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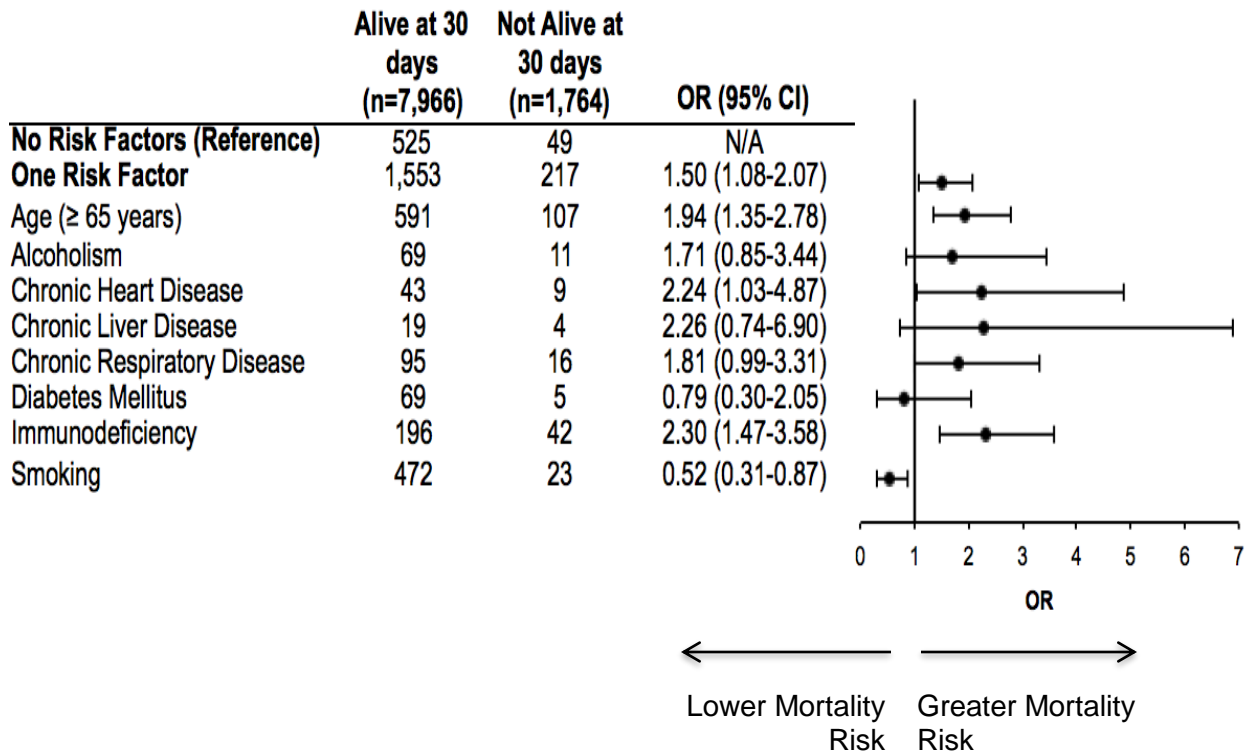
Table 1. Demographics of unvaccinated older adults with pneumococcal disease.

	Alive at 30 days (n=7,966)	Not alive at 30 days (n=1,764)
Age (years), (SD)	67 (\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.

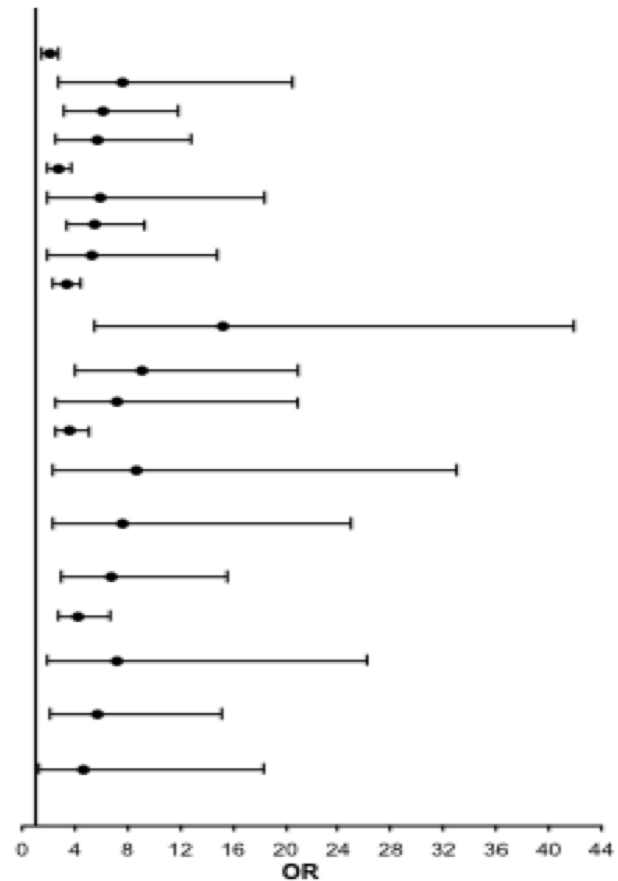
Figure 1. Risk of 30-day mortality in unvaccinated adults with one pneumococcal disease risk factor.



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)
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)



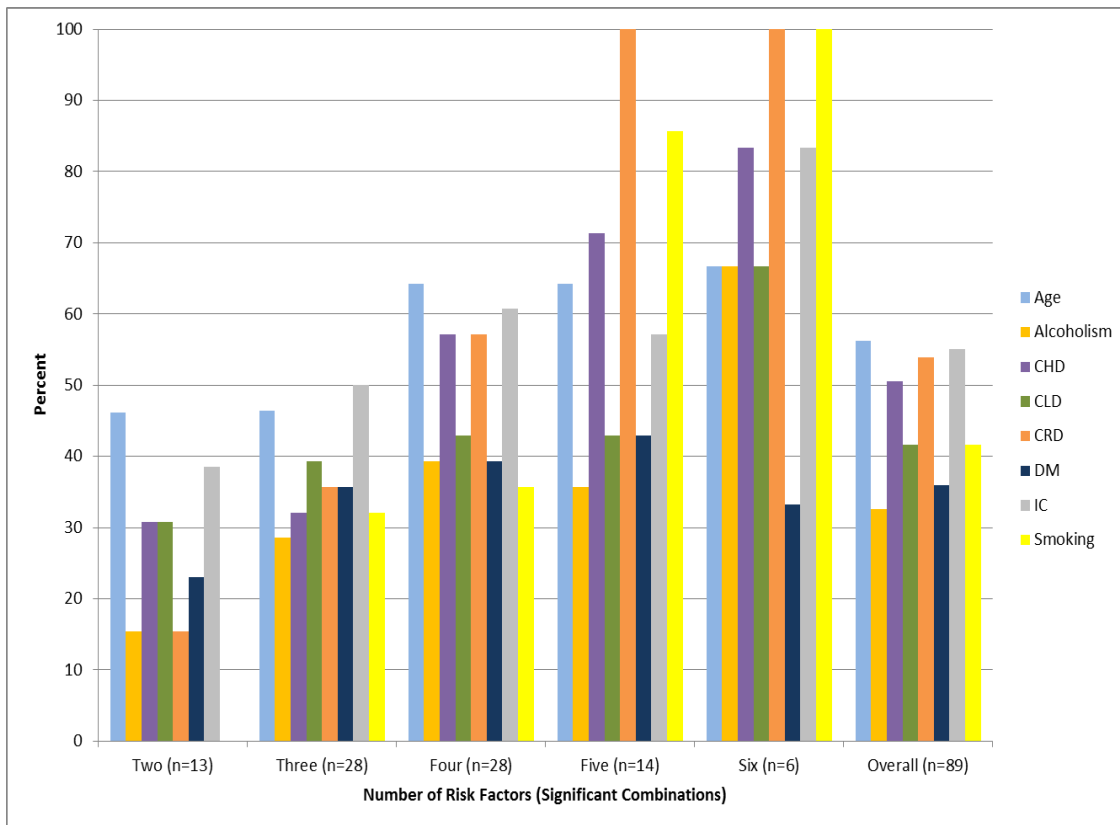
← Less Mortality Risk Greater Mortality Risk →

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.

	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.