PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Variables associated to COVID-19 severity: an observational study of non-paediatric confirmed cases from the general population of the Basque Country, Spain
AUTHORS	Vrotsou, Kalliopi; Rotaeche, Rafael; Mateo-Abad, Maider; Machón, Mónica; Vergara, Itziar

VERSION 1 – REVIEW

REVIEWER	Celal Satıcı Istanbul Yedikule Chest Disease and Chest Surgery Research and Training Hospital, University of Health Sciences, Turkey
REVIEW RETURNED	25-Jan-2021

GENERAL COMMENTS	I wrote my comments as highlighted in the manuscript – Please contact publisher for this file.

REVIEWER	Pierachille Santus University of Milan; Italy
REVIEW RETURNED	29-Jan-2021

GENERAL COMMENTS	The paper by K. Vrotsou et al entitled “Variables associated to COVID-19 severity: an observational study of >13000 confirmed cases in the Basque Country, Spain” is a retrospective observational study performed in Spain on a large general population with data that have been extracted by the electronic health records and were referred to the general population from 14 years old and over. The paper is interesting, especially in terms of GPs management and epidemiological consideration for the Health Systems. Comments - The title is not so clear and could be more appealing; for example could be better to delete >13000, underline in general population (the Authors evaluated data from 14 yo), outside the hospital and so on. - Page 4 line 27-21: the sentence “Only individuals ≥14 years old with a COVID-19 positive Polymerase Chain Reaction (PCR) or antibody test, were included” must be clarify. Should be better to explain as have been evaluated the subjects with antibody presence (mild, moderate , severe disease? Asymptomatic?). This is an important point take in account the paper objective. - Page 6 line 44-46: should be better to explain better the sentence “Most infected cases were females…..” underlining where this peoples were (at home, outside hospital and so on). Have been reported some considerations on this point in Discussion but is not so persuasive. I think that could be better annotated and - The data on the prevalence between female and male, reported in general population and PC, is unusual compared with all the other

	world data where the prevalence is the contrary (about 30% female and 70% male). This point must be clearly explained and discussed. - Regarding table 3 and related text in page 7 the respiratory diseases must be better clarify. Particularly regarding chronic obstructive pulmonary disease that identify “per se” COPD and so to report only “and allied” is not sufficient. Therefore, should be better at lest to report COPD and asthma why on asthma, particularly on allergic asthma, there are data that speculate on the possible protective role. - About drugs consumption could be interesting to know data regarding some specific drugs that have been correlate with COVID19. In specific use of chronic oral or systemic corticosteroids, inhalatory steroids, anticoagulant drugs (LMWH, Direct and Indirect oral anticoagulant, chronic immunosuppressant, drugs altering the RAA system). - Blood and blood forming organ drugs consumers what does it mean? Subjects that take Anticoagulant? Anti platelet aggregation? Anti neoplastic? Please clarify. - No data has been reporting on Oxygen prescription/use at home. Did you have data? Could be important in order to know better the disease severity and clinical management at home. - Did you have data on the respiratory failure (RF) also related to the peripheral saturation level? Did you have date on RF related to the pts recovered in Hospital? - With data for the more important drugs related to COVID19 (see the previous two points) could be interesting to create a new table with the distribution and significance across the considered categories. - Hereditary and degenerative diseases of the central nervous system include dementia? Should be interesting to report it as distinguish disease. - Page 9 line 34: “was” has been reported twofold. - Page 10 line 54-56 regarding the tools used in order to identify the risk of general population, also in a general setting and in order to promote the better clinical programs, some previous evidences could be cited (eg Early consensus management for non-ICU acute respiratory failure SARS-CoV-2 emergency in Italy: from ward to trenches. Eur Respir J. 2020 May 21;55(5):2000632). - Page 10 line 58-60 take in account the risk factors of the hospitalized pts should be important to cite also the level of respiratory failure at admission (see Severity of respiratory failure at admission and in-hospital mortality in patients with COVID-19: a prospective observational multicentre study. BMJ Open. 2020 Oct 10;10(10):e043651). - No considerations have been made on the more young population, from 14 to 45 yo, that have a very low or not mortality incidence. How affect the data/results this type of populations? Has been performed a separate analysis? Should be important to analyse this population implemented the CART with an other line regarding subjects with ≤45 yo. - The presented data in the submitted paper didn’t have a bias related to these subjects (≤45 yo)? Mandatory explanation.

REVIEWER	Irit Nachtigall Helios Kliniken, Region East, Infection prevention and Infectious diseases
REVIEW RETURNED	30-Jan-2021

GENERAL COMMENTS	I would like to thank the authors for the interesting subject and for

	the presentation of a very important data set. Data presention is well arranged and data set is adequate for the questions that might have been adressed. and that is my problem with the article. Primary question is not well defined and should get more attention. Many questions are adressed but what is missing is a red thread. The data are well wort publication since they give interesting voews especially on the problem with psychosis and that should be the main focus since a differentiation between hospital and ICU admission could not be drawn, the focus shouzld be less on this part. Another point is the language, in some parts the manuskript is written very well, but especially the introduction would benefit from a language overhaul Bute taking all together, it is a very interesting data set presented with a well done statistic work, that just needs a little more focus

REVIEWER	Adam Brufsky, MD, PhD University of Pittsburgh, Pittsburgh, PA
REVIEW RETURNED	31-Jan-2021

GENERAL COMMENTS	This is an interesting observational analysis of variables associated with COVID severity in a single health system in the Basque area Northern Spain. (1) Unfortunately the English is very stilted, making it very difficult to review the manuscript. As one example of many, the word "Exitus" is used for death throughout. There are multiple other examples. I believe this work would be best served by a complete rewrite into a less stilted English, with less jargon used. (2) Nonetheless, there are several interesting aspects to discuss. In particular, psychosis appears to be a risk factor for death. The discussion around this, as well as comparison to other literature, needs to be clarified. (3) The CART model needs to be clarified and better described. (4) The drug prescriptions also need better clarification. I think this may be an issue of English translation. (5) The combination of hospital/ICU groups changes the nature of the study, and should be better justified. Again, it is difficult to evaluate this manuscript properly, given its current language issues.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Celal Satici, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital
*** Please find comments from this reviewer in the attached file *** Comments to the Author:
I wrote my comments as highlighted in the manuscript

Answer: Thank you very much. In the attached manuscript, we found a total of 3 comments. We copy them below and answer to each one of them.

Comments as found in the attached manuscript:

- Page 5, line 12: The main problem in this study is the inclusion of an intubated patient and a hospitalized patient who does not need oxygen support and analyzed them in the same group. Is not there any data regarding oxygen support (HFNC / NIMV/ IMV / ECMO..) in the electronic health records

Answer: The reviewer is right in that merging hospitalized and ICU patients in one group is not an ideal situation. Our initial intention was to analyse them separately. But we have already explained the reasons that led to this merging. As already stated in the manuscript (current page 5 lines 2-7), the pandemic and the strain it imposed to the public health system lead to altering the established health attention plans. Emergency ICU units were set-up in many hospitals, but this "change" was not registered in the electronic health records. Thus, there is no way, from the electronic health data we handle, to know which of the included patients were admitted to an emergency ICU, in order to establish a fourth "ICU only" group. These admissions appear as Hospital admissions. Adjusting the health records registration system is something that cannot happen quickly, let alone during a pandemic situation where efforts need to focus on more pressing issues. A similar situation must have appeared in other health systems around the globe. This does not mean that we have to discard valuable data.

We should also keep in mind that observational study usually present more difficulties when it to comes to recompiling data, compared to other more controlled studies. And in order to overcome these difficulties, certain decisions need to be made. Would the reviewer have found it that problematic if with the same data set we had just explored Dead vs. Alive cases? So far, in the COVID-19 related articles many other authors have just studied Dead vs. Alive; Hospitalised vs. No Hospitalized, ICU vs. No ICU etc., working mainly with binary outcomes. Consider any of the above outcomes, but in particular the Dead vs. Alive, it becomes obvious that the merging of different patient profiles is definitely very pronounced; much more compared to ours. Alive include hospitalized and intubated, as well as those who recover at home having mild symptoms. Nonetheless binary outcomes are still of interest and value. Our intention was to move a step onward. And despite the drawbacks, which we understand and have properly addressed in the manuscript, the groups we established show a gradient of infection severity and the CART model pinpoints to the factors related to this gradient of severity. And this is precisely the great novelty of this work. For health professionals and especially health managers, knowing what patient characteristics can lead to greater hospitals/ICU admissions, as well as death can allow for better-targeted health prevention plans, focusing on specific populations.

Finally, in relation to your question about oxygen support, we need to clarify that our study has not explored the medications and treatment options offered to the COVID-19 cases. This was not among our objectives and no treatment related data were extracted. We focused the COVID-19 infection severity from a public health perspective, and we were interested in information that could be obtained for all infected cases.

- Page 5, line 47: Post-hoc analysis should be performed to understand the parameter that causes the difference.

Answer: the parameters that appear to affect the outcome are shown by the CART results, in Figure 1 and have also been discussed in the results and discussion sections. The CART methodology section has now been re-written offering an explanation which should be clearer to the non-statisticians and facilitate its understanding.

- Page 6, line 57: It was revealed that getting flu vaccination is positively correlated with disease severity. The underlying reason should be discussed and the result reported after adjustment for confoundings

Answer: this Table 1 association (current page 6, line 26), was a three-group unadjusted comparison. We do not claim that the flu vaccination affected disease severity, we just commented on this association. Usually, when the results are presented in a paper the simple and unadjusted effects are given first, before going on into reporting adjusted and in our case CART model results. The flu vaccination was not highlighted as an important factor by the CART model, which suggests that the association seen in Table 1 most likely reflects the effect of other

variables, like comorbidities, polypharmacy, age etc., which were included in the CART. The flu vaccination is precisely recommended to older people and populations at risk. Therefore, when these other variables were present flu vaccination did not appear as an important variable, which is why we have not commended any further on this initial comparison.

Reviewer: 2

Dr. Pierachille Santus, University of Milan Comments to the Author:
The paper by K. Vrotsou et al entitled "Variables associated to COVID-19 severity: an observational study of >13000 confirmed cases in the Basque Country, Spain" is a retrospective observational study performed in Spain on a large general population with data that have been extracted by the electronic health records and were referred to the general population from 14 years old and over. The paper is interesting, especially in terms of GPs management and epidemiological consideration for the Health Systems.
Comments
- The title is not so clear and could be more appealing; for example could be better to delete >13000, underline in general population (the Authors evaluated data from 14 yo), outside the hospital and so on.

Answer: Thanks a lot for the suggestion. We have now modified the title, which we hope that you find more adequate.

- Page 4 line 27-21: the sentence "Only individuals ≥14 years old with a COVID-19 positive Polymerase Chain Reaction (PCR) or antibody test, were included" must be clarify. Should be better to explain as have been evaluated the subjects with antibody presence (mild, moderate , severe disease? Asymptomatic?). This is an important point take in account the paper objective.

Answer: Thank you very much for this comment. We now state in the text (current page 4 lines 6-7) that only the health records of ≥14 years old individuals with PCR+ or antibody+ were included in our analyses.
Based on your comment we see that the distribution of the PCR+ and antibody+ should also be given to the reader, and this has now been added (current page 6 lines 18-20). As far as the system of mild-moderate-severe-asymptomatic that the reviewer suggests implies a consensus over the severity of each symptom and working with an established protocol for categorizing each and every case. But such a protocol requires an understanding over the disease, non-existing during the first pandemic wave in our health system, and probably in no other system, at least not for classifying all cases across all health attention levels. If we had worked only with hospitalized individuals, say, it may have been easier to establish such a system, even retrospectively, but our sample had cases from different health care levels. What we did instead, was to consider that the level of medical attention received represented the infection severity of the cases, and study the factors associated with it. This would be the corresponding to the mild, moderate, severe disease cases. On the other hand, as we have already stated in the manuscript the way that the COVID-19 symptoms were registered at least during the first pandemic wave, does not really allow us knowing how many asymptomatic cases we may have had. Close contacts may have been family members, household assistants or health workers. After considering all the above, we have added more information in current page 13 and have also opted for changing the limitation presented in the last bullet-point. It is more accurate to state that COVID-19 symptoms were not properly recorded.

- Page 6 line 44-46: should be better to explain better the sentence "Most infected cases were females….." underlining where this peoples were (at home, outside hospital and so on). Have been reported some considerations on this point in Discussion but is not so persuasive. I think that could be better annotated and
Answer: we have now added more details in the text (current page 6, lines 21-23) clarifying that in the current sample´s most infected cases were females and this sex was more prevalent in the Primary Care groups, i.e they did not require any hospital/ICU admission. While on the other hand more males were seen in the Hospital/ICU and Death groups.
In relation to the corresponding Discussion point the reviewer mentions, we have cited several published articles, among which a 20133 UK cases [1], a German cohort [2], two Spanish studies [3, 4] and a meta-analyses of multiple covid-19 prediction models of primary studies indicating that males

have worse COVID-19 outcomes than females [5]. In the current version of the manuscript (current page 10, lines 11-15) we have added an extra reference [6] on an investigation line over the protective effect of the low androgens levels in females. With this addition we consider that the corresponding discussion part is now more compete.

References:

1)Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study.
2) Nachtigall I, Lenga P, Jóźwiak K, Thürmann P, Meier-Hellmann A, Kuhlen R, et al. Clinical course and factors associated with outcomes among 1904 patients hospitalized with COVID-19 in Germany: an observatioal study. Clin Microbiol Infect [Internet]. 2020
3) Poblador-Plou B, Carmona-Pírez J, Ioakeim-Skoufa I, Poncel-Falcó A, Bliek-Bueno K, Cano-Del Pozo M, et al. Baseline chronic comorbidity and mortality in laboratory-confirmed COVID-19 cases: Results from the PRECOVID study in Spain. Int J Environ Res Public Health. 2020;17(14):1–14.
4) Working group for the surveillance and control of COVID-19 in Spain. The first wave of the COVID-19 pandemic in Spain : characterisation of cases and risk factors for severe outcomes , as at 27 April 2020. Eurosurveillance [Internet]. 2020;25(50):1–13.
5) Wynants L, Van Calster B, Collins GS, Riley RD, Heinze G, Schuit E, et al. Prediction models for diagnosis and prognosis of covid-19: Systematic review and critical appraisal. BMJ. 2020;369.
6) Mohamed MS, Moulin TC, Helgi, Schiöth B. Sex differences in COVID-19: the role of androgens in disease severity and progression. Endocrine [Internet]. 2020;71:3–8.

- The data on the prevalence between female and male, reported in general population and PC, is unusual compared with all the other world data where the prevalence is the contrary (about 30% female and 70% male). This point must be clearly explained and discussed.

Answer: The reviewer is right in that female/male cases of our sample present different distributions compared to other samples. Nonetheless, the 30%/70% has not been such a clear-cut. In a multicenter European study the female/male % were 42.3/57.7% [1]. *A German work reported 48.5/51.5% [2], and a USA study 45.2/54.8% [3]. Therefore, differences were not as big as 40% between sexes, at least not in all samples.*

The officially reported covid-19 data, as given by the public health system (Osakidetza report 31st of may: https://www.euskadi.eus/contenidos/informacion/boletin_coronavirus/es_def/adjuntos/31_mayo_Boletin.pdf), clarify that the distribution by sexes is the same as the one presented in our manuscript. The local data are similar to other works : Poblador-Plou B et al. [4] with female/male =58.8/41.2%; and a Spanish national surveillance study [5] with the female/male being 53%/47%. We can only hypothesize over the reasons of this distribution. The public health system of the Basque country is a free of charge and equitable system for all patients, which makes difficult to attribute this difference to a differential health attention. On the other hand, in the Spanish reality too, women are usually talking care of the younger and older members of their families, having therefore closer and more frequent contacts, compared to men. In this country women also represent a great proportion of house-care and health-care professions [6,7,8]. As we have already explained in the manuscript during the first pandemic wave only people with symptoms or close contact with infected individuals were tested, while during the end of the first wave antibody tests were performed to health related professions. The highest prevalence of women, similar to other Spanish data may be reflecting the above mentioned realities. Following the reviewer´s suggestion we have now extended the discussion (current page 13 lines 2-7) section including these considerations as possible explanations.

References:

1) Hewitt J, Carter B, Vilches-Moraga A, Quinn TJ, Braude P, Verduri A, et al. The effect of frailty on survival in patients with COVID-19 (COPE): a multicentre, European, observational cohort study. Lancet Public Heal [Internet]. 2020 Aug 1.
2) Nachtigall I, Lenga P, Jóźwiak K, Thürmann P, Meier-Hellmann A, Kuhlen R, et al. Clinical course and factors associated with outcomes among 1904 patients hospitalized with COVID-19 in Germany: an observational study. Clin Microbiol Infect [Internet]. 2020

3) Douglas Tremblay, Maaike van Gerwen, Mathilda Alsen, Santiago Thibaud, Alaina Kessler, Sangeetha Venugopal, Iman Makki, Qian Qin, Sirish Dharmapuri, Tomi Jun, Sheena Bhalla, Shana Berwick, Jonathan Feld, John Mascarenhas, Kevin Troy, Caroline Cromwell, Andrew Dunn, William K. Oh, and Leonard Naymagon. Impact of anticoagulation prior to COVID-19 infection: a propensity score–matched cohort study
4) Poblador-Plou B, Carmona-Pírez J, Ioakeim-Skoufa I, Poncel-Falcó A, Bliek-Bueno K, Cano-Del Pozo M, et al. Baseline chronic comorbidity and mortality in laboratory-confirmed COVID-19 cases: Results from the PRECOVID study in Spain. Int J Environ Res Public Health. 2020;17(14):1–14.
5) Working group for the surveillance and control of COVID-19 in Spain. The first wave of the COVID-19 pandemic in Spain : characterisation of cases and risk factors for severe outcomes , as at 27 April 2020. Eurosurveillance [Internet]. 2020;25(50):1–13.
6) Zenia Hellgren and Inma Serrano. Transnationalism and Financial Crisis: The HamperedMigration Projects of Female Domestic Workersin Spain. Soc. Sci.2017,6, 8; doi:10.3390/socsci6010008.
7) https://www.osakidetza.euskadi.eus/osakidetza-es/-/conozca-osakidetza/
8) Cristina Lázaro-Pérez, JoseÁngel Martínez-López, JoséGómez-Galán, and Eloy López-Meneses. Anxiety About the Risk of Death of Their Patients inHealth Professionals in Spain: Analysis at the Peak ofthe COVID-19 Pandemic. Int. J. Environ. Res. Public Health2020,17, 5938.

- Regarding table 3 and related text in page 7 the respiratory diseases must be better clarify. Particularly regarding chronic obstructive pulmonary disease that identify “per se” COPD and so to report only “and allied” is not sufficient. Therefore, should be better at lest to report COPD and asthma why on asthma, particularly on allergic asthma, there are data that speculate on the possible protective role.

Answer: the information the reviewer requests has now been added in Table 3. The allergic asthma did show a descending prevalence across the three groups, but percentages and frequencies were actually low. This has not been added in the results section current page 7, lines 24-26. Considering asthma and COPD separately did not alter any of our results.

- About drugs consumption could be interesting to know data regarding some specific drugs that have been correlate with COVID19. In specific use of chronic oral or systemic corticosteroids, inhalatory steroids, anticoagulant drugs (LMWH, Direct and Indirect oral anticoagulant, chronic immunosuppressant, drugs altering the RAA system).

Answer: At this point the reviewer requests more information over the treatment options offered to the COVID-19 patients. In this area a consensus does seem to exist as far as the systemic corticosteroids COVID treatment is concerned (1,2), but the inhaled steroids treatment option is under study, with randomized controlled trials currently performed in the UK and other countries (3, 4, 5). Anticoagulation treatments for fighting the disease are also recommended, when no contraindications exist (6, 7). In any case, as we explain in other replies our study did not assess data on COVID treatments options. Our interest was to explore patient baseline characteristics (socio-demographic, chronic medication, and chronic diseases). We have approached the severity of the disease from a public health perspective, as said in previous replies.

References:
1. Judith van Paassen, et al. Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes; Critical Care 24: 696 (2020).
2. https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1.
3. https://www.principletrial.org/.
4.https://www.clinicaltrials.gov/ct2/show/NCT04331054?term=inhaled+steroids&cond=Covid19&draw=2&rank=1.
5.https://www.clinicaltrials.gov/ct2/show/NCT04355637?term=inhaled+steroids&cond=Covid19&draw=2&rank=5
6. Robert D. McBane, II, MD et al. Anticoagulation in COVID-19: A SystematicReview, Meta-analysis, and Rapid GuidanceFrom Mayo Clinic; Mayo Clin Proc. 2020;95(11):2467-2486.

7. Rodriguez-Guerra M, et al. Current treatment in COVID-19 disease: a rapid review. Drugs in Context 2021; 10: 2020-10 PubMed -3. DOI: 10.7573/dic.2020-10-31 PubMed of 8I SS N : 174 0 - 439 8

- Blood and blood forming organ drugs consumers what does it mean? Subjects that take Anticoagulant? Anti platelet aggregation? Anti neoplastic? Please clarify.

Answer: The blood and blood forming organs includes antithrombotic agents, antihemorragics, antianemic preperations, blood substitutes and perfusion solution. As already stated in the manuscript, the Anatomical Therapeutic chemical classification system was used, as indicated by the WHO. In order to avoid misunderstanding we have now added the corresponding link in the text (https://www.whocc.no/atc_ddd_index/) (current page 4, line 13).

- No data has been reporting on Oxygen prescription/use at home. Did you have data? Could be important in order to know better the disease severity and clinical management at home.
- Did you have data on the respiratory failure (RF) also related to the peripheral saturation level? Did you have date on RF related to the pts recovered in Hospital?
- With data for the more important drugs related to COVID19 (see the previous two points) could be interesting to create a new table with the distribution and significance across the considered categories.

Answer: the data the reviewer requests, as already replied in previous comments, are related to the different treatment options during the COVID-19 infection. This was not one of the objectives of this study and therefore no COVID-19 treatment related data were obtained. We were interested in exploring what baseline characteristics, chronic diseases and medications may have affected the severity of the infection.

- Hereditary and degenerative diseases of the central nervous system include dementia? Should be interesting to report it as distinguish disease.
Answer: yes indeed ,the ICD-9 for this disease category includes the pathology of Dementia. Following the reviewer´s suggestion, this pathology is now presented separately in Table 3.

- Page 9 line 34: “was” has been reported twofold.
Answer: thanks, this replication has now been deleted.

- Page 10 line 54-56 regarding the tools used in order to identify the risk of general population, also in a general setting and in order to promote the better clinical programs, some previous evidences could be cited (eg Early consensus management for non-ICU acute respiratory failure SARS-CoV-2 emergency in Italy: from ward to trenches. Eur Respir J. 2020 May 21;55(5):2000632).

Answer: we are sorry to say that we are not going to include the recommended reference. This is due to various considerations that we expose below. Firstly, the suggested reference does not treat “general setting” as the reviewer seems to suggest, and at this discussion point we specifically mention the general setting. On the contrary the above reference has to do with non-ICU hospitalized patients, and we have already included 3 stratification approaches for hospitalized patients in the manuscript (current page 11, line 1). What is more, the suggested paper is an early consensus of Italian doctors (among whom, the reviewer) that during the first pandemic period tried to establish the management pathways for hospitalized patients. But there are no data in this paper, to support (or not) that this consensus actually works in practice. In addition to that, as the authors state in that paper, this consensus “is not necessarily totally in line with the World Health Organization (WHO) documents.” Given all the above we do not really see what this reference adds to our work. We would be more than happy to cite an article that discusses stratification techniques for the general population, if the reviewer has a reference that can be added in this context.

- Page 10 line 58-60 take in account the risk factors of the hospitalized pts should be important to cite also the level of respiratory failure at admission (see Severity of respiratory failure at admission and in-hospital mortality in patients with COVID-19: a prospective observational multicentre study. BMJ Open. 2020 Oct 10;10(10):e043651).

Answer: the variables that we accessed and assessed as part of this study are the one shown in Tables 1 – 3. We do not have information on the data the reviewer requests. In any case, these data would be relevant if we had worked only with infections admitted into the hospital. But our sample and scope of this work was broader. Therefore, we believe that the data the reviewer mentions would not have been useful in the context of this work, as the corresponding information would be available only for part of the sample. Our work established the severity of the COVID-19 outcome infection, based on the level of health attention received, and presented the factors that were associated with this severity levels, focusing on sociodemographic data, chronic pathologies and chronic drug consumption. The focus of our work was a public health perspective approach, by offering information that would be helpful to public health intervention programs, focusing on a broad range of different infection profiles.

- No considerations have been made on the more young population, from 14 to 45 yo, that have a very low or not mortality incidence. How affect the data/results this type of populations? Has been performed a separate analysis? Should be important to analyse this population implemented the CART with an other line regarding subjects with ≤45 yo.

VERSION 2 – REVIEW

REVIEWER	Pierachille Santus University of Milan, Milano, Italy
REVIEW RETURNED	05-Mar-2021

GENERAL COMMENTS	None.

REVIEWER	PD Dr. Irit Nachtigall Helios Kliniken, Region East, Infectious Diseases
REVIEW RETURNED	15-Mar-2021

GENERAL COMMENTS	Thank you very much for your work and good luck for the ongoing.

REVIEWER	Adam Brufsky, MD, PhD University of Pittsburgh USA
REVIEW RETURNED	17-Mar-2021

GENERAL COMMENTS	The authors have done an impressive job of clarifying the language addressing my prior concerns. In particular, they now address the limitation of the heterogeneity of combining Hospital/ICU groups together in one analysis.