Cardiology in the Young

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Risk factors and lifelong impact of community-acquired pneumonia in congenital heart disease

Patrick D. Evers[1], Dóra K. Farkas[2], Michael Khoury[3], Morten Olsen[4] and Nicolas L. Madsen[2,5]

[1]Division of Pediatric Cardiology, Oregon Health and Sciences University, Portland, OR, USA; [2]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [3]Division of Pediatric Cardiology, Department of Pediatrics, University of Alberta, Edmonton, Canada; [4]Department of Radiology, Horsens Regional Hospital, Aarhus, Denmark and [5]The Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Original Article

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Author for correspondence:
P. Evers, MD MSc, Division of Pediatric Cardiology, Oregon Health and Sciences University, 707 SW Gaines St. CDRC-P, Portland, OR 97239, USA. Tel: (503) 494-4429.
E-mail: eversp@ohsu.edu

Abstract

Introduction: The prevalence of congenital heart disease (CHD) in adults is rising necessitating a greater understanding of acquired diseases such as community-acquired pneumonia, which remains a leading cause of age-related mortality and morbidity in the general population. We hypothesise that the CHD population, given cardiopulmonary mechanics and altered immune function, bears a uniquely high risk for pneumonia-related hospitalisations and mortality. *Methods:* A countrywide cohort study was performed to calculate the relative risk and cumulative incidence of pneumonia hospitalisations and resultant 30-day mortality amongst the adult CHD population, matched 1:10 with non-CHD persons by gender, age, and adjusted for comorbidities. Cox proportional hazard regression quantified the impact of CHD severity and extracardiac defects. *Results:* The CHD cohort includes 17,162 adults. The majority demonstrate mild/moderate CHD complexity. The cumulative incidence of pneumonia hospitalisation was higher for adults with CHD (hazard ratio 1.90; 95% confidence interval: 1.74–2.06) than the comparison cohort. This risk was increased for those with extracardiac defects or a syndrome (hazard ratio: 4.34; 95% confidence interval: 3.39–5.54). Additionally, CHD individuals with severe/univentricular subtypes demonstrate a heightened risk compared to the non-CHD cohort (hazard ratio: 2.35; 95% confidence interval: 1.94–2.84), as well as compared to those with mild/moderate CHD (hazard ratio: 1.28; 95% confidence interval: 1.07–1.53). In addition, pneumonia hospitalisation mortality was elevated above the comparison population with a 30-day mortality rate ratio of 1.31 (95% confidence interval: 1.00–1.73). *Conclusion:* Adults with CHD are at elevated risk of pneumonia hospitalisations and pneumonia-associated mortality. This risk is further elevated in those with severe CHD and extracardiac defects.

The prevalence of adults living with congenital heart disease (CHD) has risen rapidly as survival out of childhood improves.[1,2] As a result, the incidence and impact of adult comorbidities, such as diabetes,[3] stroke,[4] and myocardial infarctions,[5] have garnered increased attention in the ageing and growing CHD population. Additionally, in the general population, the incidence of community-acquired pneumonia and associated morbidity and mortality have remained relatively high with advances in medical care being partially offset by an ageing population,[6] with about a 9% lifetime cumulative incidence of hospitalisation,[7] and a 30-day mortality rate of 8%.[8] The risk factors, incidence, and impact of community-acquired pneumonia in the CHD population, however, have not been previously described.

Individuals with CHD often have numerous risk factors that may contribute towards the occurrence and severity of community-acquired pneumonia, including abnormal pulmonary physiology, altered immune function, congestive heart failure, anaemia, splenomegaly, and unemployment.[9–11] Therefore, we hypothesise that the incidence of community-acquired pneumonia-related hospitalisations amongst adults with CHD is higher than the general population and thereby constitutes a considerable risk to the health of this ageing population. Additionally, we sought to evaluate the clinical and demographic factors associated with community-acquired pneumonia-related hospitalisations in the adult CHD population, as well as a comparison of the morbidity and mortality of community-acquired pneumonia-related hospitalisations between the CHD and general population cohorts.

Methods

This study was performed in Denmark using the Danish National Patient Registry which contains data on demographics and medical care pertaining to all residents dating back to 1977. Each citizen is assigned a unique 10-digit civil registration identification number at birth, allowing individual-level record linkage to the Danish Civil Registration System which includes

information pertaining to date of birth, gender, and date of death of the citizenry. Furthermore, the Danish Register of Congenital Heart Disease augments this data, identifying an additional Danish cohort of CHD individuals whose CHD status was recorded in the medical record between 1963 and 1974.[7] Therefore, exposures were captured from 1963 through 2017 – except 1974 to 1977 – while outcomes were measured from 1977 through 2017. Previous research supports the Danish National Patient Registry's sufficient scale to perform adequate case-matching for pneumonia: from 1997 to 2011, the registry identified 342,609 and 552,528 patients with first time and total community-acquired pneumonia-related hospitalisations, respectively.[12,13] No informed consent or Institutional Review Board permission was obtained, as it is not required for register-based studies in Denmark. The study was approved by the Danish Data Protection Agency the research conforms to the ethical standards of the Declaration of Helsinki.

The community-acquired pneumonia-related hospitalisations were identified through discharge diagnosis codes according to the International Statistical Classification of Diseases and Related Health Problems (ICD) 8 or ICD-10, as varied by era (Appendix). For the assessment of community-acquired pneumonia incidence, the exposed population of interest were CHD patients older than 18 years at the time of the first pneumonia hospitalisation. The CHD designation could be acquired at any age. Each CHD patient was age- and sex matched to 10 members of the general population who did not have a CHD diagnosis. Index date for the CHD cohort was the later of the CHD diagnosis date and 18th birthday. This index date was thereby assigned to the matched comparisons. Comparison patients were censored if they acquired the diagnosis of CHD after the index date. Patients with an isolated CHD diagnosis of patent ductus arteriosus and known prematurity less than 37 weeks were not included in the CHD cohort. Prematurity was not an exclusion criteria as gestational age was an identifiable variable only in a minority of the population. The severity of the CHD was stratified as mild (minor lesions such as ventricular septal defect, atrial septal defect, and patent ductus arteriosus but not requiring intervention), moderate (equivalent to the minor lesions but distinguished by requiring intervention), severe (major lesions requiring intervention but able to sustain biventricular circulation), univentricular (functionally single ventricular circulations), and unclassifiable.[7] To adjust for the impact of comorbidities, the Charlson Comorbidity Index was used as a composite comorbidity score.[14] The CHD cohort and control cohort were also analysed for the presence of extracardiac defects given the common co-occurrence of cardiac and extracardiac congenital malformations. The data set did not contain the other known risk factors for pneumonia of smoking and alcohol use and therefore these could not be controlled for.

The community-acquired pneumonia hospitalisation was identified as the first hospitalisation for each patient in which pneumonia was the primary diagnosis. A hospitalisation was excluded if a patient had been admitted to the hospital or chronic care facility for greater than or equal to two days in the 90 days prior to the pneumonia admission to exclude healthcare-associated pneumonia. To test the durability of the community-acquired pneumonia diagnosis, an alternative definition of the diagnosis was employed wherein respiratory failure was the primary discharge diagnosis and pneumonia was a secondary diagnosis (Appendix). The cumulative incidence of first pneumonia-related hospitalisation amongst the CHD cohort and the comparison cohort was performed, with death as a competing risk. Cox proportional hazard regression was used to calculate the hazard ratios and 95% confidence intervals of the occurrence of a community-acquired pneumonia hospitalisation. The adjusted HRs incorporated Charlson Comorbidity Index as a time-dependent variable.

To quantify the impact of CHD on a community-acquired pneumonia-related in-hospital mortality and length of stay, each CHD patient with pneumonia hospitalisation was matched on age and sex to 10 patients with community-acquired pneumonia hospitalisation within the same calendar year but without any previous CHD diagnosis. Given the competing nature of in-hospital mortality and hospital discharge, the cumulative incidence function of 30-day mortality and discharge were calculated with Gray's test used to test for equality.[15] To include the residual mortality risk after discharge, a time-to-event Cox regression with death as the dependent variable was used to calculated the 30-day mortality rate ratio (MRR), adjusting for Charlson Comorbidity Index at the index date. All analyses were performed using SAS 9.4 statistical software.

Results

We identified 17,162 patients with CHD who were matched on age and sex at a ratio of 1:10 to a general population cohort of 171,588 with birth years spanning from 1890 to 1999 (Table 1). Of the CHD cohort, 12,215 (71.2%) had mild/moderate severity of CHD, the most common of which were atrial septal defects (4560, 26.6%). While 19.8% (3400) had severe/univentricular CHD, only 1.3% (216) had univentricular physiology. The CHD cohort was more likely to have extracardiac defects (15.1% versus 5.2%) and comorbidities (20.6% versus 9.5%) compared with the general population. The three most common comorbidities at index date in the CHD cohort were chronic pulmonary disease (6.4%), cerebrovascular disease (5.7%), and congestive heart failure (3.5%) while that of the control cohort were chronic pulmonary disease (4.0%), tumour (1.5%), and diabetes (1.0%).

Of the CHD cohort, 754 (4.4%) had a pneumonia-related hospitalisation compared to 4135 (2.4%) in the comparison cohort. The incidence of pneumonia-related hospitalisation was higher in those with severe/univentricular CHD than mild/moderate CHD (4.8 and 4.3%, respectively). This yielded a higher cumulative incidence of pneumonia-related hospitalisations in the CHD cohort relative to the general population cohort [80 years of age: CHD 19.1% (17.7–20.5%) and general population 11.9% (11.4–12.3%)] (Fig 1). The adjusted hazard ratio for the CHD cohort was elevated above the comparison cohort (hazard ratio 1.90; 95% confidence interval 1.74–2.06), a finding that persisted in a sub-analysis of CHD cohorts by severity and age (Table 2). Furthermore, those with severe/univentricular heart disease were at elevated risk (hazard ratio 1.28; 95% confidence interval 1.07–1.53) when compared to those of the CHD cohort with mild/moderate heart disease. Finally, those of the CHD cohort with extracardiac defects were at particularly elevated risk above the general population cohort with extracardiac defects (HR 2.70; 95% CI 2.09–3.49). The sensitivity analysis using the alternative definition of community-acquired pneumonia, specifically respiratory failure as the primary diagnosis and pneumonia as the secondary diagnosis, identified negligibly few additional patients.

For the length of stay and mortality analysis, these 754 patients with CHD who were admitted for community-acquired pneumonia were matched to 7362 patients without CHD who were admitted for community-acquired pneumonia. Of CHD patients with pneumonia, 44 of 754 patients (5.8%) died during the hospitalisation, compared with 266 of 7362 (3.6%) in the comparison cohort,

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Table 1. Subject characteristics

	CHD cohort		Comparison cohort	
	n	%	n	%
Total	17,162	100	171,588	100
Gender				
Female	8730	51	87,278	51
Male	8432	49	84,310	49
Age grouping (years)				
18–34	12,489	73	124,890	73
35–49	1885	11	18,850	11
50–64	1702	10	17,020	10
>65	1086	6	10,828	6
CHD severity				
Mild (no surgery required)	890	5	–	–
Moderate (surgery required)	11,325	66	–	–
Severe	3184	19	–	–
Univentricular	216	1	–	–
Not classified	1547	9	–	–
Major CHD diagnosis				
Ventricular septal defect	4769	28	–	–
Atrial septal defect	4560	27	–	–
Anomalies of heart valve	2851	17		
Coarctation of aorta	1184	7	–	–
Tetralogy of Fallot	676	4	–	–
Atrioventricular septal defect	612	4	–	–
Transposition of great vessels	372	2	–	–
Patent ductus arteriosus	104	1	–	–
Common arterial trunk	77	0	–	–
Other	1957	11	–	–
Extracardiac defects				
No	14,577	85	162,668	95
Yes	2585	15	8920	5
Charlson comorbidity				
Low (0)	13,629	79	155,254	90
Medium (1–2)	3080	18	14,439	8
High (3+)	453	3	1895	1
Community-acquired pneumonia hospitalisation				
No	16,408	96	167,453	98
Yes	754	4	4135	2

with death at a median of 7.5 and 9.0 days in hospital, respectively. An additional 15 CHD patients and 153 comparison patients died within the 30 days following discharge. Cause of death was available in 52 of the total 59 CHD patients who died during this time and 371 of the 419 members of the comparison cohort. The causes of death were similarly distributed in the two cohorts with the highest proportion (37%) dying from infectious disease in each cohort, the next most common cause being respiratory failure resulting in 27% of the deaths in the CHD cohort, and 24% of the comparison cohort and a cardiovascular cause was the third most common at 13% of the CHD cohort and 11% of the comparison cohort. The 30-day mortality risk was elevated for the CHD population compared to the comparison cohort, with an MRR of 1.31 (1.00–1.73) (Table 3).

This risk was particularly elevated in those less than 65 years of age with an MRR of 1.59 (1.01–2.49). Examining discharge and in-hospital mortality as competing risks, the cumulative incidence functions (Fig 2) illustrate that CHD patients being more likely to experience an in-hospital mortality and less likely to experience discharge in the 30 days following admission ($p < 0.001$). This finding was consistent in both sexes but only in those less than 65 years of age at discharge; those 65 years or older had similar rates of in-hospital mortality and survival to discharge.

Discussion

This study is the first longitudinal population-based assessment of community-acquired pneumonia-related hospitalisations in the adult CHD population. We have illustrated that the risk of pneumonia hospitalisations and the resultant in-hospital and 30-day mortality risks are elevated when compared with the general population. Specifically, we found that those with CHD have a twofold risk of a community-acquired pneumonia-related hospitalisations compared to age- and sex-matched members of the general population. The cumulative incidence of a community-acquired pneumonia-related hospitalisations was 19.1% for the CHD cohort by age 80 while only 11.9% for a matched general population cohort. While this elevated risk was true regardless of CHD severity and age, the risk was highest in those with severe CHD and those younger than 65 years of age.

Other studies of the adult CHD population, including work from our previous group, have similarly illustrated the diminished risk discrepancy between the CHD cohort and the general population at very advanced age as the risk of adverse outcomes in the general population increases over time with older age.[16–18] While there are no previous studies examining the incidence of community-acquired pneumonia or its related hospitalisations in the CHD population, there is precedence that several other chronic diseases such as diabetes, dementia, chronic lung disease, and liver disease do lead to an increased pneumonia incidence.[16,19,20] This risk of community-acquired pneumonia-related hospitalisations did not appear to be limited to only those with severe/univentricular CHD, but appeared to be consistent across the spectrum of disease, even in those with mild/moderate CHD disease.

There are several hypotheses to potentially explain the elevated cumulative incidence of pneumonia in this CHD population. While the CHD cohort is likely to have more contact with the health care setting, efforts were made to exclude heath care-associated pneumonias. However, chronic exposure to health care settings with the unique pathogen microenvironment implicated therein may provide a source of important lifelong risk. In addition, it is possible that clinical characteristics commonly present in CHD increases the incidence and severity of pneumonia. For example, factors such as cardiomegaly, subclinical microembolisms from venous stasis, post-operative diaphragmatic paresis, and post-operatively impaired chest wall mechanics may lead to atelectasis and impaired airway clearance. Similarly, primary immunodeficiency or immunodeficiency secondary to chronic systemic inflammation may contribute.[21–23] It is worth noting that

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Table 2. Adjusted hazard ratios of community-acquired pneumonia-related hospitalisation in CHD adults compared with the general population

	Unadjusted hazard ratio		Adjusted hazard ratio	
	HR	95% CI	HR	95% CI
CHD versus matched comparisons				
Overall	2.42	(2.23–2.63)	1.90	(1.74–2.06)
Age<65 years	2.66	(2.42–2.94)	2.12	(1.92–2.34)
Age ≥ 65 years	1.96	(1.69–2.28)	1.49	(1.27–1.74)
Mild/moderate CHD	2.30	(2.09–2.54)	1.83	(1.65–2.02)
Severe/univentricular CHD	3.08	(2.57–3.68)	2.35	(1.94–2.84)
Without ECD/syndrome	2.18	(2.00–2.38)	1.71	(1.56–1.88)
With ECD/syndrome	5.78	(4.59–7.28)	4.34	(3.39–5.54)

Sex and birth year-matched comparisons.
Adjustment made for Charlson Comorbidity Index.
CI: confidence interval; ECD = extracardiac defects; CHD = congenital heart disease.

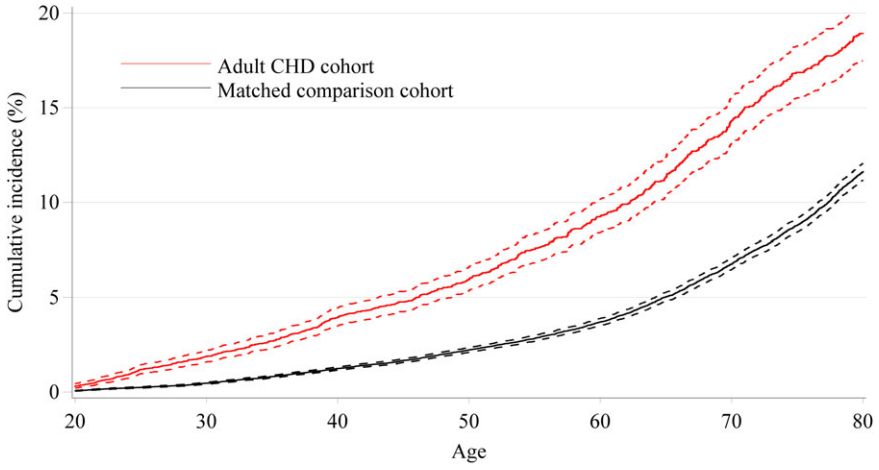

Figure 1. Cumulative incidence of community-acquired pneumonia-related hospitalisation in adults with CHD and a general population comparison cohort, with death as competing risk. General population cohort matched on age and gender. CHD = congenital heart disease.

this elevated risk remains even when examining those CHD patients and compare patients who lack any other extracardiac defect or syndrome. Finally, pharmaceutical influences in this oft-hospitalised CHD population, such as proton-pump inhibitors, may pose an additional risk for community-acquired pneumonia.[24–26]

Once admitted, those with CHD were more likely to suffer an in-hospital mortality as well as a 30-day mortality. Those under the age of 65 years illustrated particular risk, but this finding could be due to escalating risk in the older general population as well as a survival bias in the CHD population. In addition, CHD patients experienced a longer hospitalisation period prior to discharge. This highlights the reality that admissions in this population, even when unrelated to their CHD, can lead to greater incremental risk and cost, both direct and indirect, when compared to the general population.

Limitations to this analysis include the reliance on diagnostic coding to both identify the cohort of CHD patients but also the outcome of interest, community-acquired pneumonia, which itself is not an explicit ICD code, and may not be coded for as the primary hospitalisation diagnosis. In addition, the CHD diagnosis itself may be biasing the results. Specifically, if CHD patients are more frequently surveilled by the medical system, the diagnosis of pneumonia may be more frequent. However, given the outcome of interest is a community-acquired pneumonia-related hospitalisations and not simply the diagnosis of community-acquired pneumonia, this would probably very infrequently occur simply due to heighted surveillance. Similarly, given most pneumonias of sufficient severity that inpatient care is required will progress if untreated, these results from Denmark are likely valid in other medical systems in which elective care is more cost-prohibitive. Finally, while every effort was made to control for concomitant risks for pneumonia besides the CHD exposure, there are other variables which went unmeasured that may be correlated with CHD exposure and causally related to pneumonia, such as socio-economic status.

In conclusion, adults with CHD are at an elevated risk for community-acquired pneumonia-related hospitalisations compared with the general population with a significantly increased cumulative incidence over their adult lives. Moreover, these patients have an elevated risk of suffering a prolonged hospitalisation, an in-hospital mortality, and 30-day mortality following a hospitalisation. This analysis highlights the significant risk that community-acquired pneumonia poses for the adult CHD

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Table 3. Thirty-day mortality rate ratio comparing CAP patients with previous CHD diagnosis to CAP patients without previous CHD diagnosis, stratified by gender and age

	Unadjusted MRR		Adjusted MRR	
	MRR	95% CI	MRR	95% CI
Overall	**1.39**	**(1.06–1.83)**	**1.31**	**(1.00–1.73)**
Female	1.30	(0.89–1.90)	1.25	(0.85–1.84)
Male	**1.50**	**(1.01–2.22)**	1.38	(0.93–2.05)
Age < 65 years	**1.85**	**(1.19–2.86)**	**1.59**	**(1.01–2.49)**
Age ≥ 65 years	1.19	(0.83–1.69)	1.16	(0.82–1.66)

Adjustment made for Charlson Comorbidity Index.
CI = confidence interval; MRR = mortality rate ratio.
Bold: $p < 0.05$.

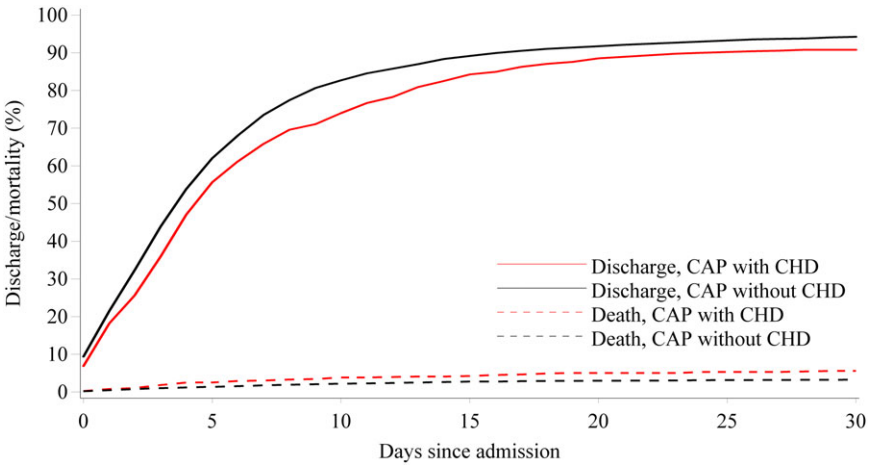

Figure 2. Cumulative incidence of discharge and death as competing risks in patients with or without CHD after admission for a community-acquired pneumonia-related hospitalisation. CAP = community-acquired pneumonia; CHD = congenital heart disease.

population and the need for ongoing vigilance and subspecialty expertise to care for these patient's through their adulthood.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/S1047951120004254

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DKF conceptualised and designed the study, performed the data curation, performed data analysis, interpreted the data analysis, drafted portions of the initial manuscript, and approved the final manuscript as submitted.

MK, MO interpreted the data analysis, drafted portions of the initial manuscript, and approved the final manuscript as submitted.

NLM acquired funding, conceptualised and designed the study, interpreted the data analysis, drafted portions of the initial manuscript, and approved the final manuscript as submitted.

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