	168.0 [151.8, 168.0]	0.40
AUMC	168.0 [64.0, 168.0]	162.0 [61.0, 168.0]	0.65

Observation time for subjects in each group and dataset. Observation was censored when subjects receive carbapenems of the other group or die. The time (hours) was described as median value with interquartile range.

Supplementary table 4: Backgrounds of the subjects without AKI at treatment start after overlap weighting

	MIMIC-III			MIMIC-IV			AUMC		
	I/C N = 45.0	NCC N = 45.0	p-value	I/C N=64.6	NCC N=64.6	p-value	I/C N=103.9	NCC N=103.9	p-value
Age (years)			0.68			0.89			0.53
18-39	2.5 (5.6%)	3.8 (8.4%)		7.7 (12.0%)	6.9 (10.7%)		11.5 (11.0%)	15.4 (14.9%)	
40-49	5.5 (12.2%)	3.7 (8.2%)		7.7 (12.0%)	6.5 (10.1%)		12.7 (12.3%)	11.8 (11.3%)	
50-59	8.2 (18.2%)	7.2 (16.0%)		9.7 (15.0%)	13.5 (20.8%)		24.1 (23.2%)	19.3 (18.6%)	
60-69	9.4 (20.8%)	9.1 (20.2%)		17.4 (26.9%)	16.3 (25.3%)		32.0 (30.8%)	28.7 (27.6%)	
70-79	9.1 (20.2%)	13.0 (28.8%)		11.5 (17.9%)	11.8 (18.2%)		20.0 (19.3%)	23.0 (22.2%)	
80+	10.3 (23.0%)	8.3 (18.4%)		10.6 (16.4%)	9.7 (14.9%)		3.6 (3.4%)	5.7 (5.4%)	
Sex			>0.99			>0.99			>0.99
Female	20.5 (45.5%)	20.5 (45.5%)		28.9 (44.7%)	28.9 (44.7%)		37.5 (36.1%)	37.5 (36.1%)	
Male	24.5 (54.5%)	24.5 (54.5%)		35.7 (55.3%)	35.7 (55.3%)		66.4 (63.9%)	66.4 (63.9%)	
ICU type			>0.99			>0.99			>0.99
Non-surgery	24.1 (53.4%)	24.1 (53.4%)		54.8 (84.9%)	54.8 (84.9%)		63.1 (60.7%)	63.1 (60.7%)	
Surgery	21.0 (46.6%)	21.0 (46.6%)		9.8 (15.1%)	9.8 (15.1%)		40.8 (39.3%)	40.8 (39.3%)	
Type of carbapenem			N/A			<0.001			N/A
Imipenem/cilastatin	45.0 (100.0%)	0.0 (0.0%)		63.6 (98.5%)	0.0 (0.0%)		103.9 (100.0%)	0.0 (0.0%)	
Imipenem/cilastatin/relebactam	0.0 (0.0%)	0.0 (0.0%)		1.0 (1.5%)	0.0 (0.0%)		0.0 (0.0%)	0.0 (0.0%)	
Meropenem	0.0 (0.0%)	45.0 (100.0%)		0.0 (0.0%)	64.0 (99.1%)		0.0 (0.0%)	103.9 (100.0%)	
Doripenem	0.0 (0.0%)	0.0 (0.0%)		0.0 (0.0%)	0.2 (0.3%)		0.0 (0.0%)	0.0 (0.0%)	
Ertapenem	0.0 (0.0%)	0.0 (0.0%)		0.0 (0.0%)	0.4 (0.6%)		0.0 (0.0%)	0.0 (0.0%)	
SOFA	4.0 (3.0, 8.0)	4.0 (2.0, 7.0)	0.67	4.0 (3.0, 6.0)	5.0 (3.0, 7.0)	0.59	7.0 (4.0, 9.0)	6.0 (4.0, 9.0)	0.34
Missing	0	0		0	0		14	19	
qSOFA	1.0 (0.0, 1.0)	1.0 (0.0, 1.0)	0.62	1.0 (0.0, 1.0)	1.0 (0.0, 1.0)	0.49	1.0 (0.0, 1.0)	1.0 (0.0, 1.0)	0.86
Missing	0	1		0	0		0	0	
SIRS	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	0.94	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	0.97	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	0.95
Blood culture	35.7 (79.2%)	35.7 (79.2%)	>0.99	49.1 (76.0%)	49.1 (76.0%)	>0.99	15.8 (15.2%)	15.8 (15.2%)	>0.99
Vancomycin usage	14.9 (33.2%)	14.9 (33.2%)	>0.99	38.8 (60.1%)	38.8 (60.1%)	>0.99	52.1 (50.1%)	52.1 (50.1%)	>0.99
Vasopressor usage	19.0 (42.2%)	19.0 (42.2%)	>0.99	3.8 (5.9%)	3.8 (5.9%)	>0.99	64.2 (61.8%)	64.2 (61.8%)	>0.99
Ventilation	30.2 (67.0%)	30.8 (68.5%)	0.83	6.7 (10.4%)	3.7 (5.8%)	0.12	68.8 (66.2%)	62.3 (59.9%)	0.18
Baseline sCr (mg/dL)	1.0 (0.6, 1.4)	0.9 (0.6, 1.4)	0.67	0.9 (0.6, 1.5)	0.9 (0.6, 1.4)	0.94	0.8 (0.6, 1.1)	0.7 (0.5, 1.1)	0.10
sCr at treatment start (mg/dL)	1.0 (0.8, 1.4)	1.0 (0.7, 1.6)	0.61	1.0 (0.6, 1.5)	0.9 (0.6, 1.4)	0.93	0.9 (0.6, 1.2)	0.8 (0.6, 1.1)	0.14

Supplementary table 5: Backgrounds of the subjects with AKI at treatment start after overlap weighting

	MIMIC-III			MIMIC-IV			AUMC		
	I/C n=14.4	NCC n=14.4	p-value	I/C n=20.2	NCC n=20.2	p-value	I/C n=35.9	NCC n=35.9	p-value
Age (years)			>0.99			0.35			0.70
18-39	0.8 (5.8%)	0.6 (4.2%)		0.0 (0.0%)	0.5 (2.4%)		3.6 (10.1%)	4.0 (11.2%)	
40-49	0.8 (5.7%)	1.4 (10.0%)		2.0 (9.8%)	1.0 (5.1%)		2.1 (5.9%)	2.3 (6.4%)	
50-59	2.3 (16.3%)	2.3 (15.7%)		1.0 (4.8%)	2.8 (14.0%)		7.0 (19.4%)	5.1 (14.2%)	
60-69	3.8 (26.4%)	3.2 (22.3%)		6.8 (33.6%)	5.2 (25.8%)		11.5 (32.0%)	11.4 (31.6%)	
70-79	4.3 (29.7%)	4.5 (31.0%)		6.7 (33.2%)	5.4 (26.9%)		9.3 (26.0%)	12.3 (34.4%)	
80+	2.3 (16.1%)	2.4 (16.7%)		3.8 (18.6%)	5.2 (25.9%)		2.3 (6.5%)	0.8 (2.2%)	
Sex			>0.99			>0.99			>0.99
Female	8.0 (55.1%)	8.0 (55.1%)		7.8 (38.4%)	7.8 (38.4%)		12.9 (35.9%)	12.9 (35.9%)	
Male	6.5 (44.9%)	6.5 (44.9%)		12.5 (61.6%)	12.5 (61.6%)		23.0 (64.1%)	23.0 (64.1%)	
ICU type			>0.99			>0.99			>0.99
Non-surgery	11.9 (82.7%)	11.9 (82.7%)		15.4 (76.4%)	15.4 (76.4%)		20.3 (56.6%)	20.3 (56.6%)	
Surgery	2.5 (17.3%)	2.5 (17.3%)		4.8 (23.6%)	4.8 (23.6%)		15.6 (43.4%)	15.6 (43.4%)	
Type of carbapenem			N/A			N/A			N/A
Imipenem/cilastatin	14.4 (100.0%)	0.0 (0.0%)		20.2 (100.0%)	0.0 (0.0%)		35.9 (100.0%)	0.0 (0.0%)	
Imipenem/cilastatin/relebactam	0.0 (0.0%)	0.0 (0.0%)		0.0 (0.0%)	0.0 (0.0%)		0.0 (0.0%)	0.0 (0.0%)	
Meropenem	0.0 (0.0%)	14.4 (100.0%)		0.0 (0.0%)	20.2 (99.9%)		0.0 (0.0%)	35.9 (100.0%)	
Doripenem	0.0 (0.0%)	0.0 (0.0%)		0.0 (0.0%)	0.0 (0.1%)		0.0 (0.0%)	0.0 (0.0%)	
Ertapenem	0.0 (0.0%)	0.0 (0.0%)		0.0 (0.0%)	0.0 (0.0%)		0.0 (0.0%)	0.0 (0.0%)	
SOFA	6.0 (4.0, 8.0)	5.0 (3.0, 7.0)	0.23	6.0 (4.0, 9.0)	8.0 (5.0, 11.0)	0.24	8.0 (5.0, 10.0)	9.0 (7.0, 11.0)	0.29
Missing	0	0		0	0		5	6	
qSOFA	1.0 (0.0, 1.0)	1.0 (0.0, 1.0)	0.44	1.0 (0.0, 1.0)	1.0 (0.0, 1.0)	0.69	1.0 (0.0, 1.0)	1.0 (0.0, 1.0)	0.90
Missing	0	1		0	0		0	0	
SIRS	2.0 (2.0, 2.0)	2.0 (1.0, 3.0)	0.69	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	0.94	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	0.81
Blood culture	12.0 (83.2%)	12.0 (83.2%)	>0.99	16.5 (81.6%)	16.5 (81.6%)	>0.99	4.4 (12.2%)	4.4 (12.2%)	>0.99
Vancomycin usage	4.1 (28.6%)	4.1 (28.6%)	>0.99	13.5 (66.7%)	13.5 (66.7%)	>0.99	18.3 (51.0%)	18.3 (51.0%)	>0.99
Vasopressor usage	5.3 (36.8%)	5.3 (36.8%)	>0.99	3.9 (19.4%)	3.9 (19.4%)	>0.99	24.9 (69.5%)	24.9 (69.5%)	>0.99
Ventilation	9.8 (67.6%)	9.3 (64.5%)	0.81	4.9 (24.2%)	3.8 (18.7%)	0.54	23.7 (66.1%)	20.5 (57.1%)	0.27
Baseline sCr (mg/dL)	0.8 (0.5, 1.4)	1.0 (0.6, 1.5)	0.80	1.3 (0.9, 1.7)	1.2 (0.8, 1.7)	0.87	1.0 (0.7, 1.3)	1.0 (0.7, 1.3)	0.99
sCr at treatment start (mg/dL)	1.3 (1.0, 1.9)	1.5 (1.1, 2.2)	0.75	2.3 (1.5, 2.7)	1.9 (1.4, 2.7)	0.75	1.6 (1.2, 2.3)	1.6 (1.2, 2.3)	0.99
AKI stage at treatment start			>0.99			>0.99			>0.99
1	12.8 (88.9%)	12.8 (88.9%)		15.4 (76.2%)	15.4 (76.2%)		28.0 (77.9%)	28.0 (77.9%)	
2	1.6 (11.1%)	1.6 (11.1%)		4.8 (23.8%)	4.8 (23.8%)		7.9 (22.1%)	7.9 (22.1%)	