

Comparative Lab Evaluation of Middle Molecule Clearance in Dialysis Patients

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Introduction and Objective

- A majority of patients with end-stage kidney disease (ESKD) in the United States are treated with thrice weekly in-center hemodialysis (ICHHD). Modern dialyzers are extremely efficient at removing small (<500 Da) water-soluble toxins like urea (60 Da), which readily diffuse across the dialyzer membrane. Despite achieving adequate dialysis by this measure, outcomes for patients treated with ICHHD remain poor, with high rates of complications, hospitalizations, and mortality.¹
- One factor that has long been hypothesized to contribute to poor outcomes in dialysis patients is the sub-optimal clearance of middle molecules: a group of uremic solutes with molecular weights ranging from approximately 500 Da to 58 kDa [i.e., β_2 -microglobulin (β_2 M), κ - and λ - free light chains, and TNF- α]. Because of their larger size, middle molecules cannot readily diffuse across dialyzer membranes and are thus less efficiently cleared from the circulation by current ICHHD treatments.²
- Accumulation of these may worsen outcomes for ESKD patients via multiple mechanisms, including promoting chronic inflammation, altering bone mineral metabolism, and causing cardiovascular damage. C-reactive protein (CRP), a pentameric acute-phase protein of approximately 115 kDa, is larger than albumin and is not itself appreciably removed by dialysis; it is measured here as an index of the systemic inflammation associated with middle molecule retention rather than as a directly cleared solute.³
- Given the intertwined roles of ineffective middle molecule clearance and chronic inflammation in driving poor outcomes among ICHHD patients, numerous approaches can be implemented in clinical practice that may result in lower burden of middle molecules in the body and attenuate systemic inflammation as reflected by CRP, including expanded hemodialysis (HD) with a dialyzer with larger pore sizes, yielding possible associated improvements in patient outcomes. Serial measurements of β_2 M are one plausible means of measuring middle molecule removal.⁴
- Two 2026 analyses established expanded HD as non-inferior to online hemodiafiltration: the randomized MOTHER HDx trial, for a composite of all-cause mortality and major cardiovascular events (IRR 0.87; 95% CI 0.63-1.19), and the interim CONCORDIA analysis, for all-cause mortality (HR 0.75; 95% CI 0.54-1.04).^{5,6} With both modalities converging on comparable hard clinical outcomes, the open question shifts from which modality to deliver toward which measurable solute signal, if any, tracks clinical benefit. However, to date, there is limited understanding of the association between β_2 M and CRP levels and clinical outcomes because these key analytes are not routinely measured as part of ESKD patient care in the US. In this study we seek to evaluate the association between longitudinal β_2 M and CRP dynamics and the risk of hospitalization and death in a large cohort of patients starting treatment with expanded HD.

Methods

- The CLEAR study is an ongoing prospective observational cohort study designed to characterize longitudinal serial β_2 M and CRP levels in dialysis clinics (n=120) that will transition to expanded HD.
- The study population will maintain a cross-sectional census of approximately 5,250 adult (≥ 18 years old) patients receiving ICHHD.
- During the sample collection period (Month 0 – Month 5), remnant blood from samples collected for monthly laboratory measurements as part of routine clinical care will be utilized for measurement of pre-dialysis (up to 6 measurements) and contemporaneous post-dialysis (up to 3 measurements) β_2 M concentration. In parallel, pre-dialysis CRP concentration will likewise be measured on remnant samples (up to 2 measurements) (Figure 1).

Figure 1: CLEAR study schematic

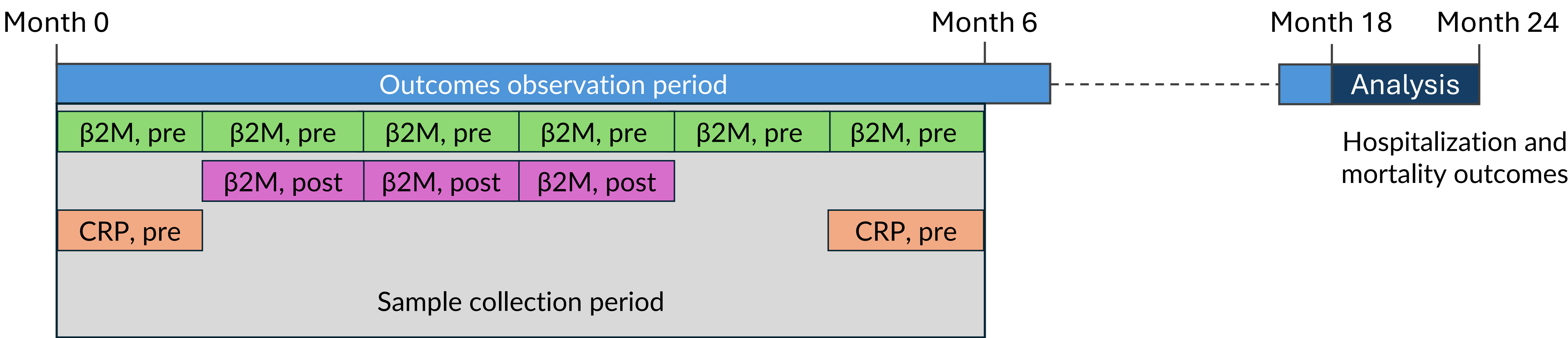


Figure 1: Within each month of the sample collection period (grey box, Month 0 – Month 5) the indicated laboratory measurements will be performed on remnant laboratory samples from participating dialysis clinics. The outcome observation period begins with the first recorded study measurement and continues until Month 18 or loss to follow-up. Following the conclusion of the observation period, data will be analyzed for outcomes. Abbreviations: β_2 M, beta 2 microglobulin; CRP, c-reactive protein; post, post-dialysis sample; pre, pre-dialysis sample.

- Patients will be followed forward through Month 18 for hospitalization and mortality events passively using existing data streams, providing at least 12 months of observation beyond each patient's final study measurement.
- β_2 M will be parameterized in multiple ways including absolute pre-dialysis levels, single treatment reduction ratios, and month-over-month change metrics. Discriminant analyses will be used to seek the parameterization that most tightly associates with the pre-specified endpoints of hospitalization and all-cause mortality. Analyses will also consider whether simultaneous consideration of Kt/V and CRP levels improves discrimination. Models will otherwise be adjusted for case-mix covariates. Analyses will be stratified by incident status: prevalent patients who were switched to expanded HD and incident patients who were started on expanded HD.

Results & Conclusions

- The first serial measurement of β_2 M and CRP levels will occur in September 2026. Earliest facilities will begin to convert at the end of September 2026. Because sample collection and the outcome observation period are ongoing, analytic results are not yet available; the principal analysis is anticipated following the close of follow-up at Month 18.
- CLEAR will provide one of the largest longitudinal characterizations of β_2 M and CRP dynamics among patients transitioning to expanded HD and will identify the β_2 M parameterization that most strongly discriminates the risk of hospitalization and death. These data will inform whether routine monitoring of middle molecule clearance can be used to guide dialysis prescription in ESKD.

References & Acknowledgements

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We specifically acknowledge Kathryn Husarek of DaVita, Inc. for editorial contributions in preparing this poster.
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Presented at the 40th Annual Meeting of the International Society of Blood Purification (ISBP) in October 2026, Rome, Italy.



40th ANNUAL MEETING OF THE
INTERNATIONAL SOCIETY OF BLOOD
PURIFICATION

