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Major Adverse Cardiovascular Events During Invasive Pneumococcal Disease Are Serotype Dependent

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Background. Up to 30% of patients admitted to hospitals with invasive pneumococcal disease (IPD) experience major adverse cardiovascular event (MACE) including new/worsening heart failure, new/worsening arrhythmia, and/or myocardial infarction. *Streptococcus pneumoniae* (*Spn*) is the most frequently isolated bacterial pathogen among community-acquired pneumonia (CAP) patients and the only etiological agent linked independently to MACE. Nevertheless, no clinical data exist identifying which serotypes of *Spn* are principally responsible for MACE.

Methods. This was an observational multicenter retrospective study conducted through the Public Health Secretary of Bogotá, Colombia. We included patients with a confirmed clinical diagnosis of IPD with record of pneumococcal serotyping and clinical information between 2012 and 2019. *Spn* were serotyped using the quellung method by the National Center of Microbiology. MACE were determined by a retrospective chart review.

Results. The prevalence of MACE was 23% (71/310) in IPD patients and 28% (53/181) in patients admitted for CAP. The most prevalent *S. pneumoniae* serotype identified in our study was the 19A, responsible for the 13% (42/310) of IPD in our cohort, of which 21% (9/42) presented MACE. Serotypes independently associated with MACE in IPD patients were serotype 3 (odds ratio [OR] 1, 48; 95% confidence interval [CI] [1.21–2.27]; $P = .013$) and serotype 9n (OR 1.29; 95% CI [1.08–2.24]; $P = .020$). Bacteremia occurred in 87% of patients with MACE. Moreover, serum concentrations of C-reactive protein were elevated in patients with MACE versus in non-MACE patients (mean [standard deviation], 138 [145] vs 73 [106], $P = .01$).

Conclusions. MACE are common during IPD with serotype 3 and 9n independently of frequency.

Keywords. major adverse cardiovascular events (MACE); invasive pneumococcal disease (IPD); serotypes; *Streptococcus pneumoniae* (*Spn*).

Community-acquired pneumonia (CAP) is a leading cause of infectious death and a principal cause of sepsis, bacteremia, and admission to the intensive care unit (ICU). CAP and its associated complications are together responsible for more than 2.56 million deaths globally, with >1 million adults in the United States seeking hospital care for CAP annually [1, 2]. Critically, the socioeconomic burden of CAP and associated invasive disease are staggering, with annual costs exceeding $17 billion in the United Sates and more than €10 billion in Europe [2–4].

Streptococcus pneumoniae (the pneumococcus, *Spn*) is the most common bacterial pathogen isolated from patients hospitalized for CAP [5, 6]. Those at risk for pneumococcal pneumonia include the very young, elderly, individuals who are immunocompromised or have comorbidities, and those experiencing ongoing or recent viral infection of the respiratory tract [7, 8]. Importantly, *Spn* produces a polysaccharide capsule that is required for virulence. Briefly, the capsule surrounds and protects the bacterium from phagocytosis, with antibodies against the capsule being highly opsonic and sufficient for protection [9]. *Spn* is known to produce 100 biochemically and serologically distinct capsules types, that is, serotypes [10, 11]. As antibodies against one serotype do not confer protection against *Spn* carrying another capsule type, individuals remain susceptible to infection until they generate sufficient antibody against conserved pneumococcal proteins. Fortunately, not all serotypes have the same propensity for human disease. Current efforts to protect against *Spn* disease are based on vaccines that elicit antibody against the 13 deadliest serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) [7, 8]. The most current vaccine consisting of purified capsular polysaccharide from these serotypes are conjugated to CRM197, a nontoxic variant of diphtheria toxin (PCV) [5, 12]. Since 2000, the widespread implementation of 7-, 10-, and 13-valent vaccine formulations have led to an overall drop in the incidence of pneumococcal

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disease, albeit this is thought to be temporary as result of ongoing serotype replacement. Serotype replacement occurs when invasive strains carrying capsule covered by the vaccine acquire genetic material encoding for the capsule type of a nonvaccine serotype. Thus, there is a consensus to expand the current vaccine to include other serotypes [9].

One important aspect of severe CAP that contributes to mortality are major adverse cardiovascular events (MACE) [13–15]. These include heart failure, cardiac arrhythmias, and myocardial infarction [13, 16–19]. Up to 30% of patients admitted to the hospital due to CAP experience MACE, and these individuals have twice the mortality of patients with CAP alone. MACE is more frequent in patients with severe CAP [18–20], typically, elderly patients with comorbid conditions. It is of note that in a review of complications associated with CAP, *Spn* bacteremia was identified to be an independent risk factor for MACE [15, 16, 19, 21, 22]. Along such lines, work by our group has demonstrated a role for direct cardiovascular damage during *Spn* infection. For instance, the bacterium's pore-forming toxin pneumolysin has been shown to kill cardiomyocytes and, along with bacterial cell wall, disrupt cardiac contractility [23]. We have shown that *Spn* have the capacity to translocate across the vascular endothelium and invade the myocardium [13, 24–28]. Within the heart of experimentally infected laboratory mice and nonhuman primates, *Spn* were observed to replicate in the myocardium, kill cardiomyocytes, acutely disrupt cardiac function, and cause cardiac damage that resulted in de novo collagen deposition and cardiac remodeling in convalescence [24, 25, 27]. Importantly, and similar to clinical data in humans, cardiac damage in mice was found to be dependent on the strain's ability to cause bacteremia [24–27, 29]. What is more, the specifics of cardiac damage among animals that developed bacteremia were also observed to be strain dependent [26, 27]. For instance, a serotype 2 strain had generalized cardiac injury and cardiomyopathy, whereas a serotype 4 strain had discrete focal points of replication and damage. Importantly, whether pneumococcal serotype influences MACE in humans is unknown, although, as indicated, the capsule has a profound effect on *Spn* virulence.

Herein we assessed clinical risk factors previously associated with MACE and determined the association between pneumococcal serotypes and the development MACE in patients hospitalized due to invasive pneumococcal disease (IPD). Information obtained from this study is important to determine so as to best inform therapeutic practice and rationale selection of serotypes for vaccine development.

METHODS

This was an observational, multicenter, retrospective study conducted in Bogotá, Colombia. We used the pneumococcal isolates reported to the Public Health Secretary under a *Spn* surveillance program. Samples of *Spn* are sent in obligatory fashion to the National Center of Microbiology, where all samples are serotyped through the quellung method [30]. Patients with confirmed IPD were those with a clinical diagnosis of pneumococcal disease (eg, pneumonia, meningitis, or primary bacteremia) and at least 1 *S. pneumoniae* isolated in a sterile fluid.

Clinical Outcomes

Primary Outcome

Outcome was the development of MACE during hospital admission.

Secondary Outcomes

Outcomes were length of hospital stay (LOS), ICU LOS, time to clinical stability in days (defined as the mechanical ventilation, or vasopressors, inotropic removal), antibiotic days, need of ICU admission, hospital mortality, and ICU mortality.

Study Population

Adult patients were hospitalized due to IPD in Bogota, with pneumococcal isolation and serotype characterization besides clinical criteria of IPD. Additionally, all clinical charts were reviewed blinded to the pneumococcal serotypes to determine clinical outcomes.

Inclusion Criteria

All adults (>18 years old) with a clinical diagnosis of IPD and pneumococcal strain identification, in which the hospital sent the clinical chart, were included in the study (Supplementary Figure 1).

Exclusion Criteria

Criteria included patients in whom clinical data were incomplete or other bacteria were isolated (ie, coinfection).

Study Definitions

International and well-accepted definitions for each variable were used for this study [28, 31]. MACE is a composed outcome, including new or worsening cardiac arrhythmia, defined as a change from the typical sequence of electrical activity recorded in the electrocardiogram (EKG), compared to the baseline EKG recorded at hospital admission. New or worsening heart failure, defined as rapid onset of symptoms and signs secondary to abnormal cardiac function, which may occur with or without previous cardiac disease documented through echocardiogram and/or biomarkers such a Pro-BNP. Myocardial infarction, was defined as a myocardial injury with clinical evidence of myocardial ischemia, rise and/or fall of serum troponin values with at least 1 value above 99th percentile of the normal reference value of each local laboratory; development of pathological Q waves and/or new ischemic changes in EKG; or evidence of coronary thrombus by angiography and/or new

loss of viable myocardium, or regional wall motion abnormality identified in the echocardiogram.

Statistical Analysis

To assess the association between MACE and *Spn* serotypes, we guided the analysis based on previously published literature; in which age, previous cardiovascular diseases, and CAP severity were identified as related factors [20]. Consequently, data from variables such as high blood pressure, heart failure, coronary heart disease, cardiac arrhythmia, dyslipidemia, diabetes mellitus, obesity, the requirement for mechanical ventilation and vasopressor or inotropic support were gathered and compared between serotypes for this study. A bivariate analysis was initially carried out to compare the quantitative variables according to their distribution. If it was normally distributed, Student *t* test was applied for independent samples; if the variable was not a normal distribution, Mann-Whitney *U* test was used. Qualitative variables were compared by χ^2 analysis. Variables were analyzed by cardiovascular risk, pneumonia severity, and pneumococcal serotypes. Later on, a logistic regression model was performed considering the outcome (MACE development) as a dichotomous variable. To apply this model, we ensured variables had supporting literature, biological plausibility and had a *P*-value of <.2. Finally, statistically significant variables were those that had a *P*-value <.05.

RESULTS

A total of 310 patients with IPD were included in the study. The median age was 61 years old (interquartile range [IQR] 45, 73), from which 45% (141/310) were female; all demographic information is presented in Table 1. CAP was the principal clinical diagnosis with 60% (186/310), meningitis 18% (58/310), and other types of presentation of IPD (primary bloodstream infection) in 21% (66/310) were included (Figure 1A). The overall prevalence of MACE was 23% (71/310) in IPD patients, 28% (53/186) among patients with primary CAP, 14% (8/58) in patients with meningitis, and 15% (10/66) of patients with other forms of IPD presentation (Figure 1B).

S. pneumoniae was isolated in blood cultures from 88% of cases (273/310), followed by cerebrospinal fluid in 14% (44/310), tracheal secretion 8% (25/310), pleural fluid 6% (20/310), bronchoalveolar lavage 6% (18/310), and ascitic fluid 1% (3/310). MACE were more frequent among patients with bacteremia when compared to nonbacteremic patients (93% [66/71] vs 86% [207/239], *P* = .08). The most frequent comorbidity identified in patients who developed MACE was hypertension in 62% (44/71), heart failure 31% (22/71), coronary heart disease in 15% (11/71), and obesity in 10% (7/71), among others (Table 1). Finally, only 3% of all patients (10/310) were vaccinated with anti-pneumococcal (either conjugate or polysaccharide) or flu vaccines.

About the physiological variables evaluated on admission, we found no difference between MACE and no-MACE patients, except in the Glasgow coma scale, which was lower in MACE patients (mean [standard deviation {SD}] 13 [3] vs 14 [3], *P* = .01). Regarding serum laboratories on admission, we found no significant differences except for blood concentration of C-reactive protein (CRP), which was higher in patients who developed MACE (mean [SD] 138 [145] vs 73 [106], *P* = .01). Importantly, serum troponin was not evaluated in all patients, this was only assessed in patients with clinical suspicious of acute myocardial infarction, at discretion of the attending physician; the complete list of physiological variables and laboratories are presented in Table 2. In terms of clinical severity scores, we found that patients that developed MACE had a more severe disease determined by higher APACHE II when compared to patients that did not develop MACE (mean [SD] 17 [6] vs 14 [7], *P* = .03); also confirmed by a higher CURB-65 score (mean [SD] 2.87 [0.96] in MACE group vs 1.86 [1.2], *P* < .01) and the pneumonia severity index (PSI) (mean [SD] 129 [26] vs 102 [45], *P* < .01) in CAP patients. As expected, some medical treatments during hospital admission were different among patients who developed MACE (Table 3). Moreover, antibiotic treatment was comparable between the two groups, except for more frequent usage of meropenem 15% (11/71) in the MACE group, which is most likely related to disease severity (Table 4).

In the MACE group, the most frequent cardiac complication was arrhythmias 58% (41/71), followed by heart failure 49% (35/71), infarction 29% (21/71), and myocardial injury 16% (12/71). It should be noted that patients may have presented more than one complication during hospital admission. The most prevalent *S. pneumoniae* strain identified in our study was the 19a, responsible for the 13% (42/310) cases, 21% (9/42) of those developed MACE. Among those with MACE, the most prevalent serotype was serotype 3 (14/71), followed by serotype 9n (6/71). The complete list of pneumococcal serotypes stratified by MACE is presented in Table 5. Variables associated to MACE were age (*P* < .018), cardiovascular disease (*P* = .032), severe pneumonia (*P* < .001) and infection with pneumococcal serotypes 3 and 9n (*P* = .040), R2: 0.263, Hosmer and Lemeshow test *P* = .513. Moreover, we found that *S. pneumoniae* serotype 3 (OR 1.48; 95% confidence interval [CI] [1.21–2.27]; *P* = .013), and serotype 9n (OR 1.29; 95% CI [1.08–2.24]; *P* = .020), were independently associated with the development of MACE in patients with IPD. Finally, mortality in the patients that required ICU was 20% in all cohort (64/310), although the MACE group was higher when compared to no-Mace patients (45% [32/71] vs 13% [32/239], *P* < .01). Hospital mortality in MACE patients was also higher than in no-MACE patients (62% [44/71] vs 19% [47/239], *P* < .01). The full comparison of clinical outcomes stratified among patients who developed MACE are present in Table 4.

Table 1. Demographic Characteristics of Patients Hospitalized Due to Invasive Pneumococcal Disease (IPD) Stratified by the Presence of Major Adverse Cardiovascular Events (MACE)

Characteristic	All Cohort n = 310	MACE n = 71	No MACE n = 239	*P*
Age, median (IQR)	61 (45, 73)	70 (60, 79)	58 (43, 69)	
Female, n (%)	141 (45)	26 (37)	115 (48)	.09
Comorbid conditions, n (%)				
Smoking	89 (29)	24 (33)	65 (27)	.28
Alcoholism	37 (12)	13 (18)	24 (10)	.06
COPD	44 (14)	15 (21)	29 (12	.05
Diabetes	50 (16)	13 (18)	37 (15)	.56
Hypertension	131 (42)	44 (61)	87 (36)	**<.01**
Heart failure	40 (13)	22 (31)	18 (7)	**<.01**
Chronic renal disease	36 (12)	10 (14)	26 (11)	.45
Liver disease	17 (5)	6 (8)	11 (15)	.21
Obesity	16 (5)	7 (10)	9 (4)	**.04**
HIV	17 (5)	2 (3)	15 (6)	.26
Coronary heart disease	26 (8)	11 (15)	15 (6)	**.01**
Dyslipidemia	27 (8)	10 (14)	17 (7)	.06
Previous hospitalization	47 (15)	21 (29)	26 (11)	**<.01**
Previous antibiotic therapy	41 (13)	15 (21)	26 (11)	**.02**
Auricular fibrillation	20 (6)	11 (15)	9 (4)	**<.01**
Auto immune disease	38 (14)	8 (11)	30 (12)	.7
Cancer	37 (12)	8 (11)	29 (12)	.8
Epilepsy	5 (2)	1 (1)	4 (2)	.8
Chronic medications, n (%)				
Anti-hypertensive drugs	131 (42)	44 (61)	87 (36)	**<.01**
Use of anti-diabetic drugs	24 (8)	8(11)	16 (7)	.29
Insulin	17 (5)	3 (4)	14 (6)	.59
Opioids	6 (2)	2 (3)	4 (2)	.53
PPIs	62 (20)	20 (28)	42 (17)	**.05**
Use of inhalators	25 (8)	10 (14)	15 (6)	**.03**
Anticoagulation	11 (4)	6 (8)	5 (2)	**.01**
Statins	44 (14)	15 (21)	29 (12)	.05
NSAID	16 (5)	5 (7)	11 (5)	.41
Corticosteroids	32 (10)	9 (13)	23 (10)	.45
Anti-convulsant drugs	6 (2)	2 (3)	4 (2)	.53
Vaccination				
Vaccine PSP23	2 (1)	0 (0)	2 (1)	.44
Pneumococcal conjugate vaccine	4 (1)	0 (0)	4 (2)	.27
Influenza vaccine	4 (1)	0 (0)	4 (2)	.27

Abbreviations: COPD, chronic obstructive pulmonary diseases; HIV, human immunodeficiency virus; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory; PBI, protons bomb inhibitor.

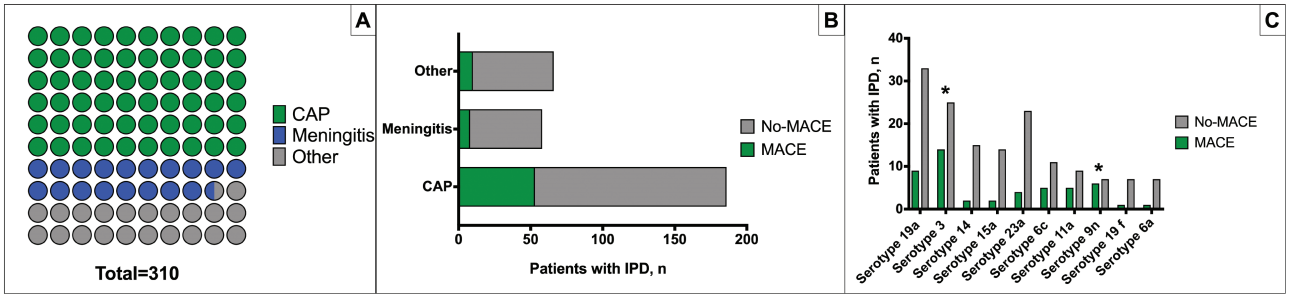

Figure 1. *A*, Graphical representation of the distribution of patients included in the study according to the diagnosis. *B*, Distribution of patients included in the study according to the diagnosis and developing of MACE. *C*, Distribution of patients included in the study according to the strain identification and developing of MACE. Abbreviations: CAP, community-acquired pneumonia; IPD, invasive pneumococcal disease; MACE, major adverse cardiovascular events.

Table 2. Physiological Variables of Patients Hospitalized Due to Invasive Pneumococcal Disease (IPD), and Separated by the Presence or Not of Major Adverse Cardiovascular Events (MACE)

Physiological Variable, Mean, (SD)	All Cohort n = 310	MACE n = 71	No MACE n = 239	*P* value
Heart rate, bpm	98 (80, 112)	98 (29)	97 (23)	.7
Systolic pressure, mmHg	117 (26)	113 (27)	118 (25)	.22
Diastolic pressure, mmHg	70 (16)	69 (17)	70 (16)	.55
MAP, mmHg	83 (23)	83 (21)	83 (24)	.95
Respiratory rate, rpm	21 (6)	21 (6)	20 (5)	.18
Oximetry, %	88 (12)	87 (8)	88 (13)	.65
Glasgow coma scale	14 (3)	13 (3)	14 (3)	**.01**
Temperature, °C	36.9 (1.9)	36 (1)	36 (2)	.85
Leucocytes, × 10^3	13.2 (8.9)	12 (8)	13 (9)	.25
Neutrophils[a], ×10^3	10 (5.2, 16.6)	8.3 (3.7, 16.9)	10.0 (5.8, 16.0)	.24
Hemoglobin, gr/dL	12.9 (3.41)	12 (3)	12 (3)	.86
Hematocrit, %	42.1 (40.2)	38 (9)	42 (45)	.42
Platelets × 10^3	215 (117)	200 (105)	220 (121)	.24
Glucose, mg/dL	138 (113)	133 (66)	140 (125)	.72
Ureic nitrogen, mg/dL	30.3 (24.5)	35 (28)	28 (23)	.05
Creatinine, mg/dL[a]	1.06 (0.76, 1.7)	1.87 (1.87)	1.2 (0.77)	.23
Sodium, mmol	133 (20)	136 (6)	131 (23)	.11
Potassium, mmol	5.5 (22)	4 (0,6)	6 (2,5)	.54
Total bilirubin, mg/dL	1.04 (0.77)	1.06 (0.5)	1.01 (0.36)	.07
Indirect bilirubin, mg/dL	0.87 (1.34)	0.84 (1)	0.88 (1,4)	.92
Direct bilirubin, mg/dl	0.37 (0.20)	1.20 (1.9)	0.57 (0.46)	.14
ALT, UI/L	86 (18)	86 (18)	85 (35)	.81
AST, UI/L	79 (27)	83 (9)	69 (19)	.83
C-reactive protein, mg/L	89 (119)	138 (145)	73 (106)	**.01**
Procalcitonin, ng/ml	26 (56)	43 (47)	20 (59)	029
Prothrombin time, sec	15 (7)	15 (6)	15 (7)	.87
Thromboplastin time, sec	34 (19)	34 (10)	34 (22)	.91
Arterial blood gases				
PH[a]	7.42 (7.34,7.47)	7.40 (7.32,7.48)	7.39 (7.32,7.49)	.56
PO2, mmHg	70 (36)	70 (43)	70 (33)	.92
PCO2, mmHg	30 (12)	31 (11)	29 (12)	.21
FiO2, %	30 (19)	29 (19)	30 (18)	.65
HCO3, meq/L[a]	18 (14, 20)	18 (15, 22.5)	18.4 (16, 23.7)	.70
Lactate, mmol/L	6 (31)	4.2 (3.1)	7 (3.6)	.63
Clinical severity scores				
SOFA	6 (3.6)	7 (3)	6 (3)	.09
Apache II	15 (7)	17 (6)	14 (7)	**.03**
Curb 65	2.4 (1.1)	2.87 (0.96)	1.86 (1.2)	**<.01**
PSI	181 (41)	129 (26)	102 (45)	**<.01**

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; bpm, beats per minute; FiO2, oxygen inspired fraction; HCO3, sodium bicarbonate; IQR, interquartile range; MAP, median arterial pressure; rpm, rate per minute; PO2, arterial oxygen pressure; PCO2, arterial carbon dioxide; PSI, pneumonia severity index; SD, standard deviation.
[a]Median, (IQR).

DISCUSSION

The data presented in this study supports the notion that the MACE is a common event during IPD. We found for the first time in the medical literature, that some *S. pneumoniae* serotypes are more prone to induce MACE in patients with IPD. Moreover, we also found that pneumococcal bacteremia seems to be required to cause MACE, an independent confirmation of results previously performed with animal experiments and prior clinical studies [24, 25, 27, 32]. We observed that development of MACE was correlated with disease severity, also with high CRP blood concentrations. As has been previously described, we observed that some patient characteristics such are chronic medical conditions and cardiovascular risk factors are related to the development of MACE [21, 29, 32, 33]. Our findings have important implications in regard to potential vaccine design and patient care.

In our study, MACE was independently associated with disease caused by serotype 3 and 9n. Increasing clinical data show that serotype 3 isolates of *Spn* are a major problem. This is despite the fact that serotype 3 capsule is included in the current 13-valent conjugate vaccine (PCV13) formulation. Serotype 3 isolates of *Spn* are distinct from other *Spn* in that they are

Table 3. Hospitalization Characteristics and Medical Interventions, in Patients Hospitalized Due to Invasive Pneumococcal Disease (IPD), With or Without Presence of Major Adverse Cardiovascular Events (MACE)

Characteristics, n (%)	All Cohort n = 310	MACE n = 71	No MACE n = 239	*P*
Mechanical ventilation	141 (45)	48 (67)	93 (38)	**<.01**
Noninvasive mechanical ventilation	16 (5)	3 (4)	13 (5)	.70
Use of norepinephrine	131 (42)	50 (70)	81 (33)	**<.01**
Use of vasopressin	50 (16)	20 (28)	30 (12)	**<.01**
Use of epinephrine	19 (6)	10 (14)	9 (4)	**<.01**
Use of dobutamine	25 (8)	18 (25)	7 (3)	**<.01**
Use of levosimendan	6 (2)	3 (4)	3 (1)	.10
Dexamethasone	42 (13)	8 (11)	34 (14)	.55
Hydrocortisone	52 (16)	19 (26)	33 (14)	**<.01**
Dopamine	9 (3)	4 (6)	5 (2)	.11
Midazolam	133 (42)	47 (66)	86 (36)	**<.01**
Fentanyl	143 (45)	49 (69)	94 (39)	**<.01**
Dexmedetomidine	26 (8)	4 (6)	22 (9)	.35
Propofol	28 (9)	10 (14)	18 (7)	.08
Remifentanil	7 (2)	3 (4)	4 (2)	.19

hyperencapsulated [12, 26, 34]. Unlike other *Spn* capsular types, serotype 3 polysaccharide is not covalently linked to the cell wall, instead loosely associated with phosphatidylglycerol residues and thus is continuously shed into the bacterium's environment [25, 27]. Capsule volume and shedding confers intrinsic resistance to antibody-independent scavenger receptor mediated phagocytosis and necessitates higher specific antibody titers for opsonophagocytosis. It is for this reason that serotype 3 strains cause necrotizing pneumonia and other severe forms of infection at higher rates than other serotypes. These more severe forms of disease might be in relation with the increased prevalence of MACE in patients infected with serotype 3, secondary to the fact that cell wall, capsule, and pneumolysin are cardiotoxic. Therefore, our finding add to the argument that serotype 3 isolates are more virulent with evidence they are more prone to cause cardiac damage.

We also found that patients infected with serotype 9n were more susceptible of MACE during IPD. Serotype 9n is not covered by the current vaccine and along with serotype 3 was associated with mortality in a recent meta-analysis. Serotype 9n belongs to a serogroup or a cluster of isolates with similar, but still serologically distinct, capsular types. One interesting aspect of serotype 9 serogroup is that its members are acetylated. Acetylation of capsule has been demonstrated to impact its susceptibility to clearance by host factors and directly impact the bacterium's virulence. The specific reasons why 9n is associated with MACE are unclear, and it may be that this property extends to other member of its serogroup. Information on the propensity of serotypes to cause MACE is highly relevant as knowledge on the infecting serotype can inform the medical team that the affected individual is more likely to develop cardiac complications. What is more, and despite difficulties with serotype 3, our finding of serotype 9n as being associated with cardiac damage suggests that its inclusion in any new vaccine formulation should be prioritized.

It is essential to highlight that all preclinical studies designed to study MACE during pneumococcal infections using mice and nonhuman primates showed that bacteremia is a crucial factor in developing pneumococcal driven cardiac damage [24, 25, 27]. This fact agrees with the findings of a prospective human study with a 10-year follow-up, conducted by Beatty et al, in which researchers found that pneumococcal bacteremia is a risk factor for adverse cardiac events [29, 35]. The above data are concordant with our findings because, in

Table 4. Clinical Outcomes of Patients Hospitalized Due to Invasive Pneumococcal Disease (IPD)

Outcomes, n (%)	All Cohort n = 310	MACE n = 71	No MACE n = 239	*P*
ICU mortality	64 (20)	32 (45)	32 (13)	**<.01**
Hospitalization mortality	94 (30)	47 (66)	47 (19)	**<.01**
ICU requirement	206 (66)	56 (79)	150 (62)	**<.01**
Hospitalization days, mean (SD)	16 (19)	18 (16)	17 (20)	.25
ICU days, mean (SD)	6,4 (12)	7 (8)	6 (13)	.73
Time to clinical stability (days), mean (SD)	6,2 (8,5)	5 (9)	6 (8)	.35
Antibiotic days, mean (SD)	11 (14)	9 (11)	12 (15)	.13

Abbreviations: ICU, intensive care unit; MACE, major adverse cardiovascular events; SD, standard deviation.

Table 5. *Streptococcus pneumoniae* Serotypes Identified in Patients Hospitalized Due to Invasive Pneumococcal Disease (IPD) and Stratified by Major Adverse Cardiovascular Events (MACE) and No MACE

Serotype, n (%)	All Cohort n = 310	MACE n = 71	No MACE n = 239	*P*
Serotype 19a	42 (13)	9(13)	33 (14)	.80
Serotype 3	39 (12)	14 (20)	25 (10)	**.03**
Serotype 14	17 (5)	2 (3)	15 (6)	.21
Serotype 15a	16 (5)	2 (3)	14 (6)	.30
Serotype 23a	16 (5)	4 (6)	12 (5)	.83
Serotype 6c	16 (5)	5 (7)	11 (5)	.41
Serotype 11a	14 (4)	5 (7)	9 (4)	.24
Serotype 9n	13 (4)	6 (8)	7 (3)	**.04**
Serotype 19f	8 (2)	1 (1)	7 (3)	.47
Serotype 6a	8 (2)	1 (1)	7 (3)	.47
Serotype 15b	7 (2)	1 (1)	6 (2)	.58
Serotype 22f	7 (2)	1 (1)	6 (2)	.58
Serotype 8	7 (2)	1 (1)	6 (2)	.58
Serotype 23b	6 (2)	1 (1)	5 (2)	.71
Serotype 1	6 (2)	1 (1)	5 (1)	.71
Serotype 10a	6 (2)	1 (1)	5 (2)	.71
Serotype 23f	6 (2)	0 (0)	6 (2)	.17
Serotype 7f	6 (2)	3 (4)	3 (1)	.11
Serotype 9v	6 (2)	0 (0)	6 (2)	.17
Serotype 34	5 (1)	0 (0)	5 (2)	.21
Serotype 6b	5 (1)	1 (1)	4 (2)	.87
Serotype 16f	4 (1)	1 (1)	3 (1)	.92
Serotype 13	4 (1)	0 (0)	4 (2)	.27
Serotype 18c	4 (1)	1 (1)	3 (1)	.92
Serotype 20	3 (1)	2 (3)	1 (0.4)	.07
Serotype 28a	3 (1)	1 (1)	2 (1)	.66
Serotype 35b	3 (1)	0 (0)	3 (1)	.34
Serotype 35f	3 (1)	1 (1)	2 (1)	.66
Serotype 37	3 (1)	0 (0)	3 (1)	.34
Serotype 7c	3 (1)	2 (3)	1 (0.4)	.07
Serotype 12b	2 (1)	1 (1)	1 (0.4)	.36
Serotype 12f	2 (1)	0 (0)	2 (1)	.43
Serotype 25f	2 (1)	1 (1)	1 (0.4)	.36
Serotype 31	2 (1)	0 (0)	2 (1)	.43
Serotype 35a	2 (1)	0 (0)	2 (1)	.43
Serotype 4	2 (1)	0 (0)	2 (1)	.43
Serotype 10f	1 (0.3)	1 (1)	0 (0)	.06
Serotype 11d	1 (0.3)	1 (1)	0 (0)	.06
Serotype 15c	1 (0.3)	0 (0)	1 (0.4)	.58
Serotype 16	1 (0.3)	0 (0)	1 (0.4)	.58
Serotype 17f	1 (0.3)	0 (0)	1 (0.4)	.58
Serotype 18a	1 (0.3)	0 (0)	1 (0.4)	.58
Serotype 19c	1 (0.3)	1 (1)	0 (0)	.06
Serotype 24f	1 (0.3)	0 (0)	1 (0.4)	.58
Serotype 29	1 (0.3)	0 (0)	1 (0.4)	.58
Serotype 4c	1 (0.3)	0 (0)	1 (0.4)	.58
Serotype 6d	1 (0.3)	0 (0)	1 (0.4)	.58
Serotype 8a	1 (0.3)	0 (0)	1 (0.4)	.58

our study, 92% of MACE patients had bacteremia. Thus, we also conclude that bacteremia is requisite for the development of MACE in patients with pneumococcal infection. Therefore, it would suggest that serotypes that are best equipped to cause bacteremia are more likely to cause MACE along with IPD patients. Moreover, physicians with patients who develop bacteremia should be aware of the risk for MACE development.

Systemic inflammation is recognized to be a risk factor for worse short- and long-term clinical outcomes in patients with CAP and sepsis [14, 16, 32, 36, 37]. CRP blood levels are directly related to disease severity and host inflammatory response; as well as the risk for developing cardiovascular complications [37]. Yende et al found that high serum interleukin (IL)-6 and IL-10, a cytokine produced to counter excessive inflammation, concentrations at hospital discharge were strongly associated with one-year mortality [38]. Mankowski et al described that there is a direct effect on atherosclerotic plaque and dysregulation in cardiomyocyte function due to persistent inflammation, which is related to cardiovascular outcomes. Corrales-Medina et al found that cardiac complications are common in patients with CAP and sepsis; this is related to an increase in short and long-term mortality and risk of developing cardiovascular diseases up to 10 years after the acute event of CAP [18–20, 33, 35, 39]. This is in concordance with our results; we found a correlation between high CRP levels and the development of MACE. Finally, our results also have shown a relation between classic cardiovascular risk factors and the development of cardiovascular complications in IPD patients, thus confirming what is widely reported in the literature.

Our study has limitations and strengths that are important to acknowledge. First, the number of patients included in the study is small. Also, we excluded some patients because of incomplete data that could be considered a selection bias. We did not include patients that did not require in-hospital care. The low number of isolations of some *Spn* serotypes could represent a limitation that could be sensitive to small changes. However, the relation among all serotypes (independently of the number of isolations) and the development of MACE was evaluated independently (χ^2) and in the multivariate analysis. MACE's definition did not include outcomes such as cardiovascular death or stroke, which represents a limitation itself. These clinical outcomes were not included because the identification of such outcomes from medical records was not possible due to the study design. Another limitation is that we did not follow up the patients over time; thus, we cannot analyze long-term outcomes. Nevertheless, the most critical risk period for MACE is within the first 30-days of hospital admission. Nonetheless and despite these limitations, this is the first multicenter study, including patients representing a whole city, which is novel and generalizable. In addition, our study also includes representative community samples of middle-aged and elderly adults and a rigorous methodology to identify MACE.

CONCLUSION

This study has important implications for patients with community-acquired pneumonia and invasive pneumococcal

disease. Patients infected with serotypes 3 and 9n are at higher risk of developing MACE, and clinicians should actively look for these complications during hospital admission of patients with IPD due to these serotypes. Patients with previous cardiovascular risk factors, bacteremia, and elevated CRP concentration during IPD hospitalization, might be more prone to develop MACE and should be carefully observed to early diagnosed and treat these life-threatening complications. Large prospective studies are needed to confirm this strain-dependent MACE in patients hospitalized due to IPD.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. L. F. R., A. B., H. F. A., and C. C. S. M. were responsible for study design, implementation, and manuscript preparation. They had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. H. F. A., C. C. S. M., P. C. R. V., I. G. B., A. B., H. A. V., S. G., A. R., C. J. O., and L. F. R. contributed substantially to the study design, data analysis, and interpretation. H. F. A., C. C. S. M., P. C. R. V., I. G. B., A. B., H. A. V., S. G., A. R., C. J. O., and L. F. R. wrote the manuscript.

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