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ORIGINAL ARTICLE

Short- and long-term outcomes after incident pneumonia in adults with chronic kidney disease: a time-dependent analysis from the Stockholm CREAtinine Measurement project

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ABSTRACT

Background. Little is known about the health sequelae of pneumonia in persons with chronic kidney disease (CKD).

Methods. We studied adults with CKD in Stockholm during 2006–11, who not previously been diagnosed with lower respiratory tract infections. We used multivariable-adjusted Cox regression with pneumonia as a time-varying exposure to estimate hazard ratios (HRs) [95% confidence intervals (CIs)] for the events of death, major adverse cardiovascular events (MACEs), acute kidney injury (AKI), CKD progression or hospitalization for urinary tract infections (UTIs)/sepsis. Cataract and knee/joint replacement served as negative control outcomes.

Results. We identified 71 931 adults (mean age 79 years, 59% women), of whom 8379 (12%) were diagnosed with pneumonia during follow-up; incident pneumonia was associated with 10 times higher adjusted mortality risk during the first 90 days [HR = 10.0, 95% confidence interval (CI) 9.5–10.5] and double the mortality beyond 90 days from pneumonia diagnosis (HR = 2.0; 95% CI 1.9–2.1). Incident pneumonia was similarly associated with higher adjusted risk of MACE (<90 days: HR = 12.6; 95% CI 12.0–13.3; ≥90 days: HR = 1.5; 95% CI 1.4–1.6). The adjusted risk of CKD progression and UTI/sepsis hospitalization was highest within 90 days from pneumonia but remained elevated thereafter. For AKI, the association with incident pneumonia was only seen within 90 days. Neither cataract nor knee/joint replacement was related to pneumonia.

Conclusions. Incident pneumonia was associated with increased risks of MACE, CKD progression, severe UTI/sepsis and death, with risks highest soon after pneumonia diagnosis but extending beyond 90 days. Our findings highlight the susceptibility for adverse outcomes of CKD patients following pneumonia diagnosis, and may inform clinical decisions regarding vaccination strategies.

Keywords: acute kidney injury, cardiovascular disease, chronic kidney disease, mortality, pneumonia

INTRODUCTION

Pneumonia is a leading cause of hospitalization and mortality worldwide, contributing to elevated healthcare and societal costs [1, 2]. Pneumonia is estimated to account for one million hospital admissions in the European Union, and 60 000 deaths in the USA annually [3–5]. In addition, pneumonia has been associated with long-term adverse sequelae, including a higher rate of cardiovascular disease (CVD) or death [6] even after 10 years from diagnosis [7]. Plausible mechanisms to explain such long-term associations involve pneumonia-induced upregulation of the sympathetic nervous system [8], persistent residual inflammation [9, 10], thrombotic-promoting status [11, 12] and scar formation [13].

Persons with chronic kidney disease (CKD) are at high risk of infectious complications [14, 15], accounting for 21% of all hospitalizations. Pneumonia is probably the most common infection in these patients [15–17]. The risk of pneumonia and of fatal pneumonia in persons with CKD is >2-fold compared with those without CKD [14, 15, 18, 19]. Despite this, there is surprisingly little evidence about possible major long-term sequelae of pneumonia among individuals with CKD. The few earlier studies may have been limited by their focus on short-term risk of acute kidney injury (AKI) [20], or the rare outcome of hemolytic uremic syndrome among pediatric patients with

proteinuria [21]. Epidemiological studies dedicated to outcomes following pneumonia in patients with CKD may have significant public health relevance, both for improving risk stratification and for motivating the implementation of vaccination campaigns in patients with CKD.

Our objective was to identify the relative rates of acute and long-term health events after incident pneumonia in a region-representative population of adults with manifest CKD. Additionally, because AKI, systemic inflammation, thrombosis and scar formation are also risk factors for CKD progression [22–25], we hypothesized that incident pneumonia may also associate with the long-term risk of kidney function decline.

MATERIALS AND METHODS

Data sources

We used data from the Stockholm CREAtinine Measurements project [26], a healthcare utilization cohort that contains all residents from the region of Stockholm that underwent serum creatinine testing in outpatient or inpatient care during 2006–11. Creatinine and other laboratory data were linked with regional and national administrative databases for information on healthcare utilization, diagnoses, dispensed drugs, validated renal replacement therapy (RRT) endpoints and death, with minimal loss to follow-up. The study used only de-identified data, and thus, individual informed consent was not required. The study was approved by regional institutional ethics review boards and adheres to the Declaration of Helsinki.

Study population

Eligible participants for this study were adults (>18 years old) with non-dialysis-dependent confirmed CKD with no history of kidney transplantation and with no prior outpatient/inpatient diagnosis of pneumonia or lower respiratory tract infections (LRTIs) (Supplementary data, Table S1). The date of the first estimated glomerular filtration rate (eGFR) measurement taken at an outpatient consultation and <60 mL/min/1.73 m^2 was considered the index date. eGFR was calculated with the CKD Epidemiology Collaboration formula [27] using isotope dilution mass spectrometry standardized serum creatinine tests performed in connection with an ambulatory health care visit. Creatinine values <0.3 and >17.0 mg/dL were considered implausible and discarded. In addition, patients undergoing maintenance dialysis or kidney transplantation were identified, and excluded from the study, via linkage with the national Swedish Renal Register. As a next step, and in order to ensure the presence of confirmed CKD, we imposed the condition to have a second ambulatory eGFR test <60 mL/min >3 months apart. After selecting all participants with confirmed non-dialysis-dependent CKD, we excluded those with creatinine tests taken during pregnancies, chronic infections, clinical history of pneumonia (including ventilator-associated pneumonia) or with a history of any other LRTIs during the preceding 5 years (see Supplementary data, Table S1 for definitions) [15]. Among 82 235 identified adults with confirmed CKD, 71 931 that did not have any history of pneumonia and fulfilled all inclusion criteria were considered for analysis in our study (see Flow Chart in Supplementary data, Figure S1).

Study exposure and covariates

The study exposure is incident pneumonia, defined as the first encountered International Classification of Diseases-10 (ICD-10) J12–J18 diagnosis reported in in- or outpatient care after index date. Study covariates included age, sex, eGFR, comorbidities and medications (definitions in Supplementary data, Tables S1–S3). Comorbid history was ascertained from preceding ICD-10 codes with no time restriction. Therapeutic procedures were identified from Nordic Medico-Statistical Committee classification codes, and pharmacy-dispensed medications by Anatomical Therapeutic Chemical Classification codes. Information on pharmacy-dispensed medications was obtained from the Dispensed Drug Registry, a nationwide register that records complete information on all prescription drugs dispensed at Swedish pharmacies. Medications were assumed to be concomitant if dispensed within the previous 5 months or 1 month after index date. Finally, CKD severity was categorized according to the KDIGO staging as follows: eGFR = 30–59 mL/min/1.73 m^2, eGFR = 29–15 mL/min/1.73 m^2 and eGFR <15 mL/min/1.73 m^2. In the statistical calculations, eGFR = 29–15 mL/min/1.73 m^2 and eGFR <15 mL/min/1.73 m^2 were merged to one group labeled eGFR <30 mL/min/1.73 m^2. Covariates were derived at index date and updated again at the time of incident pneumonia.

Study outcomes

The primary study outcomes were time to death and major adverse cardiovascular events (MACEs). Deaths were retrieved from the Swedish death registry, which is updated monthly and has complete national coverage. MACEs were defined as the composite of nonfatal stroke, myocardial infarction, heart failure, arrhythmia or death due to CVD, all of which have been associated with pneumonia in studies involving non-CKD individuals [28, 29]. The secondary study outcomes were time to CKD progression [>40% eGFR decline relative to baseline, or RRT initiation as ascertained by linkage with the Swedish Renal Register], AKI (defined by death or hospitalization attributed to N17) or other infection-related hospitalizations of importance for CKD [urinary tract infection (UTI) or septicemia].

To test the robustness of our findings and to assess the presence of residual confounding, we modeled two negative control outcomes (cataract and replacement of knee-joint surgeries—Supplementary data, Table S4) that we anticipated not to be associated with the exposure. Patients were followed from index date until occurrence of event, RRT, migration from the region, death or end of follow-up (31 December 2012), whichever occurred first.

Statistical analysis

Categorical data were expressed as proportions (%) and compared using the Chi-squared test. Continuous data were expressed as mean and standard deviation (SD) or median and interquartile ranges (IQRs). Person time was counted from the first date of available eGFR <60 mL/min/1.73 m^2.

We performed multivariable Cox proportional hazards regression models to examine the association between development of pneumonia and adverse outcomes. For this analysis, pneumonia (either diagnosed in outpatient care or requiring hospitalization) was considered as a time-updated exposure. Thus, a patient who developed pneumonia during follow-up contributed time to the nonpneumonia exposure group during the time before pneumonia had been diagnosed and thereafter, to the pneumonia-exposed group. Covariates were also time-updated at the time of incident pneumonia and included age, sex, eGFR, recent infections (Supplementary data, Table S4), comorbidities and use of relevant medications [immunosuppressive drugs, corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs)/aspirin, angiotensin-converting enzyme inhibitors (ACEi)/angiotensin II receptor blockers (ABRs), β-blockers, calcium channel blockers, mineralocorticoid receptor antagonists (MRAs), other antihypertensives, other diuretics, statins, anticoagulants and proton pump inhibitors]. When pertinent, adjustment for clinical history of AKI, MACE, UTI or sepsis was also performed.

In order to elucidate short-term versus long-term risk, we performed time-varying Cox regression analysis splitting the follow-up of the exposed period in two intervals: <90 and ≥90 days from index pneumonia. Although the majority of inpatients with pneumonia recover clinically within 1 week, we chose to conservatively define our short-term follow-up as <90 days.

Various sensitivity analyses were performed to test the robustness of our results: first, we modeled the risk association with cataract and knee-joint surgeries as negative control outcomes. Second, we performed subgroup analyses by age strata (<60 and ≥60 years), sex (men and women), presence/absence of diabetes, eGFR (<30 or ≥30 mL/min/1.73 m^2) and nature of the index pneumonia (inpatient or outpatient event). Third, we performed a further sensitivity analysis splitting the follow-up of the exposed period in three intervals: <90, 90–364 days and beyond 365 days from index pneumonia. Statistical analyses were performed using STATA version 15. Two-sided $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

The study population included 71 931 individuals with confirmed CKD (Supplementary data, Figure S1). At cohort entry, the mean (IQR) age was 79 (71–85) years old, 59% were women, 21% had diabetes and 39% had a history of CVD (Table 1). The majority had eGFR = 30–60 mL/min/1.73 m^2 (95%), and the remaining 5% had an eGFR <30 mL/min/1.73 m^2.

During a median follow-up of 3.7 years (IQR 2.1–5.0), 8379 subjects (12%) developed pneumonia. The overall pneumonia incidence was 33.3/1000 person-years (py) (95% CI 32.6–34.0), which increased across worsening CKD stages [from 30.3/1000 py (95% CI 29.6–31.0) in patients eGFR 30–60 mL/min/1.73 m^2 to 82.4/1000 py (95% CI 77.8–87.2) in patients with eGFR <30 mL/min/1.73 m^2]. Characteristics at time of pneumonia infection are detailed in Supplementary data, Table S5. The majority of pneumonia events (92%) led to a hospital admission, and only 8% of cases were completely managed in outpatient settings.

Table 1. Baseline characteristics of study participants

Demographics and medications	Overall
Number of individuals	71 931
Age, mean (IQR), years	79 (71–85)
Female, *n* (%)	42 689 (59.4)
eGFR, median (IQR), mL/min/1.73 m^2	49.4 (44.9–56.8)
eGFR ≥30 mL/min/1.73 m^2, *n* (%)	67 964 (94.5)
eGFR <30 mL/min/1.73 m^2, *n* (%)	3 967 (5.5)
Hypertension, *n* (%)	59 140 (82.2)
Diabetes, *n* (%)	15 311 (21.3)
CVD, *n* (%)	27 797 (38.6)
Myocardial infarction, *n* (%)	8 190 (11.4)
Congestive heart failure, *n* (%)	14 411 (20.0)
Peripheral vascular disease, *n* (%)	5823 (8.1)
Cerebrovascular disease, *n* (%)	11 155 (15.5)
Cancer, *n* (%)	13 688 (19.0)
Chronic obstructive pulmonary disease, *n* (%)	6834 (9.5)
Rheumatic disease, *n* (%)	4498 (6.3)
Dementia, *n* (%)	3287 (4.6)
Peptic ulcer disease, *n* (%)	2598 (3.6)
Liver disease, *n* (%)	1057 (1.5)
Hemiplegia or paraplegia, *n* (%)	364 (0.5)
Corticosteroids, *n* (%)	5953 (8.3)
Immunosuppressives, *n* (%)	1509 (2.1)
NSAID/aspirin, *n* (%)	34 683 (48.2)
ACEi/ARBs, *n* (%)	32 259 (44.9)
MRA, *n* (%)	6188 (8.6)
β-blockers, *n* (%)	32 645 (45.4)
Calcium channel blockers, *n* (%)	16 159 (22.5)
Other diuretics, *n* (%)	34 267 (47.6)
Other antihypertensive drugs, *n* (%)	705 (1.0)
Statins, *n* (%)	21, 547 (30.0)
Anticoagulant, *n* (%)	35, 277 (49.0)
Proton pump inhibitors, *n* (%)	13 534 (19.8)

Primary study outcomes

As many as 19 761 deaths and 26 446 MACE were registered (Table 2). Compared with nonpneumonia periods, incident pneumonia was associated with an increased death risk within the short-term (<90 days, hazards ratio, HR = 10.0; 95% CI 9.5–10.5) as well as ≥90 days of follow-up (HR = 2.0; 95% CI 1.9–2.1; Table 2). Similarly, the risk of MACE was highest in the acute phase after pneumonia (HR = 12.6; 95% CI 12.0–13.3), but remained elevated ≥90 days (HR = 1.5; 95% CI 1.4–1.6).

Secondary study outcomes

A higher incidence of CKD progression endpoints, AKI diagnoses and infection-related hospitalizations were also observed after development of pneumonia versus nonpneumonia periods, primarily within the first 90 days (Table 2). Developing pneumonia associated with a higher subsequent risk of CKD progression, and UTI/sepsis-related hospitalization both within the first 90 days (HR = 2.1; 95% CI 1.8–2.5 and HR = 9.7; 95% CI 8.9–10.5, respectively) and after ≥90 days (HR = 1.3; 95% CI 1.2–1.4 and HR = 1.7; 95% CI 1.6–1.8, respectively). The

Table 2. Association between incident pneumonia and subsequent health event risk within or beyond 90 days

Outcomes	Total number of events	Nonpneumonia period	<90 days after pneumonia			≥90 days after pneumonia		
		Event rate (per 1000 py)	Event rate (per 1000 py)	Crude HR (95% CI)	Adjusted HR (95% CI)	Event rate (per 1000 py)	Crude HR (95% CI)	Adjusted HR (95% CI)
Primary outcomes								
Death	19 761	60.3	1217.1	19.5 (18.6–20.5)	10.0 (9.5–10.5)	247.40	3.4 (3.3–3.6)	2.0 (1.9–2.1)
MACE	26 446	112.9	1842.5	16.7 (15.9–17.6)	12.6 (12.0–13.3)	192.90	1.9 (1.8–2.0)	1.5 (1.4–1.6)
Secondary outcomes								
CKD progression	10 741	41.8	121.1	2.8 (2.5–3.3)	2.1 (1.8–2.5)	77.70	1.7 (1.6–1.9)	1.3 (1.2–1.4)
AKI	1649	5.7	77.8	14.1 (11.7–16.9)	8.2 (6.7–9.9)	10.10	1.9 (1.5–2.3)	1.2 (1.0–1.5)
UTI or sepsis	9439	33.6	545.1	16.5 (15.3–17.8)	9.7 (8.9–10.5)	84.4	2.6 (2.4–2.9)	1.7 (1.6–1.8)
Control outcomes								
Cataract	8852	36	28.7	0.8 (0.6–1.1)	0.7 (0.5–1.0)	38.60	1.1 (1.0–1.2)	1.0 (0.9-1.1)
Replacement of knee-joint surgery	1121	4.4	3	0.8 (0.3–1.9)	1.0 (0.4–2.4)	2.20	0.6 (0.4–1.0)	0.8 (0.5–1.2)

Multivariable adjustment included age, sex, eGFR, comorbid history (recent infection, hypertension, CVD, diabetes mellitus, cancer, chronic obstructive pulmonary disease, rheumatic disease, dementia, peptic ulcer disease, liver disease, hemiplegia or paraplegia) and ongoing medications (immunosuppressive drugs, corticosteroids, NSAIDs/aspirin, ACEi/ABRs, β-blockers, calcium channel blockers, MRAs, other antihypertensives, other diuretics, statins, anticoagulants and proton pump inhibitors).

association between incident pneumonia and AKI was only seen during the first 90 days (HR = 8.2; 95% CI 6.7–9.9).

Sensitivity analyses

We found no association between pneumonia development and our negative control outcomes (Table 2). Associations were generally consistent across age groups, sex, eGFR strata, presence/absence of diabetes and inpatients/outpatients pneumonia, in both follow-up periods (Supplementary data, Figure S2 and Figure 1) following pneumonia. As expected, pneumonias that led to a hospital admission were associated with worse outcomes than pneumonias resolved through outpatient consultations. When the follow-up of pneumonia patients was split into three periods, the associations were the strongest during the first 90 days, but remained elevated both during the following year and after (Supplementary data, Table S6).

DISCUSSION

Pneumonia is common in persons with CKD, but few studies that have addressed the clinical consequences of pneumonia in these patients have exclusively focused on acute/short-term risks. Our findings corroborate and expand well-described associations between pneumonia and the short-term risk of death [19, 30] or AKI [20, 31, 32]. In addition, we present the observation of an increased MACE rate after incident pneumonia. We do also observe some increased risk of CKD progression during the first 90 days of observation, but we would call for caution in the interpretation of this finding. In our study, we defined CKD progression by relative eGFR changes calculated from outpatient creatinine measurements. This was done in an attempt to eliminate the influence that the index event (pneumonia hospitalization) has on creatinine fluctuations. However, this biomarker may still be biased during the short-term follow-up period, especially in the elderly patients.

The main novelty of our analysis is the exploration of long-term outcomes associated with incident pneumonia. Like recent evidence in the general population [6, 7, 33], we also observe that individuals surviving pneumonia are still at increased MACE and death risk in the long-term. Another novel finding in our study is an increased long-term risk of CKD progression after pneumonia. This association is intriguing and is backed-up by two recent population-based studies using administrative claims that link pneumonia with the incidence of CKD: first, an analysis from Taiwan observed an increased risk of RRT initiation in patients with inpatient pneumonia compared with healthy controls after >12 years of follow-up [34]; second, an analysis from Sweden observed that individuals with inpatient pneumonia were at higher risk of CKD diagnosis than healthy controls. This risk association was highest during the 5 years immediately after pneumonia [35]. By using a time-dependent exposure, our analysis offers some advantages over previous evidence, as it could be argued that the inpatient admission, rather than the subjacent cause, denotes a sicker/more predisposed patient to adverse outcomes. Furthermore, the use of repeated creatinine measurements to define CKD progression by validated thresholds of relative eGFR decline is another strength.

The mechanisms by which pneumonia could affect adverse outcomes in the long-term may involve inflammation and atherothrombosis. Infection is a pro-inflammatory disease that can affect the cellular composition of the atherosclerotic lesions [36] and activate the autoimmune response [37]. Interestingly, markers of systemic inflammation remain elevated after pneumonia recovery in >50% of cases [38, 39], and persistent systemic inflammatory activity may predispose to CVD [40], progression of CKD [23–25] and death [7–9, 41]. Pneumonia may also promote a pro-thrombotic environment [11, 12], while patients with pneumonia have shown higher levels of platelet activation biomarkers such as soluble P-selectin and thromboxane B2 [42], elevation in these markers after pneumonia discharge predicted the 1-year risk of (cardiovascular) death [43]. The development of AKI is also associated with greater activation of inflammation, coagulation and fibrinolysis pathways [20], and this can affect both CVD and CKD progression risk. Finally, the use in these patients of antibiotics such as macrolide [44, 45] or aminoglycosides [46] can also contribute. It could be

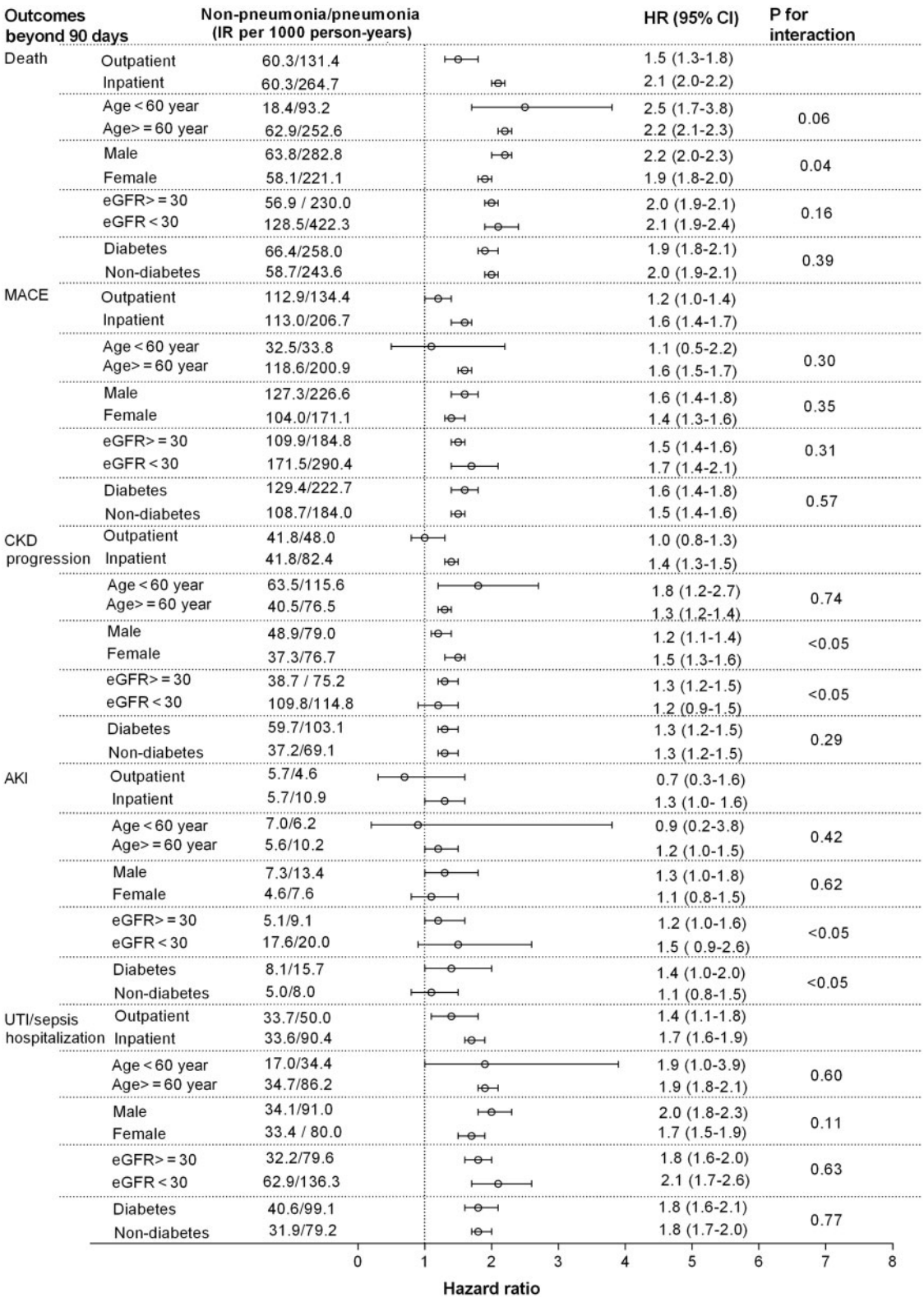

FIGURE 1: Association between incident pneumonia and long-term health event risks (beyond 90 days) in adults with non-dialysis-dependent CKD. Hazard ratios are adjusted for age, sex, eGFR, recent (90-day) infection, comorbidities (hypertension, CVDs, diabetes mellitus, cancer, chronic obstructive pulmonary disease, rheumatic disease, dementia, peptic ulcer disease, liver disease, hemiplegia or paraplegia) and medications (immunosuppressive drugs, corticosteroids, NSAIDs/aspirin, ACEi/ARBs, β-blockers, calcium channel blockers, MRAs, other antihypertensives, other diuretics, statins, anticoagulants and proton pump inhibitors). IR, incidence rate.

argued that these proposed mechanisms above are not exclusive in pneumonia but also in many other severe infections. In this sense, it is intriguing that a recent cross-sectional cohort study of advanced CKD patients from Canada associated (any) recent infection history with the risk of CVD events, initiation of RRT and death [47]. Whether this increase was attributed to pneumonia alone or to other infection types is yet to be analyzed.

Collectively, these findings evidence the need to further understand the consequences of infections in persons with CKD, for which there are established prevention strategies. Currently, pneumococcal vaccination is recommended by KDIGO to all adults with eGFR <30 mL/min/1.73 m^2 at high risk of pneumococcal infection (i.e. those with nephrotic syndrome, diabetes or under immunosuppressive medication) [48]. Interestingly, two observational studies in dialysis patients suggest improved survival among those undergoing pneumococcal vaccination compared with those without [49, 50]. Although our study cannot establish causal associations, we hope that the clinical importance of the outcome associations here evidenced motivates discussions on the value of vaccination campaigns in the broader range of persons with CKD and an adequate evaluation of costs/benefits ratio, optimal dose and vaccine delivery strategy.

Strengths of this study include its large sample size, region representativeness, careful design accounting for the background risk through nonexposed periods and virtually no loss to follow-up in a universal health care system, which is presumably less affected by socioeconomic or healthcare access bias. Our study should, nonetheless, be interpreted along with several limitations. First, we utilize clinical diagnoses, which may lead to ascertainment and misclassification biases. This said, the exposure and outcomes of interest have been validated against medical records and generally been found to possess high specificity and positive predictive values [51, 52]. Our data sources do not allow reliable differentiation of the severity of pneumonia and/or the underlying pathogen. Unknown and residual confounding are biases inherent to all observational studies, and we acknowledge the lack of information on potential confounders such as smoking habits, alcohol consumption or body mass index. Furthermore, we do not have data on antibiotics used during pneumonia hospitalizations or vaccinations. Finally, our study was conducted in Swedish residents with CKD during 2006–11, and its generalizability to other populations, countries or periods is uncertain.

We conclude that the risks of MACE, AKI, CKD progression, severe UTI/sepsis and death were independently increased after pneumonia diagnosis in a region-representative population of adults with CKD. These excess risks were found to be most pronounced in the 90 days after pneumonia, and to taper down to a lower, but still sustained risk thereafter. Our findings highlight the susceptibility for adverse outcomes of CKD patients following pneumonia diagnosis, and may inform clinical decisions regarding vaccination strategies.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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AUTHORS' CONTRIBUTIONS

G.S. and J.J.C. contributed to the research idea and study design; M.T. and J.J.C. contributed to data acquisition; G.S. and M.T. performed statistical analysis; G.S., J.I., M.T., K.M., C.S.L. and J.J.C. are responsible for results interpretation; C.S.L. and J.J.C are responsible for supervision or mentorship. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST STATEMENT

None declared.

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