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## Renal replacement therapy could be initiated in patients with severe AKI, regardless of age and critical condition

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## **Renal replacement therapy could be initiated in patients with severe AKI, regardless of age and critical condition**

### **Cover Page Footnote**

This appraisal was written in the memory of Mrs. Noor Al-Jannah. May she rest in heaven. I would like to acknowledge my mentors in life Dr. Falah Shamsa and Dr. Janan Alkilidar, this study could not have been completed without their continual guidance.

# Renal replacement therapy could be initiated in patients with severe AKI, regardless of age and critical condition

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**ABSTRACT** A clinical decision report using:

Meersch M, Küllmar M, Schmidt C, et al. Long-Term Clinical Outcomes after Early Initiation of RRT in Critically Ill Patients with AKI. *J Am Soc Nephrol*. Mar 2018;29(3):1011-1019. <https://doi.org/10.1681/asn.2017060694>

for a critically ill elderly patient with severe acute kidney injury.

**Keywords:** renal replacement therapy, elderly patient, critically ill, acute kidney injury

## Clinical-Social Context

Noor Al-Jannah [pseudonym] is a 93 year-old woman with a past medical history of stage 3b chronic kidney disease (CKD) admitted for aspiration pneumonia and respiratory failure. On admission, her creatinine was at baseline 1.2 mg/dL, BUN 70 mg/dL, and eGFR 42. IV antibiotics were initiated and respiratory symptoms improved and ventilator settings were returned to normal. BUN remained elevated and she remained lethargic, non-verbal, and cachectic despite adequate nutrition, indicating symptomatic uremia.

One week post-admission, Mrs. Al-Jannah suffered a severe upper-GI bleed. She was hypotensive (blood pressure 85/50) and kidney function tests were significantly elevated (Creatinine 4.5 mg/dL, BUN 220 mg/dL, eGFR 9). She was transported to the Surgical Intensive Care Unit (SICU) where emergent Esophagogastroduodenoscopy (EGD) was performed and an actively bleeding gastric arterio-venous malformation (AVM) was discovered and treated.

Although Mrs. Al-Jannah was hemodynamically stabilized, her uremic symptoms and kidney function tests failed to improve. Nephrology was reluctant to begin renal replacement therapy (RRT) given her other comorbidities and critical condition, and they urged for palliative care. After discussing this with the family, Mrs. Al-Jannah's daughter-in-law (her legal guardian) and the rest of the family expressed their understanding of the risks of RRT and insisted that all measures be taken to preserve and extend Mrs. Al-Jannah's life, as their religion mandated. Nephrology recommended against hemodialysis due to Mrs. Al-Jannah's history of diastolic heart failure and her critically ill condition, thus peritoneal dialysis was considered. Urgent dialysis was not initiated, and, one month later, while searching for a nursing facility where she could undergo peritoneal dialysis, Mrs. Noor Al-Jannah passed away due to massive pulmonary hemorrhage.

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## Clinical Question

Should urgent renal replacement therapy (RRT) be considered in critically ill elderly patients with severe acute kidney injury (AKI)?

## Research Article

Meersch M, Küllmar M, Schmidt C, et al. Long-Term Clinical Outcomes after Early Initiation of RRT in Critically Ill Patients with AKI. *J Am Soc Nephrol.* Mar 2018;29(3):1011-1019. <https://doi.org/10.1681/asn.2017060694><sup>1</sup>

## Description of Related Literature

UpToDate was queried by searching “chronic kidney disease management”, and the overview of management of CKD in adults article was chosen.<sup>2</sup> This article highlighted a 2007 meta-analysis of 20 studies that found that delayed referral of CKD patients to a nephrologist was associated with statistically significant increase in risk of all-cause mortality. Furthermore, the article corroborates the importance of kidney replacement therapy in patients with symptomatic uremia with end stage kidney disease (ESKD). Kidney transplantation is the first choice of treatment in ESKD, followed by hemodialysis or peritoneal dialysis. Due to Mrs. Al-Jannah’s critical condition and comorbidities, kidney transplantation is contraindicated.

PubMed was then searched using the search phrase “initiation of renal replacement therapy AND critically ill” which obtained 808 results. The search was then filtered for “Clinical Trial” and “Randomized Controlled Trial” article types, “Human” species, and “80 and over: 80+ years” and “Aged: 65+ years” age ranges, which obtained 54 results. The titles of these articles were scanned, and 47 articles were excluded as they were not related to the clinical question of this article: they focused on molecular markers of kidney disease, pharmacological therapies, and the comparison of RRTs. Next, the abstracts of each of the remaining 7 articles were read and 2 articles were excluded as they could not be applied to Mrs. Al-Jannah’s case: one article studied patients who had no urgent indication for RRT and the other analyzed the difference in survival rates between two different hemodialysis methods. Google Scholar was then searched using the title of the article chosen for critical appraisal and selecting the “Related Articles” link, resulting in 101 related articles. The titles of these articles were scanned and no additional articles that pertained to the clinical question were found.

Gaudry et al. performed a randomized trial on 620 ICU patients with stage 3 AKI (Kidney Disease: Improving Global Outcomes [KDIGO] classification) in which patients were assigned to an early RRT (RRT initiated immediately after randomization) or delayed RRT (RRT only after absolute indication) group, which found that there was no significant difference in mortality between the two groups (P=0.79) and that catheter-related bloodstream infections were higher in the early RRT group (P = 0.03).<sup>3</sup> Bellomo et al. found that there was no significant difference in survival of critically ill elderly patients (age > 65, n = 72) with severe AKI compared to younger patients with similar disease (age < 65, n = 70) after both groups were treated with continuous RRT (CRRT).<sup>4</sup> Ponce et al. found that there was no significant survival benefit in extended daily hemodialysis compared to high volume peritoneal dialysis<sup>5</sup>, indicating that peritoneal dialysis would have been an effective alternative therapy for Mrs. Al-Jannah.

Two separate studies were written on the ELAIN randomized clinical trial, which enrolled 231 critically ill patients who were randomly assigned to two groups: an early and a delayed RRT group. Zarbock et al. found that early RRT was associated with significantly reduced 90-day mortality compared to delayed RRT (P = 0.03).<sup>6</sup> The second study, Meersch et al., was chosen for critical appraisal. This study extended the length of follow-up of the same 231 patients to 1 year and found that early RRT significantly reduced major adverse kidney events (P < 0.001) and mortality (P < 0.01) and increased renal recovery at 1 year (P = 0.001).<sup>1</sup> This study was chosen for critical appraisal due to its specific patient population fitting Mrs. Al-Jannah’s clinical course and its extension on previous findings of short-term benefits of early RRT intervention to show long-term benefits as well. Though the inclusion criteria of the study limit generalizability, its specific population and findings validated by above mentioned studies will be valuable in guiding clinical decisions on situations like Mrs. Al-Jannah’s.

The strength of recommendation of the above body of evidence is Grade B, based on the Strength of Recommendation Taxonomy (SORT)<sup>7</sup>, due to the conflicting findings of Gaudry et al.<sup>3</sup> with the conclusions in Zarbock et al.<sup>6</sup> and Meersch et al.<sup>1</sup>

## Critical Appraisal

Using the SORT criteria, Meersch et al. is considered a high quality randomized controlled clinical trial with extensive follow-up with Level 1 study quality, as it uses good quality patient-oriented evidence.<sup>2</sup>

This study screened 604 critically ill patients with AKI. Inclusion criteria consisted of: (1) KDIGO stage 2 AKI, (2) plasma neutrophil gelatinase-associated lipocalin > 150 ng/ml, (3) critical illness, (4) age 18-90, (5) intention for full intensive care treatment. 348 of the screened patients did not meet these criteria. This rigorous inclusion criteria adequately selected for a representative sample of critically ill AKI patients. 3 patients declined to be included, and 22 patients were hospitalized in facilities where no CRRT machines were available. The remaining 231 patients were randomized into 2 experimental groups: 112 assigned to the early RRT group (1 of whom was lost to follow-up) and 119 assigned to the delayed RRT group. Early RRT was initiated immediately after diagnosis of KDIGO stage 2. Delayed RRT was initiated only if stage 3 AKI was reached or after an absolute indication for RRT initiation was met. There were no significant differences in the inclusion criteria variables between both groups, and most other variables were similar between the groups (age, sex, comorbidities, number of medications), thus indicating successful randomization of the patients. The study could not be blinded as patients would know which group they were assigned to based on whether they began RRT immediately (early RRT group) or only after reaching a certain AKI status (delayed RRT). If Mrs. Noor Al-Jannah was screened for this study, she would have met all inclusion criteria and would have undergone RRT initiation regardless of which experimental group she was assigned to.

At 1 year follow-up, 64.9% of patients in the early RRT group had a major adverse kidney event (death, dependence on RRT, or persistent renal dysfunction) versus 89.1% of patients in the delayed RRT group, resulting in an absolute risk reduction (ARR) of -24.2% (95% CI -34.7% to -13.7%,  $P < 0.001$ ) and an odds ratio (OR) of 0.23 (95% CI 0.11 to 0.45,  $P < 0.001$ ). Calculated number needed to treat (NNT) is 4.13 - for approximately every 4 patients who undergo early RRT initiation, 1 patient will avoid a major adverse kidney event that would have occurred had they undergone delayed RRT initiation. All-cause mortality at 1 year follow-up was also significantly lower in the early RRT group (ARR = -19.5%, 95% CI -32.0% to -7.2%; OR = 0.62, 95% CI 0.44 to 0.87;  $P < 0.01$ ), with a NNT of 5.12.

This study was successful in elucidating the long-term benefits of early RRT initiation by using an extensive follow-up time, achieving randomization, and eliminating participation bias. Publication and Funding biases were eliminated as the study was registered on the German Clinical Registry (Identifier: DRKS00004367) and the author stated that the study sponsors had no role in the design and conduct of the study. However, several weaknesses did exist. The inclusion criteria proved to be very rigorous and resulted in a limited sample size of 231 patients and a loss of generalizability to patients who do not fit the rigorous criteria. Furthermore, due to this smaller sample size, only 25 patients enrolled in the study were > 80 years old; this age group was too small to make separate conclusions in elderly patients. Lastly, the study did not analyze symptoms related to kidney disease, such as the uremic symptoms seen in Mrs. Al-Jannah, which are important indicators of morbidity outside of major adverse kidney events.

### Clinical Application

Mrs. Noor Al-Jannah was a 93 year-old critically ill woman who suffered a severe AKI. Her legal surrogate and family were in agreeance that she would have wanted all life-preserving measures to be taken. Emergent RRT was not initiated due to nephrology's input that RRT was unethical and would not improve survivability given her critical condition and elderly age. It was finally decided that peritoneal dialysis was the right treatment option, however initiation of treatment was further delayed due to limited availability of care facilities due to the COVID-19 pandemic. These ethical and social factors led to weeks of delays in treatment.

The study by Meersch et al. found that early RRT significantly reduced major renal adverse events and all-cause mortality<sup>4</sup>, allowing them to conclude that there are significant short-term and long-term survival benefits in early RRT initiation. Not only did Mrs. Al-Jannah fit the rigorous inclusion criteria of the study, her condition also met the absolute indication for RRT (BUN > 200 mg/dL) in the study, indicating that she would have immediately been placed on emergent RRT. Had this been applied to her case, this article provides strong evidence that her risk of death would have been significantly decreased. Furthermore, the massive pulmonary hemorrhage that led to her

rapid demise was likely linked to her chronic symptomatic uremic state, which could have been prevented by early RRT initiation.

## New Knowledge Related to Clinical Decision Science

With hospice care expanding in western medicine, physicians have increasingly begun to implement opinions of comfort care into their practice and clinical recommendations. However, the will of the patient (and thus their surrogate) prevails over these considerations, and physicians must be careful to understand that there will remain significant differences in opinions on comfort care, especially in many non-western cultures that call for preservation of life at all costs, and they must be prepared to adapt to these differences to lessen stress on both the patient and the family. While it is understandable that opinions on comfort care might sway a physician's recommendations, it is crucial that, as healthcare professionals, we respect the autonomy of patients who may benefit from treatment and offer them said treatment if they request it.<sup>8</sup>

Is RRT a reasonable treatment option in the elderly population? Is it effective in this population, and are its benefits worth the possible risks of decreased quality of life? These questions represent the dilemma that many nephrologists face when deciding whether to initiate RRT in an elderly patient. A review by Kjellstrand highlights that, because of this hesitancy, there is a lack of distributive justice of RRT. Elderly patients at 70 years old had less than 1/10 the chance of a 20-to-40-year-old to receive dialysis and less than 1/30 the chance of receiving a renal transplant.<sup>9</sup> This lack of distributive justice may be linked to a perceived reduced quality of life in elderly patients on dialysis and the belief that it would be cruel to start an elderly patient on RRT.<sup>8</sup> Conversely, however, self-reported quality of life of elderly patients receiving RRT was particularly high.<sup>9</sup> Furthermore, Ch'ng et al. found that, after controlling for comorbidities, dialysis reduced the hazard of death in elderly patients (age > 65) with end stage renal disease (ESRD) compared to younger ESRD patients, with hazard ratios (HR) 0.58 and 0.76, respectively.<sup>10</sup> Additionally, a review by Berger and Hedayati found showed that transplant recipients older than 70 years of age had a 41% mortality reduction compared with the rate of ESRD patients who did not receive a transplant. Elderly patients with no or mild comorbidities could benefit greatly from renal transplantation, and those with severe comorbidities who may not qualify for renal transplantation should still be considered for dialysis treatment, especially those without significant cognitive or functional disabilities.<sup>11</sup> With these findings in mind, it is important not to delay RRT in elderly patients, even those with significant comorbidities, as delayed initiation of RRT among elderly ESRD patients is associated with the development of uremic complications and increased morbidity.<sup>8</sup>

In the case Mrs. Al-Jannah, once the ethical conflicts were resolved, the next question remained: what should be done when there are limited facilities that will accept dialysis patients on a ventilator? This was the dilemma facing both the hospital team and the family, with no right answer in sight until Mrs. Al-Jannah's final complication occurred.

## Conflict Of Interest Statement

The author declares no conflicts of interest.

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