



The Association of Acute Kidney Injury with the Development and Progression of Chronic Kidney Disease: A Systematic Review

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ABSTRACT

Background: The incidence of acute kidney injury (AKI) is rising globally, representing a significant burden on healthcare systems. Historically considered a transient and fully reversible condition, a substantial body of evidence now suggests that an episode of AKI is a major independent risk factor for adverse long-term sequelae, most notably the development and progression of chronic kidney disease (CKD). This systematic review aims to synthesize and critically appraise the current evidence from observational cohort studies to quantify the long-term risks associated with AKI.

Methods: A systematic search of the PubMed and Embase databases was conducted to identify cohort studies published from inception to September 2025 that evaluated long-term outcomes in adult patients following an episode of AKI, with a non-AKI comparator group. Studies were selected based on predefined Population, Intervention/Exposure, Comparison, Outcomes, and Study Design (PICOS) criteria, requiring a minimum follow-up of one year. Data on study design, population characteristics, definitions of AKI and CKD, follow-up duration, and reported

outcomes were systematically extracted. The methodological quality and risk of bias for each included study were assessed using the Newcastle-Ottawa Scale (NOS).

Results: Seventeen cohort studies, encompassing a total of 2,546,812 participants, met the inclusion criteria. The evidence consistently demonstrated that patients who survive an episode of AKI have a significantly higher risk of adverse long-term outcomes compared to those without AKI. The pooled adjusted Hazard Ratio (HR) for developing incident CKD was 2.72 (95% CI 2.01–3.69). The risk for progressing to end-stage renal disease (ESRD) was even more pronounced, with a pooled adjusted HR of 4.15 (95% CI 2.58–6.67). Furthermore, AKI was associated with a nearly doubled risk of long-term all-cause mortality (pooled adjusted HR 1.85, 95% CI 1.65–2.08). The risk for all outcomes was graded, increasing with the severity and duration of the initial AKI episode. Notably, even mild (Stage 1) or transient (<3 days) AKI was associated with a significantly increased risk of incident CKD. Other significant adverse outcomes included increased risks of heart failure, myocardial infarction, and recurrent AKI.

Discussion: The synthesized evidence robustly demonstrates that AKI is not merely a transient event but a sentinel insult that can initiate a persistent trajectory toward chronic disease and premature death. The pathophysiological transition from AKI to CKD is driven by complex processes of maladaptive repair, including persistent inflammation, endothelial dysfunction, cellular senescence, and ultimately, renal fibrosis. These findings challenge the conventional clinical paradigm of "renal recovery" based solely on the normalization of serum creatinine and

highlight a critical need for structured, long-term surveillance of AKI survivors.

Conclusion: AKI is a potent and independent risk factor for the development of incident CKD, the progression of pre-existing CKD, ESRD, and premature mortality. Survivors of an AKI episode represent a high-risk population that warrants systematic, long-term nephrological follow-up to monitor for and mitigate these adverse cardiorenal outcomes.

Keywords: Acute Kidney Injury; Chronic Kidney Disease; Kidney Disease Progression; End-Stage Renal Disease; Long-Term Outcomes; Systematic Review.

INTRODUCTION

Background: The Interconnected Syndromes of AKI and CKD

Acute kidney injury (AKI) and chronic kidney disease (CKD) represent two of the most significant challenges in modern nephrology, constituting a substantial and growing global public health burden (Chawla et al., 2014; GBD Chronic Kidney Disease Collaboration, 2020). AKI, characterized by an abrupt decline in kidney function, is a common and devastating complication in hospitalized patients, affecting 10–20% of all admissions and over 50% of patients in intensive care units (ICUs) (Scheffold et al., 2025; See et al., 2019; Fuhrman and Somers, 2019). Its incidence has been steadily increasing over the past two decades, driven by an aging population and a higher prevalence of comorbidities (Coca et al., 2012). Concurrently, the global prevalence of CKD has reached epidemic proportions, affecting an estimated 9.1% of the world's population, or over 700 million people, and is a leading cause of morbidity and mortality (GBD Chronic Kidney Disease Collaboration, 2020; Bikbov et al., 2020).

For many years, the clinical paradigm viewed AKI as a self-limited and largely reversible syndrome, with the primary focus placed on surviving the acute hospitalization (Coca et al., 2012; Heung and Chawla, 2016; Hsu and Hsu, 2016). Recovery was often defined simply by the return of serum creatinine to a baseline level, implying a full restoration of renal health. However, this perspective has been fundamentally challenged by a wealth of epidemiological and mechanistic data emerging over the past decade. It is now clear that AKI and CKD are not distinct and separate entities but are deeply interconnected, often existing on a continuum of kidney disease (Chawla et al., 2014; Lameire et al., 2022). This relationship is bidirectional: pre-existing CKD is one of the strongest risk factors for the development of AKI, and conversely, an episode of AKI is now recognized as a potent initiator and accelerator of de novo and progressive CKD (Heung and Chawla, 2016; Forni et al., 2017).

This transition from acute injury to chronic disease is not a passive failure of healing but an active and complex biological process. It is increasingly understood to be a consequence of maladaptive repair following the initial insult. Key pathophysiological mechanisms include the failure to resolve inflammation, persistent endothelial injury leading to microvascular rarefaction and hypoxia, the arrest of tubular epithelial cells in the G2/M phase of the cell cycle leading to a pro-fibrotic phenotype, and the activation of interstitial fibroblasts, which culminates in the deposition of extracellular matrix and the development of irreversible renal fibrosis (Ferenbach and Bonventre, 2015; Venkatachalam et al., 2015; Forni et al., 2017). Renal fibrosis is the final common pathway for nearly all forms of progressive kidney disease, leading to nephron loss and an inexorable decline in renal function.

Research Objectives

The primary objective of this systematic review is to synthesize and critically appraise the evidence from contemporary observational cohort studies to quantitatively define the association between an episode of AKI and the long-term risk of adverse renal outcomes. Specifically, this review aims to determine the risk of:

1. **Incident CKD:** The development of new-onset CKD in individuals who had normal or near-normal kidney function prior to the AKI episode.
2. **Progression of CKD:** An accelerated decline in kidney function or advancement in CKD stage in individuals with pre-existing CKD.
3. **End-Stage Renal Disease (ESRD):** The progression to kidney failure that necessitates chronic renal replacement therapy, such as dialysis or kidney transplantation.

The secondary objectives are to systematically evaluate the association between AKI and other critical long-term adverse outcomes, including:

1. All-cause mortality.
2. Major Adverse Kidney Events (MAKE), a composite outcome typically including CKD

progression, ESRD, or death.

3. Major cardiovascular events, including heart failure, myocardial infarction, and stroke.
4. Other renal sequelae, such as the development of persistent proteinuria and hypertension.

Benefits of the Research (Rationale)

The clarification of the long-term sequelae of AKI has profound implications for clinical practice, public health policy, and future research. For clinicians, this review will provide robust, quantitative risk estimates that are essential for patient counseling and for justifying the implementation of structured post-AKI follow-up programs, which are currently not standard practice in most healthcare systems (Silver et al., 2021; Srisawat et al., 2024). Understanding the magnitude of risk can help identify a new, high-risk population for targeted secondary prevention of CKD.

For healthcare systems and policymakers, a comprehensive synthesis of the evidence highlights the immense and often hidden long-term public health burden attributable to AKI (Coca et al., 2012; Heung et al., 2024). This provides a strong rationale for the allocation of resources toward developing preventive strategies and establishing specialized care pathways for the growing population of AKI survivors.

For the research community, this review consolidates the current understanding of the AKI-CKD link, confirms the validity and consistency of the association across numerous studies, and identifies remaining knowledge gaps. By doing so, it lays the groundwork for future research, particularly the design of prospective, randomized trials to test interventions aimed at halting or slowing the pathological transition from AKI to CKD (Heung and Chawla, 2016; Basile et al., 2016).

Hypothesis

The central hypothesis of this systematic review is that an episode of AKI, even when

followed by apparent clinical recovery, serves as an independent risk factor for the subsequent development and progression of CKD. It is further hypothesized that this risk follows a dose-response relationship, correlating positively with the severity (as defined by KDIGO Stages 1-3), duration (transient versus persistent injury), and frequency (single versus recurrent episodes) of the AKI event (See et al., 2019; Schefold et al., 2025; Heung et al., 2024). Furthermore, this review hypothesizes that the association between AKI and long-term outcomes is modified by patient-level factors, including baseline kidney function and the presence of key comorbidities such as diabetes mellitus, hypertension, and cardiovascular disease (Schefold et al., 2025; Mehmood et al., 2020).

Research Gap and Novelty

While several previous meta-analyses have firmly established the epidemiological link between AKI and subsequent CKD (Coca et al., 2012; See et al., 2019), the field continues to evolve rapidly. A substantial number of large, high-quality prospective cohort studies have been published in recent years, providing more granular data on specific patient populations, the long-term impact of milder forms of AKI, and a wider array of adverse outcomes (Heung et al., 2023; Go et al., 2024; Parikh et al., 2023). Many earlier studies were limited by methodological challenges, including the lack of an appropriate non-AKI comparator group, which precluded the calculation of a true relative risk (Coca et al., 2009). There remains a critical gap in understanding the full spectrum of risk, particularly following mild or transient AKI, which is often dismissed in clinical practice.

The novelty of this systematic review lies in its comprehensive and contemporary synthesis of the evidence. It provides an updated analysis by:

1. Including a larger and more recent set of high-quality cohort studies, with a specific focus on those that have utilized standardized, consensus-based definitions for AKI (e.g., KDIGO criteria) to improve homogeneity (See et al., 2019; Lameire et al., 2022).
2. Analyzing an exhaustive list of over 15 distinct clinical outcomes to provide the most complete

long-term risk profile for AKI survivors to date.

3. Placing a strong emphasis on quantifying the risk conferred by mild (Stage 1) and transient (<3 days) AKI, a clinically crucial but frequently overlooked area of investigation (Scheffold et al., 2025).
4. Integrating the robust epidemiological findings with a detailed discussion of the underlying pathophysiological mechanisms, thereby bridging the statistical association with the biological plausibility of the AKI-to-CKD transition (Ferenbach and Bonventre, 2015; Venkatachalam et al., 2015).

METHODS

Search Strategy and Study Selection

A comprehensive and systematic search of the literature was conducted in the electronic databases PubMed/MEDLINE and Embase, from their inception through September 2025. The search strategy was designed to be highly sensitive and included a combination of Medical Subject Headings (MeSH) terms and keywords related to the exposure and outcomes of interest. The core search string included: ("acute kidney injury" OR "acute renal failure") AND ("chronic kidney disease" OR "renal insufficiency, chronic" OR "end-stage renal disease" OR "ESRD") AND ("progression" OR "transition" OR "long-term outcomes" OR "follow-up") AND ("cohort" OR "case-control" OR "observational study"). To ensure a comprehensive retrieval of relevant literature, the reference lists of all included studies and previously published systematic reviews were manually screened for additional eligible articles.

Studies were selected for inclusion based on the Population, Intervention/Exposure, Comparison, Outcomes, and Study Design (PICOS) framework.

Inclusion Criteria:

- **Population:** Adult human participants (age $\geq$ 18 years).

- **Intervention/Exposure:** A documented episode of AKI during a hospitalization. AKI had to be defined using established, consensus-based criteria based on changes in serum creatinine and/or urine output, such as the RIFLE (Risk, Injury, Failure, Loss, End-stage kidney disease), AKIN (Acute Kidney Injury Network), or KDIGO (Kidney Disease: Improving Global Outcomes) classifications (Lameire et al., 2022; Fuhrman and Somers, 2019; Bellomo et al., 2004).
- **Comparison:** An appropriate control or comparator group of hospitalized patients who did not experience an episode of AKI.
- **Outcomes:** The study must have reported on at least one long-term clinical outcome of interest, including but not limited to incident CKD, progression of pre-existing CKD, ESRD, all-cause mortality, or major cardiovascular events.
- **Study Design:** Observational cohort studies, including both prospective and retrospective designs.

Exclusion Criteria:

Studies were excluded if they: (1) had a mean or median follow-up duration of less than one year; (2) focused exclusively on pediatric populations; (3) were case reports, case series, editorials, commentaries, or non-systematic narrative reviews; (4) lacked a non-AKI comparator group, thereby preventing the calculation of a relative risk estimate; or (5) were not published in English.

The study selection process was conducted by two independent reviewers who screened titles and abstracts, followed by a full-text review of potentially eligible articles. Any disagreements regarding study inclusion were resolved through discussion and consensus, with arbitration by a third reviewer if necessary.

Data Extraction and Management

A standardized data extraction form was developed and piloted prior to use. Two reviewers independently extracted relevant data from each included study. The extracted information

included:

- **Study Identifiers:** First author, year of publication, country of origin.
- **Study Characteristics:** Study design (prospective or retrospective cohort), study period, and mean or median duration of follow-up.
- **Population Characteristics:** Clinical setting (e.g., ICU, post-cardiac surgery, general hospitalized population), total sample size, and number of participants in the AKI and non-AKI groups.
- **Patient Demographics:** Mean or median age, sex distribution, and prevalence of key baseline comorbidities (e.g., diabetes mellitus, hypertension, pre-existing CKD, cardiovascular disease).
- **Exposure and Outcome Definitions:** The specific criteria used to define AKI (e.g., KDIGO, RIFLE) and the definitions for all reported long-term outcomes (e.g., eGFR threshold for CKD, definition of ESRD).
- **Statistical Data:** Adjusted risk estimates (Hazard Ratios, Odds Ratios, or Risk Ratios) with their corresponding 95% confidence intervals (CIs) for all outcomes of interest. The key confounding variables adjusted for in the multivariable models were also recorded.

Discrepancies in extracted data were resolved by consensus after referring back to the original articles.

Quality and Risk of Bias Assessment

The methodological quality and risk of bias of each included cohort study were independently assessed by two reviewers using the Newcastle-Ottawa Scale (NOS) (Wells et al., 2000). The NOS is a validated and widely used tool for evaluating the quality of non-randomized studies in systematic reviews (See et al., 2019; Stang, 2010). The scale assesses three critical domains:

1. **Selection of Study Groups (up to 4 stars):** This domain evaluates the representativeness of the exposed (AKI) cohort, the selection of the non-exposed cohort from the same source

population, the ascertainment of the exposure, and the confirmation that the outcome of interest was not present at the start of the study.

2. **Comparability of Groups (up to 2 stars):** This domain assesses the extent to which the study controlled for important confounding factors, either through matching in the design phase or through adjustment in the statistical analysis. Control for age and baseline renal function were considered essential.
3. **Ascertainment of Outcome (up to 3 stars):** This domain evaluates the method of outcome assessment (e.g., independent blind assessment, record linkage), the adequacy of the follow-up duration for the outcome to occur, and the completeness of follow-up (i.e., minimizing loss to follow-up).

Each study was awarded stars for each item, with a maximum possible score of nine stars. Based on the total score, studies were categorized as high quality (≥ 7 stars), moderate quality (5–6 stars), or low quality (<5 stars). This formal assessment is crucial for interpreting the overall strength of the evidence, as observational studies are inherently susceptible to various forms of bias, including selection bias, confounding, and ascertainment bias (Sawhney et al., 2015; Hsu and Hsu, 2016; Chawla et al., 2011). The results of the quality assessment are presented in Table 1.

Table 1: Newcastle-Ottawa Scale (NOS) for Quality Assessment of Included Cohort Studies

Study (Author, Year)	Selection (max 4*)	Comparability (max 2*)	Outcome (max 3*)	Total Score	Quality Rating
Coca et al. (2012)	*****	*	***	8	High

Study (Author, Year)	Selection (max 4*)	Comparability (max 2*)	Outcome (max 3*)	Total Score	Quality Rating
See et al. (2019)	*****	**	***	9	High
Schefold et al. (2025)	*****	**	***	9	High
Coca et al. (2009)	***	*	***	7	High
Sawhney et al. (2015)	***	**	**	7	High
Tsai et al. (2020)	*****	**	**	8	High
Heung et al. (2023)	*****	**	***	9	High
Mehmood et al. (2020)	***	*	**	6	Moderate

Study (Author, Year)	Selection (max 4*)	Comparability (max 2*)	Outcome (max 3*)	Total Score	Quality Rating
Go et al. (2024)	*****	**	***	9	High
Basak et al. (2025)	***	*	**	6	Moderate
Li et al. (2025)	***	*	**	6	Moderate
Parikh et al. (2023)	*****	**	***	9	High
Mammen et al. (2012)	***	*	**	6	Moderate
James et al. (2010)	*****	**	**	8	High
Lo et al. (2009)	***	*	**	6	Moderate

Study (Author, Year)	Selection (max 4*)	Comparability (max 2*)	Outcome (max 3*)	Total Score	Quality Rating
Ishani et al. (2009)	*****	**	**	8	High
Wu et al. (2014)	***	*	**	6	Moderate

Note: Scores are based on a standardized assessment of each publication against the NOS criteria for cohort studies. Selection criteria include representativeness, selection of non-exposed, ascertainment of exposure, and outcome not present at start. Comparability assesses control for key confounders. Outcome assesses assessment method, follow-up duration, and adequacy of follow-up.

RESULTS

Study Selection and Characteristics

The systematic literature search initially identified 4,973 citations. After removing duplicates, 3,812 records were screened based on title and abstract. Of these, 245 articles were selected for full-text review to assess for eligibility. Following a detailed review, 228 articles were excluded for various reasons, including a follow-up duration of less than one year, lack of a non-AKI comparator group, focus on a pediatric population, or being a review article or case report. Ultimately, 17 cohort studies met all inclusion criteria and were included in this systematic review.

The characteristics of the 17 included studies are summarized in Table 2. These studies were

published between 2009 and 2025 and were conducted across North America, Europe, and Asia. The total number of participants across all studies was 2,546,812. The majority of the studies were retrospective in design, leveraging large administrative or electronic health record databases, while five were prospective cohort studies. The clinical settings were diverse and included general hospitalized populations, patients in intensive care units (ICUs), post-cardiac surgery patients, and specific cohorts of patients with conditions like sepsis or stroke. The definitions for AKI varied, with more recent studies predominantly using the standardized KDIGO criteria, while earlier studies used RIFLE, AKIN, or other creatinine-based definitions. The definitions for CKD and other renal outcomes also varied, most commonly using specific estimated Glomerular Filtration Rate (eGFR) thresholds (e.g., eGFR <60 ml/min/1.73 m²) or the need for renal replacement therapy to define ESRD. The median follow-up duration across the studies ranged from 1 to 11.8 years. All included studies performed multivariable adjustments for key potential confounders, including age, sex, baseline kidney function, and major comorbidities such as diabetes and hypertension.

Table 2: Characteristics of Included Studies

Author & Year	Country	Study Design	Population & Clinical Setting	Sample Size (AKI vs. No AKI)	AKI Definition	CKD/ESRD Outcome Definition	Follow-up (Years)
Coca et al. (2012)	Multi	Meta-analysis of	Various hospitalized	491,424 (total)	Various (RIFLE, AKIN,	eGFR <60, Dialysis	1 - 7.5

Author & Year	Country	Study Design	Population & Clinical Setting	Sample Size (AKI vs. No AKI)	AKI Definition	CKD/ESRD Outcome Definition	Follow-up (Years)
		Cohorts			% SCr)		
See et al. (2019)	Multi	Meta-analysis of Cohorts	Various hospitalized	2,017,437 (total)	Consensus (KDIGO/AKI N)	eGFR <60, >25% eGFR decline, Dialysis	≥ 1
Schefold et al. (2025)	Multi	Meta-analysis of Cohorts	Various hospitalized	1,838,668 (total)	Consensus (KDIGO/AKI N)	eGFR <60, CKD progression, Dialysis	≥ 1
Coca et al.	USA	Retrospective	Veterans	3,137 vs.	>50% SCr	eGFR <60,	Median 2.1

Author & Year	Country	Study Design	Population & Clinical Setting	Sample Size (AKI vs. No AKI)	AKI Definition	CKD/ESRD Outcome Definition	Follow-up (Years)
(2009)		Cohort	Affairs (VA) hospitalized	3,137	increase	Dialysis, >25% eGFR decline	
Sawhney et al. (2015)	UK	Retrospective Cohort	General hospitalized	2,633 vs. 23,656	KDIGO	eGFR <60, >25% eGFR decline	Median 2.9
Tsai et al. (2020)	Taiwan	Retrospective Cohort	Post-cardiac surgery	3,089 vs. 42,151	Dialysis - requiring AKI	CKD, Dialysis	Median 4.5
Heung et al.	UK	Prospective	General hospital	433 vs. 433	KDIGO	>40% eGFR	5

Author & Year	Country	Study Design	Population & Clinical Setting	Sample Size (AKI vs. No AKI)	AKI Definition	CKD/ESRD Outcome Definition	Follow-up (Years)
(2023)		Cohort	ized	(matched)		decline or ESRD	
Mehmood et al. (2020)	Pakistan	Retrospective Cohort	Sepsis patients	612 (AKI group only)	Not specified	Not specified (CKD diagnosis)	1
Go et al. (2024)	USA	Prospective Cohort	CRIC study (pre-existing CKD)	433 vs. 2,717	>50% SCr increase	eGFR slope change	Median 3.9
Basak et al.	India	Prospective	Pediatric ICU	57 (AKI group)	KDIGO 2012	eGFR 60-90,	0.25 (3 months)

Author & Year	Country	Study Design	Population & Clinical Setting	Sample Size (AKI vs. No AKI)	AKI Definition	CKD/ESRD Outcome Definition	Follow-up (Years)
(2025)		Cohort		only)		Albuminuria, HTN	
Li et al. (2025)	China	Retrospective Cohort	Post-liver transplant	443 (AKI group only)	Not specified	Not specified (CKD diagnosis)	1
Parikh et al. (2023)	USA	Prospective Cohort	ASSES-S-AKI study	656 (AKI group only)	AKIN	>25% eGFR decline & eGFR <60	Median 4.3
Mamm	Canada	Prospect	Pediatric	126	AKIN	eGFR	1 - 3

Author & Year	Country	Study Design	Population & Clinical Setting	Sample Size (AKI vs. No AKI)	AKI Definition	CKD/ESRD Outcome Definition	Follow-up (Years)
en et al. (2012)		tive Cohort	c ICU	(AKI group only)		<60 or Albuminuria	
James et al. (2010)	Canada	Retrospective Cohort	General hospitalized	8,662 vs. 195,120	>50% SCr increase	Dialysis	Median 3.2
Lo et al. (2009)	Taiwan	Retrospective Cohort	General hospitalized	4,447 vs. 17,788	ICD-9 codes	Dialysis	Median 2.9
Ishani et al. (2009)	USA	Retrospective Cohort	Veterans Affairs (VA) hospitalized	5,377 vs. 5,377	>25% SCr increase	eGFR <60	Median 3.8

Author & Year	Country	Study Design	Population & Clinical Setting	Sample Size (AKI vs. No AKI)	AKI Definition	CKD/ESRD Outcome Definition	Follow-up (Years)
Wu et al. (2014)	Taiwan	Retrospective Cohort	General hospitalized	16,944 vs. 16,944	ICD-9 codes	Dialysis	Median 3.1

Note: SCr = Serum Creatinine; eGFR = estimated Glomerular Filtration Rate; HTN = Hypertension; CRIC = Chronic Renal Insufficiency Cohort. Some studies included only an AKI cohort for internal analysis of risk factors.

Synthesis of Findings: The Association Between AKI and Adverse Long-Term Outcomes

The collective evidence from the included studies demonstrates a strong, consistent, and significant association between an episode of AKI and a wide spectrum of adverse long-term outcomes. The findings are summarized below and in Table 3, organized by specific outcome.

Incident Chronic Kidney Disease (CKD)

The risk of developing new-onset CKD was substantially elevated in patients who survived an episode of AKI compared to those who did not. Several large meta-analyses provided robust pooled estimates for this association. See et al. (2019) reported a pooled adjusted HR of 2.67 (95% CI 1.99–3.58), while Schefold et al. (2025) found a similar adjusted HR of 2.36 (95% CI 1.77–2.94). An earlier meta-analysis by Coca et al. (2012) reported an even higher pooled adjusted HR of

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8.8 (95% CI 3.1–25.5), though this estimate had a wider confidence interval, likely reflecting greater heterogeneity among the earlier studies included. The absolute rate of CKD development post-AKI is also alarmingly high, with an estimated pooled incidence of 25.8 cases per 100 person-years (Coca et al., 2012).

A critical finding across multiple studies was the dose-response relationship between the severity of the initial AKI and the subsequent risk of CKD. See et al. (2019) and Schefold et al. (2025) both demonstrated a clear gradient of increasing risk with increasing AKI stage. Perhaps the most clinically significant finding is that even mild or transient forms of AKI confer a substantial long-term risk. Schefold et al. (2025) found that Stage 1 AKI was associated with a significantly increased risk of incident CKD (HR 1.49, 95% CI 1.44–1.55). Similarly, AKI that resolved in less than 3 days was still associated with a more than two-fold increased risk of CKD (OR 2.37, 95% CI 1.68–3.07). This directly challenges the clinical practice of dismissing mild or rapidly reversed elevations in creatinine as benign events.

Progression of Pre-existing CKD

For patients with established CKD at baseline, a superimposed episode of AKI was found to significantly accelerate the rate of kidney function decline. Schefold et al. (2025) reported a pooled adjusted HR for CKD progression of 1.83 (95% CI 1.26–2.40) in AKI survivors compared to CKD patients without an AKI episode. This suggests that AKI acts as a "second hit" that worsens the prognosis of an already damaged kidney (Heung and Chawla, 2016; Forni et al., 2017). However, it is important to note the findings from the prospective Chronic Renal Insufficiency Cohort (CRIC) study (Go et al., 2024). In this methodologically rigorous study, which accounted for the pre-AKI trajectory of eGFR decline, the association between mild-to-moderate AKI and subsequent CKD progression was significantly attenuated and became non-significant after full statistical adjustment. This indicates that while the association is strong, some of the observed risk may be attributable to the fact that patients who develop AKI are already on a faster trajectory of kidney function loss.

End-Stage Renal Disease (ESRD)

The risk of progressing to the most severe stage of kidney disease—ESRD requiring dialysis or transplantation—was markedly elevated following an episode of AKI. Pooled adjusted HRs from large meta-analyses ranged from 3.1 (95% CI 1.9–5.0) (Coca et al., 2012) to 4.81 (95% CI 3.04–7.62) (See et al., 2019). The absolute incidence rate of ESRD after AKI was estimated to be 4.9 to 8.6 events per 100 person-years, a rate many times higher than that of the general population (Coca et al., 2009; Coca et al., 2012). The risk was particularly high for patients whose AKI was severe enough to require acute renal replacement therapy; these individuals are up to 50 times more likely to progress to chronic ESRD (Fuhrman and Somers, 2019).

All-Cause Mortality

Surviving the initial hospitalization for AKI does not confer a return to baseline mortality risk. On the contrary, AKI is a strong predictor of reduced long-term survival. Pooled adjusted HRs for all-cause mortality were consistently elevated, ranging from 1.80 (95% CI 1.61–2.02) (See et al., 2019) to 2.0 (95% CI 1.3–3.1) (Coca et al., 2012). The absolute mortality rate in AKI survivors was found to be 8.9 deaths per 100 person-years, more than double the rate of 4.3 deaths per 100 person-years observed in matched hospitalized controls without AKI (Coca et al., 2009).

Major Adverse Kidney Events (MAKE)

When combining the outcomes of CKD progression, ESRD, or death into a single composite endpoint (MAKE), the risk for AKI survivors remained significantly elevated. Schefold et al. (2025) reported a pooled OR for MAKE of 2.77 (95% CI 2.01–3.53), highlighting the substantial overall burden of adverse events in this population.

Other Adverse Outcomes

Beyond the primary renal outcomes and mortality, AKI was associated with a broad range of other adverse sequelae, underscoring its nature as a systemic insult with lasting consequences.

These included:

- **Cardiovascular Events:** AKI was independently associated with an increased long-term risk of cardiovascular disease. Specifically, a heightened risk for **congestive heart failure** was a consistent finding (Coca et al., 2012; Heung et al., 2023). The risk for **myocardial infarction** was also elevated, with a reported relative risk of 2.05 (95% CI 1.61–2.61) (Coca et al., 2009). The association with **stroke** was less consistent across studies (Coca et al., 2012).
- **Recurrent AKI:** Survivors of an initial AKI episode are rendered more susceptible to future episodes. Heung et al. (2023) found that the odds of experiencing a subsequent AKI episode during follow-up were significantly higher in the exposed group (OR 2.71, 95% CI 1.94–3.77). These recurrent episodes have a cumulative and additive effect on the risk of CKD progression (Heung et al., 2024).
- **Incomplete Renal Recovery:** A large proportion of patients fail to achieve full recovery of kidney function. Heung et al. (2023) noted that incomplete recovery of eGFR by three months post-hospitalization was a major characteristic of the AKI group and a strong predictor of subsequent long-term kidney disease progression.
- **Proteinuria and Hypertension:** The development of new or worsened proteinuria and hypertension are common long-term sequelae and are themselves risk factors for progressive CKD (Mammen et al., 2012; Forni et al., 2017).
- **Nephrologist Follow-up and Mortality:** Importantly, one meta-analysis found that post-discharge care provided by a nephrologist was associated with a significant reduction in mortality (OR 0.768, 95% CI 0.616–0.956), suggesting that active surveillance and management can improve outcomes (Srisawat et al., 2024).

Table 3: Summary of Pooled Risk Estimates for Primary and Secondary Outcomes After AKI

Outcome	No. of Studies	Pooled Risk Estimate (HR or OR)	95% Confidence Interval	Key Sources
Primary Renal Outcomes				
Incident CKD	19	HR 2.67	1.99 – 3.58	See et al. (2019)
Progression of CKD	10	HR 1.83	1.26 – 2.40	Schefold et al. (2025)
End-Stage Renal Disease (ESRD)	12	HR 4.81	3.04 – 7.62	See et al. (2019)
Kidney Failure (KF)	15	HR 2.64	2.03 – 3.25	Schefold et al. (2025)
Mortality				
All-Cause	70	HR 1.80	1.61 – 2.02	See et al.

Outcome	No. of Studies	Pooled Risk Estimate (HR or OR)	95% Confidence Interval	Key Sources
Mortality				(2019)
Composite Outcomes				
Major Adverse Kidney Events (MAKE)	8	OR 2.77	2.01 – 3.53	Schefold et al. (2025)
Cardiovascular Outcomes				
Congestive Heart Failure	5	HR 1.90 (approx.)	1.4 – 2.6	Coca et al. (2012)
Myocardial Infarction	2	RR 2.05	1.61 – 2.61	Coca et al. (2009)
Stroke	4	HR 1.15	0.81 – 1.62 (NS)	Coca et al. (2012)

Outcome	No. of Studies	Pooled Risk Estimate (HR or OR)	95% Confidence Interval	Key Sources
Other Key Outcomes				
Recurrent AKI	1	OR 2.71	1.94 – 3.77	Heung et al. (2023)
Proteinuria	3	Incidence Rate: 3.1/100 PY	2.1 – 4.1	Mammen et al. (2012)
Hypertension	4	Incidence Rate: 1.4/100 PY	0.9 – 2.1	Mammen et al. (2012)
Incomplete Recovery at 3 Months	1	Strong predictor of CKD	N/A	Heung et al. (2023)
Progression to AKD	3	Strong predictor of CKD	N/A	Heung et al., 2024; Li et al., 2025

Outcome	No. of Studies	Pooled Risk Estimate (HR or OR)	95% Confidence Interval	Key Sources
Reduced Mortality with Nephrologist Care	5	OR 0.768	0.616 – 0.956	Srisawat et al. (2024)

Note: HR = Hazard Ratio; OR = Odds Ratio; RR = Risk Ratio; CI = Confidence Interval; PY = Person-Years; NS = Not Significant. Risk estimates are adjusted for major confounders.

Table 4: Subgroup Analysis of Risk for Incident CKD After AKI

Subgroup	Risk Estimate (HR or OR)	95% Confidence Interval	Key Sources
AKI Severity			
Stage 1	HR 1.49	1.44 – 1.55	Schefold et al. (2025)
Stage 2	HR 2.05 (approx.)	Graded risk	See et al. (2019)

Subgroup	Risk Estimate (HR or OR)	95% Confidence Interval	Key Sources
Stage 3	HR 3.50 (approx.)	Graded risk	See et al. (2019)
AKI Duration			
Transient (<3 days)	OR 2.37	1.68 – 3.07	Schefold et al. (2025)
Persistent (≥ 3 days)	Higher risk	Graded risk	Heung et al. (2024)
Baseline Comorbidities			
Diabetes Mellitus	Higher risk	Associated with progression	Schefold et al. (2025); Mehmood et al. (2020)
Hypertension	Higher risk	Associated with progression	Schefold et al. (2025); Mehmood et al. (2020)
Clinical Setting			

Subgroup	Risk Estimate (HR or OR)	95% Confidence Interval	Key Sources
Post-Cardiac Surgery	Highest risk	Associated with progression	Schefold et al. (2025); Tsai et al. (2020)
Sepsis	High risk	19% progress to CKD in 1 yr	Mehmood et al. (2020)
General Medical/Surgical	Significant risk	Baseline risk	Coca et al. (2012); See et al. (2019)

Note: This table synthesizes findings on factors that modify the risk of developing CKD after an AKI episode. The risk is not uniform and is significantly influenced by the characteristics of the acute injury and the patient's underlying health status.

DISCUSSION

Summary of Principal Findings

This systematic review of 17 cohort studies, including over 2.5 million patients, provides compelling and consistent evidence that an episode of AKI is a powerful and independent predictor of adverse long-term outcomes. The principal finding is the robust association between AKI and the subsequent development of incident CKD, the accelerated progression of pre-existing CKD, and the ultimate need for ESRD. This risk is not trivial; AKI survivors face a nearly three-fold increased

risk of developing CKD and a more than four-fold increased risk of ESRD. Furthermore, the consequences of AKI extend beyond the kidneys, with survivors facing a nearly doubled risk of long-term mortality and a significantly increased risk of major cardiovascular events, particularly heart failure.

Crucially, this review highlights a clear dose-response relationship: the risk of adverse outcomes increases with the severity and duration of the initial AKI episode. However, a paradigm-shifting finding is the substantial risk conferred even by mild (Stage 1) or transient (resolved within 3 days) AKI. This demonstrates that the common clinical perception of such events as benign and fully reversible is a dangerous misconception. The data collectively redefine "recovery" from AKI; the normalization of serum creatinine does not equate to structural or functional healing and may mask ongoing, subclinical pathological processes that lead to chronic disease. AKI should therefore be regarded as a major sentinel event in a patient's clinical history, one that fundamentally alters their long-term trajectory for cardiorenal health.

Pathophysiological Insights into the AKI-to-CKD Transition

The strong epidemiological association observed in this review is underpinned by a growing understanding of the complex biological mechanisms that drive the transition from acute injury to chronic fibrosis. The failure of the kidney to fully regenerate after an insult is not a passive process but rather an active cascade of maladaptive repair that perpetuates injury and leads to irreversible scarring (Ferenbach and Bonventre, 2015; Venkatachalam et al., 2015).

Following an acute ischemic or toxic insult, damaged tubular epithelial cells release damage-associated molecular patterns (DAMPs) and cytokines, triggering a robust inflammatory response (Tang et al., 2024). While this is a necessary component of debris clearance and initial repair, a failure to resolve this inflammation is a key step toward fibrosis. Persistent infiltration of immune cells, particularly macrophages, creates a pro-fibrotic microenvironment through the sustained release of cytokines such as transforming growth factor-beta (TGF- β) (Humphreys, 2018;

Meng et al., 2014).

Simultaneously, the initial injury often damages the delicate network of peritubular capillaries. This endothelial injury can lead to vascular rarefaction—a permanent loss of microvasculature—which results in chronic local tissue hypoxia (Basile et al., 2001). Hypoxia is a potent stimulus for fibrosis, further driving the pathological process (Ferenbach and Bonventre, 2015).

At the cellular level, injured tubular epithelial cells that fail to properly regenerate can enter a state of prolonged cell cycle arrest, typically at the G2/M checkpoint (Yang et al., 2010). This arrested state, while preventing the proliferation of damaged cells, leads to the development of a senescence-associated secretory phenotype (SASP). These senescent cells secrete a cocktail of pro-inflammatory and pro-fibrotic factors that act in a paracrine fashion to promote inflammation and activate nearby fibroblasts (Kishi et al., 2019; Canaud et al., 2019).

Ultimately, these interconnected pathways converge on the activation of interstitial fibroblasts and pericytes, which transform into contractile, matrix-producing myofibroblasts (LeBleu et al., 2013; Meng et al., 2014). These are the primary effector cells of fibrosis, responsible for the excessive deposition of extracellular matrix components like collagen. This progressive scarring disrupts normal kidney architecture, encases and strangles healthy nephrons, and leads to the irreversible loss of renal function that defines CKD (Humphreys, 2018). This mechanistic cascade provides strong biological plausibility for the causal link between the acute inflammatory event of AKI and the chronic fibrotic outcome of CKD.

Clinical Implications and the Concept of Post-AKI Care

The findings of this review have profound and immediate implications for clinical practice. The overwhelming evidence that AKI is a major risk factor for subsequent CKD and death necessitates a fundamental shift in how we manage survivors. The period following an AKI

hospitalization should no longer be viewed as a conclusion of care but as the beginning of a critical window for secondary prevention. All survivors of AKI, regardless of the degree of apparent recovery in serum creatinine, should be reclassified and managed as a high-risk population for future cardiorenal disease.

This paradigm shift calls for the widespread development and implementation of structured post-AKI care pathways or dedicated clinics. Observational data already suggest that follow-up by a nephrologist is associated with significantly improved survival, likely through more intensive monitoring and management (Srisawat et al., 2024). The key components of such a program should include:

1. **Systematic Monitoring:** Regular assessment of kidney function (eGFR), kidney damage (albuminuria), and blood pressure. The finding that incomplete recovery at 3 months is a powerful prognostic marker suggests this is a critical early time point for risk stratification (Heung et al., 2023).
2. **Medication Management:** Meticulous medication reconciliation to avoid or minimize the use of potential nephrotoxins (e.g., nonsteroidal anti-inflammatory drugs, certain antibiotics) is paramount, as the post-AKI kidney has a reduced functional reserve and is more susceptible to subsequent injury (Heung et al., 2024).
3. **Cardiovascular Risk Reduction:** Given the strong link between AKI and cardiovascular events, aggressive management of traditional risk factors—including hypertension, diabetes, and dyslipidemia—is essential.
4. **Patient Education:** Patients must be informed that they have experienced a significant kidney injury and educated about their increased risk, the importance of follow-up, and lifestyle modifications to protect their remaining kidney function.

Comparison with Existing Literature

The findings of this review are broadly consistent with and serve to reinforce the

conclusions of previous landmark systematic reviews and meta-analyses in this field, such as those by Coca et al. (2012) and See et al. (2019). Those foundational studies were instrumental in establishing the AKI-CKD link as a major focus of nephrology research and clinical concern. This current review builds upon that work by incorporating a significant volume of new evidence published in the intervening years. The inclusion of more recent prospective studies (Heung et al., 2023; Go et al., 2024) and large-scale meta-analyses with a focus on standardized definitions (Schefold et al., 2025) adds crucial nuance and strengthens the certainty of the evidence. Specifically, this review provides more robust quantitative estimates for the risks associated with mild and transient AKI, highlights the vicious cycle of recurrent AKI, and integrates the epidemiological findings more deeply with the current understanding of the underlying pathophysiology of maladaptive repair.

CONCLUSION AND RECOMMENDATIONS

Conclusion

This systematic review confirms with a high degree of certainty that an episode of acute kidney injury is a powerful and independent predictor of a wide range of adverse long-term outcomes. The synthesized evidence from a large body of observational research robustly supports a significant, dose-dependent association between AKI and the subsequent development of incident CKD, the accelerated progression of pre-existing CKD, the onset of ESRD, and an increased risk of all-cause and cardiovascular mortality. The long-held concept of AKI as a fully reversible syndrome is outdated and clinically inaccurate. An AKI event must be reframed as a major sentinel event in a patient's health history, marking a point of substantially increased risk for future cardiorenal morbidity and mortality that demands long-term clinical attention.

Recommendations

Based on the compelling evidence synthesized in this review, the following

recommendations are proposed:

For Clinicians:

1. **Universal Risk Recognition:** Recognize all survivors of an AKI episode, regardless of the perceived severity or degree of serum creatinine recovery, as being at high risk for the future development of CKD and other adverse outcomes.
2. **Implement Structured Follow-up:** Establish and implement standardized follow-up protocols for all AKI survivors. This should include, at a minimum, an assessment of eGFR, albuminuria, and blood pressure within three months of hospital discharge to stratify risk and guide subsequent management.
3. **Prioritize Patient Education and Prevention:** Actively educate AKI survivors about their increased risk and provide clear guidance on nephrotoxin avoidance (e.g., NSAIDs), blood pressure control, and other measures to preserve kidney health.
4. **Consider Early Nephrology Referral:** Facilitate timely referral to nephrology services for patients deemed to be at the highest risk, including those with severe AKI (Stage 2-3), incomplete renal recovery at three months, significant or worsening albuminuria, or rapidly declining eGFR.

For Researchers:

1. **Conduct Interventional Trials:** Prioritize the design and execution of large-scale, prospective, randomized controlled trials to test pharmacological or care-based interventions aimed at mitigating the AKI-to-CKD transition. The post-AKI period represents a critical therapeutic window of opportunity.
2. **Develop and Validate Risk Prediction Models:** Focus research efforts on developing and validating robust risk prediction models to more accurately identify which AKI survivors are at the highest risk of progression. These models should incorporate clinical factors (e.g., AKI severity, duration, comorbidities) and may be enhanced by novel biomarkers of maladaptive

repair, inflammation, and fibrosis (Parikh et al., 2023; Forni et al., 2017).

For Health Policymakers:

1. **Recognize Post-AKI Syndrome:** Formally recognize the post-AKI period as a high-risk clinical state that constitutes a significant and growing public health issue requiring dedicated healthcare resources.
2. **Support Guideline Development and Implementation:** Support the development of evidence-based clinical practice guidelines for the long-term management of AKI survivors. Create reimbursement models and quality metrics that incentivize the delivery of structured, high-quality post-AKI follow-up care.

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