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Risk of stroke or myocardial infarction hospitalisation following hospitalisation for community-acquired pneumonia in Portugal: a self-controlled case series study

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ABSTRACT

Objectives We aimed to assess the risk of cardiovascular hospitalisations (stroke or myocardial infarction (MI)) following a community-acquired pneumonia (CAP) hospitalisation in a large Portuguese administrative dataset.

Design Self-controlled case series study.

Setting We used hospitalisation data from National Health Service hospitals across Portugal between 2010 and 2018.

Participants Adults hospitalised for both CAP and stroke/MI in Portugal during the 2010-2018 period (n=13 494, of which 10 400 with stroke and 3094 with MI).

Primary and secondary outcome measures We considered CAP hospitalisation as the exposure (14-, 28- and 91-day exposure periods) and acute cardiovascular (stroke or MI) hospitalisations as the outcome. Incidence rate ratios (IRR) were computed using a conditional Poisson regression (overall and by sex and age subgroups).

Results Patients were mostly male and above 75 years. Stroke/MI hospitalisation incidence was higher following CAP, compared with the baseline period. Largest differences were observed in the 14-day period after discharge (IRR for stroke: 2.55, 95% CI: 2.33–2.80; IRR for MI: 3.23, 2.78–3.75), compared with the 28-day (IRR for stroke: 2.06, 1.92–2.22; IRR for MI: 2.62, 2.32–2.95) and 91-day periods (IRR for stroke: 1.37, 1.30–1.44; IRR for MI: 1.75, 1.60–1.91). A similar trend was observed for sex and age subgroups.

Conclusions Our study shows an increased risk of stroke/MI for CAP patients, particularly during the first 2 weeks after being discharged. Effective postdischarge monitoring and follow-up, combined with efforts to prevent CAP occurrence, could improve patient outcomes.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Our study used the self-controlled case series method, where each participant serves as their own control, consequently adjusting for fixed individual covariates.
⇒ We studied a large sample using hospitalisation data from a national-level database over an 8-year period.
⇒ Some cardiovascular events may not have been captured by our study (eg, only the first episode after the CAP hospitalisation was included).

BACKGROUND

Cardiovascular diseases are a leading cause of mortality worldwide. According to the WHO, over 80% of deaths related to those diseases are attributed to heart attack and stroke.[1]

Several studies have highlighted the association between community-acquired pneumonia (CAP) and cardiovascular diseases.[2–6] The association between respiratory infections and cardiovascular disease is linked to several mechanisms, including systemic inflammation, platelet activation and direct pathogen-mediated damage. Inflammation during respiratory infections can lead to endothelial dysfunction and increased coagulation, thereby raising the risk of cardiovascular events. Platelet activation can create a prothrombotic state, heightening the likelihood of myocardial infarction (MI) or stroke. Additionally, pathogens such as *Streptococcus pneumoniae* can directly impact the cardiovascular system, contributing to conditions like myocarditis and other complications.[7 8]

Previous studies have shown increased risk of cardiovascular events, including in younger adults, following hospitalisation for respiratory infections such as pneumonia.[2–4] Meier *et al* reported a three times increase in MI risk right after infection, while Clayton *et al* found a nearly fourfold rise in both MI and stroke hospitalisations.[2–4] Similarly, Pak *et al* reported a strong association between lower respiratory tract infections and an elevated risk of cardiovascular events, with a relative incidence ratio of 4.85 (95% CI 2.44 to 9.67)

for MI and 4.94 (1.12–21.78) for stroke during the first 2 weeks after infection.[9] In a study conducted in the USA, 12% of CAP patients were readmitted within 30 days, often due to new or worsening cardiac, pulmonary or neurological conditions.[10]

While these studies provide important insights, most rely on conventional study designs, such as cohort or case-control designs, which can be limited by confounding. The self-controlled case series (SCCS) methodology, which was used for example by Pak *et al*,[9] offers an alternative approach, with a case-only design, where each participant serves as their own control, consequently adjusting for fixed individual covariates, such as sex, comorbidities or socioeconomic status.[11]

In this study, we aimed to assess the risk of cardiovascular hospitalisations (stroke or MI) following a CAP hospitalisation. Our study adds to the literature by using a SCCS methodology to provide a better understanding of the risk of cardiovascular events following pneumonia in a large population in Portugal.

METHODS

Study design

We conducted an SCCS, using a within-person analysis comparing the risk of having a stroke/MI hospitalisation following a CAP hospitalisation with the risk in the baseline period. We considered CAP hospitalisation as exposure and acute cardiovascular (stroke or MI) hospitalisations as the outcome. Similar to the approach used by others,[9 12] relevant periods were defined as follows (figure 1):

i. Observation period: This period represents the total follow-up period.[12] Each patient was followed for a total of 2 years, starting 1 year prior to the CAP discharge date. This period included both exposure and baseline periods.
ii. Exposure period: This period corresponds to the period when exposure can have a potential effect.[12] The exposure period started with a CAP discharge, and three different durations were considered (14, 28 and 91 days postdischarge) to analyse possible differences in the direction and magnitude of the effect.
iii. Baseline period: This period serves as the control for comparison with the exposure period.[12] We considered as the baseline period 1 year (52 weeks) before the CAP discharge and 50, 48 or 39 weeks after the exposure period ends (depending on the duration of the exposure period).

Data sources

Data regarding public hospital discharges were provided by the Portuguese Health System Central Administration, which collates data on hospital discharges from the National Health Service hospitals (*Base de Dados de Morbilidade Hospitalar*) for the 2010–2018 period. Data included demographics (sex and age), main and additional diagnoses (coded with International Classification of Diseases (ICD) – 9th version – Clinical Modification or with International Classification of Diseases – 10th version – Clinical Modification codes), whether diagnoses were present on admission (flag recorded after 2013), length of stay and dates of admission and discharge. Access to data on hospitalisations is subject to request and approval by the Portuguese Central Administration of the Health System (Administração Central do Sistema de Saúde). The study was approved by the NOVA National School of Public Health Ethics Committee (ref. 22/2022).

Patient and public involvement statement

None.

Study population

We started by identifying hospitalisations of adults (≥18 years old) discharged between 2010 and 2018 from

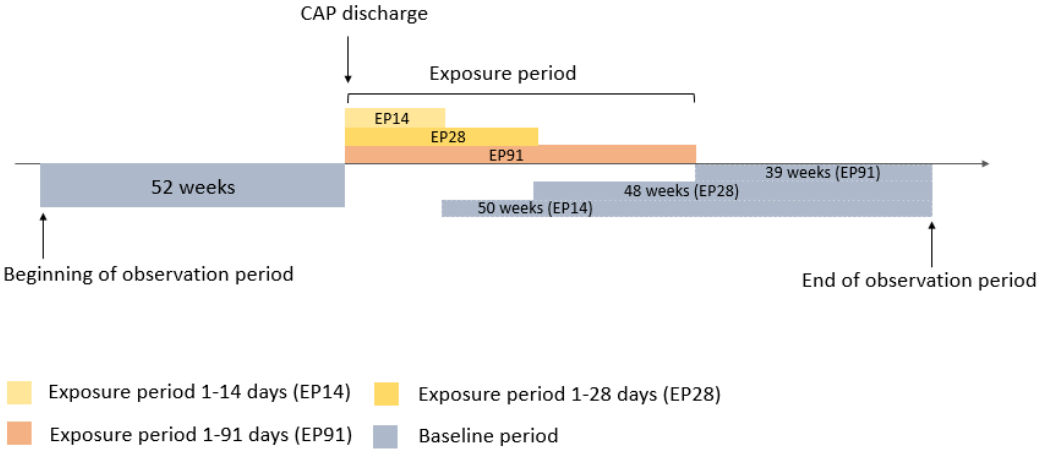

Figure 1 Observation, exposure and baseline periods for self-controlled case series study (main analysis). The sensitivity analysis considered the same events as the main analysis, but the exposure period was defined from the admission date (not discharge). CAP, community-acquired pneumonia.

Portuguese mainland public hospitals with diagnoses of CAP or stroke/MI. The main and secondary diagnoses using ICD codes were considered (online supplemental tables S1 and S2). We first identified patients who had hospitalisations for both CAP and stroke/MI, since in SCCS, all participants must have experienced the event (stroke/MI).

The exclusion criteria used to select patients or hospitalisations for each patient were the following: (1) hospitalisations of patients with codes for stroke/MI in CAP hospitalisation given the limitations to identify the order of events, (2) hospitalisations that occurred outside the observation period and (3) any hospitalisations for CAP or stroke/MI other than the first occurrence. The flowchart for the selection of the study participants is presented in online supplemental figure S1.

Variables

Demographic variables included sex and age groups (18–29, 30–49, 50–64, 65–74, 75–84 and ≥85 years). Comorbidities were studied using the Elixhauser Comorbidity Index[13] and selected based on previous studies (atrial fibrillation (AF), chronic pulmonary disease, congestive heart failure, diabetes complicated and uncomplicated, HIV/AIDS, liver disease, peripheral vascular disease, renal chronic disease, rheumatoid arthritis/collagen vascular diseases, solid tumour without metastases and metastatic tumour).[14–18] ICD codes considered for comorbidities are shown in online supplemental table S3. We also studied the length of stay. Demographic, comorbidity and length of stay data were collected from the CAP hospitalisation included.

Outcome variables were stroke/MI hospitalisations, assessed during the baseline and exposure periods.

Statistical analysis

Patients with stroke/MI hospitalisation and CAP hospitalisation exposure were described according to their sex, age, comorbidities and length of stay. The analysis included only participants with complete data.

To analyse the risk of a stroke/MI hospitalisation following a CAP hospitalisation, we employed a conditional Poisson regression, using the clogit function in R, which is part of the survival package. Incidence rate ratios (IRRs) and corresponding 95% CIs were estimated. We also estimated IRR per sex (male/female) and age subgroups (18–64 years/65 years or older) to explore potential differences between strata. To examine the potential impact of the risk exposure period used in the SCCS, a sensitivity analysis was conducted. For this sensitivity analysis, we considered the same risk periods (14, 28 and 91 days) for rehospitalisation, but starting from the admission date.

The statistical analyses were performed using R 4.1.1.[19] Descriptive analysis was conducted using the dplyr R package.[20] An SCCS was performed using biostat3,[21] survival[22] packages along with publicly available code.[23]

Table 1 Baseline characteristics of patients with community-acquired pneumonia (CAP) and stroke/MI during the 2010–2018 observation period

Baseline characteristics	Participants who had hospitalisations for stroke and CAP	Participants who had hospitalisations for MI and CAP
Number of patients	10 400	3094
Sex		
Male	5388 (51.81%)	1712 (55.33%)
Female	5012 (48.19%)	1382 (44.68%)
Age		
18–29	12 (0.12%)	2 (0.06%)
30–49	120 (1.15%)	53 (1.71%)
50–64	650 (6.25%)	320 (10.34%)
65–74	1468 (14.11%)	566 (18.29%)
75–84	4268 (41.04%)	1147 (37.07%)
≥85	3882 (37.33%)	1006 (32.51%)
Mean (SD)	80.26 (10.01)	78.24 (10.96)
Comorbidities		
Atrial fibrillation	3571 (34.34%)	894 (28.89%)
Chronic pulmonary disease	1408 (13.54%)	608 (19.65%)
Congestive heart failure	2977 (28.63%)	1429 (46.19%)
Diabetes	3289 (31.63%)	1268 (40.98%)
HIV/AIDS	23 (0.22%)	8 (0.26%)
Liver disease	355 (3.41%)	87 (2.81%)
Peripheral vascular disorders	451 (4.34%)	215 (6.95%)
Renal chronic disease	1885 (18.13%)	958 (30.96%)
Rheumatoid arthritis/collagen vascular diseases	140 (1.35%)	59 (1.91%)
Solid tumour without metastasis and Metastatic cancer	652 (6.27%)	171 (5.53%)
Length of hospital stay in days (median and IQR)	9 (6, 14)	9 (6, 14)

CAP, community-acquired pneumonia; MI, myocardial infarction.

RESULTS

In the 2010–2018 period, we identified 26 988 hospitalisations corresponding to 13 494 patients with a CAP and a stroke/MI hospitalisation during the observation period (online supplemental figure S1). Of these, 10 400 patients were included in the stroke subgroup and 3049 in the MI subgroup (table 1). Most patients were male (stroke: 51.8% and MI: 55.3%). Patients were mostly aged

Table 2 Incidence rate ratios for stroke/myocardial infarction (MI) hospitalisation following community-acquired pneumonia (CAP) hospitalisation (using discharge date as the start of the exposure period)

Outcome and periods (base analysis)	Number of patients	Incidence rate ratio (95% CI)
Stroke hospitalisation during		
Exposure period defined as 1–14 days		
Exposure period	493	2.55 (2.33 to 2.80)
Baseline period	9907	
Exposure period defined as 1–28 days		
Exposure period	788	2.06 (1.92 to 2.22)
Baseline period	9612	
Exposure period defined as 1–91 days		
Exposure period	1 691	1.37 (1.30 to 1.44)
Baseline period	8709	
MI hospitalisation during		
Exposure period defined as 1–14 days		
Exposure period	183	3.23 (2.78 to 3.75)
Baseline period	2911	
Exposure period defined as 1–28 days		
Exposure period	291	2.62 (2.32 to 2.95)
Baseline period	2803	
Exposure period defined as 1–91 days		
Exposure period	615	1.75 (1.60 to 1.91)
Baseline period	2479	

Note: Incidence rate ratio and 95% CI were calculated using the clogit function.
MI, myocardial infarction.

≥75 years in the stroke subgroup (75–84 years: 41.0% and ≥85 years: 37.3%) and the MI subgroup (75–84 years: 37.1% and ≥85 years: 32.5%). The most frequently recorded comorbidities were AF (stroke: 34.3% and MI: 28.9%), diabetes (stroke: 31.6% and MI: 41.0%), congestive heart failure (stroke: 28.6% and MI: 46.2%), chronic renal disease (stroke: 18.1% and MI: 31.0%) and chronic pulmonary disease (stroke: 13.5% and MI: 19.7%). The median of CAP hospital stay was 9 days for stroke and MI patients.

IRRs and CIs of stroke/MI hospitalisation following a CAP hospitalisation using discharge date as the start of the exposure are presented in table 2. During the initial 14-day exposure period, the incidence of stroke hospitalisations was 2.55 times (95% CI 2.33 to 2.80) the one of the baseline, being 3.23 times (95% CI 2.78 to 3.75) for MI hospitalisations. When the exposure period was extended to 28 days, the incidence of stroke hospitalisations was still higher than in the baseline period but decreased to 2.06 times (1.92–2.22) the incidence in the baseline; the incidence of MI hospitalisations also dropped to 2.62 times (2.32–2.95) the one of the baseline. By the 91-day exposure period, both types of hospitalisations were still higher than in the baseline period but lower than in shorter exposure periods (stroke: 1.37 (1.30–1.44) and MI: 1.75 (1.60–1.91)).

In the stratified IRR analysis by sex (male/female) and age subgroups (18–64 years/65 years or older), we observed a similar trend across groups, with the highest IRR observed in the initial days following discharge, then decreasing over time (table 3).

When the exposure period was defined from the admission date (sensitivity analysis), also excluding those that had stroke/MI and CAP in the same hospitalisation, there was an increased risk of stroke/MI hospitalisation after CAP hospitalisation across all periods (table 4). The risk was higher in the 28-day exposure period for both cardiovascular conditions (stroke: 1.47 (1.35–1.60) and MI: 2.09 (1.83–2.39)) compared with the 14- and 91-day exposure periods.

DISCUSSION

During the 2010–2018 period, 13 494 patients with CAP who experienced a cardiovascular (stroke/MI) hospitalisation were analysed. Most patients had a stroke, were older (≥75 years) and had multiple comorbidities. Stroke and MI incidence were higher following CAP, compared with the baseline period, especially in the 14-day period after discharge and decreasing afterwards. The same was observed for sex and age (above 65 years or not) subgroups.

Table 3 Incidence rate ratios for stroke/myocardial infarction (MI) hospitalisation following community-acquired pneumonia (CAP) hospitalisation discharge, per sex and age subgroups

Outcome and periods	Male	Female	18–64 years	≥65 years
Stroke hospitalisation during				
Exposure period defined as 1–14 days	2.33 (2.05–2.66)	2.80 (2.47–3.17)	3.43 (2.57–4.58)	2.48 (2.26–2.73)
Exposure period defined as 1–28 days	1.84 (1.66–2.05)	2.31 (2.09–2.55)	2.71 (2.14–3.43)	2.01 (1.86–2.17)
Exposure period defined as 1–91 days	1.23 (1.14–1.33)	1.52 (1.42–1.64)	1.90 (1.60–2.26)	1.33 (1.26–1.40)
MI hospitalisation during				
Exposure period defined as 1–14 days	3.02 (2.45–3.74)	3.50 (2.82–4.34)	3.83 (2.57–5.71)	3.15 (2.68–3.70)
Exposure period defined as 1–28 days	2.56 (2.17–3.02)	2.69 (2.25–3.21)	2.43 (1.70–3.48)	2.64 (2.32–3.00)
Exposure period defined as 1–91 days	1.64 (1.45–1.85)	1.89 (1.66–2.15)	1.83 (1.42–2.35)	1.74 (1.59–1.91)

Note: Incidence rate ratio (IRR) and 95% CI were calculated using the clogit function.
MI, myocardial infarction.

Our findings align with previous literature that highlights the association between respiratory infections and increased cardiovascular disease risk. Similar to our observation that the risk of cardiovascular disease is elevated after CAP, studies by Corrales-Medina *et al*, Pak *et al*, Clayton *et al* and Li *et al* reported an increased risk of cardiovascular disease following respiratory infections, particularly within the first months, with a gradual decline in risk over time.[3 4 9 24]

As previously described,[3 4 9] our analysis showed that the risk of stroke and MI was higher in the 14-day period after CAP hospitalisation and declined gradually afterwards. This higher risk may be due to the acute impact of pneumonia on the cardiovascular system, as discussed

Table 4 Sensitivity analysis: Incidence rate ratios for stroke/myocardial infarction (MI) hospitalisation following community-acquired pneumonia (CAP) hospitalisation (using admission date as the start of the exposure period)

Outcome and periods (sensitivity analysis)	Number of patients	Incidence rate ratio (95% CI)
Stroke hospitalisation during		
Exposure period defined as 1–14 days		
Exposure period	226	1.14 (1.00 to 1.30)
Baseline period	10 174	
Exposure period defined as 1–28 days		
Exposure period	574	1.47 (1.35 to 1.60)
Baseline period	9826	
Exposure period defined as 1–91 days		
Exposure period	1589	1.27 (1.21 to 1.34)
Baseline period	8811	
MI hospitalisation during		
Exposure period defined as 1–14 days		
Exposure period	110	1.90 (1.57 to 2.29)
Baseline period	2984	
Exposure period defined as 1–28 days		
Exposure period	237	2.09 (1.83 to 2.39)
Baseline period	2857	
Exposure period defined as 1–91 days		
Exposure period	618	1.76 (1.61 to 1.93)
Baseline period	2476	

Note: The sensitivity analysis considered the same events as the main analysis, but the exposure period was defined from the admission date (not discharge). Hospitalisations of patients with codes for stroke/MI and CAP were excluded given the limitations to identify the order of events. Incidence rate ratio and 95% CI were calculated using the clogit function.
MI, myocardial infarction.

in a literature review by Corrales-Medina *et al*.[25] AF is a known risk factor for stroke that may be triggered by CAP. We observed a high prevalence of AF in the individuals who experienced stroke and MI, which may partly contribute to the increased risk of cardiovascular events following CAP. The prolonged cardiovascular risk may be explained by a systemic inflammatory and prothrombotic state, even after clinical manifestation. Some studies showed that after CAP, some patients exhibited elevated levels of cytokines, such as IL-6 (interleukin-6), IL-10, IL-8 and IL-22, that remained increased weeks after the clinical recovery. In a study by Yende *et al*, high levels of IL-6 and IL-10 at hospital discharge following a CAP hospitalisation were associated with death due to cardiovascular disease over the following year.[26 27] Our results suggest the need for integrated health monitoring of patients recovering from CAP after they are discharged to reduce the risk of stroke/MI. Close monitoring of cardiovascular health is essential to prevent severe complications such as stroke or MI, especially in the first 2 weeks after CAP discharge. Implementing effective clinical follow-up strategies could also help improve patient outcomes by identifying potential cardiovascular risks early on. Pneumococcal vaccination might also protect against cardiovascular outcomes following pneumococcal CAP and should be reinforced.[28 29] In addition, influenza vaccination has also been described to possibly reduce cardiovascular events.[30] Finally, further studies are needed on the risk factors for cardiovascular events in CAP patients to define which patients should be prioritised for cardiovascular monitoring after CAP discharge. Several studies have highlighted factors such as pre-existing cardiovascular conditions, pneumonia severity and advanced age as key predictors of cardiovascular events.[28] Future studies may analyse separately stroke and MI and distinguish between ischaemic and haemorrhagic stroke, as this could be helpful to further understand the mechanisms behind CAP and cardiovascular disease association.

Our results are prior to the COVID-19 pandemic and may differ from the cardiovascular risk associated with CAP after the pandemic, specifically in terms of cardiovascular and thrombotic outcomes. COVID-19 infection has been shown to increase the risk of cardiovascular complications, regardless of age, sex or prior cardiovascular conditions.[31 32]

It is important to address the limitations of our study. First, patients with cardiovascular events during a CAP hospitalisation were not included in our analysis. This exclusion could potentially result in an underestimation of the effect of CAP, as it likely excludes episodes occurring shortly after infection. This hypothesis is also supported by the difference between our main and sensitivity analyses. Underestimation of increased risk in 28- and 90-day periods may also occur due to the inclusion of shorter post-CAP periods with increased risk in the baseline period (14 days; 14 and 28 days, respectively). Additionally, we focused exclusively on the first hospitalisation for each patient, which limits the understanding of potential patterns or outcomes associated with subsequent hospitalisations. Despite our conservative approach, we believe our results are still relevant to quantify this risk and better understand the link between CAP and cardiovascular events. Second, we cannot guarantee that patients were continuously monitored throughout the entire observation period, as we do not have complete information on utilisation of private healthcare facilities or patient deaths. While this can be a source of bias, we believe it is negligible, as it should apply to only a limited subgroup of patients as in previous studies.[9] Third, we only included CAP events of hospitalised patients. Our findings may not be generalisable to non-hospitalised patients. Fourth, we lacked data in specific years for the 'present on admission' flag (years 2010–2012), which may have led to an overestimation of the incidence rate since it was not possible to distinguish hospital-acquired pneumonia. However, a sensitivity analysis performed on a previous study with similar data indicates that it may have a minimal impact on our findings.[33] Fifth, AF was not included in the main analysis, as it was not possible to determine its exact onset. Nonetheless, we presented AF prevalence as part of our patients' characterisation. Finally, we were able to include data from 2010 to 2018, which precluded us from studying the pandemic period and afterwards.

CONCLUSION

Our study shows an increased risk of stroke/MI for CAP patients, particularly during the first 2 weeks after being discharged. Effective postdischarge monitoring and follow-up, combined with efforts to prevent CAP occurrence (eg, vaccination), have potential to improve patient outcomes.

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Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Access to data on hospitalisations is subject to request and approval by the Portuguese Central Administration of the Health System (ACSS, Administração Central do Sistema de Saúde, geral@acss.min-saude.pt).

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