Kidney disease and mortality in patients with respiratory tract infections: a systematic review and meta-analysis

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ABSTRACT

Background. Respiratory tract infections (RTIs) are a common reason for people to seek medical care. RTIs are associated with high short-term mortality. Inconsistent evidence exists in the association between the presence of kidney disease and the risk of death in patient with RTIs.

Methods. We searched the PubMed, Cochrane Library and Embase databases from inception through April 2019 for cohort and case–control studies investigating the presence of kidney disease (defined as medical diagnosis of kidney disease, reduced estimated glomerular filtration rate or creatinine clearance, elevated serum creatinine and proteinuria) on mortality in adults with RTIs in different settings including community, inpatient and intensive care units. We assessed the quality of the included studies using Cochrane Collaboration’s tool and conducted a meta-analysis on the relative risk (RR) of death.

Results. Of 5362 records identified, 18 studies involving 16 676 participants met the inclusion criteria, with 15 studies investigating pneumonia and 3 studies exploring influenza. The risk of bias in the available evidence was moderate. Most [17/18 (94.5%)] of studies reported positive associations of underlying chronic kidney disease with mortality. The pooled adjusted risk for all-cause mortality in patients with RTIs almost doubled [RR 1.96 (95% confidence interval 1.48–2.59)] in
patients with kidney disease. Associations were consistent across different timings of kidney disease assessment and provenances of RTIs (community-acquired or healthcare-associated).

Conclusions. The presence of kidney disease is associated with higher mortality among people with RTIs, especially in those with pneumonia. The presence of kidney disease might be taken into account when considering admission for patients who present with RTIs.

Keywords: chronic kidney disease, influenza, meta-analysis, mortality, pneumonia, respiratory tract infection

INTRODUCTION

Respiratory tract infections (RTIs), including pneumonia and influenza, are common and can be life-threatening if not treated promptly [1]. With >290 million episodes each year globally, RTIs are among the most common reasons why people seek healthcare [2]. Among those with lower RTIs, >2.7 million people die each year and pneumococcal pneumonia is the cause of more than half of the deaths [2]. In the current era of avoiding antibiotic resistance, antibiotic use for treating RTIs should be minimized. However, antibiotic treatment is advocated for high-risk groups, such as patients receiving dialysis, when such patients present with RTIs [3]. Thus it is important to be able to identify patients at higher risk of mortality from RTIs.

Chronic kidney disease (CKD), characterized as reduced renal function, is a major public health problem affecting ~10% of the global adult population [4]. CKD was defined in 2002 [5] after the advent of a validated formula in 1999 to measure the estimated glomerular filtration rate (eGFR) [6]. Increased risk of death from RTIs in the dialysis population is already well established [7–9]. The first mortality prediction score in RTI included renal disease in 1997, but this preceded the currently used definition of CKD and only identified people with very severe kidney dysfunction or on dialysis [10]. In recent years, accumulated evidence has suggested that an increased risk of RTI-related death extends to patients with non-dialysis-dependent CKD [11, 12]. However, results are not consistent [11–15]: the magnitude of this association varies depending on different settings and types of RTIs, and even disappeared in some studies [14, 15]. Although a number of systematic reviews have explored the association between CKD and all-cause mortality or cardiovascular mortality [16–18], none have focused on infection-related mortality.

To date, it is unknown if pre-existing CKD helps stratify the risk of death, as RTIs are common with high mortality risk related to the acute infection. Current admission scores in the guideline do not include CKD in the predictor [3] and only include symptoms such as respiratory rate. If an association between pre-existing CKD (not on dialysis) and the risk of death exists in the context of RTIs, then it has important implications for clinical care in terms of prompt antibiotic treatment and referring patients for further admission, pointing to infection prevention for reducing mortality in this population. Here we performed a systematic review to explore the impact of non-dialysis-dependent CKD on mortality among people who present with RTIs.

MATERIALS AND METHODS

The methods were pre-specified in a protocol that was registered with PROSPERO, an international prospective register of systematic reviews (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=119599).

Our systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines [19].

Search strategy

We performed a systematic literature search to identify all studies exploring kidney function and mortality in patients with RTIs. Our search strategy included the relevant key terms: ‘respiratory tract infection’, ‘kidney disease’, ‘creatinine’, ‘glomerular filtration rate’ and ‘mortality’ or ‘acute kidney injury’ (Supplementary data, Item 1). The search was conducted by two independent researchers (G.S. and X.Q.) using the Cochrane Central Register of Controlled Trials (CENTRAL, through April 2019), PubMed (1946–April 2019) and Embase (Elsevier, 1974–April 2019).

Inclusion and exclusion criteria

Studies were included if they met the following criteria: cohort or case–control studies; adult (>18 years of age) with available kidney function measurements (creatinine, cystatin C or eGFR) with or without acute kidney injury (AKI); RTIs, such as pneumonia and influenza; and mortality, including all-cause mortality and cause-specific mortality. We excluded case reports, case series, editorials and review articles. We excluded those with chronic dialysis or kidney transplantation. There was no restriction of publication year. There was no restriction of gender and duration of follow-up time. We only included studies in English, Chinese or Japanese. In the case of multiple publications covering the same study population, we only included the report with the longest follow-up.

Exposure

We accepted a wide range of definitions of kidney disease, including medical diagnosis of kidney disease, reduced eGFR or creatinine clearance, elevated serum creatinine, proteinuria, micro-albuminuria or macro-albuminuria and renal structural abnormalities.

Outcomes

The primary outcome of interest was all-cause mortality within studies with a defined duration of follow-up period. The secondary outcomes included the risk of in-hospital mortality and 30- and 90-day mortality from infection during the study periods.

Study selection and data extraction

All the systematic search records from different databases were imported in EndNote (Clarivate Analytics, Philadelphia, PA, USA). After deduplication, eligible studies were listed and assessed independently by two reviewers (G.B.S. and M.I.) using...
Kidney disease and RTI mortality

RESULTS

Study selection

We identified 5361 records from systematic searching and 1 record from reference checking of the key papers. Of these, 4043 records underwent title and abstract screening after removing duplicates. After excluding 3895 records based on title and abstract screening, 148 records remained for full-text assessment. We excluded 130 articles that did not meet inclusion criteria (abstract or no full text available (n = 22); included patients with end-stage renal disease (n = 4); language not English, Japanese or Chinese (n = 12); no data of acute RTIs (n = 20); no data on CKD or AKI (n = 20); no baseline kidney function data (n = 28); no data on mortality from RTI (n = 5); no data of CKD or AKI on mortality (n = 15) and tuberculosis (n = 4). Eighteen studies met the eligibility criteria and were considered for meta-analysis [12–15, 22–34] (Figure 1).

Study characteristics

The studies selected for evaluation enrolled a total of 16 676 participants (Table 1). The studies were from France (n = 4) [13, 22, 23, 26], Spain (n = 4) [24, 30, 32, 33], China (n = 3) [15, 28, 34], USA (n = 3) [14, 25, 27], Mexico (n = 1) [31], UK (n = 1) [12], Canada (n = 1) [11] and Qatar (n = 1) [29]. All were cohort studies except for one case–control study [31]. Intensive care was the most common study setting, followed by inpatients, emergency [33], community [11, 12] and nursing home [32]. The average age ranged from 29 to 69 years and the proportion of men ranged from 38% to 78%. Most studies ended follow-up at hospital discharge.

Fourteen studies, enrolling 16 159 patients, provided data on pneumonia and the remaining three studies [14, 29, 31], enrolling 517 patients, investigated influenza. Most of the RTI diagnoses were either from clinical diagnosis or from International Classification of Disease codes. Most of the RTIs were community acquired. Two studies [24, 28] reported that the RTIs were healthcare-associated and one [15] did not distinguish the onset of RTIs. There were various definitions of kidney disease, including the previous history of kidney disease [13, 14, 27, 30, 32], elevated serum creatinine or blood urea nitrogen (BUN) [22–26, 28, 29, 31, 34] and reduced eGFR [11, 12, 15]. Ten studies [11, 22–26, 28, 29, 31, 34] identified kidney disease prior to the onset of RTIs and the remaining eight studies reported kidney disease status on admission. All studies reported short-term all-cause mortality following a pneumonia diagnosis. Ten studies [13–15, 22–25, 27, 29, 31] reported inhospital mortality and the remaining eight studies reported 28–30 days mortality. One study [12] reported 90 days mortality.

Risk of bias assessment

The full quality assessment is reported in the Supplementary data, Table S1. Study quality was variable. Relying on routine medical history introduced a potential source of misclassification of kidney disease status for five studies [13, 14, 27, 30, 32].

Ten studies [13–15, 22–25, 27, 29, 31] reported in-hospital mortality with an unclear length of hospital stay, making the duration of follow-up unclear. All included studies identified deaths from death registers or hospital records extraction, with a low risk of misclassification of mortality. There was variable adjustment for confounding, from unadjusted crude estimates to estimates adjusted for a range of comorbidities and demographics.

The effect of kidney disease on mortality in patients with RTIs

When compared with individuals without kidney disease, the pooled adjusted risk for all-cause mortality in patients with
RTIs almost doubled [RR 1.96 (95% CI 1.48–2.59)] in those with kidney disease and with high heterogeneity ($I^2 = 86.2\%$, $P < 0.01$; Figure 2).

The effect of kidney disease on mortality in patients with influenza

In patients with influenza, the presence of kidney disease was associated with increased mortality risk. However, it did not reach conventional levels of statistical significance [RR 1.54 (95% CI 0.62–3.81)] due to low power and moderate heterogeneity ($I^2 = 2.5\%$, $P = 0.12$; Supplementary data, Figure S1).

The effect of kidney disease on mortality in patients with pneumonia

In patients with pneumonia, the all-cause mortality was more than two times higher [RR 2.02 (95% CI 1.51–2.72)] with high heterogeneity ($I^2 = 87.8\%$, $P < 0.01$; Figure 2). Higher risk of all-cause mortality in patients with pneumonia was observed in those with kidney disease, regardless of the timing of kidney disease measurement (prior to RTIs or on admission, Supplementary data, Figure S2) or setting (ICU, inpatients and others; Figure 2). The results were consistent in those with community-acquired pneumonia (CAP), healthcare-associated pneumonia (Supplementary data, Figure S3) and in-hospital or 28-/30-day
Table 1. Characteristics of studies reporting on the association between the presence of kidney disease and the risk of death in patients with RTIs

<table>
<thead>
<tr>
<th>Identity</th>
<th>Region</th>
<th>Study design</th>
<th>Setting</th>
<th>Total participants</th>
<th>Age (years), mean ± SD or median (quartile)</th>
<th>Male (%)</th>
<th>Follow-up duration</th>
<th>Types of infection</th>
<th>Onset</th>
<th>Definition of infection</th>
<th>Time of CKD assessment</th>
<th>Data source of CKD</th>
<th>Definition of CKD</th>
<th>Data source of mortality</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang et al. [34]</td>
<td>China</td>
<td>Cohort</td>
<td>Inpatient</td>
<td>186</td>
<td>68.1 ± 16.5</td>
<td>68.80</td>
<td>Until death or hospital discharge</td>
<td>Pneumonia</td>
<td>Community-acquired</td>
<td>Clinical diagnosis confirmed by chest radiographs</td>
<td>On admission</td>
<td>Hospital records</td>
<td>BUN ≥ 7.4 mmol/L</td>
<td>Hospital data</td>
<td>30-day mortality</td>
</tr>
<tr>
<td>Cecato et al. [33]</td>
<td>Spain</td>
<td>Cohort</td>
<td>Emergency department</td>
<td>739</td>
<td>63-69 (48-79)</td>
<td>IPP: 59; NIPP: 58</td>
<td>IPP: 59; NIPP: 58</td>
<td>Until death or hospital discharge, and the patients discharged alive were re-examined or at least contacted by telephone within 30-40 days from hospital discharge</td>
<td>Pneumonia</td>
<td>Community-acquired</td>
<td>Clinical diagnosis confirmed by chest radiographs and pneumococcal etiology</td>
<td>Prior to RTI</td>
<td>Unclear</td>
<td>Medical history of chronic renal failure</td>
<td>Hospital data</td>
</tr>
<tr>
<td>Su et al. [15]</td>
<td>China</td>
<td>Cohort</td>
<td>Inpatient</td>
<td>183</td>
<td>63 (49–77)</td>
<td>50.00</td>
<td>Until death or hospital discharge</td>
<td>Pneumonia</td>
<td>Not clear</td>
<td>ICD codes</td>
<td>Prior to RTI</td>
<td>Unclear</td>
<td>Medical history of chronic renal disease</td>
<td>Hospital data</td>
<td>Inhospital mortality</td>
</tr>
<tr>
<td>Mata-Marin et al. [31]</td>
<td>Mexico</td>
<td>Case-control</td>
<td>Inpatient</td>
<td>33</td>
<td>Case 29 (25–46), controls 34 (22–44)</td>
<td>38</td>
<td>Case-control, but in hospital mortality defined cases: controls were discharged</td>
<td>Influenza A/H1N1</td>
<td>Community-acquired</td>
<td>Clinical diagnosis confirmed by PCR positive for A/H1N1 influenza</td>
<td>On admission</td>
<td>Medical records</td>
<td>Serum creatinine &gt; 10 mg/dL</td>
<td>Hospital data</td>
<td>Inhospital mortality</td>
</tr>
<tr>
<td>McDonald et al. [32]</td>
<td>UK</td>
<td>Cohort</td>
<td>Community</td>
<td>474</td>
<td>50-74 (65)</td>
<td>53</td>
<td>30 days</td>
<td>Pneumonia</td>
<td>Community-acquired</td>
<td>ICD codes</td>
<td>Prior to RTI</td>
<td>Primary care test results: eGFR &gt; 60 vs &lt; 30 mL/min/1.73 m²</td>
<td>Linkage to national official statistics (death registrations)</td>
<td>28-day mortality</td>
<td></td>
</tr>
<tr>
<td>Shah et al. [34]</td>
<td>USA</td>
<td>Cohort</td>
<td>ICU</td>
<td>444</td>
<td>18-49.8 years: 115 (36.5%) age 50-64 years: 101 (23.3%) age ≥65 years: 228 (51.2%)</td>
<td>53</td>
<td>38</td>
<td>Earliest of hospital discharge or 30 days from ICU admission</td>
<td>Influenza A or B</td>
<td>Community-acquired</td>
<td>Clinical diagnosis confirmed by PCR, rapid test or viral culture</td>
<td>Prior to RTI</td>
<td>Hospital records</td>
<td>Medical history of CKD</td>
<td>Hospital data</td>
</tr>
<tr>
<td>Soub et al. [39]</td>
<td>Qatar</td>
<td>Cohort</td>
<td>ICU</td>
<td>40</td>
<td>Male 45.7, range 15-72</td>
<td>60</td>
<td>Until death or hospital discharge</td>
<td>Influenza A/H1N1</td>
<td>Community-acquired</td>
<td>Clinical diagnosis confirmed by PCR positive for influenza A H1N1 (nasopharyngeal swab or BAL)</td>
<td>On admission</td>
<td>Hospital records</td>
<td>Elevated creatinine level on admission (level not specified)</td>
<td>Hospital data</td>
<td>Inhospital mortality</td>
</tr>
<tr>
<td>Sireent et al. [30]</td>
<td>Spain</td>
<td>Cohort</td>
<td>ICU</td>
<td>242</td>
<td>56.8 ± 16.0</td>
<td>69</td>
<td>38 days</td>
<td>Pneumonia</td>
<td>Community-acquired</td>
<td>Clinical diagnosis confirmed by chest radiographs</td>
<td>Prior to RTI</td>
<td>Unclear</td>
<td>Pre-existing renal disease with documented abnormal serum creatinine level outside the period of the pneumonia episode</td>
<td>Hospital data</td>
<td>28-day mortality</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Identity</th>
<th>Study design</th>
<th>Region</th>
<th>Setting</th>
<th>Total participants</th>
<th>Age (years), mean ± SD or median (quartile)</th>
<th>Male (%)</th>
<th>Follow-up duration</th>
<th>Types of infection</th>
<th>Onset</th>
<th>Definition of infection</th>
<th>Time of CKD assessment</th>
<th>Data source of CKD</th>
<th>Definition of CKD</th>
<th>Data source of mortality</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mongardon et al. [13]</td>
<td>France</td>
<td>Cohort ICU</td>
<td>222</td>
<td>60 (48–71)</td>
<td>66 until death or hospital discharge</td>
<td>Community-acquired</td>
<td>Pneumonia</td>
<td>Clinical diagnosis confirmed by pneumococcal serology</td>
<td>Prior to RTI</td>
<td>Unclear</td>
<td>Medical history of chronic renal insufficiency</td>
<td>Hospital data</td>
<td>In-hospital mortality</td>
<td>30-day mortality</td>
<td></td>
</tr>
<tr>
<td>Chang et al. [20]</td>
<td>Taiwan</td>
<td>Cohort ICU</td>
<td>380</td>
<td>69 ± 15</td>
<td>61 until death or hospital discharge</td>
<td>Community-acquired</td>
<td>Pneumonia</td>
<td>Clinical diagnosis confirmed either by chest radiographs or by etiology</td>
<td>On admission</td>
<td>Hospital records</td>
<td>Creatinine &gt; 1.6 mg/dL</td>
<td>Hospital data</td>
<td>30-day mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>James et al. [11]</td>
<td>Canada</td>
<td>Cohort Community</td>
<td>4253</td>
<td>50.9</td>
<td>15.4–43.6</td>
<td>2.5 years</td>
<td>Pneumonia</td>
<td>ICD codes</td>
<td>Prior to RTI</td>
<td>Outpatient</td>
<td>eGFR 60-104 versus &lt; 30 mL/min 1.73 m²</td>
<td>The Alberta Vital Statistics Registry</td>
<td>30-day mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arozullah et al. [27]</td>
<td>USA</td>
<td>Cohort Inpatient</td>
<td>1415</td>
<td>39.8</td>
<td>8.5</td>
<td>Until death or hospital discharge</td>
<td>Community-acquired</td>
<td>ICD codes</td>
<td>Prior to RTI</td>
<td>Hospital records</td>
<td>Pre-existing renal disease outside the period of the pneumonia episode</td>
<td>Hospital data</td>
<td>In-hospital mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laurichesse et al. [26]</td>
<td>France</td>
<td>Cohort Inpatient</td>
<td>215</td>
<td>66.7 ± 20</td>
<td>53.00</td>
<td>30 days</td>
<td>Pneumonia</td>
<td>Community-acquired</td>
<td>Clinical diagnosis confirmed by chest radiographs</td>
<td>On admission</td>
<td>Hospital records</td>
<td>Serum creatinine ≥ 88 μmol/L</td>
<td>Hospital data</td>
<td>30-day mortality</td>
<td></td>
</tr>
<tr>
<td>Conte et al. [20]</td>
<td>USA</td>
<td>Cohort Inpatient</td>
<td>1000</td>
<td>Not provided</td>
<td>45 until death or hospital discharge</td>
<td>Community-acquired</td>
<td>Pneumonia</td>
<td>Clinical diagnosis confirmed by chest radiographs</td>
<td>On admission</td>
<td>Hospital records</td>
<td>Serum creatinine &gt; 1.5 mg/dL</td>
<td>Hospital data</td>
<td>In-hospital mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>el-Bisegy et al. [24]</td>
<td>Spain</td>
<td>Cohort ICU</td>
<td>84</td>
<td>59 ± 14</td>
<td>75 until death or hospital discharge</td>
<td>Community-acquired</td>
<td>Healthcare-associated Pneumonia</td>
<td>Clinical diagnosis confirmed by chest radiographs and Legionella serology after 72h of hospital admission</td>
<td>On admission</td>
<td>Hospital records</td>
<td>Serum creatinine &gt; 1.8 mg/dL</td>
<td>Hospital data</td>
<td>In-hospital mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levy et al. [23]</td>
<td>France</td>
<td>Cohort ICU</td>
<td>335</td>
<td>63 ± 18</td>
<td>61.00</td>
<td>Until death or ICU discharge</td>
<td>Pneumonia</td>
<td>Community-acquired</td>
<td>Clinical diagnosis confirmed by chest radiographs</td>
<td>On admission</td>
<td>Hospital records</td>
<td>Serum creatinine &gt; 1.5 mg/dL</td>
<td>Hospital data</td>
<td>In-hospital mortality</td>
<td></td>
</tr>
<tr>
<td>Levy et al. [23]</td>
<td>France</td>
<td>Cohort ICU</td>
<td>299</td>
<td>63.9 ± 17.6</td>
<td>63.00</td>
<td>Until death or ICU discharge</td>
<td>Pneumonia</td>
<td>Community-acquired</td>
<td>Clinical diagnosis confirmed by chest radiographs</td>
<td>On admission</td>
<td>Hospital records</td>
<td>Serum creatinine &gt; 1.5 mg/dL</td>
<td>Hospital data</td>
<td>In-hospital mortality</td>
<td></td>
</tr>
</tbody>
</table>

mortality (Supplementary data, Figure S4). Only one included study reported the risk of 90-day mortality as 27% higher in those with reduced eGFR than those with eGFR >60 mL/min/1.73 m² [RR 1.27 (95% CI 1.12–1.43)] [12].

Meta-regression and sensitivity analyses

A sensitivity analysis restricted to the 11 studies without OR transformation demonstrated a similar association between the presence of kidney disease and a higher risk of all-cause mortality (Supplementary data, Figure S5).

Meta-regression analyses suggested that the RRs were higher for larger studies compared with smaller studies, inpatient settings compared with intensive care settings, kidney disease assessed prior to hospitalization compared with on admission and healthcare-associated pneumonia compared with community-acquired, although CIs included the null (Table 2).

Publication bias

Publication bias was not evident from the funnel plot of included studies (P = 0.46 in the Beggs’s test, Supplementary data, Figure S6).

DISCUSSION

This meta-analysis, based on 18 studies of patients with RTIs, showed that the risk of all-cause death was increased, with a high heterogeneity between studies that was explained by study size, setting, type of RTI and timing of assessment of kidney disease status. Overall, the risk of mortality was
approximately two times higher in patients with kidney disease and pronounced in patients with pneumonia.

Our observations are in line with the evidence from previous studies. In the community setting, James et al. [11] and McDonald et al. [12] observed a graded association between reduced eGFR and a higher risk of 30-day mortality in patients hospitalized for pneumonia. This association was consistent in the meta-analysis irrespective of the context, even though the underlying illness usually drives the high risk of mortality. In line with the severity of the underlying RTI, the predicting mortality value of kidney disease was more pronounced in the patients presenting in the community and in inpatients when compared with the ICU setting. Similarly, assessment of kidney disease prior to infection was a stronger predictor than kidney function assessed on admission. Many clinical prediction tools for CAP have included BUN as an indicator of kidney disease, including the Pneumonia Severity Index [10], CURB-65 [Confusion, Urea >7 mmol/l, Respiratory rate >30/min, low systolic (<90 mm Hg) or diastolic (<60 mm Hg) Blood pressure], age >65 years [39] and minor criteria from the Infectious Diseases Society of America/American Thoracic Society guidelines [36]. These tools have been validated to identify high-risk patients and their implementation can improve patients’ outcomes [37, 38]. Our results suggest that pre-existing general practitioner health records can also inform whether to treat or to admit patients who have had previous creatinine measurements [11, 12]. These findings highlight the importance of ascertaining the type of pre-existing kidney disease and not just acute increases in urea as a result of dehydration when patients present with RTIs, especially in the community setting.

Most included studies defined kidney disease by using reduced eGFR or medical history. Fewer studies have examined albuminuria. A study by McDonald et al. [12] in the UK reported a non-significant association of proteinuria with mortality in patients with pneumonia. Meanwhile, in the Atherosclerosis Risk in Communities study, Ishigami et al. [39] observed a strong dose-response association between the urinary albumin:creatinine ratio (ACR) and the risk of death from hospitalization with infections. This association was independent of eGFR. Indeed, when assessed in the context of CKD risk stage according to the Kidney Disease: Improving Global Outcomes [40], there were multiplicative contributions of low eGFR and high ACR to mortality. The role of ACR in the risk of death in patients with RTIs requires more studies for confirmation.

Several factors might contribute to the higher all-cause mortality in patients with kidney disease in the context of RTIs. One of the links might be cardiovascular disease (CVD). Patients with CKD may have higher CVD mortality associated with RTIs, eventually contributing to higher all-cause mortality. It is well known that patients with CKD have a higher risk of CVD [16, 41]. Previous studies also showed that an episode of infection increases CVD mortality and this association was more pronounced in those with reduced renal function [42, 43]. The occurrence of CVD complications in patients with RTIs has been associated with increased short- and long-term mortality [44, 45]. The underlying mechanism is multifactorial and likely to include exacerbation of systemic inflammatory changes in atherosclerotic plaques inducing demand ischaemia, thereby leading to an increased risk of death from CVD [45-47]. Kidney disease is already associated with increased malnutrition, elevated serum inflammatory cytokines levels and oxidative stress [48, 49]. The inflammatory storm from RTIs may be more intense in patients with kidney disease. Another link might be related to AKI. Patients with kidney disease are prone to AKI, which is a well-established independent factor for CVD and death [50].

For policymakers, the results of this systematic review highlight the importance of underlying kidney disease for patients with pneumonia, which should be considered in clinical quality indicators and incentivization as well as public health policy, such as immunization drives. For clinicians, our results confirm the importance of checking pre-existing kidney disease comorbidities in patients seeking medical care for symptoms of RTIs. For guideline developers, pre-existing kidney disease might also be considered for inclusion in hospital admission scores [3]. For patients with CKD, pneumonia carries a higher risk of death, and pneumococcal and influenza vaccination should be encouraged as one of the prevention strategies. It is concerning that patients with CKD have lower and shorter protective effects from vaccination, because many people with CKD often do not receive pneumococcal vaccination and their immunity wanes over time [51, 52].

Our study has several strengths. We performed a sensitive and comprehensive search strategy, with a broad definition of kidney disease, for a thorough and inclusive search. We were able to show that the presence of kidney disease, whether assessed prior to infection or measured on admission, was associated with a higher risk of mortality in patient with pneumonia. This association was consistent in different settings and for both community-acquired and healthcare-associated infections.

We also acknowledge the limitations that need to be considered when interpreting our findings. First, most of the included studies in our systematic review only reported all-cause in-hospital mortality or 28-/30-day mortality, and we were unable to investigate long-term mortality and cause-specific mortality. Second, most of the included studies used the measurements of kidney function at admission, which might reflect pre-existing kidney function or AKI. However, subgroup analysis showed a consistent association between pre-existing kidney disease (prior to infections) and higher risk of death in those with pneumonia. Third, our analysis plan selected the most adjusted RR presented in the included studies (as representing the least confounded and therefore most conservative risk estimation), which may have resulted in outcome reporting bias. Fourth, as our meta-analysis was based on observational studies, residual or unmeasured confounding could not be eliminated. Fifth, we found overall high heterogeneity in our estimates. Heterogeneity may be attributed in part to the differences in patient characteristics (e.g. sex distribution, mean age and comorbidities such as diabetes), definition of kidney disease (medical history, eGFR, etc.) and different onset of RTIs, follow-up periods, study quality and sample sizes. However, we were unable to perform all these subgroup analyses owing to the limited data available and lack of access to the original, individual patient data. Sixth, it should be noted that only one study included pneumonia managed in the community [12], and this was limited to a study population of older adults with diabetes, thus caution is needed in applying these findings outside hospital settings. Seventh, we cannot exclude publication bias for some small studies included in this review, although most studies are large and results appear robust.

In conclusion, the presence of kidney disease is associated with a higher risk of death in patients with RTIs, especially in those with pneumonia. Clinicians should not only use the presence of kidney disease as an indication to start antibiotic therapy for RTI but also, in view of their higher mortality risk, consider that these patients may require hospital admission.
SUPPLEMENTARY DATA
Supplementary data are available at ckj online.

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AUTHORS’ CONTRIBUTIONS
All authors contributed to the study design, data acquisition and data analysis and interpretation. Specifically, G.B.S. and X.D.Q. developed and ran the search strategy. G.B.S., M.I., X.D.Q. and H.M. independently extracted data and obtained copies of studies. L.X.S. checked the data extraction. M.I. and H.M. assessed studies for inclusion and assessed the risk of bias. D.N. was the third review author who selected which studies to include when disagreements existed. C.S.L., J.J.C. and D.N. contributed to the development of data analysis strategies. G.B.S. and X.D.Q. performed the data analysis. G.B.S. and D.N. drafted the manuscript. All authors provided comments on this review and approved the final version.

CONFLICT OF INTEREST STATEMENT
None declared.

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