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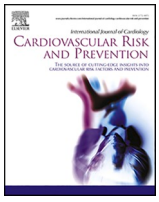

Time-dependent cardiovascular risks following pneumonia in inpatient and outpatient settings: A register-based cohort study☆

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ABSTRACT

Background: The elevated long-term cardiovascular disease (CVD) risks associated with pneumonia have been observed among inpatients, yet the risks associated with outpatients are less understood.
Methods: We used register-based data and a matched cohort design, including 98,354 pneumonia inpatients and 44,486 outpatients, as well as a 5-fold number of matched healthy controls. Associations between pneumonia presentation (in inpatient and outpatient settings) and long-term CVD risks were measured by rate difference and hazard ratio (HR) using Poisson and Cox regressions in a time-dependent manner.
Results: During a maximum follow-up period of 5.7 years of ischemic heart disease (IHD), heart failure (HF), and stroke were documented among pneumonia inpatients.
Relative to healthy controls, pneumonia patients showed increased risks of IHD, HF, and stroke. Women and young inpatients demonstrated stronger associations of CVD with pneumonia; inpatients aged 60 years or older showed the highest excessive CVD risks.
Conclusions: Pneumonia demanding outpatient and inpatient cares are intermediate-term and long-term risk factors of incident CVDs respectively, underscoring the need to plan setting-specific and time-dependent CVD-preventive cares following pneumonia presentation.

1. Introduction

Pneumonia is a respiratory infection that comprises a significant proportion of global death [1]. Pneumonia could cause mild to severe illness and its health consequences not only is confined to the lung, but also affect a range of non-respiratory organs [2–5]. Molecular evidence has suggested pneumonia could deleteriously affect cardiovascular function through direct cardiomyocyte lesions and a systemic pro-inflammatory status post-infection [2–5]. Further, population-based studies also found altered cardiovascular risks following pneumonia hospitalization where increased risks of cardiovascular diseases (CVD), including ischemic heart disease (IHD), heart failure (HF), and stroke, among pneumonia patients were observed [6–8]. Specifically, consistent evidence pointed to a time-dependent feature of the risk where increased CVD risks were highest in the short-term after pneumonia and remained an attenuating but significant trend through up to ten years [9–13].

Previous evidence on the long-term CVD risks was primarily derived from hospitalized pneumonia patients [9–13], leaving the risks associated with outpatients less understood. Only one study reported the

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long-term CVD risks among pneumonia outpatients and found a 54 % increased risk of HF among 3,163 outpatients within the first year following pneumonia [10]. However, the risks of CVDs other than HF and whether the time-dependent associations hold for pneumonia managed in the outpatient setting are still unknown. Given that a considerable number of pneumonia patients are treated in outpatient visits and they are likely to pay less attention to post-disease care after the recovery of the acute-phase infection, it is worthwhile to explore the long-term role of pneumonia as a risk factor of subsequent CVDs for outpatients.

In addition, pneumonia affects people of all ages, yet younger adults were under-represented in the related research, compared to middle-aged and older patients [9–13]. Of the previous research that explored the long-term effect of pneumonia on CVD risks, two studies used register-based data and analyzed participants above the age of 17 years and 18 years, respectively.[10 11] Yet of those studies, age-stratified effects were not estimated or estimated using a large cut-off point of 65 years, leaving the effects in younger adults uncertain.

Therefore, the present study aims to evaluate the CVD risks, including new-onset IHD, HF, and stroke, associated with pneumonia inpatients and outpatients in a time-dependent manner. We utilized a register-based and matched cohort design nested within a city-wide population, which takes advantage of a large sample size and patients with a wide spectrum of age, and aim to provide evidence on the post-discharge and post-visit care following pneumonia presentation for both the inpatient and outpatient settings.

2. Methods

2.1. Data disclosure statement

The authors are restricted from sharing the data underlying this study because of the sensitive nature of the data collected for this study. The analytic methods and study materials used in the analysis, including program scripts, are available from the author upon reasonable request.

2.2. Data source

The present study used Electronic Health Records from Shenzhen Health Information Platform, [14, 15] which collects and centralizes administrative medical information from all health institutions in Shenzhen, covering hospitals, community health service centers, and public health agencies. Briefly, all data are initially collected from individual medical and health institutions, temporarily stored in designed cache databases, undergoing quality control, and eventually uploaded to Shenzhen Health Information Platform. We analyzed Electronic Health Records from multiple databases (Fig. 1), including 1) the Medical Records collected for inpatients, outpatients, and community-based individuals who actively undergo health checkups for preventive purposes (referred to as healthy controls hereafter); 2) the Resident Records describing demographic characteristics collected for all permanent residents; and 3) the Death Records monitored and reported by Shenzhen Center for Disease Control and Prevention, of which the completeness was reported previously [16]. Electronic health records across different databases for the same individuals are linked with a unique pseudonymized identification number. All data extraction and analyses in the present study were based on centralized and quality-controlled data using Shenzhen Health Information Platform.

2.3. Study population

The study population was selected from permanent residents living in Shenzhen who had a medical record documented from 2017 January 1st to 2022 August 31st and had valid health records documented in 2022. Briefly, we included adult individuals who were diagnosed with pneumonia in the inpatient setting, had pneumonia diagnosed in the outpatient setting, and underwent health checkups as eligible pneumonia inpatients, pneumonia outpatients, and healthy controls, respectively, by employing a set of inclusion and exclusion criteria (Fig. 2). Patients or healthy controls who had a history of malignant neoplasms, immunocompromised status due to human immunodeficiency virus (HIV) infection, and cardiovascular diseases of interest to the present study (IHD, HF, and stroke) were excluded from the analyses. For those who had multiple episodes of pneumonia or health checkup recorded, the earliest record for each person was used as the index pneumonia event or index control event. Further, patients who were hospitalized with pneumonia diagnosis were excluded from the group of pneumonia outpatient; likewise, patients who were diagnosed

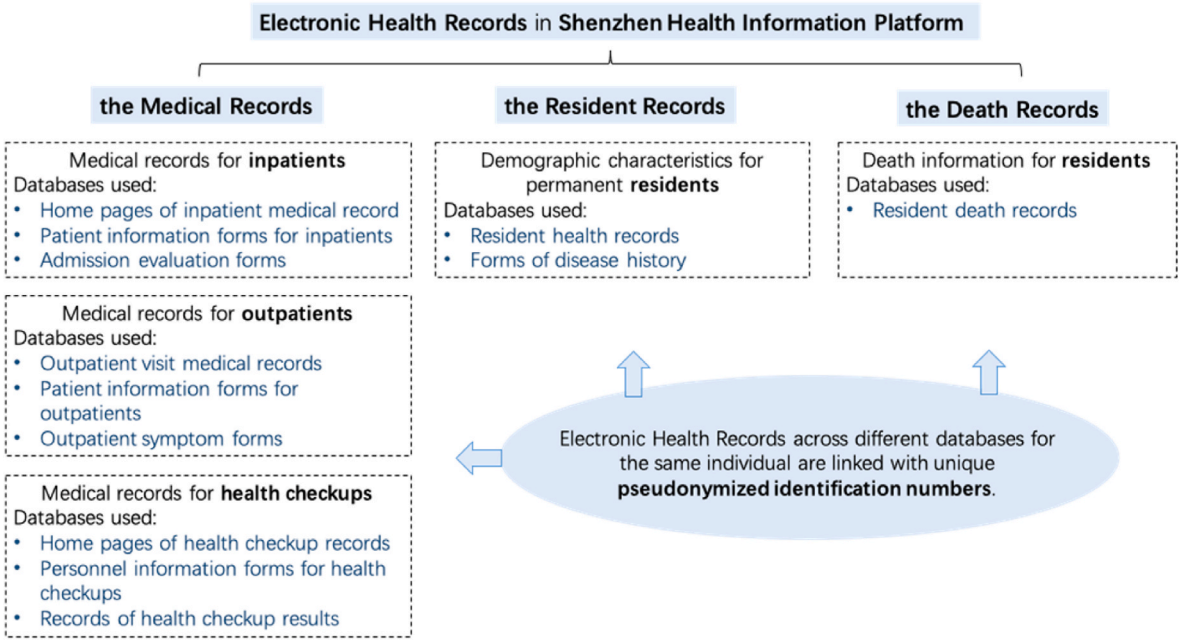

Fig. 1. Data source utilized in Shenzhen Health Information Platform. Figure legend: Electronic Health Records from multiple databases were extracted and analyzed in the present analyses, including the Medical Records, the Resident Records, and the Death Records.

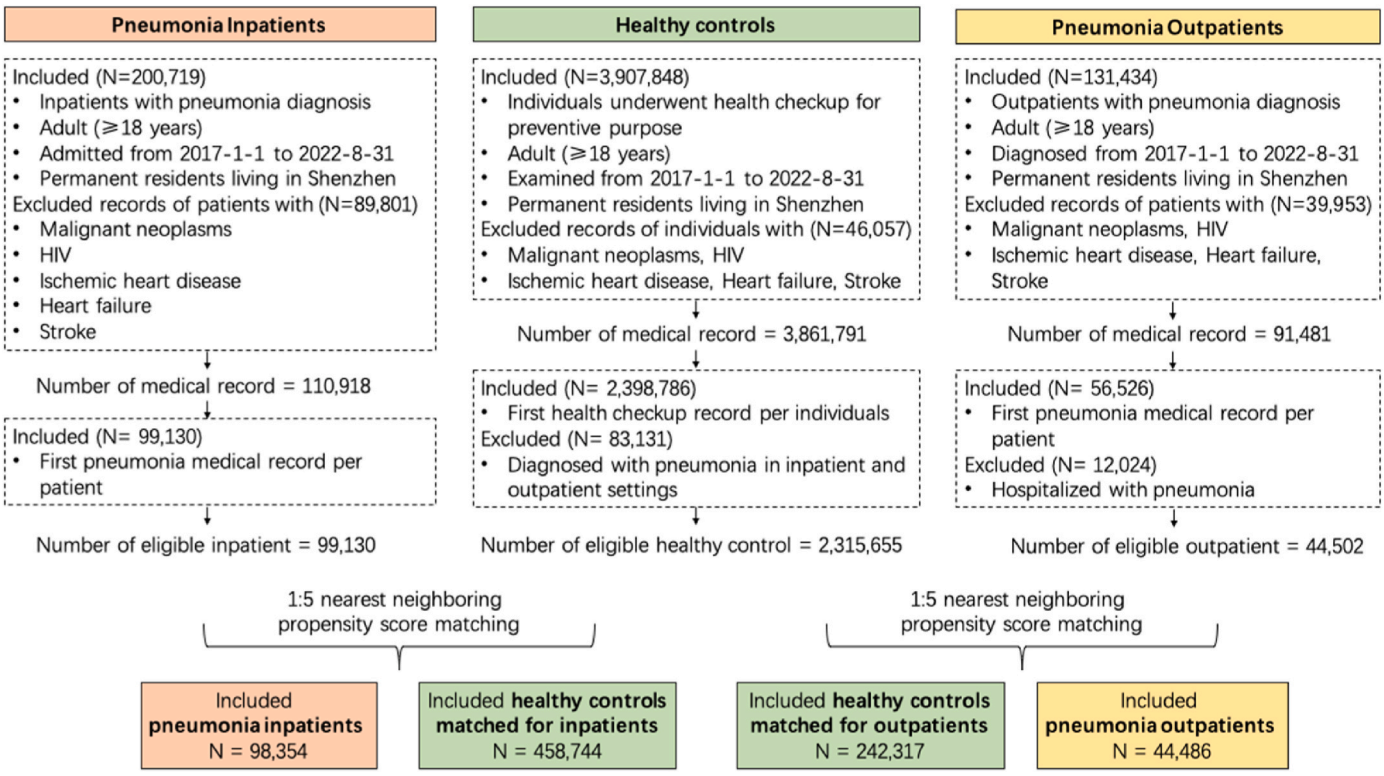

Fig. 2. Flowchart of study population selection. Figure legend: The study population was selected from adult individuals who were diagnosed with pneumonia in the inpatient setting, had pneumonia diagnosed in the outpatient setting, and underwent health checkups as eligible pneumonia inpatients, pneumonia outpatients, and healthy controls, respectively, by employing a set of inclusion and exclusion criteria. Further, we performed propensity score matching to select up to 5 healthy controls for each pneumonia patient, to balance baseline characteristics between patients and controls, including age, sex, marital status, ethnicity group, education, history of hypertension, and history of diabetes.

with pneumonia in the inpatient or outpatient setting were excluded from the group of healthy control. In total, we identified 99,130 pneumonia inpatients, 44,502 pneumonia outpatients, and 2,315,655 eligible healthy controls, respectively.

Next, to balance baseline characteristics between patients and controls, we performed propensity score matching (PSM) [17] to select up to 5 healthy controls for each pneumonia patient. Propensity scores took into account age, sex, marital status, ethnicity group, education, history of hypertension, and history of diabetes measured at the index pneumonia/control event through logistic regressions. Healthy controls were selected without replacement using the nearest neighbor matching within calipers on propensity score ($\leq$0.1) and age ($\pm$3 years) and the exact matching on sex. Eventually, 98,354 pneumonia inpatients, 458,744 healthy controls matched for inpatients, 44,486 pneumonia outpatients, and 242,317 healthy controls matched for outpatients were successfully paired and included in the present analyses. The medical ethical review committee of Southern University of Science and Technology has approved the present study (Approval Number 20210067) and a waiver of informed consent.

2.4. Assessment of exposure

Pneumonia diagnoses of inpatients and outpatients were extracted from the Home Pages of Inpatient Medical Record and the Outpatient Visit Medical Record, respectively. The 10th revision of the International Classification of Diseases (ICD-10) codes in the field of all discharge diagnoses were used to identify pneumonia inpatients; a combination of ICD-10 codes (Supplementary Table 1) and disease terminologies ("pneumonia" with an exclusion of "suspicious pneumonia") in Chinese recorded in the field of all outpatient diagnoses defined pneumonia outpatients. It's worth mentioning that the number of coronavirus disease 2019 (COVID-19) patients in Shenzhen in the study period was limited because the stringent zero-COVID-19 policy was employed before December 2022 in mainland China, leading to insufficient statistical power to estimate the COVID-19 effect. Therefore, COVID-19 infection data were excluded from the present analyses. Individuals who had a record of health checkup events in the database of Home Pages of Health Checkup Records were treated as candidates for healthy controls.

We performed a set of inclusion and exclusion criteria to select eligible pneumonia episodes and health checkup records documented from 2017 January 1st to 2022 August 31st (aforementioned in the Study Population section). For those who had multiple eligible pneumonia episodes or health checkup records, the earliest available records were used as the index event. The dates of hospital admission, outpatient visit, and health checkup were treated as the index dates for pneumonia inpatients, pneumonia outpatients, and healthy controls, respectively.

2.5. Assessment of outcomes

The outcomes of interest are new-onset CVD events, including IHD, HF, and stroke, which are ascertained through the Inpatient Medical Record and the Resident Death Record using ICD-10 codes (Supplementary Table 1). The first occurrence of IHD, HF, or stroke being listed as a discharge diagnosis in the Inpatient Medical Record or a cause of death in the Resident Death Record was considered as a new-onset outcome event, of which hospital admission date or death date was recorded as the corresponding outcome dates. All participants were followed from the index date through the time of their first CVD event or 2022 August 31st.

2.6. Assessment of covariates

Demographic characteristics, including age or date of birth, sex, education, ethnicity group, and marital status, of all permanent residents living in Shenzhen were extracted from the Resident Health Records. Education was initially recorded in six groups and then combined as a two-category variable (junior high school and lower education, senior high school and higher education) in the analyses. As a majority of the residents are of Han ethnicity, ethnicity groups were categorized as "Han" and "Non-Han". Marital status was analyzed as "married" and "unmarried" groups. Besides, the season of the index date was analyzed and classified as spring (March to May), summer (June to August), autumn (September to November), and winter (December to February).

Disease histories were ascertained through multiple sources of information, including discharge diagnoses reported in the Inpatient Medical Record, self-reported disease history documented in the Outpatient Visit Medical Record, and the Forms of Disease History recorded in the Resident Records. We evaluated the status for a set of disease histories, including malignant neoplasms, HIV infection, IHD, HF, stroke, hypertension, diabetes, and chronic obstructive pulmonary disease (COPD).

In addition, among pneumonia inpatients, we further explored the effects of comorbidity, length of hospital stay, and infection cause. The length of hospital stay was analyzed as three groups, namely 1–7 days, 8–14 days, and 15+ days. Laboratory- and/or clinical symptom-confirmed infection causes were recorded in a small proportion of the pneumonia inpatients, of whom three infection causes were analyzed, including bacterial, viral, and mycoplasma pneumonia.

A subset of study participants had height and weight examined and documented at the hospital admission, outpatient visit, or health checkup. Among those participants, the body mass index (BMI) was calculated as the weight (in units of kilogram) divided by height (in unit of meter) square.

2.7. Statistical analysis

We first described the baseline characteristics of four groups of the study population measured at the index date. Continuous and categorical variables were summarized as means (standard deviations [SD]) and proportions, respectively.

Next, we reported the absolute risk, i.e., incidence rate (IR), of three CVD events following pneumonia diagnosis or health checkup during follow-up, which started from the index date and ended at the first CVD event or death, with a maximum span of 5.7 years [18]. We also estimated the absolute risk difference, i.e., rate difference (RD), by fitting multivariate Poisson regression models with the identity link and robust variance estimation. [19, 20] Further, the strength of the associations between pneumonia and incident CVD risks were evaluated by hazard ratio (HR) and 95 % CI using multivariate Cox regression models. All multivariate regression models adjusted for demographic features (age, sex, education, marital status, and ethnic group), the season of the index date, and disease histories (hypertension, diabetes, and COPD), and Cox models were stratified by the "pneumonia patient - healthy control" pairs assigned by the PSM process in the selection of study population. The proportional hazards assumption was checked using the Schoenfeld residuals plots. As previous studies have noticed that the CVD risks following pneumonia are time-varying,[9 10] the present analyses were performed in a time-dependent manner, where IRs (95 % CIs), RDs (95 % CIs), and adjusted HRs (95 % CIs) were estimated for different follow-up periods, covering 0–3 months, 4–12 months, 1–2 years, 3–6 years after the index date.

Moreover, we tested whether the CVD risks associated with pneumonia were modified by sex and age. RDs (95 % CIs) and adjusted HRs (95 % CIs) were estimated in sub-population of different sex (men and women) and age groups (18–40 years, 41–60 years, 60–100 years). Interaction effects were estimated using the likelihood ratio test by comparing the Cox regression models with and without a multiplicative interaction term between the exposure and sex or age group. In addition, we explored the CVD risks according to different comorbidities, days of hospital stay, and infection causes among pneumonia inpatients. Risk estimates were also reported by prevalent disease status, including diabetes and hypertension. All subgroup analyses were estimated for two follow-up periods, 0–1 years and 2–6 years.

We performed several sensitivity analyses to test the robustness of the associations between pneumonia diagnosis and new-onset CVD risks. First, BMI was additionally adjusted in the Cox regression models to explore the BMI-independent effects. Second, we excluded the inpatients with ≥2 times of pneumonia hospitalization from the study population to rule out the effects due to repetitive infections (8,102 inpatients excluded). Third, a more stringent definition of pneumonia inpatients was employed where only inpatients with pneumonia listed as one of the first three discharge diagnoses were analyzed, to maximize the probability that pneumonia was the primary reason for the hospitalization (13,477 inpatients excluded). Fourth, to control the potential confounding effect arising from prevalent COPD and hyperlipidemia, inpatients with comorbidities of COPD and disorders of lipoprotein metabolism were excluded (2,514 and 9,852 and inpatients excluded, respectively).

3. Results

A total of 98,354 pneumonia inpatients and 44,486 outpatients were included in the present analyses, of which the average ages at index date were 46.5 years and 43.7 years and the proportions of women were 46.7 % and 48.3 %, respectively (Table 1). Compared to healthy controls, pneumonia inpatients were slightly older, more likely to get lower education, be unmarried, present with a history of diabetes, hypertension, and COPD, and have a slightly lower BMI. Pneumonia outpatients showed a similar pattern as with inpatients, except for presenting with a lower disease burden of diabetes and hypertension relative to the matched controls.

During a maximum follow-up period of 5.7 years (median follow-up period of 2.9 years), 9,443, 4,962, and 6,704 new-onset cases of IHD, HF, stroke were documented among pneumonia inpatients; the corresponding numbers observed for pneumonia outpatients were 504 IHDs, 260 HFs, and 285 strokes, respectively (Table 2, Supplementary Table 2). The incidence rates of all CVD outcomes were highest within the first three months and then declined across the follow-up period. Among inpatients, the IRs (95 % CIs) of IHD, HF, and stroke decreased from 14.2 (12.8,15.8), 13.2(11.8,14.8), 11.3(10.0,12.8) cases/1000 person-years in the first 3 months following pneumonia to 10.2 (9.6,10.8), 5.9(5.5,6.4), and 7.5(7.0,8.1) cases/1000 person-years in the 3–6 years. Similar descending patterns of IR were also observed for pneumonia outpatients, but with a lower absolute risk relative to that in inpatients.

Compared to healthy controls, pneumonia patients demonstrated excessive risks of all CVD outcomes estimated by RDs. Particularly, the risk showed a time-dependent feature where the RD was highest during the first 3 months following pneumonia diagnosis and then gradually reduced in the subsequent follow-up period (Fig. 3 Panel A). Pneumonia inpatients had 4.3 (3.5, 5.1), 6.6 (5.6, 7.6), 4.6 (3.8, 5.4) additional cases/1000 person-years of IHD, HF, and stroke in the first three months and excessive risks remained significant for up to six years; whereas outpatients showed lower RDs and the significant excessive risks were observed within the first two years following pneumonia presentation.

After adjustment for age, sex, index season, and other CVD risk factors, the hazards of all CVD outcomes in pneumonia patients were higher than those in the matched controls (Fig. 3 Panel B). HRs demonstrated a similar time-dependent pattern across the follow-up as with RDs. Among the pneumonia inpatients, the highest relative risks were observed for heart failure, followed by stroke and IHD. Namely, compared to healthy controls, pneumonia inpatients showed a 222 %

Table 1
Baseline characteristics of the study population.

	Pneumonia inpatients	Healthy controls for inpatients	P	Pneumonia outpatients	Healthy controls for outpatients	P
Number of individuals	98,354	458,744		44,486	242,317	
Age (years)	46.5 (15.8)	44.7 (14.4)	<0.001	43.7 (14.2)	43.8 (14.3)	0.102
18–40 years	41.8 %	44.5 %		48.3 %	48.1 %	
41–60 years	36.7 %	38.2 %		36.7 %	36.5 %	
61–100 years	21.6 %	17.3 %		15.0 %	15.5 %	
Women	46.7 %	46.9 %	0.511	48.3 %	48.5 %	0.686
Senior high school and higher education	57.7 %	61.7 %	<0.001	61.9 %	62.8 %	<0.001
Married	85.1 %	86.2 %	<0.001	84.6 %	84.3 %	<0.001
Han ethnicity	97.6 %	96.9 %	<0.001	98.6 %	97.9 %	<0.001
Disease history						
Diabetes	10.8 %	7.3 %	<0.001	3.8 %	4.4 %	<0.001
Hypertension	18.0 %	14.7 %	<0.001	9.2 %	11.5 %	<0.001
COPD	2.6 %	0.1 %	<0.001	0.6 %	0.1 %	<0.001
BMI (kg/m^2)[a]	23.8 (3.7)	24.1 (3.4)	<0.001	23.8 (3.7)	24.0 (3.4)	<0.001

COPD, chronic obstructive pulmonary disease; BMI, body mass index.
[a] 10,833, 103,417, 5,102, and 49,762 pneumonia inpatients, healthy controls for inpatients, pneumonia outpatients, and healthy controls for outpatients had BMI measurement.

Table 2
Number and incidence rate of new-onset CVD events among pneumonia inpatients and outpatients.

		Pneumonia inpatients		Pneumonia outpatients	
Outcome	Follow-up periods	No of event/ individual	IR (95% CI) /1000 person-years	No of event/ individual	IR (95% CI) /1000 person-years
IHD	0-3 months	343/98,354	14.2 (12.8,15.8)	122/44,486	11.3 (9.4,13.5)
IHD	4-12 months	690/93,930	10.5 (9.8,11.4)	135/42,510	4.7 (3.9,5.6)
IHD	1-2 years	718/80,118	9.9 (9.2,10.7)	113/33,637	4.1 (3.4,4.9)
IHD	3-6 years	1,123/64,649	10.2 (9.6,10.8)	134/21,747	4.6 (3.8,5.4)
HF	0-3 months	319/98,354	13.2 (11.8,14.8)	72/44,486	6.6 (5.2,8.4)
HF	4-12 months	496/93,955	7.6 (6.9,8.3)	75/42,559	2.6 (2.1,3.3)
HF	1-2 years	491/80,296	6.8 (6.2,7.4)	59/33,710	2.1 (1.6,2.8)
HF	3-6 years	659/64,994	5.9 (5.5,6.4)	54/21,830	1.8 (1.4,2.4)
Stroke	0-3 months	273/98,354	11.3 (10.0,12.8)	45/44,486	4.2 (3.1,5.6)
Stroke	4-12 months	561/93,999	8.6 (7.9,9.3)	86/42,585	3.0 (2.4,3.7)
Stroke	1-2 years	609/80,278	8.4 (7.7,9.1)	81/33,714	2.9 (2.3,3.6)
Stroke	3-6 years	833/64,884	7.5 (7.0,8.1)	73/21,812	2.5 (2.0,3.1)

IHD, ischemic heart disease; HF, heart failure; IR, incidence rate; CI, confidence interval.

(HR [95%CI] of 3.22[2.69,3.85]), 135 % (2.35[1.96,2.81]), 68 % (1.68 [1.45,1.94]) higher risks of new-onset HF, stroke, and IHD in the first 3 months; the corresponding risks reduced to the level of 63 %, 30 %, 26 % in the 3–6 years, respectively, but remained significant along the whole follow-up period. Among the pneumonia outpatients, pneumonia diagnosis was significantly associated with a 175 %, 122 %, and 46 % increased risk of HF, IHD and stroke in the first three months, respectively. Specifically, the elevated risks in outpatients were observed to a

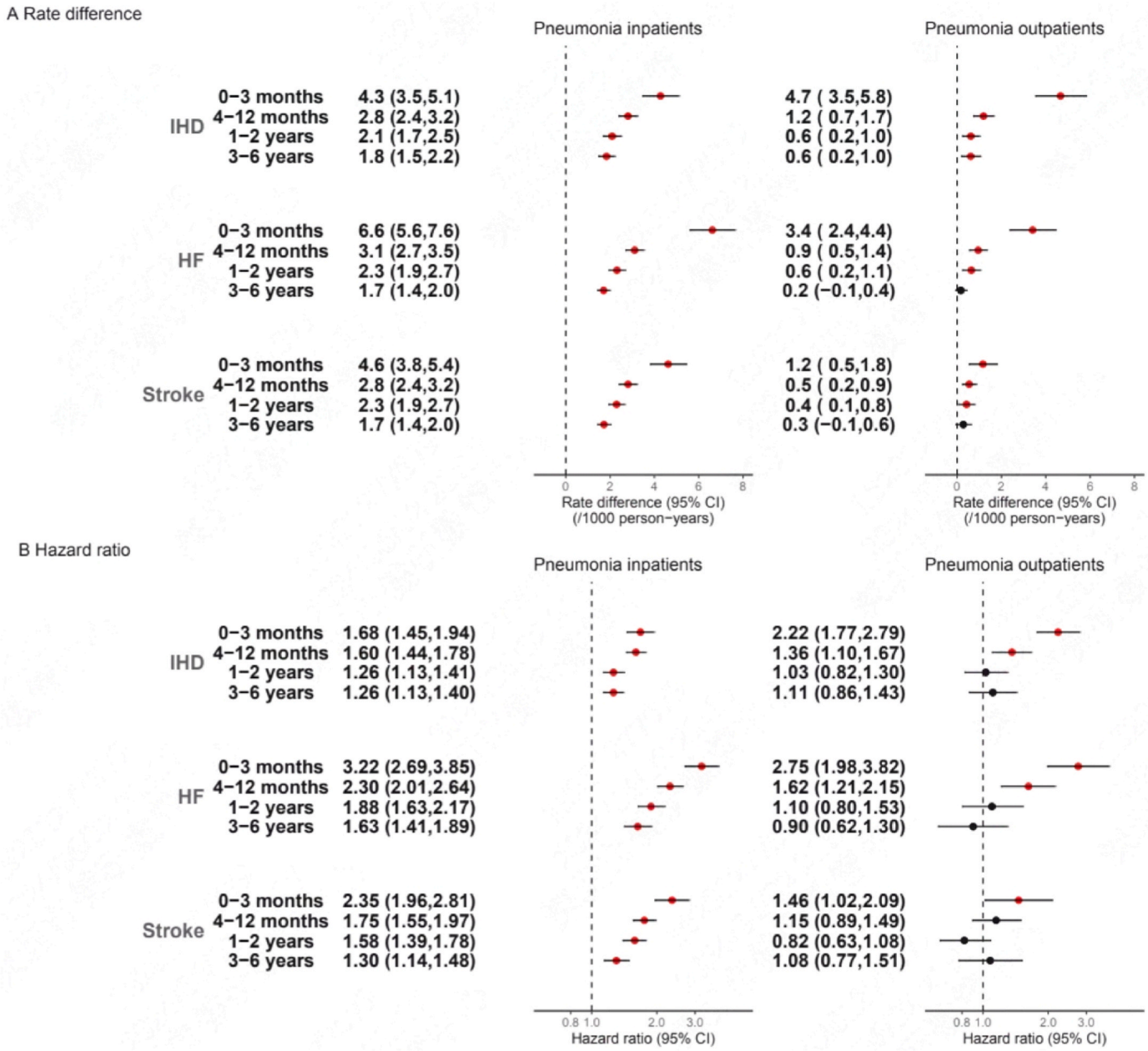

Fig. 3. Associations of cardiovascular diseases with pneumonia diagnosis among inpatients and outpatients. Figure legend: Associations between pneumonia and cardiovascular diseases were estimated via rate differences and hazard ratios using modified Poisson regression and Cox regression, respectively. All models adjusted for age, sex, education, marital status, and ethnic group, the season of the index date, and disease histories (hypertension, diabetes, and COPD), and Cox regression models were stratified by the "pneumonia patient - healthy control" pairs. Points and horizontal lines denote the point estimates and confidence intervals of HRs, respectively, where red points represent statistically significant estimates.

less degree and in a shorter period of no more than one year following pneumonia, compared to those in inpatients.

Subgroup analyses suggested a modification effect of sex and age group on the associations between pneumonia and CVD risks among inpatients (Supplementary Figs. 2–3, Fig. 4). Specifically, pneumonia inpatients demonstrated stronger associations with all CVD events among women compared with those in men. As for age groups, the highest excessive risks and lowest increased hazard were observed in the inpatients aged 60 years and higher; whereas younger inpatients (aged 18–40 years) exhibited the lowest excessive risks but highest relative risks as indicated by RDs and HRs, respectively (Fig. 4).

Longer hospital stays were associated with higher excessive risks and increased hazards of all CVD outcomes (Supplementary Table 4). Further, we tested the associations among inpatients with different infection causes and noticed increased CVD hazards associated with bacterial pneumonia (Supplementary Table 5). Firm results were not seen for viral and mycoplasma pneumonia as the sample sizes were limited. Stratified estimates indicated that the increased risks of IHD, HF, and stroke associated with pneumonia were relatively greater among participants with hypertension, compared with those observed in non-hypertensive participants (Supplementary Table 6).

The associations between pneumonia diagnosis and the subsequent new-onset CVD risks were not appreciably changed in the sensitivity analyses, including introducing additional adjustment for BMI in the Cox regression models, excluding inpatients with multiple pneumonia episodes, restricting the analyses to inpatients with pneumonia as the primary discharge diagnosis, and excluding inpatients with prevalent COPD as well as disorders of lipoprotein metabolism (Supplementary

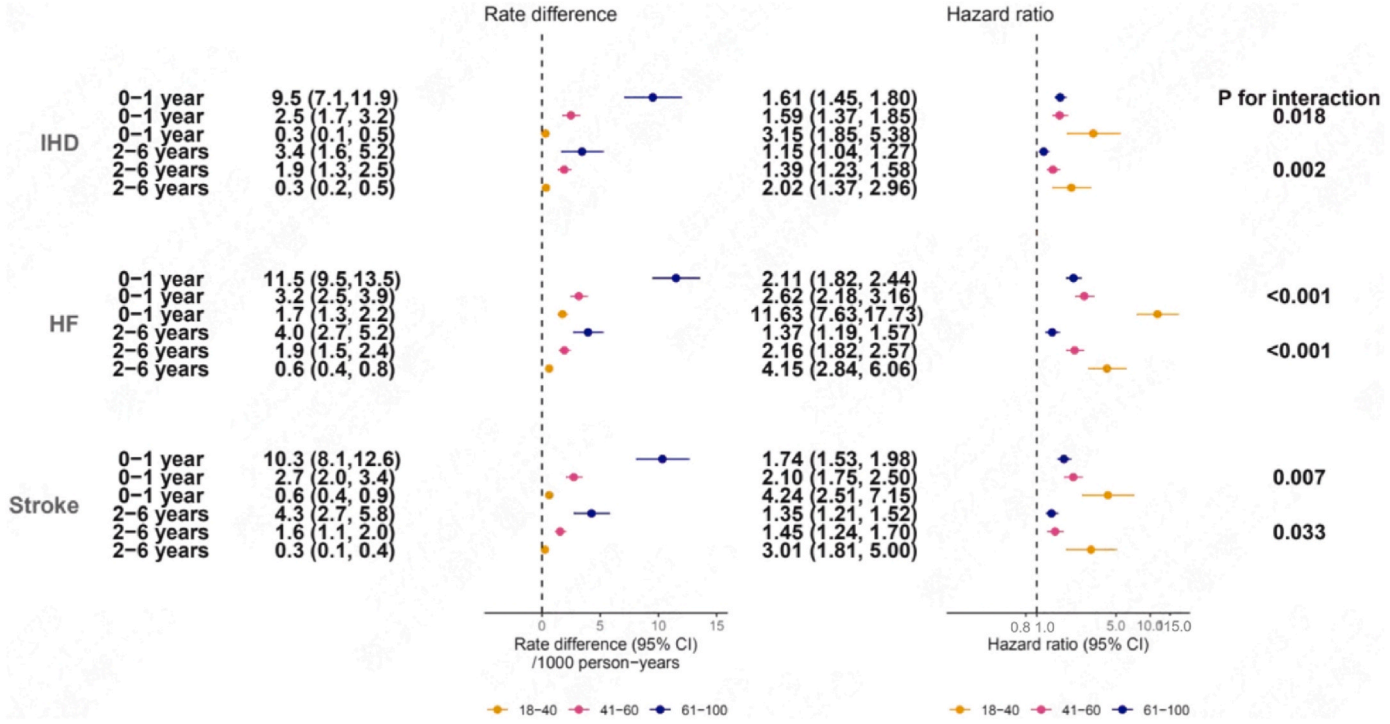

Fig. 4. Associations of cardiovascular diseases with pneumonia diagnosis among inpatients by age groups. Figure legend: Associations between pneumonia and cardiovascular diseases were estimated by age groups. All models adjusted for age, sex, education, marital status, and ethnic group, the season of the index date, and disease histories (hypertension, diabetes, and COPD), and Cox regression models were stratified by the "pneumonia patient - healthy control" pairs. Points and horizontal lines denote the point estimates and confidence intervals of HRs, respectively, where color groups represent estimates among different age groups.

Table 7).

4. Discussion

In this register-based study, we used a matched cohort design to evaluate the new-onset CVD risks of pneumonia patients identified in both inpatient and outpatient settings. Relative to healthy controls, pneumonia inpatients and outpatients showed excessive risks and increased hazards of IHD, HF, and stroke; the associations demonstrated time-dependent features, remaining highest in the first three months and declining subsequently. In particular, the increased risks persisted across the whole follow-up period for up to six years among inpatients, yet were only observed during the first one or two years following pneumonia presentation in outpatients. Women, younger, and longer hospital stay demanding inpatients presented stronger associations of CVD with pneumonia; while inpatients aged 60 years or older and discharged with hypertension had the highest excessive CVD risks.

Basic studies suggested that the infection-causing microbe and its toxins could lead to the direct damage of cardiomyocytes as well as the dysregulation of inflammatory pathways. [2, 3, 5, 21] Even after the clinical recovery, the imbalanced levels between pro-inflammatory and pro-resolving mediators contribute to a persistent inflammatory response. [2,22,23] Consistent with the above evidence, population studies also supported an elevated CVD risk in both the short- and long-term following pneumonia presentation. [7,24] However, the CVD risks of pneumonia patients treated in outpatient settings are less understood compared to those in inpatients [6–8]. Two previous studies have prospectively explored the associations between pneumonia episodes identified in outpatient visits and the subsequent CVD risks. Corrales-Medina et al. focused on the short-term (30 days) incident cardiac complications among pneumonia patients in the United States, and found heart failure, arrhythmias, and myocardial infarction are common in patients with community-acquired pneumonia [25]. Eurich et al. observed an increased long-term risk of heart failure following pneumonia presentation for up to 10 years, but did not have sufficient statistical power to estimate effects in a time-dependent manner due to a limited sample size [10]. The present study provided novel evidence with regard to the time-dependent CVD risks for pneumonia outpatients. Similar to the time-dependent features found for inpatients, CVD risks among outpatients were highest in the first three months and declined gradually. However, the increased risks of outpatients only observed for no more than one or two years, differ from those observed for inpatients which persisted for up to six years. As patients treated in the outpatient setting often present with milder symptoms and better prognoses, post-infection risks are likely to be underestimated after the outpatient visit. Given that a considerable number of pneumonia patients are treated in outpatient visits, introducing CVD-preventive knowledge and practice would be beneficial to reduce the long-term cardiovascular risks that might result from another possible respiratory disease-related epidemic in the post-COVID-19 period. Our results suggested that CVD-preventive cares after pneumonia presentation are needed especially within the first year following the outpatient visit and for up to six years following hospitalization.

Hospitalization for pneumonia has been consistently associated with higher long-term CVD risks. Previous studies have found the increased risks of IHD, HF, and stroke gradually attenuated across the follow-up but could hold up to 10 years following pneumonia hospitalization [9–13], consistent with our findings and reinforcing the need to perform long-term CVD prevention care after patients discharged from the hospital. Compared to those in the middle-aged and old-aged participants, the long-term risks for relatively younger participants are understudied. Two register-based studies covered a wide age spectrum starting from the beginning of adulthood. Bergh et al. included Swedish men aged 18 years or older but did not report the age-stratified effects [11]. Eurich et al. evaluated the relationship between pneumonia diagnosis and HF among participants aged 17 years or older and stratified the analyses by the age of 65 years, showing participants younger than 65 years had lower absolute risks but higher relative risks [10]. However, participants

younger than 65 years are still heterozygous and it is worthwhile to explore the risk among younger adults since they are susceptible to pneumonia as indicated in the COVID-19 pandemic. The present study took advantage of the register-based data and explored the associations among younger adults (18–40 years). We also found an age-dependent trend, where the younger pneumonia inpatients demonstrated the lowest risk difference but the highest hazard ratio, compared with healthy controls. Together with previous evidence, this result suggested an alert of post-discharge CVD risks could be beneficial even to younger patients hospitalized with pneumonia.

Contrary to the relative risks, i.e., hazard ratio, measuring the strength of the association, absolute risk difference, i.e., risk differences, quantifies the public health impact of the association [26]. In particular, in the subgroup analyses, we noticed that the absolute risk differences of new-onset CVD events associated with pneumonia diagnosis were more pronounced in inpatients aged 60 years or older and discharged with hypertension. This result suggested that public health strategies to reduce pneumonia hospitalization burden such as vaccination promotion could prioritize old and hypertensive individuals as the target population, as they might gain the most excessive health benefits in terms of CVD risk reduction.

The present study comes with a few strengths as we made use of city-wide register-based data, including the inclusion of a large sample size of pneumonia outpatients and participants with a wide age range, the ability to test pneumonia-CVD associations in a time-dependent manner, and the selection of controls from community-based and relatively healthy residents. We also acknowledge several limitations. First, there is a lack of information on the other behavioral CVD risk factors in the register-based data, such as smoking status. Even though we have controlled the effects of a range of demographic factors, disease histories, as well as BMI in the sensitivity analyses, further behavior-dependent effects of pneumonia on new-onset CVD risks cannot be estimated in the present analyses. Nevertheless, even without the information of behavioral factors, our main observation will not be changed that the pneumonia demanding both inpatient and outpatient cares is a risk factor for IHD, HF, and stroke in a time-dependent and setting-specific manner. Second, an inpatient record could document a maximum of 16 discharge diagnoses. We included inpatients with pneumonia listed as one of the discharge diagnoses and cannot rule out the possibility that other primary diseases were the major reasons leading to the elevated CVD risks. Therefore, we restricted the analyses to those who had pneumonia listed as the first three discharge diagnoses to maximize the possibility that pneumonia is the primary cause of hospitalization in the sensitivity analysis and the results were not appreciably changed. Third, we treated the earliest pneumonia record as the index event among those with multiple pneumonia admissions/visits, and this could lead to an overestimate of the effect as a repeated infection might indicate a worse general health status due to other underlying conditions. Thus we excluded the patients with multiple pneumonia records and the results were robust in the sensitivity analysis.

5. Conclusion

In conclusion, we observed increased risks of IHD, HF, and stroke associated with pneumonia diagnosis, where elevated risks were highest in the first three months and subsequently descended with time, lasting up to six years among inpatients and persisting about one or two years among outpatients. Pneumonia demanding outpatient and inpatient cares are intermediate-term and long-term risk factors of incident CVDs respectively, underscoring the need to perform setting-specific and time-dependent CVD-preventive cares following pneumonia presentation. In addition, aged 60 years or older and hypertensive pneumonia patients demonstrated the highest excessive CVD risks, suggesting that public health strategies targeting pneumonia such as vaccination promotion could prioritize individuals with advanced ages and hypertension in order to gain the most CVD benefits.

CRediT authorship contribution statement

Xia Li: Writing – original draft, Visualization, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Shuang Wang:** Writing – review & editing, Supervision, Methodology, Data curation, Conceptualization. **Keye Wu:** Writing – review & editing, Methodology, Conceptualization. **Chunbao Mo:** Writing – review & editing, Validation, Methodology, Formal analysis. **Furong Li:** Writing – review & editing, Validation, Methodology, Conceptualization. **Zhiyuan Cheng:** Writing – review & editing, Methodology, Conceptualization. **Fengchao Liang:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Jing Zheng:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Dongfeng Gu:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors report no relationships that could be construed as a conflict of interest.

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Appendix A. Supplementary data

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