Original Article

Cost-effectiveness analysis of statins for the treatment of hospitalized COVID-19 patients

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Contributions: (I) Conception and design: R Chow, HJ Shin; (II) Administrative support: CB Simone 2nd, EH Prsic, HJ Shin; (III) Provision of study materials or patients: R Chow, EH Prsic, HJ Shin; (IV) Collection and assembly of data: R Chow; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: A recent systematic review and meta-analysis reporting on thirteen published cohorts investigating 110,078 patients demonstrated that patients who were administered statins after their COVID-19 diagnosis and hospitalization were had a lower risk of mortality. While these findings are encouraging, given competing COVID-19 treatment approaches, it is unclear if statin use should be prioritized and if its use is a cost-effective treatment options for hospitalized COVID-19 patients. In this study, we report on a cost-effectiveness analysis of statin-containing treatment regimens for hospitalized COVID-19 patients.

Methods: A Markov model was used to compare statin use and no statin use among hospitalized COVID-19 patients from a United States healthcare perspective. The cycle length was one week, with a time horizon of 4 weeks. A Monte Carlo microsimulation with 20,000 samples were used. All analyses were conducted using TreeAge Pro Healthcare Version 2021 R1.1.

Results: The mean cost for patients receiving statins in addition to usual care was $31,623 (SD $20,331), whereas the mean cost for patients not receiving statins was $33,218 (SD $25,440). The mean effectiveness for the two cohorts were 1.73 (SD 0.96) and 1.71 (SD 1.00), respectively.

Conclusions: This analysis demonstrated that treatment of hospitalized COVID-19 patients with statins was both cheaper and more effective than treatment without statins; statin-containing therapy dominates over non-statin therapy. Statin medications for the treatment of COVID-19 should be further investigated in randomized controlled trials, especially considering its cost-effective nature. Optimistically and pending the results of future randomized trials, statins should be considered for use broadly for the treatment of hospitalized COVID-19 patients.

Keywords: Statins; COVID-19; cost-effectiveness analysis; survival; hospitalization

Submitted Sep 08, 2021. Accepted for publication Dec 02, 2021.
doi: 10.21037/apm-21-2797
View this article at: https://dx.doi.org/10.21037/apm-21-2797

Introduction

The COVID-19 pandemic, as declared by the World Health Organization on March 12, 2020 (1), has been an ongoing global health and social crisis for the past one-and-a-half years. Many potential treatments have been explored, including statins. Mechanistically, statins may inhibit 3-hydroxy-glutaryl-CoA (HMG-CoA) reductase in cells, and reduce cytokine storm-like effects from the virus (2-4).

A recent systematic review and meta-analysis reported

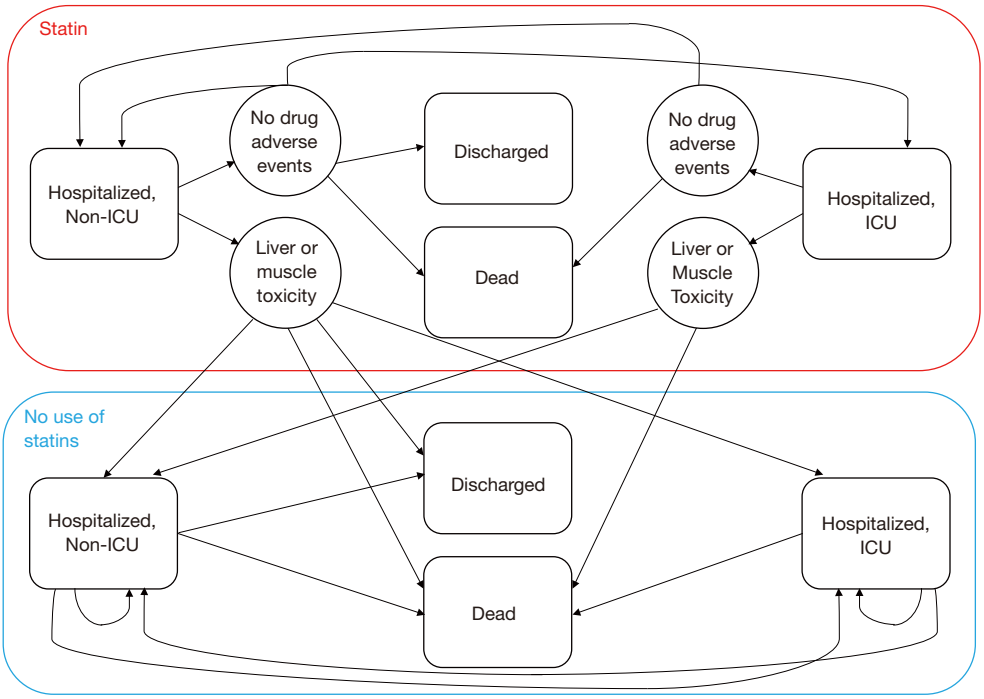

Figure 1 State-transition diagram.

on 13 published cohorts investigating 110,078 patients. That study found that patients who were administered statins after their COVID-19 diagnosis and hospitalization had a significantly lower risk of mortality—hazard ratio of 0.53 (95% CI: 0.46–0.61), and odds ratio of 0.57 (95% CI: 0.43–0.75). Given this reported superiority, and while waiting for the development of randomized controlled trial data on statin use for COVID-19, a logical next question is if statin medications are cost-effective treatment options for hospitalized COVID-19 patients.

In this study, we report on a cost-effectiveness analysis of statin-containing compared to non-statin-containing treatment regimens for hospitalized COVID-19 patients, from a United States healthcare perspective in accordance with the CHEERS reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-21-2797/rc).

Methods

The model

A Markov model was used to compare statin use and no statin use among hospitalized COVID-19 patients (*Figure 1*). For this analysis, there were four assumed health states—"Hospitalized, non-ICU", "Hospitalized, ICU", "Discharged", and "Dead". Patients treated with statin medications started in the "Hospitalized, non-ICU" health state, and may or may not have experienced a drug-related adverse event during the cycle. If patients experienced liver or muscle toxicities, statins were discontinued. Patients either remained in the "Hospitalized, Non-ICU" health state or transitioned to one of the three other health states. For patients who were admitted to the ICU, we assumed that they would be transferred back to non-ICU inpatient care prior to discharge or otherwise have died. For modeling simplicity, we also assumed that patients who were discharged would not be readmitted to the hospital for COVID-19 within 1 month.

The cycle length was one week, with a time horizon of 4 weeks. No discounting rate was used due to the acute timeline. A Monte Carlo microsimulation with 20,000 samples were used. All analyses were conducted using TreeAge Pro Healthcare Version 2021 R1.1 (Williamstown, MA, USA).

Probabilities

We sourced 1-week probability of death, discharge and ICU

admission for non-statin hospitalized COVID-19 patients from Zhang *et al.* (5) and Rodriguez-Nava *et al.* (6). From Zhang *et al.* (5), we computed the 1-week probability from their 4-week Kaplan-Meier curve statistics. We assumed that probabilities reported by Rodriguez-Nava *et al.* (6) were 4-week probabilities, and from this we computed 1-week probability. Probability of death among statin patients was computed using relative risks reported from a prior meta-analysis [Chow *et al.* (7)] and from the probability reported by Zhang *et al.* (5) for non-statin patients. Probability of discharge and ICU admissions among statin patients was also sourced from Zhang *et al.* (5); probability of death among ICU patients receiving statins was extracted from Rodriguez-Nava *et al.* (6). The probabilities for liver and muscle toxicities were sourced from Gitlin *et al.* (8). Beta distributions were used to model probabilities (*Table 1*).

Effectiveness

Utilities for non-ICU hospitalization and ICU hospitalization were noted from Cyrus *et al.* (9). We assumed utilities for those who were discharged, died, experienced liver toxicity, and experienced muscle toxicity. We conservatively assumed a disutility of –0.2 for liver and muscle toxicities, which would be a greater disutility than a patient's health state changing from non-ICU hospitalization to ICU-hospitalization. Gamma distributions were used, for utility associated with hospitalization. Triangular distributions were used, for disutility associated with liver and muscle toxicity.

Costs

We calculated the cost of statins in addition to usual care from the US Department of Health & Human Services (10), as the average cost of moderate dose statins (13)—atorvastatin 10 mg, simvastatin 40 mg, pravastatin 40 mg and lovastatin 40 mg, all commonly used drugs and dose regimens. We assumed price to range ±50%. The cost for non-ICU hospitalization was calculated using the 1-day average hospitalization cost of approximately $2,000 from the World Health Organization (11), and we varied costs ±50%. We used the one-day cost of ICU hospitalization with mechanical ventilation from the Dasta *et al.* (12) paper, and calculated a lower-bound range from the one-day cost of ICU hospitalization after stabilization on day 3. The upper-bound was calculated, to produce a symmetric range. A uniform distribution was used to represent costs.

Results

The mean cost for patients receiving statins was $31,623 (SD $20,331), whereas the mean cost for patients not receiving statins was $33,218 (SD $25,440). The mean effectiveness for the two cohorts were 1.73 (SD 0.96) and 1.71 (SD 1.00), respectively. Treatment of hospitalized COVID-19 patients with statins was both cheaper and more effective than treatment without statins; statin-containing therapy dominates over non-statin therapy.

Discussion

To our knowledge, this is the first cost-effectiveness analysis reporting on statin use for the treatment of hospitalized COVID-19 patients. We report herein that treatment with statins, relative to treatment without statins, is both cheaper and more effective.

This information is quite timely in light of the new wave of COVID-19 infections affecting all countries with the rise of viral variants and the relatively slow rollout of vaccinations in much of the world (14,15). Furthermore, variants of COVID-19 that have proved more infectious and more potent than the original virus are taxing hospital censuses and filling ICU beds throughout the world (16). In light of this, new COVID-19 cases are continue to emerge, and treatment, rather than eradication strategies, is necessary.

Currently, remdesivir, systemic glucocorticoid, tocilizumab, and monoclonal antibody treatments are recommended for patients with severe COVID-19 pneumonia (17). There is currently no universally recommended treatment for patients with non-severe COVID-19. Given the results of our prior systematic review (7), and now this cost-effectiveness analysis suggesting statin-containing treatments are both cheaper and more effective than alternative approaches, statins should be further investigated for use in non-severe COVID-19 patients. Akin to how dexamethasone is widely used for its inexpensive cost and supported by effectiveness data, statins may be a good drug to help treat hospitalized COVID-19 patients. Outside of the US, statins may also help to improve global equity, most notably in resource-poor countries. The cheap medication cost of statins might help reduce COVID-19 mortality, especially in countries which much reduced access to COVID-19 vaccination. Of note, statins are commonly used medications that are generally well tolerated. Although statin therapy may lead

Table 1 Inputs for Markov model—statin use after hospitalization

Parameter	Point estimate	Range	Source
One-week rate			
Statin arm			
Hospitalized, non-ICU	0.82	N/A	Chow *et al.* (7)
Hospitalized, ICU	0.02	N/A	Zhang *et al.* (5)
Discharge	0.15	N/A	Zhang *et al.* (5)
Death	0.01	N/A	Chow *et al.* (7)
Hospitalized, ICU			
Hospitalized, non-ICU	0.94	N/A	Rodriguez-Nava *et al.* (6)
Death	0.06	N/A	Rodriguez-Nava *et al.* (6)
Toxicity			
Liver	0.01	N/A	Gitlin *et al.* (8)
Muscle	0.1	N/A	Gitlin *et al.* (8)
Non-statin arm			
Hospitalized, Non-ICU	0.79	N/A	Zhang *et al.* (5)
Hospitalized, ICU	0.03	N/A	Zhang *et al.* (5)
Discharge	0.16	N/A	Zhang *et al.* (5)
Death	0.02	N/A	Zhang *et al.* (5)
Hospitalized, ICU			
Hospitalized, non-ICU	0.84	N/A	Rodriguez-Nava *et al.* (6)
Death	0.16	N/A	Rodriguez-Nava *et al.* (6)
Utilities			
Health states			
Hospitalized, non-ICU	0.847	0.83 to 0.87	Cyrus *et al.* (9)
Hospitalized, ICU	0.629	0.40 to 0.91	Cyrus *et al.* (9)
Discharged	1	N/A	N/A
Death	0	N/A	N/A
Toxicity			
Liver	−0.2	−0.10 to −0.30	N/A
Muscle	−0.2	−0.10 to −0.30	N/A
Costs			
Statin arm			
Added cost: statin	$0.93	$0.47 to $1.40	US Department of Health & Human Services (10)
Non-statin arm			
Hospitalized, Non-ICU	$14,000	$7,000 to $21,000	World Health Organization (11)
Hospitalized, ICU	$76,500	$28,000 to $125,000	Dasta *et al.* (12)

N/A, not applicable.

to side effects of myopathy and liver toxicities in a minority of patients, these adverse events typically reverse after discontinuation of statins (18).

While the focus of this analysis was for the use of statins as a treatment modality, we also eagerly await the results of the ongoing COLSTAT trial that is investigating colchicine/statins for the prevention of COVID-19. These results will hopefully provide insight as to whether statins are also appropriate in the prevention setting.

This study was not without limitations. Our underlying probabilities were sourced from observational studies and, therefore, patients receiving and not receiving statins may have had unbalanced characteristics that may have led to confounding. To account for such potential imbalances, we used adjusted probabilities from multivariable models. As well, much of the published evidence reports on a dataset of outpatient-documented and inpatient-documented treatment, which may lead to an imprecise effect estimate of inpatient treatment. We also used beta distributions for probabilities to account for potential variation in measured effectiveness relative to true effectiveness/efficacy. Another limitation is the omission of other possible side effects, including statin-induced dementia (13) and statin-induced diabetes (19). These adverse events are typically quite uncommon and more likely to occur with longer statin use, and they are likely of marginal concern in patients with immediate risk of COVID-19 pneumonia, where the interest of treatment is improved health state in a very acute timeline until stabilization after COVID-19 infection. This differs from prior studies and cost-effectiveness analyses of statins in other settings, which report long-term side effect of statins, including diabetes and dementia. It is also important to note that the link between dementia and statins has not been fully characterized at this time. Finally, our model assumes that patients admitted to ICU will continue statins—there may be instances in clinical care where oral statin treatment is discontinued and intravenous statin preparations are not administered, as per the rewritten medical orders upon ICU admission.

In conclusion, treatment of hospitalized COVID-19 patients led to better effectiveness, but also lower overall healthcare cost. Statin medications for the treatment of COVID-19 should be further investigated in randomized controlled trials (RCTs), especially considering its cost-effective nature. Optimistically and pending the results of future RCTs, statins should be considered for use broadly for the treatment of hospitalized COVID-19 patients.

Acknowledgments

Funding: This research was funded, in part, through the NIH/NCI Cancer Center Support (P30 CA008748).

Footnote

Reporting Checklist: The authors have completed the CHEERS reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-21-2797/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-21-2797/coif). CBS serves as the Editor-in-Chief of *Annals of Palliative Medicine*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Chow R, Simone CB 2nd, Prsic EH, Shin HJ. Cost-effectiveness analysis of statins for the treatment of hospitalized COVID-19 patients. Ann Palliat Med 2022;11(7):2285-2290. doi: 10.21037/apm-21-2797

