Intermediate and long-term risk of new-onset heart failure after hospitalization for pneumonia in elderly adults

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Background Pneumonia is associated with high risk of heart failure (HF) in the short term (30 days) postinfection. Whether this association persists beyond this period is unknown.

Methods We studied 5,613 elderly (≥65 years) adults enrolled in the Cardiovascular Health Study between 1989 and 1994 at 4 US communities. Participants had no clinical diagnosis of HF at enrollment, and they were followed up through December 2010. Hospitalizations for pneumonia were identified using validated *International Classification of Disease Ninth Revision* codes. A centralized committee adjudicated new-onset HF events. Using Cox regression, we estimated adjusted hazard ratios (HRs) of new-onset HF at different time intervals after hospitalization for pneumonia.

Results A total of 652 participants hospitalized for pneumonia during follow-up were still alive and free of clinical diagnosis of HF by day 30 posthospitalization. Relative to the time of their hospitalization, new-onset HF occurred in 22 cases between 31 and 90 days (HR 6.9, 95% CI 4.46-10.63, $P < .001$), 14 cases between 91 days and 6 months (HR 3.2, 95% CI 1.88-5.50, $P < .001$), 20 cases between 6 months and 1 year (HR 2.6, 95% CI 1.64-4.04, $P < .001$), 76 cases between 1 and 5 years (HR 1.7, 95% CI 1.30-2.12, $P < .001$), and 71 cases after 5 years (HR 2.0, 95% CI 1.56-2.58, $P < .001$). Results were robust to sensitivity analyses using stringent definitions of pneumonia and extreme assumptions for potential informative censoring.

Conclusion Hospitalization for pneumonia is associated with increased risk of new-onset HF in the intermediate and long term. Studies should characterize the mechanisms of this association in order to prevent HF in elderly pneumonia survivors. (Am Heart J 2015;170:306-312.e6)

Heart failure (HF) affects ~2% of the Western population and is a leading cause of morbidity and mortality in elderly adults (age ≥65 years).[1] Because of our aging population, it has been estimated that by 2030, 1 in 33 Americans will have HF and the annual health care cost of this condition will be ~US$70 billion.[1] Therefore, in order to design better preventive strategies, characterizing risk factors for the development of new-onset HF in elderly individuals is an important goal.

Pneumonia affects ~1.2% of the population in the northern hemisphere each year, and it is the most common single diagnosis responsible for hospital admission in North America.[2,3] Pneumonia is particularly common among elderly adults, and two-thirds (66%) of pneumonia hospitalizations occur in this age group.[4,5] Contrary to other age groups, the rates of pneumonia in elderly individuals continue to rise.[2,4]

On the basis of acutely increasing systemic metabolic demands, pneumonia has long been regarded as a trigger for HF.[6] A recent meta-analysis showed that 14% of patients hospitalized for pneumonia develop new or worsening HF within 30 days of admission.[7] Nonetheless, pneumonia survivors continue to have increased morbidity and mortality long term after the infection and cardiovascular

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Submitted December 19, 2014; accepted April 25, 2015.

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0002-8703

http://dx.doi.org/10.1016/j.ahj.2015.04.028

diseases are major contributors to this effect.[8] Moreover, recent animal studies suggest that some pulmonary pathogens can produce persistent inflammatory damage to the myocardium event when the infection is resolved.[9] These elements suggest that pneumonia can increase the risk of HF well beyond the short-term postinfection. Because of the increasing burden of HF and pneumonia in our aging population, such association would have important implications for HF prevention and the management of patients with pneumonia. However, this relationship has never been investigated.

In this study, we tested the hypothesis that hospitalization for pneumonia is independently associated with increased risk of subsequent new-onset HF not only in the short term but also in the intermediate and long term in elderly adults.

Methods

Study population and data collection

The Cardiovascular Health Study (CHS) enrolled 5,888 community-dwelling elderly adults (age ≥65 years) from 4 US communities in California, Philadelphia, North Carolina, and Maryland.[10] The baseline evaluation (1989-1994) included a standardized physical examination, diagnostic and laboratory evaluation, and questionnaires on health status, medical history, lifestyle habits, and cardiovascular risk factors.[10–12] Update of major examination components and surveillance of new cardiovascular events and hospitalizations occurred at twice-yearly contacts, alternating between telephone calls and in-person clinic visits until 1999. Beyond 1999, ascertainment of vital status and surveillance for new cardiovascular events and hospitalizations continued through semiannual telephone contacts and review of Medicare Utilization files and local newspaper obituaries.[10] In our analyses, participants were followed up through December 2010 (mean follow-up 11.9 years). The institutional review boards at each participating site approved the study. All participants gave informed consent.

Event assessment

Hospitalizations for pneumonia were adjudicated using a previously validated method based on the presence of *International Classification of Disease Ninth Revision* (*ICD-9*) codes for pneumonia in at least 1 of the first 5 discharge diagnosis fields of hospital discharge abstracts.[4,13] Our review of a subset of medical records (158) identified by this approach found documentation of clinical and radiographic diagnoses of pneumonia in 89% and 88% of cases, respectively.[14] We defined pneumonia as severe when *ICD-9* codes suggestive of severe sepsis, septic shock, or organ dysfunction were also present, as previously validated.[15] For sensitivity analyses, we used a more stringent definition of pneumonia hospitalizations in which *ICD-9* codes 481, 482, 485, or 486 (suggestive of bacterial pneumonia) were listed in the primary (first) discharge diagnosis field. This more stringent definition reduces the sensitivity of capturing all hospitalizations with pneumonia but maximizes the probability that pneumonia was indeed a reason for these admissions.[13] We did this to account for the possibility of confounding due to unrecognized cases of HF misdiagnosed as pneumonia during a hospital admission. Using this definition, our review of a subset of medical records found documentation of clinical and radiographic diagnoses of pneumonia in 94% and 96% of cases, respectively.[14]

For adjudication of HF events, medical records of potential new events were directed to a centralized CHS Events Subcommittee.[16] As per CHS protocol, diagnosis of HF required all of the following: (*a*) documentation of HF diagnosis by a treating physician; (*b*) HF symptoms (shortness of breath, fatigue, orthopnea, paroxysmal nocturnal dyspnea) and signs (edema, rales, tachycardia, gallop rhythm, displaced apical impulse), or supportive findings on echocardiography, contrast ventriculography, or chest radiography; and (*c*) medical therapy for HF (diuretics plus either digitalis or a vasodilator).[17] New-onset HF was the first HF event during study follow-up in individuals without HF at enrollment.[16]

Covariables

These included age, sex, race, coronary heart disease (prevalent at study entry and incident during the study), atrial fibrillation, diabetes, heart valve disease, smoking status, body mass index, heart rate, systolic and diastolic blood pressures, serum low-density lipoprotein cholesterol and high-density lipoprotein cholesterol, glomerular filtration rate (estimated as per the Modification of Diet in Renal Disease Study equation),[18] serum C-reactive protein, left ventricular hypertrophy by electrocardiogram, forced expiratory volume in 1 second (FEV_1; measured by spirometry), use of antihypertensive drugs, use of aspirin, and use of statins. With the exception of FEV_1, all covariables were regularly updated at study clinic visits (online Supplementary Table SI).

Statistical analyses

Because the outcome of our study was new-onset HF, patients with a clinical diagnosis of HF at baseline were excluded. The prevalence of missing values for covariables at baseline ranged from 0 to 5.3% (online Supplementary Table SII). To account for this, we used multiple imputation (with additional predictors, online Supplementary Table SII) to create 10 complete data sets of the covariables selected for analyses. To determine the risk of new-onset HF after pneumonia, we used multivariable Cox regression. Patients were censored at time of death or loss to follow-up. The main exposure variable was a time-dependent indicator corresponding to 5 prespecified time intervals after the first (index) hospitalization for pneumonia: 31-90 days, 91 days to 6 months, 6-12 months, 1-5 years, and >5 years. We included all preselected covariables (listed above) in our model. When covariables had >1 measurement during

follow-up, we treated them as time dependent and used their most recent value at any given event time. To account for changes in the hazard of pneumonia over time, we included an interaction term for pneumonia and age. We ran this model in each of the 10 imputed data sets and combined the results to produce our final estimates.[19] We repeated these procedures with pneumonia defined by its severity.

Because time after pneumonia is a continuum, we did not arbitrarily exclude the immediate (0-30 days) post-pneumonia interval from our models. However, in CHS, all incident events diagnosed during one same hospitalization were adjudicated the date of that admission as the date of their occurrence (ie, they were adjudicated the same date of occurrence). This prevented us from making any inference of precedence between pneumonia and HF events when they were diagnosed in the same hospitalization, rendering estimates of HF risk in the 0-30-day postpneumonia interval unreliable. Therefore, these estimates are not reported. To evaluate informative censoring from death and loss to follow-up, we performed sensitivity analyses under 2 extreme assumptions: (1) that censored individuals experience an HF event immediately after censoring and (2) that censored individuals have longer times to events than do uncensored individuals.[20] To explore potential confounding effects of recurrent episodes of pneumonia, we repeated our main analysis censoring patients who had >1 episode of pneumonia at the time of their second episode. To explore whether any association between hospitalization for pneumonia and subsequent new-onset HF is simply a function of individuals' frailty and/or the acute hospitalization per se (regardless of the cause), we repeated our main analyses with hospitalization for fractures (hip, *ICD-9* code 820.xx; vertebral, *ICD-9* code 805.xx; wrist, *ICD-9* codes 813.xx and 814.xx; and ribs, *ICD-9* codes 807.0x and 807.1x), and not pneumonia, as the exposure of interest. We chose these fractures because they are (similar to pneumonia) also well-recognized markers of individuals' aging and frailty, and a common cause of acute hospitalization[21–24]; however, they have no known intermediate or long-term biological effects that are shared with pneumonia.

All tests were 2 sided, and a P value less than .05 was considered statistically significant. Variables with a normal distribution were described using means and SDs, and those with a skewed distribution using medians and interquartile range (IQR). Comparisons were made using Pearson χ^2 tests, 2-sample Student t tests, or Wilcoxon 2-sample tests, as appropriate.

Analyses were implemented using SAS v.9.2 (SAS, Cary, NC) or R statistical software (R Project for Statistical Computing, http://www.r-project.org/).

Results

Of 5,888 participants in CHS, 275 had clinical diagnosis HF at enrollment and were excluded. Our analysis included 5,613 participants. During follow-up, 1,315 (23.4%) participants were hospitalized with pneumonia at least once (median time to pneumonia 8.8 years, IQR 5.3-12.5 years), whereas 1,868 participants developed new-onset HF (median time to new-onset HF 9.0 years, IQR 4.8-13.6 years). Participants who were hospitalized with pneumonia were slightly younger than the rest of participants but had a heavier burden of cardiovascular comorbidities and risk factors such as coronary heart disease, atrial fibrillation, diabetes, and smoking (Table I).

Table I. Baseline characteristics of patients with and without pneumonia

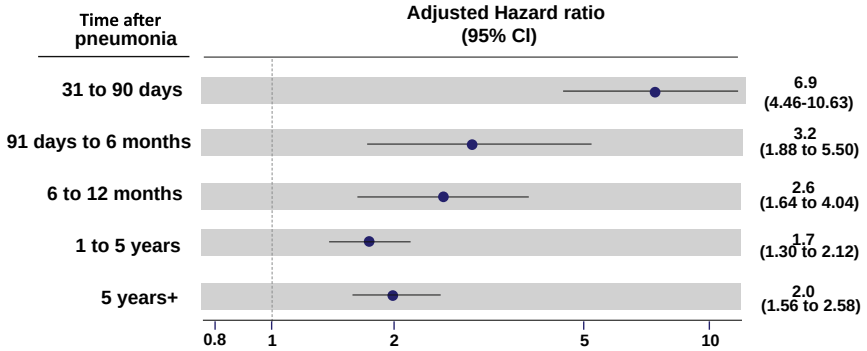
Baseline characteristics	Hospitalization for pneumonia		
	Yes (n = 1315)	No (n = 4298)	*P*
Age (y)	72.5 (5.5)	73.5 (5.6)	<.001
Male gender	611 (46.5%)	1,751 (40.7%)	<.001
Ethnicity			.024
White	1130 (85.9%)	3585 (83.4%)	
African American	174 (13.2%)	690 (16.1%)	
Other	11 (0.8%)	23 (0.5%)	
Coronary heart disease	283 (21.5%)	696 (16.2%)	<.001
Atrial fibrillation	38 (2.9%)	80 (1.9%)	.023
Diabetes	245 (18.6%)	625 (14.5%)	<.001
Valvular heart disease	75 (5.9%)	213 (5.1%)	.271
Smoking	774 (58.9%)	2,231 (52.0%)	<.001
Body mass index (kg/m^2)	26.4 (4.6)	26.8 (4.7)	.008
Heart rate (beats/min)	66 (11)	65 (11)	.002
Systolic blood pressure (mm Hg)	137 (22)	137 (22)	.618
Diastolic blood pressure (mm Hg)	70 (12)	71 (12)	.014
Serum LDL cholesterol (mg/dL)	129 (37)	131 (35)	.041
Serum HDL cholesterol (mg/dL)	54 (16)	55 (16)	.117
Glomerular filtration rate (mL/min per 1.73 m^2)	68.5 (18)	68.7 (18)	.768
Serum C-reactive protein (mg/L)	2.7 (1.3-4.8)	2.4 (1.2-4.2)	.018
LV hypertrophy by ECG	66 (5.2%)	176 (4.2%)	.138
Percent of predicted FEV_1	85.9 (23.4)	91.8 (21.6)	<.001
Use of antihypertensive medications	655 (49.8%)	1899 (44.3%)	<.001
Use of aspirin	463 (35.2%)	1406 (32.8%)	.100
Use of statins	30 (2.3%)	97 (2.3%)	.965

Data are number (%), mean (SD), or median (IQR).
Abbreviations: LDL, low-density lipoprotein; HDL, high-density lipoprotein; LV, left ventricle; ECG, electrocardiogram.

Of the 1,315 participants hospitalized for pneumonia, 315 were diagnosed as having HF before their index pneumonia hospitalization, and an additional 348 died (161), were lost to follow-up (1), or were diagnosed as having new-onset HF (186) within the first 30 days of their pneumonia admission. Thus, there were 652 pneumonia survivors who were still free of HF diagnosis at 30 days posthospitalization. Among these, the cumulative number of patients who experienced new-onset HF between 31 and 90 days, 91 days and 6 months, 6 months and 1 year, 1 to 5 years, and >5 years postinfection were 22 (3.4%), 36 (5.5%), 56 (8.6%), 132 (20.2%), and 203 (31.1%), respectively.

Hospitalization with pneumonia was associated with increased risk of new-onset HF in the intermediate and long term postinfection. The magnitude and direction of hazard ratios (HRs) for new-onset HF after hospitalization for

Figure



Intermediate and long-term risk of new-onset HF after hospitalization for pneumonia: All estimates are adjusted for age, gender, race, coronary heart disease (prevalent at study entry and incident during the study), atrial fibrillation, diabetes, heart valve disease, smoking status, body mass index, heart rate, systolic and diastolic blood pressures, serum low-density lipoprotein cholesterol, serum high-density lipoprotein cholesterol, glomerular filtration rate, serum C-reactive protein, left ventricular hypertrophy by electrocardiogram, percent of predicted FEV_1 (as measured by spirometry), use of antihypertensive drugs, use of aspirin, and use of statins. With the exception of age, gender, race, prevalent coronary heart disease at study entry, and percent of predicted FEV_1, all covariables that were regularly updated during study follow-up were treated as time dependent in the model.

pneumonia were overall concordant in unadjusted analyses, adjusted analyses with covariables measured at study entry only, adjusted analyses using complete cases only (no imputed data), and adjusted analyses with the complete data set after the imputation process and using time-updated covariables (online Supplementary Table SIII). In the latter, HRs for new-onset HF at 31 to 90 days, 91 days to 6 months, 6 months to 1 year, 1-5 years, and >5 years after pneumonia were 6.9 (95% CI 4.46-10.63, $P < .001$), 3.2 (95% CI 1.88-5.50, $P < .001$), 2.6 (95% CI 1.64-4.04, $P < .001$), 1.7 (95% CI 1.30-2.12, $P < .001$), and 2.0 (95% CI 1.56-2.58, $P < .001$), respectively (Figure). The magnitude of the association between pneumonia and intermediate and long-term risk of new-onset HF at each post-pneumonia interval was greater than or similar to other well-established risk factors for HF (online Supplementary Table SIV).

The HRs for new-onset HF after pneumonia did not substantially differ between severe and nonsevere cases, except for the period of >5 years after pneumonia (HR 3.4 [95% CI 2.47-4.72] in severe pneumonia and HR 1.3 [95% CI 0.89-1.86] in nonsevere pneumonia) (Table II).

Only a minority (14%) of new-onset HF events after hospitalization for pneumonia were preceded by coronary heart disease (online Supplementary Tables SV).

Table II. Intermediate and long-term risk of new-onset HF after hospitalization for severe and nonsevere pneumonia

Time after hospitalization for pneumonia	Severe pneumonia		Nonsevere pneumonia	
	HR	95% CI	HR	95% CI
30-90 d	6.2	2.74-13.88	7.2	4.33-11.85
91 d–6 mo	3.0	1.13-8.15	3.3	1.75-6.16
6-12 mo	1.7	0.64-4.58	2.9	1.76-4.83
1-5 y	1.9	1.25-2.77	1.6	1.16-2.09
5 y+	3.4	2.47-4.72	1.3	0.89-1.86

All estimates are adjusted for age, gender, race, coronary heart disease (prevalent at study entry and incident during the study), atrial fibrillation, diabetes, heart valve disease, smoking status, body mass index, heart rate, systolic and diastolic blood pressures, serum low-density lipoprotein cholesterol, serum high-density lipoprotein cholesterol, glomerular filtration rate, serum C-reactive protein, left ventricular hypertrophy by electrocardiogram, percent of predicted FEV_1 (as measured by spirometry), use of antihypertensive drugs, use of aspirin, and use of statins. With the exception of age, gender, race, prevalent coronary heart disease at study entry, and percent of predicted FEV_1, all covariables that were regularly updated during study follow-up were treated as time dependent in the model.

Sensitivity analyses and analysis with fracture as the exposure of interest

Sensitivity analysis using the more stringent definition of pneumonia produced estimates largely consistent with our main analyses (online Supplementary Tables SVI). Sensitivity analyses also indicated robustness against informative censoring (online Supplementary Table SVII). When patients who had ≥2 episodes of pneumonia were censored at the time of their second pneumonia episode, the HRs for new-onset HF after pneumonia remained significant up to 1 year and >5 years postinfection; however, although the HR for the 1- to 5-year postpneumonia interval also remained elevated at 1.2, its 95% CI was not statistically significant (0.91-1.67; online Supplementary Table SVIII).

Finally, when we repeated our main analysis with hospitalization for fractures as the exposure of interest, there was a significant increase in the risk of HF in the first 6 months posthospitalization but no obvious association after that (Table III). Details of the baseline characteristics of the 767 patients hospitalized with fractures in CHS and their

Table III. Intermediate and long-term risk of new-onset HF after hospitalization for fracture

Time after hospitalization for fracture	HR	95% CI	*P*
30-90 d	2.3	1.09-5.01	.029
90 d–6 mo	2.3	1.19-4.34	.012
6-12 mo	1.0	0.48-2.01	.960
1-5 y	1.2	0.85-1.56	.336
5 y+	1.2	0.86-1.72	.260

All estimates are adjusted for age, gender, race, coronary heart disease (prevalent at study entry and incident during the study), atrial fibrillation, diabetes, heart valve disease, smoking status, body mass index, heart rate, systolic and diastolic blood pressures, serum low-density lipoprotein cholesterol, serum high-density lipoprotein cholesterol, glomerular filtration rate, serum C-reactive protein, left ventricular hypertrophy by electrocardiogram, percent of predicted FEV_1 (as measured by spirometry), use of antihypertensive drugs, use of aspirin, and use of statins. With the exception of age, gender, race, prevalent coronary heart disease at study entry, and percent of predicted FEV_1, all covariables that were regularly updated during study follow-up were treated as time dependent in the model.

rates and timing of new-onset HF events after hospitalization are provided in online Supplementary Tables SIX and SX.

Discussion

In a large community-based prospective sample of elderly adults without HF at baseline, hospitalization for pneumonia was independently associated with a pronounced increase in the risk of new-onset HF in the intermediate and long term. This association was evident for patients with both severe and nonsevere pneumonia. Our results did not substantially change even when stringent case definitions for pneumonia were used or under extreme assumptions for potential informative censoring. The association between hospitalization for pneumonia and new-onset HF remained significant after removing the potential contribution from repeated episodes of pneumonia. Even in the very long term (>5 years after hospitalization for pneumonia), the magnitude of the relative risk increase of new-onset HF associated with pneumonia was comparable to or greater than the risk associated with well-established risk factors for HF. The increase in HF risk after pneumonia hospitalization was independent of traditional risk factors including coronary heart disease, and most (86%) of new-onset HF events postpneumonia were not preceded by this diagnosis. Hospitalization for fracture was also associated with increased risk of new-onset HF in the first 6 months after admission; however, in contrast to pneumonia, hospitalization for fracture was not associated with HF risk in the long-term.

Previous studies have typified the immediate short term (≤30 days) postpneumonia as a high-risk period for the development of HF.[6,25] However, to the best of our knowledge, our study is the first to describe an independent association between pneumonia and new-onset HF beyond the short term. The strength and magnitude of this association suggest that there is an opportunity for preventing a substantial number of new-onset HF events in this population. Moreover, because pneumonia survivors have increased long-term morbidity and mortality, prevention HF postpneumonia could also improve these outcomes. Finally, because of the burden of pneumonia in elderly adults, recognizing this association may also contribute to improve the assessment of HF risk in the general elderly population and it should be taken into account when estimating the cost and benefit of interventions (ie, vaccination) aimed at preventing pneumonia in this population.

The mechanisms by which pneumonia may trigger HF in the short term have been discussed elsewhere.[6,25] These mechanisms are mostly explained by the acute physiological stress associated with the acute illness and also by processes and procedures related to patients' transfer of care and inpatient management (transient interruption of stable therapeutic regimens for preexisting cardiovascular conditions, administration of large sodium loads and/or infusion volumes from commonly used intravenous medications, transfer of care back to community primary care providers, etc). These mechanisms are not specific to pneumonia, and their effect could linger after hospitalization. This could explain the highest HRs for new-onset HF in the first few months after pneumonia hospitalization and also the higher risk in the first few months after hospitalization for fractures. However, the persistent higher risk of new-onset HF in the long term after hospitalization for pneumonia suggests more complex biological interactions. Even when patients recover from the acute infection, pneumonia survivors seem to continue exhibiting elevated systemic inflammatory activation. This is important because chronic inflammatory activation has been implicated in the development and progression of HF in the general population.[26] Although >80% of patients hospitalized for pneumonia clinically recover by 1 week, >50% still show heightened markers of systemic inflammation.[27,28] Hansson et al[29] reported mean circulating C-reactive protein levels of 5 mg/L (95% CI 4-6) in 95 pneumonia survivors (mean age 70 years) at 6 months after their infection. Levels of C-reactive protein ≥3.0 mg/L have been associated with high risk of coronary artery disease and HF in nonpneumonia settings.[30,31] Moreover, elevated levels of interleukin-6 in blood at hospital discharge in pneumonia survivors are predictive of 1-year cardiovascular mortality.[32] Another potential mechanism is that acute insults to the cardiovascular system that occur during the acute infection have long-lasting effect on vascular or myocardial function. A detailed autopsy study of 67 patients with lobar pneumonia showed pathological evidence of myocarditis in 39% of cases.[33] Moreover, markers of myocardial cell injury (ie, troponins) are frequently elevated at hospital presentation in patients with pneumonia without acute coronary syndromes.[34] Therefore, it is possible that myocardial injury during pneumonia causes enduring decline in myocardial function. More recent animal studies also suggest that certain pneumonia-producing bacteria such as *Streptococcus pneumoniae* can invade the myocardium during severe infections and leave lingering foci of

myocardial inflammation even when the infection has resolved after antibiotic therapy.[9] In addition, infection can also induce acute inflammation of the arterial wall,[35] potentially leading to lasting impairment of the elastic properties of arteries, which in turn may result in lasting increments in the pulsatile left ventricular afterload.[36] Finally, acute kidney injury is common during pneumonia and its progression to chronic kidney disease could also increase HF risk.[37] A more accurate characterization of these mechanisms should help in informing the design and testing of any future strategies for the prevention of HF in elderly pneumonia survivors.

Strengths of this study include its large, community-based population, its prospective design, long follow-up, detailed and longitudinal evaluation of cardiovascular risk factors, and comprehensive methodology for surveillance and adjudication of incident HF events. Limitations include our reliance on hospital discharge *ICD-9* codes to ascertain hospitalizations for pneumonia. Although this method has been previously validated,[4,13] we performed an internal independent confirmation of its applicability to our sample[14] and completed a sensitivity analysis using a most stringent definition of pneumonia; we cannot completely rule out misclassification. Similarly, because we ascertained severity of pneumonia based on the presence specific *ICD* codes in discharge abstracts and although this strategy has also been formerly validated,[15] potential misclassification of this variable is also possible. Because we only ascertained index (first-time) hospitalizations for pneumonia, our analyses did not account for the potential cumulative effect of recurrent pneumonia events. In CHS, baseline abnormalities in participants' left ventricular function were uncommon[38] and this did not allow for meaningful stratified analyses by this factor. In addition, we did not have information regarding left ventricular function at the time of diagnosis of HF events, and therefore, we could not explore differential effects of pneumonia on new-onset HF with preserved or reduced ejection fraction. Finally, because our analyses were restricted to individuals older than 65 years and cases of pneumonia requiring hospital admission, our results should not be generalized beyond those boundaries.

Conclusion

In this large community-based sample of elderly adults, hospitalization for pneumonia was associated with subsequent increase in the risk of new-onset HF in the intermediate and long term postinfection. Future studies are needed to clearly elucidate the mechanisms of this association in order to design targeted preventive strategies.

Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Role of investigators

V.F.C.-M., M.T., S.Y., R.K., G.D., M.S.V.E., and J.A.C. designed the study; the data were gathered by R.K., A.B.N., and M.F.L.; M.T. performed the statistical analyses; V.F.C.-M., M.T., and J.A.C. vouch for the data and analysis; all authors provided critical input to the interpretations of the results; V.F.C.-M. wrote the first manuscript draft; all authors approved the final version. The authors had full access to data and full control of the decision to publish.

Disclosures

CHS was supported by contracts HHSN268201200036C, HHSN268200800007C, N01 HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, and N01HC85086 and Grant HL080295 from the National Heart, Lung, and Blood Institute, with additional contribution from the National Institute of Neurological Disorders and Stroke. Additional support was provided by AG023629 from the National Institute on Aging. A full list of principal CHS investigators and institutions can be found at CHS-NHLB.org. Dr Corrales-Medina is supported by a Recruitment Award from the Department of Medicine of The Ottawa Hospital and the Ottawa Hospital Research Institute in Ottawa, Ontario, Canada. Dr Yende is supported by K23GM083215.

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Appendix

Supplementary Table SI. Details of the time-fixed and time-varying covariables included in our analyses

Variable	Measurement scale	Time-fixed or time-varying	Observation times (year after enrollment in study)	
			Original cohort	African American cohort
Age	Continuous	Time-fixed	Y1	Y1
Gender	Dichotomous	Time-fixed	Y1	Y1
Race	Dichotomous (nonwhite vs white)	Time-fixed	Y1	Y1
Prevalent coronary heart disease	Dichotomous	Time-fixed	Y1	Y1
Time to incident coronary heart disease	Continuous (prior to pneumonia)	Time-varying	Continuous	Continuous
Diabetes status (as per ADA criteria)	Dichotomous	Time-varying	Y1, Y5, Y9	Y1, Y5
Atrial fibrillation (by electrocardiogram)	Dichotomous	Time-varying	Y1, Y3-Y11	Y1-Y7
Heart valve disease	Dichotomous	Time-varying	Y1, Y3, Y5-Y11	Y1-Y7
Smoking status	Dichotomous (ever smoked vs never)	Time-varying	Y1, Y3-Y11	Y1-Y7
Body mass index	Continuous	Time-varying	Y1, Y3-Y11	Y1-Y7
Heart rate	Continuous	Time-varying	Y1, Y4-Y11	Y1-Y7
Systolic blood pressure	Continuous	Time-varying	Y1, Y3-Y7, Y9-Y11	Y1-Y3, Y5-Y7
Diastolic blood pressure	Continuous	Time-varying	Y1, Y3-Y7, Y9-Y11	Y1-Y3, Y5-Y7
Serum LDL	Continuous	Time-varying	Y1, Y5	Y1
Serum HDL	Continuous	Time-varying	Y1, Y5	Y1
Serum C-reactive protein*	Continuous	Time-varying	Y1, Y5, Y9	Y1, Y5
Glomerular filtration rate	Continuous	Time-varying	Y1, Y5, Y9	Y1, Y5
FEV_1	Continuous	Time-fixed	Y1	Y1
Left ventricular hypertrophy by electrocardiogram	Dichotomous	Time-varying	Y1, Y3-Y11	Y1-Y7
Use of antihypertensives	Dichotomous	Time-varying	Y1, Y3-Y11	Y1-Y7
Use of aspirin	Dichotomous	Time-varying	Y1, Y3-Y11	Y1-Y7
Use of statins	Dichotomous	Time-varying	Y1, Y3-Y11	Y1-Y7

Abbreviations: American Diabetes Association; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
*Log-transformed for analysis.

Supplementary Table SII. Prevalence of baseline missing values for analysis and imputation variables

Variable	Measurement scale	Frequency (%)
Analysis variables		
Age	Continuous	0
Gender	Dichotomous	0
Race	Dichotomous	0
Prevalent coronary heart disease	Dichotomous	0
Time to incident coronary heart disease	Continuous	0
Diabetes status (as per ADA criteria)	Dichotomous	58 (1.0)
Atrial fibrillation (by electrocardiogram)	Dichotomous	10 (0.2)
Heart valve disease	Dichotomous	136 (2.4)
Smoking status	Dichotomous	6 (0.1)
Body mass index	Continuous	19 (0.3)
Heart rate	Continuous	296 (5.3)
Systolic blood pressure	Continuous	9 (0.2)
Diastolic blood pressure	Continuous	27 (0.5)
Serum LDL	Continuous	125 (2.2)
Serum HDL	Continuous	56 (1.0)
Serum C-reactive protein*	Continuous	85 (1.5)
Glomerular filtration rate	Continuous	72 (1.3)
FEV_1	Continuous	300 (5.3)
Left ventricular hypertrophy by electrocardiogram	Dichotomous	193 (0.3)
Use of antihypertensive medications	Dichotomous	7 (0.1)
Use of aspirin	Dichotomous	7 (0.1)
Use of statins	Dichotomous	7 (0.1)
Additional variables used in the imputation process		
Prevalent hypertension	Dichotomous	7 (0.1)
Prevalent angina	Dichotomous	0
Prevalent claudication	Dichotomous	0
Prevalent myocardial infarction	Dichotomous	0
Prevalent stroke	Dichotomous	0
Prevalent transient ischemic attack	Dichotomous	0
Coronary artery angioplasty at baseline	Dichotomous	45 (0.1)
Coronary bypass surgery at baseline	Dichotomous	39 (0.7)
Serum total cholesterol	Continuous	49 (0.9)
Serum triglycerides*	Continuous	49 (0.9)
Serum albumin	Continuous	72 (1.3)
Serum glucose*	Continuous	72 (1.3)
Any major electrocardiographic abnormalities	Dichotomous	178 (3.2)
Carotid US-common carotid intima media thickness*	Continuous	25 (0.4)
Carotid US-internal carotid intima media thickness*	Continuous	27 (0.5%
Carotid US-internal carotid artery stenosis	Ordinal	32 (0.6)
Use of ACE inhibitors	Dichotomous	5 (0.1)
Use of β-blockers	Dichotomous	5 (0.1)
Use of diuretics	Dichotomous	5 (0.1)
Use of vasodilators	Dichotomous	5 (0.1)
Use of calcium-channel blockers	Dichotomous	7 (0.1)
Use of nitrates	Dichotomous	7 (0.1)
Use of lipid-lowering medications other than statins	Dichotomous	7 (0.1)
Use of oral hypoglycemics	Dichotomous	7 (0.1)
Use of insulin	Dichotomous	7 (0.1)

Abbreviations: ADA, American Diabetes Association; LDL, low-density lipoprotein; HDL, high-density lipoprotein; US, ultrasound.
*Log-transformed prior to analysis.

Supplementary Table SIII. Unadjusted and adjusted HRs for time to new-onset HF from multivariable Cox models using complete cases and multiply imputed data

Time after hospitalization for pneumonia	Unadjusted HRs (multiply imputed data; n = 5613)			Adjusted for baseline covariables using complete cases only (n = 4573)		
	HR	95% CI	*P*	HR	95% CI	p-value
31-90 d	9.0	5.82-13.77	<.0001	7.3	4.53-11.88	<.0001
91 d–6 mo	4.0	2.42-6.94	<.0001	3.7	2.09-6.56	<.0001
6-12 mo	3.2	2.01-5.03	<.0001	2.9	1.82-4.68	<.0001
1-5 y	2.0	1.60-2.59	<.0001	1.7	1.30-2.35	.0002
5 y+	2.4	1.86-3.13	<.0001	2.2	1.63-2.92	<.0001

Time after hospitalization for pneumonia	Adjusted for baseline covariables (multiply imputed data; n = 5613)			Adjusted for baseline and longitudinal covariables (multiply imputed data; n = 5613)		
	HR	95% CI	*P*	HR	95% CI	*P*
31-90 d	7.6	4.85-11.68	<.0001	6.9	4.46-10.63	<.0001
91 d–6 mo	3.5	2.09-6.00	<.0001	3.2	1.88-5.50	<.0001
6-12 mo	2.8	1.76-4.31	<.0001	2.6	1.64-4.04	<.0001
1-5 y	1.8	1.42-2.29	<.0001	1.7	1.30-2.12	<.0001
5 y+	2.2	1.72-2.94	<.0001	2.0	1.56-2.58	<.0001

Supplementary Table SIV. Estimated HRs for time to new-onset HF from multivariable Cox models using n = 10 multiply imputed data sets and all baseline and longitudinal covariables

Variable	HR	LCL	UCL	*P*
Time after hospitalization for pneumonia				
30-90 d	6.9	4.46	10.63	<.0001
90 d–6 mo	3.2	1.88	5.50	<.0001
6-12 mo	2.6	1.64	4.04	<.0001
1-5 y	1.7	1.30	2.12	<.0001
5 y+	2.0	1.56	2.58	<.0001
Age	1.1	1.06	1.09	<.0001
Age by pneumonia interaction	1.0	0.97	1.01	.2468
Gender (male vs female)	1.4	1.29	1.59	<.0001
Race (white vs nonwhite)	1.0	0.84	1.17	.8823
Diabetes	1.5	1.35	1.71	<.0001
Prevalent coronary heart disease	1.7	1.47	1.86	<.0001
Incident coronary heart disease	1.4	1.09	1.71	.0073
Heart valve disease	1.8	1.48	2.09	<.0001
Smoking status (ever smoker)	1.1	0.96	1.17	.2909
Spline variables for body mass index (BMI)				
BMI	1.0	0.99	1.02	.2227
$(BMI - 20.24)^3$	1.0	1.00	1.00	.0397
Heart rate	1.0	1.01	1.02	<.0001
Serum LDL	1.0	0.99	1.00	.8716
Serum HDL	1.0	0.99	1.00	.0445
Serum C-reactive protein (log-transformed)	1.1	1.07	1.17	<.0001
Hypertension	1.4	1.29	1.59	<.0001
Use of aspirin	1.1	0.96	1.16	.2505
Use of statins	0.9	0.73	1.03	.0966
Atrial fibrillation by electrocardiogram	1.7	1.35	2.04	<.0001
Left ventricular hypertrophy by electrocardiogram	1.8	1.52	2.09	<.0001
Percent of predicted FEV_1	1.0	0.99	1.00	<.0001
Spline variables for glomerular filtration rate (GFR)				
GFR	0.98	0.984	0.992	<.0001
$(GFR - 39.72)^3$	1.0	1.00	1.00	<.0001
Average Pressure (DBP + SBP)/2	1.0	1.00	1.01	<.0001
Pressure ratio (SBP/DBP)	1.3	1.20	1.52	<.0001

Abbreviations: LCL, lower limits of 95% CIs; UCL, upper limits of 95% CIs; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SBP, systolic blood pressure; DBP diastolic blood pressure.

Supplementary Table SV. New-onset HF events preceded by coronary heart disease (prevalent or incident) in survivors of pneumonia hospitalization at different intervals after hospitalization

Interval after hospitalization for pneumonia	No. of new-onset HF events among pneumonia survivors	No. (%) of new-onset HF events preceded by coronary artery disease diagnosis (prevalent or incident)
30-90 d	22	4 (18)
90 d–6 mo	14	5 (36)
6 mo–1 y	20	4 (20)
1-5 y	76	8 (11)
5 y+	71	8 (12)
Total	203	29 (14)

Supplementary Table SVI. Sensitivity analysis of the intermediate and long-term risk of new-onset HF after hospitalization for pneumonia using more stringent definition of pneumonia

Time interval after hospitalization for pneumonia	HR	95% CI	*P*
31-90 d	5.1	2.88-8.85	<.0001
91 d–6 mo	1.7	0.75-3.78	.2047
6-12 mo	2.5	1.52-4.19	.0004
1-5 y	1.5	1.11-1.97	.0064
5 y+	1.9	1.39-2.51	<.0001

Supplementary Table SVII. Sensitivity analysis of the intermediate and long-term risk of new-onset HF after hospitalization for pneumonia under extreme assumptions about censored observations

Time after hospitalization for pneumonia	Assuming that all censored individuals experienced new-onset HF immediately after censoring (n = 5613)			Assuming that censored individuals had longer times to new-onset HF than uncensored individuals (n = 5613)		
	HR	95% CI	*P*	HR	95% CI	*P*
31-90 d	9.4	7.32-11.96	<.0001	8.6	5.57-13.16	<.0001
91 d–6 mo	4.0	2.92-5.45	<.0001	3.6	2.10-6.10	<.0001
6-12 mo	3.0	2.33-3.96	<.0001	2.7	1.71-4.21	<.0001
1-5 y	2.0	1.73-2.31	<.0001	1.4	1.09-1.78	.0071
5 y+	1.8	1.53-2.10	<.0001	0.9	0.67-1.13	.2742

Supplementary Table SVIII. Sensitivity analysis of the intermediate and long-term risk of new-onset HF after hospitalization for pneumonia with censoring at the time of recurrent pneumonia

Time after hospitalization for pneumonia	HR	95% CI	*P*
31-90 d	4.9	2.92-8.28	<.0001
91 d–6 mo	2.9	1.65-5.24	.0003
6-12 mo	1.8	1.04-3.14	.0378
1-5 y	1.2	0.91-1.67	.1805
5 y+	1.7	1.22-2.25	.0013

Supplementary Table SIX. Baseline characteristics of patients with and without fracture

Baseline characteristics	Hospitalization for fractures		*P*
	Yes (n = 767)	No (n = 4846)	
Age (y)	73.9 (5.6)	72.6 (5.6)	<.001
Male gender	215 (28.0%)	1,751 (44.3%)	<.001
Ethnicity			<.001
White	716 (93.4%)	3,999 (82.5%)	
African American	47 (6.1%)	817 (16.9%)	
Other	4 (0.5%)	30 (0.6%)	
Coronary heart disease	127 (16.6%)	852 (17.6%)	.488
Atrial fibrillation	15 (2.0%)	103 (2.1%)	.761
Diabetes	96 (12.5%)	774 (16.0%)	.014
Valvular heart disease	28 (3.7%)	265 (5.5%)	.036
Smoking	373 (48.6%)	2,635 (54.4%)	.003
Body mass index (kg/m^2)	25.5 (4.2)	26.9 (4.7)	<.001
Heart rate (beats/min)	66 (11)	65 (11)	.215
Systolic blood pressure (mm Hg)	135 (22)	137 (22)	.017
Diastolic blood pressure (mm Hg)	69 (11)	72 (11)	<.001
Serum LDL cholesterol (mg/dL)	131 (37)	130 (36)	.610
Serum HDL cholesterol (mg/dL)	57 (17)	54 (16)	<.001
Glomerular filtration rate (mL/min per 1.73 m^2)	68.4 (17)	68.7 (18)	.693
Serum C-reactive protein (mg/L)	2 · 3 (1.0-4.0)	2 · 5 (1.3-4.5)	<.001
LV hypertrophy by ECG	29 (3.8%)	218 (4.5%)	.368
Percent of predicted FEV_1	90.7 (21.3)	90.5 (22.4)	.801
Use of antihypertensive medications	327 (42.6%)	2229 (46.0%)	.082
Use of aspirin	277 (36.1%)	1596 (33.0%)	.083
Use of statins	14 (1.8%)	113 (2.3%)	.381

Data are number (%), mean (SD), or median (IQR).
Abbreviations: LDL, low-density lipoprotein; HDL, high-density lipoprotein; LV, left ventricle; ECG, electrocardiogram.

Supplementary Table SX. Timing of hospitalization for fractures and rates of new-onset HF after fracture hospitalization in CHS

No. of patients admitted to hospital with fracture during study follow-up		767
Median time to fracture (IQR)		9.4 y (5.6-14.0 y)
No. (%) of patients with fracture diagnosed as having HF before fracture hospitalization		131 (17.1)
No. (%) of patients with fracture who died, were lost to follow-up, or were diagnosed as having HF within 30 d after hospitalization		67 (8.7)
Nos. of fracture survivor patients still free of HF at 30 d after hospitalization		569
Cumulative no. (%) of new-onset HF events at different time intervals posthospitalization (using the 569 fracture survivors free of HF at 30 d after hospitalization as the denominator)		
	31-90 d	7 (1.2)
	91 d–6 mo	17 (3.0)
	6 mo–1 y	25 (4.4)
	1-5 y	81 (14.2)
	>5 y	119 (20.9)