Pre-Diagnostic Systemic Immune-Inflammation Index and Individual Cardiovascular-Kidney-Metabolic Conditions: Mechanism-Specific Associations in a Kidney Cancer Cohort

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Background. Inflammation is central to cardiovascular-kidney-metabolic (CKM) multimorbidity under the American Heart Association (AHA) framework, and is also implicated in cancer. CKM burden is high among people with kidney cancer, and cardiovascular disease is a leading non-cancer cause of death in this group. The Systemic Immune-Inflammation Index (SII), derived from platelet, neutrophil, and lymphocyte counts on a standard complete blood count (CBC), reflects innate, adaptive, and thrombotic activity in a single value obtained at no additional cost, and is an emerging prognostic biomarker in renal cell carcinoma. Its relationship to CKM disease has been examined at the syndrome or stage level and outside cancer populations, leaving two questions open. The purpose of this analysis was to test whether each of five individual CKM conditions is associated with pre-diagnostic SII, and whether cumulative CKM measures represent those condition-level associations.

Methods. Following University of Florida Institutional Review Board determination of non-human-subjects research (Protocol NH00049096), we analyzed de-identified data from the UF Health Integrated Data Repository, structured in the Observational Medical Outcomes Partnership (OMOP) common data model. Participants were 4,735 adults (18 years and older) with an incident kidney cancer diagnosis between September 2015 and February 2026 (index date). SII (platelets × neutrophils ÷ lymphocytes) was computed only from CBCs drawn before the index date and summarized as the per-patient median. The outcome in all models was SII. Predictors were hypertension, type 2 diabetes, obesity, dyslipidemia, and chronic kidney disease, each modeled separately in parallel linear regression on log-SII and quantile (median) regression on raw SII, adjusted for age, sex, race, smoking, insurance, and pre-diagnostic depression and anxiety. Benjamini-Hochberg correction was applied across ten tests per model family, and corrected values are reported as q values (false discovery rate adjusted p values). Adjusted models were restricted to the 2,896 participants with both a numeric age at index date and at least one computable pre-diagnostic SII. Separately, three-model mediation tested serum creatinine as a mediator of the chronic kidney disease association and statin exposure as a mediator of the dyslipidemia association. Two cumulative measures, a condition-count burden score (0 to 5) and AHA CKM stage, were then each tested as predictors of SII. Post-hoc sensitivity analyses repeated the chronic kidney disease model after excluding SII values drawn within one and within two months before the index date. Analyses used Python 3.10 (statsmodels, scipy) and R 4.4.3.

Results. Median age was 65 years (interquartile range, IQR, 57 to 72), 62.6% were male, 74.8% were White, and 17.1% Black or African American. Before the index date, hypertension was present in 43.4%, dyslipidemia in 30.9%, type 2 diabetes in 19.9%, chronic kidney disease in 19.4%, and obesity in 16.9%; median SII was 692.6 (IQR 452.0 to 1,133.4). AHA CKM stage could be assigned in 1,499 participants with at least three pre-diagnostic measurements. In adjusted models (n = 2,896), chronic kidney disease was the only condition associated with SII after correction: the adjusted median shift in SII was 74.9 units (95% CI 27.2 to 122.6; p = 0.002, q = 0.021). In the parallel linear model, the association did not reach significance (β = 0.053, p = 0.122, q = 0.342). SII is strongly right-skewed, which widens interval estimates, and the rule for following the median model where the two diverge was set before analysis. Serum creatinine accounted for 46.5% of this association, implicating renal dysfunction, whereas statin exposure accounted for 7.9% of the dyslipidemia estimate. Excluding SII values drawn within two months before the index date increased both the estimated median shift (77.8 to 98.7 to 132.1 units at zero, one, and two months) and its statistical significance (p = 0.035, 0.013, and 0.003); more frequent blood counts in the weeks preceding a cancer diagnosis are therefore an unlikely explanation. Neither the burden score (all q ≥ 0.34) nor AHA CKM stage (p = 0.54) was associated with SII.

Conclusions. A kidney-specific inflammatory signal was detectable at the condition level but not in cumulative CKM measures or stage. Inflammatory markers may be better interpreted condition by condition, and which renal pathways shift circulating immune cells remains a question for experimental work.