Revista Ibero-Americana de Humanidades, Ciências e Educação — REASE

doi.org/10.51891/rease.v12i9.30034

MICROVASCULAR THROMBOSIS AND ACUTE KIDNEY INJURY IN COVID-19: AN UMBRELLA REVIEW

TROMBOSE MICROVASCULAR E LESÃO RENAL AGUDA NA COVID-19: UMA REVISÃO UMBRELLA

Carolyne Assed Caires Duarte[1]
Vanessa Schnekenberg Martins Uscocovich[2]
Ivo Misael[3]
Príscila Diane Assed Caires Duarte[4]
Eduarda Baranselli Sestito[5]
Pollyanna Nicolly da Silva[6]

RESUMO: Esta revisão umbrella sintetizou evidências sobre a associação entre mecanismos microvasculares e tromboinflamatórios relacionados ao SARS-CoV-2 e lesão renal aguda (LRA), com ênfase em desfechos renais, mortalidade e terapia renal substitutiva (TRS). A revisão seguiu o PRISMA 2020 e foi registrada prospectivamente no PROSPERO (CRD42025113270l). PubMed/MEDLINE, Scopus e Embase foram pesquisados para revisões sistemáticas, meta-análises e revisões umbrella. A seleção dos estudos e a extração dos dados foram realizadas independentemente por dois revisores, o risco de viés foi avaliado com o ROBIS e a sobreposição de estudos primários entre sínteses de evidências de primeira ordem foi quantificada pela Corrected Covered Area (CCA). Seis sínteses de evidências foram incluídas. A incidência de LRA foi de 9,2% (IC 95% 4,6–13,9) em pacientes hospitalizados, 32,6% (IC 95% 8,5–56,6) em pacientes criticamente enfermos e 20% (IC 95% 14–28) em crianças com síndrome inflamatória multissistêmica. Na síntese pediátrica de MIS-C, a LRA esteve associada a maior mortalidade (OR 4,68; IC 95% 1,06–20,70). A sobreposição de estudos primários foi alta no conjunto (CCA 12,7%) e muito alta entre as sínteses de evidências em adultos (CCA 26,7%). Não foi realizado novo agrupamento estatístico nem recálculo das estimativas de efeito publicadas. As evidências atuais sustentam uma associação entre LRA relacionada à COVID-19 e desfechos adversos e são compatíveis com um papel contributivo da disfunção endotelial e da lesão tromboinflamatória, embora a inferência causal permaneça limitada pela natureza observacional das evidências, pela sobreposição e pela heterogeneidade.

Palavras-chave: COVID-19. Lesão Renal Aguda. Trombose Microvascular. SARS-CoV-2. Revisão Umbrella

[1] Acadêmica do curso de Medicina, Centro Universitário Fundação Assis Gurgacz (FAG), Cascavel, Paraná, Brasil.
[2] Médica nefrologista, Mestre e orientadora do trabalho, Centro Universitário Fundação Assis Gurgacz (FAG), Cascavel, Paraná, Brasil.
[3] Médico cirurgião vascular e orientador do trabalho, Centro Médico Vascular, Cascavel, Paraná, Brasil.
[4] Médica pediatra, Prefeitura Municipal de Toledo, Toledo, Paraná, Brasil.
[5] Acadêmica do curso de Medicina, Centro Universitário Fundação Assis Gurgacz (FAG), Cascavel, Paraná, Brasil.
[6] Acadêmica do curso de Medicina, Centro Universitário Fundação Assis Gurgacz (FAG), Cascavel, Paraná, Brasil.

ABSTRACT: This umbrella review synthesized evidence on the association between SARS-CoV-2-related microvascular and thromboinflammatory mechanisms and acute kidney injury (AKI), emphasizing renal outcomes, mortality, and renal replacement therapy (RRT). The review followed PRISMA 2020 and was prospectively registered in PROSPERO (CRD42025113270l). PubMed/MEDLINE, Scopus, and Embase were searched for systematic reviews, meta-analyses, and umbrella reviews. Study selection and data extraction were performed independently by two reviewers, risk of bias was assessed using ROBIS, and primary-study overlap among first-order evidence syntheses was quantified using the Corrected Covered Area (CCA). Six evidence syntheses were included. AKI incidence was 9.2% (95% CI 4.6–13.9) in hospitalized patients, 32.6% (95% CI 8.5–56.6) in critically ill patients, and 20% (95% CI 14–28) in children with multisystem inflammatory syndrome. In the pediatric MIS-C synthesis, AKI was associated with increased mortality (OR 4.68; 95% CI 1.06–20.70). Primary-study overlap was high overall (CCA 12.7%) and very high among adult evidence syntheses (CCA 26.7%). No de novo pooling or recalculation of published effect estimates was performed. Current evidence supports an association between COVID-19-associated AKI and adverse outcomes and is compatible with a contributory role of endothelial dysfunction and thromboinflammatory injury, although causal inference remains limited by observational evidence, overlap, and heterogeneity.

Keywords: COVID-19. Acute Kidney Injury. Microvascular Thrombosis. SARS-CoV-2. Umbrella Review

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a multisystem disorder associated with significant morbidity and mortality. Although initially characterized as a respiratory illness, accumulating evidence has demonstrated substantial extrapulmonary involvement, particularly affecting the cardiovascular, neurological, hematological, and renal systems. Among these complications, acute kidney injury (AKI) has emerged as one of the most frequent and clinically relevant manifestations, contributing to prolonged hospitalization, increased need for intensive care, and higher mortality rates (XU et al., 2021; YASEEN et al., 2021; YANG et al., 2022; TRIPATHI et al., 2023; SHAO et al., 2020; PASSONI et al., 2022; ROBBINS-JUAREZ et al., 2020; NASIRI et al., 2021).

The mechanisms underlying COVID-19-associated AKI are complex and multifactorial. Proposed pathways include direct viral invasion of renal tissues through angiotensin-converting enzyme 2 (ACE2) receptors, systemic inflammatory responses, cytokine-mediated injury, hemodynamic instability, hypoxemia, and nephrotoxic exposures.

However, increasing attention has been directed toward the role of endothelial dysfunction and microvascular thrombosis as central contributors to renal injury in patients with COVID-19.

SARS-CoV-2 infection promotes a prothrombotic state characterized by endothelial activation, complement dysregulation, platelet aggregation, and excessive inflammatory signaling. These processes contribute to thromboinflammation and the formation of microvascular thrombi in multiple organs, including the kidneys. Histopathological studies have demonstrated evidence of endothelial injury, capillary congestion, fibrin deposition, and thrombotic microangiopathy in renal tissue obtained from patients with severe COVID-19 (PRENDECKI et al., 2020; NICOLAI et al., 2020; GANDHI et al., 2022; MUKHERJEE; GHOSH; FURMENT, 2020; GHEIASI et al., 2024; BANSAL; GUBBI; MUNIYAPPA, 2020; GENCER et al., 2020; FERRARIS et al., 2020; IDILMAN et al., 2021). Such findings support the hypothesis that microvascular thrombosis may impair renal perfusion, exacerbate ischemic injury, and accelerate the progression of AKI. Despite the growing number of evidence syntheses addressing COVID-19-associated AKI, no previous review has specifically focused on integrating evidence regarding the contribution of microvascular thrombosis and thromboinflammatory mechanisms to renal injury across different evidence syntheses.

Several systematic reviews and meta-analyses have investigated the incidence, prognostic implications, and pathophysiological mechanisms of AKI in COVID-19. These studies have consistently reported associations between renal dysfunction and adverse clinical outcomes, including increased mortality and greater need for renal replacement therapy. Nevertheless, the extent to which microvascular thrombosis contributes to these outcomes remains incompletely characterized, and available evidence is dispersed across multiple evidence syntheses with varying methodologies and populations.

A comprehensive synthesis of these findings is important to clarify the relationship between microvascular thrombosis and COVID-19-associated AKI, identify consistent patterns across studies, and provide clinically relevant insights for risk stratification and patient management. Understanding the role of thromboinflammatory mechanisms may also contribute to the development of preventive and therapeutic strategies aimed at reducing renal complications in patients with COVID-19.

Therefore, the present umbrella review aimed to synthesize evidence from systematic reviews, meta-analyses, and umbrella reviews evaluating the association between SARS-CoV-

2-related microvascular thrombosis and acute kidney injury, as well as its relationship with mortality, renal replacement therapy requirements, renal function outcomes, and thromboinflammatory mechanisms.

METHODS

This study was designed as an umbrella review (overview of reviews) conducted according to the PRISMA 2020 Statement and prospectively registered in PROSPERO (CRD420251132701). The review synthesized evidence derived exclusively from previously published systematic reviews, meta-analyses, and umbrella reviews addressing the association between SARS-CoV-2-related microvascular thrombosis and acute kidney injury. No primary observational or interventional studies were directly included.

The review question was developed according to the Population, Exposure, Comparator, and Outcomes (PECO) framework. The population comprised patients with confirmed COVID-19, and the exposure of interest included microvascular thrombosis, thrombotic microangiopathy, endothelial dysfunction, and other SARS-CoV-2-associated thromboinflammatory mechanisms potentially involved in kidney injury. Comparisons, when available in the included studies, involved patients with and without thrombotic involvement or different degrees of thrombotic burden. The primary outcome was the occurrence of AKI, whereas secondary outcomes included mortality, renal replacement therapy requirements, renal function outcomes, and mechanistic evidence supporting the association between microvascular thrombosis and COVID-19-associated kidney injury. As this review synthesized evidence exclusively from previously published studies, institutional ethics committee approval was not required.

A predefined electronic literature search was conducted in PubMed/MEDLINE, Scopus, and Embase to identify systematic reviews, including meta-analyses, and umbrella reviews investigating the association between COVID-19, microvascular thrombosis, and acute kidney injury. Searches included studies published between January 2020 and March 2025, and the searches were completed in July 2025.

Search strategies combined controlled vocabulary (Medical Subject Headings [MeSH] and Emtree, when applicable) with free-text terms related to COVID-19, SARS-CoV-2, acute kidney injury, renal replacement therapy, microvascular thrombosis, thrombotic

microangiopathy, and evidence synthesis study designs. Boolean operators ("AND" and "OR") were used to combine search terms, and the syntax was adapted to the indexing requirements of each database.

Records retrieved from all databases were exported for duplicate identification before eligibility assessment. The reference lists of the included studies were manually screened to identify additional eligible publications. The complete electronic search strategies, including database-specific search strings, applied filters, search dates, and the number of retrieved records, are provided in Supplementary Material S1, in accordance with the PRISMA-S recommendations.

Eligibility criteria were established a priori according to the PECO framework. Systematic reviews, systematic reviews including meta-analyses, and umbrella reviews investigating the association between COVID-19-related thromboinflammatory or microvascular mechanisms and renal outcomes were considered eligible. Evidence syntheses including patients of any age, sex, ethnicity, geographic location, or disease severity were eligible, provided that they reported at least one predefined renal outcome.

Potential overlap of primary studies across the included evidence syntheses was formally assessed using the Corrected Covered Area (CCA), as described by Pieper et al. (2014). A citation matrix was constructed by identifying the primary studies reported in each first-order systematic review or meta-analysis. Studies were matched using author information together with sample size, study setting, and other study characteristics when necessary to distinguish publications with similar author names or sample sizes.

The CCA was calculated as $(N - r)/(rc - r)$, where N represents the total number of primary-study occurrences across the included reviews, r represents the number of unique primary studies, and c represents the number of reviews included in the overlap matrix. CCA values were interpreted as slight (0–5%), moderate (6–10%), high (11–15%), or very high (>15%) overlap.

The primary CCA analysis included the four evidence syntheses that directly incorporated and reported primary studies (Xu et al. (2021), Passoni et al. (2022), Shao et al. (2020), and Tripathi et al. (2023)). Yaseen et al. (2021) and Yang et al. (2022) were not incorporated into the primary CCA matrix because both were higher-order evidence syntheses. Yaseen et al. synthesized systematic reviews, whereas Yang et al. conducted an umbrella

review that additionally updated selected meta-analyses using a broader cohort-study evidence base. These structures were not directly comparable with the first-order systematic reviews used to construct the primary-study citation matrix; their inclusion in the same CCA calculation could therefore have mixed different levels and scopes of evidence and distorted the overlap estimate.

Because Tripathi et al. (2023) exclusively evaluated pediatric patients with multisystem inflammatory syndrome in children (MIS-C), whereas Xu et al. (2021), Passoni et al. (2022), and Shao et al. (2020) predominantly evaluated adult COVID-19 populations, an additional population-stratified CCA analysis was performed for the three adult evidence syntheses. The complete citation matrix and calculations are provided in Supplementary Material S2.

The primary outcome was acute kidney injury. Secondary outcomes included mortality, renal replacement therapy, renal function parameters, histopathological evidence of renal microvascular injury, and other clinically relevant renal outcomes associated with COVID-19. Narrative reviews, editorials, conference abstracts, expert opinions, protocols, case reports, case series, experimental animal studies, in vitro studies, and publications without relevant quantitative outcome data were excluded. Duplicate records were removed before screening, and, when overlapping evidence syntheses were identified, they were retained when they contributed clinically or methodologically relevant information; the degree of underlying primary-study overlap was subsequently quantified and explicitly considered during evidence interpretation.

Following duplicate removal, two reviewers independently screened all retrieved records in two sequential stages according to the predefined eligibility criteria. First, titles and abstracts were assessed to identify potentially relevant studies. Subsequently, the full texts of all eligible publications were independently evaluated to confirm study eligibility. Disagreements regarding study selection were resolved through discussion until consensus was reached, guided by the predefined inclusion and exclusion criteria. The study selection process was documented using the PRISMA 2020 flow diagram, including the number of records identified, screened, excluded, and included at each stage.

Data extraction was independently performed by two reviewers using a standardized data extraction form. The following information was collected from each included study: first author, year of publication, country, study design, number of included primary studies, sample

size, characteristics of the study population, renal outcomes, mortality, renal replacement therapy requirements, reported effect measures, methodological characteristics, and the main conclusions. Discrepancies were resolved through discussion until consensus was achieved. Potential overlap among systematic reviews was recorded during data extraction and subsequently quantified using the CCA rather than being used as an automatic exclusion criterion.

Risk of bias in the included evidence syntheses was assessed using the Risk Of Bias In Systematic Reviews (ROBIS) tool. ROBIS was applied across the four methodological domains of study eligibility criteria, identification and selection of studies, data collection and study appraisal, and synthesis and findings. Domain-level judgments were categorized as low, high, or unclear concern, and an overall risk-of-bias judgment was assigned based on whether the identified concerns were considered likely to materially affect the findings of each evidence synthesis. Unclear judgments were used when the published report did not provide sufficient information to support a definitive low- or high-risk classification. Detailed domain-level judgments and their methodological rationale are provided in Supplementary Material S3.

Evidence was synthesized using a structured narrative approach complemented by quantitative summary estimates extracted directly from the included evidence syntheses. No de novo meta-analysis of primary studies, statistical pooling across reviews, or recalculation of published pooled effect estimates was performed. Reported effect estimates and corresponding 95% confidence intervals for clinically relevant renal outcomes were summarized descriptively and graphically to facilitate comparison across evidence syntheses.

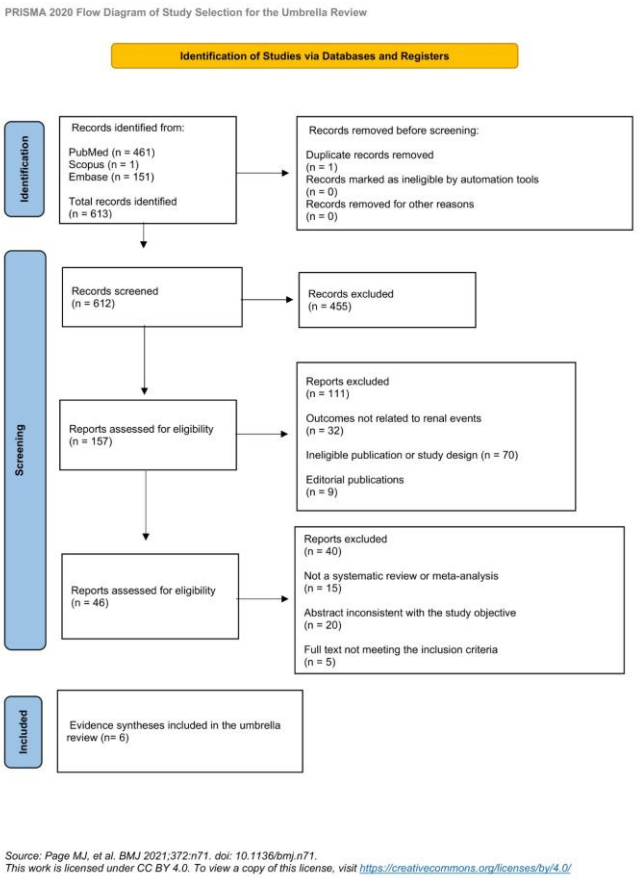
The direction, consistency, magnitude, and precision of the reported associations were interpreted while considering risk of bias, heterogeneity, and primary-study overlap. When multiple reviews addressed substantially overlapping populations or outcomes, concordant results were not treated as statistically independent replication of evidence. Greater interpretative weight was given to more comprehensive and methodologically robust evidence syntheses.

RESULTS

The electronic search conducted in PubMed/MEDLINE, Scopus, and Embase identified 613 records. After removal of one duplicate, 612 records underwent title and abstract

screening. Of these, 455 records were excluded because they did not meet the predefined eligibility criteria. A total of 157 reports were assessed for eligibility, of which 111 were excluded because they were unrelated to renal outcomes, had an editorial design, or did not meet the methodological scope of the review. Among the remaining 46 reports, 40 were further excluded because they were not systematic reviews or meta-analyses (n = 15), had abstracts inconsistent with the objective of the study (n = 20), or presented full texts incompatible with the inclusion criteria (n = 5). Ultimately, six evidence syntheses met all eligibility criteria and were included in the umbrella review. The study selection process is shown in the PRISMA 2020 flow diagram (Figure 1).

Figure 1. PRISMA 2020 flow diagram illustrating the identification, screening, eligibility assessment, and inclusion of evidence syntheses in the umbrella review.



The six included studies (XU et al., 2021; YASEEN et al., 2021; YANG et al., 2022; TRIPATHI et al., 2023; SHAO et al., 2020; PASSONI et al., 2022) were published between 2020

and 2023 and comprised systematic reviews, systematic reviews with meta-analysis, and umbrella reviews evaluating renal outcomes, thrombotic events, and microvascular mechanisms associated with COVID-19. The included evidence syntheses addressed adult hospitalized patients, critically ill patients admitted to intensive care units, and pediatric patients with multisystem inflammatory syndrome in children (MIS-C). The main characteristics and findings of the included studies are summarized in Table 1.

Table 1. Characteristics of evidence syntheses included in the umbrella review.

Author (Year)	Study Design	Population	Population Scope	AKI Definition	Primary Renal Outcomes	Main Findings
Xu Z et al. (2021)	Systematic Review and Meta-analysis	Hospitalized Adults with COVID-19	16,199 participants	KDIGO Criteria	Acute Kidney Injury (AKI) Incidence, Renal Replacement Therapy (RRT) Requirement, and Mortality	AKI was significantly associated with increased mortality; higher incidence was observed among critically ill patients.
Yaseen MO et al. (2021)	Systematic Review of Systematic Reviews	Adults with COVID-19	15 systematic reviews	Variable Definitions (Predominantly KDIGO-Based)	AKI, RRT Requirement, and Mortality	Renal complications were frequent; AKI emerged as a negative prognostic marker.
Passoni R et al. (2022)	Systematic Review and Meta-analysis	Hospitalized and Critically Ill Adults with COVID-19	18,043 participants	KDIGO Criteria	AKI, RRT Requirement, and Mortality	AKI incidence was 9.2% in general hospitalized cohorts and 32.6% among critically ill patients.

Author (Year)	Study Design	Population	Population Scope	AKI Definition	Primary Renal Outcomes	Main Findings
Tripathi AK et al. (2023)	Systematic Review and Meta-analysis	Children with Multisystem Inflammatory Syndrome (MIS-C)	6,186 pediatric patients	Pediatric KDIGO Criteria	AKI, Mortality, and Disease Severity	The pooled incidence of AKI was 20%; AKI was associated with an increased risk of mortality.
Shao M et al. (2020)	Systematic Review and Meta-analysis	Hospitalized Adults with COVID-19	24,527 participants	KDIGO Criteria	AKI, Mortality, and Disease Severity	AKI was associated with severe COVID-19 and increased mortality.
Yang L et al. (2022)	Umbrella Review	Patients with COVID-19 and populations with pre-existing kidney disease	103 reviews identified; 30 low-risk reviews included in narrative synthesis; 10 meta-analyses updated with 119 cohort studies	Variable across included reviews	AKI, CKD, kidney transplantation, mortality, and disease severity	AKI was associated with increased mortality and severe COVID-19; kidney disease was consistently associated with adverse clinical outcomes.

Four of the six included evidence syntheses directly incorporated and reported primary studies and were therefore eligible for quantitative overlap assessment. Across Xu et al. (2021), Passoni et al. (2022), Shao et al. (2020), and Tripathi et al. (2023), 116 primary-study occurrences were identified, corresponding to 84 unique primary studies. The overall Corrected Covered Area was 12.7%, indicating high overlap.

Overlap was concentrated in the adult COVID-19 evidence base. Xu et al. (2021), Passoni et al. (2022), and Shao et al. (2020) collectively contained 92 primary-study occurrences corresponding to 60 unique studies, resulting in a CCA of 26.7%, classified as very high overlap. None of the 24 pediatric MIS-C primary studies included by Tripathi et al. overlapped with the adult primary-study evidence base. Yaseen et al. (2021) and Yang et al. (2022) were analyzed

as higher-order evidence syntheses and were therefore not incorporated into the primary-study CCA calculation. The complete citation matrix is provided in Supplementary Material S2.

Risk of bias varied across the six included evidence syntheses. Tripathi et al. (2023) was judged to have low overall risk of bias. Xu et al. (2021), Yang et al. (2022), and Shao et al. (2020) were judged to have unclear overall risk of bias, primarily because of incomplete reporting of selected methodological procedures or restrictions whose influence on the findings could not be determined. Yaseen et al. (2021) and Passoni et al. (2022) were judged to have high overall risk of bias. In Yaseen et al. (2021), the principal concerns involved partially subjective eligibility criteria and quantitative synthesis across systematic reviews without formal assessment of underlying primary-study overlap. In Passoni et al. (2022), the principal concern involved post-selection exclusion of two eligible studies from the quantitative synthesis after they were considered statistical outliers, with the stated purpose of reducing heterogeneity. Detailed domain-level ROBIS assessments and methodological justifications are provided in Supplementary Material S3.

The high degree of overlap, particularly among the adult evidence syntheses, was explicitly considered during interpretation so that concordant findings arising from shared primary studies were not treated as independent replication of evidence.

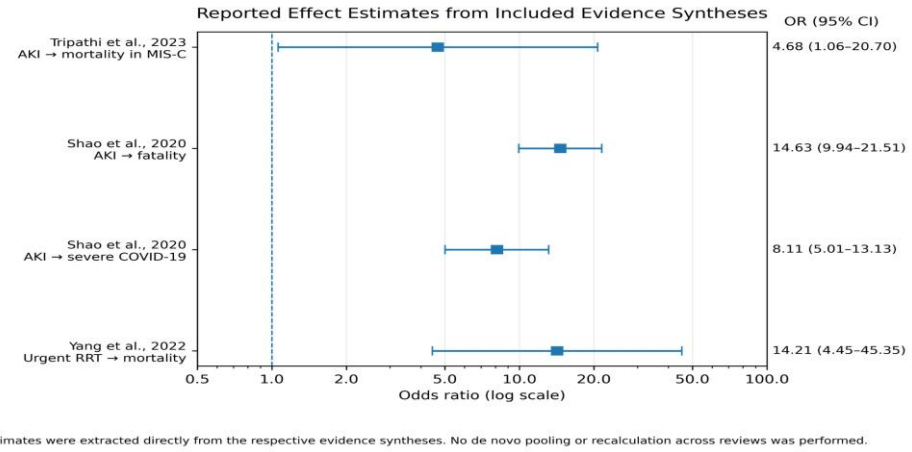
Acute kidney injury (AKI) definitions were predominantly based on Kidney Disease: Improving Global Outcomes (KDIGO) criteria, although some variability was observed across studies. The most frequently reported comorbidities among patients with AKI included hypertension, diabetes mellitus, and pre-existing chronic kidney disease.

The incidence of AKI varied according to clinical setting and disease severity. In general hospitalized cohorts, pooled AKI incidence was 9.2% (95% CI 4.6–13.9). Among critically ill patients, AKI incidence was substantially higher, reaching 32.6% (95% CI 8.5–56.6). In pediatric populations with MIS-C, the pooled incidence of AKI was 20% (95% CI 14–28). The requirement for renal replacement therapy (RRT) ranged from 3.2% to 15% across the included evidence syntheses. Mortality among patients with AKI showed wide variability, ranging from 17.0% to 83.9%, with a pooled estimate of 50.4% (95% CI 17.0–83.9).

Selected quantitative effect estimates that could be directly verified in the included evidence syntheses are summarized in Figure 2. In the pediatric MIS-C synthesis by Tripathi et al. (2023), AKI was associated with increased mortality (OR 4.68; 95% CI 1.06–20.70). Shao

et al. (2020) reported associations between AKI and both fatality (OR 14.63; 95% CI 9.94–21.51) and severe COVID-19 (OR 8.11; 95% CI 5.01–13.13). In the umbrella review by Yang et al. (2022), urgent renal replacement therapy was associated with increased mortality (OR 14.21; 95% CI 4.45–45.35). These estimates were extracted directly from the respective evidence syntheses and were not recalculated or statistically pooled across reviews. Accordingly, Figure 2 represents a descriptive graphical comparison of previously reported effect estimates rather than a de novo meta-analysis.

Figure 2. Reported effect estimates for adverse outcomes associated with acute kidney injury and renal replacement therapy across included evidence syntheses.



Note: Effect estimates and corresponding 95% confidence intervals were extracted directly from the respective evidence syntheses. The figure provides a descriptive graphical summary only; no de novo pooling, recalculation, or statistical combination of estimates across reviews was performed. AKI, acute kidney injury; MIS-C, multisystem inflammatory syndrome in children; OR, odds ratio; RRT, renal replacement therapy.

DISCUSSION

The findings of this umbrella review reinforce that acute kidney injury (AKI) is one of the most clinically relevant extrapulmonary complications of COVID-19 and should be interpreted within the broader framework of systemic endothelial dysfunction and thromboinflammation. Across the included evidence syntheses, AKI was consistently associated with increased mortality, greater renal replacement therapy (RRT) requirements, and worse clinical outcomes. Importantly, thrombotic and microvascular events were also associated with unfavorable renal outcomes, supporting the biological plausibility that renal microcirculatory injury contributes substantially to COVID-19-associated kidney dysfunction.

Since the early stages of the pandemic, it has become increasingly clear that COVID-19 extends beyond respiratory involvement and affects multiple organ systems through complex inflammatory and vascular pathways. SARS-CoV-2 infection has been associated with endothelial activation, complement dysregulation, platelet activation, and a sustained prothrombotic state. Within the kidney, these alterations may compromise microcirculatory integrity through glomerular and peritubular microvascular injury, impairing tissue perfusion and favoring tubular dysfunction. Histopathological reports describing endothelial injury, fibrin deposition, capillary congestion, renal infarction, and thrombotic microangiopathy provide biological plausibility for the associations observed in the present review.

The substantial variation in AKI incidence according to disease severity further highlights the multifactorial nature of renal involvement in COVID-19. While pooled incidence remained relatively lower among general hospitalized populations, rates increased considerably among critically ill patients. This pattern likely reflects the combined effects of systemic inflammation, hemodynamic instability, hypoxemia, endothelial dysfunction, coagulation abnormalities, and microvascular injury. Rather than acting independently, these mechanisms appear to amplify one another, creating a biological environment particularly favorable to renal injury and disease progression.

From a nephrology practice perspective, these findings reinforce the importance of early and repeated renal assessment in patients with moderate-to-severe COVID-19, particularly among those admitted to intensive care units or presenting with markers of systemic inflammation, coagulation activation, hemodynamic instability, or pre-existing kidney disease. Standardized AKI definitions, especially KDIGO criteria, remain essential for early diagnosis, staging, prognostic assessment, and comparability across clinical studies. Routine monitoring of serum creatinine, urine output, and other KDIGO-recommended parameters may facilitate earlier recognition of AKI and timely nephrology consultation. The consistent association between AKI and mortality observed across evidence syntheses supports the need for structured renal monitoring protocols in high-risk patients.

Particularly noteworthy was the reported association between AKI and mortality. These findings suggest that AKI should not be viewed solely as a marker of disease severity, but also as a clinically meaningful component of the pathophysiological cascade associated with multiorgan dysfunction. Acute impairment of kidney function may contribute to fluid

overload, electrolyte disturbances, acid-base imbalance, accumulation of inflammatory mediators, and worsening systemic homeostasis, all of which may further compromise organ function in critically ill patients. This interpretation is consistent with previous evidence syntheses in which AKI emerged as an important prognostic marker among hospitalized patients with COVID-19.

The association between AKI and increased RRT requirements has direct implications for nephrology services and critical care planning. During the most critical phases of the pandemic, many healthcare systems experienced increased demand for dialysis resources, particularly in intensive care settings. The present findings support the need for early nephrology involvement when renal function deteriorates, careful fluid and hemodynamic management, avoidance of nephrotoxic exposures whenever possible, and timely preparation for kidney replacement therapy in patients at higher risk of progression.

An important aspect of the present review is the inclusion of pediatric evidence, particularly studies involving multisystem inflammatory syndrome in children (MIS-C). Although children generally experience lower mortality rates than adults, AKI was not uncommon among patients with MIS-C and was associated with clinically significant adverse outcomes. The intense inflammatory response characteristic of MIS-C may promote endothelial activation and microvascular injury through mechanisms that partially overlap with those observed in severe adult disease. These findings highlight the importance of maintaining vigilance for renal complications across different age groups and clinical presentations.

The relationship between thrombotic and microvascular injury and renal outcomes deserves particular emphasis. In this context, renal thrombotic microangiopathy may represent an important pathophysiological link connecting endothelial injury, coagulation abnormalities, and kidney dysfunction. The interaction between viral-mediated endothelial damage and activation of thromboinflammatory pathways may help explain why some patients develop severe renal complications even in the absence of overt macrovascular thrombosis or profound systemic hypotension.

From a mechanistic perspective, the interaction between SARS-CoV-2 and angiotensin-converting enzyme 2 (ACE2) receptors may contribute directly and indirectly to renal injury through endothelial dysfunction, apoptosis, inflammatory activation, and exposure of

procoagulant factors. The resulting heterogeneity of renal perfusion may explain the discrepancy occasionally observed between extensive structural injury and preserved global renal function during the early stages of disease. Taken together, these observations support the characterization of severe COVID-19 as a systemic thromboinflammatory disorder with important microvascular renal manifestations.

The findings reported here are broadly consistent with previous systematic reviews and meta-analyses describing elevated rates of AKI, increased mortality, and greater use of RRT among patients with COVID-19. However, the present study expands current knowledge by specifically emphasizing the contribution of microvascular injury and thrombotic mechanisms to renal dysfunction and by integrating evidence from systematic reviews, meta-analyses, and umbrella reviews. This approach provides a broader perspective on the interaction between endothelial dysfunction, thrombosis, and kidney injury throughout the clinical spectrum of COVID-19.

The heterogeneity observed across studies likely reflects differences in patient populations, disease severity, healthcare settings, diagnostic criteria for AKI, and temporal phases of the pandemic. Such variability is expected in evidence derived from multiple countries and healthcare systems and should be considered when interpreting pooled estimates. Nevertheless, the principal associations showed a broadly consistent direction across populations, although the high degree of primary-study overlap indicates that this consistency should not be interpreted as entirely independent replication of evidence.

Risk of bias was assessed using ROBIS, and primary-study overlap was formally quantified using the Corrected Covered Area (CCA). The study protocol was prospectively registered in PROSPERO, the review was conducted according to PRISMA 2020 recommendations, and a predefined search strategy was applied across PubMed/MEDLINE, Scopus, and Embase. These procedures allowed the findings to be interpreted while explicitly considering risk of bias, heterogeneity, and the non-independence of overlapping evidence syntheses.

The translational relevance of these findings lies in the recognition that COVID-19-associated AKI may reflect not only systemic illness severity but also a potentially targetable microvascular phenotype. Endothelial injury, complement activation, platelet activation, and coagulation abnormalities may interact to impair renal perfusion and promote tubular injury.

Better characterization of these pathways may help identify biomarkers of renal risk, guide individualized anticoagulation or anti-inflammatory strategies, and support future trials focused on prevention of microvascular kidney injury.

A relevant methodological finding of the present umbrella review was the substantial overlap among the underlying primary studies. The overall CCA of 12.7% indicated high overlap across first-order evidence syntheses, whereas the population-stratified analysis demonstrated very high overlap among adult COVID-19 reviews (CCA 26.7%). This finding indicates that concordant results across adult evidence syntheses cannot be interpreted as entirely independent replication because several reviews relied on the same underlying cohorts. Conversely, the pediatric MIS-C evidence base showed no overlap with the adult primary studies, reflecting a distinct clinical population. Formal quantification of overlap therefore allowed the consistency of evidence to be interpreted without overestimating the independence of repeated primary data.

Risk-of-bias assessment further demonstrated that the methodological strength of the available evidence syntheses was heterogeneous. Only one included synthesis was judged at low overall risk of bias, three were classified as unclear because important methodological procedures were incompletely reported or their potential influence could not be determined, and two were judged at high risk of bias. These findings reinforce the need to interpret concordance across reviews in conjunction with both methodological quality and primary-study overlap rather than considering the number of concordant reviews alone as an indicator of evidentiary strength.

Some limitations should be acknowledged. First, the methodological quality of the included evidence syntheses was variable, with two reviews judged at high overall risk of bias and three with unclear risk because of incomplete methodological reporting or unresolved concerns. Second, despite formal quantification and explicit consideration of primary-study overlap, repeated inclusion of the same underlying cohorts across different evidence syntheses remains an inherent limitation of umbrella reviews. Accordingly, concordant findings from overlapping reviews were not interpreted as statistically independent confirmation of an association. Third, much of the available evidence originated during earlier phases of the pandemic and may not fully reflect the influence of emerging viral variants, vaccination, and evolving therapeutic strategies. Finally, although the available evidence consistently supports

an association between microvascular injury and AKI, the predominantly observational nature of the underlying evidence precludes definitive causal inference.

Taken together, the available evidence suggests that AKI in COVID-19 represents more than an isolated renal complication and should be considered a clinically relevant manifestation of systemic thromboinflammatory injury in which endothelial dysfunction and microvascular damage play central roles. Improved understanding of these mechanisms may contribute to earlier identification of high-risk patients, more effective risk stratification, and the development of targeted therapeutic strategies aimed at mitigating renal and systemic complications associated with COVID-19.

CONCLUSION

This umbrella review supports a consistent association between SARS-CoV-2-related microvascular and thrombotic injury and adverse renal outcomes, reinforcing the importance of endothelial dysfunction and thromboinflammatory mechanisms in COVID-19-associated acute kidney injury. Across the available evidence syntheses, AKI was consistently associated with increased mortality, greater renal replacement therapy requirements, and worse clinical outcomes.

Renal involvement in COVID-19 should therefore be interpreted within the broader context of systemic microvascular and thromboinflammatory injury rather than as an isolated organ complication. Recognition of these mechanisms has important clinical implications, particularly for early identification of renal dysfunction, careful monitoring of kidney function and coagulation parameters, and implementation of kidney-protective strategies in high-risk patients.

However, the very high degree of primary-study overlap among adult evidence syntheses should be considered when interpreting the apparent consistency of findings. Further well-designed studies are warranted to clarify causal mechanisms and evaluate interventions targeting endothelial and microvascular injury in patients with COVID-19.

ACKNOWLEDGEMENTS

The authors have no acknowledgements to declare.

ETHICAL APPROVAL

Ethics committee approval was not required because this umbrella review synthesized previously published evidence and did not involve direct participation of human subjects or access to identifiable individual patient data.

CONSENT TO PARTICIPATE

Not applicable. This study analyzed data from previously published studies and did not involve direct recruitment of participants.

CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

DATA AVAILABILITY STATEMENT

All data used in this umbrella review were derived from previously published evidence syntheses. The primary-study citation matrix used for the Corrected Covered Area analysis, together with the corresponding overlap calculations, is provided in Supplementary Material S2, allowing independent verification of the overlap assessment.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

AI STATEMENT

Artificial intelligence tools were used exclusively to improve language and editorial clarity. All scientific content, interpretation, critical revision, and final approval were performed by the authors, who assume full responsibility for the manuscript.

REFERENCES

BANSAL, R.; GUBBI, S.; MUNIYAPPA, R. Metabolic syndrome and COVID-19: endocrine-immune-vascular interactions shape clinical course. Endocrinology, v. 161, n. 10, bqaa112, 2020. Disponível em: https://doi.org/10.1210/endocr/bqaa112. Acesso em: 24 ago. 2026.

FERRARIS, L. E. et al. Mesenteric artery thrombosis, microvascular intestinal endotheliitis, and Guillain-Barré syndrome in the same SARS-CoV-2 patient. Cureus, v. 12, n. 11, e11326, 2020. Disponível em: https://doi.org/10.7759/cureus.11326. Acesso em: 24 ago. 2026.

GANDHI, B. et al. Thrombotic microangiopathy with multiorgan involvement following COVID-19. Proceedings (Baylor University. Medical Center), v. 35, n. 2, p. 204-206, 2022. Disponível em: https://doi.org/10.1080/08998280.2021.1997054. Acesso em: 24 ago. 2026.

GENCER, S. et al. Immunoinflammatory, thrombohaemostatic, and cardiovascular mechanisms in COVID-19. Thrombosis and Haemostasis, v. 120, n. 12, p. 1629-1641, 2020. Disponível em: https://doi.org/10.1055/s-0040-1718735. Acesso em: 24 ago. 2026.

GHEIASI, B. et al. Thrombocytopenia secondary to COVID-19: outcomes analysis in terms of thrombotic microangiopathy, acute kidney injury, and mortality. International Journal of Hematology-Oncology and Stem Cell Research, v. 18, n. 1, p. 7-13, 2024. Disponível em: https://doi.org/10.18502/ijhoscr.v18i1.14740. Acesso em: 24 ago. 2026.

IDILMAN, I. S. et al. Lung and kidney perfusion deficits diagnosed by dual-energy computed tomography in patients with COVID-19-related systemic microangiopathy. European Radiology, v. 31, n. 2, p. 1090-1099, 2021. Disponível em: https://doi.org/10.1007/s00330-020-07155-3. Acesso em: 24 ago. 2026.

MUKHERJEE, A.; GHOSH, R.; FURMENT, M. M. COVID-19-associated renal infarction and ascending aortic thrombosis: case report. American Journal of Tropical Medicine and Hygiene, v. 103, n. 5, p. 1989-1992, 2020. Disponível em: https://doi.org/10.4269/ajtmh.20-0869. Acesso em: 24 ago. 2026.

NASIRI, N. et al. Kidney complications of COVID-19: a systematic review and meta-analysis. Journal of Research in Health Sciences, v. 21, n. 1, e00503, 2021. Disponível em: https://doi.org/10.34172/jrhs.2021.39. Acesso em: 24 ago. 2026.

NICOLAI, L. et al. Immunothrombotic dysregulation in COVID-19 pneumonia is associated with respiratory failure and coagulopathy. Circulation, v. 142, n. 12, p. 1176-1189, 2020. Disponível em: https://doi.org/10.1161/CIRCULATIONAHA.120.048488. Acesso em: 24 ago. 2026.

PASSONI, R. et al. Occurrence of acute kidney injury in adult patients hospitalized with COVID-19: a systematic review and meta-analysis. Nefrología, v. 42, n. 4, p. 404-414, 2022. Disponível em: https://doi.org/10.1016/j.nefro.2021.09.002. Acesso em: 24 ago. 2026.

PIEPER, D. et al. Systematic review finds overlapping reviews were not mentioned in every other overview. Journal of Clinical Epidemiology, v. 67, n. 4, p. 368-375, 2014. Disponível em: https://doi.org/10.1016/j.jclinepi.2013.11.007. Acesso em: 24 ago. 2026.

PRENDECKI, M. et al. Temporal changes in complement activation in haemodialysis patients with COVID-19 as a predictor of disease progression. Clinical Kidney Journal, v. 13, n. 5, p. 889-896, 2020. Disponível em: https://doi.org/10.1093/ckj/sfaa192. Acesso em: 24 ago. 2026.

ROBBINS-JUAREZ, S. Y. et al. Outcomes for patients with COVID-19 and acute kidney injury: a systematic review and meta-analysis. American Journal of Kidney Diseases, v. 76, n. 6, p. 719-727.e1, 2020. Disponível em: https://doi.org/10.1053/j.ajkd.2020.09.002. Acesso em: 24 ago. 2026.

SHAO, M. et al. Acute kidney injury is associated with severe infection and fatality in patients with COVID-19: a systematic review and meta-analysis of 40 studies and 24,527 patients. Pharmacological Research, v. 161, 105107, 2020. Disponível em: https://doi.org/10.1016/j.phrs.2020.105107. Acesso em: 24 ago. 2026.

TRIPATHI, A. K. et al. Acute kidney injury following multisystem inflammatory syndrome associated with SARS-CoV-2 infection in children: a systematic review and meta-analysis. Pediatric Nephrology, v. 38, p. 357-370, 2023. Disponível em: https://doi.org/10.1007/s00467-022-05701-3. Acesso em: 24 ago. 2026.

XU, Z. et al. Systematic review and subgroup analysis of the incidence of acute kidney injury (AKI) in patients with COVID-19. BMC Nephrology, v. 22, 52, 2021. Disponível em: https://doi.org/10.1186/s12882-021-02244-x. Acesso em: 24 ago. 2026.

YANG, L. et al. Kidney health in the COVID-19 pandemic: an umbrella review of meta-analyses and systematic reviews. Frontiers in Public Health, v. 10, 963667, 2022. Disponível em: https://doi.org/10.3389/fpubh.2022.963667. Acesso em: 24 ago. 2026.

YASEEN, M. O. et al. A systematic review of systematic reviews on the incidence of acute kidney injury in COVID-19 patients. Pharmacophore, v. 12, n. 4, p. 92-102, 2021. Disponível em: https://doi.org/10.51847/PD4wBgNnfm. Acesso em: 24 ago. 2026.