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Population-based disease-group analysis of Spanish excess mortality in the early COVID-19 pandemic period

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ABSTRACT

Background and aim Increased mortality during the COVID-19 pandemic is not explained exclusively by COVID-19 infection and its complications. We analysed non-COVID-19 causes of mortality in a population analysis based on data from the Spanish National Institute of Statistics.

Methods Using monthly mortality data in Spain (January 2010–December 2020), we analysed deaths associated with cancer, blood, endocrine, mental, nervous, cardiovascular, respiratory and digestive diseases and explored the COVID-19 impact using a difference-in-difference strategy. We calculated monthly interannual variations in mortality and computed percentage change in terms of the log of deaths in month *h* of year *t* minus the log of deaths in month *h* in the previous year *t–1*.

Results In 2020 in Spain, mortality increased 17.9% compared with 2019. COVID-19 was the leading cause of death (n=60 358), followed by ischaemic heart disease (n=29 654). Throughout 2020, monthly interannual variations in cardiovascular mortality showed an average upward trend of 1.7%, while digestive, cancer and blood diseases showed a downward trend.

Conclusions During the COVID-19 pandemic in Spain in 2020, excess mortality was primarily related to cardiovascular mortality while mortality associated with digestive, cancer and blood diseases was reduced.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The increased mortality observed in Western countries during the COVID-19 pandemic is not explained exclusively by the COVID-19 infection and its complications.

WHAT THIS STUDY ADDS

⇒ The most important cause of non-COVID-19 mortality was cardiovascular diseases. While viral infection may have impacted on inflammatory and thrombotic alterations, healthcare system capacity adaptations to COVID negatively impacted chronic and acute care for patients with cardiovascular conditions.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study highlights the importance of maintaining standards of care for all patients in a pandemic scenario. During the COVID-19 pandemic, healthcare systems focused on COVID-19 care and the prevention of the transmission of the virus to the detriment of acute and chronic care for patients with other diseases, especially cardiovascular.

INTRODUCTION

Since COVID-19, an infectious disease caused by SARS-CoV-2, was reported in Wuhan (China) in December 2019,[1] much has been published on the associated mortality and morbidity.[2] Factors associated with higher mortality in patients infected with COVID-19 are age, the male sex, chronic obstructive pulmonary disease and cardiovascular (CV) diseases.[3] Mortality in the elderly is further aggravated by living conditions, especially the fact of living in a residence.[4]

However, excess mortality during the COVID-19 pandemic, described in all Western countries,[5] was not only due to COVID-19 and its complications but also to delayed healthcare associated with a reduction in emergency room visits and hospital admissions for non-COVID-19 diseases.[6]

Increased mortality associated with CV diseases[7] is largely due to delayed acute care for acute myocardial infarction (AMI),[8] bearing in mind that CV mortality in Spain has been greatly reduced as a consequence of the optimal times historically achieved by the ST-segment elevation acute coronary syndrome approach.[9]

It has been observed, for chronic pathologies such as heart failure (HF), that telemedicine strategies are effective in reducing hospitalisation and mortality[10] and in improving follow-up.[11] Telemedicine during the worst months of the COVID-19 pandemic compensated to some extent for the cancellation of follow-up visits and cardiac rehabilitation programmes.[12]

Table 1 Average death rates for different disease groups before and after COVID-19 onset

	Total	Cancer	Blood	Endocrine	Mental	Nervous	CV	Respiratory	Digestive
Before	0.91	0.62	3.05	0.54	4.57	3.25	−0.34	1.25	1.58
After	0.59	−0.87	2.52	17.18	−5.15	6.32	4.28	−13.65	−3.14
DID		−1.16	−0.20	16.97	−9.39	3.39	4.94	−14.58	−4.40

This table reports average values for the outcome variable (the rate of increase in mortality) before and after COVID-19 onset for the control group (total) and the treated groups reflecting different disease groups. DID is the sample difference variable for the average difference between treated and control groups after and before COVID-19 onset for the outcome variable.
CV, cardiovascular.DID, difference in difference;

Our primary aim was to determine whether there genuinely was an increase in mortality at the population level in Spain in 2020 by analysing non-COVID-19 causes of increased monthly mortality rates in a population analysis based on data obtained from the Spanish National Institute of Statistics (INE). A secondary aim was to identify possible determining factors associated with excess mortality.

METHODS

Spanish population data 2020

The total Spanish population was 47 398 695 inhabitants (23 227 282 men and 24 171 413 women) on 1 January 2020 and 47 332 614 habitants (23 199 313 men and 24 133 301 women) by year-end, accounting for a vegetative balance of −66 081 inhabitants. In terms of changes by age group, numbers changed as follows: children (up to 15 years old) increased from 7 258 083.6 to 7 369 817.7, young-middle-aged adults (16–65 years) decreased from 30 769 691.1 to 30 695 480.9, older adults (65–80 years) decreased from 6 826 195.3 to 6 644 087.7, and the elderly population (>80 years) increased from 2 544 724.8 to 2 623 227.5.

Mortality analysis

Using a difference-in-difference (DID) strategy that exploits the fact that we had data on the total number of deaths due to COVID-19, we examined how the COVID-19 pandemic impacted mortality in 2020 associated with different pathologies, considering a control group (predicted trend) and treated groups (pandemic trend). Accordingly, we constructed a synthetic control group based on the total number of deaths in the periods before and after the pandemic onset in March 2020, but excluding deaths attributable to COVID-19. As for the treated groups, these were based on mortality associated with specific diseases (eg, cancer). The causal impact of the pandemic on deaths associated with specific diseases was calculated by comparing differences in deaths between the treated and control groups before and after the pandemic onset. Differences were tested for using a DID framework, based on the following linear regression Eq. 1:

$$D_{gt} = \alpha + \beta G_{gt} + \gamma Time_t + \theta COVID_t + \delta\ G_{gt} \cdot COVID_t + \varepsilon_{gt}$$

where D_{gt} is the outcome (dependent variable), denoting the rate of change in mortality in the control ($g=0$) and treated ($g=1$) groups at time t; G_{gt} is a dummy variable taking the value 1 for the treated groups, and 0 otherwise; $Time_t$ is a temporal variable that accounts for the temporal effect on deaths; and $COVID_t$ is a dummy variable that takes the value of 1 for time period t after the pandemic onset, and 0 otherwise.

Regarding the regression equation parameters, α is a constant that accounts for average mortality over the sample period; β accounts for differences in the expected value of the outcome variable between the treated and control groups before the pandemic onset, that is, $\alpha+\beta+\gamma-(\alpha+\gamma)$ while the expected differences during the pandemic period are given by $\beta+\delta$, that is, $\alpha+\beta+\gamma+\theta+\delta-(\alpha+\gamma+\theta)$. Thus, δ linked to the interaction variable $G_{gt} \cdot COVID_t$ is the DID parameter that yields the COVID-19 impact on deaths associated with specific disease (eg, cancer), with positive (negative) values indicating that COVID-19 caused an increase (decrease) in mortality. Note that estimates of the DiD parameter relied on the parallel trend assumption.[13]

Statistical data

For Spain, we compiled monthly data on total deaths associated with different diseases, namely, cancer, blood, endocrine, mental, nervous, CV, respiratory and digestive diseases. The data included 74 839 deaths recorded as specifically, and suspected to be, due to COVID (n=60 358 and n=14 481, respectively) from March 2020 to December 2020. Using the compiled data, we calculated the monthly annual rate of change in mortality, computed on a percentage basis as the log of deaths in month h of year t minus the log of deaths in month h in the previous year $t-1$.

RESULTS

Spanish COVID-19 mortality 2020

COVID-19 was the leading cause of death in Spain in 2020, with 60 358 deaths (32 498 men and 27 860 women), which, per 100 000 deaths, represented male and female mortality rates of 140 and 115.4. To that number can be added 14 481 suspected COVID-19 deaths due to clinical symptoms not microbiologically confirmed. The second cause of death was ischaemic heart disease (29 654 deaths), followed by CV diseases (25 817 deaths) and lung cancer (21 893 deaths).

Table 2 Difference-in-differences estimates

	α	β	γ	θ	δ	R^2
Cancer	1.881 (1.37)	−0.298 (0.99)	−0.017 (0.01)	0.719 (1.74)	−1.163 (1.81)	0.015
Blood	2.117 (1.74)	2.135 (1.83)	−0.021 (0.02)	0.974 (2.08)	−0.203 (4.09)	0.014
Endocrine	1.800 (1.65)	−0.375 (1.87)	−0.015 (0.02)	0.631 (2.02)	16.967*** (3.71)	0.124
Mental	3.111* (1.89)	3.656* (1.88)	−0.039 (0.02)	2.048 (2.28)	−9.394** (4.19)	0.074
Nervous	3.359** (1.68)	2.340 (1.67)	−0.044** (0.02)	2.316 (2.02)	3.392 (4.53)	0.046
Cardiovascular	2.190 (1.54)	−1.254 (1.38)	−0.022 (0.02)	1.053 (0.55)	4.943** (2.42)	0.029
Respiratory	3.945* (2.30)	0.339 (2.54)	−0.054 (0.03)	2.951 (2.48)	−14.575*** (5.14)	0.069
Digestive	0.925 (1.47)	0.668 (1.24)	−0.000 (0.016)	−0.314 (1.89)	−4.396 (3.14)	0.021

This table reports parameter estimates for the regression model in Eq. (1). White robust SEs are indicated in parentheses.
*Denote significance at the 10% levels.
**Denote significance at the 5% levels.
***Denote significance at the 1% levels.

The months with the highest COVID-19 mortality in Spain were March (11 313 deaths) and April (18 252 deaths), followed by November (9891 deaths) and December (6185 deaths). The main COVID-19 complications in deceased patients were respiratory failure (57.5%) and pneumonia (32.7%), and the most frequent comorbidities were arterial hypertension (12.8%) and chronic kidney disease (9.6%).

In addition to deaths directly attributable to COVID-19, COVID-19 indirectly contributed to 3770 deaths, mainly due to ischaemic heart disease (278 deaths), lung cancer (263 deaths) and cerebrovascular diseases (216 deaths).

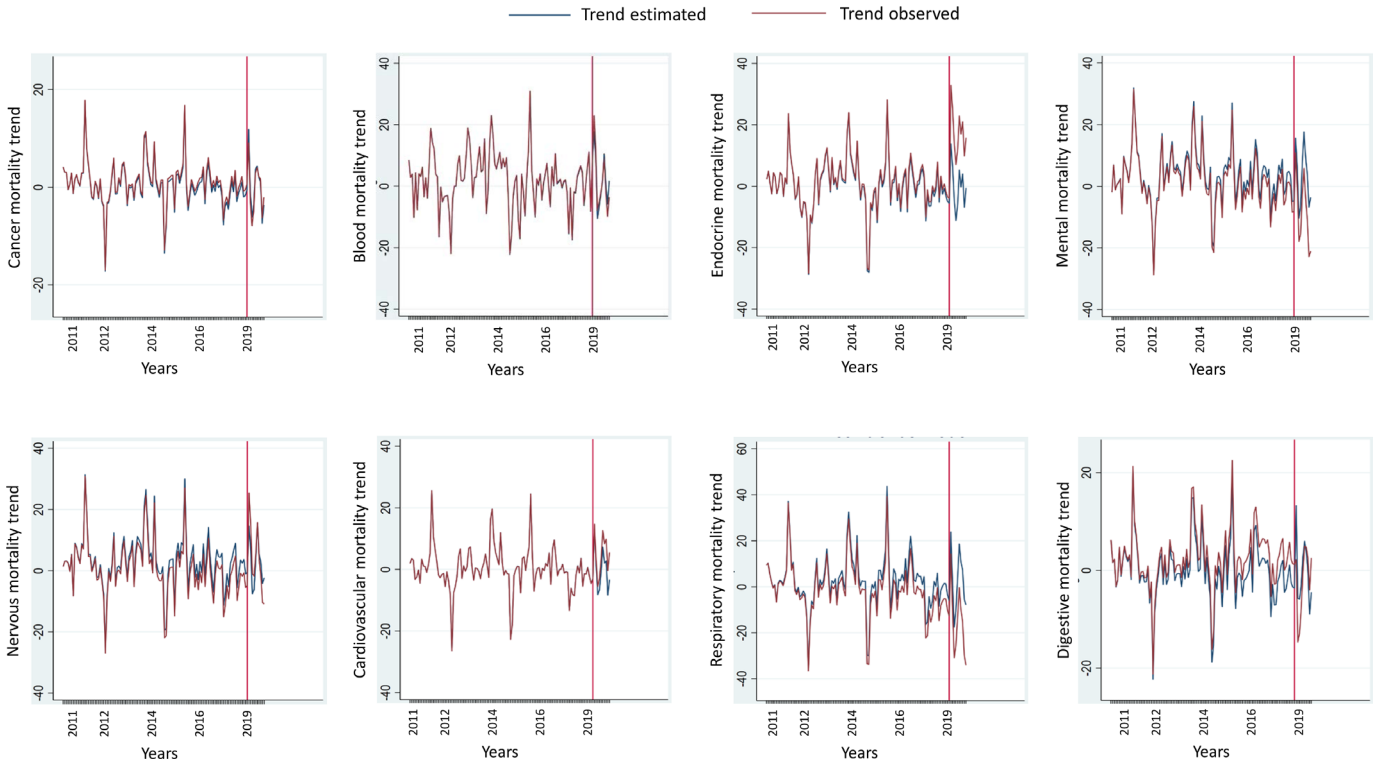

Figure 1 Linear-trend model showing changes in disease-related mortality rates 2010–2020.

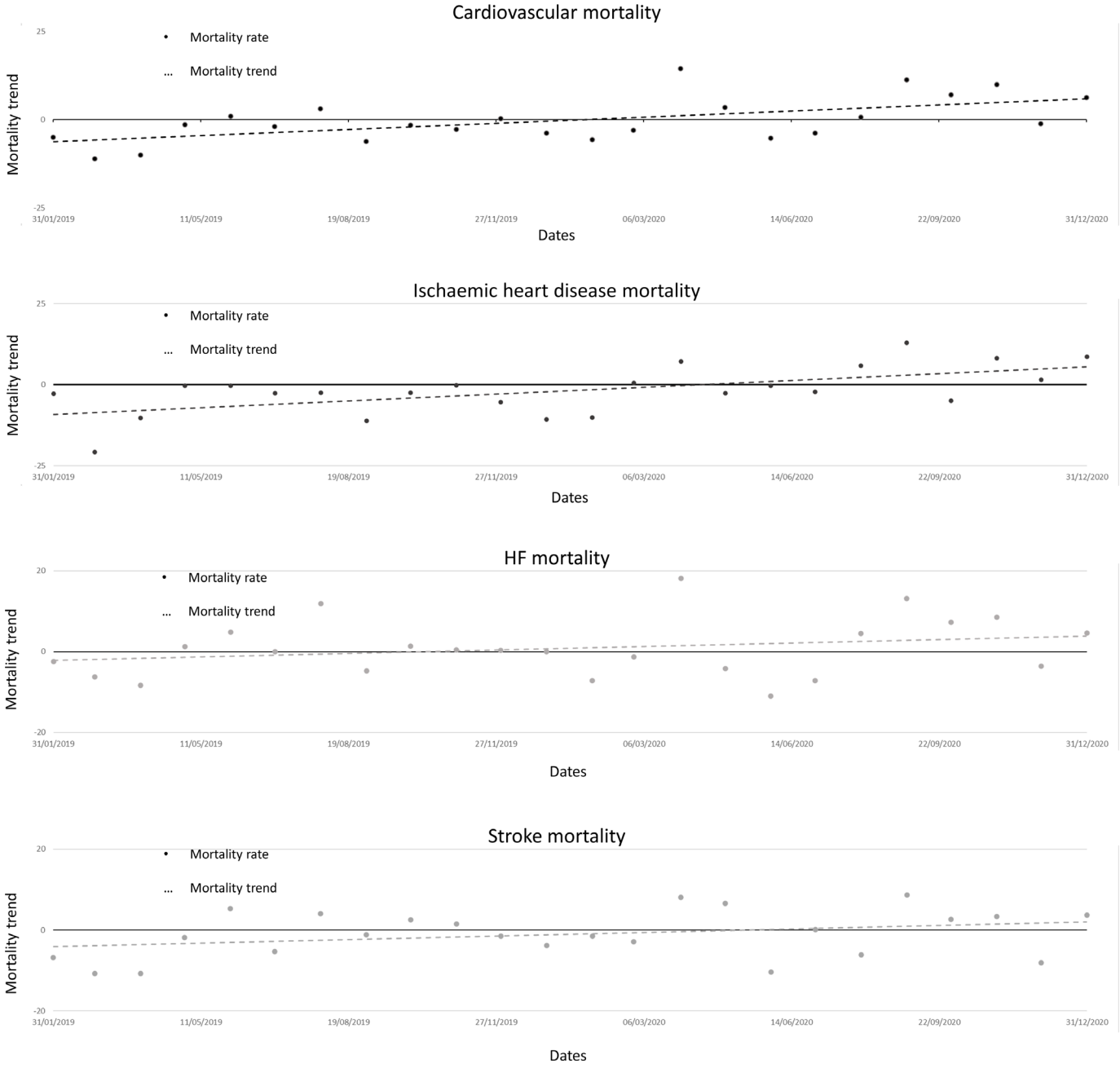

Figure 2 Interannual mortality variations for cardiovascular diseases, including ischaemic heart disease, heart failure (HF) and stroke.

Spanish total mortality 2020

In 2020 in Spain, deaths were 493 776, an increase of 17.9% over 2019. The annual number of deaths from 2010 to 2020 showed that CV diseases accounted for 24.3% of deaths in 2020, an increase of 2.8% over 2019, followed by cancer (22.8%, a decrease of 0.3%), and infectious diseases, including confirmed or suspected COVID-19 cases (16.4%, an increase of 1.2%). Respiratory and nervous system diseases were less represented in the increased mortality, at 8.6% and 5.6%, respectively.

Table 1, which reports average mortality rates for different diseases for COVID-19 preonset and postonset periods, shows a postonset downward trend for digestive, cancer and blood diseases, but a significant upward trend for CV diseases. Table 2 shows DID estimates for the different disease groups. Figure 1, representing trend changes over the years 2010–2020, shows that postonset, mortality rates increased for CV and endocrine diseases but decreased for respiratory diseases.

CV mortality 2020

Figure 2 shows that monthly interannual variations in CV mortality increased by 1.7% throughout 2020; coinciding with COVID-19 pandemic waves in Spain, the increases were especially high in April and September (R^2=0.3432). Mortality from AMI reflected a similar trend (1.7% monthly interannual variation in 2020, and especially high in April and September: R^2=0.3647). Monthly

interannual variation also increased for HF and stroke, by 2.1% and 0.8%, respectively, and again tending to rise in April and September. However, the increase was much lower than for AMI, with the regression lines showing the poorest fit (R^2=0.0633 and R^2=0.1041, respectively).

DISCUSSION

Our findings, based on data published by the Spanish health authorities, show that COVID-19 not only caused deaths directly but also indirectly increased CV mortality in 2020. We also observed decreased mortality rates attributable to digestive, cancer and blood diseases. Our results reflect mortality in early pandemic waves, however, so it would be important to also analyse medium-term and long-term impacts on different groups of diseases.

In a bibliographic review, we retrieved numerous studies that analysed excess mortality in 2020 and 2021 in relation to different waves of COVID-19, with many pointing to causes other than COVID-19.[5] However, as far as we are aware, our study is the first to analyse the specific sources of excess mortality. We found that the primary reason for the increased excess mortality was CV diseases, mainly acute diseases such as AMI and stroke, but also a worsening of chronic diseases such as HF.

Confinement and social isolation necessary to control the high rate of COVID-19 infection and the corresponding morbidity and mortality rates led to changes in healthcare activity, whose full impact on populational health, although temporary, is unknown. A systematic review by Pina and Castelletti[12] reported an association between the suspension of non-urgent services (such as cardiac rehabilitation and chronic cardiology care) and an increase in hospital admissions due to late complications of CV diseases. In addition, confinement in the home led to changed and often less healthy or different dietary and exercise habits, that undoubtedly had a negative effect on prognosis.[14] The pandemic also had a psychological impact that led patients to avoid seeking medical help for fear of being exposed to infection.[8 15] Those reasons combined may explain the increased CV-related mortality, more related to acute events and more affected by confinement, dietary and exercise habits, and healthcare capacity adaptation to the pandemic.

One possible explanation, as previously mentioned, is delayed healthcare and a greater incidence of acute complications associated with coronary events.[8] Also affected were cardiology follow-up, complementary testing and interventions with an impact on prognosis.[15] The fact that primary care attention to the population, where CV preventive care is more usual, was reduced due to COVID-19 saturation[16] may also have affected the incidence of new CV events. Those facts may explain the increased mortality associated with acute AMI and CV-related events, as reported by us and corroborated by other authors.[17]

We also observed an increase in HF-associated mortality, which, although of a lesser magnitude, contributed to the increased mortality observed for all CV diseases. Many authors have described the effectiveness of telemedicine monitoring systems for patients with HF,[18] as they reduce the associated mortality and hospitalisations.[19] Pandemic findings regarding telemedicine have demonstrated the benefits for patients,[20] although digital literacy gaps mean that those findings cannot be generalised to all patients.[21 22] Nonetheless, it has been demonstrated by our group, over almost a decade of development, that a telemedicine system reduces admissions and mortality in patients with HF,[23] and furthermore, that there was no deterioration in effectiveness associated with the COVID-19 pandemic period.[24]

We also found that mortality associated with digestive, cancer and blood diseases was reduced, possibly explained, relative to CV diseases, by a longer latency period and less sensitivity to the urgently implemented pandemic-related capacity adaptations and changes mentioned above. However, further longer-term studies are necessary to analyse excess mortality patterns as observed in Spain and apparently normalising as of around July 2022,[25] especially considering the success of COVID-19 vaccination programmes.

Our findings coincide with known and proven information on the pathophysiology of COVID-19 research and so would appear to yield convincing findings, especially considering the source of our data and the methodology. The main limitation is that the data were treated in an aggregated manner since they were obtained from the Spanish INE, with no breakdown of events and possible associated variables. Despite this, the data are public and our results are corroborated by results published locally by a number of hospitals.

CONCLUSIONS

Excess mortality in Spain, in the pandemic waves of 2020, was not only related to COVID-19 and its complications, but also indirectly to other diseases, most importantly CV diseases, while mortality due to digestive, cancer and blood diseases was reduced. It remains necessary to explore whether these trends have changed since 2020 and what knock-on effects may result from a lack of control of risk factors and other pathologies during the main pandemic waves when healthcare systems needed to deal with the care of patients with COVID-19.

Contributors FR-S: conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualisation, writing–original draft and writing–manuscript review and editing and garantor; JCRN: data curation, formal analysis, investigation, methodology, software, supervision, validation, visualisation, writing–original draft; RMG-A: data curation, formal analysis, investigation, methodology, software, supervision, validation, visualisation, writing–original draft; SC-S: conceptualisation, investigation, supervision, validation, visualisation, writing–original draft and writing–manuscript review and editing; JRGJ: conceptualisation, investigation, supervision, validation, writing–manuscript review and editing.

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