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 Editor

Significant increase in the incidence of high-risk pulmonary embolism during the COVID-19 shutdown: The pandemic response causes serious collateral consequences

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Dear Editors,

When the novel coronavirus disease (COVID-19) started to spread globally in December 2019 and COVID-19 related deaths continued to increase rapidly [1], the World Health Organization (WHO) declared a pandemic [2]. In response, governments around the world initiated country-wide shutdowns, mandating curfews and strict social contact restrictions. Several weeks in to the shutdown in Austria, physicians noticed a worrying trend: The strict stay-at-home order, as well as fear of contracting the virus, was apparently stopping patients from seeking timely medical attention [3]. As a result, patients with a variety of health complaints presented very late, which may in some cases have led to more serious health consequences than those which would have been caused by COVID-19 [4,5].

Pulmonary embolism (PE) is a leading cause of death worldwide; however, early diagnosis and prompt administration of anticoagulant treatment can effectively reduce morbidity and mortality in these patients [5,6]. The European Society of Cardiology (ESC) has established treatment guidelines for PE, which were updated in 2019 [7]. Assessment of PE-related severity and risk of early death according to these guidelines is based on clinical presentation and factors reflecting acute right ventricular (RV) dysfunction, which contributes to haemodynamic collapse in acute pulmonary embolism. In addition, patients with pre-existing diseases such as cancer, chronic heart failure or pulmonary disease are known to have an increased risk of early death [7]. In the case of hemodynamic instability, patients are classified as high-risk, due to severely reduced hemodynamic reserve. For high risk patients, rapid systemic fibrinolytic therapy is recommended to reduce the risk of cardiovascular collapse and early death [7,8].

By retrospective data analysis we explored the incidence of PE patients, defined as high-risk according to the 2019 ESC-guidelines for the diagnosis and management of acute PE at our emergency department in the period from March 16 to April 30, 2020 (forty-six days) during the countrywide shutdown that was initiated by the Austrian government. Based on these guidelines, patients were separated into four groups: low risk (LR), intermediate low risk (IML), intermediate high risk (IMH) and high risk (HR). The presence of haemodynamic instability was the main determinant to classify patients as having a high risk PE. According to these guidelines, for patients with no hemodynamic instability, signs of RV dilation and positive troponin were included in the risk stratification as well as Pulmonary Embolism Severity Index (PESI) score was assigned based on the variables of age, sex, previous PE, cancer, comorbidities, O_2-saturation, systolic blood pressure and heart rate. The time from onset of symptoms to hospital admission was also documented. As COVID-19 might be an additional risk factor for PE, the co-existence of a COVID-19 infection was excluded by reverse-transcriptase–polymerase-chain-reaction (PCR) assay performed using nasal and pharyngeal swab specimens. We compared percentages of patients admitted with high risk PE between the shutdown period (March 16 to April 30, 2020) and two control periods when no pandemic was present: an earlier period during the same year (January 1 to February 15, 2020; “control period 1”) and a corresponding period during the previous year (March 16 to April 30, 2019; “control period 2”). The study protocol was approved by the Ethics Committee (EK 32-399 ex 19/20) of the Medical University of Graz.

The primary outcome was the incidence of high-risk PE in the defined time periods and the secondary outcome was the time from symptomatic PE to hospital admission. Data are presented as absolute and relative frequencies or as median and interquartile range (IQR, 1st to 3rd quartile). To compare the data from the three time periods, we performed Fisher's exact test or Mann-Whitney U test. A p-value < 0.05 was considered statistically significant. The statistical analysis was conducted using R version 3.6.1 (https://www.r-project.org).

The main finding of our retrospective data analysis was a significant increase in hospital admissions of patients with life-threatening high-risk PE during the shut-down period (March 16 – April 30, 2020; 33.3%) compared to both the period before the shutdown in 2020 (“control period 1”; 3.8%, $p = 0.011$) and the same time period in 2019 (“control period 2”; 0%, $p = 0.003$) (Table 1) (Fig. 1). Systemic fibrinolytic therapy was applied in six of the nine (66.7%) high-risk PE patients presenting during the shut-down period. In the other three high-risk PE patients (33.3%), fibrinolytic therapy was waived due to severe comorbidities, contraindications or an unfavourable prognosis. By contrast, in control period 1, there was only one high risk PE case which necessitated fibrinolytic therapy; no high-risk PE was observed in control period 2. The days from onset of symptoms to hospital admission were significantly higher in the shutdown period (median 4.0, IQR 2.5-7.0) compared to control period 2 (2.0, 1.0-4.8, $p = 0.046$) and control period 1 (2.0, 1.0-4.8, $p = 0.044$), respectively (Table 1) (Fig. 1). We observed three deaths in total, all in 2020: two in the shut-down period and one in control period 1 (Table 1).

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Table 1
Risk assessment, delay to hospital admission and outcome during the three investigated time-periods.

	Shut down period Mar 16-Apr 30, 2020 (*N* = 27)	Control period 1 Jan 1-Feb 15, 2020 (*N* = 26)	Control period 2 Mar 16-Apr 30, 2019 (*N* = 22)	p[a]	p[b]
Risk[e]				0.011	0.003
High risk (HR)	9 (33.3%)	1 (3.8%)	0 (0.0%)		
Intermediate high risk (IMH)	3 (11.1%)	4 (15.4%)	6 (27.3%)		
Intermediate low risk (IML)	8 (29.6%)	11 (42.3%)	8 (36.4%)		
Low risk (LR)	7 (25.9%)	10 (38.5%)	8 (36.4%)		
Delay				0.044	0.046
Median (Q1, Q3)	4.0 (2.5, 7.0)	2.0 (1.0, 4.8)	2.0 (1.0, 4.8)		
Outcome				1.000	0.495
alive	25 (92.6%)	25 (96.2%)	22 (100.0%)		
death	2 (7.4%)	1 (3.8%)	0 (0.0%)		

[a] Comparison of shut down period (March 16 to April 30, 2020) and control period 1 (January 1 to February 15, 2020).
[b] Comparison of shut down period (March 16 to April 30, 2020) and control period 2 (March 16 to April 30, 2019).
[e] *p*-values are for the comparison of HR vs. rest.

In anticipation of an overwhelming impact of COVID-19, many medical resources have been re-directed towards the COVID-19 pandemic response, hindering other patients from timely receiving important medical procedures or therapies [3,9]. Although many concerns have been voiced regarding the economic impact of the pandemic, little is known about health-related collateral consequences caused by the social shutdown [10]. Metzler et al. [3] recently reported a decline in acute coronary syndrome admissions in Austria since the outbreak of COVID-19, which might be a perilous response to the pandemic. In our daily clinical practice, we have noticed a worrying number of non-COVID-19 patients being seriously affected by the pandemic, including the currently-reported increase in high-risk PE admissions to our hospital. Several factors might explain this important observation. These include patients´ misinterpretation of PE-related symptoms such as sudden shortness of breath, coughing, dyspnoea or sharp chest pain as being related to an acute respiratory infection. Given the strict containment efforts, as well as fear of nosocomial infections, people with such symptoms may have stayed at home longer, thus allowing low-risk cases of PE to progress to potentially life-threatening high-risk PE cases. Fortunately, the majority of our patients survived after administration of fibrinolytic therapy; however, this treatment is precluded for certain high-risk PE patients due to its high bleeding risk [7].

Regarding our data, it is conceivable that such delays in seeking medical attention had an impact on individual outcomes. This observation underlines our assumption that delays in seeking medical attention might lead to disease progressions.

In the current pandemic, healthcare decision-makers have been understandably focused on immediate actions to prevent further disease transmission and to provide adequate facilities for critical COVID-19 cases. This is not meant to be a criticism of the decisions made, since decisions in such exceptional times are extremely challenging, requiring great courage and responsibility. Nonetheless, the current report underscores the importance of providing adequate treatment to other critically ill patients during the pandemic.

Although only limited data is available, first observations suggest a decline or a delay in the admission of critically ill patients to the hospital during the shutdown period. As there is no comparable previous experience, the long-term consequences of the COVID-19 crisis cannot be estimated. The fact that the current situation prevents patients, even those with life-threatening conditions, from seeking timely medical attention may lead to a significant increase in mortality caused by non-COVID-19 causes. In a recent publication, Italian researchers made similar observations to Metzler et al. [3] in Austria, and in addition emphasized a significant increase in mortality during the shutdown period that was not fully explained by COVID-19 cases alone [9]. Our study has limitations, since it is based on a retrospective data analysis from a single medical centre. However, our results should encourage other researchers to address this important research question in further studies. In conclusion, delayed hospital admission led to a significant increase in high-risk PE patients during the COVID-19 shutdown in Austria. In the event of a second shutdown, patients should be encouraged to seek timely medical attention, in order to avoid further unnecessary deaths.

Ethical approval and consent to participate

The study protocol was approved by the Ethics Committee (EK 32-399 ex 19/20) of the Medical University of Graz. Our analysis looked retrospectively at outcomes. All data analysed were collected as part of routine diagnosis and treatment. Therefore, the need for written informed consent has been waived by the approval of the ethics committee of the Medical University of Graz.

Consent for publication

The Authors grant the Publisher the sole and exclusive license of the full copyright in the Contribution, which license the Publisher hereby accepts.

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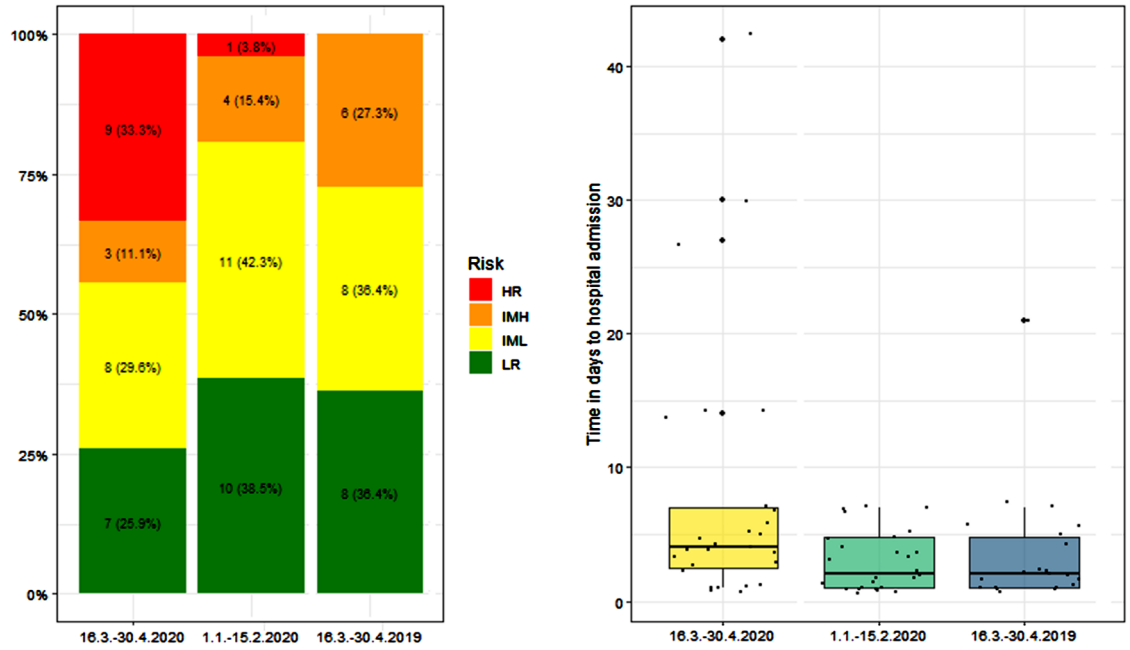

Fig. 1. Distribution of risk groups within the investigated time periods and boxplots showing the delay to hospital admission for the investigated time periods. HR = high risk, IMH = intermediate high risk, IML = intermediate low risk, LR = low risk.

Declaration of Competing Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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References

[1] Livingston E, Bucher K. Coronavirus disease 2019 (COVID-19) in Italy. JAMA 2020;323:1335.
[2] Sohrabi C, Alsafi Z, O'Neill N, Khan M, Kerwan A, Al-Jabir A, Iosifidis C, Agha R. World Health Organization declares global emergency: a review of the 2019 novel coronavirus (COVID-19). Int J Surg 2020;76:71–6.
[3] Metzler B, Siostrzonek P, Binder RK, Bauer A, Reinstadler SJ. Decline of acute coronary syndrome admissions in Austria since the outbreak of COVID-19: the pandemic response causes cardiac collateral damage. Eur Heart J 2020;41:1852–3.
[4] Galarza M, Gazzeri R. Letter: collateral pandemic in face of the present COVID-19 pandemic: a neurosurgical perspective. Neurosurgery 2020;87:E186–8.
[5] Cohen AT, Agnelli G, Anderson FA, Arcelus JI, Bergqvist D, Brecht JG, Greer IA, Heit JA, Hutchinson JL, Kakkar AK, Mottier D, Oger E, Samama MM, Spannagl M. VTE Impact Assessment Group in Europe (VITAE). Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. Thromb Haemost 2007;98:756–64.
[6] Laporte S, Mismetti P, Décousus H, Uresandi F, Otero R, Lobo JL. Clinical predictors for fatal pulmonary embolism in 15,520 patients with venous thromboembolism: findings from the Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) Registry. Circulation 2008;117:1711–6.
[7] Konstantinides SV, Meyer G. The 2019 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 2019;40:3453–5.
[8] Chopard R, Ecarnot F, Meneveau N. Catheter-directed therapy for acute pulmonary embolism: navigating gaps in the evidence. Eur Heart J Suppl 2019;21:I23–30.
[9] De Filippo O, D'Ascenzo F, Angelini F, Bocchino PP, Conrotto F, Saglietto A, Secco GG, Campo G, Gallone G, Verardi R, Gaido L, Iannaccone M, Galvani M, Ugo F, Barbero U, Infantino V, Olivotti L, Mennuni M, Gili S, Infusino F, Vercellino M, Zucchetti O, Casella G, Giammaria M, Boccuzzi G, Tolomeo P, Doronzo B, Senatore G, Grosso Marra W, Rognoni A, Trabattoni D, Franchin L, Borin A, Bruno F, Galluzzo A, Gambino A, Nicolino A, Truffa Giachet A, Sardella G, Fedele F, Monticone S, Montefusco A, Omedè P, Pennone M, Patti G, Mancone M, De Ferrari GM. Reduced rate of hospital admissions for ACS during Covid-19 outbreak in Northern Italy. N Engl J Med 2020;383:88–9.
[10] Kittleson MM. The invisible hand - medical care during the pandemic. N Engl J Med 2020;382:1586–7.

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