Original Article

Immunization status in chronic obstructive pulmonary disease: A multicenter study from Turkey

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Abstract:

OBJECTIVE: The purpose of this study is to detect the prevalence and the factors associated with influenza and pneumococcal vaccination and outcomes of vaccination during 2013–2014 season in patients with chronic obstructive pulmonary disease (COPD) in Turkey.

METHODS: This was a multicenter retrospective cohort study performed in 53 different centers in Turkey.

RESULTS: During the study period, 4968 patients were included. COPD was staged as GOLD 1-2-3-4 in 9.0%, 42.8%, 35.0%, and 13.2% of the patients, respectively. Influenza vaccination rate in the previous year was 37.9%; and pneumococcus vaccination rate, at least once during in a life time, was 13.3%. Patients with older age, higher level of education, more severe COPD, and comorbidities, ex-smokers, and patients residing in urban areas had higher rates of influenza vaccination. Multivariate logistic regression analysis showed that advanced age, higher education levels, presence of comorbidities, higher COPD stages, and exacerbation rates were associated with both influenza and pneumococcal vaccination. The number of annual physician/outpatient visits and hospitalizations due to COPD exacerbation was 2.73 ± 2.85 and 0.92 ± 1.58 per year, respectively. Patients with older age, lower education levels, more severe COPD, comorbid diseases, and lower body mass index and patients who are male and are residing in rural areas and vaccinated for influenza had significantly higher rates of COPD exacerbation.

CONCLUSIONS: The rates of influenza and pneumococcal vaccination in COPD patients were quite low, and the number of annual physician/outpatient visits and hospitalizations due to COPD exacerbation was high in Turkey. Advanced age, higher education levels, comorbidities, and higher COPD stages were associated with both influenza and pneumococcal vaccination.

Keywords:

Chronic obstructive pulmonary disease, chronic obstructive pulmonary disease exacerbation, influenza vaccine, pneumococcal vaccine

Chronic obstructive pulmonary disease (COPD) is highly prevalent illness, and the prevalence varies throughout the world. An overall COPD prevalence of 7.8%–19.7% is reported in adult population.[1-7] Patients usually suffer from cough, sputum, dyspnea, and sometimes acute worsening of these symptoms, termed as COPD exacerbation, especially in winter season. Acute COPD exacerbations, which can lead to more frequent physician/hospital admissions, hospitalizations, life-threatening complications, and death, are mostly associated with tracheobronchial infections and air pollution.[8] Acute exacerbations are

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more common in severe COPD cases, and those cases are reported to be referred to the hospital 1.5–2.5 times per year.[9]

Of the infectious COPD exacerbations, 40%–60% are known to be related to bacterial infections and 30% are related to respiratory viral infections (rhinoviruses, influenza viruses, etc.).[10] Influenza vaccination has been shown to reduce outpatient visits, hospitalizations, and mortality rates due to COPD exacerbations.[11,12] Pneumococcal vaccine has also been shown to decrease pneumococcal pneumonia in COPD patients.[13,14] In current practice, GOLD guidelines recommend influenza vaccination in all COPD patients to reduce serious illness.[15] Similarly, conjugate and polysaccharide (PCV13 and PPSV23, respectively) pneumococcal vaccines are recommended for all COPD patients aged ≥65 years. PPSV is also recommended for younger patients (<65 years) with significant comorbid conditions including chronic heart or lung diseases.[15]

The purpose of this study is to detect the prevalence and the factors associated with influenza and pneumococcal vaccination and outcomes of vaccination during 2013–2014 season in COPD patients in Turkey.

Methods

Study design

This multicenter retrospective cohort study was carried out in 53 different centers in Turkey between December 1, 2014, and January 31, 2015, following approval by the ethics committee.

Study population

During the study period, all patients (>40 years of age) who were admitted to these centers with at least 1 year history of COPD, diagnosed according to the GOLD criteria, and agreed to participate in the study were included.[15] Demographic characteristics and patients symptoms were collected, and modified Medical Research Council (mMRC) dyspnea scale was filled for each patient by physicians using a standard questionnaire, which was completed by face-to-face interviews. Whether patients had influenza vaccination in the recent year (Have you been vaccinated for influenza in the last year?) and pneumococcal vaccination at least once in a lifetime (Have you ever received the pneumococcal vaccine?) were questioned. COPD exacerbation was defined as worsening of respiratory symptoms requiring a physician or a hospital visit or hospitalization (How many times have you been admitted to a physician or a hospital due to worsening of your respiratory symptoms?/How many times have you been hospitalized due to worsening of your respiratory symptoms?). Physician/hospital visits and/or hospitalizations due to COPD exacerbation were also recorded.

Statistical analysis

Data analysis was performed using SPSS software (version 13.01, SPSS Inc., Chicago, IL, USA). The Chi-square test was used to compare categorical variables. The Kolmogorov–Smirnov test was used to test for normal distribution of variables. The parametric student's *t*-test was used for comparing mean or median values of normally distributed data, and the nonparametric Mann–Whitney U-test was used to compare data that were not normally distributed. Factors that were potential contributors to vaccination (age, gender, education, smoking, body mass index, residential area, comorbidities, and COPD severity) were analyzed using logistic regression. Multivariate logistic regression analysis was used as a stepwise descending method from predictive factors with a significance <0.05 in the univariate analysis.

Results

A total of 5135 patients were collected from the study centers. However, after exclusion of 167 patients due to younger age (≤40 years), repeated records, and patients with missing data, 4968 patients were analyzed. Of all patients, 4196 were male (84.5%) and the mean age was a 66.5 ± 10.0 years (male: 66.6 ± 9.8, female: 66.1 ± 10.7). Other demographic characteristics are summarized in Table 1.

Influenza and pneumococcal vaccination rate

Overall rate of influenza vaccination was 37.9% (1885/4968, 95% confidence interval [CI]: 0.366–0.393) during 2013–2014 seasons. Vaccination rates were 41.4% (852/2060, 95% CI: 0.392–0.435) and 39.7% (324/816, 95% CI: 0.364–0.431) in COPD D and C and 36.0% (363/1009, 95% CI: 0.330–0.389) and 32.4% (343/1059, 95% CI: 0.296–0.352) in COPD B and A, respectively ($P < 0.001$). Patients with older age, higher education, more severe COPD, and comorbid diseases and also patients who are ex-smokers and residing in urban area had significantly higher rates of influenza vaccination [Table 1].

Overall rate of pneumococcal vaccination was 13.3% (659/4966, 95% CI: 0.123–0.142) at least once during in a life time. Similar to influenza, pneumococcal vaccination rates were also significantly higher in ex-smokers (15.1% vs. 9.1%, $P < 0.001$), patients with higher education (university: 29.8%, secondary/high school: 20.0%, elementary school: 11.3% vs. uneducated: 8.3%, $P < 0.001$), patients with comorbid diseases (15.4% vs. 10.4%, $P < 0.001$), and patients residing in urban area (15.1% vs. 8.8%, $P < 0.001$), except COPD severity (COPD D: 15.2%, COPD C: 12.3%, COPD B:

Table 1: Demographic characteristics of chronic obstructive pulmonary disease patients according to the influenza vaccination status

Variables	Influenza vaccinated, *n* (%)	Influenza unvaccinated, *n* (%)	Total, *n* (%)	*P*
Age (4968 patients)				
<65years	666 (35.3)	1358 (44.0)	2024 (40.7)	<0.001
≥65 years	1219 (64.7)	1725 (56.0)	2944 (59.3)	
Gender (4968 patients)				
Male	1609 (85.4)	2587 (83.9)	4196 (84.5)	0.172
Female	276 (14.6)	496 (16.1)	772 (15.5)	
Education (4967 patients)				
Uneducated	220 (11.7)	537 (17.4)	757 (15.2)	<0.001
Elementary school	1127 (59.8)	1965 (63.8)	3092 (62.3)	
Secondary/high school	404 (21.4)	479 (15.5)	883 (17.8)	
University	134 (7.1)	101 (3.3)	235 (4.7)	
Smoking (4957 patients)				
Nonsmoker	212 (11.3)	374 (12.2)	586 (11.8)	<0.001
Ex-smoker	1319 (70.1)	1775 (57.7)	3094 (62.4)	
Smoker	351 (18.7)	926 (30.1)	1277 (25.8)	
Residence (4933 patients)				
Rural	489 (26.2)	941 (30.7)	1430 (29.0)	0.001
Urban	1379 (73.8)	2124 (69.3)	3503 (71.0)	
mMRC score (4967 patients)				
0	90 (4.8)	158 (5.1)	248 (5.0)	0.004
1	530 (28.1)	1021 (33.1)	1551 (31.2)	
2	504 (26.7)	760 (24.7)	1264 (25.4)	
3	506 (26.8)	743 (24.1)	1249 (25.1)	
4	255 (13.5)	400 (13.0)	655 (13.2)	
GOLD category (4608 patients)				
GOLD 1	152 (8.7)	264 (9.3)	416 (9.0)	0.007
GOLD 2	708 (40.3)	1264 (44.3)	1972 (42.8)	
GOLD 3	634 (36.1)	979 (34.3)	1613 (35.0)	
GOLD 4	262 (14.9)	345 (12.1)	607 (13.2)	
GOLD groups (4769 patients)				
Group A	394 (22.0)	785 (26.4)	1179 (24.7)	0.004
Group B	343 (19.2)	542 (18.2)	885 (18.6)	
Group C	220 (12.3)	385 (12.9)	605 (12.7)	
Group D	833 (46.5)	1267 (42.5)	2100 (44.0)	
Comorbidity (patients)				
At least one (4968)	1181 (62.7)	1701 (55.2)	2882 (58.0)	<0.001
Hypertension (4836)	723 (39.6)	982 (32.6)	1705 (35.3)	<0.001
Hearth failure (4913)	299 (16.1)	414 (13.5)	713 (14.5)	0.013
Diabetes mellitus (4812)	345 (19.0)	405 (13.5)	750 (15.6)	<0.001
Allergy-Atopy (4876)	224 (12.1)	332 (11.0)	556 (11.4)	0.206
Other (2810)	462 (40.6)	688 (41.1)	1150 (40.9)	0.795
COPD exacerbation				
Exacerbation ≥2	1053 (58.8)	1653 (55.5)	2706 (56.7)	0.023
Exacerbation <2	737 (41.2)	1327 (44.5)	2064 (43.3)	
BMI (4863 patients)*				
Low	131 (7.1)	229 (7.6)	360 (7.4)	0.417
Normal	590 (31.8)	1013 (33.7)	1603 (33.0)	
Overweighed	678 (36.5)	1061 (35.3)	1739 (35.8)	
Obese	456 (24.6)	705 (23.4)	1169 (23.9)	

*Low (BMI <20 kg/m^2), Normal (BMI: 20-24.9 kg/m^2), Overweighed (BMI: 25-29.9 kg/m^2), Obese (BMI ≥30 kg/m^2). BMI=Body mass index, COPD=Chronic obstructive pulmonary disease, mMRC=Modified Medical Research Council, GOLD=Global Initiative for Chronic Obstructive Pulmonary Disease

13.9%, and COPD A: 14.4%, $P = 0.270$). Furthermore, female patients had significantly higher rates of pneumococcal vaccination (16.0% vs. 12.8%, $P = 0.017$). Multivariate logistic regression analysis showed that advanced age (odds ratio [OR]: 1.519, 95% CI: 1.327–1.738, $P < 0.001$ and OR: 1.309, 95% CI: 1.084–1.580,

$P = 0.005$), higher education levels (OR: 4.217, 95% CI: 2.990–5.947, $P < 0.001$ and OR: 6.200, 95% CI: 4.033–9.533, $P < 0.001$), presence of comorbidities (OR: 1.207, 95% CI: 1.060–1.374, $P = 0.004$ and OR: 1.357, 95% CI: 1.126–1.635, $P < 0.001$), and higher COPD stages and exacerbation rates (OR: 1.175, 95% CI: 1.028–1.342, $P = 0.018$ and OR: 1.518, 95% CI: 1.263–1.824, $P < 0.001$) were found to be associated with both influenza and pneumococcal vaccination, respectively [Table 2]. Multivariate logistic regression analysis also showed female gender as a factor that contributing to (OR: 1.675, 95% CI: 1.288–2.178, $P < 0.001$) pneumococcal vaccination. On the contrary, active smoking was associated with lower influenza and pneumococcal vaccination rates (OR: 0.638, 95% CI: 0.501–0.813, $P < 0.001$ and OR: 0.679, 95%CI: 0.474–0.972, $P = 0.034$).

Among influenza-vaccinated patients, 86.3% (1627/1885, 95% CI: 0.846–0.877), 6.3% (119/1885, 95% CI: 0.053–0.075), and 7.3% (139/1885, 95% CI: 0.062–0.086) said that they had been vaccinated after the recommendation of their physicians, pharmacists, or others, respectively. In contrast, among the patients unvaccinated, 53.1% (1645/3026, 95% CI: 0.525–0.561) stated that their physician did not recommend vaccination, 12.6% (390/3026, 95% CI: 0.117–0.141) said that the vaccine was ineffective, and 34.3 (991/3026, 95% CI: 0.311–0.344) reported other reasons.

Annual chronic obstructive pulmonary disease exacerbation and hospitalization rates

Annual number of COPD exacerbation requiring physician/outpatient visit was 2.73 ± 2.85 times per year and requiring hospitalization was 0.92 ± 1.58 times per year. Patients with older age (>65), lower education levels, more severe COPD, comorbid diseases, and lower BMI and patients who are male and are residing in rural area and vaccinated for influenza had significantly higher rates of COPD exacerbation rates [Table 3].

Discussion

In this study, we found that the overall prevalence of influenza vaccination among COPD patients during 2013–2014 season was 37.9% and pneumococcal vaccination at least once in a lifetime was 13.3%. A recent study which was performed in western cities of Turkey showed similar vaccination rates (36.5% for influenza and 14.1% for the pneumococcus).[16] Influenza and pneumococcus vaccination rates were found to be unchanged during this 8-year period after a study which was performed in Eastern Black Sea Region of Turkey during 2006/2007 season, and in that previous study, vaccination rates were detected as 33.3% and 12.0%, respectively.[17] Despite vaccine recommended groups are well defined and vaccines were reimbursed by Social Security Institution, vaccination rates remain low in Turkey. There are varying vaccination rates in COPD patients worldwide. In the PLATINO study which was conducted in 2003 in five different Latin American countries, influenza vaccination rate reported to be lower in Caracas (Venezuela) and higher in Santiago (Chile) as 5.1% and 52%, respectively.[18] A study from Italy by Chiatti *et al*. showed that the influenza vaccination rate to be 30.5% during 2004/2005 season.[19] One another study from Germany showed 46.5% of patients received influenza vaccine and 14.6% received pneumococcal vaccine during 2002/2003 season.[20] On the other hand, higher influenza vaccination rates were reported from Norway (59%, during 2006/2007 season) and from

Table 2: Multivariate logistic regression analysis of demographic parameters contributing influenza and pneumococcal vaccination

Variables*	Influenza vaccination			Pneumococcal vaccination		
	OR	95.0% CI	*P*	OR	95.0% CI	*P*
Age ≥65 years	1.519	1.327-1.738	<0.001	1.309	1.084-1.580	0.005
Gender (female)	-	-	-	1.675	1.288-2.178	<0.001
Residence (Urban area)	0.934	0.807-1.082	0.364	1.526	1.218-1.911	<0.001
Education						
Uneducated	Reference	-	-	Reference	-	-
Elementary school	1.538	1.247-1.897	<0.001	1.704	1.235-2.351	0.001
Secondary/high school	2.563	1.996-3.291	<0.001	3.625	2.531-5.193	<0. 001
University	4.217	2.990-5.947	<0.001	6.200	4.033-9.533	<0.001
Smoking						
Nonsmoker	Reference	-	-	Reference	-	-
Ex-smoker	1.118	0.902-1.387	0.309	1.164	0.841-1.611	0.361
Smoker	0.638	0.501-0.813	<0.001	0.679	0.474-0.972	0.034
Comorbidity	1.207	1.060-1.374	0.004	1.357	1.126-1.635	<0.001
COPD exacerbation ≥2	1.175	1.028-1.342	0.018	1.518	1.263-1.824	<0.001
GOLD grade (3 and 4)	1.232	1.082-1.403	0.002	-	-	-

*Only variables, derived from predictive factors with a significance ≤0.05 in the univariate analysis, were included. COPD=Chronic obstructive pulmonary disease, CI=Confidence interval, OR=Odds ratio, GOLD=Global Initiative for Chronic Obstructive Pulmonary Disease

Table 3: The number of physician/policlinic visits and hospitalizations due to chronic obstructive pulmonary disease exacerbations per year

Variables*	Number of exacerbation/year		*P*	Number of hospitalization/year		*P*
	Mean±SD	Median-range		Mean±SD	Median-range	
Age (years)						
<65	2.40±2.69	2 (0-12)	<0.001	0.70±1.40	0 (0-12)	<0.001
≥65	2.95±2.94	2 (0-12)		1.07±1.67	0 (0-12)	
Gender						
Male	2.89±2.81	2 (0-12)	0.005	0.90±1.49	0 (0-12)	0.581
Female	2.70±2.86	2 (0-12)		0.92±1.59	0 (0-12)	
Education						
Uneducated	3.82±3.16	3 (0-12)	<0.001	1.51±1.92	1 (0-12)	<0.001
Elementary school	2.80±2.88	2 (0-12)		0.94±1.59	0 (0-12)	
Secondary/high school	1.98±2.35	1 (0-12)		0.54±1.18	0 (0-10)	
University	1.35±1.70	1 (0-10)		0.31±0.77	0 (0-5)	
Residence						
Rural	3.30±3.02	2 (0-12)	<0.001	1.28±1.78	1 (0-10)	<0.001
Urban	2.49±2.75	2 (0-12)		0.78±1.47	0 (0-12)	
GOLD category						
GOLD 1	1.73±2.18	1 (0-1)	<0.001	0.34±0.91	0 (0-8)	<0.001
GOLD 2	2.01±2.38	1 (0-12)		0.53±1.12	0 (0-10)	
GOLD 3	3.02±2.90	2 (0-12)		1.06±1.65	0 (0-12)	
GOLD 4	4.27±3.24	3 (0-12)		1.78±1.96	1 (0-10)	
GOLD groups						
Group A	0.42±0.49	0 (0-1)	<0.001	0.07±0.26	0 (0-2)	<0.001
Group B	0.57±0.49	1 (0-1)		0.20±0.40	0 (0-1)	
Group C	3.43±2.05	3 (2-12)		0.67±1.12	0 (0-8)	
Group D	4.74±2.82	4 (2-12)		1.77±1.96	1 (0-12)	
Comorbidity (patients)						
At least one co-morbidity	2.85±2.89	2 (0-12)	<0.001	1.00±1.63	0 (0-12)	<0.001
Hypertension (4836)	2.98±2.94	2 (0-12)	<0.001	1.06±1.67	0 (0-12)	<0.001
Hearth failure (4913)	3.24±3.02	2 (0-12)	<0.001	1.18±1.70	1 (0-12)	<0.001
Diabetes mellitus (4812)	3.08±2.95	2 (0-12)	<0.001	1.25±1.96	1 (0–10)	<0.001
Allergy-Atopy (4876)	2.90±2.89	2 (0-12)	0.105	0.77±1.42	0 (0-10)	0.001
Other (2810)	2.64±2.88	2 (0-12)	<0.001	0.88±1.52	0 (0-10)	0.015
BMI*						
Low	3.16±2.93	2 (0-12)	0.011	1.20±1.64	1 (0-10)	<0.001
Normal	2.86±2.99	2 (0-12)		1.01±1.67	0 (0-12)	
Overweighed	2.51±2.72	2 (0-12)		0.80±1.47	0 (0-10)	
Obese	2.66±2.80	2 (0-12)		0.86±1.57	0 (0-12)	
Influenza vaccination						
No	2.69±2.88	2 (0-12)	0.036	0.87±1.56	0 (0-12)	<0.001
Yes	2.79±2.82	2 (0-12)		1.01±1.60	0 (0-10)	
Pneumococcal vaccination						
No	2.73±2.87	2 (0-12)	0.339	0.92±1.58	0 (0-12)	0.436
Yes	2.74±2.75	2 (0-12)		0.93±1.53	0 (0-10)	

*Low (BMI<20 kg/m^2), Normal (BMI: 20-24.9 kg/m^2), Overweighed (BMI: 25-29.9 kg/m^2), Obese (BMI ≥30 kg/m^2). BMI=Body mass index, SD=Standard deviation, GOLD=Global Initiative for Chronic Obstructive Pulmonary Disease

France (73%, during 2010/2011 season).[21,22] More acceptable vaccination rates were reported from Spain in 2003 for influenza (84.2%) and for pneumococcus (65%).[23] However, a recent study reported a small decrease in overall prevalence of influenza vaccination (62.7%) in Spain.[24]

Patients with older age, higher level of education, more severe COPD, and comorbidities and patients who were ex-smokers and residing in urban areas had higher rates of influenza vaccination. Similarly, ex-smokers, patients with a higher level of education and comorbidities, patients residing in urban area, and also female patients had higher rates of pneumococcus vaccination. Similar to our results, the vaccination rates were found to be higher among the higher educational levels,[16,20,24-27] elder patients and those with concomitant disease,[16,19,21] and were found to be lower among active smokers.[17,19,21]

Ariñez-Fernandez *et al*. also concluded that the most important determinants of pneumococcus vaccination are female gender, advanced age, and severity of COPD.[28] In addition to the some demographical characteristics, vaccine recommendation by physician seems to be an important determinant of vaccination. We detected that, of the patients being vaccinated, 86.3% reported that they took into consideration of their physician's advice, while 53.1% of patients being unvaccinated reported that their physician gave no advice. Some studies also emphasize the importance of physicians' recommendation in vaccination rates.[16,22] However, some other studies underline the role of patients not believing the effectiveness of vaccines.[29]

Our study showed that the annual number of COPD exacerbations requiring physician/outpatient visits or hospitalizations (2.73 ± 2.85 and 0.92 ± 1.58, respectively) was higher than those previous studies.[30,31] For example, in the TORCH and the UPLIFT studies, the annual rate of exacerbations was 0.85 and 0.73 in treatment groups and 1.13 and 0.85 in placebo groups, respectively.[30,31] Our results also showed that patients with older age (>65), lower education levels, more severe COPD, comorbid diseases and lower BMI, patients who are male, and patients who are residing in rural area and vaccinated for influenza had significantly higher rates of COPD exacerbation. Although we did not investigate the role of prior exacerbations, analysis of the ECLIPSE study showed that the single best predictor of exacerbations, across all GOLD stages, was a past history of exacerbations.[32] Consistent to our results, increasing age, severity of airflow limitation, prior asthma diagnosis, eosinophilia, and comorbid conditions were also previously confirmed to be predictors of frequent exacerbations.[33-37] On the contrary, we showed that higher levels of education and residence in urban areas were found to be associated with reduced risk of exacerbation. The association between higher level of education and less exacerbation rate was not surprising as well as the residential area. We believe that the lower rates of exacerbations in residents of urban areas are mostly associated with more viable and comfortable living conditions and a higher quality of life. Thus, Suzuki *et al*. and Hurst *et al*. reported poorer quality of life to be associated with frequent exacerbations.[33,34] On the other hand, we think that the higher rates COPD exacerbations in patients vaccinated for influenza might be associated with the tendency of vaccination among more severe COPD patients.

Our study has some limitations. Despite high number of study population, our data are mostly dependent on self-reporting of vaccination and exacerbation rates. The validity of self-reported vaccination status has not been assessed in Turkish population; however, some studies reported that self-reported vaccination status is adequate in Australian and American patients.[38,39] On the other hand, especially recall of pneumococcal vaccination may be difficult since it is performed >5 years intervals (until this study, only polysaccharide type [PPSV23] was available). Similar to vaccination status, number of exacerbations and hospitalizations especially in frequent exacerbators might be difficult to remember.

Conclusions

Our results demonstrated that influenza and pneumococcal vaccination rates remained suboptimal during 2013–2014 season among COPD patients and the number of annual outpatient visits and hospitalizations due to COPD exacerbations was high in Turkey. Advanced age, higher education levels, presence of comorbidities, higher COPD stages, and exacerbation rates were associated with both influenza and pneumococcal vaccination.

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Conflicts of interest
There are no conflicts of interest.

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