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MORNING BRIEF

Scientific Review

10 July 2020

The purpose of the Morning Brief is to summarize and present key information, research articles and other relevant publications pertaining to critical care and COVID-19.

Stellenbosch University Research Response Team

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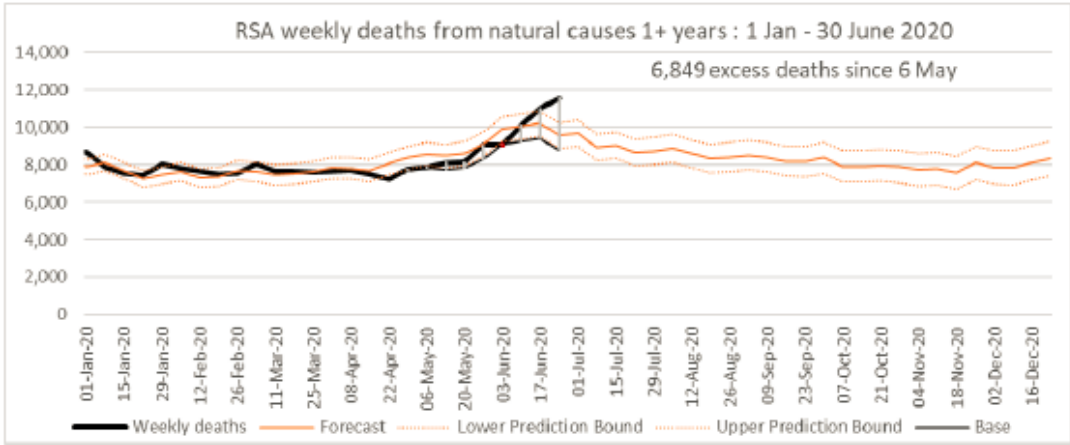
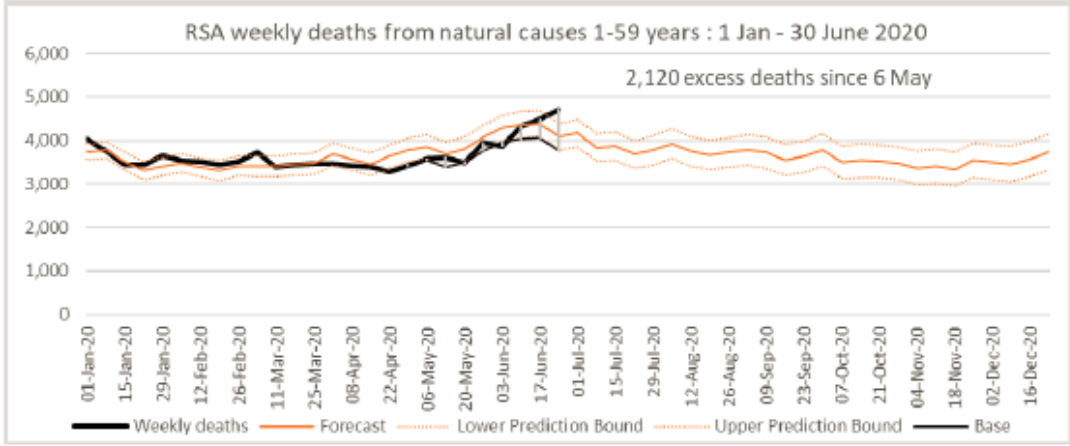
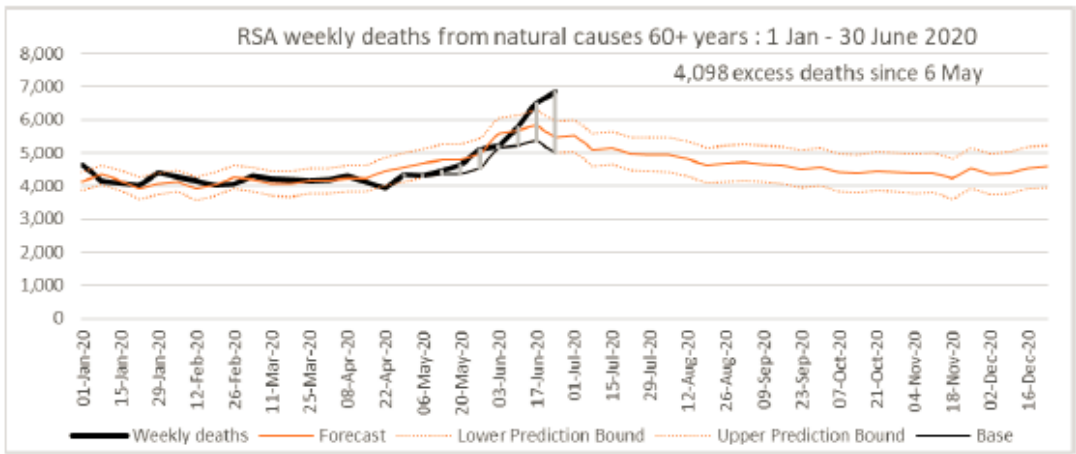
Content

Statistics
Statins and COVID-19







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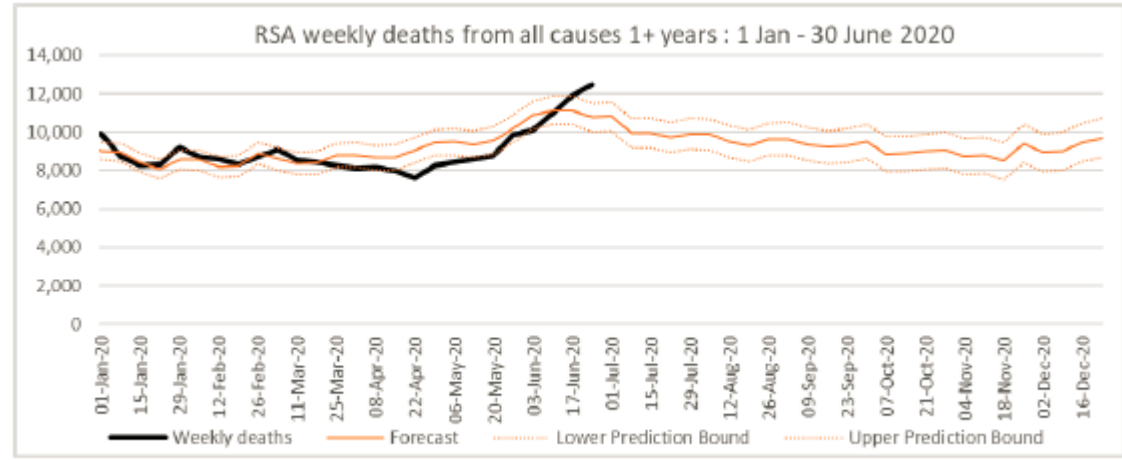
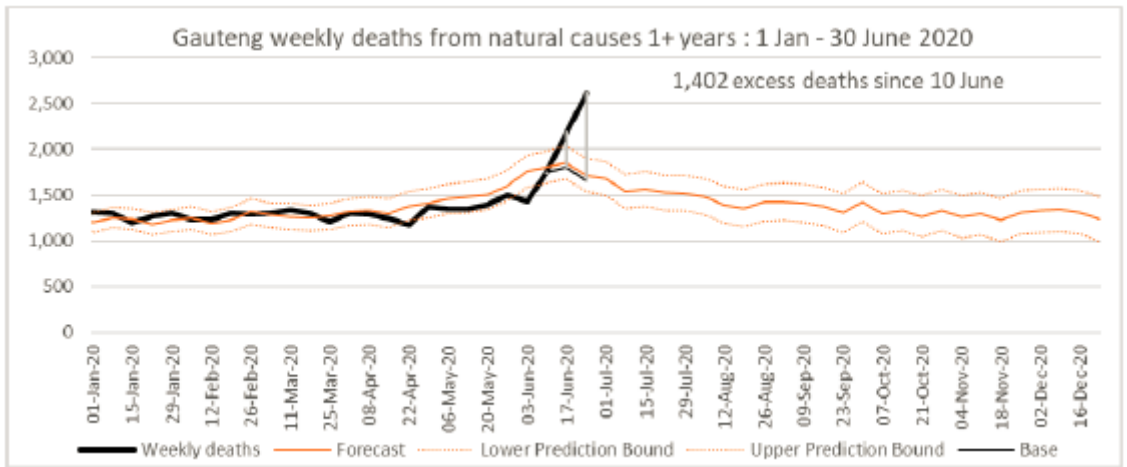


lumbers have been scaled to the estimated actual number of death and for the last week has been adjusted for delayed registrations



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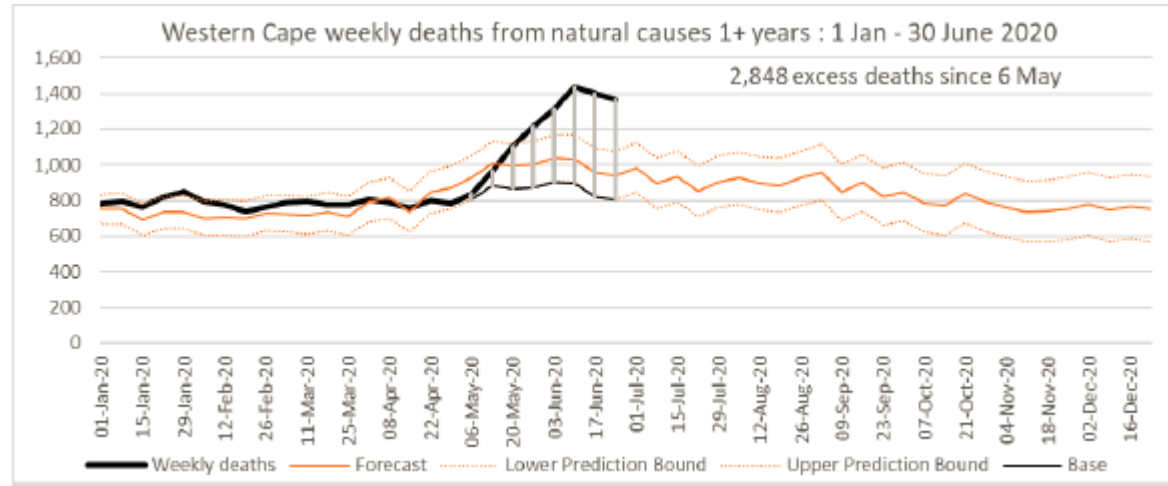

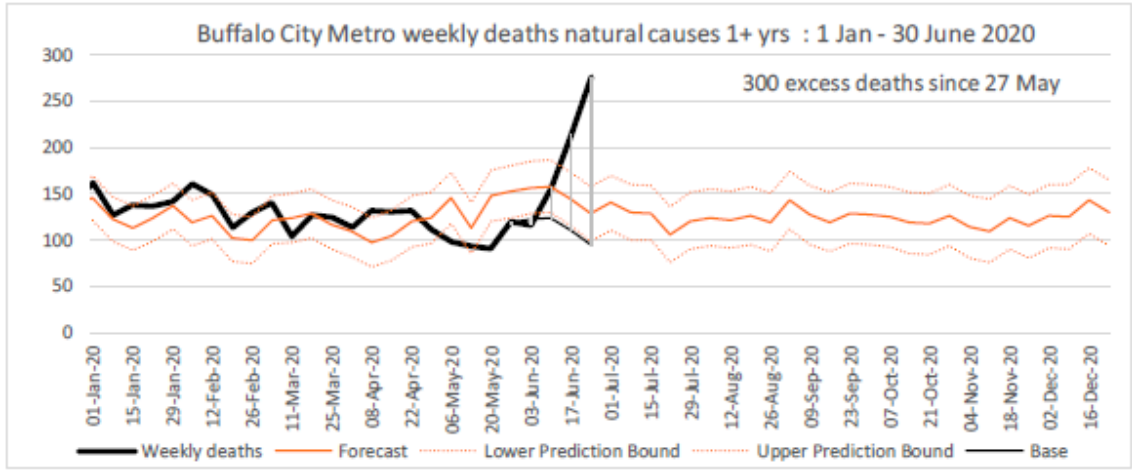

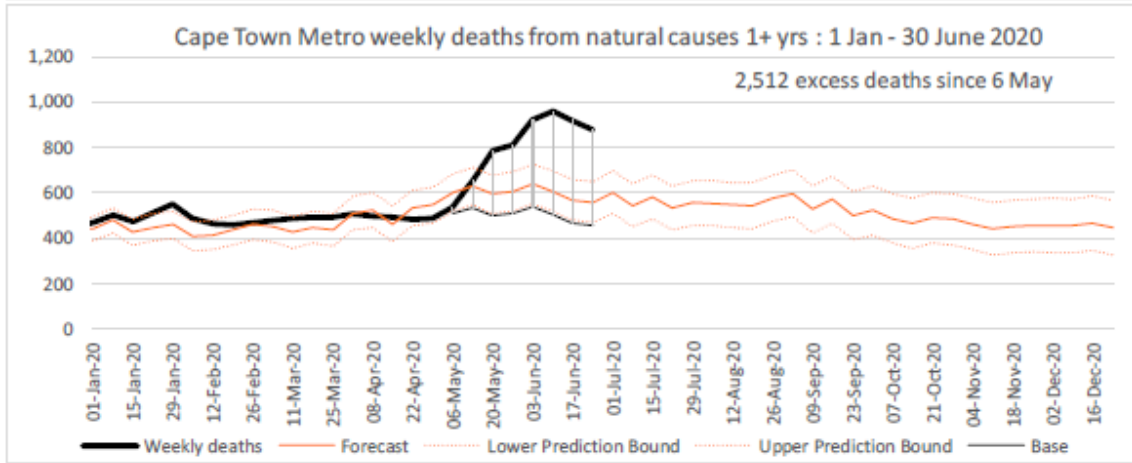

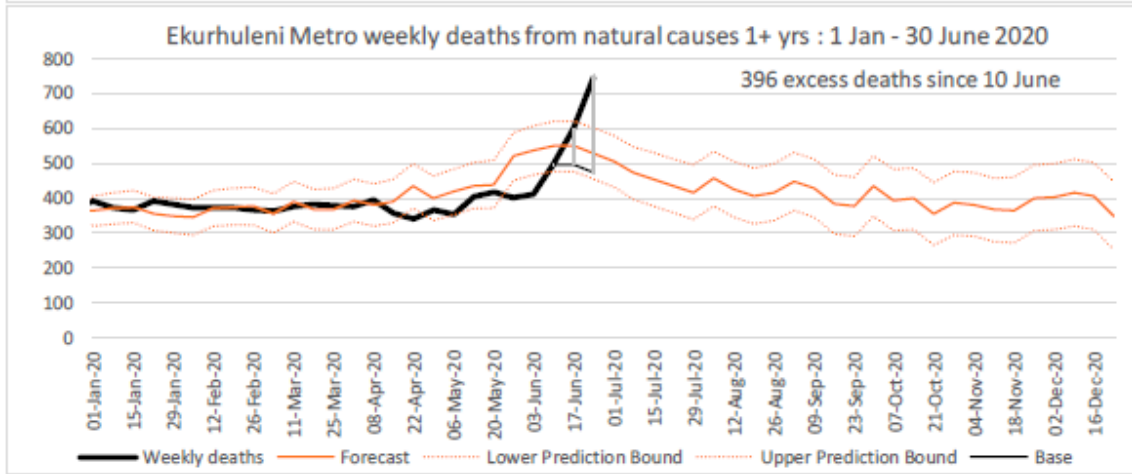

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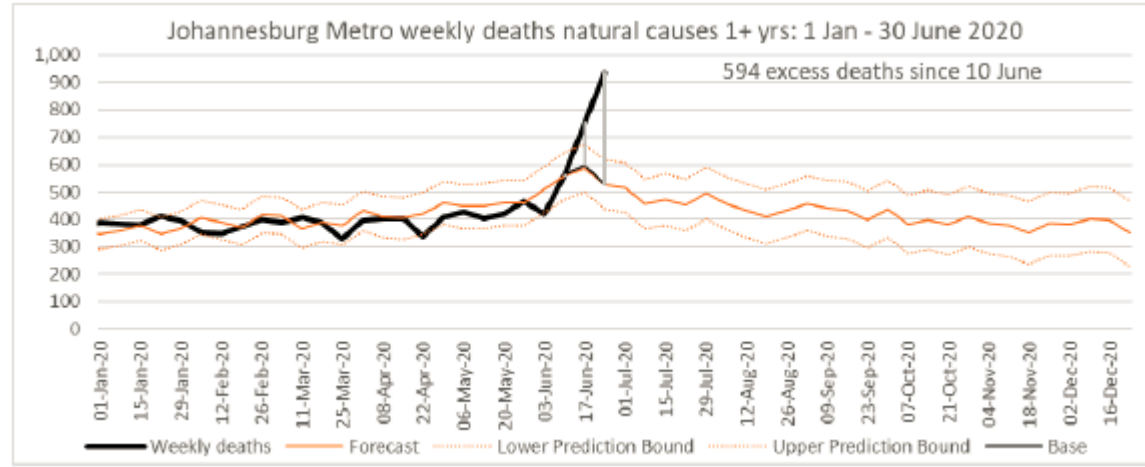

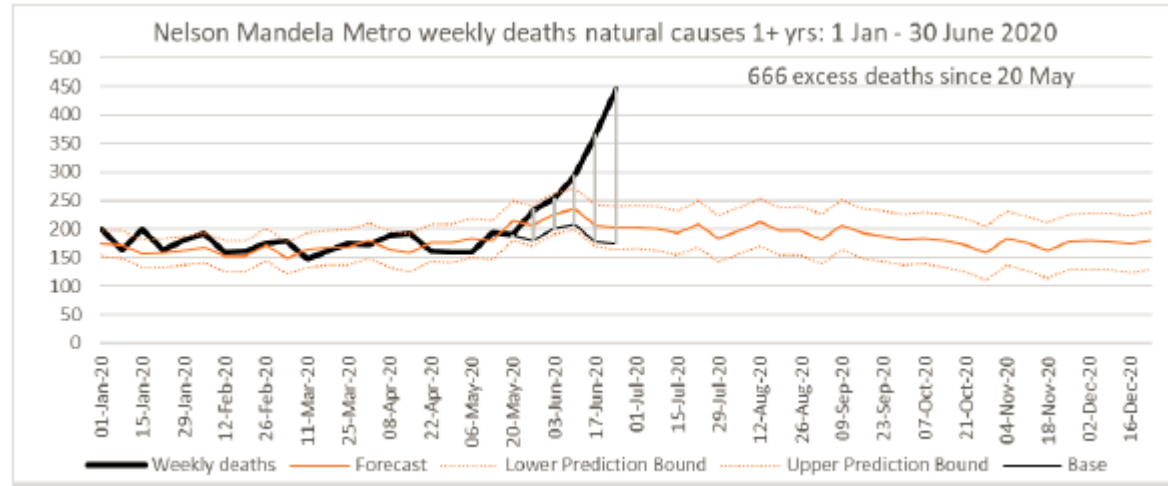

Cell Metabolism

CellPress

Clinical and Translational Report

In-Hospital Use of Statins Is Associated with a Reduced Risk of Mortality among Individuals with COVID-19

Xiao-Jing Zhang,[1,2,3,31] Juan-Juan Qin,[1,2,31] Xu Cheng,[1,2,31] Lijun Shen,[1,2,31] Yan-Ci Zhao,[1,2,31] Yufeng Yuan,[4] Fang Lei,[2] Ming-Ming Chen,[1,2] Huilin Yang,[1,2] Liangjie Bai,[2] Xiaohui Song,[2] Lijin Lin,[1,2] Meng Xia,[2] Feng Zhou,[2,3] Jianghua Zhou,[1,2] Zhi-Gang She,[1,2] Lihua Zhu,[1,2] Xinliang Ma,[5] Qingbo Xu,[6] Ping Ye,[7] Guohua Chen,[8] Liming Liu,[9] Weiming Mao,[10] Youqin Yan,[11] Bing Xiao,[12] Zhigang Lu,[13] Gang Peng,[14] Mingyu Liu,[15] Jun Yang,[16] Luyu Yang,[17] Changjiang Zhang,[1,18]

WHY LOOK AT STATINS IN COVID19?

- Re-purposing existing approved drugs to mitigate the severity of COVID-19 is viewed as a cost-effective and time-sensitive strategy to combat the pandemic of coronavirus.
- Statins are first-line lipid-lowering therapies with well-tolerated side effects, are low in cost, and are broadly available worldwide.
- The potent anti-inflammatory and immunomodulatory effects of statins suggest they could be beneficial to counter corona viral infections, including for SARS-CoV-2

- Observational studies and randomized controlled trials (RCTs) have demonstrated a significant protective effect of statins on improving pro-inflammatory cytokine release and immune cell functions among individuals with viral and bacterial pneumonia.
- A recent report based on molecular docking analysis showed that statins might inhibit SARS-CoV-2 entry into host cells by directly binding the main protease of the coronavirus.
- These data led to speculation regarding the potential therapeutic benefits of statins for the treatment of COVID-19 (Arabi et al., 2020; Bifulco and Gazzerro, 2020).
- However, concerns have been raised regarding whether individuals on statins are at a greater risk for SARS-CoV-2 infection and COVID-19 exacerbation, as this class of drugs has been shown to increase the expression of angiotensin-converting enzyme 2 (ACE2), the receptor for the virus, in lab animals.

AIMS:

- Recruit 13,981 clinically confirmed cases of COVID-19 to determine the association of in-hospital use of statins with clinical outcomes, obtaining clinical evidence urgently needed to answer the question as to whether statin use is detrimental or beneficial in hospitalized individuals with COVID-19
- In the subgroup analysis, further investigate the additional effects of combining ACEi/ARB with statins on the clinical outcomes of COVID-19.

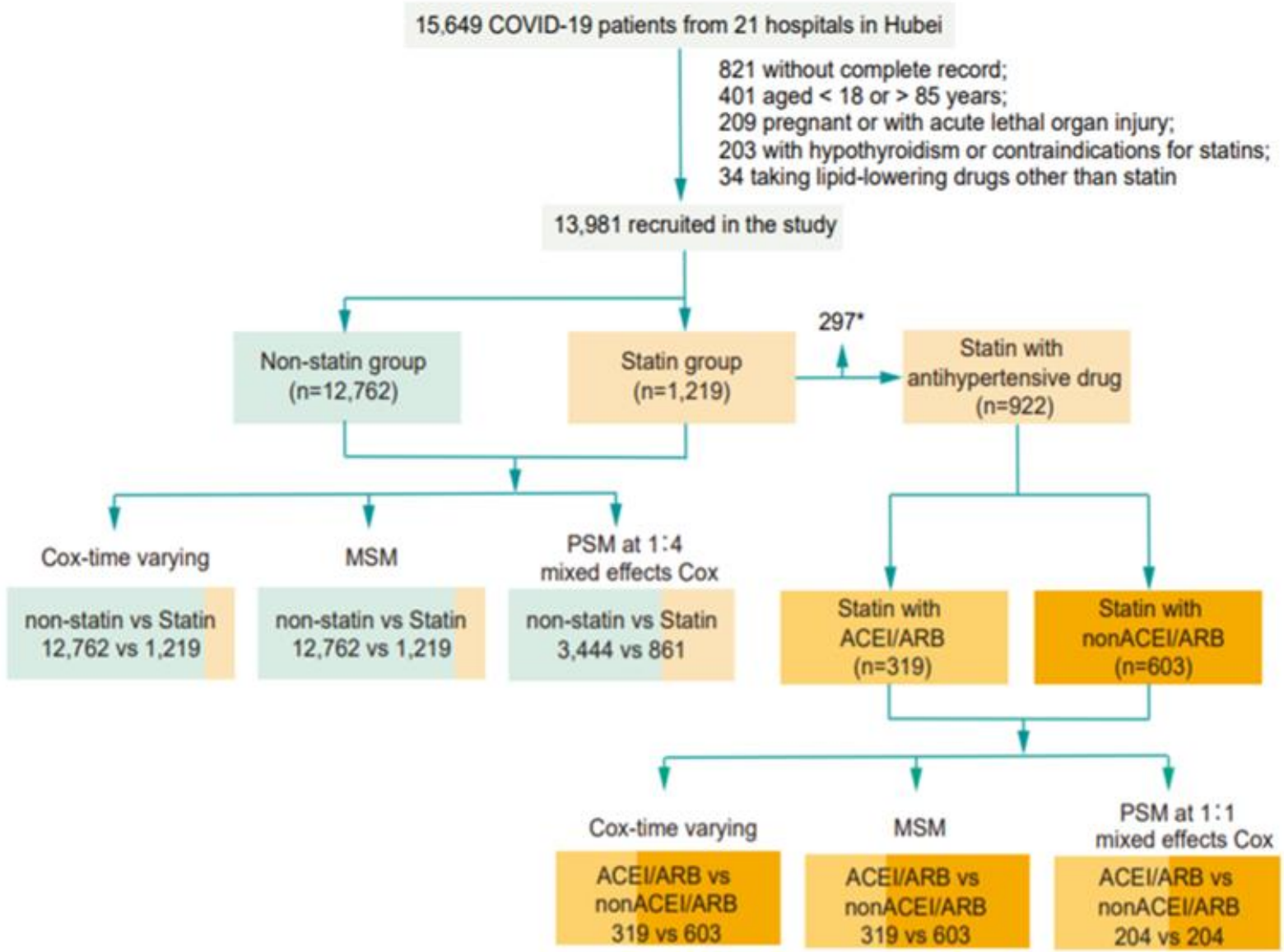

Figure 1. The Flowchart Showing the Strategy of Participant Enrollment

A schematic overview illustrating participant enrollment and the exclusion and inclusion criteria.

*297 participants without a medical history of hypertension or with hypertension but not taking antihypertensive medication were excluded from subgroup analyses.

RESULTS AND DISCUSSION:

The time-varying Cox model, marginal structure model (MSM), and propensity score-matching analysis consistently showed a lower risk of all-cause mortality of COVID-19 in individuals with statin use versus statin non-use.

Baseline Characteristics in Participants with and without Statin Treatment

1,219 had in-hospital use of statins (statin group) and the remaining 12,762 had no statin treatment (non statin group)

In comparison to non-statin using participants, those that received statin treatment were

- ❑ Older (66.0 versus 57.0 years of age, $p < 0.001$) and
- ❑ Statin patients had higher prevalence of chronic medical conditions, including:
  - hypertension (81.5% versus 30.3%, $p < 0.001$),
  - diabetes mellitus (DM) (34.0% versus 14.6%, $p < 0.001$),
  - coronary heart disease(36.3% versus 5.7%, $p < 0.001$),
  - cerebrovascular diseases (8.8% versus 2.3%, $p < 0.001$), and
  - chronic kidney diseases(5.2% versus 3.1%, $p < 0.001$)

- **Chest CT**: bilateral pulmonary lesions were more common in the statin group compared with that in the non-statin group (89.5% versus 83.7%, $p < 0.001$)
- Larger proportions of subjects in the statin group showed increased neutrophil counts, procalcitonin levels, and D-dimer compared with the non-statin group.
- At baseline Inflammatory markers, abnormal serum biochemistry, including increased ALT and AST levels and decreased estimated glomerular filtration rate (eGFR), indicated more prevalent organ impairments in the participants with statin therapy compared to non-statin use.
- The frequencies of individuals with increased low-density lipoprotein cholesterol (LDL-c) and total cholesterol (TC) levels were higher among the statin group versus the non-statin group at admission. In terms of the whole hospitalization period, lipid profiles were comparable between the two groups
- Days from onset of symptom to hospitalization and the median follow-up days were longer in the individuals on statin treatment compared to the non-statin group

Propensity Score Matching (PSM) model

For subjects enrolled in the propensity score-matching (PSM) model that was conducted to minimize the differences in baseline characteristics, 861 participants from the statin group were matched at a 1:4 ratio to 3,444 participants from the non-statin group.

The baseline characteristics were comparable between the two groups, except the proportion of individuals with $SpO2 < 95\%$ was lower in statin group than the non-statin group

Lipid profiles also were comparable during hospitalization between statin and non-statin groups after PSM

Hypertension and anti-hypertensives:

- Among the participants on statin therapy, 993 (81.5%) had hypertension.
- Of these 319 were also treated with ACE inhibitors or an ARB regimen
- 603 were on non ACEi/ARB antihypertensive drugs
- Age and gender distribution were comparable between the two groups.
- The systolic blood pressure (SBP) levels and prevalence of DM were higher, while the prevalence of COPD was lower, in individuals on statin + ACEi/ARB, compared to those on the combination of statin and other types of antihypertensive drugs.
- To further examine the influence of anti hypertensive treatment, 204 individuals in the statin+ACEi/ARB group were matched at a 1:1 ratio to 204 individuals in the statin + nonACEi/ARB group. The baseline characteristics were comparable between the two groups

In-Hospital Use of Statins and Combination of Statins and ACEi/ARB:

- Atorvastatin was the most frequently prescribed (83.2%), followed by rosuvastatin (15.6%)
- Statin treatment started at the day of hospital admission. The dose differences among statins were converted to an equivalent dose of atorvastatin.
- The therapeutic duration for individuals in the statin group was 22.0 (14.0–28.0) days, with an atorvastatin equivalent dose at 20.0 (18.9–20.0) mg per day .
- There were 26.2% individuals also treated with ACEi/ARB in the statin group compared to 6.6% for the non-statin group
- In the PSM cohort, the percentage of individuals on ACEi/ARB treatment was comparable between the statin and non-statin groups. The median (IQR) day of starting ACEi/ARB treatment was 3.0 days after admission, and the median (IQR) therapeutic duration was 17.0 (9.5–25.0) days
- In the PSM cohort, the median (IQR) ACEi/ARB starting time was 4.0 days after admission, and the median (IQR) therapeutic duration was 16.0 days

In-Hospital Use of Statins Was Associated with a Lower Risk of All-Cause Mortality

- The incidence rate of death during a 28-day follow-up was 0.21 cases 100-person-day in the statin group (the mortality rate at 5.5%) versus 0.27 100-person-day in the non-statin group (the mortality rate at 6.8%)
- In the PSM cohort, the crude incidence of death in the statin group (IR, 0.20 cases 100-person-day; death rate 5.2%) was markedly lower than that in the non-statin group (IR, 0.37 100-person-day; death rate 9.4%).

To minimize the potential bias in this study, various models and sensitivity tests were done to evaluate the reliability of our study results.

In this study, individuals who received statins did not have earlier initiation of medical therapy or hospital admission than statin nonusers (14.0 days in the statin group versus 11.0 days in the non-statin group), implying unlikely imbalanced access to the health system-related lower risk of COVID-19 mortality in the statin group.

The COVID-19-associated medical expenses were covered by the Chinese government during the pandemic, which largely reduced the impact of the socio-economic level on in-hospital treatment.

Regarding the potential bias from survivor treatment selection, we performed a Cox model with time-varying exposure to adjust for potential bias caused by differences in the initial time of treatment.

Meanwhile, we calculated the average hospitalization period for individuals discharged in the statin and the non-statin groups, which were similar (15.0 days versus 16.0 days), indicating unlikely prolonged benefit from hospital treatment in the statin group

Competing medical issues, such as clinicians being more likely to arrange urgent therapy in critically ill patients versus those less critically ill, could lead to a bias resulting in an association between not using statins with poor outcomes. Therefore, an MSM analysis were conducted and adjusted for time-varying confounders that simultaneously influence the time of statin initiation and risk of mortality.

Cox models with and without time-varying exposure and MSM analysis were also performed in the patient populations excluding those who were admitted to the ICU or died within 48 h after admission.

Despite extensive efforts to utilize multiple models with rigorous controls, there still could be possible biase that can impact the magnitude of the statin use-associated benefits on all cause mortality among individuals with COVID-19, thus calling for the need of further validations via RCT studies

The Combination of Statins and ACEi/ARB Utilization Was Not Significantly Associated with the Risk of All-Cause Mortality among Individuals with COVID-19 and Hypertension

Results indicated that using ACEi/ARB in combination with statins conferred neither additive beneficial nor detrimental effects in 28-day mortality compared to the combined use of non-ACEi/ ARB plus statins among subjects with pre-existing hypertension

In-Hospital Usage of Statins and Combination Usage of Statins and ACE Inhibitors or ARBs Did Not Increase the Risk of Organ Damage and Other Adverse Effects

After adjusted baseline differences, Cox model analysis showed that statin usage was associated with a lower prevalence of using
mechanical ventilation (aHR, 0.37; 95% CI, 0.26–0.53, p <0.001),
ICU admission (aHR, 0.69; 95% CI, 0.56–0.85, p =0.001), and
ARDS (aHR, 0.83; 95% CI, 0.72–0.97, p = 0.015) In individuals with COVID-19
After matching baseline differences in two groups by PSM, the statin group still showed a lower incidence of invasive mechanical ventilation compared to the non-statin group (aHR, 0.51; 95% CI, 0.34–0.78, p =0.002)
Statin therapy was not significantly associated with other secondary outcomes (e.g., acute kidney injury, liver injury, and cardiac injury) and increased serum CK or transaminase levels in the PSM cohort
Among the individuals with COVID-19 and pre-existing hypertension, there were no significant associations between all observed secondary outcomes and statins with or without ACE inhibitors or ARB treatment in unmatched subjects
There were no significant associations between the co-treatment of statin with ACEi/ARB and other secondary outcomes or the raised serum CK or transaminase levels

Conclusion

The use of statins in hospitalized subjects with COVID-19 was associated with a lower risk of all-cause mortality and a favourable recovery profile. Due to the nature of such retrospective studies, these results should be interpreted with caution; however, these data provide supportive evidence for the safety of statin or combination of a statin with ACEi/ARB for treatment in patients with COVID-19. Further RCTs to prospectively explore the efficacy of statins on COVID-19 outcomes are urgently needed.

LIMITATIONS:

1. retrospective study makes it impossible to infer causality in the association between the use of statins and ACEi/ARB and the ameliorated severity and mortality in COVID-19.
2. Even while using multiple statistical models to adjust for potential bias and performed sensitivity analyses to show that the overall unmeasured confounders were unlikely to undermine the main conclusion, some unforeseen confounders (e.g., prehospital medication and socioeconomic status) may still potentially alter the magnitude of statin effects on all-cause mortality of COVID-19.
3. Marginal structural models require the availability of time-varying data on each day surrounding the initiation of statin exposure. The data for time-varying confounders for each day were not fully available, and imputation for days with missing data would also lead to uncertain bias to the conclusion.
However, participants started on statin treatment in a very early phase after admission would thus minimize the impact of imputation.
4. The BMIs in the statin and non-statin groups were comparable and thus were not adjusted in the following statistical analysis. Moreover, due to the urgent status of the COVID-19 pandemic, BMI was not always measured and has a relatively high missing proportion. This might lead to an uncertainty of the impact of BMI on the associations between statin use and lower risk of all-cause mortality.
5. the role of different types of statins on COVID-19 outcomes was not fully analyzed since the majority of the cases were taking atorvastatin and rosuvastatin, while the number of individuals taking other types of statins was relatively small.
6. study population included only hospitalized subjects,

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This summary was prepared by Dr A Hiemstra as part of the daily brief to the TBH ICU team.