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From Comorbidity to Phenotype: Redefining Risk in Cardiorenal Acute Kidney Injury

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Abstract

Acute kidney injury (AKI) in hospitalized patients is increasingly recognized as part of a broader cardiorenal metabolic process rather than an isolated renal event. Heart failure (HF) and diabetes mellitus (DM) frequently coexist among patients at risk for AKI and contribute to hemodynamic, neurohormonal, and metabolic disturbances that influence clinical outcomes. However, current risk stratification approaches often evaluate these conditions independently, potentially overlooking their interactive effects.

Emerging evidence suggests that HF and DM define distinct patterns of risk among patients with AKI. HF consistently identifies a subgroup with greater illness severity, including higher risks of mortality and need for advanced supportive care. Mechanistically, reduced cardiac output, venous congestion, and neurohormonal activation contribute to renal vulnerability and impaired recovery. In contrast, DM demonstrates more heterogeneous associations. Although some observational studies have reported lower short-term mortality among patients with DM, this finding should not be interpreted as evidence of a protective effect, given the persistent susceptibility to clinically significant renal injury. Notably, the coexistence of HF and DM is associated is associated with a disproportionate increase in dialysis initiation, suggesting synergistic cardiorenal vulnerability. Collectively, these findings support a more integrated approach to risk assessment and reinforce the importance of multidisciplinary cardiorenal care in high-risk patients.

Keywords: Acute kidney injury, Cardiorenal syndrome, Heart failure, Diabetes mellitus, Risk stratification, Dialysis initiation, Cardiorenal metabolic phenotype

Commentary

Acute kidney injury (AKI) in hospitalized patients is increasingly recognized not as an isolated renal event, but as part of a broader cardiorenal metabolic process. Heart failure and diabetes mellitus frequently coexist among patients at risk for AKI, creating a complex physiological milieu characterized by hemodynamic instability, neurohormonal activation, and microvascular vulnerability [1–3]. Despite their well-established associations with adverse outcomes, these conditions are often evaluated as independent comorbidities rather than interacting determinants of cardiorenal risk. Such a reductionist approach may obscure clinically meaningful differences in prognosis and disease trajectory. In this context, emerging evidence suggests that heart failure and diabetes differentially, and in some cases synergistically, modify AKI-related outcomes [4]. These observations support a broader view of AKI as a manifestation of interconnected cardiovascular and renal dysfunction.

Phenotype-Specific Risk Patterns in AKI

Within this evolving framework, recent work examining cardiorenal metabolic phenotypes among hospitalizations complicated by acute kidney injury provides important insight into how overlapping comorbid conditions shape in-hospital outcomes. Distinct patterns emerge when heart failure and diabetes mellitus are evaluated both individually and in combination [4]. Heart failure consistently identifies a subgroup with greater illness severity, including higher risks of mortality and need for organ support, reinforcing its role as a major determinant of short-term outcomes. In contrast,

diabetes mellitus demonstrates more heterogeneous associations. Although some observational cohorts have reported lower short-term mortality among patients with diabetes, this finding should be interpreted cautiously and not viewed as evidence of a protective effect. Importantly, diabetes remains associated with substantial renal vulnerability and risk of clinically significant kidney injury. Notably, the coexistence of heart failure and diabetes reveals a disproportionate increase in the risk of dialysis initiation, suggesting a synergistic interaction that extends beyond the additive effects of either condition alone. Collectively, these observations suggest that risk in AKI is not uniformly distributed, but instead varies according to underlying cardiorenal metabolic profiles, challenging traditional approaches based on isolated comorbidity assessment.

Limitations of Current Risk Paradigms

Despite growing recognition of the bidirectional relationship between cardiac and renal dysfunction, contemporary risk stratification models in cardiology and nephrology still tend to evaluate comorbid conditions in isolation. In heart failure populations, risk prediction tools commonly incorporate renal function as a static variable without adequately accounting for the dynamic interactions among cardiac performance, metabolic disease, and susceptibility to acute kidney injury [5–7]. Likewise, many AKI prediction models focus primarily on procedural exposures or acute illness severity while underrecognizing the influence of underlying cardiometabolic disease [8–10]. As a result, the complexity of cardiorenal interactions is often reduced to discrete variables rather than viewed as part of an integrated physiological process. Emerging evidence suggests that a more integrated cardiorenal metabolic framework may better reflect real-world patient presentations, particularly among hospitalized individuals with overlapping cardiovascular and metabolic disease.

Heart Failure as a Central Driver of Risk

From a cardiovascular perspective, the prominent role of heart failure in shaping AKI-related outcomes is both biologically plausible and clinically consistent with the broader framework of cardiorenal syndrome. Heart failure increases renal vulnerability through a combination of impaired forward flow, venous congestion, and maladaptive neurohormonal activation involving the renin–angiotensin–aldosterone and sympathetic nervous systems [11–13]. These hemodynamic and hormonal perturbations not only predispose patients to kidney injury but may also impair renal recovery once injury occurs.

Importantly, the association between heart failure and adverse outcomes in AKI extends beyond kidney-specific endpoints. Patients with concomitant heart failure often exhibit greater overall physiological instability, with increased susceptibility to respiratory failure, need for mechanical ventilation, and mortality [14,15]. In this setting, AKI may be viewed less as an isolated renal process and more as a manifestation of systemic circulatory dysfunction, with heart failure serving as a major upstream contributor to illness severity and clinical trajectory.

At the same time, the bidirectional nature of cardiorenal interactions should also be recognized. Although heart failure commonly acts as a precipitating driver of renal dysfunction in hospitalized patients, primary renal diseases—including glomerular and toxic nephropathies—may themselves provoke hemodynamic instability, neurohormonal activation, and secondary cardiac dysfunction consistent with cardiorenal syndrome. Such conditions should therefore be considered when interpreting phenotype-based risk patterns centered on cardiovascular disease. This broader perspective reinforces the importance of integrated cardiorenal assessment in patients with AKI, particularly among those with underlying or decompensated heart failure.

Synergistic Risk in Heart Failure and Diabetes

The observed amplification of dialysis risk among patients with coexisting heart failure and diabetes mellitus further underscores the importance of considering interactive pathophysiology within the cardiorenal axis. Although each condition independently predisposes to renal dysfunction, their coexistence appears to confer a level of vulnerability that expected effects of either disease alone, particularly with respect to progression to severe AKI requiring renal replacement therapy [16,17].

This pattern likely reflects the convergence of hemodynamic stress and impaired renal reserve. In heart failure, renal perfusion is compromised by reduced cardiac output and venous congestion, whereas diabetes contributes chronic microvascular injury, endothelial dysfunction, and metabolic stress that diminish the kidney's adaptive capacity [18–21]. Together, these processes may lower the threshold for irreversible injury and accelerate progression from mild to severe AKI.

Clinical factors may also contribute to this association. Patients with combined heart failure and diabetes frequently present with greater volume-management complexity and metabolic derangements, which may influence thresholds for dialysis initiation. Importantly, this interaction identifies a subgroup of patients in whom AKI is not only more likely to occur, but also more likely to progress to advanced stages requiring organ support. These findings reinforce the need for heightened vigilance and proactive multidisciplinary management in this high-risk population.

Clinical Implications for Risk Stratification and Management

These risk patterns have important implications for the management of hospitalized patients with AKI. The findings suggest that clinicians should move beyond a checklist approach to comorbidities and instead adopt a more integrated assessment of cardiorenal metabolic status when estimating short-term risk. In particular, the presence of heart failure, especially when coexisting with diabetes mellitus, should prompt heightened concern for adverse clinical trajectories, including progression to dialysis and need for advanced supportive care.

Patients with combined heart failure and diabetes may benefit from earlier nephrology involvement, closer hemodynamic assessment, and more proactive optimization of volume status to reduce the risk of further renal deterioration. At the same time, reports of lower observed short-term mortality among patients with diabetes in certain observational analyses should be interpreted cautiously and not mistaken for a benign clinical course, given the persistent risk of clinically significant renal complications [4].

Incorporating cardiorenal metabolic risk profiles into bedside decision-making may improve prognostic precision and support earlier multidisciplinary collaboration between cardiology and nephrology in high-risk patients with AKI.

Future Directions and a Phenotype-Based Framework

These findings support a shift toward more integrated approaches to risk assessment and management in patients with acute kidney injury. Prospective studies incorporating granular clinical data, including hemodynamics, biomarkers, and standardized AKI staging, are needed to validate these observations and better define the temporal relationship between cardiac dysfunction and renal injury. Incorporating cardiorenal metabolic profiles into clinical risk models may improve prognostic accuracy and help identify patients most likely to benefit from targeted preventive or therapeutic strategies, particularly among individuals with coexisting heart failure and diabetes mellitus.

In parallel, therapies with established cardiovascular and renal benefits, including agents that modulate neurohormonal pathways and metabolic stress, warrant further investigation in the context of AKI prevention and recovery. These observations also reinforce the importance of early multidisciplinary collaboration between cardiology and nephrology, recognizing that AKI frequently reflects systemic cardiorenal dysfunction rather than isolated kidney injury. Viewed through this broader lens, AKI may be more effectively approached as part of an interconnected cardiovascular–renal disease process, supporting more precise and patient-centered care.

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Author Contributions

Brent Tai: Conceptualization, Investigation, Writing - Original Draft, Writing - Review & Editing; Chijioke Okonkwo: Writing - Original Draft, Writing - Review & Editing; Yaroslav Zuyev: Writing - Original Draft, Writing - Review & Editing; Derek Synder: Supervision, Writing - Review & Editing.

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