Early Initiation of Renal Replacement Therapy in Intensive Care Unit Patients with Acute Respiratory Distress Syndrome and Sepsis with or without Renal Failure: A Retrospective Cohort Study Based on Propensity Score Matching

Haoyue Zhang
Tianjin Medical University
Ziping Li
Tianjin Medical University
Weiqiang Zheng
Tianjin Medical University
Tianqi Yang
Tianjin Medical University
Linlin Zhang
Tianjin Medical University
Yonghao Yu (yyu@tmu.edu.cn)
Tianjin Medical University General Hospital

Research Article

Keywords: Acute respiratory distress syndrome, sepsis, renal replacement therapy, intensive care unit, oxygenation

Posted Date: June 21st, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1730069/v2

Abstract

Background

It is unknown whether the early renal replacement therapy (RRT) initiation strategy in intensive care unit (ICU) patients with acute respiratory distress syndrome (ARDS) and sepsis with or without renal failure provides clinical benefit.

Patients and methods:

A total of 745 patients with ARDS complicated by sepsis admitted to the ICU of Tianjin Medical University General Hospital were included in the analysis. Early RRT was defined as initiating the RRT strategy within 24 hours of admission. The relationship between early RRT and clinical outcomes, including primary (30-day mortality) and secondary (90-day mortality, serum creatinine level, oxygenation index, duration of invasive mechanical ventilation, cumulative fluid output, and cumulative fluid balance), was primarily compared using propensity score matching (PSM).

Results

A total of 263 patients (35.3% of the total population) received an early RRT initiation strategy before PSM. After PSM, a cohort of 130 patients with early CRRT and 130 patients without early CRRT with matched baseline characteristics was constructed. Early RRT was not significantly associated with 30- [hazard ratio (HR): 1.37, 95%CI: 0.91–2.06, $P = 0.127$] or 90-day mortality (HR: 1.29, 95%CI: 0.89–1.88, $P = 0.182$). At each time point within 72 hours after admission, there was no significant difference in oxygenation index and duration of invasive mechanical ventilation between the early RRT group and the no early RRT group. Early RRT significantly increased total output at all time points within 72 h of admission but only reached a statistically significant negative fluid balance at 72 h ($P = 0.016$).

Conclusions

Early RRT initiation strategies had no statistically significant survival benefit in ICU patients with ARDS and sepsis, with or without renal failure, nor did they significantly improve oxygenation or shorten the duration of mechanical ventilation. The use and timing of RRT in these patients should be thoroughly investigated.

Background

Renal replacement therapy (RRT) is the standard management for acute kidney injury (AKI) in intensive care units (ICU). Regardless of the presence of renal insufficiency, RRT may have clinical benefits for two common and intertwined syndromes in intensive care settings: acute respiratory distress syndrome

(ARDS) and sepsis. The theory that ARDS patients benefit from negative fluid balance [1] stems from the fact that, in the case of fluid overload, non-cardiogenic pulmonary edema caused by increased permeability of the alveolar-capillary barrier may be exacerbated by increased intravascular hydrostatic pressure [2, 3]. Clinical evidence from ARDS patients revealed that fluid overload could lead to longer mechanical ventilation, longer ICU stays, and increased mortality [4, 5]. Therefore, early RRT, which can rapidly relieve fluid overload and establish acid-base balance, may be an attractive treatment [6].

In the context of sepsis, on the other hand, there are excessive septic inflammatory processes [7], such as strong activation of the innate immune system [8–10], uncontrolled complement activation [11], tissue factor and coagulation activation [12], and neutrophil extracellular trap release [13]. Therefore, hemofiltration has been proposed as a strategy to reduce excessive inflammation by removing circulating toxins and inflammatory cytokines from the patient's circulation [7, 14]. Preclinical studies have shown that high-volume hemofiltration can effectively remove inflammatory cytokines and endotoxins, as well as reverse septicemic induced immune paralysis [15–17]. These are theoretical grounds for the clinical benefit of early RRT initiation in ICU patients with ARDS and sepsis, regardless of renal function.

Consider the growing trend toward early or preemptive use of RRT before the onset of late complications. However, despite the lack of evidence of practice in the entire population, based on previous experience with AKI patients, early RRT initiation strategies may expose patients who can achieve renal function recovery with conservative therapy alone to potential RRT-related risks, these include life-threatening complications such as thrombosis, infections associated with dialysis access, hemorrhagic hypotension, and membrane biocompatibility. At the same time, clinical study findings on the beneficial effects of early RRT initiation strategies in AKI patients are contradictory [18–20]. According to a recent *post hoc* analysis of the AKIKI trial involving a total of 618 critically ill patients randomized to severe acute kidney injury, early RRT initiation strategies were not associated with any improvement in 60-day mortality in AKI and a subgroup of sepsis or ARDS patients, nor with improved hydration status or duration of invasive mechanical ventilation in ARDS patients [20]. Therefore, despite the theoretical basis for improved prognosis, clinical evidence from AKI patients suggests that early RRT initiation strategies, including in the case of sepsis and ARDS, are not promising for improved prognosis. The optimal strategy for initiating RRT in patients with or without AKI in the context of ARDS and sepsis remains unclear. In light of this, we used a statistical algorithm of propensity score matching (PSM) to construct baseline matched cohort data, including serum creatinine, from observational cohort data, allowing us to conclude the clinical benefits of early RRT initiation in ICU patients with ARDS complicated with sepsis.

Methods

1.1 Study design, patients

This was a single-center, retrospective observational study on discharged patients from the comprehensive, intensive care unit of Tianjin Medical University General Hospital from January 2019 to February 2022. Patients with the following conditions were excluded: (1) those discharged within 72

hours of admission; (2) those who did not have admission arterial blood gas analysis measurements; (3) those who were not diagnosed with ARDS or sepsis; and (4) those who had multiple admissions. The diagnosis of ARDS at admission was made according to the criteria established by the American-European Consensus Conference (AECC) [21]. The diagnostic criteria of sepsis were based on the consensus Sepsis-3 definitions at admission [22]. The early RRT was defined as initiating the RRT strategy within 24 hours of admission. The choice of RRT modalities was left to the discretion of the clinician. The plasma lactate concentration was measured every six hours from admission for 48 hours by a COBAS B-123 POC system (Roche Diagnostics, Rotkreuz, Switzerland) using arterial catheterization. Besides the initial lactate measurement, missing values were allowed for the other time points. The patients were followed up through outpatient visits, telephone calls, and hospital readmission records. This study was approved by the Ethics Committee of Tianjin Medical University General Hospital (IRB2022-YX-041-01) and conducted in accordance with the Declaration of Helsinki's ethical standards. The need for informed consent was waived due to the retrospective nature of our study. The study was reported in accordance with the guidelines outlined in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[23].

1.2 Study Variables

For multivariate adjustment and propensity score matching, the following 20 variables were used as covariates: patient demographics (age, sex), past medical history [hypertension, diabetes, coronary artery disease (CAD), ischemic stroke, and cancer], clinical characteristics upon admission [levels of systolic and diastolic blood pressure (SBP and DBP), heart rate, serum creatinine, oxygenation index, Glasgow Coma Scale (GCS) [24], and Sequential Organ Failure Assessment (SOFA) score [25], emergency surgical operation, invasive mechanical ventilation, and other inpatient treatment within 24 hours of admission [antibiotics, sedative/analgesic, vasoactive medications, and blood component transfusion]. The definition of the above study variables is listed in **Supplemental Table 1**. All the above parameters were included as covariables in the adjustment.

We imputed missing data for variables with missing values using MissForest, a random forest imputation algorithm for missing data implemented in R software, version 3.2.3. (R Foundation for Statistical Computing) [26]. The missing rates of the study variables are shown in **Supplemental Table 2**.

1.3 Study Outcomes

The primary outcome was 30-day mortality, defined as death within 30 days of admission. Secondary outcomes included :(1) 90-day mortality, defined as death within 90 days of admission; (2) serum creatinine levels at 24, 48, and 72 hours after admission; (3) oxygenation index at 24, 48, and 72 hours after admission; (4) duration of invasive mechanical ventilation (only patients with invasive mechanical ventilation); (5) cumulative fluid output at 24, 48, and 72 hours after admission, which encompasses cumulative urine output and cumulative volume of ultrafiltration during RRT; (6) cumulative fluid balance (difference between cumulative fluid intake and cumulative fluid output) at 24, 48, and 72 hours after admission.

1.4 Statistical Analysis

STATA 17.0 (StataCorp, College Station, TX) was used for statistical analysis. A two-tailed $P < 0.05$ was considered statistically significant. The baseline characteristics of early RRT status were reported as the means (± SD) for normally distributed data and medians with 25th and 75th percentiles for non-parametric data. Categorical variables were summarized using percentages. For categorical variables, Fisher's exact test was used to compare differences between groups with a binomial distribution. For continuous variables, the Mann-Whitney U test and unpaired t-test were used to compare differences between groups with skewed and normal distributions, respectively.

For PSM analyses, we performed a 1-to-1 matching for early RRT vs. no early RRT in the total population based on the 20 baseline covariates. We used the Stata command "calipmath" to perform a greedy matching algorithm with no replacement for all propensity score matching. A caliper width of 0.04 of the standard deviation of the logit of the propensity score was used for all matching [27]. The absolute standardized difference (ASD) is recommended to compare baseline covariates. ASD is superior to rank-sum test or t-test since it is independent of sample size, and between-group imbalances were considered to be ideal if it was less than 10% (Stata command "stddiff") [28].

We performed the following sensitivity analyses: (1) another PSM with a maximal matching ratio of 1-to-2 for early RRT vs. no early RRT; (2) a multivariate Cox proportional hazard model for early RRT vs. no early RRT; (3) excluding patients with the delay strategy of RRT based on the 1-to-1 matching cohort; (4) excluding the patients with the previous history of renal failure based on the 1-to-1 matching cohort; (5) excluding the patients with the previous history of regular RRT based on the 1-to-1 matching cohort; (6) excluding the patients with absolute indications for early RRT based on the 1-to-1 matching cohort. Among them, the absolute indications for early RRT initiation strategies were defined as: (1) oliguria or anuria ≥ 72 hours after admission; (2) azotemia with blood urea nitrogen 40 mmol/L; (3) hyperkaliemia with serum potassium ≥ 6 mmol/L or ≥ 5.5 mmol/L (concurrent with medical management), (4) pure metabolic acidosis with pH ≤ 7.15 and $PaCO_2$ < 35 mmHg; (5) acute pulmonary edema requiring emergency ultrafiltration as judged by the physician at admission.

Finally, we performed the following interaction tests and subgroup analyses based on matched population, including age (< 65 years and ≥ 65 years), sex, mean arterial pressure (MAP < 65 mmHg and ≥ 65 mmHg), estimated glomerular filtration rate (eGFR ≤ 60 mL/min/1.73m^2 and > 60 mL/min/1.73m^2; eGFR was calculated according to the equation by Chronic Kidney Disease Epidemiology Collaboration [29]), ARDS Severity (mild ARDS is defined as an oxygenation index > 200 mmHg, moderate as an oxygenation index of 100–200 mmHg, and severe as an oxygenation index < 100 mmHg), SOFA score (subgroups according to the SOFA score were categorized into tertials: 5–9, 10–13, and 14–28).

Results

2.1 Patient Characteristics

From January 2019 to February 2022, 1,510 patients were discharged from the comprehensive ICU of Tianjin Medical University General Hospital. As shown in Fig. 1, 745 patients were included in the final analysis. A total of 263 patients (35.3%) received the early RRT initiation strategy. In addition, between the early and no early RRT groups, 87 (33.1%) and 155 (32.2%) patients died within 30 days, respectively. There were no cases of loss to follow-up.

Before the PSM algorithm, early RRT patients had a higher prevalence of hypertension; higher levels of SBP, admission serum creatinine, oxygenation index, and SOFA score; a higher rate of blood component transfusion; a lower prevalence of cancer; lower rate of emergency surgical operation, invasive mechanical ventilation, antibiotics, sedative and analgesic as compared with no early RRT patients. The baseline characteristics before and after PSM are shown in **Supplemental Table 3**. Following PSM, a cohort composed of 130 early RRT patients (49.4% of the total early RRT population) and 130 no early RRT patients was constructed, with well-balanced demographics, previous history, on-admission clinical characteristics, and in-hospital management strategies. There was no significant difference observed in serum creatinine between RRT groups after PSM. This means that there is no difference in the use of RRT initiation strategies due to differences in renal function. The baseline characteristics after PSM are shown in Table 1, and the ASD before and after PSM are shown in Fig. 2.

Table 1
Baseline characteristics between patients with early RRT v.s. no early RRT after PSM.

Characteristics	Total n = 260	Early RRT n = 130	No Early RRT n = 130	*P Value*
Demographics				
Age, year	58.5 ± 17.7	58.8 ± 17.2	58.1 ± 18.2	0.750
Male, n (%)	141 (54.2)	69 (53.1)	72 (55.4)	0.800
Previous history				
Hypertension, n (%)	135 (51.9)	66 (50.8)	69 (53.1)	0.800
Diabetes, n (%)	83 (31.9)	41 (31.5)	42 (32.3)	1.000
CAD, n (%)	49 (18.8)	23 (17.7)	26 (20.0)	0.750
Ischemic stroke, n (%)	48 (18.5)	24 (18.5)	24 (18.5)	1.000
Cancer, n (%)	27 (10.4)	15 (11.5)	12 (9.20)	0.680
On-admission clinical characteristics				
SBP, mmHg	131 ± 36.0	132 ± 37.5	131 ± 34.6	0.890
DBP, mmHg	67.2 ± 19.2	67.0 ± 20.0	67.3 ± 18.5	0.900
Heart rate, bpm	105 ± 25.5	104 ± 26.8	105 ± 24.3	0.700
Serum creatinine, umol/L	188 ± 124	192 ± 123	184 ± 125	0.600
Oxygenation index, mmHg	176 ± 67.5	179 ± 69.2	173 ± 66.0	0.480
GCS Score	13 (6.5 to 15)	13.5 (5 to 15)	13 (7 to 15)	0.690
SOFA Score	11 (9 to 15)	11 (9 to 16)	11.5 (9 to 15)	0.940
Emergency surgical operation, n (%)				
	26 (10.0)	12 (9.20)	14 (10.8)	0.840
Invasive mechanical ventilation, n (%)				
	163 (62.7)	80 (61.5)	83 (63.8)	0.800
Other in-hospital treatment within 24 hours of admission				
Antibiotics, n (%)	226 (86.9)	113 (86.9)	113 (86.9)	1.000
Sedative and analgesic, n (%)	149 (57.3)	72 (55.4)	77 (59.2)	0.620
Vasoactive medications, n (%)	102 (39.2)	48 (36.9)	54 (41.5)	0.530

Characteristics	Total n = 260	Early RRT n = 130	No Early RRT n = 130	*P Value*
Blood component transfusion, n (%)	89 (34.2)	45 (34.6)	44 (33.8)	1.000

2.2 Associations between Early RRT Strategy Initiation and Clinical Outcomes

Early initiation of RRT did not have a statistically significant association with 30-day mortality (Hazard ratio (HR): 1.37, 95% CI: 0.91 to 2.06, $P = 0.127$), nor, similarly, with 90-day mortality (HR: 1.29, 95% CI: 0.89 to 1.88, $P = 0.182$) as shown in Table 2. The Kaplan-Meier curves for 30- and 90-day mortality are shown in Fig. 3. Baseline serum creatinine after PSM remained consistent between early RRT groups. The early RRT initiation strategy reduced serum creatinine by 27% within 48 hours, a statistically significant difference compared with early RRT ($P = 0.015$). At 72 hours, serum creatinine showed a slight rebound. Patients who were enrolled improved in their oxygenation index regardless of whether RRT was started early or late. However, there was no significant difference between the early RRT group and the no early RRT group at any time point within 72 hours of admission. There was also no significant difference in duration between invasive mechanical ventilation patients ($P = 0.760$). Early RRT significantly increased patients' total output at all time points within 72 hours of admission but only reached a statistically significant negative fluid balance at 72 hours when compared with no early RRT ($P = 0.016$).

Table 2
Analyses of primary and secondary outcomes.

	Early RRT (n = 130)	No Early RRT (n = 130)	*P* Value
Primary Outcome			
30-day Mortality	HR and 95%CI: 1.37 (0.91 to 2.06)		
	53 (40.8)	41 (31.5)	0.160
Secondary Outcome			
90-day Mortality	HR and 95%CI: 1.29 (0.89 to 1.88)		
	60 (46.2)	50 (38.5)	0.260
Serum Creatinine (umol/L)			
Baseline	192 ± 123	184 ± 125	0.600
24 hours	157 ± 125	182 ± 134	0.120
48 hours	140 ± 97.5	177 ± 139	0.015
72 hours	153 ± 124	166 ± 138	0.440
Oxygenation Index (mmHg)			
Baseline	178 ± 69.2	173 ± 66.0	0.480
24 hours	219 ± 104	216 ± 100	0.800
48 hours	227 ± 102	230 ± 99.0	0.800
72 hours	234 ± 99.4	224 ± 90.4	0.410
Duration of invasive mechanical ventilation (days)			
	8.7 (4.10 to 18.0)	9.11 (3.95 to 16.1)	0.760
Total Output (mL)			
24 hours	4407 (2267 to 7866)	2691 (1797 to 4339)	< 0.001
48 hours	4950 (2990 to 7700)	2775 (1900 to 3650)	< 0.001
72 hours	4887 (2700 to 7800)	2995 (2200 to 3600)	< 0.001
Fluid Balance (mL)			
24 hours	444 (-987 to 2905)	642 (-663 to 1866)	0.680
48 hours	-261 (-1159 to 1124)	277 (-564 to 1034)	0.180
72 hours	-196 (-1258 to 870)	106 (-434 to 877)	0.016

2.3 Sensitivity and Subgroup Analysis

There was no statistically significant difference between early RRT initiation strategy and 30- (Fig. 4) and 90-day mortality (**Supplementary Fig. 1**), whether based on the propensity score matching of a maximal ratio of 1-to-2 (the covariate characteristics after PSM are shown in **Supplemental Table 4**; covariate balance before and after matching was shown in **Supplemental Fig. 2**), multivariable Cox proportional hazard analysis, or excluding patients with the delay strategy of RRT, patient with the previous history of renal failure, patient with the previous history of regular RRT and patient with absolute indications for early RRT based on the 1-to-1 matching cohort. However, there was no statistically significant clinical benefit from early RRT compared with no RRT, except in patients with delayed RRT initiation. In addition, the results remained consistent except for patients with absolute indications for RRT, who are known to have a higher risk of mortality (Fig. 4).

Apart from the SOFA score subgroups, early initiation of the RRT strategy remained roughly consistent across subgroups compared with no early initiation, regardless of 30- (Fig. 4) or 90-day mortality (**Supplementary Fig. 1**), and there was no significant interaction was observed among subgroups. The subgroup with the highest SOFA score (14–28) showed the contribution of early RRT to increased mortality with a significant interaction.

Discussion

Our results indicate that early RRT initiation had no statistically significant survival benefit in ICU patients with ARDS and sepsis, with or without renal failure, when compared to no early RRT initiation or even no RRT initiation. Early RRT initiation strategies also did not significantly improve oxygenation or shorten mechanical ventilation time. This implies that although RRT is the standard treatment for AKI and there may be a theoretical basis for improving prognosis, an early RRT initiation strategy aimed at improving hydration status, oxygenation, and even clearing excessive inflammatory mediators in patients with ARDS combined with sepsis does not provide any clinical benefit, regardless of patients' renal function. "*Primum non nocere*," the adage seems to suggest that the RRT should be delayed or even reduced unless it is really needed [30]. To our knowledge, this is the only clinical study to investigate the clinical benefits of an early RRT initiation strategy in a specific patient population of ARDS and sepsis with or without renal failure.

As mentioned above, patients with ARDS seem to benefit from early RRT initiation, which may promote rapid fluid negative balance. Han *et al*. compared oxygenation of continuous renal replacement therapy (CRRT) in a total of 53 ARDS patients with early initiation (within 12 hours after ARDS onset) and late initiation of CRRT (48 hours after ARDS onset) and found that oxygenation was significantly improved, and mechanical ventilation time was shortened in the early CRRT group [6]. There were no hard-end points in this small sample study. Another single-center retrospective study compared the hard endpoints of early (≤ 48 hours postintubation) versus late (> 48 hours postintubation) RRT initiation in patients with ARDS, suggesting that the timing of RRT initiation was not associated with a survival benefit [31]. But

none of these studies compared hydration status. Our analysis of secondary outcomes showed that early RRT initiation with early onset may control fluid overload and achieve a negative balance 72 hours after admission, but this negative balance is insufficient to improve oxygenation index and shorten mechanical ventilation duration, or even improve survival. Gaudry *et al.* demonstrated in a post-hoc analysis of the AKIKI trial that it is preferable to use a diuretic rather than initiate RRT if the goal is only to control fluid balance.[20], while patients without AKI may respond better to diuretic administration. Although the surge of pro-inflammatory mediators during sepsis can theoretically be removed by blood filtration [14], preclinical studies have also provided plenty of positive evidence [15–17]. Cole *et al*. found that in a total of 24 patients with early septic shock or infectious organ dysfunction, RRT did not reduce circulating levels of several cytokines and allergic toxins associated with organ dysfunction after septic shock or severe sepsis [32]. Therefore, the effect of routine RRT on inflammatory molecules may be small, and higher flow RRT strategies may be required [14], but the impact on clinical outcomes remains uncertain [33–35]. The findings of our study are consistent with guidelines not to use renal replacement therapy in patients with sepsis or septic shock unless there is a clear indication [36]. Furthermore, despite the increased severity of sepsis-related multiple organ failure, the proportion of early RRT use increased but did not improve survival outcomes (Fig. 4).

In the subgroup analysis, despite the small sample size, the survival benefit of early RRT was almost equal to that of delayed or even no RRT initiation in patients with eGFR $\leq$ 60 mL/min/1.73m^2 (Fig. 4). Although patients delineated by baseline eGFR alone cannot completely replace the definition of AKI, this is broadly consistent with current results based on large multicenter randomized controlled trials (RCT) [19, 20]. In renal function, starting with the matched baseline serum creatinine level, although the early RRT initiation strategy resulted in statistically different serum creatinine levels compared to no early RRT at 48 hours, the difference disappeared at 72 hours. This suggests that the improvement in renal function brought about by the early RRT initiation strategy is delayed and transient. This finding does not support the faster recovery of renal function associated with the early initiation of RRT strategies. In fact, a growing body of evidence supports the hypothesis of renal injury induced by the artificial kidney [30], including RRT-related hemodynamic instability [37], biological incompatibility between blood and synthetic dialyzer membrane [38, 39], catheter-related complications (bleeding, infection), [19, 40] and other potential mechanisms involved in RRT-induced renal injury [30]. It may even be an important factor in eliminating or even reversing the possible early RRT in promoting the improvement of prognosis.

The main advantage of this study is that the statistical method of PSM was used to construct a simulated RCT cohort. In fact, it is difficult to compare the advantages and disadvantages of the early RRT strategy to construct RCT in patients without considering renal function status. However, our study has the following limitations. First, these findings are based on an observational study that cannot determine a causal effect between early RRT and improved clinical outcome and still needs to be confirmed in randomized clinical trials, if at all; second, although we used PSM to minimize the bias, we could not rule out the effect of unmeasured confounders, but we assessed the robustness of the association with unmeasured or uncontrolled confounders by calculating an E-value [41] of 1.79 for early

RRT and 1.67 for 30- and 90-day mortality, respectively. To our knowledge, unmeasured/unknown confounders would be less likely to have an association with both early RRT and study outcomes (30- and 90-day mortality) to an extent by having HRs exceeding 1.79 and 1.67, respectively; third, we could not use the Berlin definition [42] to define patients with ARDS due to lack of information (e.g., bilateral invasion on chest X-ray); fourth, there is a lack of circulatory and pulmonary fluid measurements measured by cardiac catheterization to directly evaluate whether early RRT alleviates pulmonary edema by reducing intravascular hydrostatic pressure, and serum inflammatory mediators and cytokines to directly evaluate whether early RRT alleviates overactivated inflammatory responses; fifth, due to the large heterogeneity of baseline characteristics of patients in intensive care Settings, the percentage of successful matches in the 1-to-1 matched cohort was low (49.4% of all patients with early RRT). However, the consistency of our results using multiple statistical methods and sensitivity analysis ensures the robustness of the results of the small sample cohort as much as possible.

Conclusions

Early RRT initiation strategies had no statistically significant survival benefit in ICU patients with ARDS and sepsis, with or without renal failure, nor did they significantly improve oxygenation or shorten the duration of mechanical ventilation. The use and timing of RRT in these patients should be thoroughly investigated.

Abbreviations

AECC = American-European Consensus Conference

ARDS = acute respiratory distress syndrome

AKI = acute kidney injury

CAD = coronary artery disease

CI = confidence interval

CRRT = continuous renal replacement therapy

DBP = diastolic blood pressure

eGFR = estimated glomerular filtration rate

GCS = Glasgow Coma Scale

HR = hazard ratio

ICU = intensive care units

MAP = mean arterial pressure

PSM = propensity-score matched

RRT = renal replacement therapy

SBP = systolic blood pressure

STROBE = Strengthening the Reporting of Observational Studies in Epidemiology

SOFA = Sequential Organ Failure Assessment

Declarations

Ethics approval and consent to participate

This study was approved by the Ethical Committee of Tianjin Medical University General Hospital (IRB2022-YX-041-01) in accordance with the Declaration of Helsinki, with a waiver for informed consent.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interest.

Funding

Not applicable.

Authors' contributions

LZ and YY conceived and designed the study, supervised the analysis process, interpreted the data, and revised the manuscript. HZ, and ZL analyzed the data and drafted the manuscript. WZ and TY analyzed the data and generated tables and figures. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

References

1. Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, Deboisblanc B, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 2006;354:2564–75.
2. Meyer NJ, Gattinoni L, Calfee CS. Acute respiratory distress syndrome. Lancet 2021;398:622–637.
3. Sibbald WJ, Short AK, Warshawski FJ, Cunningham DG, Cheung H. Thermal dye measurements of extravascular lung water in critically ill patients. Intravascular Starling forces and extravascular lung water in the adult respiratory distress syndrome. Chest 1985;87:585–92.
4. Van Mourik N, Metske HA, Hofstra JJ, Binnekade JM, Geerts BF, Schultz MJ, et al. Cumulative fluid balance predicts mortality and increases time on mechanical ventilation in ARDS patients: An observational cohort study. PLoS One 2019;14:e0224563.
5. Rosenberg AL, Dechert RE, Park PK, Bartlett RH. Review of a large clinical series: association of cumulative fluid balance on outcome in acute lung injury: a retrospective review of the ARDSnet tidal volume study cohort. J Intensive Care Med 2009;24:35–46.
6. Han F, Sun R, Ni Y, Hu X, Chen X, Jiang L, et al. Early initiation of continuous renal replacement therapy improves clinical outcomes in patients with acute respiratory distress syndrome. Am J Med Sci 2015;349:199–205.
7. Van Der Poll T, Van De Veerdonk FL, Scicluna BP, Netea MG. The immunopathology of sepsis and potential therapeutic targets. Nat Rev Immunol 2017;17:407–420.
8. Chan JK, Roth J, Oppenheim JJ, Tracey KJ, Vogl T, Feldmann M, et al. Alarmins: awaiting a clinical response. J Clin Invest 2012;122:2711–9.
9. Deutschman CS, Tracey KJ. Sepsis: current dogma and new perspectives. Immunity 2014;40:463–75.
10. Wiersinga WJ, Leopold SJ, Cranendonk DR, Van Der Poll T. Host innate immune responses to sepsis. Virulence 2014;5:36–44.
11. Guo RF, Ward PA. Role of C5a in inflammatory responses. Annu Rev Immunol 2005;23:821–52.
12. Diehl JL, Borgel D. Sepsis, and coagulation. Curr Opin Crit Care 2005;11:454–60.
13. Sørensen OE, Borregaard N. Neutrophil extracellular traps - the dark side of neutrophils. J Clin Invest 2016;126:1612–20.
14. Venkataraman R, Subramanian S, Kellum JA. Clinical review: extracorporeal blood purification in severe sepsis. Crit Care 2003;7:139–45.
15. Yekebas EF, Eisenberger CF, Ohnesorge H, Saalmüller A, Elsner HA, Engelhardt M, et al. Attenuation of sepsis-related immunoparalysis by continuous veno-venous hemofiltration in experimental porcine pancreatitis. Crit Care Med 2001;29:1423–30.
16. Rimmelé T, Assadi A, Cattenoz M, Desebbe O, Lambert C, Boselli E, et al. High-volume haemofiltration with a new haemofiltration membrane having enhanced adsorption properties in septic pigs. Nephrol Dial Transplant 2009;24:421–7.

17. Bellomo R, Kellum JA, Gandhi CR, Pinsky MR, Ondulik B. The effect of intensive plasma water exchange by hemofiltration on hemodynamics and soluble mediators in canine endotoxemia. Am J Respir Crit Care Med 2000;161:1429–36.
18. Zarbock A, Kellum JA, Schmidt C, Van Aken H, Wempe C, Pavenstädt H, et al. Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury: The ELAIN Randomized Clinical Trial. Jama 2016;315:2190–9.
19. Gaudry S, Hajage D, Schortgen F, Martin-Lefevre L, Pons B, Boulet E, et al. Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit. N Engl J Med 2016;375:122–33.
20. Gaudry S, Hajage D, Schortgen F, Martin-Lefevre L, Verney C, Pons B, et al. Timing of Renal Support and Outcome of Septic Shock and Acute Respiratory Distress Syndrome. A Post Hoc Analysis of the AKIKI Randomized Clinical Trial. Am J Respir Crit Care Med 2018;198:58–66.
21. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994;149:818 – 24.
22. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). Jama 2016;315:801–10.
23. Vandenbroucke JP, Von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. PLoS Med 2007;4:e297.
24. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet 1974;2:81–4.
25. Moreno R, Vincent JL, Matos R, Mendonça A, Cantraine F, Thijs L, et al. The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care. Results of a prospective, multicentre study. Working Group on Sepsis related Problems of the ESICM. Intensive Care Med 1999;25:686–96.
26. Stekhoven DJ, Bühlmann P. MissForest–non-parametric missing value imputation for mixed-type data. Bioinformatics 2012;28:112–8.
27. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat 2011;10:150–61.
28. Mamdani M, Sykora K, Li P, Normand SL, Streiner DL, Austin PC, et al. Reader's guide to critical appraisal of cohort studies: 2. Assessing potential for confounding. Bmj 2005;330:960–2.
29. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12.
30. Benichou N, Gaudry S, Dreyfuss D. The artificial kidney induces acute kidney injury: yes. Intensive Care Med 2020;46:513–515.
31. Dill J, Bixby B, Ateeli H, Sarsah B, Goel K, Buckley R, et al. Renal replacement therapy in patients with acute respiratory distress syndrome: a single-center retrospective study. Int J Nephrol Renovasc Dis 2018;11:249–257.

32. Cole L, Bellomo R, Hart G, Journois D, Davenport P, Tipping P, et al. A phase II randomized, controlled trial of continuous hemofiltration in sepsis. Crit Care Med 2002;30:100–6.
33. Heering P, Morgera S, Schmitz FJ, Schmitz G, Willers R, Schultheiss HP, et al. Cytokine removal and cardiovascular hemodynamics in septic patients with continuous venovenous hemofiltration. Intensive Care Med 1997;23:288–96.
34. Cole L, Bellomo R, Journois D, Davenport P, Baldwin I, Tipping P. High-volume haemofiltration in human septic shock. Intensive Care Med 2001;27:978–86.
35. Oudemans-Van Straaten HM, Bosman RJ, Van Der Spoel JI, Zandstra DF. Outcome of critically ill patients treated with intermittent high-volume haemofiltration: a prospective cohort analysis. Intensive Care Med 1999;25:814–21.
36. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med 2021;47:1181–1247.
37. Conger JD. Does Hemodialysis Delay Recovery from Acute Renal Failure? Seminars in Dialysis 1990;3:146–148.
38. Alonso A, Lau J, Jaber BL. Biocompatible hemodialysis membranes for acute renal failure. Cochrane Database Syst Rev 2008;2008:Cd005283.
39. Itoh S, Susuki C, Tsuji T. Platelet activation through interaction with hemodialysis membranes induces neutrophils to produce reactive oxygen species. J Biomed Mater Res A 2006;77:294–303.
40. Buetti N, Ruckly S, Lucet JC, Mimoz O, Souweine B, Timsit JF. Short-term dialysis catheter versus central venous catheter infections in ICU patients: a post hoc analysis of individual data of 4 multi-centric randomized trials. Intensive Care Med 2019;45:1774–1782.
41. Vanderweele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. Ann Intern Med 2017;167:268–274.
42. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin Definition. Jama 2012;307:2526–33.

Figures

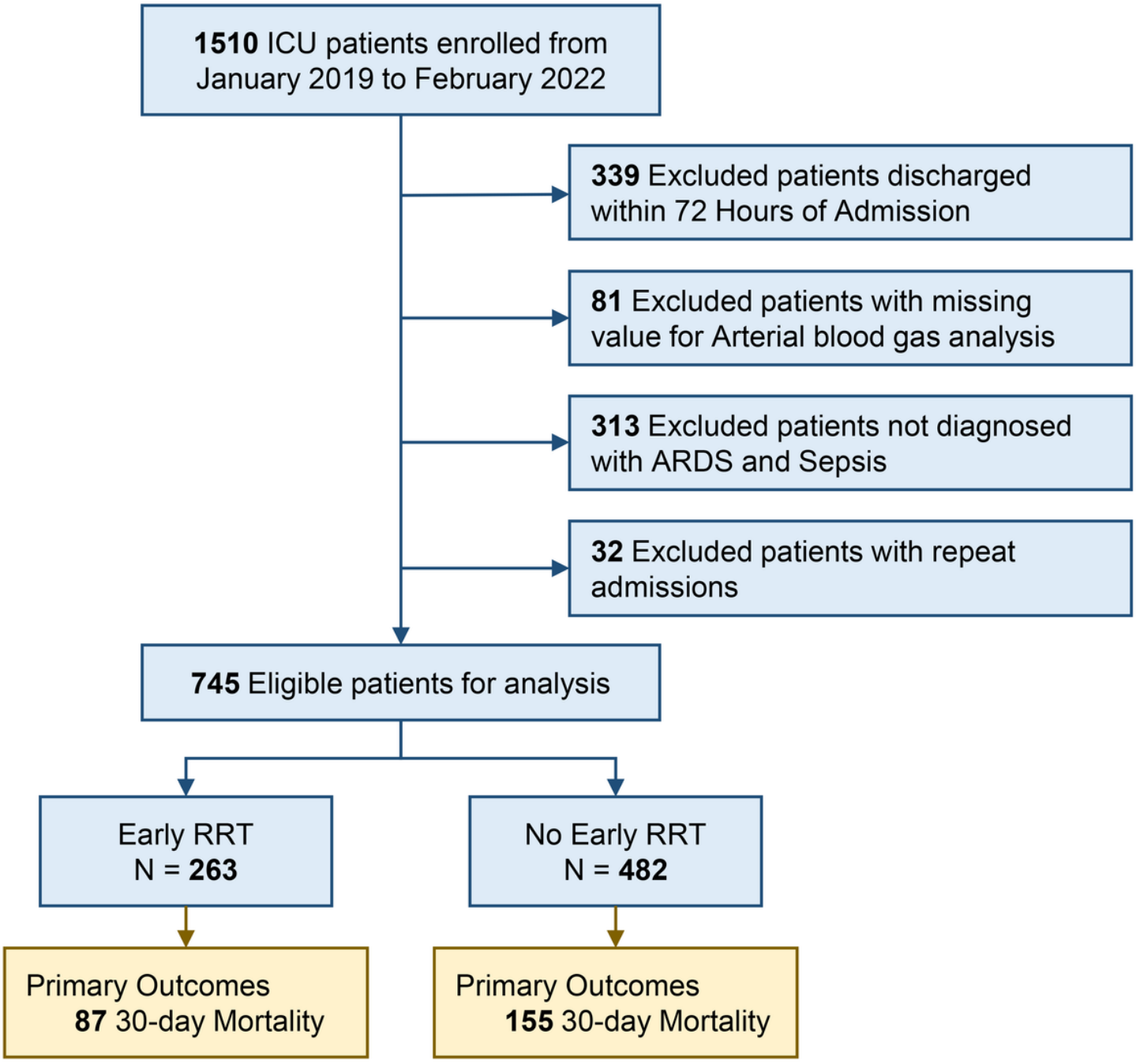

Figure 1

A schematic overview illustrating participant enrollment and the exclusion and inclusion criteria.
Abbreviations: ARDS, acute respiratory distress syndrome; ICU, intensive care unit; RRT, renal replacement therapy.

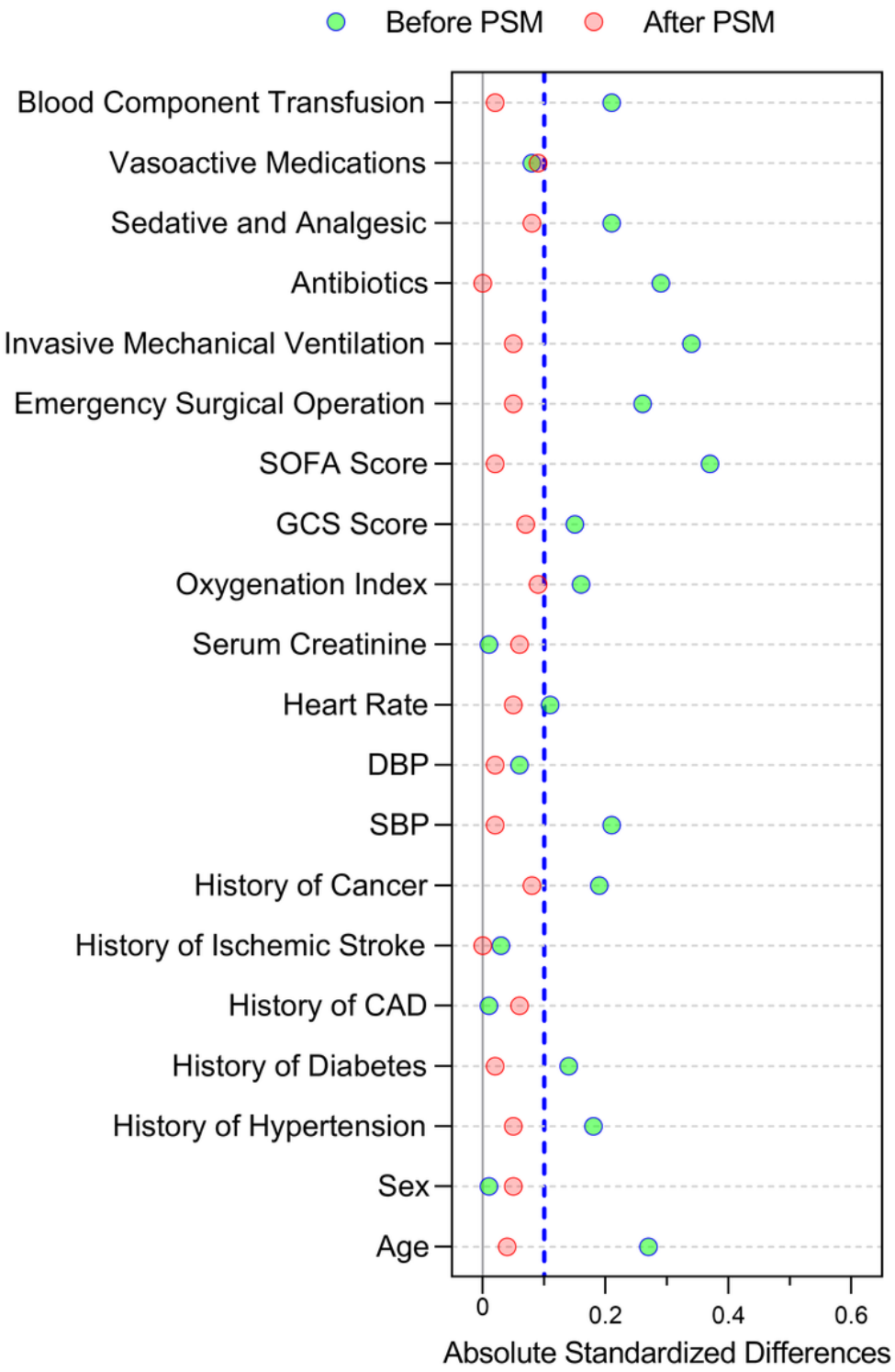

Figure 2

A Love-Plot illustrating the effect of matching were evaluated by comparing the absolute standardized difference. Abbreviations: CAD, coronary heart disease; DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; SBP, systolic blood pressure; SOFA, Sequential Organ Failure Assessment.

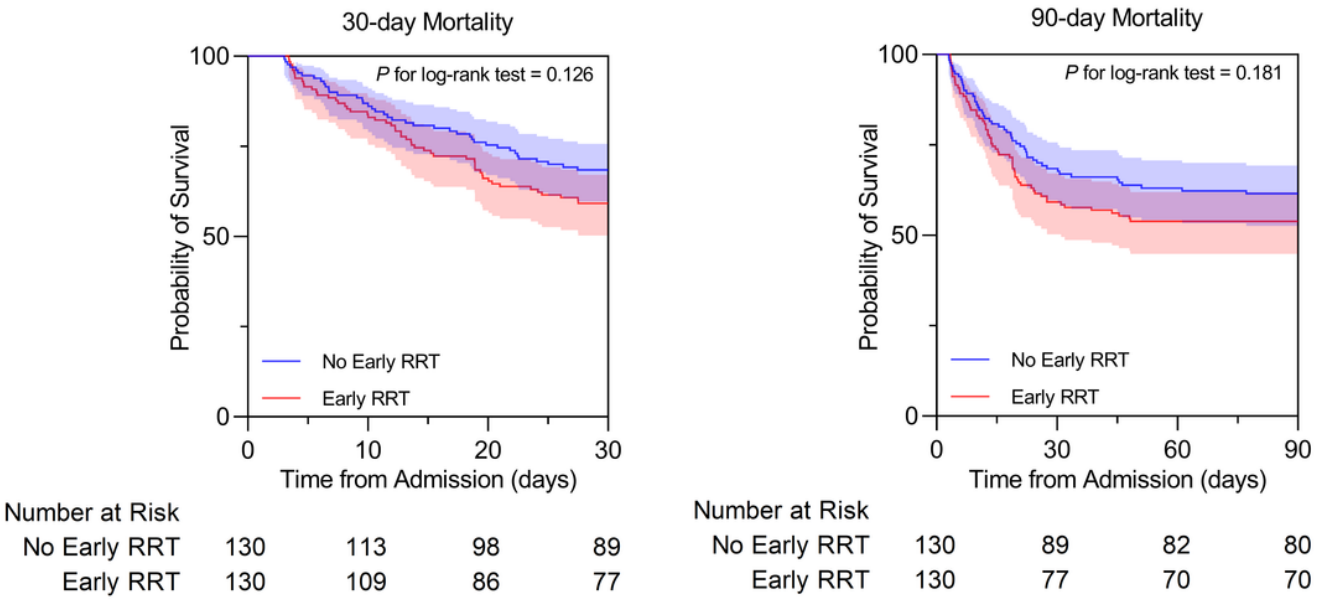

Figure 3

Survival analysis by early RRT status. Kaplan-Meier curves of the probability of survival by early RRT status with respect to 30- (left) and 90-day mortality (right). Numbers at risk are shown below each graph. Abbreviations: CI, confidence intervals; HR, hazard ratio; RRT, renal replacement therapy.

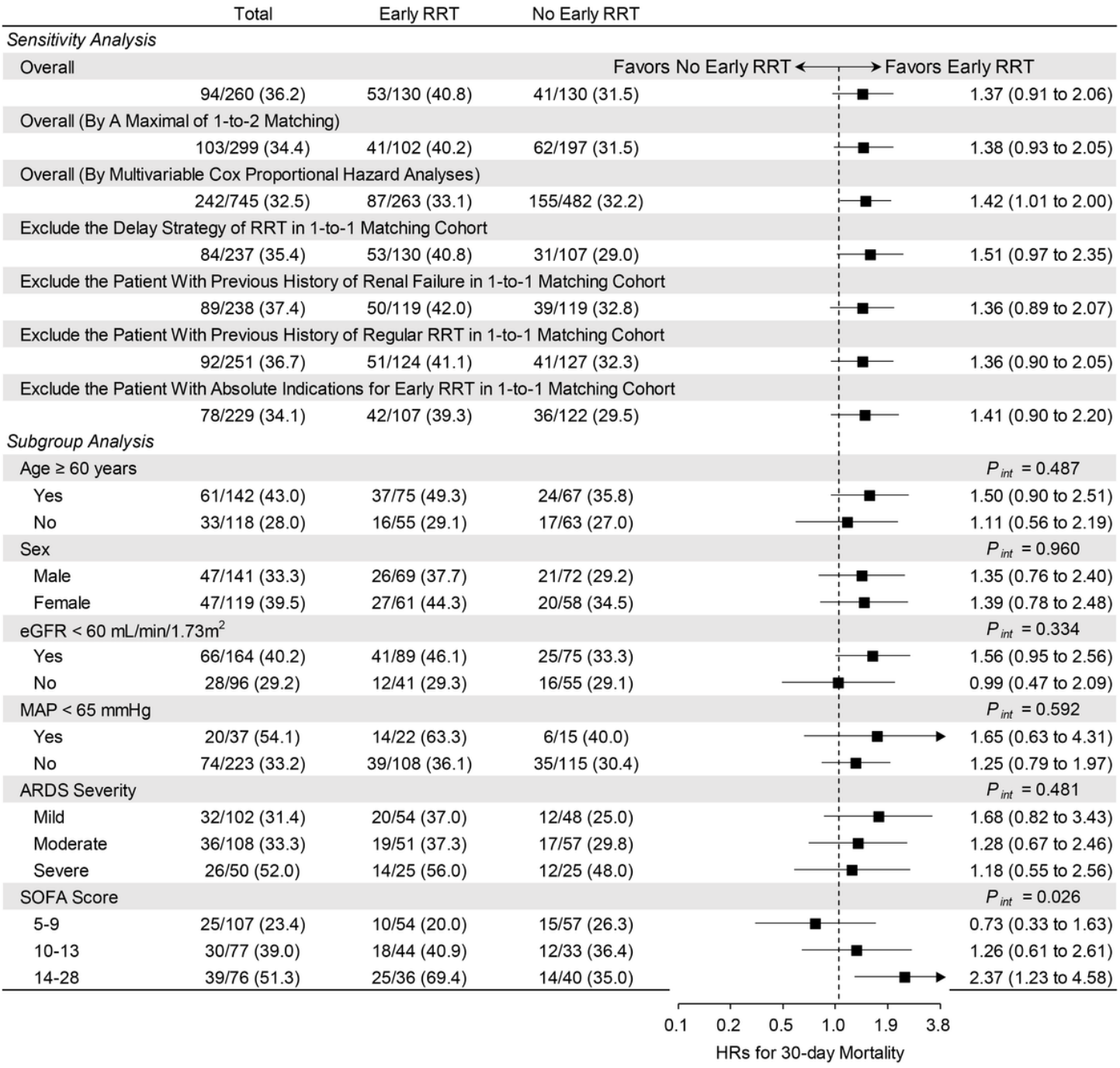

Figure 4

Forest plot of the sensitivity and subgroup analysis for primary outcome. Abbreviations: ARDS, acute respiratory distress syndrome; CI, confidence intervals; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MAP, mean arterial pressure; RRT, renal replacement therapy.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementalMaterial.docx