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Risk stacking of pneumococcal vaccination indications increases mortality in unvaccinated adults with Streptococcus pneumoniae infections

Risk stacking of pneumococcal vaccination indications increases mortality in unvaccinated adults with *Streptococcus pneumoniae* infections

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Abstract

Background: Several chronic disease states have been identified as pneumococcal vaccination indications due to their ability to increase pneumococcal disease development and subsequent mortality. However, the risk of mortality according to the number of these disease states present is unknown. We sought to determine the impact of concomitant, multiple risk factors (stacked risks) for pneumococcal disease on 30-day mortality in adults.

Methods: This was a national case-control study of unvaccinated older Veterans (≥50 years of age) admitted to Veterans Affairs medical centers from 2002 to 2011 with serious pneumococcal infections (pneumonia, bacteremia, meningitis) based on positive *S. pneumoniae* blood, cerebrospinal fluid, or respiratory cultures, respectively. Cases were those not alive 30 days following culture, while controls were alive. Using logistic regression, we quantified risk of 30-day mortality among patients with stacked risk factors, including age ≥ 65 years, alcohol abuse, chronic heart disease, chronic liver disease, chronic respiratory disease, diabetes mellitus, immunodeficiency, and smoking.

Results: We identified 9,730 serious pneumococcal infections, with an overall 30-day mortality rate of 18.6% (1,764 cases, 7,966 controls). Infection types included pneumonia (62%), bacteremia (26%), and bacteremic pneumonia (11%). Along with eight individual risk factors, we assessed 247 combinations of risk factors. Most cases (85%) and controls (74%) had at least two risk factors. Mortality

increased as risks were stacked, up to six risk factors (one: OR 1.5, CI 1.08-2.07; two: OR 2.01, CI 1.47-2.75; three: OR 2.71, CI 1.99-3.69; four: OR 3.27, CI 2.39-4.47; five: OR 3.63, CI 2.60-5.07; six: OR 4.23, CI 2.69-6.65), with each additional risk factor increasing mortality an average of 55% (±13%).

Conclusions: Among adults ≥ 50 years with serious pneumococcal disease, mortality risk increased approximately 55% as vaccination indications present increased. Mortality with six stacked indications was double that of two indications.

Keywords: Risk Stacking, Pneumococcal Vaccination, *Streptococcus pneumoniae,* Mortality

Introduction

Serious *Streptococcus pneumoniae* infections, including pneumonia, bacteremia, and meningitis, are a major cause of morbidity and mortality among older adults.[1-3] Since the 1980s, vaccines to prevent pneumococcal disease have been used on a global scale to mitigate the risks associated with these bacterial infections.[4] The Advisory Committee on Immunization Practices (ACIP) recommends administration of the pneumococcal vaccination to adults with certain risk factors for pneumococcal disease, including age ≥ 65 years, alcoholism, heart disease and heart failure, chronic respiratory disease, hepatic dysfunction, immunodeficiency, and smoking, in an effort to prevent invasive pneumococcal disease (IPD) and subsequent poor outcomes.[3]

Recent research has revealed that the presence of multiple, concomitant risk factors (risk stacking), particularly those conditions identified by ACIP as indications for pneumococcal vaccination, increases the likelihood of developing pneumococcal disease beyond the risk posed by individual risk factors alone.[5, 6] As our population ages, it is becoming more common for patients to have two or more risk factors.[6] However, the impact of risk stacking on outcomes, namely mortality, of adults who end up developing pneumococcal disease remains unknown. Furthermore, current data on risk stacking are limited in that there is no information regarding the impact of risk stacking “at-risk” conditions (e.g., alcoholism, heart disease, liver disease, cigarette smoking) with “high-risk” conditions (e.g., immunodeficiency).[5-7] As such, the purpose of this study was

to quantify the impact of stacking risk factors for developing pneumococcal disease on 30-day mortality among unvaccinated older adults.

Methods

Using national Veterans Health Administration databases, we conducted a nested case-control study of older Veterans (age ≥ 50 years) with positive *S. pneumoniae* blood, cerebrospinal fluid, or respiratory cultures between January 1, 2002 and December 31, 2011. We defined serious pneumococcal infections as culture-positive pneumonia, bacteremia, and meningitis. Cases were those individuals who died from any cause within 30 days of positive culture, and controls were those alive at 30 days. Patients were allowed to be included in the study multiple times if they had multiple positive cultures. Positive cultures from the same patient within a 30-day period were considered the same infection. We utilized national VA datasets, created from electronic medical records and administrative data, to collect patient demographics, health factors, medical history, vaccination history, medication use, clinical outcomes, and culture data. Pneumonia was identified from positive sputum cultures in addition to International Disease Classification, Ninth Revision (ICD-9) diagnosis codes. Bacteremia and meningitis were defined by positive blood and cerebrospinal fluid cultures, respectively. Patients receiving a pneumococcal vaccination within five years of positive culture were excluded. We utilized ICD-9 and procedure codes to identify the presence of disease states within one year of the positive culture date. Medication use within 30 days of positive culture, particularly the use of immunosuppressants

(corticosteroids, monoclonal antibodies, antineoplastic agents), was also assessed.

We quantified the impact of individual, as well as combinations of multiple risk factors (stacked risks) for developing pneumococcal disease on 30-day all-cause mortality. Selected risk factors were those that were previously identified as commonly occurring among older Veterans with pneumococcal disease, and that were also indications for pneumococcal vaccination identified by ACIP.[1, 3] These included age ≥ 65 years (age), alcohol abuse, chronic heart disease including chronic heart failure (CHD), chronic liver disease (CLD), chronic respiratory disease, including asthma and chronic obstructive pulmonary disease (CRD), diabetes mellitus (DM), immunodeficiency (IC), and smoking.[3] Age was included as a dichotomous variable, as opposed to a continuous variable, to reflect the actual vaccination indication of age ≥ 65 years. Immunodeficiency was defined as the presence of a solid malignancy, hematologic malignancy, HIV, or an AIDS-defining illness within one year of positive culture. Smoking status was defined as documentation of active cigarette smoking, smoking cessation counseling, or receipt of smoking cessation prescription products (varenicline, nicotine replacement products) within one year of positive culture. We determined all possible two, three, four, five, six, seven, and eight indication combinations and defined each combination as a unique variable. Odds ratios (ORs) and 95% confidence interval (CIs) were calculated using logistic regression. Separate models were run for each mutually exclusive combination of vaccine indications. The reference group for each model consisted of those individuals without any of

the aforementioned risk factors. This common reference group was selected in order to quantify the impact of stacking different combinations of indications as compared to those with none of the aforementioned indications for vaccination. Risk factors were deemed significant at a two-tailed *p*-value of 0.05 or less. All statistical analyses were performed with SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Approval by the Institutional Review Board and Research and Development Committee of the Providence Veterans Affairs Medical Center was obtained prior to initiating the study.

Results

We identified 9,730 serious pneumococcal infections in 9,468 unvaccinated individuals, with a 30-day mortality rate of 18.6% (1,764 cases and 7,966 controls; Table 1). The primary infection types, determined from positive cultures, included pneumonia (cases n=871, 49.4%; controls n=5,204, 65.3%), bacteremia (cases n=585, 33.2%; controls n=1,969, 24.7%), and bacteremic pneumonia (cases n=305, 17.3%; controls n=755, 9.5%). Meningitis accounted for <1% of infections among cases and among controls.

There were 574 episodes (5.9%; 49 cases, 2.8%, 525 controls, 6.6%) of pneumococcal disease among individuals with none of the eight aforementioned risk factors. In addition to the eight individual risk factors, there were 247 unique combinations of risk factors. There were three individual risk factors (age, CHD, and IC) and 89 stacked risks significantly associated with an increased risk of

mortality (Figure 1 and Figure 2). One risk factor (smoking) was associated with a decreased risk of mortality (OR 0.52, CI 0.31 – 0.87).

The risk of 30-day mortality among patients with one of any of the eight risk factors was 50% higher compared to those with none of the eight risk factors (OR 1.50 95% CI 1.08-2.07). The risk of 30-day mortality increased as risk factors were stacked, up to six risk factors (one: OR 1.50, CI 1.08-2.07; two: OR 2.01, CI 1.47-2.75; three: OR 2.71, CI 1.99-3.69; four: OR 3.27, CI 2.39-4.47; five: OR 3.63, CI 2.60-5.07; six: OR 4.23, CI 2.69-6.65). The addition of each risk factor increased the risk of 30-day mortality by an average of 55% (±13%; median: 56%, interquartile range 51%-60%), with the greatest increase between two and three stacked risk factors (70%). There were no statistically significant odds ratios among patients with seven (OR 1.65, CI 0.36-7.52) or eight (OR 2.14, CI 0.25-18.71) risk factors.

Among the 89 significant stacked risks, age was the most common risk factor present (50/89; 56.2%), followed by IC (49/89, 55.1%), CRD (48/89, 53.9%), CHD (45/89, 50.6%), CLD and smoking (both 37/89, 41.6%), DM (32/89, 36%), and alcohol abuse (29/89, 32.6%). All risk factors were present at least once in significant two, three, four, five, and six stacked risks with the exception of smoking, which was not present in any two risk-factor combinations. Figure 3 shows the distribution of each risk factor according to the number of risk factors present.

Of all significant individual risk factors, immunodeficiency was the strongest predictor of 30-day mortality (OR 2.30, CI 1.47-3.58). Among stacked risks,

alcoholism + CLD (OR 6.20, 3.25-11.92), Age + CLD + IC (OR 42.90, CI 4.69-390.98), alcoholism + CLD + DM + IC (OR 32.10, CI 3.28-314.3), age + CLD + CRD + IC + smoking (OR 16.07, CI 2.62-98.5), and Age + Alcoholism + CLD + CRD + IC + smoking (OR 21.40, CI 1.91-240.56) were the strongest predictors of mortality for those with two, three, four, five, or six risk factors, respectively (Figure 2). Results for all stacked risks are available in Appendix A.

Discussion

We quantified the impact of stacking pneumococcal disease risk factors on 30-day mortality in unvaccinated older Veterans with serious pneumococcal infections. Of the 8 individual risk factors assessed, 37.5% of them significantly increased the risk of death and of the 247 stacked risks, 35% significantly increased the risk of death. Current literature regarding predictors of mortality in the setting of pneumococcal disease is primarily related to the impact of individual predictors, particularly in the immunocompromised population, as well as those with invasive pneumococcal disease.[8-16] However, there is a dearth of information regarding outcomes of patients with multiple risk factors for pneumococcal disease and the subsequent impact of this risk stacking. To our knowledge, this study is the first to analyze the effect of risk factor combinations on mortality. As the current body of literature strongly supports the association between vaccination preventing invasive infections and subsequent mortality in the setting of individual risk factors, the importance of disease prevention in patients with multiple risk factors cannot be overstated.[1-3, 8, 10, 16]

Mortality increased in each phase of risk stacking, up to six risk factors. Compared to patients with none of the eight risk factors for the development of pneumococcal disease, those with two risk factors were twice as likely to die at 30 days. Those with six risk factors were more than four times as likely to die compared to those with no risk factors, and almost three times more likely to die as those with a single risk factor. No seven or eight risk factor combinations were statistically significant. However, this is likely due to smaller sample sizes in the seven (n=16) and eight (n=6) stacked risk groups. As pointed out in a recent risk stacking study, combining the effects of two independent risk factors as odds ratios leads to a multiplicative effect, as odds ratios are calculated on a log scale.[5, 17] Risk factors that are not entirely independent, however, may not be multiplicative. Several risk factors we analyzed may often be seen together, including alcohol abuse and liver disease, as well as smoking and respiratory and/or heart disease. Our results demonstrated that as the odds ratio increased as risk factors were stacked. However, the increased risk was not multiplicative, as would be expected in the presence of related conditions.

Interestingly, smoking was associated with a lower risk of mortality in our study. However, it should be noted that these were also individuals without any of the other risk factors for pneumococcal disease, including heart disease or respiratory disease, which are well-established consequences of smoking and also contribute to mortality. Furthermore, we were unable to quantify the degree to which individuals smoked. To be considered a smoker, documentation of smoking cessation counseling, use of smoking cessation medication, or an ICD-9 diagnosis

code within one year were necessary. As such, these patients may not have been smokers at the time of infection. Collectively, these caveats require that the association between smoking and risk of mortality within our study be interpreted with caution.

The results of our study demonstrate the impact of increasing numbers of pneumococcal disease risk factors on mortality among patients with serious pneumococcal infections. Once individuals develop a pneumococcal infection, there is a lasting negative impact. A recent study within the Veteran population found that patients with pneumococcal pneumonia who survived at least 30 days beyond infection had increased mortality compared to the expected survival for the average Veteran with similar demographics for up to ten years after recovering from the infection.[18] Furthermore, decreases in survival at ten years ranged from 15% to 50% according to increases in pneumonia severity index (PSI), which accounts for risk factors also assessed in our study, including age, cardiac disease, and hepatic dysfunction.[18, 19] As such, disease prevention may have an extended positive impact on mortality.

Pneumococcal vaccination may be particularly important in patients with multiple risk factors for pneumococcal disease. While the ACIP already recommends that individuals with the risk factors assessed in our study be vaccinated to prevent the development of pneumococcal disease, many adults remain unvaccinated.[1, 3] This may be due, in part, to a lack of a focused strategy for identifying those most at risk for poor outcomes. A study of 1,177 patients who developed invasive pneumococcal disease and also had an indication for the

polysaccharide pneumococcal vaccination demonstrated that 52% were unvaccinated, and that 92% of these unvaccinated individuals had at least one opportunity to receive the vaccination in the 2 years prior to infection. Multivariate analysis revealed that alcohol abuse, metastatic malignancy, and those ≥ 65 years of age with no other indication were predictive of being unvaccinated, while chemotherapy and non-HIV immune dysfunction were predictive of previous vaccination.[20]

According to current ACIP pneumococcal vaccination recommendations, patients in our study with cardiac, respiratory, and hepatic disease, along with those who smoke, and have diabetes mellitus or alcoholism would have been eligible to receive the 23-valent, pneumococcal polysaccharide vaccine (PPSV-23). In addition, those 65 years of age and older, and those with immunocompromising conditions are recommended to receive both the PPSV-23 and the 13-valent, pneumococcal conjugate vaccine (PCV-13). [3, 21] Further, all children 6 weeks and older are currently recommended to receive PCV-13 (PCV-7 during our study period), thereby impacting development of pneumococcal disease at the population level through herd immunity.[22, 23] In the general population, pneumococcal vaccination, particularly with the conjugate vaccines, has been associated with substantial reductions in disease incidence through indirect protection.[23] However, the impact of herd immunity in the older Veteran population remains unclear, and further studies are needed to determine if these findings are consistent in this high-risk population.

Considering that each additional risk factor in our study increased the risk of mortality by 55% in the presence of pneumococcal disease, thorough evaluation of a patient's medical history must be performed to ensure that, barring any contraindications, all individuals with these risk factors are vaccinated. Furthermore, it is important to note that the greatest increase between stacked combinations occurred as patients went from two to three risk factors. Interestingly, our findings are consistent with two other risk stacking studies assessing the risk of developing pneumococcal disease, which showed that the greatest increase in the risk of disease development occurred when increasing from two to three disease states present.[6, 21] Increases in disease development ranged from 67% to 265% moving from two to three disease states across all age ranges.[6, 24] As such, our study provides further evidence that risk stacking poses a substantial threat in older adults, in whom multiple, chronic disease states are common.[1, 6, 25] Furthermore, the results of our study may assist future efforts to increase pneumococcal vaccination by providing healthcare practitioners with an estimate of the quantified risk of mortality for patients with different combinations of risk factors for developing pneumococcal disease.

Limitations of our study included the assessment of risk factors identified by ACIP as necessitating pneumococcal vaccination. However, there may be other conditions, or combinations of conditions, that collectively increase the risk of mortality in the setting of pneumococcal disease which were not assessed in our study. We utilized ICD-9 diagnosis to identify disease states, allowing for the possibility of misclassification bias due to potential inaccuracies. Also, our study

likely underestimated the true number of patients with pneumococcal pneumonia, as we only included patients with a positive sputum culture and ICD-9 diagnosis code. Further, pneumococcal pneumonia may have been the source for some pneumococcal bacteremias, but without positive respiratory cultures, was not categorized as such Next, patients with multiple episodes of pneumococcal infection that were included in the study multiple times may have had a different risk profile than those with a single episode of infection. However, this impact is likely negligible, as the vast majority of patients only had one episode of infection (9,730 infections in 9,468 patients). Determining the risk of mortality in patients with more than six stacked risk factors was limited by small sample sizes within these groups. However, we believe the risk of mortality to likely be much higher than healthy individuals, as mortality increased in stacked risk factor groups with larger numbers. Next, as odds ratios only approximate relative risk, actual mortality risk may differ. It should also be noted that our analysis did not specifically adjust for pneumonia disease severity, such as with the Pneumonia Severity Index score. However, given that many of the risk factors included in our study are also part of this severity index, it is likely that pneumococcal disease severity also increased with the number of stacked risks. [26] Lastly, as we studied an older Veteran population, generalizability to the U.S. population as a whole is limited.

Conclusion

In unvaccinated older Veterans with serious pneumococcal disease, the presence of multiple ACIP risk factors for developing pneumococcal disease was associated with higher 30-day all-cause mortality. The more indications for vaccination present, the greater the risk of death, which was almost three times higher among those with six stacked risk factors as opposed to a single risk factor. As multiple risk factors for pneumococcal disease are common among older adults, effective vaccination strategies for the prevention of infection are needed.

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Table 1. Demographics of unvaccinated older adults with pneumococcal disease.

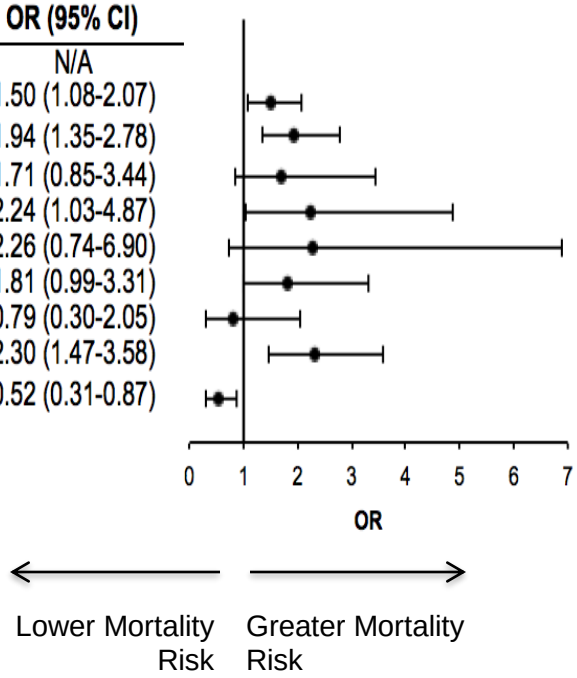
	Alive at 30 days (n=7,966)	Not alive at 30 days (n=1,764)
Age (years), (SD)	67 (± 11)	71 (± 11)*
Gender, Male	7,795 (97.5)	1,740 (98.6)*
Race		
American Indian	98 (1.2)	14 (0.8)
Asian or Pacific Islander	63 (0.8)	11 (0.6)
Black	1,054 (13.2)	238 (13.5)
White	6,297 (79.0)	1,354 (76.8)*
Unknown	454 (5.7)	147 (8.3)*
Pneumococcal Disease Risk Factors within previous year		
Alcohol abuse	1,261 (15.8)	313 (17.7)*
Chronic heart disease	1,999 (25.1)	611 (34.6)*
Chronic heart failure	1,324 (16.6)	489 (27.7)*
Chronic liver disease, any severity	705 (8.9)	320 (18.1)*
Chronic respiratory disease	3,609 (45.3)	911 (51.6)*
Diabetes mellitus	1,709 (21.5)	476 (27.0)*
Immunodeficiency	2,535 (31.8)	747 (42.3)*
Cigarette smoking	3,777 (47.4)	674 (38.2)*

Note: Results reported as n (%) unless otherwise specified

*$p < 0.05$.

Figure 1. Risk of 30-day mortality in unvaccinated adults with one pneumococcal disease risk factor.

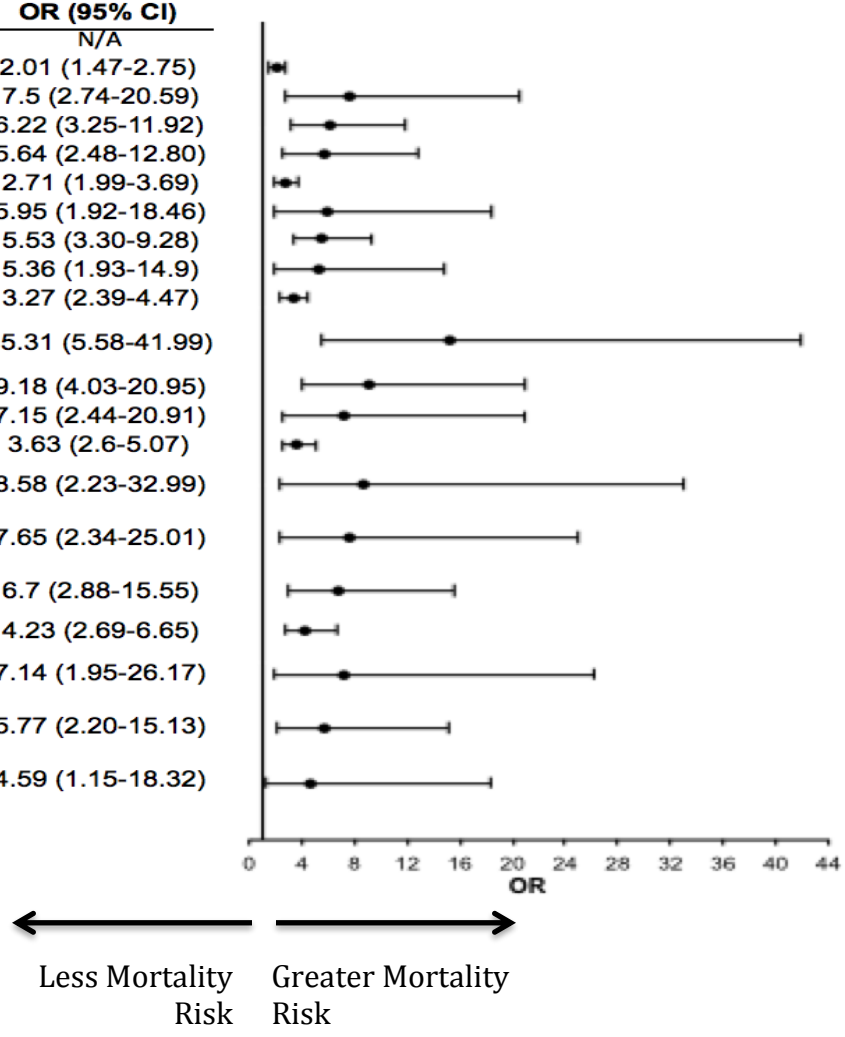
	Alive at 30 days (n=7,966)	Not Alive at 30 days (n=1,764)	OR (95% CI)
No Risk Factors (Reference)	525	49	N/A
One Risk Factor	1,553	217	1.50 (1.08-2.07)
Age (≥ 65 years)	591	107	1.94 (1.35-2.78)
Alcoholism	69	11	1.71 (0.85-3.44)
Chronic Heart Disease	43	9	2.24 (1.03-4.87)
Chronic Liver Disease	19	4	2.26 (0.74-6.90)
Chronic Respiratory Disease	95	16	1.81 (0.99-3.31)
Diabetes Mellitus	69	5	0.79 (0.30-2.05)
Immunodeficiency	196	42	2.30 (1.47-3.58)
Smoking	472	23	0.52 (0.31-0.87)



CI, Confidence Interval; OR, Odds Ratio

Figure 2. Risk of 30-day mortality in unvaccinated adults with multiple pneumococcal disease risk factors.

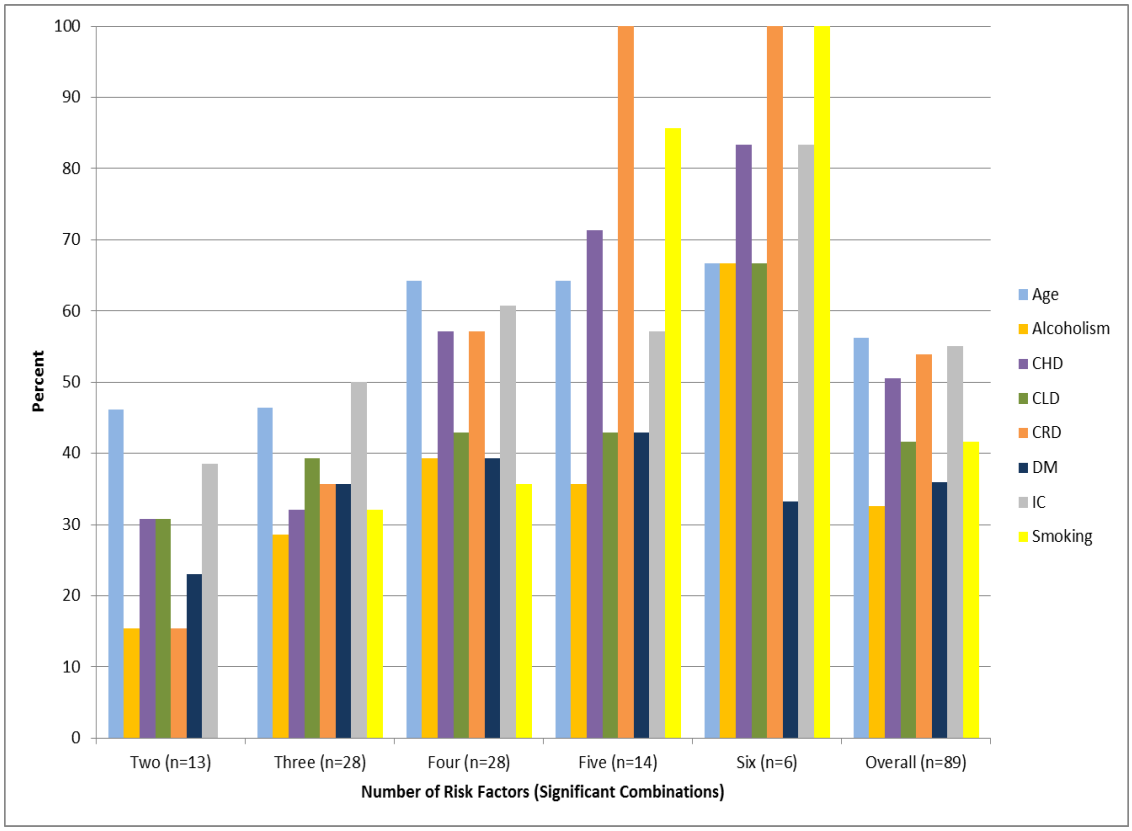
	Alive at 30 days (n=7,966)	Not Alive at 30 days (n = 1,764)	OR (95% CI)
No Risk Factors (Reference)	525	49	N/A
Two Risk Factors*	1969	370	2.01 (1.47-2.75)
CLD + IC	10	7	7.5 (2.74-20.59)
Alcoholism + CLD	31	18	6.22 (3.25-11.92)
DM + IC	19	10	5.64 (2.48-12.80)
Three Risk Factors*	1897	480	2.71 (1.99-3.69)
Alcoholism + CLD + IC	9	5	5.95 (1.92-18.46)
Age + CHD + IC	62	32	5.53 (3.30-9.28)
Age + Alcoholism + CRD	12	6	5.36 (1.93-14.9)
Four Risk Factors*	1307	399	3.27 (2.39-4.47)
Alcoholism + CLD + DM + Smoking	7	10	15.31 (5.58-41.99)
Alcoholism + CRD + DM + IC	14	12	9.18 (4.03-20.95)
Age + Alcoholism + CHD + CRD	9	6	7.15 (2.44-20.91)
Five Risk Factors*	584	198	3.63 (2.6-5.07)
Age + Alcoholism + CHD + CRD + DM	5	< 5	8.58 (2.23-32.99)
Age + CHD + CLD + CRD + Smoking	7	5	7.65 (2.34-25.01)
Alcoholism + CLD + CRD + IC + Smoking	16	10	6.7 (2.88-15.55)
Six Risk Factors*	114	45	4.23 (2.69-6.65)
Alcoholism + CHD + CLD + CRD + IC + Smoking	6	< 5	7.14 (1.95-26.17)
Age + Alcoholism + CHD + CRD + IC + Smoking	13	7	5.77 (2.20-15.13)
Alcoholism + CHD + CLD + CRD + DM + Smoking	7	< 5	4.59 (1.15-18.32)



Age, Age ≥ 65 years; CHD, Chronic heart disease; CI, Confidence Interval; CLD, Chronic liver disease; CRD, Chronic respiratory disease; DM, Diabetes mellitus; IC, Immunodeficiency; OR, Odds Ratio

*Includes 3 selected statistically significant OR (CI does not contain 1) from each numerical category of risk factors present. No statistically significant seven or eight risk factor combinations. See supplemental appendix for risk for all unique combinations.

Figure 3. Frequency of stacked pneumococcal disease risk factors in unvaccinated adults.



Age, Age ≥ 65 years; CHD, Chronic Heart Disease; CLD, Chronic Liver Disease; CRD, Chronic Respiratory Disease; DM, Diabetes Mellitus; IC, Immunodeficiency

Includes only stacked risk combinations which significantly increased the risk of 30-day mortality ($p < 0.05$). No statistically significant seven or eight risk factor combinations.

Appendix A. Risk of 30-day mortality for all combinations of risk factors for developing pneumococcal disease.

	Alive at 30 days (n=7,966)	Not alive at 30 days (n=1,764)	OR[a]	95% CI
No Risk factors	**525 (6.6)**	**49 (2.8)**	**Reference**	**Reference**
Two Risk factors	**1,969 (24.7)**	**370 (21.0)**	**2.01**	**1.47-2.75***
Age + Alcoholism	22 (0.3)	9 (0.5)	4.38	1.91-10.04*
Age + CHD	111 (1.4)	51 (2.9)	4.92	3.16-7.66*
Age + CLD	< 5	< 5	16.07	2.62-98.49*
Age + CRD	262 (3.3)	57 (3.2)	2.33	1.55-3.51*
Age + DM	75 (0.9)	29 (1.6)	4.14	2.47-6.96*
Age + IC	323 (4.1)	56 (3.2)	1.86	1.24-2.79*
Age + Smoking	217 (2.7)	16 (0.9)	0.79	0.44-1.42
Alcoholism + CHD	6 (0.08)	< 5	1.79	0.21-15.13
Alcoholism + CLD	31 (0.4)	18 (1.0)	6.22	3.25-11.92*
Alcoholism + CRD	24 (0.3)	< 5	1.34	0.39-4.61
Alcoholism + DM	< 5	0	n/a	n/a
Alcoholism + IC	14 (0.2)	0	n/a	n/a
Alcoholism + Smoking	141 (1.8)	14 (0.8)	1.06	0.57-1.98
CHD + CLD	< 5	< 5	10.71	1.48-77.69*
CHD + CRD	32 (0.4)	6 (0.3)	2.01	0.80-5.04
CHD + DM	33 (0.4)	11 (0.6)	3.57	1.70-7.50*
CHD + IC	18 (0.2)	10 (0.6)	5.95	2.60-13.60*
CHD + Smoking	48 (0.6)	< 5	0.67	0.20-2.23
CLD + CRD	6 (0.08)	< 5	1.79	0.21-15.13
CLD + DM	9 (0.1)	< 5	1.19	0.15-9.59
CLD + IC	10 (0.1)	7 (0.4)	7.50	2.74-20.59*
CLD + Smoking	27 (0.3)	< 5	0.79	0.18-3.44
CRD + DM	24 (0.3)	< 5	0.45	0.06-3.37
CRD + IC	35 (0.4)	14 (0.8)	4.23	2.16-8.51*
CRD + Smoking	224 (2.8)	13 (0.7)	0.62	0.33-1.17
DM + IC	19 (0.2)	10 (0.6)	5.64	2.48-12.80*
DM + Smoking	54 (0.7)	5 (0.3)	0.99	0.38-2.60
IC + Smoking	197 (2.5)	27 (1.5)	1.47	0.89-2.42
Three Risk factors	**1,897 (23.8)**	**480 (27.2)**	**2.71**	**1.99-3.69***
Age + Alcoholism + CHD	5 (0.06)	< 5	2.14	0.25-18.71

Age + Alcoholism + CLD	5 (0.06)	< 5	2.14	0.25-18.71
Age + Alcoholism + CRD	12 (0.2)	6 (0.3)	5.36	1.93-14.90*
Age + Alcoholism + DM	< 5	0	n/a	n/a
Age + Alcoholism + IC	5 (0.06)	< 5	6.43	1.49-27.7*
Age + Alcoholism + Smoking	25 (0.3)	< 5	0.86	0.19-3.73
Age + CHD + CLD	< 5	< 5	5.36	0.96-29.99
Age + CHD + CRD	249 (3.1)	90 (5.1)	3.87	2.65-5.66*
Age + CHD + DM	110 (1.4)	41 (2.3)	3.99	2.51-6.35*
Age + CHD + IC	62 (0.8)	32 (1.8)	5.53	3.30-9.28*
Age + CHD + Smoking	28 (0.4)	9 (0.5)	3.44	1.54-7.71*
Age + CLD + CRD	< 5	< 5	32.10	3.28-314.30*
Age + CLD + DM	< 5	< 5	2.68	0.29-24.44
Age + CLD + IC	< 5	< 5	42.86	4.69-390.98*
Age + CLD + Smoking	< 5	< 5	21.43	1.91-240.56*
Age + CRD + DM	70 (0.9)	16 (0.9)	2.45	1.32-4.54*
Age + CRD + IC	145 (1.8)	43 (2.4)	3.18	2.03-4.98*
Age + CRD + Smoking	186 (2.4)	27 (1.5)	1.56	0.95-2.56
Age + DM + IC	38 (0.5)	14 (0.8)	3.95	2.00-7.79*
Age + DM + Smoking	29 (0.4)	< 5	1.48	0.50-4.38
Age + IC + Smoking	123 (1.5)	24 (1.4)	2.09	1.24-3.54*
Alcoholism + CHD + CLD	< 5	< 5	10.71	1.48-77.69*
Alcoholism + CHD + CRD	10 (0.1)	< 5	2.14	0.46-10.06
Alcoholism + CHD + DM	< 5	< 5	2.68	0.29-24.44
Alcoholism + CHD + IC	< 5	0	n/a	n/a
Alcoholism + CHD + Smoking	21 (0.3)	< 5	1.02	0.23-4.48
Alcoholism + CLD + CRD	12 (0.2)	5 (0.3)	4.47	1.51-13.20*
Alcoholism + CLD + DM	< 5	< 5	8.04	1.75-36.96*
Alcoholism + CLD + IC	9 (0.1)	5 (0.3)	5.95	1.92-18.46*
Alcoholism + CLD + Smoking	52 (0.7)	18 (1.0)	3.71	2.01-6.83*
Alcoholism + CRD + DM	0	0	n/a	n/a
Alcoholism + CRD + IC	7 (0.09)	< 5	3.06	0.62-15.14
Alcoholism + CRD + Smoking	128 (1.6)	5 (0.3)	0.42	0.16-1.07
Alcoholism + DM + Smoking	0	0	n/a	n/a
Alcoholism + DM + Smoking	23 (0.3)	< 5	1.40	0.41-4.82
Alcoholism + IC + Smoking	40 (0.5)	13 (0.7)	3.48	1.75-6.95*
CHD + CLD + CRD	< 5	< 5	2.68	0.29-24.44
CHD + CLD + DM	< 5	< 5	10.71	2.10-54.51*
CHD + CLD + IC	< 5	< 5	5.36	0.48-60.14
CHD + CLD + Smoking	< 5	< 5	2.68	0.29-24.44
CHD + CRD + DM	51 (0.6)	9 (0.5)	1.89	0.88-4.07
CHD + CRD + IC	25 (0.3)	< 5	1.29	0.38-4.41

CHD + CRD + Smoking	87 (1.1)	17 (1.0)	2.09	1.15-3.80*
CHD + DM + IC	13 (0.2)	4 (0.2)	3.30	1.04-10.50*
CHD + DM + Smoking	36 (0.5)	< 5	0.89	0.27-3.01
CHD + IC + Smoking	15 (0.2)	5 (0.3)	3.57	1.25-10.24*
CLD + CRD + DM	< 5	< 5	7.14	1.17-43.78*
CLD + CRD + IC	6 (0.08)	< 5	1.79	0.21-15.13
CLD + CRD + Smoking	17 (0.2)	< 5	1.26	0.28-5.62
CLD + DM + IC	< 5	< 5	7.14	1.17-43.78*
CLD + DM + Smoking	10 (0.1)	0	n/a	n/a
CLD + IC + Smoking	17 (0.2)	< 5	2.52	0.82-7.79
CRD + DM + IC	12 (0.2)	< 5	3.57	1.11-11.49*
CRD + DM + Smoking	50 (0.6)	< 5	0.43	0.10-1.82
CRD + IC + Smoking	101 (1.3)	23 (1.3)	2.44	1.42-4.18*
DM + IC + Smoking	19 (0.2)	7 (0.4)	3.95	1.58-9.85*
Four Risk factors	**1,307 (16.5)**	**399 (22.6)**	**3.27**	**2.39-4.47***
Age + Alcoholism + CHD + CLD	< 5	< 5	10.71	2.11-54.51*
Age + Alcoholism + CHD + CRD	9 (0.1)	6 (0.3)	7.15	2.44-20.91*
Age + Alcoholism + CHD + DM	< 5	< 5	3.57	0.37-34.99
Age + Alcoholism + CHD + IC	0	< 5	n/a	n/a
Age + Alcoholism + CHD + Smoking	6 (0.08)	< 5	5.36	1.30-22.09*
Age + Alcoholism + CLD + CRD	< 5	< 5	8.04	1.75-36.96*
Age + Alcoholism + CLD + DM	0	< 5	n/a	n/a
Age + Alcoholism + CLD + IC	< 5	0	n/a	n/a
Age + Alcoholism + CLD + Smoking	< 5	< 5	2.68	0.29-24.44
Age + Alcoholism + CRD + DM	< 5	< 5	10.71	2.11-54.51*
Age + Alcoholism + CRD + IC	8 (0.1)	< 5	4.02	1.03-15.64*
Age + Alcoholism + CRD + Smoking	39 (0.5)	7 (0.4)	1.92	0.82-4.53
Age + Alcoholism + DM + IC	< 5	0	n/a	n/a
Age + Alcoholism + DM + Smoking	< 5	< 5	10.71	0.66-173.96
Age + Alcoholism + IC + Smoking	9 (0.1)	< 5	2.38	0.50-11.33
Age + CHD + CLD + CRD	< 5	< 5	21.43	1.91-240.56*
Age + CHD + CLD + DM	< 5	< 5	10.71	2.60-44.17*
Age + CHD + CLD + IC	< 5	< 5	16.07	2.62-98.50*
Age + CHD + CLD + Smoking	< 5	< 5	5.36	0.48-60.14
Age + CHD + CRD + DM	172 (2.2)	56 (3.2)	3.49	2.29-5.31*

Age + CHD + CRD + IC	152 (1.9)	53 (3.0)	3.74	2.43-5.73*
Age + CHD + CRD + Smoking	162 (2.0)	47 (2.7)	3.11	2.01-4.81*
Age + CHD + DM + IC	45 (0.6)	18 (1.0)	4.29	2.31-7.97*
Age + CHD + DM + Smoking	24 (0.3)	5 (0.3)	2.23	0.82-6.11
Age + CHD + IC + Smoking	24 (0.3)	8 (0.5)	3.57	1.52-8.37*
Age + CLD + CRD + DM	< 5	0	n/a	n/a
Age + CLD + CRD + IC	< 5	< 5	7.14	1.17-43.78*
Age + CLD + CRD + Smoking	< 5	0	n/a	n/a
Age + CLD + DM + IC	6 (0.08)	0	n/a	n/a
Age + CLD + DM + Smoking	< 5	0	n/a	n/a
Age + CLD + IC + Smoking	< 5	< 5	10.71	0.66-173.96
Age + CRD + DM + IC	44 (0.6)	9 (0.5)	2.19	1.01-4.76*
Age + CRD + DM + Smoking	43 (0.5)	6 (0.3)	1.50	0.61-3.69
Age + CRD + IC + Smoking	120 (1.5)	36 (2.0)	3.22	2.00-5.16*
Age + DM + IC + Smoking	15 (0.2)	6 (0.3)	4.29	1.59-11.55*
Alcoholism + CHD + CLD + CRD	5 (0.06)	< 5	4.29	0.81-22.68
Alcoholism + CHD + CLD + DM	< 5	< 5	3.57	0.37-34.99
Alcoholism + CHD + CLD + IC	< 5	0	n/a	n/a
Alcoholism + CHD + CLD + Smoking	15	< 5	2.86	0.91-8.95
Alcoholism + CHD + CRD + DM	< 5	0	n/a	n/a
Alcoholism + CHD + CRD + Smoking	57 (0.7)	< 5	0.38	0.09-1.59
Alcoholism + CHD + DM + IC	0	< 5	n/a	n/a
Alcoholism + CHD + DM + Smoking	9 (0.1)	0	n/a	n/a
Alcoholism + CHD + IC + Smoking	10 (0.1)	< 5	1.07	0.134-8.55
Alcoholism + CLD + CRD + DM	< 5	< 5	5.36	0.48-60.14
Alcoholism + CLD + CRD + IC	5 (0.06)	< 5	6.43	1.49-27.71*
Alcoholism + CLD + CRD + Smoking	37 (0.5)	6 (0.3)	1.74	0.70-4.32
Alcoholism + CLD + DM + IC	< 5	< 5	32.10	3.28-314.30*
Alcoholism + CLD + DM + Smoking	7 (0.1)	10 (0.6)	15.31	5.58-41.99*
Alcoholism + CLD + IC + Smoking	14 (0.2)	12 (0.7)	9.18	4.03-20.95*
Alcoholism + CRD + DM + IC	< 5	0	n/a	n/a
Alcoholism + CRD + DM + Smoking	14 (0.2)	< 5	0.77	0.10-5.94
Alcoholism + CRD + IC + Smoking	40 (0.5)	13 (0.7)	3.48	1.75-6.95*

Alcoholism + DM + IC + Smoking	< 5	< 5	2.68	0.29-24.44
CHD + CLD + CRD + DM	5 (0.06)	< 5	2.14	0.25-18.71
CHD + CLD + CRD + IC	< 5	< 5	21.43	1.91-240.56*
CHD + CLD + CRD + Smoking	11 (0.1)	< 5	1.95	0.42-9.04
CHD + CLD + DM + IC	< 5	< 5	10.71	1.48-77.69*
CHD + CLD + DM + Smoking	< 5	0	n/a	n/a
CHD + CLD + IC + Smoking	< 5	0	n/a	n/a
CHD + CRD + DM + IC	13 (0.2)	7 (0.4)	5.77	2.20-15.13*
CHD + CRD + DM + Smoking	53 (0.7)	17 (1.0)	3.44	1.85-6.39*
CHD + CRD + IC + Smoking	38 (0.5)	13 (0.7)	3.67	1.83-7.34*
CHD + DM + IC + Smoking	12 (0.2)	0	n/a	n/a
CLD + CRD + DM + IC	< 5	< 5	10.71	0.66-173.96
CLD + CRD + DM + Smoking	< 5	0	n/a	n/a
CLD + CRD + IC + Smoking	9 (0.1)	< 5	2.38	0.50-11.33
CLD + DM + IC + Smoking	< 5	0	n/a	n/a
CRD + DM + IC + Smoking	9 (0.1)	< 5	1.19	0.15-9.59
Five Risk factors	**584 (7.3)**	**198 (11.2)**	**3.63**	**2.60-5.07***
Age + Alcoholism + CHD + CLD + CRD	5 (0.06)	< 5	4.29	0.81-22.68
Age + Alcoholism + CHD + CLD + DM	0	0	n/a	n/a
Age + Alcoholism + CHD + CLD + IC	0	0	n/a	n/a
Age + Alcoholism + CHD + CLD + Smoking	0	< 5	n/a	n/a
Age + Alcoholism + CHD + CRD + DM	5 (0.06)	< 5	8.58	2.23-32.99*
Age + Alcoholism + CHD + CRD + IC	7 (0.09)	< 5	1.53	0.19-12.70
Age + Alcoholism + CHD + CRD + Smoking	29 (0.4)	11 (0.6)	4.06	1.91-8.63*
Age + Alcoholism + CHD + DM + IC	< 5	0	n/a	n/a
Age + Alcoholism + CHD + DM + Smoking	< 5	0	n/a	n/a
Age + Alcoholism + CHD + IC + Smoking	5 (0.06)	< 5	4.29	0.81-22.68
Age + Alcoholism + CLD + CRD + DM	0	0	n/a	n/a

Age + Alcoholism + CLD + CRD + IC	< 5	< 5	5.36	0.48-60.14
Age + Alcoholism + CLD + CRD + Smoking	11 (0.1)	0	n/a	n/a
Age + Alcoholism + CLD + DM + IC	< 5	0	n/a	n/a
Age + Alcoholism + CLD + DM + Smoking	< 5	0	n/a	n/a
Age + Alcoholism + CLD + IC + Smoking	< 5	< 5	5.36	0.48-60.14
Age + Alcoholism + CRD + DM + IC	< 5	0	n/a	n/a
Age + Alcoholism + CRD + DM + Smoking	5 (0.06)	0	n/a	n/a
Age + Alcoholism + CRD + IC + Smoking	14 (0.2)	8 (0.5)	6.12	2.45-15.31*
Age + Alcoholism + DM + IC + Smoking	< 5	0	n/a	n/a
Age + CHD + CLD + CRD + DM	< 5	< 5	3.57	0.37-34.99
Age + CHD + CLD + CRD + IC	5 (0.06)	< 5	2.14	0.25-18.71
Age + CHD + CLD + CRD + Smoking	7 (0.09)	5 (0.3)	7.65	2.34-25.01*
Age + CHD + CLD + DM + IC	0	0	n/a	n/a
Age + CHD + CLD + DM + Smoking	0	0	n/a	n/a
Age + CHD + CLD + IC + Smoking	0	< 5	n/a	n/a
Age + CHD + CRD + DM + IC	81 (1.0)	39 (2.2)	5.16	3.19-8.35*
Age + CHD + CRD + DM + Smoking	79 (1.0)	19 (1.1)	2.58	1.443-4.60*
Age + CHD + CRD + IC + Smoking	118 (1.5)	34 (1.9)	3.09	1.91-4.99*
Age + CHD + DM + IC + Smoking	16 (0.2)	< 5	2.68	0.86-8.33
Age + CLD + CRD + DM + IC	< 5	0	n/a	n/a
Age + CLD + CRD + DM + Smoking	< 5	0	n/a	n/a
Age + CLD + CRD + IC + Smoking	< 5	< 5	16.07	2.62-98.50*
Age + CLD + DM + IC + Smoking	0	0	n/a	n/a
Age + CRD + DM + IC + Smoking	26 (0.3)	11 (0.6)	4.54	2.11-9.73*

Alcoholism + CHD + CLD + CRD + DM	< 5	0	n/a	n/a
Alcoholism + CHD + CLD + CRD + IC	< 5	< 5	10.71	0.66-173.96
Alcoholism + CHD + CLD + CRD + Smoking	13 (0.2)	< 5	3.30	1.04-10.50*
Alcoholism + CHD + CLD + DM + IC	0	0	n/a	n/a
Alcoholism + CHD + CLD + DM + Smoking	< 5	< 5	3.57	0.37-34.99
Alcoholism + CHD + CLD + IC + Smoking	< 5	< 5	10.71	0.66-173.96
Alcoholism + CHD + CRD + DM + IC	< 5	0	n/a	n/a
Alcoholism + CHD + CRD + DM + Smoking	18 (0.2)	< 5	0.60	0.08-4.55
Alcoholism + CHD + CRD + IC + Smoking	16 (0.2)	< 5	0.67	0.09-5.16
Alcoholism + CHD + DM + IC + Smoking	< 5	0	n/a	n/a
Alcoholism + CLD + CRD + DM + IC	< 5	< 5	10.71	0.66-173.96
Alcoholism + CLD + CRD + DM + Smoking	10 (0.1)	< 5	2.14	0.46-10.06
Alcoholism + CLD + CRD + IC + Smoking	16 (0.2)	10 (0.6)	6.70	2.88-15.55*
Alcoholism + CLD + DM + IC + Smoking	< 5	< 5	5.36	0.48-60.14
Alcoholism + CRD + DM + IC + Smoking	7 (0.09)	0	n/a	n/a
CHD + CLD + CRD + DM + IC	< 5	< 5	10.71	0.66-173.96
CHD + CLD + CRD + DM + Smoking	8 (0.1)	< 5	4.02	1.03-15.64*
CHD + CLD + CRD + IC + Smoking	< 5	< 5	7.14	1.17-43.78*
CHD + CLD + DM + IC + Smoking	5 (0.06)	< 5	4.29	0.81-22.68
CHD + CRD + DM + IC + Smoking	37 (0.5)	17 (1.0)	4.92	2.58-9.38*
CLD + CRD + DM + IC + Smoking	0	< 5	n/a	n/a
Six Risk factors	**114 (1.4)**	**45 (2.6)**	**4.23**	**2.69-6.65***

Age + Alcoholism + CHD + CLD + CRD + IC	< 5	< 5	10.71	0.66-173.96
Age + Alcoholism + CHD + CLD + CRD + Smoking	5 (0.06)	< 5	4.29	0.81-22.68
Age + Alcoholism + CHD + CLD + CRD + DM	< 5	< 5	10.71	0.66-173.96
Age + Alcoholism + CHD + CLD + DM + IC	0	0	n/a	n/a
Age + Alcoholism + CHD + CLD + DM + Smoking	< 5	0	n/a	n/a
Age + Alcoholism + CHD + CLD + IC + Smoking	0	< 5	n/a	n/a
Age + Alcoholism + CHD + CRD + DM + IC	0	0	n/a	n/a
Age + Alcoholism + CHD + CRD + DM + Smoking	11 (0.1)	< 5	2.92	0.79-10.83
Age + Alcoholism + CHD + CRD + IC + Smoking	13 (0.2)	7 (0.4)	5.77	2.20-15.13*
Age + Alcoholism + CHD + DM + IC + Smoking	0	0	n/a	n/a
Age + Alcoholism + CLD + CRD + DM + IC	0	< 5	n/a	n/a
Age + Alcoholism + CLD + CRD + DM + Smoking	< 5	< 5	10.71	0.66-173.96
Age + Alcoholism + CLD + CRD + IC + Smoking	< 5	< 5	21.43	1.91-240.56*
Age + Alcoholism + CLD + DM + IC + Smoking	0	0	n/a	n/a
Age + Alcoholism + CRD + DM + IC + Smoking	< 5	0	n/a	n/a
Age + CHD + CLD + CRD + DM + IC	< 5	< 5	5.36	0.96-29.99
Age + CHD + CLD + CRD + DM + Smoking	< 5	0	n/a	n/a
Age + CHD + CLD + CRD + IC + Smoking	< 5	< 5	10.71	2.11-54.51*
Age + CHD + CLD + DM + IC + Smoking	0	0	n/a	n/a
Age + CHD + CRD + DM + IC + Smoking	34 (0.4)	10 (0.6)	3.15	1.47-6.76*

Age + CLD + CRD + DM + IC + Smoking	< 5	< 5	5.36	0.48-60.14
Alcoholism + CHD + CLD + CRD + DM + IC	< 5	0	n/a	n/a
Alcoholism + CHD + CLD + CRD + DM + Smoking	7 (0.09)	< 5	4.59	1.15-18.32*
Alcoholism + CHD + CLD + CRD + IC + Smoking	6 (0.08)	< 5	7.14	1.95-26.17*
Alcoholism + CHD + CLD + DM + IC + Smoking	< 5	0	n/a	n/a
Alcoholism + CHD + CRD + DM + IC + Smoking	5 (0.06)	< 5	2.14	0.25-18.71
Alcoholism + CLD + CRD + DM + IC + Smoking	< 5	< 5	5.36	0.96-29.99
CHD + CLD + CRD + DM + IC + Smoking	< 5	0	n/a	n/a
Seven Risk factors	**13 (0.2)**	**< 5**	**2.47**	**0.68-8.98**
Age + Alcoholism + CHD + CLD + CRD + DM + IC	< 5	0	n/a	n/a
Age + Alcoholism + CHD + CLD + CRD + DM + Smoking	0	< 5	n/a	n/a
Age + Alcoholism + CHD + CLD + CRD + IC + Smoking	< 5	0	n/a	n/a
Age + Alcoholism + CHD + CLD + DM + IC + Smoking	0	< 5	n/a	n/a
Age + Alcoholism + CHD + CRD + DM + IC + Smoking	< 5	0	n/a	n/a
Age + Alcoholism + CLD + CRD + DM + IC + Smoking	< 5	< 5	10.71	0.66-173.96
Age + CHD + CLD + CRD + DM + IC + Smoking	< 5	0	n/a	n/a
Alcoholism + CHD + CLD + CRD + DM + IC + Smoking	< 5	0	n/a	n/a
Eight Risk factors	**5 (0.06)**	**< 5**	**2.14**	**0.25-18.71**
Age + Alcoholism + CHD + CLD + CRD + DM + IC + Smoking	5 (0.06)	< 5	2.14	0.25-18.71

Age, Age ≥ 65 years; CHD, Chronic Heart Disease; CLD, Chronic Liver Disease; CRD, Chronic Respiratory Disease; CI, Confidence Interval; DM, Diabetes Mellitus; IC, Immunodeficiency; OR, Odds Ratio

*$p < 0.05$.