

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Effects of healthcare system transformations spurred by the coronavirus disease 2019 pandemic on management of stroke and STEMI: A registry-based cohort study in France
AUTHORS	Lesaine, Emilie; Francis, Florence; Domecq, Sandrine; Bijon, Marine; Cetrin, Laura; Coste, Pierre; Lhuire, Quentin; Miganeh-Hadi, Sahal; Pradeau, Catherine; Rouanet, François; Sevin, Floriane; Sibon, Igor; Saillour, Florence; AVICOVID Group, AVICOVID Group

VERSION 1 – REVIEW

REVIEWER	Olié, Valérie Santé publique France
REVIEW RETURNED	17-Feb-2022

GENERAL COMMENTS	<p>This study conducted on two large cohorts evaluate the impact of the healthcare system transformations due to COVID-19 pandemic on stroke and STEMI management in the Nouvelle Aquitaine region. The data used in this analysis are of very good quality, with an exhasutivity of hospitalized cases and a wealth of information collected, particularly on the various delays in management. This study provides some original results, not yet described in the literature, on the impact of Covid19 on the management of other pathologies, even if the results are not completely extrapolable to regions more affected by Covid than Nouvelle Aquitaine. The statistical analyses are appropriate and robust, The limitation of the study are correctly discussed by the authors.</p> <p>However, several points should be raised. The main one concerns the assumption made by the authors that it is the « Plan Blanc » that has led to an improvement in the management of STEMI patients by reducing management delays significantly for STEMI and borderline significantly for Stroke. Is it possible to consider that the significant decrease in admissions for these two pathologies during the first wave, observed in other French studies, could have contributed to a decrease in delays thanks to a fluidification of the STEMI and Stroke pathway? Please discuss this hypothesis</p> <p>The authors give numbers of patients for each period. The periods having very different lengths, it is difficult to perceive this significant decrease in the number of daily patients admitted during the first lockdown. Could they add the average numbers of patients per day or per week over these three periods. Is this parameter related to management delays?</p> <p>Strokes admitted during the wave have different characteristics than those admitted before the wave. They are younger, have fewer risk factors (diabetes, hypertension, dyslipidemia) and have less severe strokes. This result may seem surprising. Indeed, one of the hypotheses to explain the decrease in hospitalizations for stroke</p>
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	<p>during the first lockdown would be that only the most serious strokes were admitted to hospital and that less serious strokes with small deficits would have remained at home. This should result in more severe patients being selected for hospitalization. This has been observed at the national level in France but does not seem to be the case in Nouvelle-Aquitaine. Do the authors have an explanation for the less severe profile of strokes during the first wave?</p> <p>Is the origin of the strokes (home, nursing home) indicated in the 2 databases? Was it modified during the wave? This could provide information on the different profile of stroke patients in the first wave. Finally, do the authors have access to hospital mortality for these 2 diseases? Was it modified during this period?</p>
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REVIEWER	<p>Danchin, Nicolas Hôpital Européen Georges Pompidou, Université René Descartes, Department of Cardiology</p> <p>None, except that one of the co-authors previously participated in a study that we led on AMI admissions during the COVID lock-down in France.</p>
REVIEW RETURNED	28-Feb-2022

GENERAL COMMENTS	<p>The question raised in this study is important, and the authors should be congratulated to try and provide answers. However, I have major issues with the article such as presented.</p> <p>Methods:</p> <p>The wording of the sentence “The two cohorts were constituted of all adult patients, living in metropolitan France, with recent stroke or STEMI, admitted to a care structure involved in the CNV registry between January 1st 2019 and August 31 2020” may be confusing, giving the feeling that all patients with STEMI or stroke in France were included in the study. I suggest the following wording: “The two cohorts were constituted of all adult patients, living in metropolitan France, and admitted to a care structure involved in the CNV registry with recent stroke or STEMI, between January 1st 2019 and August 31 2020”.</p> <p>A major effort should be made to simplify the description of the methods, which is currently extremely difficult to understand, beginning by explaining what type of institutions participate in the CNV registry. This is a major issue, to understand how the current findings may be representative (or not) of what was observed in all institutions in France during the period studied. In other words, are the cohorts population-based or not?</p> <p>Definition of the pre-, per- and post-wave periods: why were those specific dates chosen? In particular why choose the 10th of February to define the beginning of the first wave? On the 17th of February, only 12 cases were confirmed in France (Le Monde, 17 Feb 2020), and the lock-down was implemented mid-March ...</p> <p>Conversely, the post-wave period includes the month of August, which is holiday season, which may modify management patterns. The definition of the 3 periods is a major issue; including one month with only few documented cases in the “per-wave” period will result in the dilution of the end-point variables.</p> <p>First paragraph of the Results. Provide minimal details for the STEMI cohorts (and not only for the stroke cohorts).</p> <p>Second paragraph: avoid using “Only trends could be observed”. There were no statistically significant differences in any of the characteristics studied. Likewise, later on, avoid “tended to increase”, “trends” etc. Please remain factual, and not interpretative, in the results.</p>
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	<p>Discussion: Comparison with the literature. A previously published French study (ref 7) showed no change in the time from symptom onset to admission in STEMI patients during the lock-down period. Strengths and limitations: the authors spend too much time complimenting themselves on their work, and not enough describing its true limitations. For instance, only those STEMI patients admitted within 24 hours of symptom onset were included. It can't be excluded that the proportion of patients admitted more than 24 hours after onset may have been higher during the pandemic. Also, they did not analyze the number of hospital admissions for stroke or STEMI on a weekly basis during the different periods.</p> <p>The authors use too many abbreviations, many of which are unconventional and therefore difficult to understand.</p>
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VERSION 1 – AUTHOR RESPONSE

Our responses to comments of the first Reviewer - Dr. Valérie Olié, Santé publique France – The French Public Health Agency

Comments to the Author:

This study conducted on two large cohorts evaluate the impact of the healthcare system transformations due to COVID-19 pandemic on stroke and STEMI management in the Nouvelle Aquitaine region. The data used in this analysis are of very good quality, with an exhasutivity of hospitalized cases and a wealth of information collected, particularly on the various delays in management. This study provides some original results, not yet described in the literature, on the impact of Covid19 on the management of other pathologies, even if the results are not completely extrapolable to regions more affected by Covid than Nouvelle Aquitaine. The statistical analyses are appropriate and robust, The limitation of the study are correctely discussed by the authors. However, several points should be raised.

1. The main one concerns the assumption made by the authors that it is the « Plan Blanc » that has led to an improvement in the management of STEMI patients by reducing management delays significantly for STEMI and borderline significantly for Stroke. Is it possible to consider that the significant decrease in admissions for these two pathologies during the first wave, observed in other French studies, could have contributed to a decrease in delays thanks to a fluidification of the STEMI and Stroke pathway? Please discuss this hypothesis

We thank the Reviewer for the comment that leads us to a better analysis of mechanisms of the impact of the hospital reorganizations.

We think our data don't support the reviewer's hypothesis in favor of an improvement of management delays linked to a coming down of patient hospital admissions. Our response to the reviewer features three main points:

At first. As pointed out by the reviewer, we have found that the « plan blanc » has led to an improvement in the management of STEMI and in a lesser degree of strokes. This finding resulted from a multivariate model analyzing the independent effect of the "plan blanc", taking into account confounding factors identified by the DAG method. Hospital activity (Emergency services activity) was included into the models. So, the positive effect of the "plan blanc" on the management delays was independent of the variations of the hospital activity.

This comment led us to better point out in the discussion that the multivariate models took into account hospital activity as confounding variables.

In the discussion (Strength and weaknesses): "The explanatory analyses present robust results, including appropriate confusion variables identified by the DAG method. The large panel of data collected allowed the integration of a large variety of confusion factors, including clinical characteristics, socio-geographical factors, and acute care management pathway data and hospital activity." p15

Second. In the descriptive analysis, we did not find any global decreasing of the management delays during the per-wave period; they have reduced in the SCA ST+ cohort and they have rather increased in the stroke cohort. So, the management delays variations during the per-wave period was not uniform; that is not consistent with the hypothesis so that management delays variations would be the result, even in part, of the patient admission decrease.

Third. Our data are not consistent with a global decrease of STEMI and stroke patient admissions during the per-wave period. Indeed, we have found a first decrease at the beginning of the per-wave period followed by a progressive increase till the end of lockdown period. Our data are completely consistent with those of a regional emergency services monitoring (ORU NA) and with national data recently published in the journal Stroke. So, the hypothesis of an effect of patient admission decrease is not valuable in our study because no uniform decrease was observed during the whole per-wave period.

This valuable comment led us, in the result section, to better present the evolutions of stroke and STEMI patient inclusions, particularly during the per-wave period, and, in the discussion section, to discuss this findings.

Result section: "Study sample included a total of 9,218 patients: 6,008 in the pre-wave period, 1,487 in the per-wave period and 1,723 in the post-wave period. Patient inclusion was stable during the pre and post-wave periods (weekly mean number (SD) of inclusions: 32 (6) STEMI patients pre-wave, 32 (5) STEMI patients post-wave, 83 (8) stroke patients pre-wave, 75 (7) stroke patients post-wave); in the beginning of the per-wave period (week 7 to week 15) was observed a coming down of inclusions of stroke (lowest weekly number of stroke inclusions: 75 patients) and STEMI patients (lowest weekly number of STEMI inclusions: 24 patients), followed by a slow increase till the end of the per-wave period." p7

In the discussion (comparison with the literature): "Contrarily to studies having found a global decrease of STEMI and stroke patient admissions during the per-wave period (31), we have highlighted variation of these admissions in two steps, with a first decrease at the beginning of the per-wave period followed by a progressive increase till the end of lockdown period. Our data that are completely consistent with those of the regional emergency services observatory producing information about the daily admissions number in each emergency service in the Aquitaine region (ORU NA) and of a French study on the evolution of stroke admission during the first lockdown period, can be explained by the weak spread of the Covid-19 virus in the Aquitaine region during the first wave of the pandemic.(32,33)". p14

2. The authors give numbers of patients for each period. The periods having very different lengths, it is difficult to perceive this significant decrease in the number of daily patients admitted during the first lockdown. Could they add the average numbers of patients per day or per week over these three periods. Is this parameter related to management delays?

We thank the Reviewer for her suggestion. In the result section, we have added information on the weekly mean number of stroke and STEMI inclusions in each period. As the inclusion rhythm was stable during the pre and post-wave periods, we added the weekly mean number of inclusions of the whole both periods. The inclusion rhythm was not so stable during the per-wave period: indeed,

weekly inclusion number decreased deeply at the beginning of the period (between week 7 and week 15) and increased afterward to reach about the pre-wave period level at the end of the lockdown (week 18). So, we have added for each cohort the lowest weekly mean inclusion number of the period.

The variations of inclusion weekly number observed during the per-wave period are consistent with these retrieved by the ORU NA which is a regional observatory of the emergency services producing information on the daily admission number of each emergency service in the Aquitaine region and these of a French study on the evolution of stroke admission during the first lockdown period. This information has been added in the discussion section.

As mentioned in the previous response, the variations of inclusion weekly numbers during the per-wave period were not linked to the management delays that either increased (stroke cohort) or decreased (STEMI cohort).

Result section: "Study sample included a total of 9,218 patients: 6,008 in the pre-wave period, 1,487 in the per-wave period and 1,723 in the post-wave period. Patient inclusion was stable during the pre and post-wave periods (weekly mean number (SD) of inclusions: 32 (6) STEMI patients pre-wave, 32 (5) STEMI patients post-wave, 83 (8) stroke patients pre-wave, 75 (7) stroke patients post-wave); in the beginning of the per-wave period (week 7 to week 15) was observed a coming down of inclusions of stroke (lowest weekly number of stroke inclusions: 75 patients) and STEMI patients (lowest weekly number of STEMI inclusions: 24 patients), followed by a slow increase till the end of the per-wave period." p7

In the discussion (comparison with the literature): "Contrarily to studies having found a global decrease of STEMI and stroke patient admissions during the per-wave period (31), we have highlighted variation of these admissions in two steps, with a first decrease at the beginning of the per-wave period followed by a progressive increase till the end of lockdown period. Our data that are completely consistent with those of the regional emergency services observatory producing information about the daily admissions number in each emergency service in the Aquitaine region (ORU NA) and of a French study on the evolution of stroke admission during the first lockdown period, can be explained by the weak spread of the Covid-19 virus in the Aquitaine region during the first wave of the pandemic.(32,33)". p14

3. Strokes admitted during the wave have different characteristics than those admitted before the wave. They are younger, have fewer risk factors (diabetes, hypertension, dyslipidemia) and have less severe strokes. This result may seem surprising. Indeed, one of the hypotheses to explain the decrease in hospitalizations for stroke during the first lockdown would be that only the most serious strokes were admitted to hospital and that less serious strokes with small deficits would have remained at home. This should result in more severe patients being selected for hospitalization. This has been observed at the national level in France but does not seem to be the case in Nouvelle-Aquitaine. Do the authors have an explanation for the less severe profile of strokes during the first wave?

Our descriptive results highlighted that stroke patients were younger, had fewer risk factors and had less severe strokes during the per-wave period compared to the pre-wave period. If some studies and particularly one meta-analysis retrieved more severe and older patients during the first wave of the pandemic, several other studies found consistent results with ours. Three studies found a higher proportion of patients with low NIHSS during the per-wave period and three studies found that stroke patients were younger during this wave. Wallace and al interpreted these results as a consequence of the variations between regions of the virus spread and of the fear of contracting Covid-19 at the hospital. Another explanation is linked to the various inclusion criteria. Indeed, most studies, having found different results on stroke patient profile during the per-wave period, included patients with transient ischemic attacks; this condition was excluded from ours. These patients with resolving and

lighter symptoms were more likely to avoid hospital admission by fear of contracting the Covid-19 virus at the hospital. The first wave little affected the Aquitaine region, the fear of going to the hospital was probably less present. There were no problems of bed availability, emergency physicians were available to better identify mild strokes.

In the method section, we have more precisely noticed the inclusion criteria, especially of the patients with transient ischemic attacks.

“The stroke cohort included recent ischemic or haemorrhagic stroke patients diagnosed by brain imaging with validation by a neurovascular physician (exclusion of transient ischemic attacks), managed in 5 of the 6 EMS and 14 (including 7 stroke units) of the 20 hospitals caring more than 30 strokes per year in Aquitaine.” p5

In the discussion section, we have added a paragraph on this issue.

“Our descriptive results highlighted that stroke patients were younger, had fewer risk factors and had less severe strokes during the per-wave compared to the pre-wave period. If some studies including one meta-analysis retrieved more severe and older patients during the first wave of the pandemic, several others found consistent results with ours.(31,33–37) Three authors found a higher proportion of patients with low NIHSS during the per-wave period and three studies agreed to found younger stroke patients during this wave. Wallace and al interpreted these results as a consequence of the variations between regions of the virus spread and of the fear of contracting Covid-19 at the hospital. The first wave little affected the Aquitaine region, the fear of the hospital was probably less present.. Another explanation is linked to the various inclusion criteria. Indeed, most studies, having found different results from ours on stroke patient profile during the per-wave period, included patients with transient ischemic attacks; this condition was excluded from ours. These patients with resolving and lighter symptoms were more likely to avoid hospital admission by fear of contracting the Covid-19 virus at the hospital.”p14

4. Is the origin of the strokes (home, nursing home) indicated in the 2 databases? Was it modified during the wave? This could provide information on the different profile of stroke patients in the first wave.

We agree with the reviewer, the origin of the stroke patients would have been very useful to better understand the evolution of stroke patient profile during the first wave. However, this information is not available in the CNV registry database.

Nous have added a sentence in the discussion section highlighting the issue raised by the absence of information:

In the discussion (comparison with the literature): “Lastly, the knowledge of the origin of hospitalized patients (home, nursing homes, other hospital) would have been useful to analyze this result; this information was however not available.” p14

5. Finally, do the authors have access to hospital mortality for these 2 diseases? Was it modified during this period?

This manuscript is the first of a three-step project on the impact of the COVID-19 pandemic on stroke and STEMI patient management. Two other questions are arising concerning:

1) the clinical and social health inequalities in stroke and STEMI patient management, induced or reinforced by the Covid-19 crisis; An article is in progress.

2) the impact of the COVID-19 pandemic on the stroke and STEMI patient long term mortality and morbidity; The CNV registry has the opportunity to link with the national mortality and PMSI databases. Analyses will begin as soon as the PMSI 2021 databases are available, i.e. during the summer.

Other research questions using the SNDS databases are under consideration.

These points are mentioned in the chapter "perspectives" in the discussion:

"This is the first of a three-step project on the impact of the COVID-19 pandemic on stroke and STEMI patient management. Two other questions are arising concerning: 1) the clinical and social health inequalities in stroke and STEMI patient management, induced or reinforced by the Covid-19 crisis. 2) the impact of the COVID-19 pandemic on the stroke and STEMI patient long term mortality and morbidity."p16

Our responses to comments of the second reviewer - Dr. Nicolas Danchin, Hôpital Européen Georges Pompidou, Université René Descartes

Comments to the Author:

The question raised in this study is important, and the authors should be congratulated to try and provide answers. However, I have major issues with the article such as presented.

Methods:

1. The wording of the sentence "The two cohorts were constituted of all adult patients, living in metropolitan France, with recent stroke or STEMI, admitted to a care structure involved in the CNV registry between January 1st 2019 and August 31 2020" may be confusing, giving the feeling that all patients with STEMI or stroke in France were included in the study. I suggest the following wording: "The two cohorts were constituted of all adult patients, living in metropolitan France, and admitted to a care structure involved in the CNV registry with recent stroke or STEMI, between January 1st 2019 and August 31 2020".

We thank the Reviewer for the suggestion. We have modified the quoted sentence of the previous article version (method section) with the following one:

"The two cohorts were constituted of all adult patients, living in metropolitan France, and admitted to a care structure involved in the CNV registry with recent stroke or STEMI, between January 1st 2019 and August 31 2020." p4-5.

2. A major effort should be made to simplify the description of the methods, which is currently extremely difficult to understand, beginning by explaining what type of institutions participate in the CNV registry. This is a major issue, to understand how the current findings may be representative (or not) of what was observed in all institutions in France during the period studied. In other words, are the cohorts population-based or not?

This comment give us the opportunity to improve the presentation of the method, which omitted to present participating hospitals. We have added this information at the beginning of the method and in the discussion:

Method section: "The STEMI cohort included recent STEMI patients less than 24h from symptoms onset, managed in all the 6 EMS, 14 emergency unit (EU) and 11 cathlabs of Aquitaine. The stroke cohort included recent ischemic or haemorrhagic stroke patients diagnosed by brain imaging with validation by a neurovascular physician (exclusion of transient ischemic attacks), managed in 5 of the 6 EMS and 14 (including 7 stroke units) of the 20 hospitals caring more than 30 strokes per year in Aquitaine." p5

Discussion section: "Our study is based on the analysis of two high quality databases including a large number of stroke and STEMI patients managed in a large panel of care structures in the Aquitaine region: all the EMS, EU, and cathlabs involved in the management of STEMI patients in Aquitaine and a representative sample of care structures involved in the management of stroke patients in Aquitaine."p15

We have also removed abbreviations and some unhelpful details.

“1) in EMS, data previously entered in electronic care records are extracted from the hospital information system,

2) in emergency units (EU), data are entered prospectively by physicians in a dedicated paper or electronic care records then extracted or collected retrospectively by clinical research assistants,

3) in cathlabs or in stroke hospitalization units, data are entered prospectively by physicians in then extracted.

Data of the two cohorts are consolidated and incorporated into one data warehouse allowing the reconstructing of the whole patient STEMI or stroke management pathway. ” p5

3. Definition of the pre-, per- and post-wave periods: why were those specific dates chosen? In particular why choose the 10th of February to define the beginning of the first wave? On the 17th of February, only 12 cases were confirmed in France (Le Monde, 17 Feb 2020), and the lock-down was implemented mid-March ... Conversely, the post-wave period includes the month of August, which is holiday season, which may modify management patterns. The definition of the 3 periods is a major issue; including one month with only few documented cases in the “per-wave” period will result in the dilution of the end-point variables.

We thank the Reviewer for this his comment, which gives us the opportunity to better justify the setting up of the per-wave period time limits that is a major methodological issue of our study. Our objectives were to analyze the impact of changes in hospital organizations and use of care, spurred by the first wave of the COVID-19 pandemic. The time limits of the per-wave period had so to be defined according to the implementation of the health care reorganizations and society functioning transformations to fight against the Covid-19 pandemic. They couldn't be defined according neither to the only lockdown nor to the evolution of Covid-19 cases incidence. Indeed, if the national lockdown was the major society functioning transformation decision made to prevent the epidemic spread, health care reorganizations have already been decided and implemented before, that had changed hospital functioning and patients' management. Nor was the COVID cases incidence, underestimated in the early pandemic, right witnesses of the per-wave period beginning. Therefore, we have make the choice to make the per-wave period begin in the same time with the first hospital reorganizations implementation. First reorganizations have been implemented from early February 2020, “call to the emergency services” activity began to increase in week 8 and emergency units activity began to decline in week 7, reason why we've chosen the 10th of February (week 7) as the start of the first wave.

The end of the lockdown on May 10, 2020, corresponded with the restoration of a more sustained hospital activity and the beginning of the gradual reduction of reorganizations. It has been decided this date would correspond to the end of our per-wave period.

The post-wave period was a main issue of our study to analyze the evolution of patient management and of the impact of hospital reorganizations and use of care. However, while the CNV registries proceed to continuous data collection and inclusion, we had to stop follow-up period at the end of august, to be able to produce not too late results. The inclusion of the summer period was inescapable but we think it did raise any bias because no summer season variation have been shown neither in stroke and STEMI inclusion nor in stroke and STEMI management delays during the previous years.

To better explain these choices, we have modified the methods and the discussion as follow:

Method section: “Analyses were performed separately for each cohort. Three periods were defined according to the dates of implementation of first hospitals reorganizations in mid-February and termination of national lockdown on May 10, 2020: pre-wave (from January 1, 2019 to February 9, 2020), per-wave (from February 10 to May 10, 2020), and post-wave (from May 11 to August 31, 2020).” p7

Discussion section: "A major methodological issue consisted in the setting up of the per-wave period time limits, that, in consistency with our objectives, had to be defined according to the implementation of the health care reorganizations and society functioning transformations to fight against the Covid-19 pandemic. Therefore, we have made the choice to make the per-wave period begin in the same time with the first hospital reorganizations implementation. The date of the end of the per-wave period was decided as the one of the end of the lockdown (May 10, 2020), corresponding with the restoration of a more sustained hospital activity and the beginning of the gradual reduction of reorganizations. The post-wave period was an important issue of our study to analyze the evolution of patient management. However, while the CNV registries proceed to continuous data collection and inclusion, we had to stop follow-up period at the end of august, to be able to produce not too late results. The inclusion of the summer period was inescapable but we think it did generate any bias because no summer season variation has been shown neither in stroke and STEMI inclusion nor in stroke and STEMI management delays during the previous years."p15-16

Results

4. First paragraph of the Results. Provide minimal details for the STEMI cohorts (and not only for the stroke cohorts).

We thank the Reviewer for the suggestion. We have added descriptive elements of the sample included in the STEMI cohort (beginning of the result section).

Result section: "STEMI patient mean age was close in the three period. A lower proportion of women (24.1% vs. 27.6% and 26.6%) and a higher proportion of patient with hypertension history (54.1% vs. 48.0% and 47.1%) were observed during the per-wave period compared to the pre and post-wave periods." p7

5. Second paragraph: avoid using "Only trends could be observed". There were no statistically significant differences in any of the characteristics studied. Likewise, later on, avoid "tended to increase", "trends" etc. Please remain factual, and not interpretative, in the results.

We agree with the Reviewer's comment. We've deleted some non-significant results that were not clinically relevant and modified the phrasing of other non-significant results on "Use of care" and "Care management quality" that were relevant to the study, by avoiding the "trend" phrasing.

Result section: "During the per-wave with regard to the pre-wave period, were observed in both cohorts an increase in calls to emergency services (stroke cohort: 65.5% versus 61.5%; STEMI cohort: 81.8% versus 77.4%) and in median time from symptoms-to-care time (stroke cohort: 139 minutes versus 121 minutes; STEMI cohort: 84 minutes versus 76 minutes). These findings returned to their previous levels during the post-wave period, with the exception of calls to emergency services for stroke, which remained high." p8

"There was an increase in median EU admission-to-imaging time (91 minutes vs. 83 minutes) and a decrease in median FMC-to-procedure time (95 minutes vs. 100 minutes) during the per-wave with regard to the pre-wave period. This management time remained high for stroke (88 minutes) and increased for STEMI (102 minutes) in the post-wave period. Specifically in the stroke cohort, the proportion of IVT decreased during the per-wave compared to the pre and post-wave periods (all ischemic strokes: 14.6% vs. 19.4% and 16.7%, $p=0.011$; IVT alert patients: 31.3% vs. 42.4% and 38.8%, $p=0.011$) and the proportion of patients with an optimal pathway (call to the emergency services / MICU transport/EU) was higher during the per-wave period (59.5%) compared to the pre (57.3%) and post-wave periods (58.3%, $p=0.040$)." p11-12

The discussion was also modified:

"Globally, the stroke management times deteriorated during the pandemic, but this deterioration did not seem to be directly related to the reorganizations implemented."p13

“In both STEMI and stroke cohorts, more frequent calls to emergency services and longer times to health care system were observed during the per-wave period with regard to the pre-wave period.”p13

“Our results showing an increase in the times taken by stroke and STEMI patients to contact the health care system during the COVID pandemic are consistent with the literature, both internationally and in France.(6,13,30)”p14

Discussion:

6. Comparison with the literature. A previously published French study (ref 7) showed no change in the time from symptom onset to admission in STEMI patients during the lock-down period.

We thank the Reviewer for the comment. The referenced article 7 focused on the delay from symptoms onset to hospital admission. This global time, evaluated at median of 180 minutes, includes the patient-related alert time but also part of the pre-hospital care time. Our study was examining the evolution of symptoms-to-care time defined as the time between symptoms onset and start of management by the healthcare system (call to emergency services or emergency unit admission in case of no call to emergency services). This time, ranging from a median of 75 to 84 minutes depending on the period, includes only patient-related alert time.

The periods of time comparison also differed between these two studies. In the referenced article 7, periods were defined according to the lockdown implementation point on the March 16th, 2020: pre-lockdown (from mid-February to mid-March) and post-lockdown (from mid-March to mid-April). In our study, symptoms-to-care time was analyzed over 3 periods according to the dates of implementation of first hospitals reorganizations and changes in hospital activities: pre-wave (from January 1, 2019 to February 9, 2020), per-wave (from February 10 to May 10, 2020), and post-wave (from May 11 to August 31, 2020). So, the per-wave period in our study involved several weeks of the pre and post-lockdown periods in the referenced article 7.

In addition, inclusion criteria were also different (STEMI patients admitted to intensive cardiac care units with symptom onset fewer than 48 h before hospital admission in the referenced article 7 and STEMI patients less than 24h from symptoms onset), which may influence the time to care.

Therefore, the comparison of these times between these two studies appears difficult. We have integrated this issue in the discussion “Comparison with the literature”:

“J Mesnier et al, in a French cohort of 1,167 STEMI patients, found stable symptom onset to hospital admission times along the study period (from 4 weeks before to 4 weeks after the lockdown implementation). However, any comparison between our two studies is made difficult by differences in the management times studied and the study periods.(7)” p14

7. Strengths and limitations: the authors spend too much time complimenting themselves on their work, and not enough describing its true limitations. For instance, only those STEMI patients admitted within 24 hours of symptom onset were included. It can't be excluded that the proportion of patients admitted more than 24 hours after onset may have been higher during the pandemic.

We agree with the Reviewer's suggestion. We have tried to reduce the length of paragraphs about our strength (for examples the paragraph about the survey of hospital reorganization collection or about the strength of the models). We think we already strive to fairly analyze our weaknesses.

However, in the discussion section, we have developed the issue pointed out by the reviewer by analyzing the risk of selection bias linked to our inclusion criteria in the STEMI cohort:

“Moreover, the STEMI cohort included recent STEMI patients less than 24 hours old. Literature found a higher proportion of « late comers » STEMI (admitted over 24h after the symptom onset) during the COVID-19 pandemic, with more mechanical complications and higher mortality.(41) The exclusion of these patients from our study may have generated a selection bias inducing a risk of underestimation of the increase delay to use of care.” p15

We have also further balanced and reduced our positive comments on the strengths of the study:

“The explanatory analyses present robust results, based on models of good performance, including appropriate confusion variables identified by the DAG method.” p15

“However, we cannot exclude errors in the answers given in the questionnaires field by the health care professionals, particularly concerning the dates on which organizations were implemented or terminated, due to memory bias.” p15

8. Also, they did not analyze the number of hospital admissions for stroke or STEMI on a weekly basis during the different periods.

We thank the Reviewer for her suggestion. In the result section, we have added information on the weekly mean number of stroke and STEMI inclusions in each period. As the inclusion rhythm was stable during the pre and post-wave periods, we added the weekly mean number of inclusions of the whole both periods. The inclusion rhythm was not so stable during the per-wave period: indeed, weekly inclusion number decreased deeply at the beginning of the period (between week 7 and week 15) and increased afterward to reach about the pre-wave period level at the end of the lockdown (week 18). So, we have added for each cohort the lowest weekly mean inclusion number of the period.

The variations of inclusion weekly number observed during the per-wave period are consistent with these retrieved by the ORU NA which is a regional observatory of the emergency services producing information on the daily admission number of each emergency service in the Aquitaine region and these of a French study on the evolution of stroke admission during the first lockdown period. This information has been added in the discussion section.

As mentioned in the previous response, the variations of inclusion weekly numbers during the per-wave period were not linked to the management delays that either increased (stroke cohort) or decreased (STEMI cohort).

Result section: “Study sample included a total of 9,218 patients: 6,008 in the pre-wave period, 1,487 in the per-wave period and 1,723 in the post-wave period. Patient inclusion was stable during the pre and post-wave periods (weekly mean number (SD) of inclusions: 32 (6) STEMI patients pre-wave, 32 (5) STEMI patients post-wave, 83 (8) stroke patients pre-wave, 75 (7) stroke patients post-wave); in the beginning of the per-wave period (week 7 to week 15) was observed a coming down of inclusions of stroke (lowest weekly number of stroke inclusions: 75 patients) and STEMI patients (lowest weekly number of STEMI inclusions: 24 patients), followed by a slow increase till the end of the per-wave period.” p7

In the discussion (comparison with the literature): “Contrarily to studies having found a global decrease of STEMI and stroke patient admissions during the per-wave period (31), we have highlighted variation of these admissions in two steps, with a first decrease at the beginning of the per-wave period followed by a progressive increase till the end of lockdown period. Our data that are completely consistent with those of the regional emergency services observatory producing information about the daily admissions number in each emergency service in the Aquitaine region (ORU NA) and of a French study on the evolution of stroke admission during the first lockdown period, can be explained by the weak spread of the Covid-19 virus in the Aquitaine region during the first wave of the pandemic.(32,33)”. p14

9. The authors use too many abbreviations, many of which are unconventional and therefore difficult to understand.

We agree with the Reviewer’s comment. We have changed all EDO (emergency dispatch offices) and ALS (advanced life support) abbreviations in the manuscript by these ones: call to the emergency services and MICU (mobile intensive care units). Due to the large number of corrections, they are not

detailed.

We have also removed some unnecessary abbreviations “electronic care records (ECR)”, “hospital information system (HIS)” and “clinical research assistants (CRA)” in the method:

“1) in EMS, data previously entered in electronic care records are extracted from the hospital information system,

2) in emergency units (EU), data are entered prospectively by physicians in a dedicated paper or electronic care records then extracted or collected retrospectively by clinical research assistants,

3) in cathlabs or in stroke hospitalization units, data are entered prospectively by physicians then extracted.

Data of the two cohorts are consolidated and incorporated into one data warehouse allowing the reconstructing of the whole patient STEMI or stroke management pathway. “ p5

VERSION 2 – REVIEW

REVIEWER	Olié, Valérie Santé publique France
REVIEW RETURNED	05-May-2022
GENERAL COMMENTS	Thank you for these precisions and response. Nice job!