

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Patients awaiting surgery for neurosurgical diseases during the first wave of the COVID-19 pandemic in Spain: a multicentre cohort study.
AUTHORS	Castaño-Leon, Ana; Paredes, Igor; Lagares, Alfonso; Gomez, Pedro A; González-Leon, Pedro; Perez-Nuñez, Angel; Jiménez-Roldán, Luis; Delgado-Fernández, Juan; Eiriz Fernández, Carla; García-Pérez, Daniel; Moreno-Gómez, Luis; Esteban-Sinovas, Olga; Delgado-López, Pedro; Martín-Alonso, Javier; Kaen, Ariel; Tirado-Caballero, Jorge; Ordóñez-Carmona, Marta; Arteaga-Romero, Francisco; González-Pombo, Marta; F Alén, José; Gil-Simoes, Ricardo; Torres, Cristina; Navas-García, Marta; Blasco García de Andoain, Guillermo; Frade-Porto, Natalia; González-Tarno, Patricia; Martín Segura, Adrian; Gelabert-González, Miguel; Menéndez-Cortezón, Beatriz; Rodríguez-Botana, Brais; Pérez-Alfayate, Rebeca; Fernández-García, Carla; Ferrández-Pujante, Borja; Vargas-Jiménez, Andres; Cotúa, Carlos; de la Lama, Adolfo; Calero Félix, Lourdes; Ruiz-Juretschke, Fernando; García-Leal, Roberto; Valera-Melé, Marc; Casitas Hernando, Vicente; Rivero, Belén; Orduna-Martínez, Javier; Casado Pellejero, Juan; Fustero De Miguel, David; Díaz Molina, Jorge; Moles Herbera, Jesús; Castelló-Ruiz, Maria; Gomar-Alba, Mario; García-Pérez, Fernando; Hernández-García, Borja; Villaseñor-Ledezma, Jorge; Otero-Rodríguez, Álvaro; Ailagás de las Heras, Juan; Gonçalves-Estella, Jesus; Sousa-Casasnovas, Pablo; Pascual-Argente, Daniel; Ruiz Martín, Laura; Roa Montes de Oca, Juan; Arandía Guzmán, Daniel; García Martín, Andoni; Torres Carretero, Luis; Garrido Ruiz, Alejandra; Calvo, Marta; Miranda-Lloret, Pablo; Rodríguez-Cadarso, Miguel; Antón, Joan; Roca Barber, Amparo; Quiroz-Tejada, Arnold; Carbayo-Lozano, Guillermo; Bermúdez, Garazi; Paternain Martin , Clara; De la Fuente Villa , Pablo; Fidalgo De la Rosa, Marina; Sistiaga-Gracia, Íñigo; Zabalo, Gorka

VERSION 1 – REVIEW

REVIEWER	Thelin, Eric Karolinska Institutet, Department of Clinical Neuroscience
REVIEW RETURNED	10-Mar-2022
GENERAL COMMENTS	<p>Title: Patients awaiting surgery for neurosurgical diseases during the first wave of the COVID-19 pandemic in Spain: a nationwide cohort study.</p> <p>Main message: Through a questionnaire circulated among neurosurgical clinics in Spain, the authors collected retrospective information concerning why neurosurgery was postponed during the Covid19 pandemic's first wave. In general, surgery was not</p>

	<p>performed in healthier (except respiratory issues, and in heavier) patients. Degenerative spinal and functional surgery were primarily affected, deterioration was seen in many of these patients. Surgery did not increase the risk of Covid19. Independent risk factors of delayed surgery were levels of Covid19 in the community (and having a degenerative spinal injury and having non-acute conditions in general).</p> <p>English language: Needs to be revised, there are several spelling mistakes/grammatical errors throughout the text.</p> <p>Main issues:</p> <ol style="list-style-type: none"> Spain has a population of about 50 million inhabitants, you included hospitals covering an area of approximately 10 million. Can you really call that a “nationwide” study? You point this out in the limitation as well, please consider changing the title. I would call it a retrospective questionnaire study This is primarily a study on patients waiting for surgery to perform degenerative spinal surgery and to be honest, I think it would make perfect sense to postpone elective degenerative spinal surgery during a healthcare crisis, would not the authors agree? I think this should be elaborated on better in the study. The pandemic was a general health care crisis, and priorities had to be made (and I think this signals that Spain did a pretty good job at doing that). How many patients usually get to wait because of bed/resource shortages etc. in Spain? How common is it for instance to have a degenerative spine surgery delayed when not in a Covid19 pandemic? This needs to be included somehow to get an understanding of how bad the numbers look. To me, these numbers do not look to bad. Only two patients died (and the oncology patient might have died either way, and the degenerative spine patient probably did not die from the spine injury) Figure 2, please add a normal year for reference (or even better, an average the last five years) as to see if the patient burden was significantly different from any other year. <p>Specific issues:</p> <ol style="list-style-type: none"> I recommend to authors to read the author guidelines at https://bmjopen.bmj.com/pages/authors/#research as there are currently some formatting errors in the text (e.g the incorrect text is entered in subheading) On page 16, there is a part of a Table heading that needs to be added to Table 2.
--	---

REVIEWER	Inamasu, Joji Fujita Health University Hospital, Neurosurgery
REVIEW RETURNED	09-Jun-2022

GENERAL COMMENTS	<p>1. The word [deterioration] needs to be used carefully, because its meaning differs from disease to disease. While deterioration in degenerative spine diseases may only mean worsening of leg pain, deterioration in brain tumors may mean worsening in mental status with unfavorable consequences. In this study, how [deterioration] had been evaluated/confirmed in each case has</p>
-------------------------	---

	<p>been mentioned only briefly. The difference in the follow-up method from disease to disease might have influenced the accuracy of the deterioration rate: in tumor patients, the authors described that all patients were followed by clinical telephone interviews and imaging (P13L274-5). On the other hand, spine disease patients seem to have been followed differently (P13L270-2). Therefore, the lack of uniformity in the degree of [deterioration] could be another limitation of this study,</p> <p>2. In relation to the deterioration, the authors reported relatively high frequency of deterioration in functional diseases. The functional disease category is actually broad, and many functional diseases are not rapidly progressive. Why the frequency had been high (39.5%) in your cohort? Because your cohort had included many Parkinson disease patients?</p> <p>3. The quality of English language was suboptimal, requiring extensive review by a professional language editor,</p>
--	--

VERSION 1 – AUTHOR RESPONSE

Formatting Amendments (where applicable):

***Please delete the ‘Acknowledgements’ statement and please change the heading ‘Availability of data and materials’ to ‘Data availability statement’.**

Response:

We deleted Acknowledgements statement and change the heading as suggested.

Editorial comments:

1. Please revise the abstract to ensure that it is formatted according to our Instructions for Authors (<http://bmjopen.bmj.com/pages/authors/#research>), including all relevant subheadings and required details. Note that this should include a ‘Design’ section between the ‘Objective’ and ‘Setting’ section (some of the information currently in the ‘Participants’ section should be in the ‘Design’ section). The ‘Setting’ section should describe the study setting (eg, geographical scope and timing) only; background information should be included in the ‘Objective’ section before the aim of the study is stated. ‘Primary and secondary outcome measures’ should be a separate subsection from ‘Participants’.

Response:

Abstract has been edited to fulfil the format and content required by BMJ open

“Objective: The large number of infected patients requiring mechanical ventilation has led to the postponement of scheduled neurosurgical procedures during the first wave of the COVID-19 pandemic. The aim of this study was to investigate the factors that influence the decision to postpone scheduled neurosurgical procedures and to evaluate the effect of the restriction in scheduled surgery adopted to deal with the first outbreak of the COVID-19 pandemic in Spain on the outcome of patients awaiting surgery.

Design: This was an observational retrospective study.

Settings: A tertiary-level multicentre study of neurosurgery activity between March 1 and June 30, 2020.

Participants: A total of 680 patients awaiting any scheduled neurosurgical procedure were enrolled. 470 patients (69.1%) were awaiting surgery because of spine degenerative disease, 86 patients

(12.6%) due to functional disorders, 58 patients (8.5%) due to brain or spine tumours, 25 patients (3.7%) due to cerebrospinal fluid (CSF) disorders and 17 patients (2.5%) due to cerebrovascular disease.

Primary and secondary outcome measures: The primary outcome was mortality due to any reason and any deterioration of the specific neurosurgical condition. Second, we analysed the rate of confirmed SARS-CoV-2 infection.

Results: More than one-quarter of patients experienced clinical or radiological deterioration. The rate of worsening was higher among patients with functional (39.5%) or CSF disorders (40%). Two patients died (0.4%) during the waiting period, both because of a concurrent disease. We performed a multivariate logistic regression analysis to determine independent covariates associated with maintaining the surgical indication. We found that community SARS-CoV-2 incidence (OR=1.011, $p < 0.001$), degenerative spine (OR=0.296, $p = 0.027$) and expedited indications (OR=6.095, $p < 0.001$) were independent factors for being operated on during the pandemic.

Conclusions: Patients awaiting neurosurgery experienced significant collateral damage even when they were considered scheduled procedures.”

2.The ‘Results’ section of the abstract does not seem to align with the ‘Primary and secondary outcome measures’, as the Results section does not report on mortality or COVID infection. Please revise to clarify and to ensure the object, outcomes, and results all align, both in the abstract and in the main text.

Response:

Results section has been edited to ensure alignment with the aims and primary/secondary measures. “Results: More than one-quarter of patients experienced clinical or radiological deterioration. The rate of worsening was higher among patients with functional (39.5%) or CSF disorders (40%). Two patients died (0.4%) during the waiting period, both because of a concurrent disease. We performed a multivariate logistic regression analysis to determine independent covariates associated with maintaining the surgical indication. We found that community SARS-CoV-2 incidence (OR=1.011, $p < 0.001$), degenerative spine (OR=0.296, $p = 0.027$) and expedited indications (OR=6.095, $p < 0.001$) were independent factors for being operated on during the pandemic.”

3.Please update the abstract Results section to include numerical data, including measures of statistical significance (if appropriate), for all reported findings.

Response:

We have included numerical data and statistical significance in the results section of the abstract.

“We found that community SARS-CoV-2 incidence (OR=1.011, $p < 0.001$), degenerative spine (OR=0.296, $p = 0.027$) and expedited indications (OR=6.095, $p < 0.001$) were independent factors for being operated on during the pandemic.”

4.Please revise the ‘Strengths and limitations of this study’ section of your manuscript (after the abstract). This section should contain up to five short bullet points, no longer than one sentence each, that relate specifically to the methods. The novelty, aims, results or expected impact of the study should not be summarised here.

Response:

We edited the Strengths and limitations of this study as you recommended

- “• This was a multicentre, tertiary-level, observational retrospective study of patients awaiting any neurosurgical procedure during the first wave of the SARS-CoV-2 pandemic in Spain.
- The primary outcome was mortality due to any reason and any deterioration of the specific neurosurgical condition.
- This study is a snapshot of an evolving pandemic with huge variation of its effects between centres according to the community SARS-CoV-2 incidence at the time of the first peak of the pandemic and hospital size.
- The quality of the data depends on the accuracy of data collection by the collaborators, although active supervision and discussion of discordant information was performed during the study.”

5. Please ensure that you have highlighted the key methodological limitations of the study in the ‘Strengths and limitations of this study’ section and that you have fully discussed these and other relevant limitations in the Discussion section of the main text.

Response:

The third and fourth points covered limitations of the study that were also discussed in the main text.

“This study is a snapshot of an evolving pandemic with huge variation of its effects between centres according to the community SARS-CoV-2 incidence at the time of the first peak of the pandemic and hospital size.

- The quality of the data depends on the accuracy of data collection by the collaborators, although active supervision and discussion of discordant information was performed during the study.”

6. The second sentence in the ‘Patient and Public Involvement’ statement is confusing – how could the results be shared with the participants in a way that elicits information that contribute to the results? This does not make sense. Please revise to clarify.

Response:

We edited this sentence for better understanding

“After the publication of the study, there are plans for the results to be disseminated to the patient community affected by this research, which would help to motivate them to inform their physician when they experience any kind of worsening”

7. Please update the ‘Ethics approval and consent to participate’ statement to include the name of the coordinator center.

Response:

We included the name of the coordinator center.

“The institutional review board (IRB) of the coordinator centre (Hospital universitario 12 de Octubre) gave ethical approval (CEIM 20/217), and then local principal investigators were responsible for endorsing ethical approval in their IRB. Informed consent was waived by the principal investigator’s IRB.”

8. Please complete a thorough proofread of the text and correct any spelling and grammar errors that you identify. It may be useful to ask a native English-speaking colleague to assist you or to enlist the help of a professional copy-editing service, if possible, to ensure any English grammar issues or problems with respect to clarity of meaning are identified and addressed.

Response:

The manuscript has been reviewed by professional editors to check for grammar, spelling, and clarity problems.

Reviewer: 1

Dr. Eric Thelin, Karolinska Institutet

Comments to the Author:

Title: Patients awaiting surgery for neurosurgical diseases during the first wave of the COVID-19 pandemic in Spain: a nationwide cohort study.

Main message: Through a questionnaire circulated among neurosurgical clinics in Spain, the authors collected retrospective information concerning why neurosurgery was postponed during the Covid19 pandemic's first wave. In general, surgery was not performed in healthier (except respiratory issues, and in heavier) patients. Degenerative spinal and functional surgery were primarily affected, deterioration was seen in many of these patients. Surgery did not increase the risk of Covid19. Independent risk factors of delayed surgery were levels of Covid19 in the community (and having a degenerative spinal injury and having non-acute conditions in general).

English language: Needs to be revised, there are several spelling mistakes/grammatical errors throughout the text.

Response:

The manuscript has been reviewed by professional editors to check for grammar, spelling, and clarity problems.

Main issues:

1. Spain has a population of about 50 million inhabitants, you included hospitals covering an area of approximately 10 million. Can you really call that a “nationwide” study? You point this out in the limitation as well, please consider changing the title. I would call it a retrospective questionnaire study

Response

We totally agree with your comment about the limited coverage of the national situation by our data. We discussed it in the main text as you mentioned and pointed it out in the “Strengths and limitations” section after the abstract. We have changed the title to “Patients awaiting surgery for neurosurgical diseases during the first wave of the COVID-19 pandemic in Spain: a multicentre cohort study” and deleted the term “nationwide” along the main text. We prefer to not use your suggested title because it can lead to misunderstanding of the methods we have used. All the collaborator centres collected patients’ data individually and reviewed the clinical outcome at the end of the study. We analysed all these data available in a common electronic web database. Questionnaires usually ask experts about their protocols, impression or opinions but are not based in individually collection of data as we did.

2. This is primarily a study on patients waiting for surgery to perform degenerative spinal surgery and to be honest, I think it would make perfect sense to postpone elective degenerative spinal surgery during a healthcare crisis, would not the authors agree? I think this should be elaborated on better in the study. The pandemic was a general health care crisis, and priorities had to be made (and I think this signals that Spain did a pretty good job at doing that).

Response

In a health care system crisis like the first wave of the COVID pandemic, we did not regret to have postpone scheduled degenerative spine procedure as resources were extremely limited. However, the aim of this study is to evaluate the consequences of that measure on patient's outcome and be aware of the further effect of going on this measure during the future waves. Although degenerative spine disease is not a life-threatening condition, a delayed treatment can be associated with loss of functional recovery and increase of indirect costs due to work absenteeism for a society struggling with the economic consequences of the lock-down.

We have elaborated more this issue in the main text:

“According to our data, the largest shift to being nonoperated during the first peak of the pandemic was experienced by patients with spine degenerative disease, and it remained the only clinical condition independently associated with postponed procedures. When we compared the pre-pandemic and pandemic conditions (Figure 3), the median waiting time of these patients raised significantly, especially in centres with high burden of COVID patients. Of these patients, 27% experienced deterioration during the waiting period even when telephone follow-up was provided to them. We could not imagine the application of another triage structure that would have allowed these procedures to be performed when resources were extremely limited. However, the aim of this study is to evaluate the consequences of that measure on patient outcomes and to be aware of the further effect of going on this measure during future waves. Although these conditions are not life-threatening, delayed treatment can influence definite loss of functionality²³ and increase indirect costs related to work absenteeism. Consequently, psychological symptoms such as anger and sadness and the economic impact due to surgical cancellation of elective surgeries have also been documented²⁴.”

3. How many patients usually get to wait because of bed/resource shortages etc. in Spain? How common is it for instance to have a degenerative spine surgery delayed when not in a Covid19 pandemic? This needs to be included somehow to get an understanding of how bad the numbers look. To me, these numbers do not look to bad. Only two patients died (and the oncology patient might have died either way, and the degenerative spine patient probably did not die from the spine injury)

Response

Only 2 patients died during the study period, one oncology patient and one degenerative spine disease patient, both deaths were related to concurrent diseases. We suggest that telephone supervision is effective to detect life-threatening worsening that could be managed even during health care crisis. We have added this comment into the discussion.

“Only 2 patients died during the study period, one oncology patient and one degenerative spine disease patient, and both deaths were related to concurrent diseases. We consider that telephone supervision is effective in detecting life-threatening worsening that could be managed even during health care crises. However, more than a quarter of the patients awaiting surgery during this period of the pandemic experienced a deterioration of their clinical condition that could not be dealt with during the pandemic.”

On the other hand, we totally agree with you that a reference to the pre-pandemic situation is needed. We have asked for an additional effort to the collaborator centres to collect the median waiting time for degenerative spine disease before and after the beginning of the pandemic (2019 and 2020). Also, the total number of patients that were waiting for a scheduled procedure (all diseases) at the end of 2019 and 2020 were compared. We have observed a significant increase in the median time that patients were waiting to be operated for degenerative spine disease, especially for those centres with higher burden of COVID patients.

“In Figure 2, we display for each epidemiological week the number of new inclusions in the surgical list, number of patients being operated on and the remaining number of patients waiting for surgery and its relationship with community SARS-CoV-2 incidence. Data regarding the epidemiological weeks before the start of data collection in this study are limited to those patients who were included in the surgical list during those weeks and were not operated on by the end of the timeframe of this study. Thus, we found that there was a reduction in the number of new inclusions in the surgical list while the first wave of the pandemic evolved. This occurred even when the community SARS-CoV-2 incidence declined significantly, leading to a partial recovery of scheduled surgical activity. However, we have also compared the total number of patients who were waiting for a scheduled procedure at

the end of 2019 and 2020 and the median waiting time for degenerative spine disease for the same periods (data available from our Ministry of Health. We detected an important increase in median time that patients were waiting to be operated on for degenerative spine disease proportional to the COVID-19 burden (Figure 3)”

4. I Figure 2, please add a normal year for reference (or even better, an average the last five years) as to see if the patient burden was significantly different from any other year.

Response

As we have mentioned, we added an additional figure to show the differences in the total number of patients waiting for surgery (all diseases) and the median days that were waiting until surgery for degenerative spine disease in 2019 and 2020. The effect has been related to the grade of burden of the pandemic for each center. In figure 2 data are displayed for each epidemiological week to follow the change in the rate of COVID19 infections but we consider it was clearer to see the cumulative change for a year period as you suggested using a different figure.

Specific issues:

1. I recommend to authors to read the author guidelines

at <https://bmjopen.bmj.com/pages/authors/#research> as there are currently some formatting errors in the text (e.g the incorrect text is entered in subheading)

Response

We edited the manuscript following editorial comments.

2. On page 16, there is a part of a Table heading that needs to be added to Table 2.

Response

Unfortunately, we do not understand this comment. Table 2 and 3 did not share any heading.

Reviewer: 2

Dr. Joji Inamasu, Fujita Health University Hospital

Comments to the Author:

1. The word [deterioration] needs to be used carefully, because its meaning differs from disease to disease. While deterioration in degenerative spine diseases may only mean worsening of leg pain, deterioration in brain tumors may mean worsening in mental status with unfavorable consequences. In this study, how [deterioration] had been evaluated/confirmed in each case has been mentioned only briefly. The difference in the follow-up method from disease to disease might have influenced the accuracy of the deterioration rate: in tumor patients, the authors described that all patients were followed by clinical telephone interviews and imaging (P13L274-5). On the other hand, spine disease patients seem to have been followed differently (P13L270-2). Therefore, the lack of uniformity in the degree of [deterioration] could be another limitation of this study,

Response

We understand your consideration, but the aim of the study was to describe the outcome (mortality, deterioration or SARSCoV2 infection) of those patients that were waiting for surgery between March and June of 2020. All patients irrespectively of their specific type of neurosurgical pathology were followed up by telephone calls and serial neuroimaging studies were done in case of suspicion of worsening. The definition of deterioration is based on the opinion of the attending neurosurgeon for each patient, and we were not able to discern the symptoms or radiological changes experienced by each patient.

We have edited the explanation about how the follow up was done and added the broad definition of deterioration as a limitation of the study.

“Patient outcomes were reviewed at least up to the end of the period of inclusion of the study. All patients were followed by clinical telephone interviews, and imaging studies were performed in cases of suspicion of worsening according to the attending neurosurgeon..”

“This study has some limitations. First, this study is a snapshot of an evolving pandemic with huge variation of its effects between centres according to the community SARS-CoV-2 incidence at the

time of the first peak of the pandemic and hospital size. Although we launched a national call to collaborate, the registry covered data from neurosurgical departments from 6 out of 17 Spanish main regions; thus, there is a risk of bias to overrepresentation of centres more severely affected by the first wave of the pandemic, as represented by the percentage of total beds dedicated to COVID-19 patients. Second, the definition of deterioration is based on the opinion of the attending neurosurgeon for each patient, and we were not able to discern the symptoms or radiological changes experienced by each patient.”

2. In relation to the deterioration, the authors reported relatively high frequency of deterioration in functional diseases. The functional disease category is actually broad, and many functional diseases are not rapidly progressive. Why the frequency had been high (39.5%) in your cohort? Because your cohort had included many Parkinson disease patients?

Response

Thank you for your suggestion. We have reviewed the details of the patients with functional disease, and we found that 60% were patients with chronic pain (such as chronic back pain, complex regional pain syndrome, trigeminal neuralgia), 28% were patients with refractory epilepsy and 12% were patients with Parkinson disease or other movement disorders. Among these three main categories, the group with the higher rate of worsening was the epilepsy subgroup of patients (45,8% experienced deterioration)

We have added this information into the main text:

“The subgroups of patients with the highest rate of deterioration were those waiting for functional neurosurgery (39.5%) and those with CSF disorders (40%). Among functional neurosurgical diseases, 60% were patients with chronic pain (such as chronic back pain, complex regional pain syndrome, trigeminal neuralgia), 28% were patients with refractory epilepsy and 12% were patients with Parkinson’s disease or other movement disorders. Among these three main categories, the group with the highest rate of worsening was the epilepsy subgroup of patients (45.8% experienced deterioration).”

3. The quality of English language was suboptimal, requiring extensive review by a professional language editor,

Response

The manuscript has been reviewed by professional editors to check for grammar, spelling, and clarity problems.