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Cardiovascular events after invasive pneumococcal disease: a retrospective cohort study

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ABSTRACT

Objectives: This study aims to understand the magnitude of and mechanisms underlying the development of cardiovascular events (CVEs) in patients with invasive pneumococcal disease (IPD). We aimed to identify factors that contribute to the occurrence of CVEs within 1 year after admission and discuss implications for patient care.

Methods: A multicentered cohort study included adult patients from four Dutch hospitals who had a positive blood culture for *Streptococcus pneumoniae* and any type of clinical manifestation between 2012 and 2020. Disease characteristics and microbiological data were systematically collected from electronic patient files. The main outcome measures were the occurrence of stroke and acute coronary syndromes (ACS).

Results: Of 914 eligible patients, 4.2% experienced a CVE within 1 year after admission for IPD. ACS mainly occurred in the first 2 weeks, whereas stroke developed throughout follow-up. Although ACS was positively associated with disease severity, the sole independent predictor was alcohol abuse (odds ratio [OR] 3.840, 95% confidence interval [CI] 1.108-13.303). Although stroke occurred in 6.3% of meningitis cases, the best clinical predictor of stroke was a body temperature >39.5 °C at admission (OR 3.117 [1.154-8.423]). In the adult IPD population aged <70 years, pneumococcal serotypes were the primary predictors of ACS (7F; OR 15.733 [1.812-136.632]) and stroke (22F; OR 7.320 [1.193-44.903]).

Conclusions: Adverse CVEs were not uncommon after IPD diagnosis and deserve attention, especially in the high-risk groups we identified in our study population. Whether specific serotypes play a role in the development of CVE requires substantiation in further research.

Introduction

Streptococcus pneumoniae is the most frequent cause of community-acquired pneumonia (CAP) [1], and pneumococcal infections have contributed to a higher mortality than all other etiologies combined [2]. Severe CAP carries a 5-15% risk for adverse cardiovascular events (CVEs), which are major contributors to mortality and permanent vascular complications in patients with invasive pneumococcal disease (IPD) [3–5]. Although several mechanisms that could lead to CVEs in pneumococcal infections have been hypothesized, it is unclear whether specific patients carry a particular risk.

The risk of death is higher in pneumonia caused by *S. pneumoniae* compared to other infectious causes, and the bacteria itself has been directly linked to adverse cardiac events [6]. Africano et al. [7] report a large cohort of patients with IPD in which up to 30% experienced new or worsened cardiac problems. The pneumococcus is also well-established as causing cerebral infarctions in meningitis, especially compared with other pathogens [8]. It has been described as the etiology with the most severe long-term

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complications in meningitis [9]. One potential underlying mechanism is based on the procoagulant properties of the pneumococcus. In porcine models, it has been shown that IPD induces platelet activation [10]. A small placebo-controlled trial with 185 patients found that aspirin reduced the occurrence of CVE in patients with CAP from 10.6% to 1.1% [11].

Generally agreed mechanisms resulting in CVE during pneumonia are a combination of reduced oxygen supply from the lungs and increased oxygen requirements resulting from the inflammation. This promotes thrombogenesis and myocardial stress [12,13].

Persistent inflammation after pneumonia can also contribute to subsequent progression to cardiovascular disease, as well as a persistent procoagulant inflammatory state. Higher levels of coagulation markers at hospital discharge have been associated with an increased risk of cardiovascular deaths [13]. Other possible mechanisms for experiencing CVE have been described as well, as briefly outlined below.

Coagulopathy and endothelial damage induced by a septic state have been described as possibly promoting myocardial infarction and pulmonary thromboembolism [5]. Septic emboli can also cause cerebrovascular accidents. Another common etiology for cerebrovascular problems in patients with sepsis is vasculitis, resulting in arterial narrowing that has been reported in bacterial meningitis [14]. The development of cerebral infarctions appears to occur even weeks after initial recovery from pneumococcal meningitis [15].

The management of sepsis itself might also pose a cardiovascular threat to patients. Several antibiotics could potentially affect the development of CVEs, predominantly because of their effect on QT intervals. This has been mostly described for macrolides and fluoroquinolones.

Especially older adult patients with a history of cardiovascular disease are prone to QT prolongation [16].

In addition to this effect, some fluoroquinolones have been found to induce the expression of platelet-binding protein pblB that contributes to microvascular obstruction if excessively activated [10]. In contrast, it has been hypothesized that tetracyclines could be useful in preventing myocardial infarctions by inhibiting matrix metalloproteinase-2 [17].

Taken together, sepsis in general and pneumonia specifically have been repeatedly associated with CVE. Because of the identified mechanisms suggesting a direct relationship to pneumococcal pneumonia and IPD, it can reasonably be expected that the risk for CVE is increased in this etiologic subgroup of patients than in the previously described cohort in JAMA [4]. Although serotypes of *S. pneumoniae* have been associated with the occurrence of CVE [7], it is unclear how these relate to other risk factors contributing to CVE in these specific patients. Therefore, our aims were to verify what proportion of patients aged ≥45 years with IPD experienced CVEs within 1 year after infection and to investigate which factors contributed to this adverse outcome.

Methods

Study design

We performed an observational retrospective multicentered cohort study, including three general and one academic hospital in the east of the Netherlands: Rijnstate Hospital (in Arnhem), Canisius Wilhelmina Hospital (Nijmegen), Maasziekenhuis Pantein (Beugen), and the Radboud University Medical Center (Nijmegen). Together, these hospitals provide care for >800.000 inhabitants of their region. All patients with a proven *S. pneumoniae* bacteremia (by positive blood culture) admitted to any of the hospitals between January 01, 2012 and June 01, 2020, were included in the BACON (Bacteraemia Collection East Netherlands) study cohort. The non-applicability of the Medical Research Involving Human Subjects Act (WMO) to the study design was confirmed by the regional ethics committee and the study procedures were approved by the local ethics committee of each participating hospital.

Selection of participants

Patients aged ≥45 years on the day of blood culture collection were selected from the BACON study cohort. Given the rare nature of CVE in younger patients, we reasoned the mechanisms underlying these CVEs were likely to be different and, therefore, not part of this study. Patients with evidence of relevant (either infectious or cardiologic) medical examination or treatment in a non-participatory hospital or insufficiently complete medical files were excluded. Less than 2% of all patients met the exclusion criteria. The starting point of this cohort was a proven *S. pneumoniae* bacteremia, and no specific clinical manifestations were excluded.

Data collection

We designed an electronic case record form in the Castor electronic data capture environment to build a digital database for the BACON cohort without identifiable patient information. Existing clinical data were extracted from electronic patient records, which also included letters from primary care physicians. Positive blood cultures for pneumococcus, including susceptibility and serotype information, were found using laboratory information systems. Working as a team of three researchers to gather these data, regular discussion provided consensus on how to interpret our findings, ensuring comparable methods of data entry, as documented in an electronic case record form guidance document. This also avoided the need to exclude patients who were transferred between participatory hospitals, as the entire course of admission was clear to each researcher. A coding system clearly marked the distinction between researchers and hospitals.

Outcome measures

The primary outcome was the incidence of CVEs within 1 year after pneumococcal bacteremia, defined as both ST-elevation myocardial infarction and non-ST-elevation myocardial infarction, and unstable angina pectoris (taken together as ACS) and stroke, including both transient ischemic attacks and cerebrovascular attacks. Events were detected if documented in the electronic patient file.

Covariates

For an overview of the variables collected, please refer to Supplementary Methods 1. All laboratory values were measured at admission, with the exception of albumin and lipids (taken from a timeframe of 1.5 months before or after admission). Serotypes of the blood culture isolates were determined using the Quellung reaction and confirmed by genetic annotation of their genetic capsular loci using seroBA [18]. This information was available for 780 patients in this cohort (85%).

Information in the electronic patient files on out-patient mortality was updated with a national registry and, therefore, reliable.

Statistical analysis

Statistical analysis was performed using SPSS version 26 (IBM SPSS Statistics for Windows, Version 26.0). Baseline characteristics were compared between the participating hospitals using X^2 tests for proportions and one-way analysis of variance or Kruskal-Wallis tests for scale variables. Variables were compared between patient

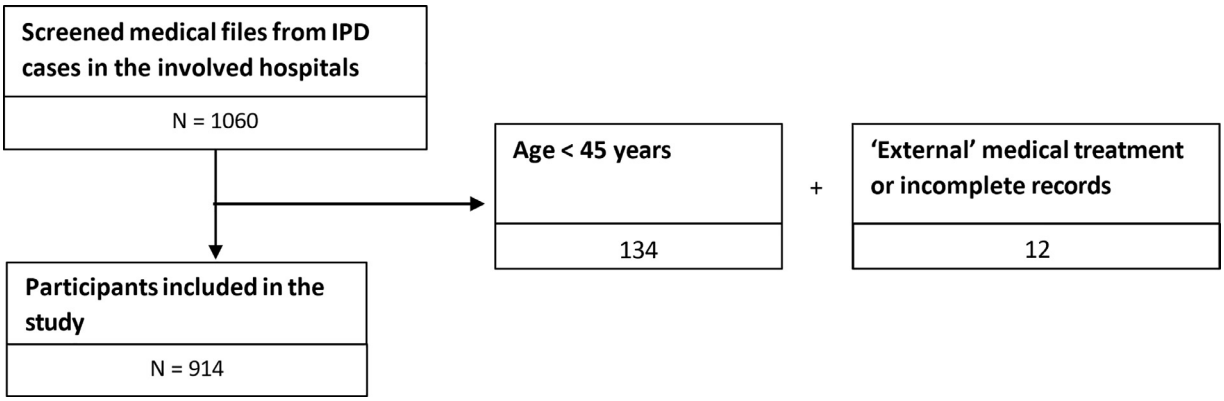

Figure 1. Inclusion flowchart of all consecutive positive blood cultures for *Streptococcus pneumoniae*. IPD, invasive pneumococcal disease.

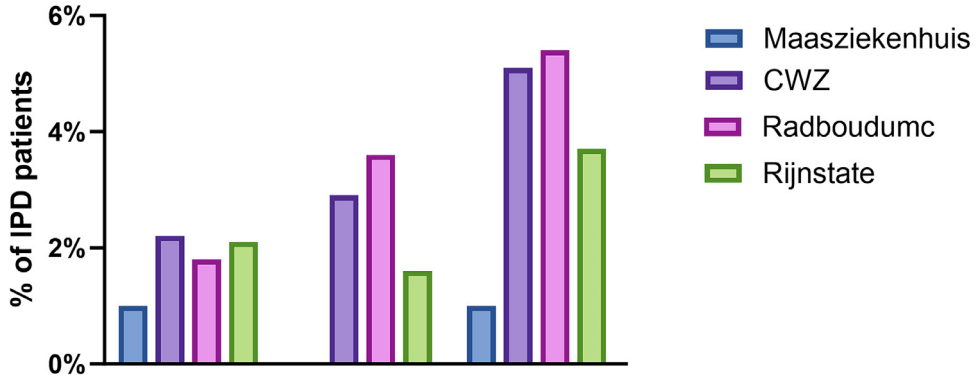

Figure 2. Cardiovascular events within 1 year after IPD, per hospital. IPD, invasive pneumococcal disease.

categories with and without CVEs and statistically tested using X^2 tests, Fisher's exact tests, or (non-parametric) t-tests for independent samples as appropriate for their distribution. Univariate analysis was used to compare quantitative variables between patients with and without CVE. We performed a binary logistic regression (method: enter) to model ACS and stroke separately and for a subgroup of patients aged <70 years. Covariates to include in the regression model were based on biologic plausibility and a significant *P*-value in the univariate analysis. Variables with >50% missing values were excluded from regression analysis. All statistical tests were performed in a two-sided manner, and a *P*-value <0.05 was considered statistically significant.

Results

From the complete BACON cohort, including all consecutive patients who experienced pneumococcal bacteremia, as proven by a positive blood culture, 914 out of 1,060 participants met the eligibility criteria (see Figure 1). The median age at admission was 70 years, 53.0% (n = 484) was male, and the majority (83%) was diagnosed with pneumonia. Of all patients, 39.2% (n = 358) had a history of cardiovascular disease and 11.1% (n = 102) had experienced at least one cerebrovascular event in their past. During 1 year follow-up, the in-hospital mortality was 12.0% (n = 110) and out-of-hospital mortality was 8.9% (n = 81). One participant was diagnosed with a SARS-CoV-2 co-infection (data not shown). Other baseline characteristics are listed in Table 1.

Occurrence of cardiovascular events

In a follow-up period of 1 year, 38 patients (4.2%) experienced a CVE (Figure 2).

The occurence of either ACS or stroke was reported in 18 (2.0%) and 20 (2.2%) cases, respectively. No profound differences in the occurrence of either event were seen across the participating hospitals ($P = 0.761$). ACS developed almost solely within 12 days after admission (Figure 3). The cumulative number of patients that were diagnosed with stroke 30 days after admission was nine (45%), at half a year was 13 (65%), and at 1 year was 20 (100%). Serotype distribution for patients with and without any CVE is shown in Supplementary Figure 1.

Predictors of acute coronary syndromes

In univariate analysis, the development of ACS was significantly associated with baseline variables alcohol abuse ($P = 0.009$), male sex ($P = 0.033$), and use of ADP-receptor antagonists ($P = 0.023$). In addition, patients who later developed ACS more often presented with chest pain ($P = 0.049$), had higher disease severity scores ($P = 0.003$) and serum creatinine levels ($P = 0.029$), and pneumococcal serotype 19A was significantly more abundant compared with those without ACS ($P = 0.040$). Age, smoking, and a history of other medical conditions were not significantly different between patients who developed ACS and those who did not (Supplementary Table 1). After regression analysis, only alcohol abuse contributed independently to the development of ACS (odds ratio [OR] = 3.8, 95% confidence interval [CI] 1.11-13.30) (Table 2). In addition, 6.5% of patients with reported alcohol abuse developed ACS, whereas 1.6% in the group with reported non-abuse. There was a trend for the systemic inflammatory response syndrome (SIRS) score to be positively associated with the risk for ACS: 1.3% (11/817) patients with a score <4 compared with 7.7% (7/91) for a 4-point score ($P < 0.0001$).

Table 1
Baseline characteristics.

No. (%)	Overall (n = 914)	Maasziekenhuis (n = 101)	CWZ (n = 272)	Radboudumc (n = 167)	Rijnstate (n = 374)
Included during COVID-19 pandemic[a]	*19 (2.1%)*	*1 (1.0%)*	*6 (2.2%)*	*2 (1.2%)*	*10 (2.7%)*
Demographics					
Age, years (mean, SD)	70 (11)	70 (11)	72 (11)	68 (10)	70 (11)
Male	484 (53.0%)	57 (56.4%)	148 (54.4%)	87 (52.1%)	192 (51.3%)
Smoking (current)	183 (20.0%)	20 (19.8%)	63 (23.2%)	34 (20.4%)	66 (17.6%)
Smoking (former)	238 (26.0%)	23 (22.8%)	119 (43.8%)	44 (26.3%)	52 (13.9%)
Alcohol abuse	62 (6.8%)	9 (8.9%)	16 (5.9%)	12 (7.2%)	25 (6.7%)
Body mass index (median, interquartile range) *(37% missing)*	25.2 (14-37)	25.6 (19-43)	26.6 (13-42)	24.5 (16-36)	25.1 (15-36)
Medical history					
Cardiovascular disease	358 (39.2%)	45 (44.6%)	134 (49.3%)	76 (45.5%)	103 (27.5%)
Congestive heart failure	201 (22.0%)	17 (16.8%)	106 (39.0%)	33 (19.8%)	45 (12.0%)
Cerebrovascular disease	104 (11.4%)	11 (10.9%)	39 (14.3%)	10 (6.0%)	44 (11.8%)
Hypertension	344 (37.6%)	34 (33.7%)	123 (45.2%)	60 (35.9%)	127 (34.0%)
Diabetes II	189 (20.7%)	19 (18.8%)	71 (26.1%)	23 (13.8%)	76 (20.3%)
Diabetes I	9 (1.0%)	0 (0.0%)	2 (0.7%)	5 (3.0%)	2 (0.5%)
Immunocompromised - limited	96 (10.5%)	0 (0.0%)	33 (12.1%)	10 (6.0%)	53 (14.2%)
Immunocompromised - severe	123 (13.5%)	10 (9.9%)	44 (16.2%)	42 (25.1%)	27 (7.2%)
Renal disease	105 (11.5%)	2 (2.0%)	45 (16.5%)	16 (9.6%)	42 (11.2%)
Chronic usage anticoagulants					
Aspirin	209 (22.9%)	24 (23.8%)	79 (29.0%)	38 (22.8%)	68 (18.2%)
ADP-receptor antagonists	46 (5.0%)	6 (5.9%)	18 (6.6%)	4 (2.4%)	18 (4.8%)
Vitamin K-antagonists and DOACs	177 (19.4%)	22 (21.8%)	62 (22.8%)	32 (19.2%)	61 (16.3%)
Other	6 (0.7%)	0 (0.0%)	1 (0.4%)	3 (1.8%)	2 (0.5%)
Usage of statins	306 (33.5%)	31 (30.7%)	118 (43.4%)	49 (29.3%)	108 (28.9%)
Diagnosis					
Pneumonia	757 (82.8%)	83 (82.2%)	233 (85.7%)	124 (74.3%)	317 (84.8%)
Meningitis	63 (6.9%)	6 (5.9%)	12 (4.4%)	14 (8.4%)	31 (8.3%)
Arthritis	34 (3.7%)	3 (3.0%)	9 (3.7%)	6 (3.6%)	16 (4.3%)
Endocarditis	11 (1.2%)	2 (2.0%)	1 (0.4%)	4 (2.4%)	4 (1.1%)
Severity scores (mean)					
SIRS score	2.5	2.4	2.5	2.4	3.6
qSOFA	0.9	0.8	0.7	0.9	0.9
CURB-65 (within pneumonia patients)	2.0	1.8	2.1	1.8	2.2

[a] In the Netherlands, the first COVID-19 case was reported on 27-02-2020.
One-way analysis of variance was used to compare means of normally distributed scale values; Kruskal-Wallis was used to compare medians. Proportions are compared using chi-square tests.
BMI, body mass index; DOAC, direct oral anticoagulants; IQR, interquartile range; qSOFA, quick sequential organ failure assessment.

Table 2
Logistic regression coefficients of factors potentially predictive of cardiovascular events in patients with IPD (ACS upper half; Stroke lower half).

Acute coronary syndrome model Patients included: 897/914; Cases 18/18	B	Std. Error	Sig.	Odds ratio (95% confidence interval)
Alcohol abuse	1.345	0.634	.034*	3.840 (1.108-13.303)
SIRS score	0.525	0.298	.078	1.691 (0.942-3.033)
Male sex	0.970	0.585	.097	2.637 (0.838-8.299)
ADP-receptor antagonist use	1.118	0.713	.117	3.058 (0.756-12.367)
Chest pain	0.784	0.502	.119	2.190 (0.818-5.860)
Serotype 7F	1.094	0.703	.120	2.986 (0.752-11.854)
Serotype 19A	0.852	0.644	.186	2.344 (0.663-8.290)
Serum creatinine	0.002	0.002	.193	1.002 (0.999-1.005)
Serotype 8	-1.367	1.064	.199	0.255 (0.032-2.051)
Nagelkerke R^2: 0.168				
Input variables: male sex, alcohol abuse, ADP-receptor antagonists, serum creatinine, SIRS score, chest pain at admission, serotype 7, 8 and 19A. Method = enter.				
Stroke model Patients included: 893/914; Cases 19/20	B	Std. Error	Sig.	Odds ratio (95% confidence interval)
Temperature ≥39.5 °C	1.137	0.507	0.025*	3.117 (1.154-8.423)
Serotype 22F	1.207	0.676	0.074	3.344 (0.889-12.575)
Headache	0.692	0.658	0.293	1.998 (0.550-7.259)
Nuchal rigidity	1.124	1.100	0.307	3.076 (0.356-26.579)
Serum creatinine	-0.003	0.004	0.457	0.997 (0.989-1.005)
Meningitis diagnosis	-0.124	1.036	0.905	0.883 (0.116-6.731)
Nagelkerke R^2: 0.091				

Input variables: headache, nuchal rigidity, temperature >39.5 °C, serum creatinine, meningitis diagnosis, serotype 22F. Method = enter.
ACS, acute coronary syndrome; ADP, adenosine diphosphate; IPD, invasive pneumococcal

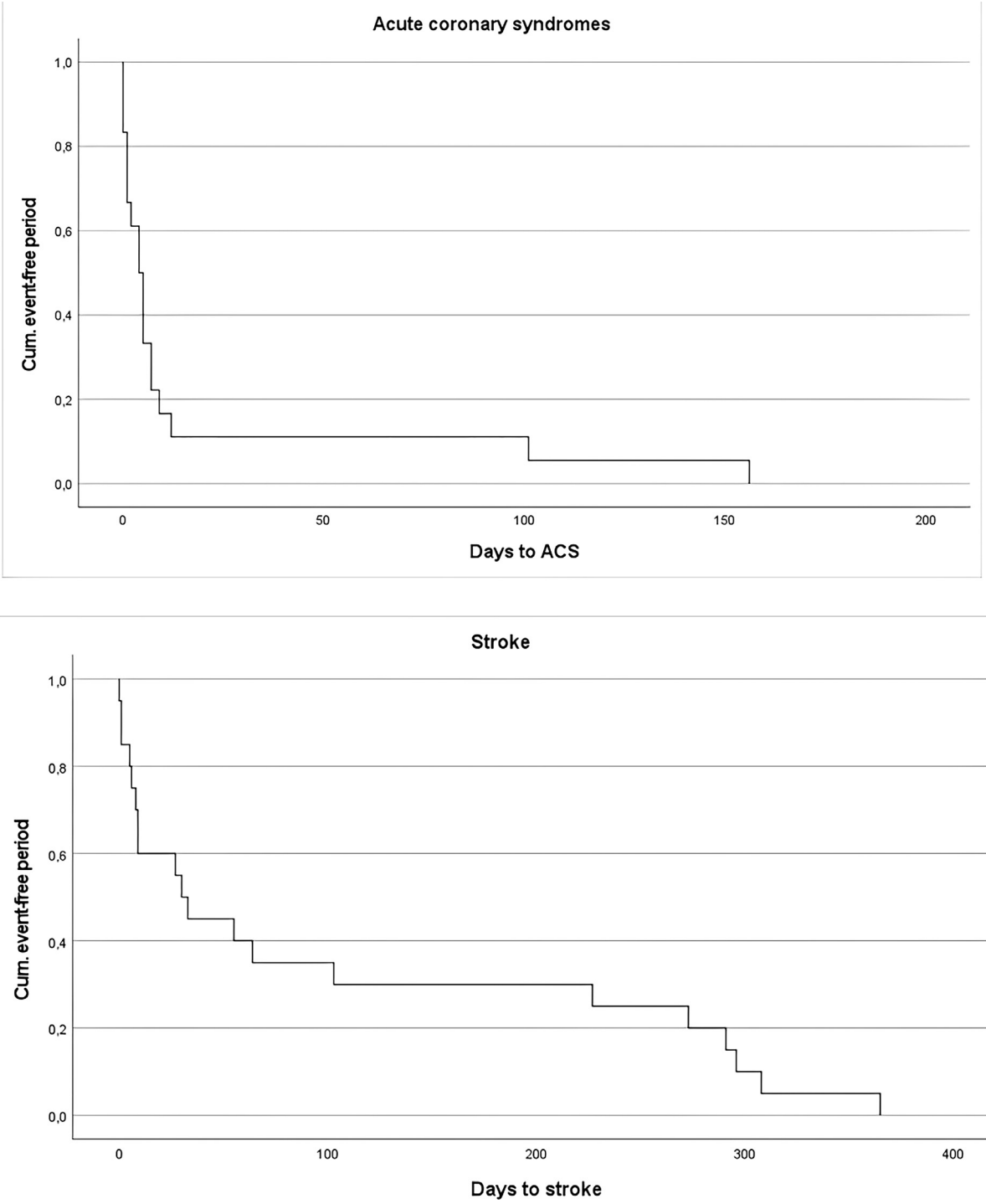

Figure 3. Time-to-event analysis of ACS and stroke. ACS, acute coronary syndrome.

Predictors of stroke

In univariate analysis, patients who developed stroke after IPD had more often been diagnosed with meningitis ($P = 0.019$) and complained of a headache at admission ($P = 0.047$). On average, they had lower serum creatinine ($P = 0.003$) and higher temperature ($P = 0.026$) compared with patients with IPD who did not experience stroke (Supplementary Table 1). Of patients diagnosed with meningitis, 6.3% developed stroke compared with 1.9% in patients with IPD with a different clinical diagnosis, but meningitis did not prove to be the best clinical predictor. The only independent predictor of stroke was a body temperature >39.5 °C at admission (OR = 3.117 [1.15-8.42]; Table 2), with 5.4% stroke among patients with high fever compared with 1.5% in those without ($P = 0.002$; Figure 4). Of note, patients with meningitis had a higher fever on average compared with IPD patients without meningitis (Supplementary Figure 2).

Subgroup analysis: cardiovascular event in patients aged <70 years

A total of 468 of 914 included patients were younger than 70 years at the time of infection (51.2%) and together, comprised

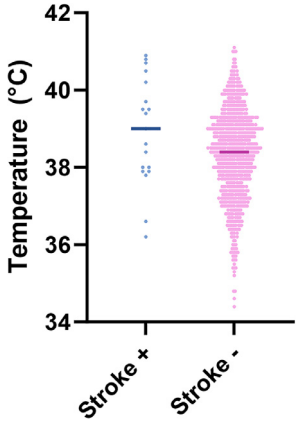

Figure 4. Body temperatures at admission in patients with and without stroke development. Depicted median values.

six cases of ACS and 10 cases of stroke. In this subgroup, specific serotypes were the primary independent predictors of CVE: serotype 7F for ACS (OR 15.733, 95% CI 1.81-136.63) and serotype 22F for stroke (OR 7.320 [1.19-44.90]) (Supplementary Table 2).

Discussion

In this study, in 4.2% of patients with IPD, a CVE was reported within 1 year after admission. Alcohol abuse was the sole independent predictor for ACS, whereas high fever was for stroke. Pneumococcal serotypes were pronounced predictors for CVE in younger adult patients. We found no evidence that the choice of antibiotic treatment contributes to the development of CVE.

We consider our large cohort of patients with broad inclusion criteria and spanning four hospitals a representative group of patients with IPD in the Netherlands. This cohort predominantly consists of patients with pneumococcal pneumonia, which is the most common clinical manifestation of IPD in the Netherlands. In our analyses, unlike most previous studies, we have adjusted for a multitude of clinical variables, including antibiotic treatment and disease severity scores. Although we have meticulously scanned all available information in the electronic patient files, we cannot rule out having missed a diagnosis of CVE. This mainly pertains to patients who died at home after they were discharged. Cases of stroke were still regularly reported after discharge, but it is likely there are missed CVEs in this setting where late ACS may have contributed to the 8.9% out-of-hospital mortality. This makes our ACS analyses primarily valid for early postinfectious events. The chances of being treated for CVE in a non-participatory hospital without reporting and thus missing the events were negligible, as the four hospitals involved are the main medical centers in the study area.

Although alcohol abuse is a well-established risk factor for IPD, we identified it as an independent predictor for ACS during IPD. The predisposing effect of alcohol abuse on pneumococcal infections has been extensively studied in both clinical and *in vitro* studies. Alcohol abuse may favor microaspiration, interact with pneumococcal virulence factors in a way that facilitates infection, hamper hepatic clearance, and suppress both the innate and adaptive immune system [19,20]. In addition, infection with *S. pneumoniae* is more frequent in CAP patients with alcohol abuse compared with those without [20]. Alcohol abuse has also been reported to be associated with a higher mortality in both patients with CAP [21,22] and those with IPD [19], although it is unclear whether this was mediated by CVEs. Although the protective effects of moderate consumption of alcohol on cardiovascular disease are still much debated, excessive consumption is a known risk factor for ACS [23]. Previous authors reported a higher number of patients with IPD complaining of chest pain among patients with a history of alcohol abuse, but whether a proportion of these complaints could be attributed to ACS remains uncertain [21]. As alcohol abuse is still under-reported [23], its contribution to pneumococcal-induced CVE might be even greater than can be deduced from our study.

The risk of ACS was the highest within the first 12 days after admission for IPD. This is consistent with previous studies describing the relation between infectious disease and vascular events as most marked within the first few days after infections [24]. The findings of Ramirez et al. [25], who described the presence of myocardial infarction in a significant number of patients with severe CAP while still being hospitalized, also confirm this. It has been reported in patients with pneumococcal pneumonia that the occurrence of a new cardiac event was often unrecognized during hospital stay [12]. It is not inconceivable that this happened in our cohort as well, since various patients with IPD presented with chest pain at admission but got diagnosed with an ACS days later. As the average age of patients experiencing ACS in our study was 72 years old, attention should be paid to an atypical presentation of retrosternal pain, and careful consideration is required before attributing symptoms to the concurrent infectious disease rather than a coronary problem [25].

It is plausible that disease severity contributed to early ACS in patients with IPD because sepsis comes with a systemic inflammatory response that affects endothelial function and destabilizes atherosclerotic plaques, in combination with an increased hemodynamic demand. Although we used the SIRS score and the quick sequential organ failure assesment (qSOFA) score as these are valid metrics for the entire adult IPD population, previous research described the same relation between severity and ACS for subpopulations using the confusion, urea, respiratory rate, blood pressure (and age >65) (CURB-65), pneumonia severity index (PSI), and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores [7]. Although the association between pre-existing cardiovascular disease and the development of ACS in our cohort was not statistically significant, the marked difference between both groups suggests a relevant factor, nevertheless, as has been described previously by many [26].

The contribution of meningitis to the development of stroke is a known causal factor, with Schut et al. [27] reporting stroke in 36% of a pneumococcal meningitis cohort. The authors identify older age and an immunocompromised state as additional risk factors and describe more frequent fever, a lower cerebrospinal fluid white cell count, and a higher erythrocyte sedimentation rate in patients with stroke compared with those without. A meningitis diagnosis was a univariate predictor in our study as well. However, the sole independent predictor of stroke was a body temperature ≥39.5 °C at admission. Although fever is a common symptom of thromboembolic events, the origin of such high fever could also reflect high levels of acute phase proteins like procoagulant fibrinogen that pose a risk for stroke. Unfortunately, very few disseminated intravascular coagulation-associated markers have been measured in our population, and it would be advisable to do so in future prospective studies. In addition, it is possible that high fever had been merely an indication for cerebral imaging in our study population instead of an actual risk factor for stroke. This could best be partitioned by a prospective series of cerebral imaging in patients with IPD suspected of neurologic involvement with and without the presence of high fever. Finally, within patients who used a vitamin K antagonist, stroke was related to a relatively low INR level.

To consider the direct effect of the causative agent *S. pneumoniae* on CVE, we compared our findings to the previously described study by Corrales-Medina et al. on CAP from any etiology [4]. They

found CVEs after pneumonia in 15% and 3% (in two distinct cohorts, aged ≥65 years and 45-64 years) of their participants. An increased sensitivity for CVE in the JAMA study could be an explanation for the difference in our results, as differences in patient characteristics do not adequately explain the differences in outcomes, and our study could not include study visits, death certificates, and telephone follow-up to identify CVE. In conclusion, from this comparison we cannot infer whether pneumococcal etiology is an independent risk factor for CVE.

As infection by different pneumococcal serotypes can lead to very different clinical phenotypes, it is interesting to look at the course of disease and occurrence of CVE for the distinct types. The paper by Africano et al. identified an independent association between serotype 3 and 9N and CVE in Colombian patients with IPD [7]. The hyperencapsulated type 3 is more resistant to phagocytosis and antibody responses, which could lead to more severe disease and, therefore, more cardiovascular damage. Although serotype 3 was isolated in several cases in our cohort, we only found a significant relation between the development of ACS and serotype 19A. As described previously, serotype 19A is related to several clonal complexes that were associated with a higher incidence of CVE [28]. The authors suggested that genotype and not serotype might have been the most relevant factors contributing to the occurrence of CVE. Notably, the influence of serotype was significantly stronger in the younger half of our cohort. Both type 7F and 22F were independent predictors of CVE, suggesting that different mechanisms are at play in different subpopulations. Finally, Shenoy et al. [29] concluded that not all pneumococci seemed capable of cardiac involvement and reported cardiac damage only after high-grade bacteremia in mice caused by serotypes 2, 3, 4, and 6A. Although the most relevant serotypes from our cohort were not included in this study (19A, 22F, 7F, and 8), intrinsic bacterial density is a factor to consider as well.

As there are over 100 pneumococcal serotypes currently known, even a cohort including 900 individuals will be underpowered to capture all serotype-specific effects. Despite this, we were able to identify serotypes that were more or less frequent in patients with CVE with *P*-values that fluctuate approximately 0.1. As serotypes are known proxies of other risk factors like disease severity, their relative importance in a prediction model does not prove causality [30]. To overcome this, future epidemiologic studies would do well to aggregate their cohorts based on serotypes, in particular for relatively younger patients. Because of the current vaccine coverage and novel compositions, it is especially important to monitor the different serotypes.

It is important to emphasize that although our inclusion period spanned a period during the COVID-19 pandemic, the patients in our cohort were IPD patients without SARS-CoV-2 co-infections. The rate of CVEs in a specific COVID-19 patient population has been reported to be higher (5-20%), likely because of the overlap in risk factors for both COVID-19 infection and CVEs and the additional effects of COVID-19 on coagulation [31,32]. Bacterial co-infections with *S. pneumoniae* in patients with COVID-19 are uncommon, though reported [33]. In the Netherlands, the instant drop in pneumococcal diagnoses during the first months of the pandemic might be explained by the decreased transmission of respiratory viruses or reduced testing [34]. Medical care such as antibiotics has been given more often in an ambulant setting, resulting in an unreliable context to study IPD during this time.

Conclusion

We observed that CVEs in patients with IPD are not uncommon. Special attention should be paid to the sometimes atypically presented ACS in the first 2 weeks after admission and the possibility of stroke should be considered in patients with fever ≥39.5 °C. Causal effects of specific pneumococcal serotypes remain an important focus for further research, especially in younger adult IPD populations.

Declarations of competing interest

The authors have no competing interests to declare.

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Author contributions

ED, MS, and KD collected the study data. ED wrote the first draft. SV, KD, CS, HW, MdJ, and AC revised the manuscript. AC supervised the work. All authors had access to the data and agree with the decision to submit the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2024.107185.

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