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## Scientific letter

## The impact of time to impose lockdown on COVID-19 cases and deaths in European countries<sup>☆</sup>



### El impacto del tiempo hasta el confinamiento en los casos y la mortalidad por COVID-19 en países europeos

To the Editor:

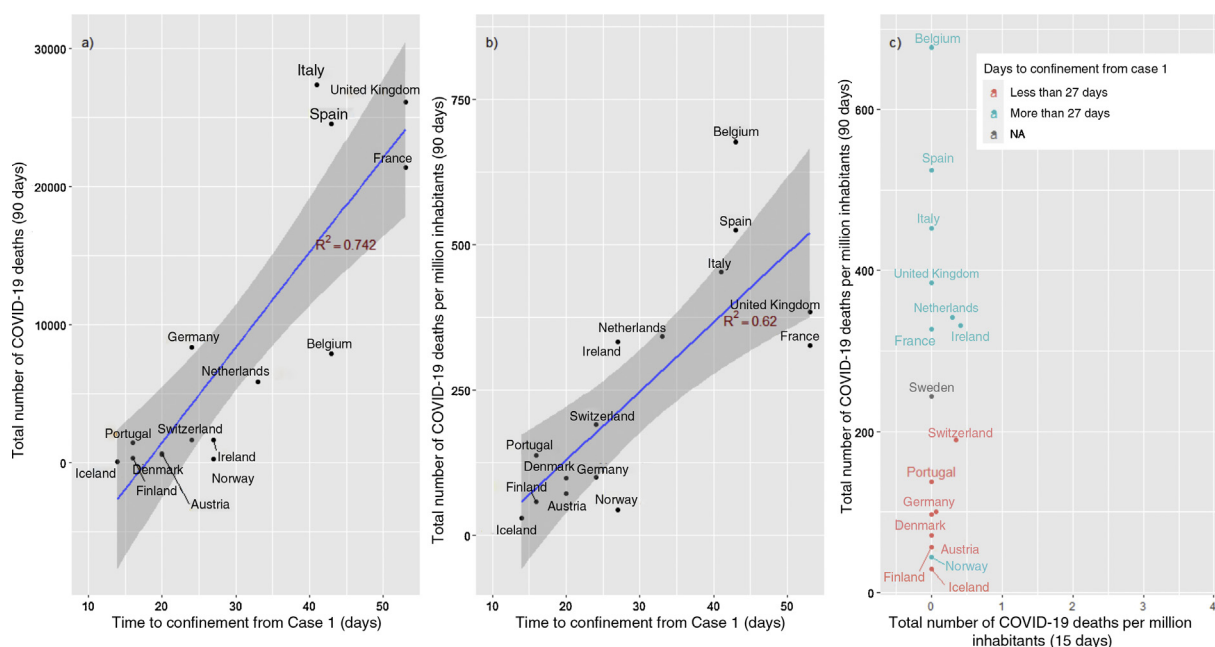
In December 2019, the infection by the SARS-CoV-2 coronavirus that causes the COVID-19 disease, characterised by its highly contagious nature, was described for the first time. Its global expansion has led to a public health crisis unprecedented in modern times.

The control measures employed in the SARS epidemic in 2003, appear to have been more successful than those currently used for COVID-19. Possible reasons for this could be that SARS-CoV-2 is far

more transmissible, plus the existence of asymptomatic patients who transmit the disease.<sup>1</sup>

Many European countries have implemented severe epidemiological measures to control the pandemic, such as early detection of cases and case isolation, comprehensive contact monitoring and quarantine, and social distancing and lockdown measures.<sup>2</sup> In fact, implementing lockdown seems to have had an effect in the reduction of deaths reported daily just 2–3 weeks after its inception.<sup>2</sup>

Regarding the number of cases and deaths related to COVID-19, differences have been documented between countries such as Norway, Finland or Portugal, and others, such as Italy, United Kingdom or Spain. One possible hypothesis is the existence of a direct relationship between the consequences of the pandemic (number of cases and deaths) and the time that elapsed between the first case and the introduction of social distancing measures.



**Fig. 1.** Relationship between the time until lockdown and the absolute and relative number of deaths from COVID-19. Univariate linear models developed with data from the 16 European countries included in the study for a) total number of deaths from COVID-19, and b) total number of deaths per million inhabitants 90 days after the first case was detected in each country, including the number of days that elapsed from that first case to the declaration of lockdown therein. c) Evolution of the number of deaths from COVID-19 relative to the population of each country between days 15 and 90 after detecting the first case of the disease. The colour scale separates those countries that declared lockdown within 27 days of the first case detected, or after 27 days. Significant differences were detected between these groups for the number of deaths per million inhabitants registered on day 90 after the first case (ANOVA,  $p = 0.0015$ ), while on day 15 there were no such differences between countries (ANOVA,  $p = 0.712$ ).

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For this reason, our study objective is to investigate the effect of the time until social distancing measures were introduced, on the number of declared cases of COVID-19 and mortality in European countries. For this, data was collected from 16 European countries (Belgium, Denmark, Finland, France, Austria, Germany, Iceland, Ireland, Italy, Norway, Holland, Portugal, Spain, Sweden, Switzerland and the United Kingdom) until 30 June 2020.<sup>3</sup> The study variables were time until social distancing (date of entry into force of social distancing measures and the date of the first case detected) and time until lockdown (date of entry into force of lockdown measures and the date of the first case detected). The result variables were the total number of cases and deaths, both absolute and relative, adjusted to the total population of each country, related to COVID-19 registered 90 days after the first case of the disease declared in each country. Adjusted and univariate linear regression models (stepwise backwards) were used for the number of tests performed and the number of cases and deaths up to the date of the start of the most demanding social distancing measure, that is, lockdown.

The results showed that there is a close correlation between the number of deaths from COVID-19, total and per million inhabitants, in relation to the days elapsed until lockdown ( $R^2$  adjusted 0.722 and 0.590, respectively) (Fig. 1). The results on social distancing had a lower correlation ( $R^2$  0.588 and 0.477, respectively) with the outcome variables (data not shown).

Regarding the total number of cases, a high correlation coefficient ( $R^2$  adjusted 0.726) was documented in relation to the time that elapsed until lockdown together with the number of tests performed.

Finally, panel c) of Fig. 1 shows how different the evolution of the pandemic has been (in terms of the number of deaths per million inhabitants) between the data at the beginning of the pandemic (15 days after detection of the first case) and the data collected 90 days after that first case in each country based on the time that elapsed until lockdown.

In conclusion, the results of this paper show that there is a strong direct relationship between the number of deaths from COVID-19 in Europe (to a lesser extent with the number of cases declared) and the time that elapsed between the declaration of the first case and

introducing the lockdown decision during the COVID-19 pandemic. It is true that these findings should be considered with caution as it is an observational study where cause-effect relationships cannot be established as there are many other biological, environmental, social and individual factors that could mediate as indirect factors of transmission. Additionally, observational learning by countries where the epidemic started later may be a partial reason for the data collected.

### Authorship

The authors CMV and JDM have contributed equally to this article.

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## Neuroendocrine tumors in rare locations: Description of 27 cases



### Tumores neuroendocrinos de localización atípica: descripción de 27 casos

Dear Editor,

Neuroendocrine tumors (NETs) are a type of uncommon cancer. The annual incidence varies between 2 and 5 per 100,000 patients.<sup>1,2</sup> The incidence has increased in the last decades, probably due to improved diagnostic techniques and to refinement of histological classification.

The most frequent locations are the gastrointestinal tract/pancreas (around 65%) and the bronchopulmonary tree (around 25%), the rest of locations being very infrequent.<sup>3</sup>

The aim of this study is to present a case series of 27 patients diagnosed of a NET in a rare location diagnosed between 2000 and 2017 in the University Hospital Clínico San Carlos, Madrid. This study was approved by the local Ethics Committee. Of the 27 patients included, 14 (52%) were men and 13 (48%) women. The most common locations of primary tumors were genitourinary (11 patients, 37%: 6 urinary bladder, 3 kidney, 1 urethra and 1 prostate tumor), followed by gynecological (6 patients, 22%: 2 ovarian, 2 cervix, 1 endometrium and 1 vulva tumor) and head and neck tumors (5 patients, 19%: 3 nasosinusual, 1 larynx and 1 parotid tumor). Furthermore, there were two patients with breast tumors, two with bile duct tumors and one patient with a thymic

neuroendocrine tumor. The gender distribution varied depending on the location of the primary tumor, with males predominating in genitourinary (82%) and head and neck tumors (60%). The median age at diagnosis was 70 years (range 26–87 years). Gynecological tumors were diagnosed at younger ages (median age at diagnosis: 49 years).

No patient presented with hormone hypersecretion symptoms. The clinical presentation depended mainly on the tumor location. Incidental diagnosis occurred in 18% of cases. Octreoscan<sup>®</sup> was done in 22% of patients and somatostatin receptors were found in 33% of them. At diagnosis, tumors were localized in 63% of patients and had distant metastases in 37%. The most common sites of metastases were distant lymph nodes (73%), liver (33%) and peritoneum, bone and lung (20% each). All patients with head and neck tumors had distant lymph node metastases.

According to the WHO classification (2010), we found five patients with grade 1 tumors (18,5%), four patients (14,8%) with grade 2 tumors and 16 patients with grade 3 tumors (59,3%). Grade information was not available in two patients. Grade 3 and 2 tumors presented most frequently with distant disease at diagnosis, 38% and 25% respectively. All patients with grade 1 tumors presented with early tumor stage at diagnosis. Regarding primary tumor location, we found more frequently high-grade tumors in head and neck and genitourinary locations, 100% and 61% respectively, in contrast to the lower grade of gynecological tumors (33%).

With a median follow-up of 29 months (range 7–146), fourteen patients had died (52%). The median overall survival for all