Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editors-in-Chief

Hospitalizations, resource use and outcomes of acute pulmonary embolism in Germany during the Covid-19 pandemic

To the Editor:

Covid-19 infections are associated with a high prevalence of venous thromboembolism, particularly pulmonary embolism [1]. In this respect, it is with great interest that we have followed the discussion in this journal evolving around the emergence of different phenotypes of Covid-19-associated thromboembolic disease, i.e. acute pulmonary embolism vs pulmonary thrombosis, different phenotypes of in situ thrombosis and a rising incidence of hospitalizations for pulmonary embolism in England [2–5].

The Helios hospital group is the largest hospital network in Germany serving about 7% of the German population. We have established a continuous surveillance program to monitor and report the effects of the Covid-19 pandemic on hospital admissions, resource use and outcomes [6–10]. With this correspondence, we wish to complement this discussion by providing hospitalization, treatment and in-hospital outcome data for pulmonary embolism during the 2020 Covid-19 pandemic and a corresponding 2016–2019 control period.

We performed a retrospective analysis of claims data of Helios hospitals in Germany. Consecutive cases with a hospital admission between January 1 and December 15, 2020 (study period) were analyzed and compared to a corresponding period covering the same weeks in 2016–2019 (control period). Hospitalizations were selected based on the discharge diagnosis of pulmonary embolism (I26) according to the International Statistical Classification of Diseases and Related Health Problems [ICD-10-GM (German Modification)]. In-hospital treatments were defined according to the German procedure classification ("Operationen- und Prozedurenschlüssel", OPS) for intensive care (OPS 8-980, 8-98f or duration of intensive-care stay >0 days), mechanical ventilation (OPS 8-70x, 8-71x or duration of ventilation >0 h), thrombolytic therapy (OPS 8-836.78, 8-020.8), thrombectomy (OPS 5-380.42, 8-836.88) and inferior vena cava filter placement (OPS 8-839.1), and length of stay and in-hospital mortality were calculated. For the latter only completed hospitalizations were included, i.e. patients were discharged or died in hospital (exclusion of hospital transfers).

Crude rates for admissions and treatments were calculated by dividing the number of cumulative events by the number of days for each time period. Crude-rate ratios or odds ratios (OR) were calculated using Poisson mixed regression to model the number of hospitalizations and logistic mixed regression to model the proportions of treatments per period specifying hospitals as random factor, respectively. To identify admission trends over time, rolling crude-rate ratios were calculated for 12-week intervals with 11-week overlap resulting in one ratio every week. For the analysis of relative risk (RR), we used Poisson regression und calculated incidence rates with respect to the underlying population of inpatient cases. Patient characteristics were compared with ANOVA for numerical and Chi2 test for categorical variables. We report RR or OR (calculated by exponentiation of the regression coefficients) together with 95% confidence intervals (CI) and *P* values for the comparisons of different periods. For all tests, we apply a two-tailed 5% error criterion for significance.

This study was approved by the Ethics Committee at the Medical Faculty, Leipzig University (#490/20-ek). Due to the retrospective study of anonymized data, informed consent was not obtained.

There were 3699 cases with PE as primary and 6375 with PE as primary or secondary diagnosis out of 1,036,126 total hospitalizations in 2020 as opposed to 14,015 and 24,113 PE cases out of 4,648,771 hospitalization between 2016 and 2019 (Fig. 1).

Hospital admissions and new SARS-CoV-2 infections in Germany are depicted in Fig. 1. As previously reported for other emergent medical conditions, there was a hospitalization deficit coinciding with the 1st pandemic wave. Beginning with the 12-week interval May 6 – July 28, there was a stable surplus of hospital admissions in 2020. Standardized incidence rates of admissions during this surplus period (May 6 – December 15, 2020) are summarized in Table 1. Adjustment for age, sex and SARS-CoV-2 infection, made no significant difference to the direction or magnitude of the relative increase in admissions. Admissions were more frequent among those with SARS-CoV-2 infection.

In patients with a pulmonary embolism as primary diagnosis excluding 45 SARS-CoV-2 cases (1.8%), age during the 2020 surplus was similar (69.0 ± 15.3 vs. 68.4 ± 15.4 years, $P = 0.11$) when compared to a corresponding control period in 2016–2019, however, with more octogenarians (30.1 vs 26.5%, $P < 0.01$). There was an observable, but non-significant change in sex distribution with more males in 2020 than in 2016–2019 (51.2 vs. 49.1%, $P = 0.07$). While overall comorbidities expressed as weighted AHRQ Elixhauser Comorbidity Index (14.1 ± 10.1 vs. 13.9 ± 10.3, $P = 0.28$), the presence of thrombosis (46.1 vs 45.4%, $P = 0.55$) and surgery (3.8 vs. 4.3%, $P = 0.33$) were comparable, coagulopathy (3.3 vs 4.5%, $P = 0.01$) and metastatic cancer (3.0 vs 4.0%, $P = 0.03$) as contributing factors were less frequently observed during the 2020 surplus. Interventional treatments (thrombolytic therapy, thrombectomy or inferior vena cava filter placement) were less frequently used (4.7 vs 6.6%, OR 0.72, 95% CI 0.58–0.89, $P < 0.01$) which was mainly driven by thrombolytic therapy (4.7 vs 6.4%, OR 0.74, 95% CI 0.60–0.91, $P < 0.01$). Similarly, intensive care (35.1 vs 38.8%, OR 0.83, 95% CI 0.75–0.92, $P < 0.01$) and mechanical ventilation utilization (7.2 vs 8.1%, OR 0.88, 95% CI 0.74–1.04, $P = 0.14$) as well as in-hospital-mortality rates (7.8 vs 9.8%, OR 0.76, 95% CI 0.64–0.90, $P < 0.01$) were lower in 2020 compared with 2016–2019. This was associated with a shorter length of hospital stay (6.4 ± 5.4 vs. 7.2 ± 5.7 days, $P < 0.01$) during the 2020 surplus period.

By analyzing claims data of the German-wide Helios hospital network, we have identified an increase in cases with pulmonary embolism since

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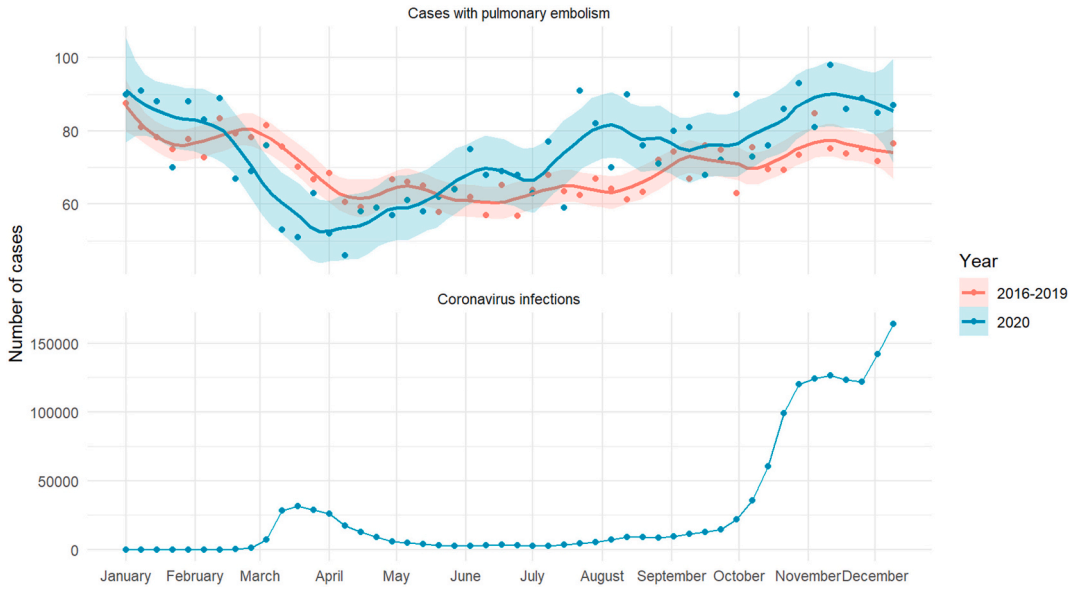

Fig. 1. Total weekly hospital admissions for pulmonary embolism at 75 Helios hospitals (upper panel) and new SARS-CoV-2 infections in Germany (lower panel). Smooth curves for weekly admission rates were fitted via Locally Weighted Scatterplot Smoothing (LOESS) with a degree of smoothing of $\alpha = 0.2$. Shaded areas represent 95% confidence intervals (CI).

Table 1
Incidence rates of PE cases per 100,000 admissions and relative risk estimates.

	2016–2019	2020	Unadjusted relative risk (95% CI)	P value	Adjusted relative risk (95% CI)	P value
PE as main diagnosis						
Total	298	373	1.25 (1.19–1.31)	<0.001	1.22[a] (1.16 – 1.28)	<0.001
SARS-CoV-2 -	–	371				
SARS-CoV-2 +	–	525	1.42 (1.05–1.90)	0.0208	1.27[b] (0.95 – 1.71)	0.1125
PE as main or secondary diagnosis						
Total	511	643	1.26 (1.22–1.30)	<0.001	1.20[a] (1.16 – 1.24)	<0.001
SARS-CoV-2 -	–	625				
SARS-CoV-2 +	–	1994	3.19 (2.74–3.72)	<0.001	2.86[b] (2.45 – 3.33)	< 0.001

[a] Adjusted for age, sex and SARS-CoV-2 infection for the comparison of the surplus periods in 2016–2019 versus 2020.
[b] Adjusted for age and sex for the comparison of SARS-CoV-2 - versus SARS-CoV-2 + cases in the 2020 surplus period.

early May 2020 compared to corresponding periods in 2016–2019. This supports similar observations made in England [5]. Interestingly, there was a slight shift in patient characteristics with respect to age and sex distribution, and less contributing factors such as coagulopathy and metastatic cancer. Although overall comorbidity burden was almost identical between cohorts, in-hospital treatments and outcomes were suggestive of less severe disease. As in a comparable study in England [5], only a minority of cases were associated with PCR-confirmed Covid-19 but this does not rule out preceding or undetected SARS-CoV-2 infection.

There are several possible, non-exclusive explanations. For instance, it has been reported that Covid-19 associated pulmonary emboli are more likely to be located in the peripheral lung segments and are less extensive resulting in less frequent and severe right heart dysfunction compared to those in patients without Covid-19 pneumonia [2]. The existence of in situ pulmonary thrombosis as one additional mechanism in patients with Covid-19 has been suggested by the absence of deep venous thrombosis, the higher incidence of pulmonary embolism but not venous thrombosis in patients with Covid-19 compared to those without Covid-19, and pathologic findings of thrombosis within the pulmonary arteries in the absence of venous thrombosis in autopsies [2–4]. While the in-hospital course with reduced intensive care utilization, mechanical ventilation, length of stay and in-hospital mortality suggests a milder disease, the increased incidence of hospitalizations for pulmonary embolism is of special concern and could also be associated with preceding Covid-19 infections [11]. In fact, pulmonary embolism has been identified as reason for readmission after a Covid-19 hospitalization in 0.6% of patients [12,13]. Although this event rate seems rather low, the magnitude of Covid-19 infections worldwide may result in a substantial number of effected individuals.

Alternatively or additionally, the raised awareness of respiratory symptoms that overlap between pulmonary embolism and Covid-19 such as cough or shortness of breath [2] may have prompted more hospital admissions. In addition, change in hospital protocols for the use of contrast-enhanced computed tomography in suspected Covid-19 cases may have detected incidental pulmonary embolism more frequently. Moreover, less mobility and the heat wave in 2020 may have contributed. Finally, changes in population-at-risk characteristics and catchment areas of the hospitals over time as well as more frequent diagnosis of low-risk embolism due to more sensitive tests cannot be ruled out. Although, the results of our and the study from England are comparable, the magnitude of the hospitalization increase was higher in England most likely due to lower baseline rate. How

this is impacted by coding regimen and the use of different ICD-10 versions is unknown although a large code overlap (e.g. I26) exists.

If the increased incidence of hospitalizations for pulmonary embolism is a signal for a rising incidence of this condition in the public, this could at least in part explain the observed excess mortality in Germany between late July and mid October 2020 not related with Covid-19 cases [14]. This finding requires immediate attention, close surveillance and further studies.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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