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Original Article

Incremental risk of long-term mortality with increased burden of comorbidity in hospitalized patients with pneumonia

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ABSTRACT

Background: Patients hospitalized for pneumonia often have concurrent comorbid conditions (CCs). The influence of CCs on the risk of subsequent death is not fully understood.
Methods: We examined adults hospitalized for pneumonia between 1996 through 2015 at Mayo Clinic for the presence of 20 priori selected CCs. We estimated cumulative all-cause mortality by number of CCs using multivariable Cox regression model.
Results: Study comprised of 9580 adults (age 70 ± 17.0 years, men 53%, whites 88%) with median number of CCs 3 (interquartile 1–4), and overall deaths 6032 (62.9%) during 50,934 person-years of follow up (118.5 deaths/1000 person-years). After adjustment, any single comorbid condition was associated with 9% greater risk of death (95% confidence interval 1.08–1.11, P < 0.0001). When study cohort was stratified according to number of comorbidities (none, 1, 2, 3, 4, 5, and ≥6 CCs), the risk of death increased as the number of CCs increased (33 for no CCs vs 252 deaths for ≥6 CCs per 1000 person-years).
Conclusions: Long-term mortality after hospitalization for pneumonia increases as the burden of comorbidities increases. Therefore, a simple comorbidity count help improve prognostic accuracy in identifying patients at increased risk of death following an episode of pneumonia.

1. Introduction

The US Healthcare Cost and Utilization Project (HCUP) estimated that after live born, pneumonia is the most common reason for hospitalization with aggregate annual hospital cost of $9.5 billion in the United States. Pneumonia is associated with excess mortality compared with many other acute conditions [1] and adversely impacts survival far beyond the initial acute care hospitalization [2–4]. However, published data on predictors of long-term mortality following incident pneumonia were contradictory [2,5–13]. Risk-prediction models for pneumonia were primarily developed to improve the decision about hospitalization [14,15] and to estimate in-hospital [16–19] or short-term mortality [20]. In contrast, the data on long-term mortality after an episode of pneumonia requiring hospitalization are limited [3]. Risk prediction models such as pneumonia severity index [18] and CURB-65 [19] have incorporated a limited number of comorbid conditions (CCs) and did not include many prevalent CCs of contemporary patient population. The widely used Charlson index [21] was based on a small heterogeneous group of hospitalized patients and developed 30 years ago incorporating 17 conditions including those with little and no influence on mortality. Although, validated in predicting short-term mortality, these models did not perform well in predicting the long-term mortality [22]. In contrast to ambulatory patients, those hospitalized for pneumonia have a broad range of CCs [5,7,12,13]. Previous studies assessing the prognosis were limited by number of included CCs [9,12,23,24], sample size [5–7,25–28] shorter follow up interval [6,9,12], and dependence on complex calculations [17]. Whereas short-term mortality may be directly related to the severity of pneumonia, the long-term mortality may be influenced by multiple CCs [7,13,26,29–31]. A recent report examining mortality at one year after pneumonia hospitalization indicated that recurrent pneumonia accounted for only 5% deaths while the remaining deaths were attributed to other conditions [30].

To address these gaps in knowledge, we investigated a cohort of adults hospitalized for pneumonia to estimate 1) the prevalence of 20 CCs-specified by the Department of Health and Human Services

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(DHHS), 2) the strength of association of anyone of these CCs with the long-term mortality, and 3) the long-term mortality risk associated with increased number of comorbidities.

2. Materials and methods

2.1. Study population

The study cohort consisted of all adults aged 18 years or more who were hospitalized with the primary discharge diagnoses of pneumonia between 8/1/1995 and 9/17/2015 at Mayo Clinic, Rochester, Minnesota. The presence or absence of co-existing CCs at the time of discharge was identified from the listings of secondary diagnoses from the patient's electronic medical record. The diagnoses were identified by the *International Classification of Diseases*, *Ninth Revision*, *Clinical Modification* (ICD-9-CM) codes. Experienced professionals abstracted data related to patient demographics, admission and discharge dates, length of hospital stay (LOS), primary and secondary discharge diagnoses, and death by day. Previous studies have demonstrated a high positive predictive value of ICD-9-CM codes for the discharge diagnoses [32,33]. The study was approved by the Mayo Clinic Institutional Review Board, which granted a waiver for informed consent.

2.2. Selection of comorbid condition

A comorbid condition is defined as the long-term conditions requiring medical attention [34]. We identified a panel of 20 CCs, specified by the Department of Health and Human Services (DHHS). The presence or absences of these concurrent CCs were identified using Clinical Classifications Software (CCS) codes (Clinical Classifications Software) developed by HCUP. Patients were stratified into 7 comorbidity groups according to number of concurrent CCs from 0 (none) to 1, 2, 3, 4, 5, and 6 or more.

2.3. Follow up

All patients were followed up until death or censoring date of 9/17/2016.

2.4. Statistical analysis

Baseline characteristics were described as percentages for categorical variables, mean ± standard deviation (SD) for continuous variables with normal distribution, and median and interquartile range for continuous variables with non-normal distribution. Comorbidity risk groups were compared in baseline characteristics by Wilcoxon signed-rank, Kruskal-Wallis, and chi-square tests as appropriate. The unadjusted cumulative incident all-cause mortality was compared across the comorbidity risk groups by Kaplan-Meier curves. We determined hazard ratio (HR) for mortality for each comorbidity risk group with no comorbidity as the referent by multivariable Cox proportional regression model accounted for age, gender, race, length of stay and other CCs. For all analyses, two-tailed tests were used and $P < 0.05$ was considered statistically significant. Statistical analyses were performed by Statistical Analysis System (SAS Institute) version 9.4.

3. Results

The baseline characteristics of study population are presented according to comorbidity groups in Table 1. The study cohort (Fig. 1) consisted of 9580 adults hospitalized for pneumonia (streptococcus pneumoniae 371 [4%], other specified bacteria 734 [8%], viruses 355 [4%], unspecified 8120 [85%]) with or without one or more of 20 DHHS-specified CCs: the mean (standard deviation) age was 69.8 (± 17.0) years, 5105 (53%) were men, 8451 (88%) whites, and median length of stay 3 days (interquartile range [IQR] 2–6). None of the patient in the study cohort had autism. Of total patient-population, only 931 (10%) patients had no comorbid condition at hospitalization, 1849 (19%) had one, and the remaining 6800 (71%) were multi-morbid. As shown in Table 1, prevalence of comorbid conditions were increased with age and significantly greater in men than in women (mean 2.9 vs 2.7, 95% confidence interval [CI] 2.65–2.76, $P < 0.0001$) and in whites than in non-whites (2.2 vs 2.9, 95% CI 2.14–2.36, $P < 0.0001$).

Median follow up was 3.6 years (IQR 1.0–8.3 years, and range 0–19.8 years from initial patients enrolment to death or censoring date). Between 1996 and 2015 (20-year period) 6032 (62.9%) all-cause deaths occurred during 50,934 person-years of follow up (118 per 1000 person-years). Compared to patients without comorbidity, the presence of any single CCs was associated with increased all-cause mortality, independent of age, gender, race, and length of hospital stay, and other comorbid conditions (hazard ratio [HR] 1.091, 95% CI 1.076–1.107, $P < 0.0001$). As shown in Fig. 1 and Fig. 2 the all-cause mortality after index hospitalization for pneumonia increased, as the number of CCs increased from 1 to 6 or more, in a dose-dependent fashion. The mortality was increased from 80% for a single CC (95% CI 1.56–2.01, $P < 0.0001$) to 250% for 6 or more CCs (HR 2.50, 95% CI 2.17–2.87 $P < 0.0001$) with no comorbid condition as the referent.

4. Discussion

This study demonstrated two important findings with potential clinical implications. First, in patients hospitalized with pneumonia the presence of any of the 20 DHHS-specified CCs except autism conferred an increased mortality independent of age, gender, race, length of hospital stay, and other CCs. Second, we found a dose-dependent relationship between all-cause mortality and numbers of CCs from 1 to 6 or more.

The findings of the present study updated and expanded the results of previous studies on long-term mortality after pneumonia. Our results broadly support the findings of a few previous studies [2,6,12]. In a small observational study examining 141 patients hospitalized for pneumonia, Brancati et al. reported increasing 2-year mortality with increasing comorbidity burden stratified as mild, moderate, and severe [6]. In a similar analysis of 1555 patients with pneumonia (both hospitalized and ambulatory), Mortensen et al. reported increased long-term mortality as the Charlson comorbidity scores were increased [2]. Several other studies showed increased long-term mortality risk associated with specific CCs such as cardiovascular disease [12,25,35] cerebrovascular disease [12], and cancer [9]. The findings of our study complements previously published reports by analyzing a broader panel of CCs including arrhythmia, asthma, depression, dyslipidemia, hypertension, osteoporosis, substance abuse, hepatitis, and schizophrenia, which were not the focus of earlier investigations.

The results of the present study and those of numerous other studies raise the questions: how CCs interact with initial bout of pneumonia and how an acute hospitalization for pneumonia sets in motion a host of pathophysiological processes that potentially persists long after recovery and eventually influence long-term mortality. Several possible explanations exist for increased mortality associated with CCs following pneumonia. Among patients hospitalized for pneumonia, short-term mortality, in general, is directly related to the severity pneumonia and physiological variables at the time of presentation, whereas long-term mortality is often associated with CCs and other yet unknown candidate predictors. Compared to physiological and laboratory variables which are important predictors of short-term mortality, CCs remained independent correlates for both short- and long-term mortality [20] implying a steady long-term influence of CCs after initial bout of pneumonia. Additionally, comorbid conditions may have a cause and effect relationship with pneumonia in contributing to its long-term mortality. Many of the CCs that are associated with pneumonia, also, increase its predisposition [36,37]. Conversely, hospitalization for pneumonia is associated with increased short- and long-term risk of incident major