PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Influence of prior comorbidities and chronic medications use on the risk of COVID19 in adults: a population based cohort study in Tarragona, Spain
AUTHORS	Vila-Córcoles, Angel; Ochoa-Gondar, Olga; Satué, EVA; Torrente-Fraga, Cristina; Gomez-Bertomeu, Frederic; Vila-Rovira, Angel; Hospital-Guardiola, Immaculada; de Diego-Cabanes, Cinta; Bejarano, Ferran; Basora-Gallisà, Josep

VERSION 1 – REVIEW

REVIEWER	Anna Ssentongo Pennsylvania State University
REVIEW RETURNED	15-Jul-2020

GENERAL COMMENTS	Vila-Corcoles and colleagues did a comprehensive analysis looking at the effects of multiple conditions and drugs on the risk of developing COVID-19. They included several very detailed tables and were very detailed in the number of conditions that they included. They found increasing Age, nursing-home residence, pre-existing cancer, chronic respiratory and cardiac disease were more common in adults who developed COVID19. Smoking, receiving rennin-angiotensin-aldosterone system inhibitors, antihistamine and influenza vaccination in prior autumn were less common in those who developed COVID-19 infection. A few suggestions: 1. Reread through the manuscript for English. Some sentences are not clear. 2. In addition it would be nice to see which anti-histamine and rass inhibitors were most commonly used. Or most protective.

REVIEWER	Toan Ha University of Pittsburgh, USA
REVIEW RETURNED	23-Jul-2020

GENERAL COMMENTS	This paper investigated the association between existing conditions and risk for COVID-19 infection among middle-age and older population. While the results are not novel, it findings are of interest and can be used as the base for further study. The study found that receiving ACA-inhibitors, flu vaccination in the autumn and smoking appeared to be associated with reduced risk of COVID-19 infection, while chronic respiratory diseases, cardiac diseases and cancer related to increased the risk. I have some minor comments as below: - Add some literature regarding the association between COVID-19 infection risk and pre-existing conditions among this population

	-Please use lower case for the word " WHEREAS" in the abstract. - Line 36, under method, please use : participating primary care centers instead of participant primary cares centers. - It would be more helpful to include education and marital status of the participants in the regression models.

REVIEWER	Jonathan D. Turner Luxembourg Institute of Health, Grand Duchy of Luxembourg
REVIEW RETURNED	04-Aug-2020

GENERAL COMMENTS	The manuscript of Vila-Corcoles et al is a retrospective examination of the role that sociodemographic and medical variables play in the susceptibility to COVID-19 disease. The authors have taken a convenience cohort of 79,083 people, 77,676 of whom were community-dwelling and 1407 were nursing-home residents. This was then broken down into those that had received a PCR diagnostic test (2324 cohort members, 380 positive 1944 negative) and those that had not received a PCR test but presented to the medical system with signs/symptoms of COVID-19 disease and were presumed positive (377 cohort members). Given the uncertainty around the possible factors predisposing/protecting against SARS-COV-2 infection the study authors aimed to investigate the relationship between prior medical conditions/treatments and COVID19 infection risk among middle-aged and older adults. Overall, the paper is well organized and easy to follow and the statistical analysis well presented, but there are many points that need to be addressed before the manuscript can be considered suitable for publication. 1. The Introduction is very brief. There are now many nice peer reviewed articles highlighting many of the comorbidities studied in the manuscript and for the ease of understanding by the reader it would be good to revise and make the Introduction more detailed. There are, for example, two peer reviewed papers highlighting the need to collect sociodemographic data that the author's manuscript goes some way to answer. Conversely, the Discussion is too long, and in many places is a repetition of the results. Please shorten the Discussion and place the novel finding of this study into the wider context. 2. The authors need to ensure that they differentiate SARS-CoV-2 infection and COVID-19 disease correctly throughout the manuscript. The cover letter (the first thig I read) had this mistake. 3. The authors need to make it very clear throughout the manuscript how many participants were used in each type of calculation. Although the cohort was initially very large (79k members), only 2324 members were PCR tested. This significantly reduces the power and interest of the study, making the headline figure of 79k cohort members somewhat disingenuous. The authors need to make it clear in which calculation the clinically diagnosed (but not laboratory tested) COVID-19 patients were included in. The real numbers of people in the tested cohort need to be highlighted in the Abstract to make it more balanced and less biased. 4. The cohort (and manuscript) is fundamentally flawed. The authors try and draw conclusions on COVID-19 disease in the population, however, in their cohort, they most probably have only the cases that were severe enough to warrant medical attention

	during the epidemic. There is no consideration of the cohort members that will have been asymptomatic but SARS-CoV-2 infected, those that are oligosymptomatic, and those that had mild symptoms, that in accordance with the recommendations of the health authorities at the time were in self isolation and self-medicating. This is a major bias and flaw in the study design that must absolutely be addressed. 5. As the “real” cohort was only 2324 members, the authors need to prove that this is statistically representative of the local population (i.e. a fully representative subset not only of the 79k member cohort, but of the local population) in terms of age / gender / type of residence / comorbidities / residence location. If it is not, then the authors need to examine why there was a bias in the PCR tested cohort – this in itself might be the most interesting result that comes out of the study – why that skewed / biased population was tested. 6. Given the published data on morbidity and mortality from COVID-19, where there are many “unexplained” severe/fatal cases below age 50, the authors need to clearly argue why they only included cohort members over age 50. 7. Please discuss and defined why/how you have chosen the comorbidities included in the manuscript. 8. Regarding statistical analyses - the authors must clearly define how time was included in the HR calculation. From my reading of the manuscript, the authors were just interested in whether a study member had a positive PCR test during the 12-week study period. If this is correct, then statistically, time is not an important factor, and the correct calculation technique should be Relative Risk (aka Risk Ratio). Normally HR would be used when there is a defined time-lapse or time period from exposure to disease. As there is no contact-tracing, or consideration of when participants were exposed to SARS-CoV-2 then the use of Time and Hazard Ratio needs to be very clearly explained, or replaced, by the correct RR. 9. Statistical power – as point three above – This appears to have been calculated on the complete study. Surely this should have only been calculated on the PCR tested cohort members. Please revise accordingly. 10. Please provide statistical evidence that your study is actually representative of your geographical region / population. This was given as one of the aims of your study in the introduction and your data collected and presented to not address this.

REVIEWER	Sarah Cuschieri The University of Malta, Malta
REVIEW RETURNED	12-Sep-2020

GENERAL COMMENTS	It is an interesting article to read. The discussion section is mainly a repetition of the results. It is always recommended that the discussion (as the name implies) discusses the results (& not repeat them) by considering the "Why" and the "How" results presented as they did. Even if there isn't much information on the subject, a hypothetical reason with adequate scientific background should be mentioned. Such as why do you think that smoking was negatively associated? etc. It would

	be ideal that from your findings, recommendations that are both clinical and public health-oriented are proposed. Not just recommend more research to be done.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Anna Ssentongo
Institution and Country: Pennsylvania State University
Competing interests or state 'None declared': None declared
Please leave your comments for the authors below
Vila-Corcoles and colleagues did a comprehensive analysis looking at the effects of multiple conditions and drugs on the risk of developing COVID-19. They included several very detailed tables and were very detailed in the number of conditions that they included. They found increasing Age, nursing-home residence, pre-existing cancer, chronic respiratory and cardiac disease were more common in adults who developed COVID-19. Smoking, receiving rennin-angiotensin-aldosterone system inhibitors, antihistamine and influenza vaccination in prior autumn were less common in those who developed COVID-19 infection. A few suggestions:
1. Reread through the manuscript for English. Some sentences are not clear.
*Authors' Response (AR): Ok, the revised manuscript has been checked by a native english speaker.
2. In addition it would be nice to see which anti-histamine and rass inhibitors were most commonly used. Or most protective.
*AR: We do not know because our research database do not discriminate it. Supplementary data would be needed to explore it.

Reviewer: 2
Reviewer Name: Toan Ha
Institution and Country: University of Pittsburgh, USA
Competing interests: No conflict of interest
Please leave your comments for the authors below
This paper investigated the association between existing conditions and risk for COVID-19 infection among middle-age and older population. While the results are not novel, it findings are of interest and can be used as the base for further study. The study found that receiving ACA-inhibitors, flu vaccination in the autumn and smoking appeared to be associated with reduced risk of COVID-19 infection, while chronic respiratory diseases, cardiac diseases and cancer related to increased the risk. I have some minor comments as below:
1.-- Add some literature regarding the association between COVID-19 infection risk and pre-existing conditions among this population
Authors Response: Ok. According to the reviewer's comment, in the revised version of the manuscript (Introduction section) we have added a new paragraph and new literature references regarding the association between COVID-19 infection risk and pre-existing conditions/comorbidities (highlighted in red in the revised manuscript).
2-Please use lower case for the word "WHEREAS" in the abstract.
*AR: Ok, it has been changed.
3.-Line 36, under method, please use: participating primary care centers instead of participant primary cares centers.
*AR: Ok, it has been changed.

4.-- It would be more helpful to include education and marital status of the participants in the regression models.
*AR: We recognize that this data may be important but, unfortunately, it was not available for us.

Reviewer: 3
Reviewer Name: Jonathan D. Turner
Institution and Country: Luxembourg Institute of Health, Grand Duchy of Luxembourg
Competing interests: None Declared
Please leave your comments for the authors below
The manuscript of Vila-Corcoles et al is a retrospective examination of the role that sociodemographic and medical variables play in the susceptibility to COVID-19 disease. The authors have taken a convenience cohort of 79,083 people, 77,676 of whom were community-dwelling and 1407 were nursing-home residents. This was then broken down into those that had received a PCR diagnostic test (2324 cohort members, 380 positive 1944 negative) and those that had not received a PCR test but presented to the medical system with signs/symptoms of COVID-19 disease and were presumed positive (377 cohort members). Given the uncertainty around the possible factors predisposing/protecting against SARS-COV-2 infection the study authors aimed to investigate the relationship between prior medical conditions/treatments and COVID-19 infection risk among middle-aged and older adults. Overall, the paper is well organized and easy to follow and the statistical analysis well presented, but there are many points that need to be addressed before the manuscript can be considered suitable for publication.
1. The Introduction is very brief. There are now many nice peer reviewed articles highlighting many of the comorbidities studied in the manuscript and for the ease of understanding by the reader it would be good to revise and make the Introduction more detailed. There are, for example, two peer reviewed papers highlighting the need to collect sociodemographic data that the author's manuscript goes some way to answer. Conversely, the Discussion is too long, and in many places is a repetition of the results. Please shorten the Discussion and place the novel finding of this study into the wider context.
*Authors Response (AR): Ok, according to the reviewer's comment, in the revised manuscript we have shortened the Discussion and have revised the Introduction adding some paragraphs and new references as the reviewer requires. Changes are highlighted in red in the revised manuscript.

2. The authors need to ensure that they differentiate SARS-CoV-2 infection and COVID-19 disease correctly throughout the manuscript. The cover letter (the first thing I read) had this mistake.
*AR: Ok, according to the reviewer's comment, it has been revised throughout the manuscript.

3. The authors need to make it very clear throughout the manuscript how many participants were used in each type of calculation. Although the cohort was initially very large (79k members), only 2324 members were PCR tested. This significantly reduces the power and interest of the study, making the headline figure of 79k cohort members somewhat disingenuous. The authors need to make it clear in which calculation the clinically diagnosed (but not laboratory tested) COVID-19 patients were included in. The real numbers of people in the tested cohort need to be highlighted in the Abstract to make it more balanced and less biased.
*AR: Ok. This is a population-based study involving 79,083 persons >50 years-old who were retrospectively followed from 01/03/2020 until 23/05/2020 (the first wave of COVID-19 epidemic period in the study setting), observing an amount of 380 persons who suffered PCR-confirmed infection during the study period. All 79,083 subjects were the cohort members (77,676 community-dwelling and 1407 nursing-home residents), being all of them used as denominator to calculate incidence rates (number of events in the numerator) in the study cohort (table 1). All of them were also used (it is methodologically necessary) to calculate risks of infection (HRs) in the total study

cohort (table 2) and, consequently, all 79,083 were included in the Cox regression model to evaluate the risk for developing the outcome of interest (PCR-confirmed infection in our study). We used 77,676 participants to calculate COVID-19 incidence and risk of PCR-confirmed infection assessing community-dwelling individuals in our population (tables 3 and 4) and used 1407 subjects assessing exclusively nursing-home residents in our cohort (table 5). These numbers are exhaustively described in the Methods and Results sections throughout the manuscript and noted in the title of each table. On the other hand, as the reviewer points out, it is true that PCR testing was performed in 2324 persons of the total 79,083 cohort members (with 380 positive and 1944 negative result). This data is also described in the Results section of the manuscript (which reports positive and negative PCR testing for all people as well as for community-dwelling and nursing-home residents). This data was not highlighted in the Abstract because it was not considered as a main result and considering space restrictions. Nevertheless, following the reviewer' comment, we note it (2324 PCR tested with 1944 negative and 380 positive results) in a new sentence included in the revised abstract.

4. The cohort (and manuscript) is fundamentally flawed. The authors try and draw conclusions on COVID-19 disease in the population, however, in their cohort, they most probably have only the cases that were severe enough to warrant medical attention during the epidemic. There is no consideration of the cohort members that will have been asymptomatic but SARS-CoV-2 infected, those that are oligosymptomatic, and those that had mild symptoms, that in accordance with the recommendations of the health authorities at the time were in self isolation and self-medicating. This is a major bias and flaw in the study design that must absolutely be addressed.
*AR: We already addressed and commented this bias in the Discussion section of our initial manuscript (limitations paragraph which said: "The availability of PCR tests was scarce at the beginning of the epidemic period in our setting and they were not routinely performed for all presumptive cases, being PCR tests prioritized for hospitalised or severe cases. Obviously, residual confounding in incidence and risk estimates related to selection bias may not be excluded considering that PCR testing was not uniformly performed"
Nevertheless, to better clarify it, in the present revised manuscript we have added a new complementary paragraph including the reviewer's comment on this concern (highlighted in red in the Discussion section) which says: "Of note, most cases included were those who were severe enough to warrant medical attention during the epidemic period. Thus, it must be highlighted that those cohort members who were asymptomatic but SARS-CoV-2 infected, those that were oligosymptomatic, and those that had mild symptoms (who mostly were in self isolation and self-medicating in accordance with the recommendations of the health authorities at the time) were largely underestimated in the present study.

5. As the "real" cohort was only 2324 members, the authors need to prove that this is statistically representative of the local population (i.e. a fully representative subset not only of the 79k member cohort, but of the local population) in terms of age / gender / type of residence / comorbidities / residence location. If it is not, then the authors need to examine why there was a bias in the PCR tested cohort – this in itself might be the most interesting result that comes out of the study – why that skewed / biased population was tested.
*AR: Sorry, but we disagree about this reviewer's comment. The real cohort were the 79,083 study subjects/cohort members (who are extensively described by age groups, sex, residence, pre-existing comorbidities and chronic medications use in table 1). The 2324 persons mentioned by the reviewer are the numerator if we examine the proportion (prevalence) of PCR-tested persons in the study population (which is not the main objective of the present study). Logically, as we already comment in the manuscript (as in the Methods as well as in the limitations paragraph of the Discussion) there is a bias linked with the fact that "PCR testing was scarce across study period in the study area and it was not uniformly performed in the study population, being prioritized for hospitalised or severe cases (related with increasing age) and outbreaks occurred in nursing-home residences (also related with

greater age). As mentioned above, we comment it in the Methods section and recognize this limitation in the manuscript.
Nevertheless, considering this reviewer's comment, we have added a new paragraph in the Results section providing data required. This paragraph (highlighted in red letter) says: "As compared with the structure of the study population (54% aged 50-64 years vs 44% aged ≥65 years, 47.6% men vs 52.4% women, 98.2% community-dwelling vs 1.8% nursing-home residents), PCR testing was more frequently performed among elderly people and nursing-home residents. Indeed, PCR was tested (positive plus negative results) In 930 (40%) people aged 50-64 years vs 1394 (60%) in aged ≥65 years ($p<0.001$), 1023 (44%) in men vs 1301 (56%) in women ($p=0.007$) and 1789 (77%) in community-dwelling vs 535 (23%) in nursing-home residents ($p<0.001$)".

6. Given the published data on morbidity and mortality from COVID-19, where there are many "unexplained" severe/fatal cases below age 50, the authors need to clearly argue why they only included cohort members over age 50.
*AR: The study protocol was constructed at the beginning of epidemic period in Spain (March 2020) and very scarce data about COVID-19 was known. Available data reported until then indicated that major comorbidities and older age supported the greatest burden of severe disease and deaths. Thus, we chose to construct a cohort including persons aged 50 years or older. In addition, we chosen this age cut-off point considering feasibility and emergency criteria to quickly update and use a pre-existing Research Database already used in a previous cohort study assessing clinical effectiveness of pneumococcal and influenza vaccinations among middle-aged and older adults in the study area (CAPAMIS cohort, listed reference number 11). This is noted in the data source's paragraph of the Methods section in the manuscript.

7. Please discuss and defined why/how you have chosen the comorbidities included in the manuscript.
*AR: Comorbidities were chosen on the basis of immunocompromise degree and risk for severe respiratory illness as usually used in other studies about community-acquired pneumonia (same above mentioned reference).

8. Regarding statistical analyses - the authors must clearly define how time was included in the HR calculation. From my reading of the manuscript, the authors were just interested in whether a study member had a positive PCR test during the 12-week study period. If this is correct, then statistically, time is not an important factor, and the correct calculation technique should be Relative Risk (aka Risk Ratio). Normally HR would be used when there is a defined time-lapse or time period from exposure to disease. As there is no contact-tracing, or consideration of when participants were exposed to SARS-CoV-2 then the use of Time and Hazard Ratio needs to be very clearly explained, or replaced, by the correct RR.
*AR: Sorry, but the use of hazard ratios in this study cohort is correct according to our statistician, to other 3 reviewers evaluating this manuscript and other 3 reviewers reviewing other peer-reviewed article recently published by us involving a subset of the cohort (37,000 hypertensive people) that used the same statistical methodology [reference Vila-Corcoles et al; J Clin Hypertension 2020] Perhaps the wording of the main outcome can be confusing. We have changed it, both in the abstract and in the Methods section of main manuscript in this way: instead of "Primary outcome was PCR-confirmed COVID-19 occurred among cohort members across 01/03/2020-23/05/2020" we wrote: "Primary outcome was time (from study start) to COVID-19 confirmed by positive polymerase chain reaction test (PCR) among cohort members throughout study period (from 01/03/2020 to 23/05/2020)". In fact, given the short follow-up period, the HR and RR will probably be very similar, but we have considered it more appropriate to use Cox regression, which takes time into account (whitin an epidemic period).

9. Statistical power – as point three above – This appears to have been calculated on the complete study. Surely this should have only been calculated on the PCR tested cohort members. Please revise accordingly.
*AR: Our responses to points 3 and 8 can also answer this question

10. Please provide statistical evidence that your study is actually representative of your geographical region / population. This was given as one of the aims of your study in the introduction and your data collected and presented to not address this.
*AR: To clarify it, in the present revised manuscript we have rewritten the first paragraph of the Methods section (Design, setting and study population) which currently says: “This is a retrospective cohort study involving 79,083 persons ≥50 years-old in the region of Tarragona (a residential-industrial urban area in Southern Catalonia, Spain, with an overall population of 210,672 all-age inhabitants). Cohort members were all persons >50 years-old (birth day data before 01/01/1970) affiliated in the 12 participating primary care centres (PCCs) managed by the Institut Català de la Salut (ICS) in the study area. In the study setting (concretely “Tarragonés”, “Alt Camp” and “Conca de Barberà” counties) there are 16 PCCs overall. Of them, 12 PCCs (those included in this study) are managed by the ICS, whereas the remaining 4 PCCs are managed by other providers and were not included in the present study. The study cohort represents approximately a 75% of overall inhabitants aged 50 years or older in the study area according to census data.[new reference number 9: IDESCAT 2020]

Reviewer: 4
Reviewer Name: Sarah Cuschieri
Institution and Country: The University of Malta, Malta
Competing interests: None Declared
Please leave your comments for the authors below
It is an interesting article to read. The discussion section is mainly a repetition of the results. It is always recommended that the discussion (as the name implies) discusses the results (& not repeat them) by considering the "Why" and the "How" results presented as they did. Even if there isn't much information on the subject, a hypothetical reason with adequate scientific background should be mentioned. Such as why do you think that smoking was negatively associated? etc. It would be ideal that from your findings, recommendations that are both clinical and public health-oriented are proposed. Not just recommend more research to be done.
*Authors’ Response (AR): We thank the reviewer your valuable comments. Dealing with the first comment, in the present revised manuscript we have shortened the Discussion removing reiterative paragraphs about results. On the second, following the reviewer’s comment, we have rephrased the last paragraph of our initial Discussion which currently says: “Since a clinical and public health-oriented point of view, meanwhile an efficacious treatment or vaccination against COVID-19 will be available, universal influenza vaccination, RAAS-inhibitors in cardiovascular patients and possibly antihistamine drugs in allergic patients could be complementary tools partially protecting against COVID-19”.

VERSION 2 – REVIEW

REVIEWER	Anna Ssentongo Penn State University
REVIEW RETURNED	11-Nov-2020

GENERAL COMMENTS	Excellent Manuscript. Statistics are sound. I recommend a native English speaker improve flow.

	introduction: Please reword "In this context, this study was aimed to analyse incidence and risk for suffering COVID-19 in relation with pre-existing comorbidities and, especially, common chronic medications use among the general adult population over 50 years in Tarragona (Southern Catalonia, Spain) across the first 12-weeks pandemic period in the study area." to "In this context, this study aimed to analyse the incidence and risk of suffering from COVID-19 in adults over 50 years in Tarragona (Southern Catalonia, Spain) with pre-existing comorbidies or using chronic medications, over the first 12-weeks pandemic period in the study area." Methods: Please change "This is a retrospective cohort study involving 79,083 persons ≥50 years-old in the region of Tarragona (a residential-industrial urban area in Southern Catalonia, Spain, with an overall population of 210,672 all-age inhabitants). " to "This is a retrospective cohort study involving 79,083 people ≥50 years-old in the region of Tarragona (a residential-industrial urban area in Southern Catalonia, Spain, with an overall population of 210,672 all-age inhabitants). ' Please reword: "Cohort members were all persons >50 years-old (birth day data before 01/01/1970) affiliated in the 12 participating primary care centres (PCCs) managed by the Institut Català de la Salut (ICS) in the study area. " to say "The cohort consisted of individuals >50 years-old (birth day data before 01/01/1970) affiliated in the 12 participating primary care centres (PCCs) managed by the Institut Català de la Salut (ICS) in the study area. Please change "sociodemographical" to sociodemographic Results: Instead of saying "cohort members" please use "the cohort consisted of...." Discussion: Please change "sociodemographical" to sociodemographic Please change "None comorbidity" to "no comorbiditeis" Please change "Hypertension, diabetes and/or obesity did not emerge independently associated with a significant increasing risk for suffering COVID-19 in our adjusted analyses." to "Hypertension, diabetes and/or obesity were not independently associated with a significantly increased risk for developing COVID-19 in our adjusted analyses." Consider adding the following meta-analysis to your introduction. https://openheart.bmj.com/content/7/2/e001353.abstract Ssentongo, A. E., Ssentongo, P., Heilbrunn, E. S., Lekoubou, A., Du, P., Liao, D., ... & Chinchilli, V. M. (2020). Renin–angiotensin–aldosterone system inhibitors and the risk of mortality in patients with hypertension hospitalised for COVID-19: systematic review and meta-analysis. Open Heart, 7(2), e001353.

REVIEWER	Toan Ha Graduate School of Public Health University of Pittsburgh, Pennsylvania, USA
REVIEW RETURNED	28-Oct-2020

GENERAL COMMENTS	This is an interesting and useful study and the authors have addressed all concerns that I and co-authors have pointed out.

REVIEWER	Jonathan D. Turner Luxembourg Institute of Health, Luxembourg
REVIEW RETURNED	12-Oct-2020

GENERAL COMMENTS	No further comments

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Comments to the Author

1. Excellent Manuscript. Statistics are sound. I recommend a native English speaker improve flow.

Authors' response: Ok, it has been revised by a native English.

2. Introduction: Please reword "In this context, this study was aimed to analyse incidence and risk for suffering COVID-19 in relation with pre-existing comorbidities and, especially, common chronic medications use among the general adult population over 50 years in Tarragona (Southern Catalonia, Spain) across the first 12-weeks pandemic period in the study area." to "In this context, this study aimed to analyse the incidence and risk of suffering from COVID-19 in adults over 50 years in Tarragona (Southern Catalonia, Spain) with pre-existing comorbidies or using chronic medications, over the first 12-weeks pandemic period in the study area."

Authors' response: Ok, it has been reworded.

3. Methods: Please change "This is a retrospective cohort study involving 79,083 persons ≥50 years-old in the region of Tarragona (a residential-industrial urban area in Southern Catalonia, Spain, with an overall population of 210,672 all-age inhabitants). " to "This is a retrospective cohort study involving 79,083 people ≥50 years-old in the region of Tarragona (a residential-industrial urban area in Southern Catalonia, Spain, with an overall population of 210,672 all-age inhabitants). '

Authors' response: Ok, it has been changed.

4. Please reword: "Cohort members were all persons >50 years-old (birth day data before 01/01/1970) affiliated in the 12 participating primary care centres (PCCs) managed by the Institut Català de la Salut (ICS) in the study area. " to say "The cohort consisted of individuals >50 years-old (birth day data before 01/01/1970) affiliated in the 12 participating primary care centres (PCCs) managed by the Institut Català de la Salut (ICS) in the study area.

Authors' response: Ok, it has been reworded.

5. Please change "sociodemographical" to sociodemographic

Authors' response: Ok, it has been changed.

6. Results: Instead of saying "cohort members" please use "the cohort consisted of...."

Authors' response: Ok, it has been reworded.

7. Discussion: Please change "sociodemographical" to sociodemographic

Authors' response: Ok, it has been changed.

8. Please change "None comorbidity" to "no comorbiditeis"

Authors' response: Ok, it has been changed.

9. Please change "Hypertension, diabetes and/or obesity did not emerge independently associated with a significant increasing risk for suffering COVID-19 in our adjusted analyses." to "Hypertension, diabetes and/or obesity were not independently associated with a significantly increased risk for developing COVID-19 in our adjusted analyses."

Authors' response: Ok, it has been changed.

10. Consider adding the following meta-analysis to your introduction. https://openheart.bmj.com/content/7/2/e001353.abstract Ssentongo, A. E., Ssentongo, P., Heilbrunn, E. S., Lekoubou, A., Du, P., Liao, D., ... & Chinchilli, V. M. (2020). Renin–angiotensin–aldosterone system inhibitors and the risk of mortality in patients with hypertension hospitalised for COVID-19: systematic review and meta-analysis. Open Heart, 7(2), e001353.

Authors' response: Ok, this interesting meta-analysis has been included within the Discussion section commenting relationship between RAAS-inhibitors and reduced risk of COVID-19 mortality (current reference 33).

Reviewer: 2

Comments to the Author: This is an interesting and useful study and the authors have addressed all concerns that I and co-authors have pointed out.

Authors' response: Ok.

Reviewer 3

Comments to the Author: No further comments

Authors' response: Ok