

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Assessing Relative Coronavirus Disease 2019 Mortality: A Swiss Population-based Study
AUTHORS	Hothorn, Torsten; Bopp, Matthias; Günthard, Huldrych; Keiser, Olivia; Roelens, Maroussia; Weibull, Caroline; Crowther, Michael

VERSION 1 – REVIEW

REVIEWER	Baud, David University Hospital in Lausanne
REVIEW RETURNED	22-Jul-2020

GENERAL COMMENTS	<p>This study reports relative mortality rates comparing a cohort of symptomatic and confirmed covid-19 patients to the general population aged between 35 and 95 at time of testing, during the same calendar period from previous years, using population based data from Switzerland.</p> <p>For the first time, this study give relative risk in direct relation to the mortality in the general population, which is new in the literature. Moreover, it give age- and sex- adjusted risks.</p> <p>Despite I am not a statistician, the paper is easy to understand for a broad audience as the readers of the BMJ. I congratulate the authors for this aspect.</p> <p>My only concern are pregnant women. Despite it seems there was no maternal death in Switzerland during the study period, we now know this population is at increased risk of severe COVID-19, ICU admission, intubation and death. See for example:</p> <p>Ellington S, Strid P, Tong VT, Woodworth K, Galang RR, Zambrano LD, et al. Characteristics of Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status - United States, January 22-June 7, 2020. <i>MMWR Morb Mortal Wkly Rep.</i> 2020;69(25):769-75.</p> <p>Collin J, Bystrom E, Carnahan A, Ahrne M. Public Health Agency of Sweden's Brief Report: Pregnant and postpartum women with severe acute respiratory syndrome coronavirus 2 infection in intensive care in Sweden. <i>Acta Obstet Gynecol Scand.</i> 2020;99(7):819-22.</p> <p>Also, pregnant women have the same risks than the “general population”, the latest being older than pregnant women (see Favre GP, L.; Baud, D. Coronavirus disease 2019 during pregnancy: do not underestimate the risk of maternal adverse outcomes. <i>AJOG MFM.</i> 2020.)</p> <p>I would recommend the authors to add a small paragraph on this important aspect.</p>
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REVIEWER	Sergi Trias-Llimós Centre d'Estudis Demogràfics, Catalonia
REVIEW RETURNED	10-Sep-2020

GENERAL COMMENTS	<p>The paper provides a very relevant assessment on the impact of COVID-19 on group-specific mortality as compared to the population level mortality rate in Switzerland. The analyses for the COVID-19 cohort focus on the time period between February 24th and May 14th 2020. The project has several strengths and its main limitation is the selection in the covid-19 cohort. I have some comments that may help the authors improving the paper.</p> <ul style="list-style-type: none"> - The critical issue in this study is the definition of individuals selected to take part of the so-called Swiss covid-19 cohort. A description on that is available on page 6, lines 13 and onwards. Overall, this should be described in more detail. For example 1) Are asymptomatic persons who tested positive (to control local outbreaks in hospital or nursing homes) included in the cohort? How much they are? 2) Are asymptomatic individuals who did the test as they were a close contact of a positive case included in the cohort in case of being tested positive? Some of these issues are also mentioned in the discussion, but not referring to the Swiss covid-19 cohort. - Furthermore, it is mentioned that “The Swiss covid-19 cohort excluded persons with known increased mortality risks (those tested posthumously or while being hospitalized), as well as very old and thus a priori frail persons”. Could you please describe more precisely the exclusion criteria? This could a priori be a relevant issue at older ages and thus require additional discussion an acknowledging the required caution when interpreting these results (for example when comparing mortality risks in the Swiss covid-19 between age groups 90+ -potentially frail- and ages below, say, 60 years of age. - Sex differences. In pages 8-9 the authors state that “more than half of the hazard increase observed in male and older patients could be attributed to the generally increased population mortality in these groups”. Whereas this is something that can be calculated, the authors did not do that, nor they refer to the specific results on that. <p>Minor comments:</p> <ul style="list-style-type: none"> - Abstract/Introduction: The aim of the paper should be clear here as well. - Page 6, line 4 and 34. The Swiss cohorts for 2014-2016 are in my view not relevant for the main results, as they are not used as main results. In other sections, and in the appendix, this information is provided sufficiently. - Page 6, line 60. Please further explain how 95% CI were calculated and add a reference. - Page 7 line 18. Are you referring to R Programming? - Figure 3. Ylab is on absolute mortality in relative terms (%) is confusing. I suggest labeling it as the probability of dying. Same in the title. - Table 4. - I would state a bit more clearly in different key parts of the paper that these results were based on results from the “first wave”? <p>Things are evolving quite quickly and the paper should be appropriately read after some weeks/months as well. Spain, for</p>
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	<p>example, is observing much lower mortality in the 2nd wave covid-19 positive cases.</p> <p>- Some pre-print references are now published. I suggest checking the list of references.</p>
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REVIEWER	Charlie Zhang University of Louisville, USA
REVIEW RETURNED	18-Sep-2020

GENERAL COMMENTS	<p>This is a timely research that investigates age-gender differentials in Covid-19 mortalities in Switzerland. The comparative method used in this paper is helpful to reveal the risks and severity of the coronavirus. However, I have identified a number of issues that undermined the quality of this manuscript.</p> <ol style="list-style-type: none"> 1. It is helpful for the readers to better understand this work if the authors clearly describe the research hypothesis in the introduction section. 2. Explain what age densities mean in Figure 2 and other figures and how they were calculated. It was described as probabilities of death in the methodology section though. Such discrepancies do cause confusions for the readers when reviewing this research work. 3. Whilst examining age-gender differentials in Covid-19 induced mortalities is useful, it would be more meaningful and insightful to reveal racial/ethnic inequalities in the death tolls within the Swiss population. Since individual death records were used in this study, I suppose race/ethnicity identity of the diseased collected was collected. Since the pandemic started, numerous studies worldwide have identified ethnic minorities and low-income residents have being disproportionately hit by the coronavirus. Moreover, examining urban/rural/suburban differences in mortality risk is another way to identify spatial disparities if locational information was available in the mortality data (I suppose it is there). 4. Scholars have highlighted elevated risks of people with preexisting conditions in the face of the pandemic, this study will be more valuable if this covariate is controlled for. 5. My last concern is about confidentiality of individual death records that were used in this study to generate population-level statistics regarding age, gender, and mortality. it is not mentioned in the article regarding if institutional review board (IRB) approval is obtained in order to protect private information of human subjects. <p>Overall, I recommend this paper be Accepted with major revisions.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1: David Baud

This study reports relative mortality rates comparing a cohort of symptomatic and confirmed covid-19 patients to the general population aged between 35 and 95 at time of testing, during the same calendar period from previous years, using population based data from Switzerland. For the first time, this study give relative risk in direct relation to the mortality in the general population, which is new in the literature. Moreover, it give ageand sex-adjusted risks.

Despite I am not a statistician, the paper is easy to understand for a broad audience

as the readers of the BMJ. I congratulate the authors for this aspect. My only concern are pregnant women. Despite it seems there was no maternal death in Switzerland during the study period, we now know this population is at increased risk of severe COVID-19, ICU admission, intubation and death. See for example:

Ellington S, Strid P, Tong VT, Woodworth K, Galang RR, Zambrano LD, et al. Characteristics of Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status - United States, January 22-June 7, 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(25):769-75.

Collin J, Bystrom E, Carnahan A, Ahrne M. Public Health Agency of Sweden's Brief Report: Pregnant and postpartum women with severe acute respiratory syndrome coronavirus 2 infection in intensive care in Sweden. *Acta Obstet Gynecol Scand.* 2020;99(7):819-22.

Also, pregnant women have the same risks than the general population, the latest being older than pregnant women (see Favre GP, L.; Baud, D. Coronavirus disease 2019 during pregnancy: do not underestimate the risk of maternal adverse outcomes. *AJOG MFM.* 2020.) I would recommend the authors to add a small paragraph on this important aspect.

Thank you very much for this comment. We absolutely agree, and a similar issue was also raised by Reviewer 3, in points 3 and 4 regarding differential risk for patient subgroups with preexisting conditions, ethnic minorities and low-income patients. Unfortunately, we did not have access to corresponding data on these potential factors. This lack of information is now explicitly mentioned as limitation of our study, in the "Strengths and Limitations" section and also in the discussion. Relevant references were added to the discussion.

1 Reviewer 2: Sergi Trias-Llimós

The paper provides a very relevant assessment on the impact of COVID-19 on groupspecific mortality as compared to the population level mortality rate in Switzerland. The analyses for the COVID-19 cohort focus on the time period between February 24th and May 14th 2020. The project has several strengths and its main limitation is the selection in the covid-19 cohort. I have some comments that may help the authors improving the paper.

- The critical issue in this study is the definition of individuals selected to take part of the so-called Swiss covid-19 cohort. A description on that is available on page 6, lines 13 and onwards. Overall, this should be described in more detail. For example 1) Are asymptomatic persons who tested positive (to control local outbreaks in hospital or nursing homes) included in the cohort? How much they are? 2) Are asymptomatic individuals who did the test as they were a close contact of a positive case included in the cohort in case of being tested positive? Some of these issues are also mentioned in the discussion, but not referring to the Swiss covid-19 cohort.

Thank you very much for raising this important point. We now present all information regarding the definition of the study population in the Methods section. In more detail, 1) yes, all positive cases are included (and we do not know if a person developed symptoms during the cause of the disease), 2) yes, all positive cases are included.

- Furthermore, it is mentioned that The Swiss covid-19 cohort excluded persons with known increased mortality risks (those tested posthumously or while being hospitalized), as well as very old and thus a priori frail persons. Could you please describe more precisely the exclusion criteria? This could a priori be a relevant issue at older ages and thus require additional discussion an acknowledging the required caution when interpreting these results (for example when comparing mortality risks in the Swiss covid-19 between age groups 90+ -potentially frail- and ages below, say, 60 years of age.

We excluded persons younger than 35 years because no deaths were observed in this

group. Persons older than 95 years have a very high absolute mortality risk and we were mainly interested in the additional risk otherwise “low-risk” persons experience by an infection. It is important to note that our models treat age as a continuous variable and, unlike many other analyses, we do not report results for age groups (60-65 years old, or older than 90 years, for example). It was necessary to categorise results for presentation in Table 4, but Figure 3 presents absolute and relative mortalities as smooth functions of age.

- Sex differences. In pages 8-9 the authors state that more than half of the hazard increase observed in male and older patients could be attributed to the generally increased population mortality in these groups. Whereas this is something that can be calculated, the authors did not do that, nor they refer to the specific results on that.

Indeed, this statement lacked corresponding information in the text of the Results section and we thank you for raising this point. We now discuss this finding in more detail: On the additive log-hazard ratio scale, two-thirds of the sex effect seen when comparing covid-19 patients only can be traced back to general population risk. The additional sex effect is borderline relevant, completely missing in an interaction model, and thus questionable.

Minor comments

- Abstract/Introduction: The aim of the paper should be clear here as well.

The abstract was completely revised to meet BMJ Open guidelines.

- Page 6, line 4 and 34. The Swiss cohorts for 2014-2016 are in my view not relevant for the main results, as they are not used as main results. In other sections, and in the appendix, this information is provided sufficiently.

Yes, thank you. We removed the 2014-2017 cohorts from the first paragraph and explain that this data is used in a sensitivity analysis in the second paragraph.

- Page 6, line 60. Please further explain how 95% CI were calculated and add a reference.

The multcomp package was used and corresponding references were added to Section A.2. R and Stata code reproducing the results is available from gitlab and provides complete transparency regarding the methods applied.

- Page 7 line 18. Are you referring to R Programming?

Yes. Two typos (R and Stata were missing) in this sentence were fixed.

- Figure 3. Ylab is on absolute mortality in relative terms (%) is confusing. I suggest labeling it as the probability of dying. Same in the title Table 4.

Indeed, the term absolute mortality refers to the probability of dying and is therefore also relative (number of deaths / number of people at risk). We explain this interpretation in the Results section and also in the caption of Figure 3. Lacking better terms contrasting “absolute” and “relative” mortalities (the latter being a ratio of probabilities) we are now using these terms throughout the manuscript.

- I would state a bit more clearly in different key parts of the paper that these results were based on results from the first wave? Things are evolving quite quickly and the paper should be appropriately read after some weeks/months as well. Spain, for example, is observing much lower mortality in the 2nd wave covid-19 positive cases. Thank you for this useful suggestion. We mention that data from the first wave only was analysed in Abstract and Methods.

- Some pre-print references are now published. I suggest checking the list of references. Three preprints have been published in the meantime (original references 6, 8, 12) and we updated the corresponding references.

Reviewer 3: Charlie Zhang

This is a timely research that investigates age-gender differentials in Covid-19 mortalities in Switzerland. The comparative method used in this paper is helpful to reveal the risks and

severity of the coronavirus. However, I have identified a number of issues that undermined the quality of this manuscript.

1. It is helpful for the readers to better understand this work if the authors clearly describe the research hypothesis in the introduction section.

The research question is an assessment of relative covid-19 mortality. This is now better reflected in the title, the abstract, and introduction.

2. Explain what age densities mean in Figure 2 and other figures and how they were calculated. It was described as probabilities of death in the methodology section though. Such discrepancies do cause confusions for the readers when reviewing this research work.

Thank you very much, this indeed was a source of confusion. Table 2 and Figure 2 compare the sex- and age distributions between the two cohorts in an exploratory analysis. We added a paragraph to the Methods section explaining this reasoning.

3. Whilst examining age-gender differentials in Covid-19 induced mortalities is useful, it would be more meaningful and insightful to reveal racial/ethnic inequalities in the death tolls within the Swiss population. Since individual death records were used in this study, I suppose race/ethnicity identity of the diseased collected was collected. Since the pandemic started, numerous studies worldwide have identified ethnic minorities and low-income residents have being disproportionately hit by the coronavirus. Moreover, examining urban/rural/suburban differences in mortality risk is another way to identify spatial disparities if locational information was available in the mortality data (I suppose it is there).

We are aware of reports on such mortality differentials from the US and other countries. To some extent, similar findings may also be expected in Switzerland, however, to a much lesser degree due to a highly developed social security system including mandatory health care insurance. Nevertheless, the sparse evidence on spatial disparities in Covid-19 incidence and prevalence in Switzerland suggests higher rates rather in more affluent than in the less privileged areas. However, racial or ethnical information was not recorded in our data. We discuss this limitation now explicitly in the Discussion section and also in the “Strengths and Limitations” box.

4. Scholars have highlighted elevated risks of people with preexisting conditions in the face of the pandemic, this study will be more valuable if this covariate is controlled for.

We absolutely agree that such an analysis would provide valuable information. Unfortunately, data on comorbidities are not available for the general population data obtained from the Swiss Federal Statistical Office. This limitation is now also mentioned.

5. My last concern is about confidentiality of individual death records that were used in this study to generate population-level statistics regarding age, gender, and mortality. it is not mentioned in the article regarding if institutional review board (IRB)

approval is obtained in order to protect private information of human subjects.

Patient data was collected by the Swiss Federal Office of Public Health (Bundesamt fr Gesundheit) under epidemic law, not needing institutional approval. Furthermore, data this report is based upon was fully anonymized. The following variables entered the models: Year of birth (NOT: day of birth), sex, day of death, and (for the covid19 cohort) day of positive SARS-CoV-2 test. Other information, such as names, addresses, social security numbers etc, allowing to identify and link persons were not available to us at any time.

Overall, I recommend this paper be Accepted with major revisions.

VERSION 2 – REVIEW

REVIEWER	Sergi Trias-Llimós Centre d'Estudis Demogràfics, Barcelona
REVIEW RETURNED	12-Nov-2020

GENERAL COMMENTS	<p>The paper provides a very relevant assessment on the impact of COVID-19 on group specific mortality as compared to the population level mortality rate in Switzerland. The analyses for the COVID-19 cohort focus on the time period between February 24th and May 14th 2020. The main strength of the analysis is that is a population-level analysis without selection restrictions over an 80-day period. The main limitation is that this cohort was selected (mostly symptomatic people). I acknowledge the effort from the authors improving the paper after the revision and the critical discussion of the main limitations in the discussion section. A few tiny comments should be considered by the authors before publication:</p> <ul style="list-style-type: none">- Abstract/Results: “The highest relative risks were...” Did the authors wanted to say HR?- Methods/Study design: The swiss covid-19 cohort includes “an unselected group of individuals tested positively for SARS-CoV-2 during the first wave between 2020-02-24 and 2020-05-15” from the Swiss Federal Office of Public Health. I suggest to mention whether it includes all data from tests (PCR?, others?) performed in Switzerland.- Page 7. Line 8. 60 days seems a typo error. 80 days?- Discussion. The authors start the discussion summarising our main results: “the at least nine fold increase in probability of death found in female and male...”. However, this information is currently omitted in the abstract.
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REVIEWER	Charlie Zhang University of Louisville, USA
REVIEW RETURNED	23-Nov-2020

GENERAL COMMENTS	The authors have addressed my concerns and suggestions in the resubmitted manuscript.
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VERSION 2 – AUTHOR RESPONSE

Response to additional comments 2021-01-27:

- > 1.The institution of corresponding author at account level is not
- > validated by Ringgold, please login using your ScholarOne's account and
- > follow these tips. The institution should not contain an exclamation
- > point indicating it is Ringgold validated.

Thank you, Universität Zürich is validated by Ringgold and there is no exclamation mark.

> 2. Identifiable information in Table 4

>

> Your article has been flagged during editorial processing as it includes potentially identifiable patient information and/or reports on patients and a signed BMJ consent form has not been uploaded.

>

> [...]

Table 4 presents information about cohorts of `_hypothetical_` patients, ie 100'000 males / females of a certain age. The rows do NOT correspond to any real person and the numbers are projections computed from the model reported on in the results part.

We highlighted this fact by changing "100'000 males or females with corresponding age" to "100'000 hypothetical males or females with corresponding age".

The article does not include identifiable patient information and/or reports on single patients in any form.

> 3. • Supplementary file citations should be in ascending order.

Thank you, we now cite Table S3 before Figures S3-S10.

Response to referee comments:

We would like to thank Dr. Trias-Llimós for his careful assessment of our

revision and respond to the additional comments as follows:

- > Abstract/Results: "The highest relative risks were..." Did the authors
> wanted to say HR?

No. "Relative risk" refers to relative mortality risk (formula "RM" in the supplement) and not the hazard ratio, the latter being only a modelling device to estimate the former. We changed "relative risks" to "relative mortality risks" in the abstract to highlight the difference.

- > Methods/Study design: The swiss covid-19 cohort includes "an unselected
> group of individuals tested positively for SARS-CoV-2 during the first wave
> between 2020-02-24 and 2020-05-15" from the Swiss Federal Office of Public
> Health. I suggest to mention whether it includes all data from tests (PCR?,
> others?) performed in Switzerland.

Yes. Federal law requires all tests (PCR at the time, this is explained in the 2nd paragraph in "Study design and data sources") to be reported to the Federal Office of Public Health. We changed "an unselected group of" to "all".

- > Page 7. Line 8. 60 days seems a typo error. 80 days?

No. The study period is 80 days (2020-02-24 - 2020-05-14) but we used a 60 day period to assess probability of death (see Statistical Analysis and supplementary material).

- > The authors start the discussion summarising our main results: "the at
> least nine fold increase in probability of death found in female and male...".
> However, this information is currently omitted in the abstract.

The "Results" part in the abstract reports this finding: "A confirmed SARS-CoV-2 infection substantially increased the probability of death across all patient groups at least nine-fold."