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

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

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1 **Abstract**

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

8

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

18

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

24 increased as risks were stacked, up to six risk factors (one: OR 1.5, CI 1.08-2.07;  
25 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-  
26 4.47; five: OR 3.63, CI 2.60-5.07; six: OR 4.23, CI 2.69-6.65), with each additional  
27 risk factor increasing mortality an average of 55% ( $\pm 13\%$ ).

28

29 **Conclusions:** Among adults  $\geq 50$  years with serious pneumococcal disease,  
30 mortality risk increased approximately 55% as vaccination indications present  
31 increased. Mortality with six stacked indications was double that of two indications.

32

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

35

36 **Introduction**

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

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

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

60

## 61 **Methods**

62 Using national Veterans Health Administration databases, we conducted a  
63 nested case-control study of older Veterans (age  $\geq$  50 years) with positive *S.*  
64 *pneumoniae* blood, cerebrospinal fluid, or respiratory cultures between January 1,  
65 2002 and December 31, 2011. We defined serious pneumococcal infections as  
66 culture-positive pneumonia, bacteremia, and meningitis. Cases were those  
67 individuals who died from any cause within 30 days of positive culture, and controls  
68 were those alive at 30 days. Patients were allowed to be included in the study  
69 multiple times if they had multiple positive cultures. Positive cultures from the same  
70 patient within a 30-day period were considered the same infection. We utilized  
71 national VA datasets, created from electronic medical records and administrative  
72 data, to collect patient demographics, health factors, medical history, vaccination  
73 history, medication use, clinical outcomes, and culture data. Pneumonia was  
74 identified from positive sputum cultures in addition to International Disease  
75 Classification, Ninth Revision (ICD-9) diagnosis codes. Bacteremia and meningitis  
76 were defined by positive blood and cerebrospinal fluid cultures, respectively.  
77 Patients receiving a pneumococcal vaccination within five years of positive culture  
78 were excluded. We utilized ICD-9 and procedure codes to identify the presence of  
79 disease states within one year of the positive culture date. Medication use within  
80 30 days of positive culture, particularly the use of immunosuppressants

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

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



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

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

113

## 114 **Results**

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

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

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

129         The risk of 30-day mortality among patients with one of any of the eight risk  
130 factors was 50% higher compared to those with none of the eight risk factors (OR  
131 1.50 95% CI 1.08-2.07). The risk of 30-day mortality increased as risk factors were  
132 stacked, up to six risk factors (one: OR 1.50, CI 1.08-2.07; two: OR 2.01, CI 1.47-  
133 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  
134 2.60-5.07; six: OR 4.23, CI 2.69-6.65). The addition of each risk factor increased  
135 the risk of 30-day mortality by an average of 55% ( $\pm$ 13%; median: 56%,  
136 interquartile range 51%-60%), with the greatest increase between two and three  
137 stacked risk factors (70%). There were no statistically significant odds ratios  
138 among patients with seven (OR 1.65, CI 0.36-7.52) or eight (OR 2.14, CI 0.25-  
139 18.71) risk factors.

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

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

150 alcoholism + CLD (OR 6.20, 3.25-11.92), Age + CLD + IC (OR 42.90, CI 4.69-  
151 390.98), alcoholism + CLD + DM + IC (OR 32.10, CI 3.28-314.3), age + CLD +  
152 CRD + IC + smoking (OR 16.07, CI 2.62-98.5), and Age + Alcoholism + CLD +  
153 CRD + IC + smoking (OR 21.40, CI 1.91-240.56) were the strongest predictors of  
154 mortality for those with two, three, four, five, or six risk factors, respectively (Figure  
155 2). Results for all stacked risks are available in Appendix A.

156

## 157 **Discussion**

158 We quantified the impact of stacking pneumococcal disease risk factors on  
159 30-day mortality in unvaccinated older Veterans with serious pneumococcal  
160 infections. Of the 8 individual risk factors assessed, 37.5% of them significantly  
161 increased the risk of death and of the 247 stacked risks, 35% significantly  
162 increased the risk of death. Current literature regarding predictors of mortality in  
163 the setting of pneumococcal disease is primarily related to the impact of individual  
164 predictors, particularly in the immunocompromised population, as well as those  
165 with invasive pneumococcal disease.[8-16] However, there is a dearth of  
166 information regarding outcomes of patients with multiple risk factors for  
167 pneumococcal disease and the subsequent impact of this risk stacking. To our  
168 knowledge, this study is the first to analyze the effect of risk factor combinations  
169 on mortality. As the current body of literature strongly supports the association  
170 between vaccination preventing invasive infections and subsequent mortality in the  
171 setting of individual risk factors, the importance of disease prevention in patients  
172 with multiple risk factors cannot be overstated.[1-3, 8, 10, 16]

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

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

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

200 The results of our study demonstrate the impact of increasing numbers of  
201 pneumococcal disease risk factors on mortality among patients with serious  
202 pneumococcal infections. Once individuals develop a pneumococcal infection,  
203 there is a lasting negative impact. A recent study within the Veteran population  
204 found that patients with pneumococcal pneumonia who survived at least 30 days  
205 beyond infection had increased mortality compared to the expected survival for the  
206 average Veteran with similar demographics for up to ten years after recovering  
207 from the infection.[18] Furthermore, decreases in survival at ten years ranged from  
208 15% to 50% according to increases in pneumonia severity index (PSI), which  
209 accounts for risk factors also assessed in our study, including age, cardiac  
210 disease, and hepatic dysfunction.[18, 19] As such, disease prevention may have  
211 an extended positive impact on mortality.

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

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

226         According to current ACIP pneumococcal vaccination recommendations,  
227 patients in our study with cardiac, respiratory, and hepatic disease, along with  
228 those who smoke, and have diabetes mellitus or alcoholism would have been  
229 eligible to receive the 23-valent, pneumococcal polysaccharide vaccine (PPSV-  
230 23). In addition, those 65 years of age and older, and those with  
231 immunocompromising conditions are recommended to receive both the PPSV-23  
232 and the 13-valent, pneumococcal conjugate vaccine (PCV-13). [3, 21] Further, all  
233 children 6 weeks and older are currently recommended to receive PCV-13 (PCV-  
234 7 during our study period), thereby impacting development of pneumococcal  
235 disease at the population level through herd immunity.[22, 23] In the general  
236 population, pneumococcal vaccination, particularly with the conjugate vaccines,  
237 has been associated with substantial reductions in disease incidence through  
238 indirect protection.[23] However, the impact of herd immunity in the older Veteran  
239 population remains unclear, and further studies are needed to determine if these  
240 findings are consistent in this high-risk population.

241           Considering that each additional risk factor in our study increased the risk  
242 of mortality by 55% in the presence of pneumococcal disease, thorough evaluation  
243 of a patient's medical history must be performed to ensure that, barring any  
244 contraindications, all individuals with these risk factors are vaccinated.  
245 Furthermore, it is important to note that the greatest increase between stacked  
246 combinations occurred as patients went from two to three risk factors. Interestingly,  
247 our findings are consistent with two other risk stacking studies assessing the risk  
248 of developing pneumococcal disease, which showed that the greatest increase in  
249 the risk of disease development occurred when increasing from two to three  
250 disease states present.[6, 21] Increases in disease development ranged from 67%  
251 to 265% moving from two to three disease states across all age ranges.[6, 24] As  
252 such, our study provides further evidence that risk stacking poses a substantial  
253 threat in older adults, in whom multiple, chronic disease states are common.[1, 6,  
254 25] Furthermore, the results of our study may assist future efforts to increase  
255 pneumococcal vaccination by providing healthcare practitioners with an estimate  
256 of the quantified risk of mortality for patients with different combinations of risk  
257 factors for developing pneumococcal disease.

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

264 likely underestimated the true number of patients with pneumococcal pneumonia,  
265 as we only included patients with a positive sputum culture and ICD-9 diagnosis  
266 code. Further, pneumococcal pneumonia may have been the source for some  
267 pneumococcal bacteremias, but without positive respiratory cultures, was not  
268 categorized as such. Next, patients with multiple episodes of pneumococcal  
269 infection that were included in the study multiple times may have had a different  
270 risk profile than those with a single episode of infection. However, this impact is  
271 likely negligible, as the vast majority of patients only had one episode of infection  
272 (9,730 infections in 9,468 patients). Determining the risk of mortality in patients  
273 with more than six stacked risk factors was limited by small sample sizes within  
274 these groups. However, we believe the risk of mortality to likely be much higher  
275 than healthy individuals, as mortality increased in stacked risk factor groups with  
276 larger numbers. Next, as odds ratios only approximate relative risk, actual mortality  
277 risk may differ. It should also be noted that our analysis did not specifically adjust  
278 for pneumonia disease severity, such as with the Pneumonia Severity Index score.  
279 However, given that many of the risk factors included in our study are also part of  
280 this severity index, it is likely that pneumococcal disease severity also increased  
281 with the number of stacked risks. [26] Lastly, as we studied an older Veteran  
282 population, generalizability to the U.S. population as a whole is limited.

283

284

285 **Conclusion**



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

293

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312

313

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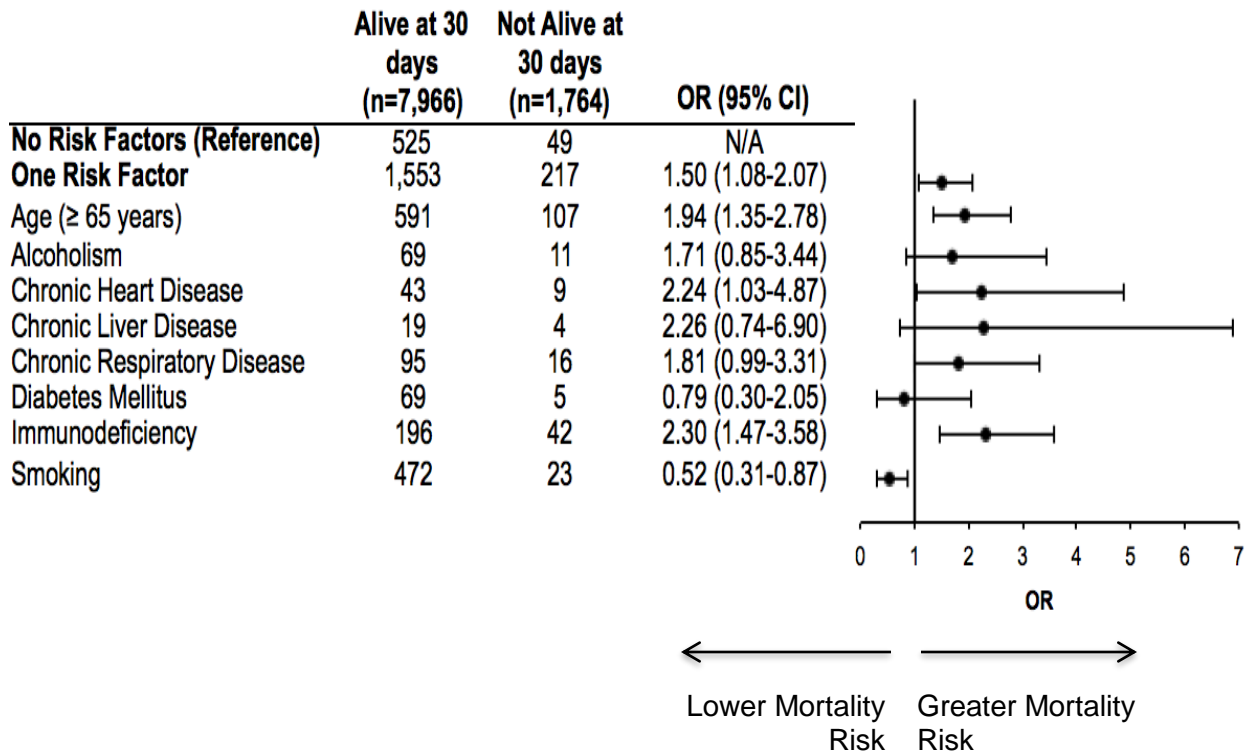
**Table 1. Demographics of unvaccinated older adults with pneumococcal disease.**

	<b>Alive at 30 days (n=7,966)</b>	<b>Not alive at 30 days (n=1,764)</b>
Age (years), (SD)	67 ( $\pm$ 11)	71 ( $\pm$ 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.**

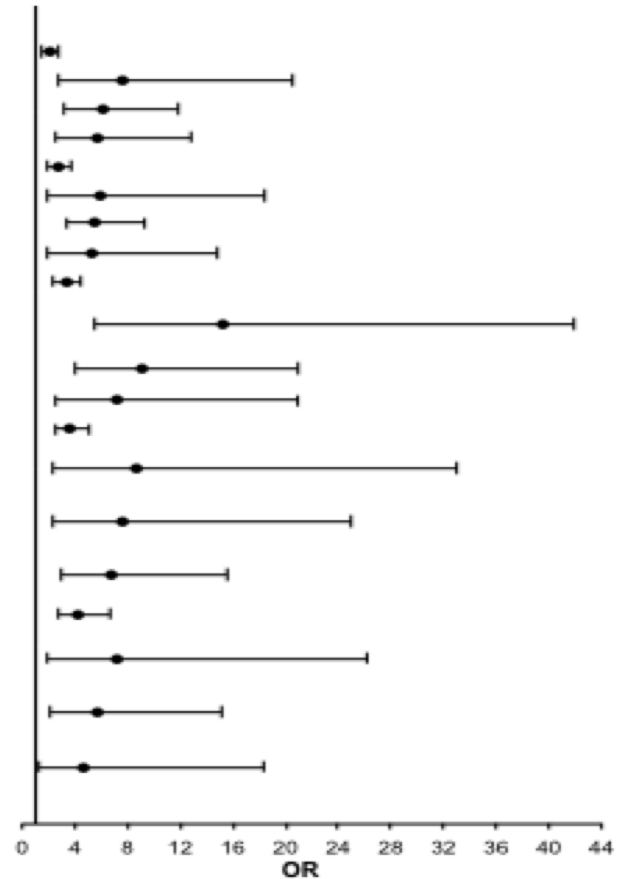


CI, Confidence Interval; OR, Odds Ratio



**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)
<b>No Risk Factors (Reference)</b>	525	49	N/A
<b>Two Risk Factors*</b>	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)
<b>Three Risk Factors*</b>	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)
<b>Four Risk Factors*</b>	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)
<b>Five Risk Factors*</b>	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)
<b>Six Risk Factors*</b>	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)



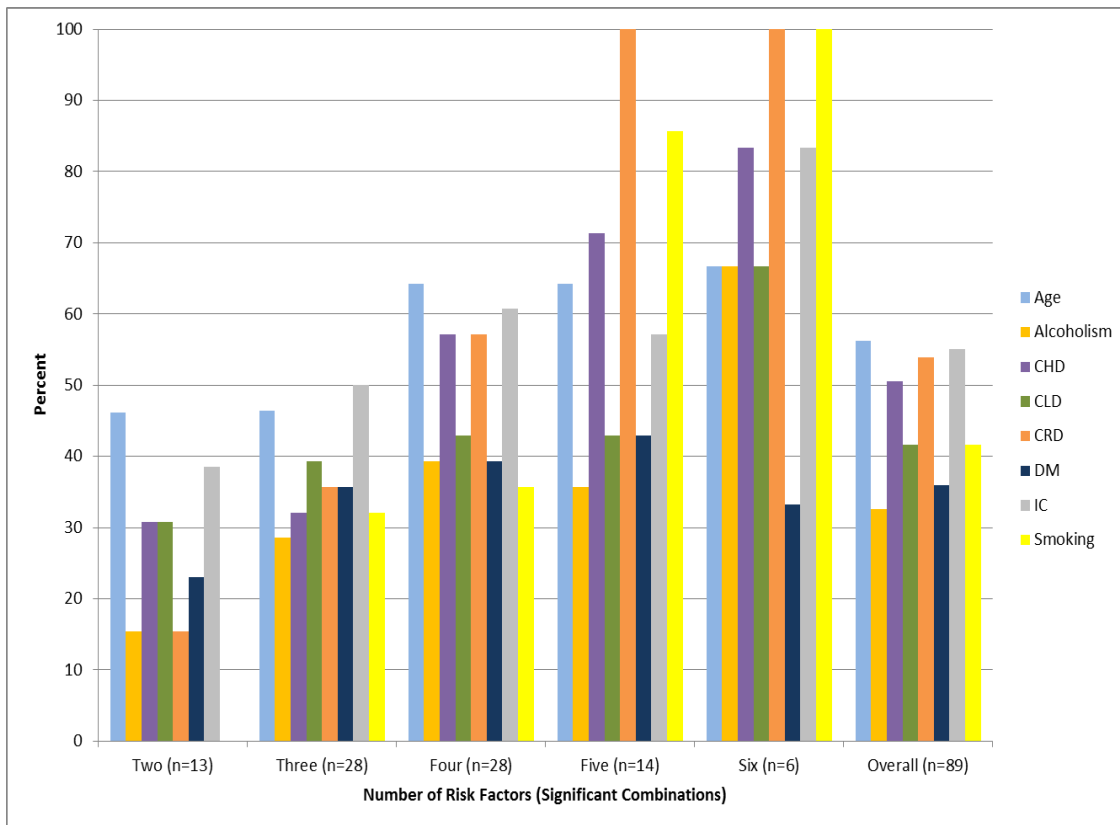
← Less Mortality Risk      Greater Mortality Risk →

Age, Age  $\geq$  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  $\geq 65$  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.**

	<b>Alive at 30 days (n=7,966)</b>	<b>Not alive at 30 days (n=1,764)</b>	<b>OR<sup>a</sup></b>	<b>95% CI</b>
<b>No Risk factors</b>	<b>525 (6.6)</b>	<b>49 (2.8)</b>	<b>Reference</b>	<b>Reference</b>
<b>Two Risk factors</b>	<b>1,969 (24.7)</b>	<b>370 (21.0)</b>	<b>2.01</b>	<b>1.47-2.75*</b>
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
<b>Three Risk factors</b>	<b>1,897 (23.8)</b>	<b>480 (27.2)</b>	<b>2.71</b>	<b>1.99-3.69*</b>
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*
<b>Four Risk factors</b>	<b>1,307 (16.5)</b>	<b>399 (22.6)</b>	<b>3.27</b>	<b>2.39-4.47*</b>
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
<b>Five Risk factors</b>	<b>584 (7.3)</b>	<b>198 (11.2)</b>	<b>3.63</b>	<b>2.60-5.07*</b>
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
<b>Six Risk factors</b>	<b>114 (1.4)</b>	<b>45 (2.6)</b>	<b>4.23</b>	<b>2.69-6.65*</b>

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
<b>Seven Risk factors</b>	<b>13 (0.2)</b>	<b>&lt; 5</b>	<b>2.47</b>	<b>0.68-8.98</b>
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
<b>Eight Risk factors</b>	<b>5 (0.06)</b>	<b>&lt; 5</b>	<b>2.14</b>	<b>0.25-18.71</b>
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.