CHEST Original Research

Tobacco Smoking Increases the Risk for Death From Pneumococcal Pneumonia [AQ1]

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Background: **Active smoking increases the risk of developing community-acquired pneumonia (CAP) and invasive pneumococcal disease, although its impact on mortality in pneumococcal CAP outcomes remains unclear. The aim of this study was to investigate the influence of current smoking status on pneumococcal CAP mortality.**

Methods: **We performed a multicenter, prospective, observational cohort study in 4,288 hospitalized patients with CAP. The study group consisted of 892 patients with pneumococcal CAP: 204 (22.8%) current smokers, 387 (43.4%) nonsmokers, and 301 (33.7%) exsmokers.**

Results: **Mortality at 30 days was 3.9%: 4.9% in current smokers vs 4.3% in nonsmokers and 2.6% in exsmokers. Currently smokers with CAP were younger (51 vs 74 years), with more alcohol abuse and fewer cardiac, renal and asthma diseases. Current smokers had lower CURB-65 (confusion, uremia, respiratory rate, BP, age ≥ 65 years) scores, although 40% had severe sepsis at diagnosis. Current smoking was an independent risk factor (OR, 5.0; 95% CI, 1.8-13.5; *P* = .001) for 30-day mortality of pneumococcal CAP, after adjusting for age (OR, 1.06; *P* = .001); liver disease (OR, 4.5); sepsis (OR, 2.3); antibiotic adherence to guidelines; and first antibiotic dose < 6 h. The independent risk effect of current smokers remained when compared only to nonsmokers (OR, 4.0; 95% CI, 1.3-12.6; *P* = .015) or to exsmokers (OR, 3.9; 95% CI, 1.09-4.95; *P* = .02).**

Conclusions: **Current smokers with pneumococcal CAP often develop severe sepsis and require hospitalization at a younger age, despite fewer comorbid conditions. Smoking increases the risk of 30-day mortality independently of tobacco-related comorbidity, age, and comorbid conditions. Current smokers should be actively targeted for preventive strategies.**

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Abbreviations: CAP = community-acquired pneumonia; CURB-65 = confusion, uremia, respiratory rate, BP, age ≥ 65 years; PPV23 = 23-valent pneumococcal polysaccharide vaccine

The deleterious effect of tobacco smoke compounds the development of several respiratory diseases and its impact on all deaths has been considered by the World Health Organization as a global health threat. Its multiple adverse effects include increasing evidence of alteration of the innate and adaptive immune response of the host against infections.[1-8]

There is a considerable amount of information concerning the association of active smoking with increased risk for community-acquired pneumonia (CAP). In fact, even in immunocompetent patients without smoking-related comorbidities such as COPD, active smoking has been found to be an independent risk factor.[9] Moreover, the amount of tobacco exposure (cigarettes per day and packs per year) showed a dose-response effect on CAP risk that may decrease after smoking cessation.[10,11] In a population-based study, Baik et al[12] reported that the smoking-related CAP risk was independent of sex. Furthermore, the relationship between smoking and causal microorganisms has been proved for invasive pneumococcal disease[13] and for *Legionella pneumophila*.[14]

In contrast, the impact of smoking on the outcome of infections is scarce and, specifically in CAP, is not well known. Prior studies have reported unreliable results.[15] While some studies showed increased

mortality due to CAP,[16-19] other studies[20-23] and two meta-analyses[24,25] reported a negative or inconsistent association. Possible explanations for this are the difficulties in finding a clear association, because CAP mortality depends on many different host factors, mainly when some important comorbidities are also tobacco related. Moreover, causal microorganisms also have different mortality rates[26] and different cytokine profiles[27] that influence prognosis and outcome. Hence, CAP studies include fairly heterogeneous populations. We hypothesized that the impact of current smoking on CAP mortality should be studied in a more homogeneous population—patients with pneumococcal CAP—after adjusting for initial severity and tobacco comorbidities. To our knowledge, there is no consistent information about the smoking effect on 30-day pneumococcal CAP mortality including both invasive and noninvasive episodes.

Our aim was to investigate the influence of active tobacco smoking on the outcome of pneumococcal CAP, considering host comorbid conditions and severity at diagnosis. A worse prognosis in pneumococcal CAP in smokers would imply a greater need for recommending vaccination in this population.

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Materials and Methods

Design and Study Population

The current study is a secondary analysis and the whole prospective cohort has been published.[28] In brief, inclusion criteria were adults aged >18 years with a new radiographic infiltrate compatible with the presence of acute pneumonia, and at least two signs or symptoms of CAP. Exclusion criteria were admission within the previous 15 days, solid organ transplantation, hematologic malignancies, immunosuppressive treatment and/or chronic corticosteroid treatment (≥ 20 mg/d), and HIV infection. The study was approved by the ethic committee (ISS, Hospital La Fe, Valencia, Spain; July 15, 2004; approval number 5/2004) and the patients provided written informed consent.

We recorded data on age, sex, prior antibiotic treatment of the same episode, tobacco use, comorbidities (eg, COPD; heart, liver, neurologic, and renal diseases; diabetes mellitus), nursing home residence, previous influenza and pneumococcal vaccine, alcohol intake (>80 g/d), previous steroid therapy (<20 mg/d), antibiotic regimen according to Spanish guidelines,[28] and first antibiotic dose ≤6 h. Initial severity assessment was measured by the CURB-65 (confusion, uremia, respiratory rate, BP, age ≥ 65 years)score and by considering sepsis and severe sepsis criteria. Follow-up was performed after discharge to assess evolution and mortality after 30 days.

Microbiologic Studies

Microbiologic tests were performed and included blood culture, urinary antigens for *Streptococcus pneumoniae* and *L pneumophila*, Gram stain and culture of quality sputum, tracheobronchial aspirate, protected specimen brush and BAL (where available), and serologic studies for respiratory viruses and atypical bacteria. Diagnosis of pneumococcal CAP was considered if one of the following criteria was met: isolation of *S pneumoniae* from blood or pleural fluid; bacterial growth ≥ 10^3 or ≥ 10^4 CFU/mL from a protected specimen brush or BAL, and urinary antigen test positive for *S pneumoniae*, isolation of a predominant *S pneumoniae* culture from a validated sputum or tracheal aspirate.

Definitions

Smoking status: Current or past smoking history, including number of packs per year, was classified as follows[13]: current (active) smokers, exsmokers, and nonsmokers. Current smokers were considered those who had smoked ≥ 100 cigarettes in their lifetime and still smoked daily on admission or had quit smoking within the previous year. Exsmokers were patients who had smoked >100 cigarettes in their lifetime but quit smoking >1 year earlier. Nonsmokers were those who had smoked <100 cigarettes or had never smoked.

Sepsis: Sepsis and severe sepsis were evaluated at CAP diagnosis following previously accepted criteria,[29] which have been published elsewhere.[30] Sepsis was defined as the presence of pneumonia and systemic inflammatory response syndrome. Severe sepsis was considered if criteria for sepsis were met and there was at least one acute organ failure with the following criteria: arterial hypoxemia (PaO_2/FIO_2 <300), creatinine level >2 mg/dL, acute confusion or hypotension (systolic arterial tension <90 mm Hg).

Statistical Studies

Univariate Analysis: Statistical analyses were performed using the SPSS version 19 software package (IBM Corp). Categorical

variables were compared using the χ^2 test. Continuous variables were analyzed using the Student *t* and Kruskal-Wallis tests. Values of $P < .05$ were considered statistically significant.

Multivariate Analysis: The independent risk effect of current smoking on 30-day mortality as a dependent variable was evaluated with three logistic regression models. In the first model, current smokers were compared with exsmokers and nonsmokers; in the second, they were compared with nonsmokers (after excluding exsmokers); in the third, current smokers were compared with exsmokers (after excluding nonsmokers). Independent variables included in the models were those found statistically significant in the univariate analyses: age, liver diseases, initial severity measured by CURB-65 score, severe sepsis, and first antibiotic dose within 6 h. We also included as independent variables some others considered clinically relevant, such as influenza vaccination and antibiotic adherence to Spanish guidelines. CURB-65 score was dichotomized as low (0-1) or high severity (≥ 2). The Hosmer and Lemeshow goodness-of-fit test was used to evaluate the adequacy of the models.

Results

General Characteristics

We recruited 4,374 patients with CAP in the whole cohort study; 86 were excluded due to missing data. A total of 913 patients had pneumococcal CAP (21.3%), of whom 83 had mixed etiology (pneumococcus-involved mixed etiology) and 21 lost to follow-up were excluded. The study group comprised 892 patients with pneumococcal CAP (Table 1). Main patient characteristics, habits, vaccination status, comorbid conditions, sepsis status, and CURB-65 score are shown in Table 2. Of these patients, 204 (22.8%) were current smokers, 301 (33.7%) were exsmokers, and 387 (43.4%) were nonsmokers. Initial antibiotic treatment was adherent to Spanish guidelines in 81.3% (Table 2). However, only four patients (0.45%) received inappropriate antibiotic (considering pneumococcal coverage according to resistance). The regimens in those patients were as follows: ciprofloxacin plus amikacin, clindamycin plus azithromycin, azitromycin plus aztreonam, and ceftazidime plus aztreonam.

Smoking Status: Demographic Characteristics, Comorbid Condition, Vaccination, and Initial Severity

Current smokers differed in several demographic characteristics, age, and comorbid conditions, as shown in Table 3. The percentage of smokers with pneumococcal CAP was higher in men than in women, and these patients were significantly younger (51.9 ± 16.2 years). Current smokers had also fewer cardiac, renal, and asthma comorbid conditions, with no differences in terms of COPD and diabetes. However, current smokers had more significant alcohol abuse (33.2%) and more liver disease.

Initial severity assessment measured by CURB-65 score showed significantly lower scores in smokers compared with the other groups. Nevertheless, when severe sepsis criteria were evaluated, a similar percentage was found in smokers and nonsmokers. Current smokers had a higher rate of bacteremic CAP than nonactive smokers. [AQ10]

Current smokers had significantly lower vaccination rates regarding influenza (27.1% vs 55% in exsmokers; $P < .001$) and pneumococcal infection [AQ11] (5.6% vs 11.8%; $P < .0016$) (Table 3). Bacteremia was [AQ12] slightly lower in those who had received the 23-valent pneumococcal polysaccharide vaccine (PPV23) but not significantly so (21.3% vs 27.1%; p:0.334). The [AQ13] rate of PPV23 vaccination was low and no significant association was found with initial severe sepsis (30 of 79 patients [38%] vs 278 of 686 patients [40.5%]; p:0.66).

30-day Mortality

Univariate Analyses: Mortality at 30 days was 3.9% (35 of 892 patients): 10 of 204 (4.9%) were smokers, 17 of 387 (4.3%) were nonsmokers, and eight of 301 (2.6%) were exsmokers ($P > .05$). Demographic characteristics, comorbid conditions, initial severity, time of first antibiotic dose, antibiotic adequacy, bacteremia, and severe sepsis related to mortality are shown in Table 4. Patients who died were older and included fewer current smokers,

Table 1—*Positive Microbiologic Test for* Streptococcus pneumoniae *Identification*

[AQ20] Test	Study Group: Active Smokers (n = 204)	Nonsmokers (n = 387)	Exsmokers (n = 301)	Total (n = 892)	*P* Value
Blood culture	51/155 (32.9)	70/271 (25.83)	41/196 (20.92)	162/622 (26.05)	.039
Sputum	76/98 (77.55)	115/137 (83.94)	98/128 (76.56)	289/363 (79.61)	.276
Urine antigen	173/201 (86.07)	334/372 (89.78)	262/297 (88.22)	769/870 (88.39)	.413
BAS	14/17 (82.35)	11/14 (78.57)	10/14 (71.43)	35/45 (77.78)	.764
BAL	4/5 (80)	6/7 (85.71)	2/3 (66.67)	12/15 (80)	…
Pleural fluid	20/26 (76.92)	25/33 (75.76)	18/20 (90)	63/79 (79.75)	.416
Protected brushing	1/2 (50)	2/3 (66.67)	2/2 (100)	5/7 (71.43)	…

[AQ21] Data given as patient no./total no. (%). BAS = ■■■.

[AQ19]

Table 2—*Demographic, Comorbidities, Prior Treatment, and Initial Severity in Pneumococcal CAP*[a]

Characteristic	Pneumococcal CAP (n = 892)
Demographic and toxic habits	
Age[b]	70 (27)
Male sex	564/892 (63.2)
Active smoking	204/892 (22.9)
Alcohol	127/840 (15.1)
Nursing home	47/892 (5.3)
Vaccines	
Pneumococcal vaccine	79/765 (10.3)
Influenza vaccine	376/776 (48.5)
Comorbidities	
Diabetes	189/891 (21.2)
Liver disease	52/888 (5.9)
Cardiac failure	101/889 (11.4)
Renal disease	46/890 (5.2)
COPD	191/870 (21.9)
Asthma	33/495 (6.7)
Treatment	
Corticosteroid therapy < 20 mg/d	24/885 (2.7)
Antibiotic adherence to guidelines	714/889 (80.3)
First antibiotic dose ≤ 6 h	689/860 (80.1)
Severity assessment	
CURB-65 score ≥ 2	697/892 (78.1)
Sepsis	658/892 (73.8)
Severe sepsis	362/892 (40.9)
Pneumococcal bacteremia	162/622 (26)

Data given as patient no./total no. (%). CAP = community-acquired pneumonia. CURB-65 = confusion, uremia, respiratory rate, BP, age ≥ 65 years.

[a]Mixed etiologies are not included.

[b]Age is presented as median and interquartile range.

although these data did not reach statistical significance. Regarding comorbid conditions, there was more liver disease in the nonsurvivor group. A significantly higher CURB-65 score and severe sepsis were found in those who died.

Multivariate Analyses: In the multivariate models to predict 30-day mortality in patients with pneumococcal CAP, we found that current smoking was an independent risk factor after adjusting for age, pneumococcal and influenza vaccines, comorbidities (alcohol-related, heart, renal, cerebrovascular, and neoplastic diseases), initial severity (based on CURB-65 score), severe sepsis, antibiotic adherence to Spanish guidelines, and first dose within 6 h. Table 5 summarizes the results of the multivariate regression analyses. In the first model, current smokers were compared with the nonsmokers and exsmokers. The independent risk effect of current smokers was maintained after excluding exsmokers or nonsmokers in the two additional regression models. Other independent risk factors for mortality were age (OR, 1.06; $P = .000$), chronic liver disease (OR, 4.5; $P = .01$), and severe sepsis (OR, 2.3; $P = .02$), while receiving the influenza vaccine was found to be a protective independent significant factor (OR, 0.31; $P = .02$) (Table 5).

Discussion

The main findings of our study are the following:

1. Current smokers developed sepsis and require hospitalization for pneumococcal CAP at a younger age than noncurrent smokers. [AQ14]
2. Active smoking is an independent mortality risk factor (OR, 5.0) in patients with pneumococcal CAP after adjusting for age, influenza and pneumococcal vaccination, comorbidities (alcohol-related, heart, kidney, cerebrovascular, and neoplastic diseases), initial severity measured by CURB-65 score, severe sepsis, antibiotic adherence to Spanish guidelines, and first dose within 6 h.
3. The independent effect of smoking was shown after excluding exsmokers and/or nonsmokers.

Tobacco smoking has been identified as risk factor for CAP[20,30]; however, its impact on mortality has not been adequately elucidated, probably because it is also linked to comorbidities, and studies on CAP rely on fairly heterogeneous populations. In our study, we found that current smokers admitted to the hospital with pneumococcal CAP represented a different population. In fact, they were much younger and had fewer comorbid conditions (eg, cardiac diseases and asthma) than admitted patients who were not active smokers. Current smokers also had worse health habits, with more alcohol abuse and lower vaccination rates. It has been reported that cigarette smokers, due to a nicotine-induced mechanism, also have increased alcohol intake,[31] along with lower influenza and pneumococcal vaccination rates.[32]

Severity on presentation, on the other hand, showed that approximately 40% of current smokers had severe sepsis at CAP diagnosis, although they had a lower percentage of comorbidities and lower CURB-65 scores (ie, current smokers developed more severe episodes, with a higher percentage of bacteremia [OR, 1.57]),[13,33] than would correspond to older and more debilitated patients. Our results reinforce that cigarette smoking is one of the strongest independent risk factors for invasive pneumococcal disease among immunocompetent, nonelderly adults.[13]

These findings highlight the relationship between tobacco and severe pneumococcal CAP episodes, even in younger patients with fewer comorbidities.[13,19,34] Tobacco inhibits some key innate immune-response components, such as Toll-like receptor 2,[35] nuclear

Table 3—*Demographic and Clinical Data of 892 Patients with Pneumococcal CAP, Comparing Active Smokers With Noncurrent Smokers*[a]

Characteristic	Current Smokers	No Current Smokers	*P* Value	OR (95% CI)
Demographics, toxins, and vaccines				
Age[b]	51 (24)	74 (20)	< .001	…
Male sex	149/204 (73.0)	415/688 (60.3)	.001	1.78 (1.26-2.52)
Alcohol	63/190 (33.2)	64/650 (9.8)	< .001	4.54 (3.05-6.76)
Nursing home	4/204 (1.9)	43/688 (6.2)	.016	0.3 (0.11-0.85)
Pneumococcal vaccine	10/180 (5.6)	69/585 (11.8)	.016	0.44 (0.22-0.87)
Influenza vaccine	49/181 (27.1)	327/595 (54.9)	< .001	0.30 (0.21-0.44)
Comorbid conditions				
Diabetes	43/204 (21.1)	146/687 (21.2)	.958	…
Chronic liver disease	24/204 (11.8)	28/684 (4.1)	< .001	3.12 (1.77-5.52)
Cardiac failure	11/204 (5.4)	90/685 (13.1)	.002	0.38 (0.19-0.72)
Chronic renal failure	5/204 (2.5)	41/686 (5.9)	.046	0.39 (0.15-1.01)
Neoplasia < 1 y	9/204 (4.4)	32/688 (4.6)	.886	…
Cardiovascular disease	10/204 (4.9)	76/688 (11.0)	.009	0.41 (0.21-0.82)
COPD	43/199 (21.6)	148/671 (22.1)	.893	…
Asthma	2/110 (1.8)	31/385 (8.0)	.021	0.21 (0.05-0.89)
Corticosteroid therapy < 20 mg/d	3/201 (1.5)	21/684 (3.1)	.226	…
Initial severity and treatment				
Antibiotic adherence	168/204 (82.3)	546/685 (79.7)	.404	…
First antibiotic dose ≤ 6 h	164/199 (82.4)	525/661 (79.4)	.355	…
CURB-65 score ≥ 2	116/204 (56.9)	581/688 (84.4)	< .001	0.24 (0.17-0.34)
Sepsis	151/204 (74.0)	507/688 (73.7)	.926	…
Severe sepsis	82/204 (40.2)	280/688 (40.7)	.898	…
Pneumococcal bacteremia	51/155(32.9)	111/467(23.8)	.025	1.57 (1.06-2.34)

See Table 2 legend for expansion of abbreviations.

[a]Nonsmokers and exsmokers.

[b]Age is presented as median and interquartile range.

factor κB, dendritic cell maturation,[36] and decreases opsonization and phagocytosis.[37,38] In vitro experimental models have shown impaired lung bacterial clearance and phagocytosis of *S pneumoniae*.[39] In fact, the risk of bacterial (mainly pneumococcal) pneumonia is reduced to the level of nonsmokers after 1 year of smoking abstinence,[40] and smoking cessation reduces the risk of hospitalization for pneumonia.[41]

The available information about the impact of tobacco on infection outcome, specifically in CAP, is not firmly established and findings are contradictory.[16-18,24,25] This may be due to several reasons, including the lack of data on smoking status in the studies,[15] the heterogeneous populations,[22,24] the impact of confounding variables such as comorbidities,[15] and the distinct microorganisms involved.[25] In our study, we found that current tobacco smoking was independently associated with 30-day mortality in patients with pneumococcal CAP after adjusting for age, comorbidities,[42] initial severity, vaccination status, antibiotic adherence to guidelines, and timing of first dose of antibiotic. Because smokers are younger and because mortality in CAP is highly dependent on age, the independent risk of smoking only appeared after eliminating the age effect. Moreover, we also incorporated some other important confounding variables in the model, such as comorbid conditions related or not to tobacco, to reinforce our findings. Our studies showed evidence for the negative impact on outcome, in line with some prior cohort studies, with the addition of including many other host variables and severity. Although two meta-analyses showed no influence of smoking on mortality,[24,25] in the first of these meta-analyses, only age was considered for adjustment,[24] and in the second, a minority of studies (eight of 127), some of them with univariate analyses, were included.[25]

The independent effect of current smoking was confirmed in two different models: (1) after elimination exsmokers and nonsmokers in the whole cohort of pneumococcal CAP, to eliminate the impact of a possible distinct population, and (2) exsmokers. Interestingly, the mortality independent risk effect of current smokers remained in the two different analyses, thus, corroborating our main finding. It is plausible that the deleterious effect of tobacco smoke on modifying Th1 responses[1,43] especially against *S pneumoniae*, with modulation of intracellular epithelial and immune signaling, and suppression of adaptive immune cell activation,[1,44] provoked a clear disadvantage for the host. In fact, the clinical relevance of smoking for mortality had been confirmed for the most severe episodes of pneumococcal CAP with septic shock[34] and in bacteremic pneumococcal pneumonia.[19]

Table 4—*Pneumococcal CAP 30-d Mortality: Univariate Statistical Results*

	Pneumococcal CAP (n = 892)			
Characteristic	Deceased 35 (3.9%) No/Total (%)	Survivors 857 (96.1%) No/Total (%)	*P* Value	OR (95% CI)
Demographic				
Age (mean)	78 (18)	70 (27)	0.001	…
Male sex)	26/35 (74.3)	538/857 (62.8)	0.16	…
Pneumococcal vaccine	4/23 (17.4)	75/742 (10.1)	0.25	…
Influenza vaccine	11/24 (45.8)	365/752 (48.5)	0.79	…
Toxic habits				
Current smoker	10/35 (28.8)	194/857 (22.6)	0.41	…
Alcohol abuse	6/35 (17.1)	121/857 (14.1)	0.61	…
Comorbidities				
COPD	10/35 (28.6)	181/835 (21.1)	0.33	…
Cardiac disease	4/35 (11.4)	97/854 (11.4)	0.99	…
Chronic renal failure	2/35 (5.7)	44/855 (5.1)	0.70	…
Diabetes	9/35 (25.7)	180/856 (21.0)	0.50	…
Asthma	0/15 (0)	33/750 (4.4)	0.61	…
Chronic liver disease	5/35 (14.3)	47/814 (5.8)	0.04	2.96 (1.09-7.9)
Initial severity assessment				
CURB 65 ≥ 2	34/35 (97.1)	663/857 (77.4)	0.006	9.95 (1.35-73.1)
Sepsis criteria	29/35 (82.9)	629/857 (73.4)	0.21	…
Severe sepsis	21/35 (60.0)	341/857 (39.8)	0.01	2.27 (1.14-4.53)
Bacteremia	10/28 (35.7)	152/594 (25.6)	0.233	…
Initial antibiotic				
Adherence	25/32 (78.1)	664/828 (80.2)	0.77	…
First dose ≤ 6 h	23/35 (67.7)	691/854 (80.9)	0.02	0.45 (0.22-0.93)

See Table 2 legend for expansion of abbreviations.

The limitations of our study are the following: (1) We had no information about the number of cigarettes per day patients smoked and, therefore, were unable to evaluate a possible dose-response relationship with 30-day mortality; (2) we obtained no information on pneumococcal serotypes, which is important when considering preventive strategies; (3) there are no precise and unanimously accepted definitions of smoker and exsmoker, and we used concepts previously used in the literature[13]; and (4) the low PPV23 vaccination rates in the smokers (5.6%) precludes evaluation of its possible impact on 30-day CAP mortality. The serotype coverage of the new conjugate pneumococcal vaccine, PCV13, in the adult population with and without comorbidities is high,[45] and smokers have been recently included in the targeted population as a risk group.[46]

Our study has also several strengths. We focused on a homogeneous subset of CAP, as it is pneumococcal pneumonia, including a wide range of potentially confounding variables (comorbidities, initial severity, antibiotic adherence to guidelines, and first initial antibiotic dose) that provided us with an accurate identification of independent risk factors. Moreover, we proved our findings after excluding exsmokers in the multivariate analyses.

In summary, to our knowledge, this is the first study to find a strong association between active smoking and

Table 5—*Multivariate Regression Analyses for 30-d Mortality in Pneumococcal CAP Concerning Current Smokers in the Whole Population and After Excluding Exsmokers or Nonsmokers*

[AQ22]

	Current vs Exsmokers and Nonsmokers[a]		Current vs Exsmokers[b]		Current vs Nonsmokers[c]	
Characteristic	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Current smokers	5.0 (1.8-13.5)	.001	3.9 (1.2-12.3)	.021	4.0 (1.3-12.6)	.015
Age	1.06 (1.02-1.10)	.001	1.03 (0.99-1.08)	.13	1.06 (1.02-1.10)	.002
Influenza vaccine	0.31(0.12-0.85)	.02	0.6 (0.1-2.4)	.5	0.20 (0.06-0.69)	.01
Liver disease	4.5 (1.4-14.5)	.01	6.1 (1.7-21.5)	.005	4.9 (1.3-18.5)	.01
CURB-65 score ≥ 2	5.9 (0.7-50.2)	.1	6.7 (0.7-57.9)	.08	5.8 (0.6-50.7)	.1
Severe sepsis	2.3 (1.09-4.95)	.02	1.3 (0.4-3.6)	.57	3.7 (1.4-9.4)	.006
Antibiotic adherence	0.6 (0.29-1.41)	.27	0.88(0.3-2.55)	.8	0.81(0.3-2.14)	.66
First dose ≤ 6 h	0.62 (0.24-1.5)	.29	0.56(0.16-1.9)	.37	0.59(0.19-1.80)	.35

See Table 2 legend for expansion of abbreviations.

30-day mortality in pneumococcal CAP, including both bacteremic and noninvasive pneumonia, not related to tobacco-induced comorbidities. This finding suggests an independent role for tobacco in worsening the outcome of pneumococcal CAP, and provides additional information about its role on severity at presentation. Current smokers had lower pneumococcal vaccination rates, developed sepsis or bacteremia, and required hospitalization for pneumococcal CAP at a younger age. Influenza vaccine appeared as an independent preventive factor for mortality in smokers, and this group should be considered as a target population for preventive strategies and firm cessation advice. Smokers have been considered by several scientific societies as a target population for the new pneumococcal conjugate vaccine, PCV13, considering its wide serotype coverage and its beneficial effect. Our study provides a new reason to encourage smokers, even young people, to quit smoking and to get vaccinated.

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Author contributions: S. B., R. M., and A. T. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. S. B. served as principal author. S. B., R. M., and A. T. contributed to the study design; S. B., R. M., A. T., S. R., R. Z., A. C., J. A., L. B., J. J. M.-V., I. A., R .d. C.-F., J. R., L. M., and J. R.-M contributed to data acquisition; S. B., R. M., and A. T. contributed to data analysis and interpretation; S. B., R. M., A. T., S. R., R. Z., A. C., J. A., L. B., J. J. M.-V., I. A., R .d. C.-F., J. R., L. M., and J. R.-M contributed to drafting and revising the manuscript.

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References

1. Arnson Y, Shoenfeld Y, Amital H. Effects of tobacco smoke on immunity, inflammation and autoimmunity. *J Autoimmun*. 2010;34(3):J258-J265.
2. Edwards D. Immunological effects of tobacco smoking in "healthy" smokers. *COPD*. 2009;6(1):48-58.
3. Ouyang Y, Virasch N, Hao P, et al. Suppression of human IL-1β, IL-2, IFN-γ, and TNF-α production by cigarette smoke extracts. *J Allergy Clin Immunol*. 2000;106(2):280-287.
4. Mehta H, Nazzal K, Sadikot RT. Cigarette smoking and innate immunity. *Inflamm Res*. 2008;57(11):497-503.
5. Manzel LJ, Shi L, O'Shaughnessy PT, Thorne PS, Look DC. Inhibition by cigarette smoke of nuclear factor-κB-dependent response to bacteria in the airway. *Am J Respir Cell Mol Biol*. 2011;44(2):155-165.
6. Strulovici-Barel Y, Omberg L, O'Mahony M, et al. Threshold of biologic responses of the small airway epithelium to low levels of tobacco smoke. *Am J Respir Crit Care Med*. 2010;182(12):1524-1532.
7. Feng Y, Kong Y, Barnes PF, et al. Exposure to cigarette smoke inhibits the pulmonary T-cell response to influenza virus and Mycobacterium tuberculosis. *Infect Immun*. 2011;79(1):229-237.
8. Bagaitkar J, Demuth DR, Scott DA. Tobacco use increases susceptibility to bacterial infection. *Tob Induc Dis*. 2008;4:12.
9. Almirall J, Bolíbar I, Balanzó X, González CA. Risk factors for community-acquired pneumonia in adults: a population-based case-control study. *Eur Respir J*. 1999;13(2):349-355.
10. Almirall J, González CA, Balanzó X, Bolíbar I. Proportion of community-acquired pneumonia cases attributable to tobacco smoking. *Chest*. 1999;116(2):375-379.
11. Almirall J, Bolíbar I, Serra-Prat M, et al; Community-Acquired Pneumonia in Catalan Countries (PACAP) Study Group. New evidence of risk factors for community-acquired pneumonia: a population-based study. *Eur Respir J*. 2008;31(6):1274-1284.
12. Baik I, Curhan GC, Rimm EB, Bendich A, Willett WC, Fawzi WW. A prospective study of age and lifestyle factors in relation to community-acquired pneumonia in US men and women. *Arch Intern Med*. 2000;160(20):3082-3088.
13. Nuorti JP, Butler JC, Farley MM, et al; Active Bacterial Core Surveillance Team. Cigarette smoking and invasive pneumococcal disease. *N Engl J Med*. 2000;342(10):681-689.
14. Den Boer JW, Nijhof J, Friesema I. Risk factors for sporadic community-acquired Legionnaires' disease. A 3-year national case-control study. *Public Health*. 2006;120(6):566-571.
15. Huttunen R, Heikkinen T, Syrjänen J. Smoking and the outcome of infection. *J Intern Med*. 2011;269(3):258-269.
16. Gupta PC, Pednekar MS, Parkin DM, Sankaranarayanan R. Tobacco associated mortality in Mumbai (Bombay) India. Results of the Bombay Cohort Study. *Int J Epidemiol*. 2005;34(6):1395-1402.
17. Doll R, Peto R, Wheatley K, Gray R, Sutherland I. Mortality in relation to smoking: 40 years' observations on male British doctors. *BMJ*. 1994;309(6959):901-911.
18. Inoue Y, Koizumi A, Wada Y, et al. Risk and protective factors related to mortality from pneumonia among middleaged and elderly community residents: the JACC Study. *J Epidemiol*. 2007;17(6):194-202.
19. Naucler P, Darenberg J, Morfeldt E, Örtqvist A, Henriques Normark B. Contribution of host, bacterial factors and antibiotic treatment to mortality in adult patients with bacteraemic pneumococcal pneumonia. *Thorax*. 2013;68(6):571-579.
20. Lange P, Vestbo J, Nyboe J. Risk factors for death and hospitalization from pneumonia. A prospective study of a general population. *Eur Respir J*. 1995;8(10):1694-1698.
21. Garau J, Baquero F, Pérez-Trallero E, et al; NACER Group. Factors impacting on length of stay and mortality of community-acquired pneumonia. *Clin Microbiol Infect*. 2008;14(4):322-329.
22. Jha P, Jacob B, Gajalakshmi V, et al; RGI-CGHR Investigators. A nationally representative case-control study of smoking and death in India. *N Engl J Med*. 2008;358(11):1137-1147.
23. Sitas F, Urban M, Bradshaw D, Kielkowski D, Bah S, Peto R. Tobacco attributable deaths in South Africa. *Tob Control*. 2004;13(4):396-399.
24. Katanoda K, Marugame T, Saika K, et al. Population attributable fraction of mortality associated with tobacco smoking in Japan: a pooled analysis of three large-scale cohort studies. *J Epidemiol*. 2008;18(6):251-264.
25. Fine MJ, Smith MA, Carson CA, et al. Prognosis and outcomes of patients with community-acquired pneumonia. A meta-analysis. *JAMA*. 1996;275(2):134-141.

26. Cillóniz C, Polverino E, Ewig S, et al. Impact of age and comorbidity on cause and outcome in community-acquired pneumonia. *Chest*. 2013;144(3):999-1007.
27. Menéndez R, Sahuquillo-Arce JM, Reyes S, et al. Cytokine activation patterns and biomarkers are influenced by microorganisms in community-acquired pneumonia. *Chest*. 2012;141(6):1537-1545.
28. Menéndez R, Torres A, Reyes S, et al. Initial management of pneumonia and sepsis: factors associated with improved outcome. *Eur Respir J*. 2012;39(1):156-162.
29. Dremsizov T, Clermont G, Kellum JA, Kalassian KG, Fine MJ, Angus DC. Severe sepsis in community-acquired pneumonia: when does it happen, and do systemic inflammatory response syndrome criteria help predict course? *Chest*. 2006;129(4):968-978.
30. LaCroix AZ, Lipson S, Miles TP, White L. Prospective study of pneumonia hospitalizations and mortality of US older people: the role of chronic conditions, health behaviors, and nutritional status. *Public Health Rep*. 1989;104(4):350-360.
31. Britt JP, Bonci A. Alcohol and tobacco: how smoking may promote excessive drinking. *Neuron*. 2013;79(3):406-407.
32. Pearson WS, Dube SR, Ford ES, Mokdad AH. Influenza and pneumococcal vaccination rates among smokers: data from the 2006 Behavioral Risk Factor Surveillance System. *Prev Med*. 2009;48(2):180-183.
33. Shariatzadeh MR, Huang JQ, Tyrrell GJ, Johnson MM, Marrie TJ. Bacteremic pneumococcal pneumonia: a prospective study in Edmonton and neighboring municipalities. *Medicine (Baltimore)*. 2005;84(3):147-161.
34. Garcia-Vidal C, Ardanuy C, Tubau F, et al. Pneumococcal pneumonia presenting with septic shock: host- and pathogen-related factors and outcomes. *Thorax*. 2010;65(1):77-81.
35. Droemann D, Goldmann T, Tiedje T, Zabel P, Dalhoff K, Schaaf B. Toll-like receptor 2 expression is decreased on alveolar macrophages in cigarette smokers and COPD patients. *Respir Res*. 2005;6:68.
36. Mortaz E, Kraneveld AD, Smit JJ, et al. Effect of cigarette smoke extract on dendritic cells and their impact on T-cell proliferation. *PLoS ONE*. 2009;4(3):e4946.
37. Qvarfordt I, Riise GC, Andersson BA, Larsson S. IgG subclasses in smokers with chronic bronchitis and recurrent exacerbations. *Thorax*. 2001;56(6):445-449.
38. Guzik K, Skret J, Smagur J, et al. Cigarette smoke-exposed neutrophils die unconventionally but are rapidly phagocytosed by macrophages. *Cell Death Dis*. 2011;2:e131.
39. Phipps JC, Aronoff DM, Curtis JL, Goel D, O'Brien E, Mancuso P. Cigarette smoke exposure impairs pulmonary bacterial clearance and alveolar macrophage complement-mediated phagocytosis of *Streptococcus pneumoniae*. *Infect Immun*. 2010;78(3):1214-1220.
40. Bénard A, Mercié P, Alioum A, et al; Groupe d'Epidémiologie Clinique du Sida en Aquitaine. Bacterial pneumonia among HIV-infected patients: decreased risk after tobacco smoking cessation. ANRS CO3 Aquitaine Cohort, 2000-2007. *PLoS ONE*. 2010;5(1):e8896.
41. Cecere LM, Williams EC, Sun H, et al. Smoking cessation and the risk of hospitalization for pneumonia. *Respir Med*. 2012;106(7):1055-1062.
42. Viasus D, Garcia-Vidal C, Castellote J, et al. Community-acquired pneumonia in patients with liver cirrhosis: clinical features, outcomes, and usefulness of severity scores. *Medicine (Baltimore)*. 2011;90(2):110-118.
43. Vassallo R, Tamada K, Lau JS, Kroening PR, Chen L. Cigarette smoke extract suppresses human dendritic cell function leading to preferential induction of Th-2 priming. *J Immunol*. 2005;175(4):2684-2691.
44. Modestou MA, Manzel LJ, El-Mahdy S, Look DC. Inhibition of IFN-gamma-dependent antiviral airway epithelial defense by cigarette smoke. *Respir Res*. 2010;11:64.
45. Grau I, Ardanuy C, Calatayud L, et al. Invasive pneumococcal disease in healthy adults: increase of empyema associated with the clonal-type Sweden(1)-ST306. *PLoS ONE*. 2012;7(8):e42595.
46. Picazo JJ, González-Romo F, García Rojas A, et al. [Consensus document on pneumococcal vaccination in adults with risk underlying clinical conditions]. *Rev Esp Quimioter*. 2013;26(3):232-252.

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