Trends and seasonal variation of hospitalization and mortality of interstitial lung disease in the United States from 2006 to 2016

An Ho (nhatan01@gmail.com)
Saint Louis University https://orcid.org/0000-0003-3155-7568
Artem Shmelev
Saint Agnes Hospital
Edward Charbek
Saint Louis University

Research

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Abstract

Background

In the recent years, the overall trends in hospital admission and mortality of interstitial lung disease (ILD) are unknown. In addition, there was some evidence that interstitial lung disease death rate highest in the winter but this finding was only available in one study. This study will investigate the trend and seasonal variations in hospital admission and mortality rates of ILD from 2006 to 2016.

Method

From the Nationwide Inpatient Sample database, we collected all cases with the International Classification of Diseases (ICD)-9 or ICD-10 codes of ILD excluding identifiable external causes (drug, organic or inorganic dusts) from 2006 to 2016. Hospitalization rates of each year were calculated based on U.S Census population data. Monthly hospitalization and in-hospital mortality rates were analyzed by seasonal and trend decomposition.

Results

From 2006 to 2016, there was a downtrend in all cause hospital admissions but in-hospital mortality rate did not change, with or without the presence of pneumonia. Highest hospital admission rates of ILD per 100000 of population were from January to May. The average number of hospitalizations in spring, summer, fall and winter months were 7447.9 ± 932.0, 6643.0 ± 840.5, 6551.3 ± 922.6 and 7110.3 ± 866.1 respectively. All-cause in-hospital mortality ranges from 7.13% ± 0.79% in the summer to 8.13% ± 0.60% in the winter with winter months having the highest mortality rate (p=0.018). The seasonal variations of hospital admission and mortality was not changed when infectious pneumonia cases were ruled out.

Conclusion

From 2006 to 2016, admission rates of ILD declined but in-hospital mortality remained unchanged. All-cause hospital admissions and mortality of ILD have a strong seasonal variation. Hospital admissions are highest in the period from January to May, in-hospital death was highest in the winter.

Introduction

Interstitial lung disease (ILD) is a group of lung disorders characterized by abnormalities within the interstitium with or without extensive alteration of alveoli and airways [1]. There have been multiple forms of interstitial lung disease described, most of which lead to progressive lung scarring and dyspnea if left untreated [2, 3]. Idiopathic pulmonary fibrosis (IPF) is one of the most well described ILD with overall very poor prognosis and median survival of 3 to 5 years [4-6]. ILD remains still one of the most challenging respiratory entities to fully understand effectively treat and requires high healthcare utilization. In the past decade, there have been multiple new treatments and knowledge of this complex group of lung disorder. However, study on the overall trend of hospital admission and mortality over the last decade is still needed.

Seasonal variations can play a major role in the general health and wellbeing of patients with respiratory conditions. Winter season can impact lung function and increase the risk of acute exacerbations[7]. The mechanisms of this observation are complex and not fully understood [8]. Pulmonary conditions other than

interstitial lung disease such as chronic obstructive pulmonary disease (COPD) have been well studied showing significant seasonal variation [9-11]. Understanding how respiratory diseases change with seasonal variation could guide medical professionals in more effective health resource allocation and to direct future studies on the pathogenesis of this complex entity.

Using a large administrative database, we aimed to analyze the trends and seasonal association of hospital admission and all-cause mortality of ILD in the past 10 years.

Methods

We obtained the study population from Nationwide Inpatient Sample (NIS) of Agency for Healthcare Resource and Quality (AHRQ) Healthcare Cost and Utilization Project, years 2006 to 2016. All data contained in these database files have previously been de-identified and are off public record, therefore, our institutional review board decided no approval for the study was necessary.

Appropriate weighting was used to produce accurate nation-wide estimates.

Study population was limited to adult patients (age ≥ 18), admitted with the primary diagnosis of interstitial lung disease (ILD) of all causes excluding the identifiable external causes (drug, asbestos, silicosis, pneumoconiosis, hypersensitivity pneumonitis due to organic dusts). (International Classification of Diseases, ninth revision, clinical modification (ICD-9-CM) diagnostic codes 516.30 through 516.37 and 515); ICD-10-CM codes J84.1 through J84.117). A complete list of used ICD codes with description is available in the Appendix. Annual population estimates were obtained from U.S Census Bureau, to account for growing U.S population.

Statistical Analysis

Weighted annual and monthly hospitalization and in-hospital mortality rates were calculated. Hospitalization rates within each year were calculated based on U.S. Census population estimates for a given year. In-hospital mortality rates were calculated with admission number as denominators and in-hospital death numbers as numerators. Monthly hospitalization or mortality rates represent a time series and can be analyzed by seasonal and trend decomposition procedures to reveal long-term trends, seasonality, and random fluctuations. Seasons were defined in a standard manner (“winter” includes December through February, “spring” – March through May, “summer” – June through August, and “fall” – September through November).

We performed two separate subgroup analyses. The first group included all cases with the primary diagnoses of IDL or PF. In second group, we excluded all records with diagnostic codes for infectious pneumonia of any etiology (see ICD codes in the Appendix section).

Inter-seasonal differences of mean number of hospitalizations was assessed by ANOVA.

Significance and magnitude of observed annual trends was evaluated by Mann-Kendall test and Sen’s slope (Sen PK, 1968).

Results

Hospital admissions

Average monthly number of in-hospital admissions and average monthly hospitalization rate per 100,000 population is demonstrated in **Table 1**. The months from January to April had higher number of admissions compared to the remaining months of the year (**Figure 1**). Seasonal pattern of hospitalization rate was the same between subgroups of included and excluded pneumonia.

After merging of months into seasons, mean (±SD) number of hospitalizations in spring, summer, fall and winter were 7447.9 ± 932.0, 6643.0 ± 840.5, 6551.3 ± 922.6 and 7110.3 ± 866.1 respectively (**Figure 2**). Inter-seasonal differences did not reach statistical significance (ANOVA p = 0.079). However, the difference was found to be significant (independent samples t-test p-value = 0.035) by comparison of number of hospitalizations during spring (7447.9 ± 932.0) with other seasons (summer, fall, winter) combined (6768.2 ± 884.8).

Crude monthly hospitalization rate and trend (by LOESS seasonal decomposition) over 11 years (2006 – 2016) is demonstrated in **Figure 3**. The observed descending trends were statistically significant ($p < 0.001$ on Mann-Kendall test) in both subgroups (with and without exclusion of admissions with PNA). Corresponding Sen's slopes were similar: −0.00133 in group without exclusion of PNA admissions and −0.001167 in group with PNA exclusion. Please note, that National Inpatient Sample switched to ICD-10 system in the third quarter of 2015 database, which could affect reporting of multiple diseases and conditions including PF, despite careful translation of ICD-9 diagnostic codes.

Mortality

Seasonal variation on in-hospital mortality is summarized in **Table 1** and **Figure 4**. In general, it was lower in the subgroup that excluded PNA. The presence or absence of diagnosis of infectious pneumonia did not significantly affect seasonal variation of mortality. The highest mortality was noted in December and February, while lowest was from March through September.

Mortality rate in spring, summer, fall and winter were 7.61% ± 0.67%, 7.13% ± 0.79%, 7.57% ± 0.69% and 8.13% ± 0.60% respectively (**Figure 5**). Observed differences were significant (ANOVA p = 0.018). Again, the highest mortality predisposition to winter was re-demonstrated.

Trend in mortality rate over 11 years are demonstrated in **Figure 6**. Observed trends were not significant (Mann-Kendall p = 0.7144 in subgroup without exclusion of PNA admissions, and 0.2218 in subgroup of excluded PNA admissions).

Discussion

To the best of our knowledge, our study is the first to describe both seasonal variations of hospital admission and in-hospital mortality for IPF and non-IPF ILD in the United States in the 11 year- period from 2006 to 2016. Our primary findings are that mortality of all types of ILD is highest in winter, up to 8.13% ± 0.60% and average admission rate is highest in Spring and in months of January to May. The seasonal variation of hospital admission and mortality do not change when we exclude all cases with infectious pneumonia diagnosis. From 2006 to 2016, all-cause hospital admission rate of patients with interstitial lung disease declined but their mortality remained unchanged, even when infectious lung etiologies were excluded.

Our finding of highest all-cause mortality in the winter, even when pneumonia was excluded, was the findings by Olson et al which used a different database for analysis [12]. The two most common explanations for winter mortality are respiratory infection and cold temperature. Cold air could hypothetically induce hyperpnoea, subsequently cause drying of the airways [13] and inducing proinflammatory substances production leading to epithelial injury [8]. Infectious etiology was suggested because strong seasonal variations have been reported in COPD, pneumonia and recognized viral illness [14]. There is some evidence that a colder environment could also prolong the life span of viruses. Many viruses such as *influenza A*, RSV and *mycoplasma pneumonia* which cause infections in humans almost exclusively in winter to early spring [15, 16].

The most immediate causes of death in patients with ILD were pulmonary fibrosis progression and pneumonia. Respiratory causes of death accounted for 64 %-89% in patients with ILD [17-19]. IPF and non-IPF interstitial lung disease both have very high and similar mortality rates after admission for respiratory distress [20]. Based on a study in Finland, ischemic heart disease, heart failure and lung cancer were the other causes of death [21]. All of those conditions also have been reported to have higher mortality in winter time in the general population [12, 22], which may explain the higher mortality in IPF and non IPF ILD patients in winter time

Of note, the in-hospital mortality of interstitial lung disease was noted to be significantly higher than the similar study in chronic obstructive lung disease (COPD) and asthma patients using the same national database ,8% vs 2%, 8% vs 1% respectively[23, 24]. interestingly enough, the mortality rate was 14% higher in the winter compared to the summer, which was less pronounced than the seasonal variations of all cause of deaths of COPD patients (25% to 50% higher in the winter) [12, 25]. Although both COPD and interstitial lung disease are both progressive illnesses with the pathogenesis involving accelerated cellular senescence[26]. This finding suggests that the impact of weather and viral illness on mortality might not be as pronounced in ILD, compared to COPD.

One of the utmost important roles of physicians is to prevent hospital admission for ILD patients. ILD and especially IPF related admissions are significant events after which the lung function of patients will significantly deteriorate with the mean survival only from 2.8 months to 27.7 months [27]. From our study, we found that all cause admission rates in the last 11 years were highest in the months from January to May. Spring in general had highest admission rates compared to the average of other seasons, even when infectious lung diseases were ruled out. Moineddin et al in their study in the primary care settings found a higher office visits due to respiratory disease in the months from December to April [28].

In the period of 11 years from 2006 to 2016, we observed a decrease in admissions rate for all cause hospital admission for ILD with the rise in population taken into account. The sharp decrease in 2016 hospital admissions might be a result of incomplete report of administrative data possibly due to the transition from ICD-10 system in the third quarter of 2015. Despite these encouraging results, the all-cause mortality rate from interstitial lung disease from 2006 to 2016 has been unchange although many advances have been introduced in diagnosis and treatment of interstitial lung disease [29] as well as in hospital management in reducing hospital admissions [30]

Our study has limitations. We did not include all types of interstitial lung disease We excluded the interstitial lung disease group with identifiable external agents (organic dust, drug, asbestos, silicosis, pneumoconiosis) because of two reasons. Firstly, it is for the comparison with the results of the study by Olson et al for the

interstitial lung disease group from 1992 to 2003 [12] and secondly, including ILD group with identifiable external agents with different pathogenesis will create more heterogeneity to our population. Although we have included all ICD-9-CM and ICD-10-CM codes for interstitial lung disease, the results are inevitably susceptible to errors from coding inaccuracies. We also did not focus on a single disease but on both IPF and non-IPF causes of ILD. Nevertheless, this study has provided with an important and objective overview on the seasonal variations and trends in admissions and mortality of this entity spectrum over a long period of time.

Conclusion

All cause hospital admission and mortality of interstitial lung disease have a strong seasonal variation in 11 years from 2006 to 2016. Hospital admissions are highest in the period from January to May, in-hospital death was highest in the winter. All- cause hospital admission of patients with interstitial lung disease declined but their mortality remained unchanged, with or without the presence of infectious pneumonia.

Declarations

Ethics approval and consent to participate: this is a study based on large national administrative database that is available for public. Consent and ethics approval was waived and not applicable.

Consent for publication: not applicable

Availability of data and materials: all data were stored in the national inpatient sample database

Competing interests: The authors declare no conflict of interest

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Authors' contribution: all authors contributed equally to the manuscript

Acknowledgement: not available

Abbreviations

ILD: Interstitial Lung Disease

IPF: Idiopathic Pulmonary Fibrosis

PF: Pulmonary Fibrosis

NIS: Nationwide Inpatient Sample

ICD-9CM: International Classification of Diseases, ninth revision, clinical modification

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Table

Table 1. Average monthly number of in-hospital admissions for pulmonary fibrosis, hospitalization rate (per 100,000 population), and in-hospital mortality; including and excluding cases with codes for infectious pneumonia.

Month	Including admissions with codes for infectious PNA			Excluding admissions with codes for infectious PNA		
	Number of hospitalizations, monthly (mean ± SD)	Monthly hospitalization rate, per 100,000 population (mean ± SD)	In-hospital mortality, % (mean ± SD)	Number of hospitalizations, monthly (mean ± SD)	Monthly hospitalization rate, per 100,000 population (mean ± SD)	In-hospital mortality, % (mean ± SD)
Jan	2,437 ± 312	0.79 ± 0.11	7.81 ± 1.49	1,951 ± 253	0.63 ± 0.09	5.83 ± 1.44
Feb	2,456 ± 313	0.79 ± 0.11	8.23 ± 1.39	2,002 ± 261	0.65 ± 0.09	6.28 ± 1.16
Mar	2,458 ± 315	0.79 ± 0.11	7.87 ± 1.04	2,001 ± 277	0.65 ± 0.10	5.73 ± 0.67
Apr	2,482 ± 337	0.80 ± 0.12	7.56 ± 0.73	2,052 ± 290	0.66 ± 0.10	5.83 ± 0.75
May	2,353 ± 293	0.76 ± 0.10	7.37 ± 0.93	1,948 ± 262	0.63 ± 0.09	5.50 ± 1.31
Jun	2,202 ± 321	0.71 ± 0.11	7.25 ± 1.09	1,825 ± 270	0.59 ± 0.09	5.38 ± 0.91
Jul	2,151 ± 304	0.69 ± 0.10	6.92 ± 1.45	1,802 ± 263	0.58 ± 0.09	5.25 ± 1.23
Aug	2,149 ± 227	0.69 ± 0.08	7.23 ± 0.90	1,802 ± 199	0.58 ± 0.07	5.57 ± 0.87
Sep	2,154 ± 245	0.69 ± 0.09	6.85 ± 1.20	1,801 ± 199	0.58 ± 0.07	5.16 ± 1.20
Oct	2,197 ± 368	0.71 ± 0.13	8.12 ± 1.33	1,813 ± 308	0.58 ± 0.11	6.19 ± 1.12
Nov	2,131 ± 363	0.68 ± 0.13	7.72 ± 1.17	1,763 ± 295	0.57 ± 0.10	5.75 ± 1.01
Dec	2,207 ± 296	0.71 ± 0.10	8.45 ± 1.56	1,785 ± 258	0.57 ± 0.09	6.25 ± 1.40

Figures

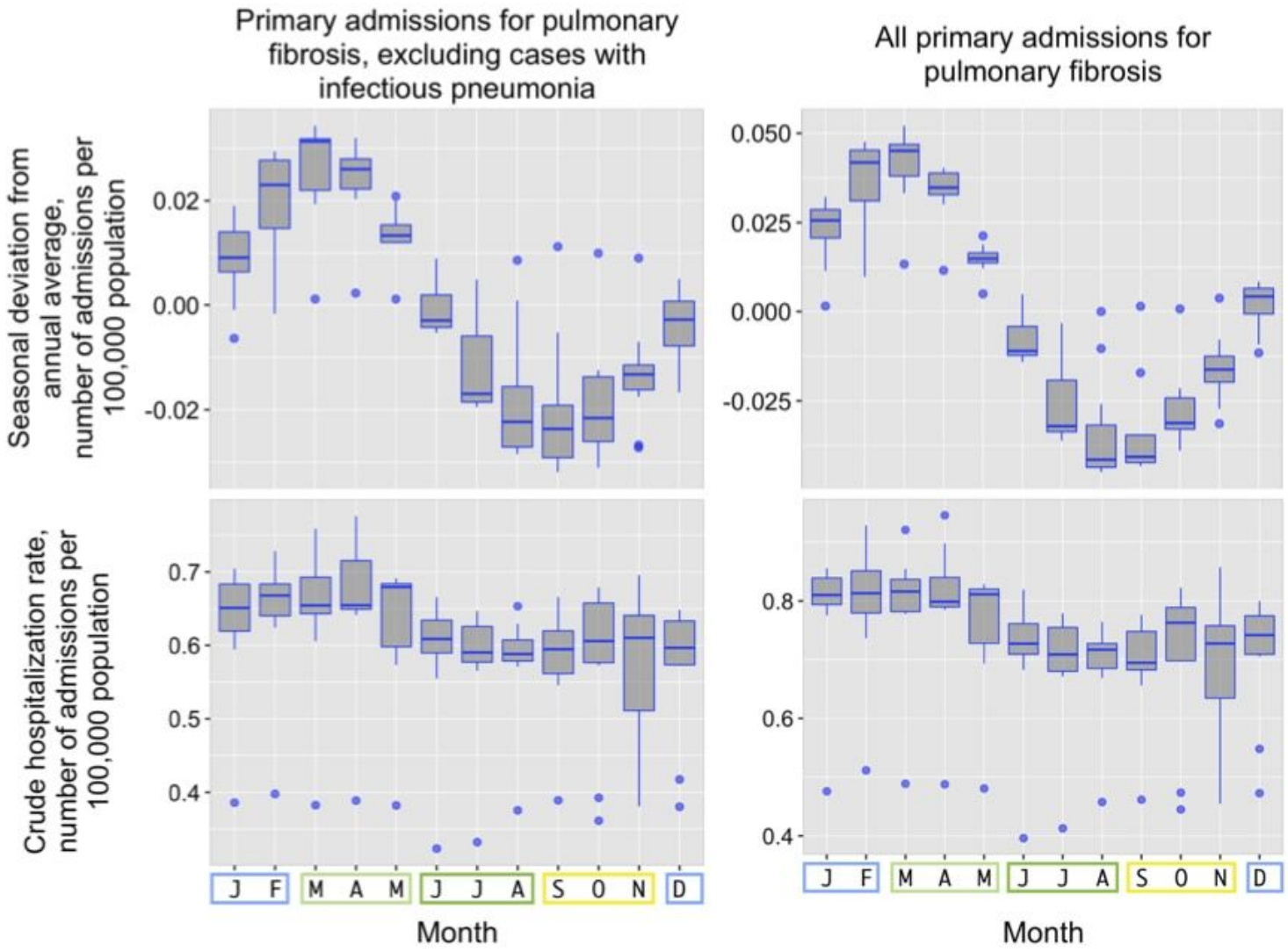

Figure 1

Crude hospitalization rates for PF (primary diagnosis; per 100,000 population) and seasonal deviation from annual average; including and excluding admissions with PNA.

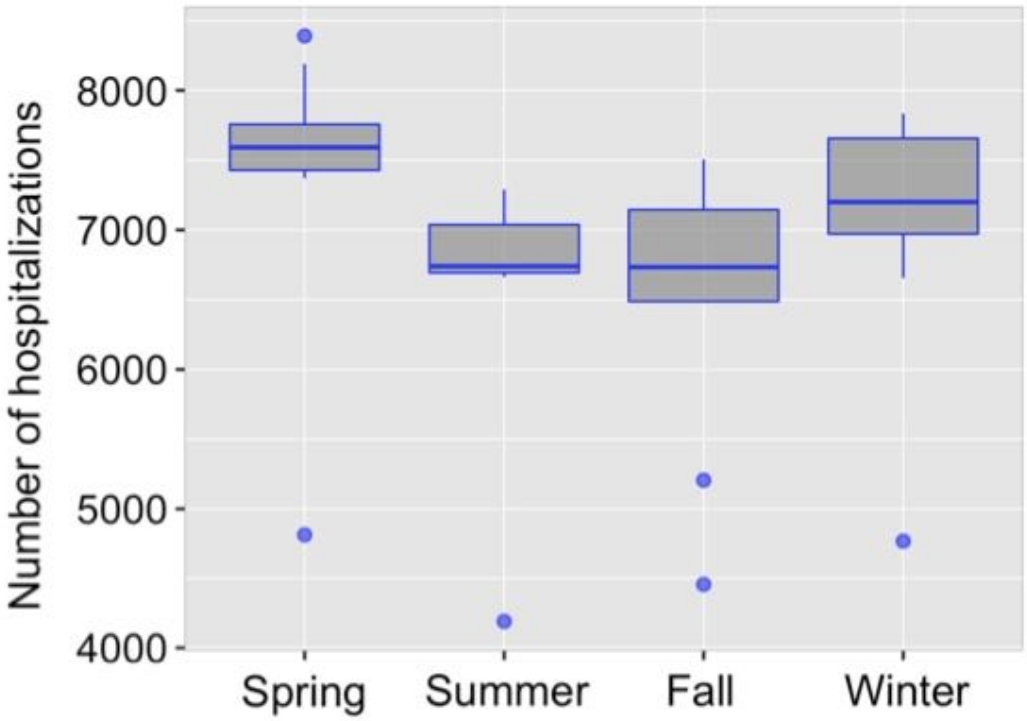

Figure 2

Number of hospitalizations for PF (regardless of presence of PNA), grouped by season.

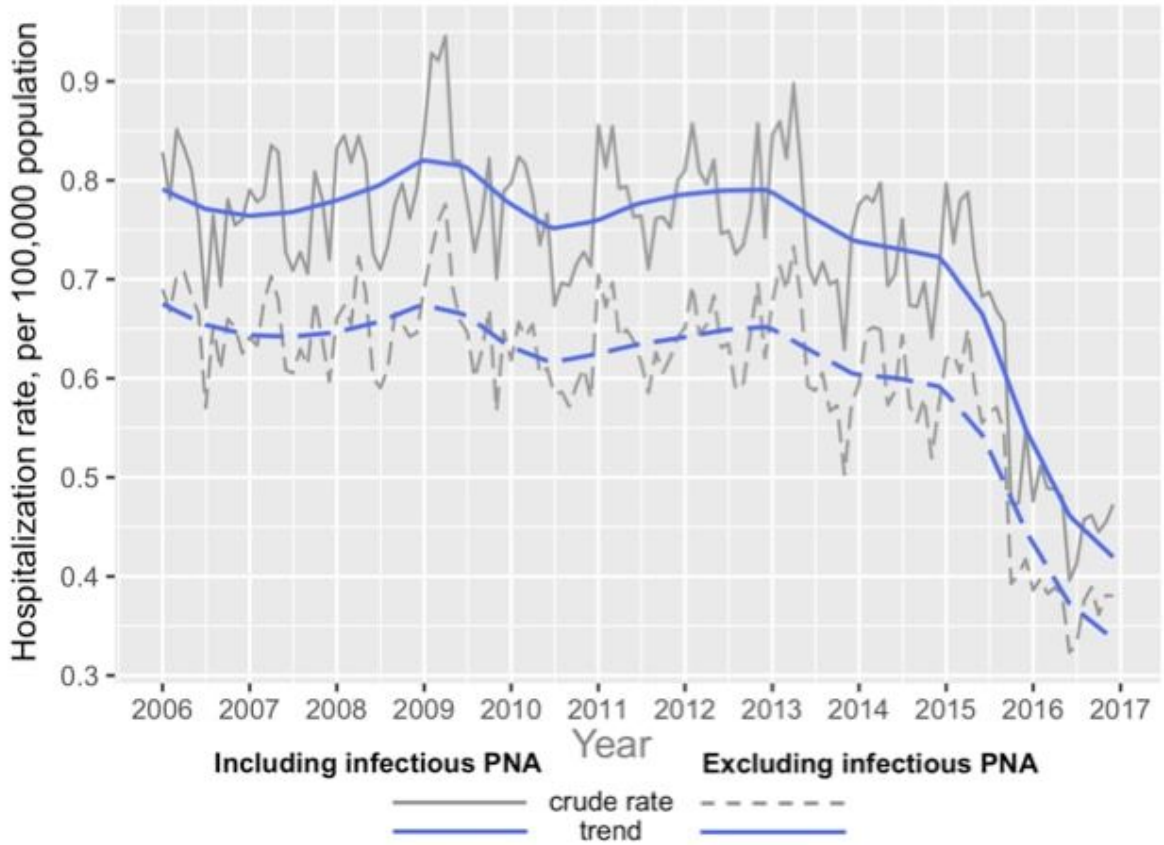

Figure 3

Crude hospitalization rates for PF and trend (seasonal LOESS decomposition), per 100,000 population, with and without exclusion of PNA, 2006 – 2016.

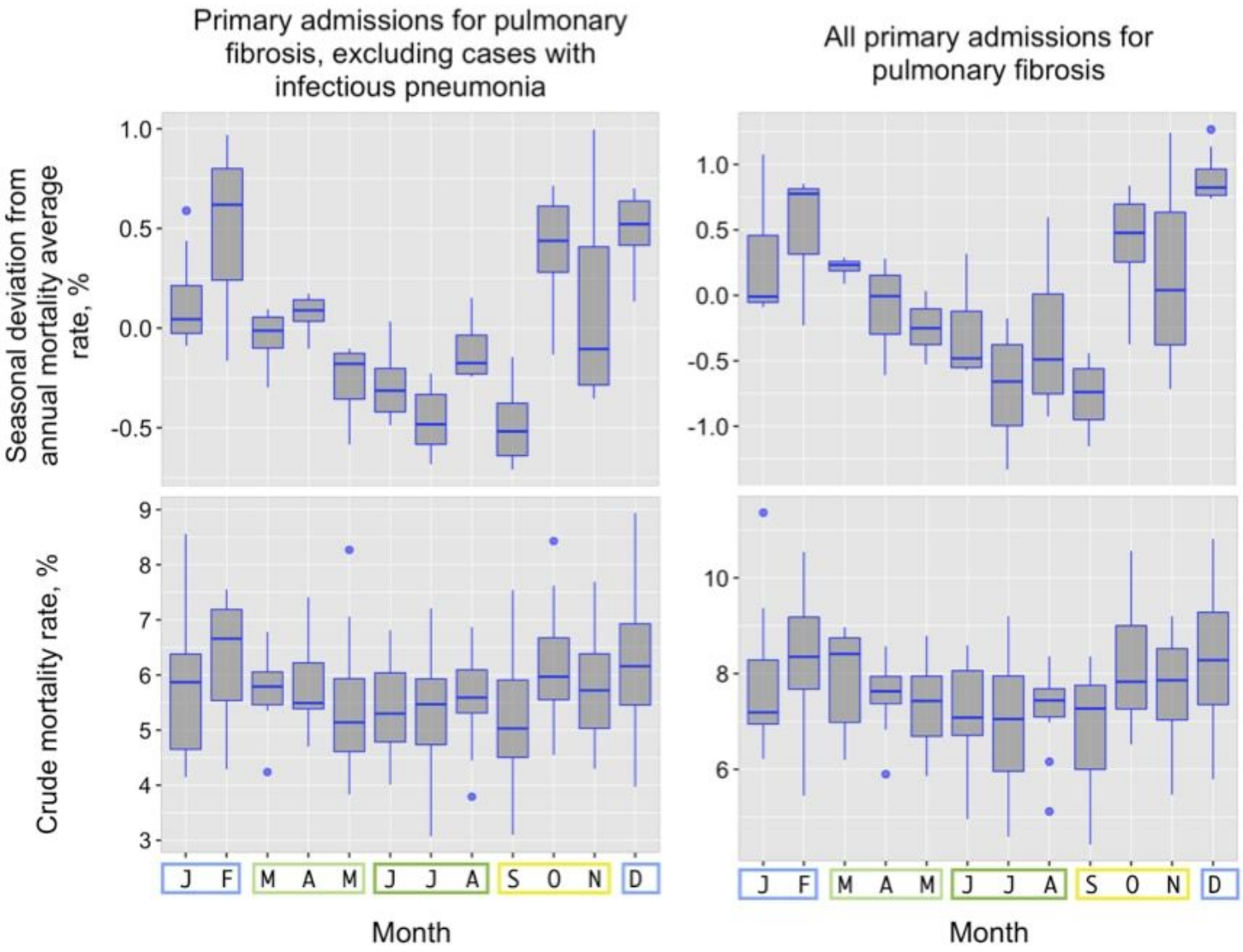

Figure 4

Crude in-hospital mortality rates of patients admitted with primary diagnosis of PF and seasonal deviation from annual mortality average; including and excluding admissions with PNA.

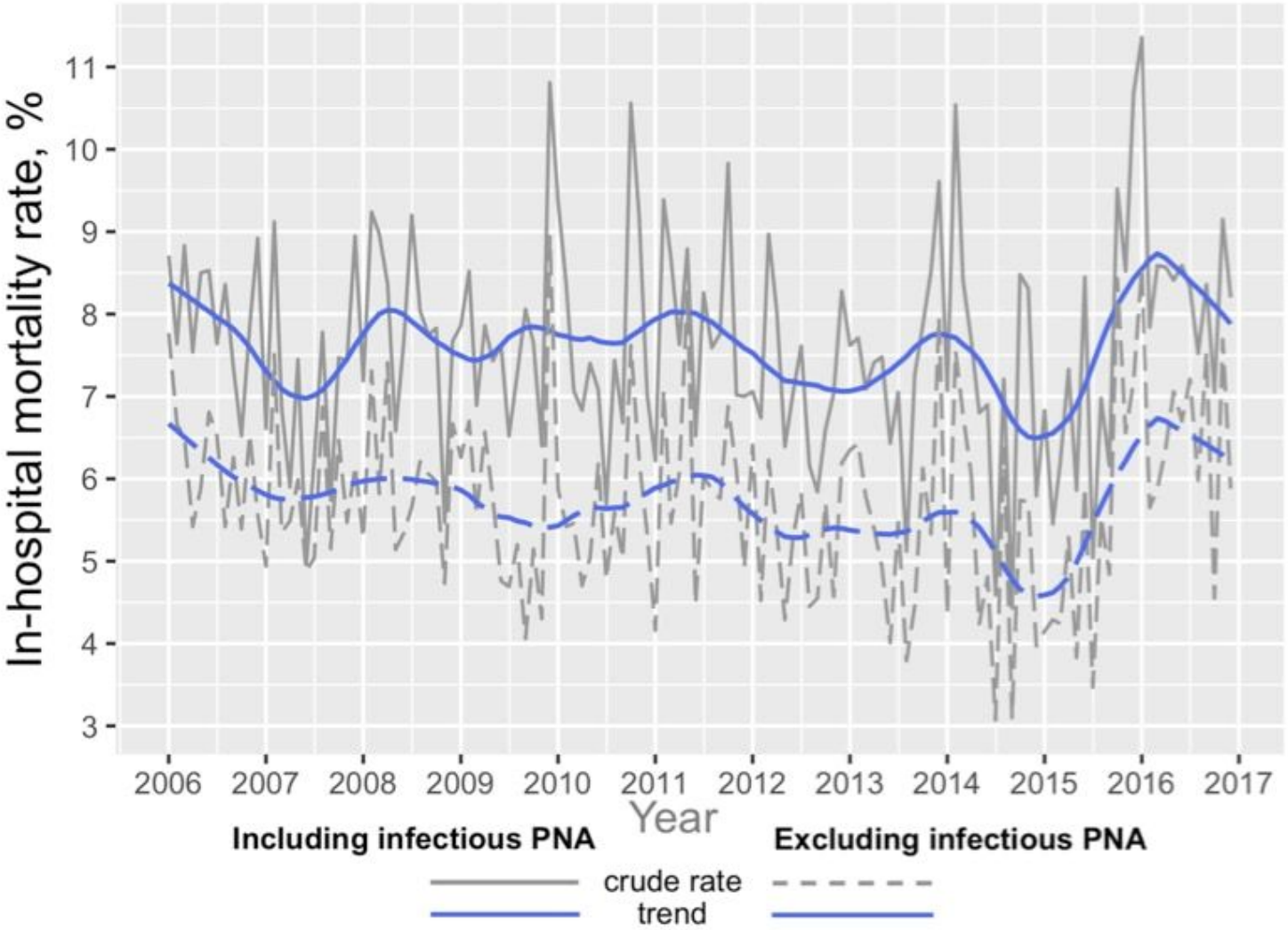

Figure 5

Crude in-hospital mortality rate and trend (seasonal LOESS decomposition), with and without exclusion of PNA, 2006 – 2016.

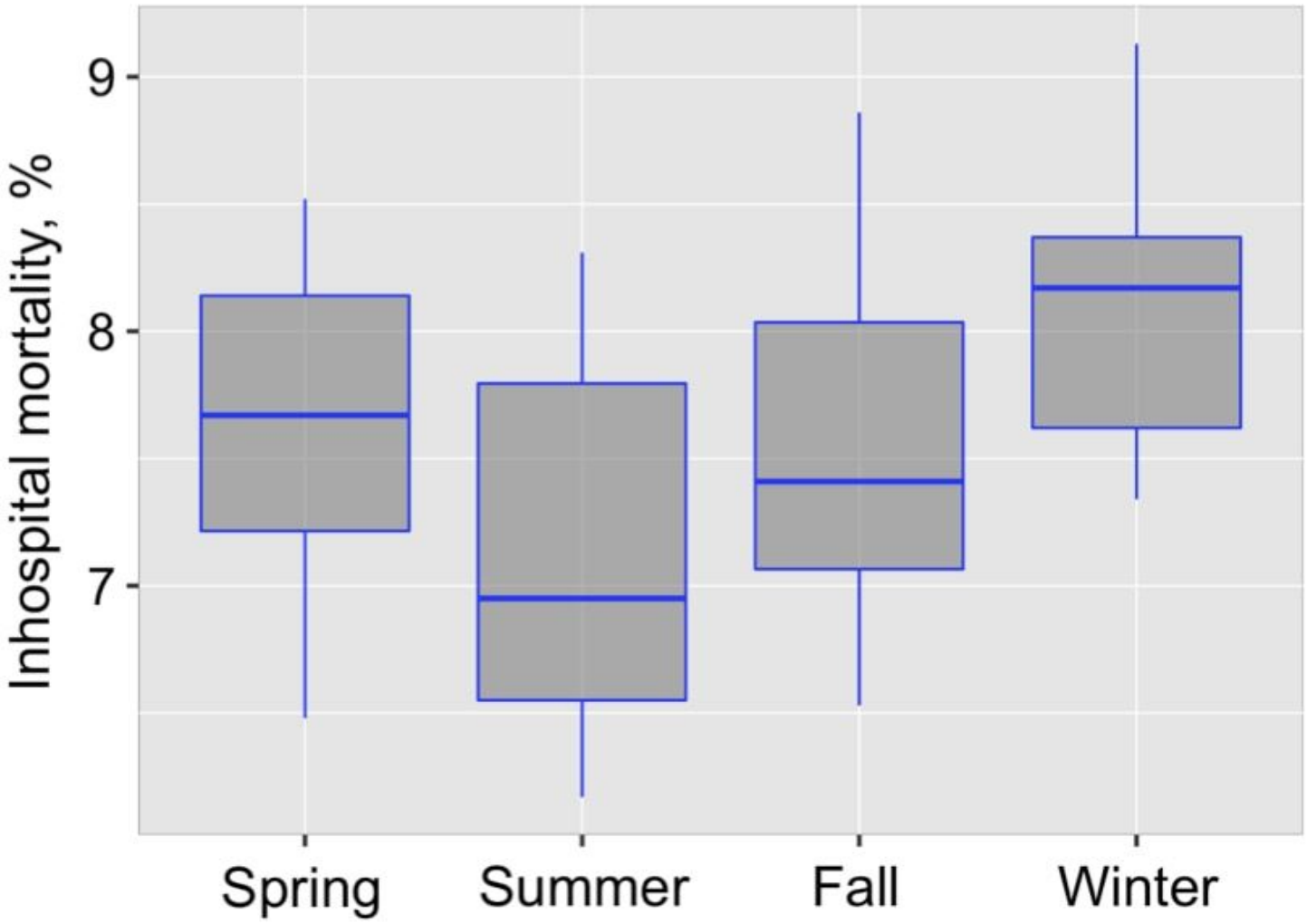

Figure 6

In-hospital mortality by season, %.