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ORIGINAL ARTICLE

The Association of Serum Free Light Chains With Mortality and Progression to End-Stage Renal Disease in Chronic Kidney Disease: Systematic Review and Individual Patient Data Meta-analysis

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Abstract

Objective: To clarify the associations between polyclonal serum free light chain (sFLC) levels and adverse outcomes in patients with chronic kidney disease (CKD) by conducting a systematic review and individual patient data meta-analyses.

Patients and Methods: On December 28, 2016, we searched 4 databases (MEDLINE, Embase, CINAHL, and PubMed) and conference proceedings for studies presenting independent analyses of associations between sFLC levels and mortality or progression to end-stage renal disease (ESRD) in patients with CKD. Study quality was assessed in 5 domains: sample selection, measurement, attrition, reporting, and funding.

Results: Five prospective cohort studies were included, judged moderate to good quality, involving 3912 participants in total. In multivariable meta-analyses, sFLC (kappa+lambda) levels were independently associated with mortality (5 studies, 3680 participants; hazard ratio [HR], 1.04 [95% CI, 1.03-1.06] per 10 mg/L increase in sFLC levels) and progression to ESRD (3 studies, 1848 participants; HR, 1.01 [95% CI, 1.00-1.03] per 10 mg/L increase in sFLC levels). The sFLC values above the upper limit of normal (43.3 mg/L) were independently associated with mortality (HR, 1.45 [95% CI, 1.14-1.85]) and ESRD (HR, 3.25 [95% CI, 1.32-7.99]).

Conclusion: Higher levels of sFLCs are independently associated with higher risk of mortality and ESRD in patients with CKD. Future work is needed to explore the biological role of sFLCs in adverse outcomes in CKD, and their use in risk stratification.

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Chronic kidney disease (CKD) is common, with an estimated prevalence of 3% to 17% in Europe and 15% in the United States.[1,2] It is associated with adverse health outcomes, including acute kidney injury, progression to end-stage renal disease (ESRD), cardiovascular disease (CVD), and mortality.[3-6] Estimated glomerular filtration rate (eGFR) and albuminuria are well-established prognostic factors in CKD that are measured routinely in clinical practice and used for risk stratification. However, there is major interest in the study of novel prognostic factors and biomarkers that could potentially improve current risk stratification methods and that may provide insights into the underlying mechanisms of adverse outcomes associated with CKD and, thereby, identify potential therapeutic targets.[7]

Polyclonal serum free light chains (sFLCs) are produced by cells of the B-cell lineage and undergo renal metabolism. Thus, sFLC levels are increased in CKD, and there are plausible mechanisms by which they may be directly

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implicated in the associated risks of mortality and ESRD.[8] However, studies published to date have reported results that are inconsistent, with variable adjustment for confounding factors, and so there remains uncertainty whether sFLC levels are independently associated with adverse outcomes in CKD.

To address this issue, we performed a systematic review and meta-analysis of individual patient data to summarize and synthesize published data on the association between sFLC levels and mortality as well as progression to ESRD in patients with CKD.

PATIENTS AND METHODS

This study was conducted in accordance with published guidelines for systematic review, analysis, and reporting of meta-analyses of observational studies.[9] It was registered a priori with PROSPERO, an international database of prospectively registered systematic reviews (accessible at http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42015025195).

Studies meeting the following criteria were included:

- Types of studies: Quantitative studies presenting an independent analysis of the association between sFLCs and mortality or ESRD in humans with CKD. Case reports and qualitative studies were not included. No restrictions on language, publication date, or publication status were imposed.
- Participants: Individuals with CKD. Participants were excluded if they were receiving dialysis or if they had monoclonal gammopathy (monoclonal gammopathy of undetermined significance or multiple myeloma).
- Exposure: Polyclonal sFLC concentration.
- Outcomes: 1) All-cause mortality and 2) ESRD, defined as initiation of renal replacement therapy (RRT).

Literature Review

We searched 4 databases (MEDLINE, 1946-present; Embase, 1947-present; CINAHL; and PubMed) using terms for CKD and immunoglobulin light chains using MeSH and related terms as free text, and we also included a term to exclude studies with *myeloma* in the title. The full search strategy for MEDLINE is shown in the Supplemental Figure (available online at http://www.mayoclinicproceedings.org). We also searched the Cochrane Library and the Centre for Reviews and Dissemination (University of York). Grey literature searching included conference proceedings and abstracts for 3 major nephrology conferences from 2012 through 2015 (UK Renal Association, European Renal Association/European Dialysis and Transplant Association, and the American Society of Nephrology Kidney Week). Authors of abstracts were contacted if relevant. We conducted reference follow-up of full-text papers. We also searched trial registers (ClinicalTrials.gov). The last search was performed on December 28, 2016. Searches and study selection processes were performed independently by 2 investigators (S.D.S.F. and A.F.) using titles and abstracts. The decision regarding inclusion was based on prespecified eligibility criteria, with differences resolved by discussion.

Data Collection

Two reviewers (S.D.S.F. and A.F.) extracted data for each study using a standardized form (based on the STROBE [Strengthening the Reporting of Observational Studies in Epidemiology] Statement checklist), including study date, location, primary aim, participant characteristics (number, CKD stage), setting (eg, primary or secondary care), main outcome, sampling method and potential sampling bias, potential confounders, presence of sample size calculation, main results (measure and magnitude of effect), method of sFLC analysis, missing data, loss to follow-up, and evidence of reporting bias, including funding source.[10] A risk-of-bias tool similar to that recommended in the Cochrane Handbook was used to judge study quality, attributing low, moderate, or high risk of bias status based on sample selection (including risk of residual confounding), measurement, attrition, reporting, and funding (S.D.S.F. and A.F. independently, with final study quality status agreed on by discussion [Supplemental Table 1, available online at http://www.mayoclinicproceedings.org]).[11]

Outcome Measures

Primary outcome measures were the adjusted hazard ratio (HR) for all-cause mortality and progression to ESRD.

Statistical Analyses

Individual patient data were obtained from all the included studies. All the studies had