Protocol for a Systematic Review and Meta-Analysis: Hemodialysis vs. Peritoneal Dialysis in COVID-19 AKI

Title page:

Research Tile: Compare the Clinical Outcome of Hemodialysis versus Peritoneal Dialysis in AKI inPatients with COVID-19

Protocol Acronym: SAMCov19-HDvPD

ABSTRACT

Background:Acute Kidney Injury (AKI) is pervasive in COVID-19 patients, affecting up to 50% of hospitalized individuals and posing graver risks for the critically ill. Renal Replacement Therapy (RRT), often necessary, involves Hemodialysis (HD) or Peritoneal Dialysis (PD). The optimal choice between HD and PD, particularly their impact on mortality, remains uncertain, creating a crucial knowledge gap. This systematic review and meta-analysis aim to address this gap by thoroughly examining existing evidence and comparing clinical outcomes, specifically mortality, in COVID-19 patients necessitating RRT.

Objectives: aims to: Compare clinical outcomes between hemodialysis and peritoneal dialysis in COVID-19 AKI patients.

Methods: Following the Cochrane Handbook for Systematic Reviews of Interventions, we will search electronic databases, screen studies using Rayyan software with independent reviewers, and extract data with standardized forms. To ensure rigor, Revman software will be used for pooled effect size calculations and heterogeneity assessment.

Significance: By transparently comparing modalities and exploring mortality determinants, SAMcov19-HDvPD will provide valuable insights to inform clinical decision-making and improve care for COVID-19 AKI patients requiring dialysis.

Keywords: Acute Kidney Injury, COVID-19, Renal Dialysis, Treatment Outcome

Systematic Review Registration

PROSPERO: CRD42023324394 (Compare the Clinical Outcome of Hemodialysis versus Peritoneal Dialysis in AKI in Patients with COVID-19)

1. Background:

Acute kidney injury (AKI) is a frequent and severe complication in patients with Coronavirus Disease 2019 (COVID-19), impacting a substantial proportion of hospitalized patients, ranging from 30% to nearly 50%. The incidence rate is even higher in critically ill individuals, reaching 38.4 per 1,000 patient-days (Chan et al., 2021; Ng et al., 2021; Silver et al., 2021). According to a study conducted by Chan et al.(Chan et al., 2021), within the cohort of COVID-19 patients experiencing acute kidney injury (AKI), 19% necessitated dialysis. Kidney involvement in patients with COVID-19 is associated with increased mortality, prolonged hospital stay, and higher healthcare costs (Geetha et al., 2022; Shao et al., 2020). The mortality rate of patients with COVID-19-related AKI exhibits significant variability, influenced by a multitude of factors beyond the underlying kidney injury. The timeframe of the study, geographic location of the outbreak (including the country of origin), and the specific modality of renal replacement therapy (hemodialysis versus peritoneal dialysis) all play a crucial role in shaping this variability(Kooman & van der Sande, 2021). Notably, distinct mortality patterns emerge within the dialysis patient population, suggesting additional factors at play. When AKI develops, renal replacement therapy (RRT) becomes necessary to remove waste products and fluids from the body, supporting recovery and preventing further complications.

The two main RRT modalities for AKI are hemodialysis (HD) and peritoneal dialysis (PD). Choosing between HD and PD for COVID-19 patients with AKI is crucial, as it can significantly impact clinical outcomes. Both modalities have advantages and disadvantages, and the optimal choice depends on various patient-specific factors and healthcare resource availability.

Rationale for Comparing HD and PD in COVID-19-AKI:

Several factors highlight the importance of comparing HD and PD in the context of COVID-19-AKI:

1. Increased AKI burden in COVID-19: As mentioned above, AKI is a frequent complication in COVID-19 patients, necessitating RRT in a significant proportion of cases. Understanding the optimal RRT modality for this specific population is critical for improving patient outcomes.
2. Potential benefits of PD in critically ill patients: PD offers several advantages over HD in critically ill patients, including:
    - Reduced hemodynamic instability: PD avoids the rapid fluid shifts associated with HD, potentially minimizing hemodynamic stress and improving cardiovascular stability. This is particularly important for COVID-19 patients, who often have pre-existing cardiovascular complications.
    - Continuous Solute and Fluid Removal: Peritoneal Dialysis (PD) offers a sustained process of solute and fluid removal, providing potential benefits for patients with dynamically changing fluid and electrolyte requirements. PD is typically conducted over extended periods, spanning both day and night, allowing for a continuous therapeutic approach. In contrast, Intermittent Hemodialysis (IHD) involves shorter and sporadic sessions, catering to the specific needs of patients requiring a more intermittent treatment regimen.
3. On the other hand, hemodialysis boasts several advantages over peritoneal dialysis
    - Rapid Fluid and Toxin Removal**:** HD typically allows for more rapid removal of excess fluid and toxins from the body compared to PD. This can be advantageous in patients who require more aggressive fluid management.
    - Greater Efficiency in Clearing Urea**:**HD is often more efficient in clearing urea, a waste product that accumulates in the blood in kidney failure. This may be particularly important in patients with elevated urea levels.

4. Limited research on optimal RRT modality in COVID-19-AKI: While the use of RRT in COVID-19-AKI is increasing, high-quality evidence comparing HD and PD in this specific population is limited. Existing

studies have reported conflicting results, and further research is needed to determine the optimal RRT modality for this growing patient group.

While studies comparing HD and PD for AKI in COVID-19 patients have provided valuable insights, significant knowledge gaps remain. These gaps include the need for robust clinical trials, investigations into specific patient subgroups, and a deeper understanding of the interplay between COVID-19 and RRT effectiveness. Filling these gaps can significantly improve the management of AKI in COVID-19 patients.:
Several gaps in research exist regarding the comparison of HD and PD for AKI in COVID-19 patients:

1) Lack of large-scale randomized controlled trials: Most existing studies are retrospective or observational, making it difficult to draw definitive conclusions about the superiority of one modality over the other. Large-scale randomized controlled trials are needed to provide robust evidence on the clinical outcomes of HD and PD in COVID-19-AKI.
2) Limited data on specific COVID-19 subpopulations: Existing research often lacks data on specific subpopulations within the COVID-19-AKI population, such as patients with pre-existing chronic kidney disease or severe respiratory failure. Further research is needed to understand the optimal RRT modality for these high-risk subgroups.
3) Incomplete understanding of COVID-19's pathophysiology on RRT outcomes: The specific mechanisms by which COVID-19 affects RRT outcomes are not fully understood. More research is needed to elucidate the pathophysiology of COVID-19-AKI and how it interacts with different RRT modalities.

There is a gap in understanding the specific advantages or disadvantages between PD and HD in critically ill patients, especially in the context of acute kidney injury related to COVID-19. While general comparisons exist, a clear assessment of these differences in the specific scenario of AKI associated with COVID-19 remains elusive, highlighting a gap in the current knowledge. Addressing these research gaps is crucial for optimizing clinical care for AKI patients with COVID-19. Well-designed studies and further exploration of underlying mechanisms can improve the evidence base for guiding renal replacement therapy decisions and enhance patient outcomes.

2. **Objective**:

To systematically review and meta-analyze the comparative clinical outcomes of hemodialysis and peritoneal dialysis in patients with COVID-19-associated acute kidney injury.

3. **Designate Contractor & Responsible Party**:

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5. Study Design:

This study will employ a systematic review and meta-analysis design to comprehensively assess and synthesize existing evidence regarding the clinical outcomes of hemodialysis and peritoneal dialysis in patients with COVID-19-associated acute kidney injury (AKI). This focused approach will enable a rigorous examination within the inherent limitations of a systematic review and meta-analysis framework.

6. Data Sources:

To comprehensively identify relevant articles, this study will employ a systematic search strategy. This will involve searching electronic databases such as PubMed, Embase, and the Cochrane Library. Additionally, clinical trial registries and reference lists of included studies will be hand-searched to ensure no relevant studies are missed. This multifaceted approach will establish a robust data foundation for the planned systematic review and meta-analysis. Informed by Jeffrey C. Valentine's insights (Valentine et al., 2010), our forthcoming meta-analysis transcends the limitations of power analysis by highlighting the multifaceted value of confidence intervals. We propose that commencing with a minimum of two studies fosters transparency, establishes methodological validity, and lays a robust foundation for subsequent synthesis. This approach aligns with Valentine's assertion that two studies represent the critical threshold for meaningful quantitative analysis, ensuring that the synthesized findings rest upon a solid and verifiable foundation.

7. Eligibility Criteria:

To comprehensively assess the comparative clinical outcomes of hemodialysis and peritoneal dialysis in COVID-19-associated AKI, we plan to conduct a systematic review and meta-analysis. This study will include studies published in English that meet the following eligibility criteria:

- *Study design:* Randomized controlled trials, observational studies, or cohort studies.
- *Population:* Adult participants diagnosed with COVID-19-associated AKI.
- *Intervention:* Comparison of hemodialysis and peritoneal dialysis.
- *Outcomes:* Reported clinical outcomes relevant to patient care in COVID-19-associated AKI.

8. Data Extraction:

In our anticipated systematic review and meta-analysis, we acknowledge the potential for heterogeneity and methodological variations across studies. To address this, our approach involves a meticulous data extraction process conducted by multiple independent reviewers (a minimum of two). These

reviewers will extract data encompassing study characteristics, patient demographics, detailed information on interventions (including hemodialysis and peritoneal dialysis), and a comprehensive array of clinical outcomes relevant to COVID-19-associated AKI.

To maintain consistency and minimize bias, a standardized data extraction form will be employed. Any discrepancies between reviewers will be resolved through thorough discussion and consensus, ensuring a robust foundation for accurate data synthesis and analysis.

Additionally, we plan to integrate the Rayyan software into our methodology to streamline and manage the screening and review process, which will involve multiple reviewers. The initial screening will evaluate search results based on title and abstract. In the subsequent screening phase, full-text articles passing the first review and those lacking sufficient information will undergo a comprehensive evaluation, emphasizing effect sizes and methodology. This systematic approach guarantees a comprehensive and efficient selection process for our upcoming study.

9. Outcomes:

The primary outcome will be all-cause mortality rate, reflecting the critical importance of patient survival in COVID-19-associated AKI. followed by secondary outcomes such as duration of hospitalization and need for intensive care. Additionally, we will explore the feasibility of analyzing renal recovery rate and dialysis-related complications based on the quality and consistency of data reported in the included studies. To address potential inconsistencies in outcome definitions, we will employ standardized definitions and utilize appropriate statistical methods to handle missing data, ensuring a robust and reliable analysis of patient outcomes.

10. Quality Assessment:

Recognizing the importance of transparency and potential variations in study designs, we plan to adopt a rigorous approach to quality assessment in our future systematic review and meta-analysis. We will primarily utilize the Cochrane Risk of Bias tool for randomized controlled trials and the Newcastle-Ottawa Scale for observational studies. However, depending on the specific characteristics of the included studies, we may also consider employing additional validated tools or adapting existing criteria (e.g., Meta-analysis Of Observational Studies in Epidemiology ;MOOSE) to ensure a comprehensive and nuanced evaluation of study quality. We will clearly document our quality assessment procedures and rationale for any adaptations chosen, contributing to the overall transparency and trustworthiness of our analysis.

11. Statistical Analysis:

11.1 Building on established principles:

This systematic review and meta-analysis will adhere to established principles for robust data synthesis. In the initial stage, we will calculate a summary statistic for each study, such as the odds ratio or a risk ratio for dichotomous data, to represent the observed intervention effect on mortality uniformly across studies. We plan to incorporate the statistical analysis methodology outlined by Jonathan J. Deeks (2019) in the Cochrane Handbook for Systematic Reviews of Interventions (Deeks et al., 2019) as our theoretical framework. This principle will serve as a cornerstone for our subsequent analytical processes. We also have selected RevMan 5, a comprehensive and widely-used meta-analysis software (https://training.cochrane.org/online-learning/core-software/revman/revman-5-download), to facilitate the calculation of pooled effect sizes within

our analysis. This software offers robust features and seamless integration with our methodological framework.

11.2 Weighted average and considerations:

We will then calculate a weighted average of intervention effects across studies, incorporating the varying precision of each study through weights (W_i), as shown in the equation below (Equation 1)(Deeks et al., 2019).This ensures studies with larger sample sizes or lower variability exert a greater influence on the overall estimate. Importantly, as the main outcome is a dichotomous event (mortality), we will employ appropriate statistical methods specifically tailored for risk or odds ratios.

A weighted average of intervention effects estimated in individual studies will be calculated as following equation:

$$\text{Weighted Average} = \frac{\sum_i (Y_i W_i)}{\sum_i W_i} \quad \text{.....(Eq.1)}$$

In this formula, Y_i represents the estimated intervention effect in the ith study, W_i denotes the weight assigned to the ith study, and the summation encompasses all studies.

11.3 Heterogeneity and potential biases:

Recognizing the potential for heterogeneity in intervention effects across studies, we will employ a random-effects model during meta-analysis. This accounts for between-study variability beyond random sampling error and allows for a more realistic estimate of the generalizable effect size. To investigate potential sources of heterogeneity within our data, we plan to employ both Cochran's Q test and I^2 statistics during the upcoming meta-analysis (Equation 2). This comprehensive approach will enable us to statistically evaluate whether observed differences in intervention effects across studies can be attributed to chance or meaningful moderators, informing our hypotheses regarding underlying factors influencing clinical outcomes. Additionally, we will implement meta-analytic methods to assess potential biases, including publication bias and selective reporting, ensuring the robustness and trustworthiness of our findings.

$$Q = \sum_{i=1}^{k} w_i (C_i - \bar{C})^2 \quad \text{.....(Eq.2)}$$

where:

- Q is the Cochran's Q statistic,
- k is the number of studies,
- w_i is the weight assigned to the i^{th} study,
- C_i is the effect size estimate of the i^{th} study,
- $\bar{C}$ is the overall effect size estimate.

11.4 Addressing missing data and visualization:

We will carefully consider the potential impact of missing data, particularly losses to follow-up or exclusions, and apply appropriate strategies to minimize their influence on the analysis. Finally, we will utilize forest plots to visually represent the individual study results alongside the overall meta-analysis estimate, providing a clear and transparent presentation of the findings.

12. Ethics and Dissemination:

Ethics approval is not applicable as this study involves the analysis of published data. Findings will be disseminated through peer-reviewed publications and conference presentations.

13. Conclusion:

This systematic review and meta-analysis aim to provide evidence-based insights into the comparative clinical outcomes of hemodialysis and peritoneal dialysis in AKI patients with COVID-19. The results will contribute to informed decision-making in the management of these critically ill patients.

14. Competing interests*:*

We declare that the authors have no competing interests.

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