Cost-effectiveness of remdesivir plus usual care versus usual care alone for hospitalized patients with COVID-19 as part of the Canadian treatments for COVID-19 (CATCO) randomized clinical trial

Vincent I. Lau, MD, MSc, FRCPC[1]
Robert Fowler, MDCM, MS, FRCPC[2]
Ruxandra Pinto, PhD[3]
Alain Tremblay, MDCM, FRCPC[4]
Sergio Borgia, MSc, MD, FRCPC[5,6]
François M. Carrier, MD, MSc[7]
Matthew P. Cheng, MD, SM[8]
John Conly, CM, MD, FRCPC[9]
Cecilia T. Costiniuk, MD, MSc, FRCPC[10]
Peter Daley, MD, MSc, FRCPC[11]
Erick Duan, MD, MSc, FRCPC[12,13,14]
Madeleine Durand, MD MSc, FRCPC[15]
Patricia S. Fontela, MD, PhD[16]
George Farjou, MD, FRCPC[17]
Mike Fralick, MD, PhD, FRCPC[18]
Anna Geagea, MD, FRCPC[19]
Jennifer Grant, MD, CM FRCPC[20]
Yoav Keynan, MD, PhD, FRCPC[21]
Kosar Khwaja, MD, MBA, MSc, FRCSC, FACS[22]
Nelson Lee, MD, MBBS, MRCP(UK), FRCP(Lond), FRCP(Edin), FIDSA[23]
Todd C. Lee, MD, MPH, FIDSA[24]
Rachel Lim, MD, FRCPC[4]
Conar R O'Neil, MD, MSc, FRCPC[25]
Jesse Papenburg, MDCM, MSc, FRCPC[26]
Makeda Semret, MD, FRCPC[18]
Michael Silverman, MD, FRCPC[27]
Wendy Sligl, MD, MSc, FRCPC[1]
Ranjani Somayaji, MD MPH FRCPC[9]
Darrell H. S. Tan, MD FRCPC PhD[28]
Jennifer LY Tsang, MD, PhD, FRCPC[12,13]
Jason Weatherald, MD, MSc, FRCPC[4]
Cedric Philippe Yansouni, MD, FRCPC, DTM&H[29]
Ryan Zarychanski MD MSc FRCPC[30]
Srinivas Murthy, MD, MSc, FRCPC[31]
For the E-CATCO authors, AMMI Clinical Research Network, and Canadian Critical Care Trials Group

[1]Department of Critical Care Medicine, Faculty of Medicine and Dentistry, University of Alberta and Alberta Health Services, Edmonton, Alberta, Canada
[2]Interdepartmental Division of Critical Care Medicine, University of Toronto, Ontario, Canada
[3]Department of Critical Care Medicine, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
[4]Division of Respiratory Medicine, Department of Medicine, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada
[5]Division of Infectious Diseases, William Osler Health System, Brampton, Ontario, Canada
[6]Division of Infectious Diseases, Department of Medicine, McMaster University, Hamilton, Ontario, Canada

[7]Department Anesthesiology and Department of Medicine, Division of Critical Care Medicine, Centre hospitalier de l'Université de Montréal, Montréal, Québec, Canada
[8]Department of Medicine, Infectious Diseases and Medical Microbiology, McGill University Health Centre, Montreal Quebec, Canada
[9]Division of Infectious Diseases, Department of Medicine, Cumming School of Medicine, University of Calgary and Alberta Health Services, Calgary, Alberta, Canada
[10]Department of Medicine, Division of Infectious Diseases and Chronic Viral Illness Service, McGill University Health Centre, Montreal, Quebec, Canada
[11]Department of Medicine and Laboratory Medicine, Memorial University, St. John's, Newfoundland, Canada
[12]Division of Critical Care, Department of Medicine, McMaster University, Hamilton, Ontario, Canada
[13]Department of Medicine, Niagara Health, St. Catharines, Ontario, Canada
[14]Department of Critical Care, St Joseph's Healthcare, Hamilton, Ontario, Canada
[15]Internal Medicine Service, Centre Hospitalier de l'Université de Montréal (CHUM), Montréal, Québec, Canada
[16]Division of Pediatric Critical Care, Department of Pediatrics, McGill University, Montréal, Québec, Canada
[17]Division of Infectious Disease, Department of Medicine, Niagara Health, St. Catharines, Ontario
[18]Department of Medicine, Sinai Health, University of Toronto, Toronto, Ontario, Canada
[19]Division of Critical Care Medicine, Department of Medicine, North York General Hospital, Toronto, Ontario, Canada
[20]Division of Medical Microbiology, Division of Infectious Diseases, Department of Medicine, University of British Columbia, Vancouver, BC, Canada
[21]Section of Infectious Diseases, Rady Faculty of Health Sciences, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada
[22]Departments of Surgery and Critical Care Medicine, McGill University, McGill University, Montreal, Québec, Canada
[23]Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada
[24]Clinical Practice Assessment Unit, Department of Medicine, McGill University, Montreal, Quebec, Canada
[25]Division of Infectious Diseases, Department of Medicine, Faculty of Medicine and Dentistry, University of Alberta
[26]Division of Pediatric Infectious Diseases, Dept. of Pediatrics, Montreal Children's Hospital, Div. of Microbiology, Dept. of Clinical Laboratory Medicine, McGill University Health Centre, Montréal, Québec, Canada
[27]Division of Infectious Diseases, Department of Medicine, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada
[28] Division of Infectious Diseases, St. Michael's Hospital, Toronto, Ontario, Canada
[29]J.D. MacLean Centre for Tropical Diseases, Division of Infectious Diseases, Department of Medical Microbiology, McGill University Health Centre, McGill University, Montréal, Québec, Canada
[30]Department of Internal Medicine, Sections of Hematology/Medical Oncology and Critical Care, Rady Faculty of Health Sciences, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada
[31]Division of Infectious Diseases, Department of Pediatrics, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada

Corresponding Author: Vincent Lau, Department of Critical Care, Faculty of Medicine and Dentistry, University of Alberta, 8440 112 Street, Edmonton, Alberta, Canada; vince.lau@ualberta.ca

Key Words: Remdesivir; COVID, mortality; economic; cost-effectiveness; mechanical ventilation; CATCO

Manuscript word count: 2500

Abstract word count: 241

Abstract

Background: The role of remdesivir in the treatment of hospitalized patients with COVID-19 remains uncertain. A cost-effectiveness analysis was conducted alongside the Canadian Treatments for COVID-19 (CATCO) open-label, randomized clinical trial evaluating remdesivir.

Methods: Patients with COVID-19 in Canadian hospitals between (August 14, 2020, and April 1, 2021) were randomized to remdesivir versus placebo (plus usual care). In-hospital outcomes and healthcare resource utilization were collected alongside estimated unit costs in 2020 Canadian Dollars (CAD) over a time horizon from randomization to hospital discharge or death from a public healthcare payer's perspective.

Results: Data from a total of 1281 adults admitted to 52 hospitals in 6 Canadian provinces were examined. Total mean costs (± standard deviation [SD]) per patient were $37,918 ± 42,413 for patients randomized to remdesivir group compared with $38,026 ± 46,021 in patients receiving usual care (incremental cost, -$108 [95% CI: -$4,746 to 4,962]; p=0.97). Remdesivir was the dominant intervention (with only mildly less costly and mildly lower mortality) with a non-calculable incremental cost effectiveness ratio. For willingness-to-pay thresholds of $0, $20,000, $50,000 and $100,000/mortality averted, a strategy using remdesivir was cost-effective in 60%, 67%, 74% and 79% of simulations, respectively. The difference between costs in the two treatment arms were primarily driven by intensive care and ward hoteling and nursing costs and remdesivir.

Interpretation: From a healthcare payer perspective, treating hospitalized patients with COVID-19 with remdesivir and usual care should be preferred to treating with usual care alone.

Registration: ClinicalTrials.gov number: **NCT04330690**

Funding: Canadian Institutes of Health Research, the Vancouver Coastal Health Research Institute, the Northern Alberta Clinical Trials and Research Centre, Covenant Health Research Centre, the St. Joseph's Health Care Foundation, and the London Health Sciences Foundation.

Background

The role of remdesivir in treating hospitalized patients with Coronavirus Disease-2019 (COVID-19) remains uncertain.(1–3) Remdesivir, a repurposed antiviral medication, has received regulatory approval from Health Canada for treatment of patients with COVID-19. This was based on clinical trial data documenting faster time-to-recovery.(4) Its impact on other clinical outcomes, including mortality and post-hospitalization outcomes, has yet to be defined.(5) Recommendations have varied for or against the use of remdesivir in COVID-19 patients by different governing bodies. (1–3)

The World Health Organization (WHO) SOLIDARITY trial (5) is a global pragmatic clinical trial examining the effects of various therapeutics in COVID-19, with final remdesivir results pending publication.(5) CATCO (Canadian Treatments for COVID-19) is the Canadian arm of SOLIDARITY, which demonstrated remdesivir has a modest but significant reduction on the need for mechanical ventilation, but not a significant difference in hospital mortality.(6) There are substantial drug acquisition costs for remdesivir, and with only modest outcome effects demonstrated in CATCO, this supports the need for a health economic evaluation. Other jurisdictions have demonstrated cost-effectiveness or dominance of remdesivir to supportive care, (7) although most were model-based.(8,9)

We conducted a cost-effectiveness analysis (E-CATCO) alongside the CATCO trial assessing remdesivir plus supportive care versus supportive care alone by measuring healthcare resource utilization and costs and clinical outcomes in the two treatment arms for hospitalized adults with COVID-19.

Methods

Design

The primary objective of E-CATCO was to estimate the incremental costs per survivor associated with the use of remdesivir plus usual care (remdesivir group) versus usual care alone (usual care group) in patients hospitalized for COVID-19. Our secondary objective assessed the cost-effectiveness of preventing one episode of invasive mechanical ventilation (IMV).(6) We performed the economic evaluation from the public healthcare payer's perspective, over the time horizon from randomization to discharge or in-hospital death (Table 1).(10)

We developed the economic evaluation according to cost-effectiveness analysis recommendations (11), including from the Canadian Agency for Drugs and Technologies in Health (CADTH),(12) and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS)(13) checklist (Supplemental Table 1). This study was approved by local research ethics boards and coordinated by Sunnybrook Research Institute at the University of Toronto. The CATCO trial was conducted in accordance with Good Clinical Practice guidelines of the International Council for Harmonization. (14) *A priori* informed or deferred consent for participation to the CATCO trial was obtained from each trial participant or their substitute decision maker,(6) and no additional patient-specific data was collected in conducting the cost-effectiveness sub-study.

Patients

CATCO was a pragmatic, adaptive, multi-centre randomized controlled trial, where multiple agents were compared against the available standard of care in an open-label fashion. Detailed eligibility criteria are described elsewhere.(6)

Eligible patients were randomized in a 1:1 ratio to remdesivir plus usual care (remdesivir group) versus usual care alone (usual care group) during periods when remdesivir was available. Patients randomized to remdesivir received 200 milligrams (mg) intravenously (IV) initially, followed by 100 mg for up to 9 additional days (or until discontinued by the treatment team or hospital discharge, whichever came first) plus usual care. Patients randomized to the control arm

received usual care without remdesivir. Usual care was left to the treating clinician, including co-interventions, such as dexamethasone, therapeutic anticoagulation, tocilizumab, etc. Usual care was dynamic and left to local standards and clinical discretion for each group. Patients were discharged when they were deemed clinically eligible by the treating team, and the study intervention was stopped if this was prior to completion of a full treatment course.(6)

From August 14, 2020, to April 1, 2021, 1282 adult, hospitalized, laboratory-confirmed COVID-19 patients (full CONSORT diagram presented elsewhere) were randomized in CATCO (remdesivir domain).(6) Patients were enrolled in one of 52 hospitals from 6 Canadian provinces (British Columbia, Alberta, Manitoba, Ontario, Quebec, Newfoundland and Labrador). We determined unit costs after the last patient was recruited in CATCO, and prior to conducting the primary CATCO outcome analyses. One patient was excluded from analyses due to incomplete data collection. In the final analysis, 1281 patients were included: 634 in the remdesivir group and 647 in usual care only group.(6)

Clinical outcomes

We collected the clinical effects, frequencies or proportions, and per-patient event rates for all randomized patients as part of the CATCO trial. The primary clinical outcome underpinning this economic evaluation was the difference in mortality, measured as in-hospital discharge or death. Secondary clinical outcomes included episodes of invasive mechanical ventilation. Given the in-hospital time horizon and emphasis on mortality, health-related quality of life was not measured, and we did not estimate quality-adjusted life-years [QALY] or extrapolate lifetime outcomes.

Unit costs and health resource use

Based on a predefined list of items (based on CATCO case-report forms), the E-CATCO steering committee reviewed the relative importance of cost variables before analysis to guide the number of variables included. Similar methodology has been described elsewhere.(15)

A line-item list of unit costs and healthcare resource use was devised, using categories including: medications, personnel, diagnostic radiology/laboratory testing, operations/procedures and per-day hospital (e.g. hoteling) costs not otherwise encompassed, in accordance with recommendations on measuring resource use.(10,16–18) Total costing (resource use multiplied by unit cost) methodology is similarly described elsewhere.(15) Duplicate disaggregated unit costs reported at a site level were removed, to avoid double-counting.(15)

We preferentially recorded unit costs published by public healthcare payers (e.g. provincial schedule of benefits, formularies from jurisdictions) as an estimation of unit costs.(12) A jurisdiction was defined as an area (e.g. province) which is responsible for the costing and delivery of healthcare in that region.(12) For unit costs not available through the public sources, we extracted unit costs from the main operational study site (Sunnybrook Hospital). We obtained costing data with assistance from hospital unit managers, accounting, human resources, pharmacy, radiology, or laboratory departments, where possible. If a specific line-item unit cost was not attainable for a specific jurisdiction, we used a mean unit cost approach for the jurisdictions that reported unit costs (with estimated standard errors). (15,19,20)

Costing, primary cost-effectiveness analysis and subgroup/sensitivity analyses

We used descriptive epidemiologic analyses, including means (with standard deviations [SD]), counts, and proportions to describe baseline characteristics, effect, and cost estimates. We adjusted all costs to 2020 CAD dollars.(21)

For our base-case primary analysis, individual resource utilization was multiplied by jurisdiction unit costs to calculate individual patient total costs. We estimated appropriate ‘standard dose’ for non-titrated medications (e.g. antibiotics) and a clinically appropriate ‘medium dose’ for various titratable medications (e.g. vasoactive medications, sedatives, analgesics,

neuromuscular blockers, etc.). Supplemental Table 2 outlines assumptions for estimating other resource utilization.

We calculated total costs for remdesivir and usual care groups by summing each of the individual patient costs, and then divided by the number of patients in that jurisdiction to calculate the mean cost per patient for each group. Incremental costs were defined as the difference in mean per-patient costs between groups and incremental effects as the difference in proportions of clinical outcomes between groups (given differing sample sizes between groups).(15)

The incremental cost-effectiveness ratio (ICER) measured the ratio of incremental costs of remdesivir group versus usual care group per incremental clinical outcome (e.g. mortality, IMV averted). (10,13) If ICERs were negative, incremental costs and incremental effects were reported separately. Similar methodology has been previously described. (15,19,20)

We conducted prespecified subgroup analyses according to: age (< 55 years, ≥55 years); sex (male, female); and illness severity at randomization based on the WHO Ordinal Scale (5,6)

To assess the uncertainty associated with cost and effects estimation, we used non-parametric bootstrapping with replacement techniques to generate 1,000 simulated pairs of costs and effects for remdesivir plus supportive care and supportive care alone groups for all outcomes. These were plotted on cost-effectiveness planes. Cost-effectiveness acceptability curves (CEAC) were used to present the probability of remdesivir being cost effective over a wide range of willingness-to-pay (WTP) thresholds. A Tornado diagram was constructed to describe the major cost drivers.(10)

We performed multiple sensitivity analyses with variations of estimates of pairs of potentially influential variables (e.g. ranges of remdesivir cost, hoteling costs, ICU and ward nursing ratios) across plausible ranges to determine if different estimates change the overall results. All analyses were performed using Excel version 14.0.6 (Microsoft Corp, Redmond Washington, US), and SAS version 9.4 (Cary, North Carolina, US).

Results

Characteristics of study population

The characteristics of the patients included in the E-CATCO study are as published in the main CATCO trial report.(6) The full CEA dataset (including cost-effectiveness planes, CEACs and non-parametric bootstrap sampling) are presented in Supplemental Appendix 1.

Clinical outcomes and incremental effects

The difference in proportions of in-hospital mortality events between remdesivir versus usual care groups was -3.9% [18.7% vs. 22.6%, 95% confidence interval (CI): -8.3% to 1.0%, p=0.09]. The difference in proportions of incident IMV events between groups was -7.0% [8.0% vs. 15.0%, 95% CI: -10.6% to -3.4%, p=0.0002], whereas the difference in proportions of total IMV events between groups was -5.7% [16.4% vs. 22.1%, 95% CI: -10.0% to -1.4%, p=0.01] (Table 3, Supplemental Appendix 1).(6)

Healthcare resource use and costs

Resource utilization and mean unit cost are outlined in Table 2. Healthcare resource use varied in key areas between remdesivir versus usual care groups as might be expected due to an incremental reduction in need for mechanical ventilation, ICU admission and length of stay in ICU: (total: 2,340 vs. 3,045 days, absolute difference: -705 days, mean: 3.7 ± 6.8 vs. 4.7 ± 8.1 days, mean difference: -1.0 days/patient [95% CI: -0.2 to -1.8 days], p=0.02).

The mean costs per patient were $37,918 ± 42,413 for the remdesivir group compared with $38,026 ± 46,021 for usual care. The incremental cost per patient between groups was -$108 ± 62,584 [95% CI: -$4,746 to 4,962]; p=0.97) (Table 2).

Cost-effectiveness, subgroup and sensitivity analyses

For the primary, base-case analysis for remdesivir versus usual care (Table 3) for mortality averted, the ICER was incalculable due to dominance of remdesivir (less costly, more effective) over usual care alone on the cost-effectiveness plane (Figure 1, Table 3, Supplemental Appendix 1), albeit only mildly for both costs and effects. The ICERs and cost-effectiveness plots for IMV (secondary objective) are presented in Table 2 and Supplemental Figure 1. The ICER was also incalculable due to dominance of remdesivir (less costly, more effective).

Reported separately, incremental costs were -$108 [95% CI: -$4,746 to 4,962, p=0.92] in favour of remdesivir. Incremental effects for mortality were -3.9% [18.7% vs. 22.6%, 95% CI: -8.3% to 1.0%, p=0.09], in favour of remdesivir. Incremental effects for IMV were -7.0% [8.0% vs. 15.0%, 95% CI: -10.6% to -3.4%, p=0.0002], in favour of remdesivir.

The cost-effectiveness acceptability curves (CEACs) are presented in Figure 2 for mortality. Across a WTP threshold of $0, $20,000, $50,000 and $100,000 per mortality averted, a strategy using remdesivir was economically attractive in 60% (60% cost-savings, 0% cost-effective), 67% (60% cost-saving, 7% cost-effective under $20,000), 74% (60% cost-savings, 14% cost-effective under $50,000) and 79% of simulations (60% cost-savings, 19% cost-effective under $100,000), respectively (Figure 2).

Cost-effectiveness acceptability curves for IMV prevention are shown in Supplemental Figure 2. Across a WTP threshold of $0, $20,000, $50,000 and $100,000/IMV averted, a strategy using remdesivir was economically attractive in 58% (58% cost-savings, 0% cost-effective), 66% (58% cost-savings, 8% cost-effective under $20,000), 75% (58% cost-savings, 17% cost-effective under $50,000) and 82% (58% cost-savings, 24% cost-effective under $100,000) of simulations, respectively.

Our pre-specified subgroup analyses (age, sex, illness severity on admission by WHO Ordinal Scale) revealed no significant subgroup interactions (Supplemental Table 3).

In sensitivity analyses, cost-neutrality (based on ~$0 WTP threshold) for remdesivir is achieved at the base-case $2,925 CAD per patient course. However, if the price of remdesivir was increased to $3,791 (increase of $866 per patient), $4,928 (increase of $2,003/patient), and $6,823 (increase of $3,898/patient) per course, the WTP threshold would increase the ICERs for those scenarios to $20,000, $50,000 and $100,000/death, respectively.

Our base-case analysis kept patient to nursing ratios at 1:1 in ICU, and 4:1 on the ward (incremental costs: -$108 per patient). However, if patient to nurse ratios changed to ICU 1.5:1 and ward 5:1, incremental costs increased $196 ± 59,327 (difference of +$304) as compared to the base case, and had a calculable ICER of $5,178/death. If ratios changed to ICU 1.5:1 and ward 6:1, incremental costs increased $161 ± 59,363 (difference of +$269) with an ICER of $4,246/death averted.

In our base-case analysis, mean ICU hoteling costs were $3,495 among all jurisdictions (incremental costs: -$108). If ICU hoteling was reduced to $2,000, incremental costs would decrease to $722 (increase of +$830 per patient) [ICER: $19,061/death averted]. If ICU hoteling was increased to $5,000 (replicating more expensive health systems), incremental costs would decrease to -$2,257 (decrease -$2,365 per patient), where remdesivir was dominant.

An aggregated Tornado Diagram (Figure 3) and full Tornado diagram (Supplemental Figure 5) demonstrate the major cost drivers in E-CATCO. The top five major cost drivers were: ICU hoteling, ward hoteling, other drugs, ICU nursing (all lower in remdesivir group), and remdesivir drug cost (higher in remdesivir group).

Discussion

In this economic analysis performed alongside the CATCO clinical trials, we found that remdesivir plus supportive care is the preferred treatment strategy (lower costs with similar-to-increased survival and less need for mechanical ventilation) compared to usual supportive care alone, for hospitalized adults with COVID-19. Lower costs associated with a treatment strategy

using remdesivir were predominantly due to reductions in ICU hoteling, ward hoteling, ICU nursing, ward nursing, and use of other drugs, despite the drug acquisition cost for remdesivir.

Our findings from E-CATCO provide economic context to the clinical effects of remdesivir. (6) Despite the non-significant reduction in mortality due to remdesivir, less need for new mechanical ventilation and ICU and lower resource utilization offset remdesivir drug costs. Our economic findings augment the clinical effects of remdesivir for adult, hospitalized, COVID-19 patients.(1–3,6) These findings are in-keeping with cost-effectiveness analyses of remdesivir in the literature from other jurisdictions and using model-based designs (7–9).

Despite similar median hospital length of stay in the two arms of CATCO,(6) there were meaningful reductions in the remdesivir group for both new need for mechanical ventilation and total days in ICU. The additional time in ICU for patients in supportive care only group was the largest incremental cost-driver. This analysis exemplifies how numerically but non-significant clinical differences in length of stay may still have an important impact on incremental cost estimation in a health economic evaluation.(15,19)

This economic analysis also highlights the value of considering both clinical effectiveness alongside costs and resource use. Every dollar spent for a non-beneficial or cost-ineffective intervention is an opportunity cost lost for other interventions in a health system with finite resources, with the potential for indirect harms to other patients.(22)

Finally, it is important to emphasize that we focused upon a base case patient hospitalized with COVID-19, finding treatment with remdesivir to be economically attractive (albeit with mainly cost-neutrality and mild-modest effects). However, upstream strategies to prevent infection and hospitalization (e.g. infection prevention through public health measures including vaccination) are generally the most effective strategies in improving health outcomes and lowering costs that health systems have at their disposal. Accordingly, health policymakers and clinicians need to consider expenditures on upstream and downstream resource use and medications from this broader population budgetary perspective.(23–27)

Strengths and Limitations

There are several strengths of this study. It was conducted in accordance with CEA guidelines, CADTH, GRADE and CHEERS recommendations,(11–13,18) using similar methodology to other CEAs conducted alongside in the Canadian context.(15,19) Clinical effects and costs are based on patient-level data from a randomized trial rather than model-based, hypothetical cohorts with inputs incorporated from multiple sources, increasing the internal validity for both costs and effects. Capturing jurisdictional costs and effects with their own distributions and variance allowed for a more precise estimate of between-group differences, which enhances the generalizability of these findings.

This analysis also has limitations. The short-time horizon (randomization to in-hospital discharge/death) may miss additional costs associated with downstream health consequences secondary to COVID. This is potentially important due to the likelihood of a legacy of long COVID.(28,29) There may be over-estimation (e.g. sedation, paralytics, antibiotics), and under-estimation (e.g. unmeasured resource use) in certain line-items; however, assumptions were applied equally between groups. This health economic evaluation derived data from a randomized trial may not represent the same treatment effects and costs as in routine clinical practice.(15) Finally, future research gaps to be addressed include differences in costs and effects of 5 vs. 10 days remdesivir therapy,(30) timing of remdesivir initiation post symptom onset, influence of vaccination status and new variants on remdesivir, and unit cost estimation at the time of analysis (e.g. if remdesivir becomes generic, could be cheaper over time). External validity is limited to the Canadian healthcare perspective but is likely comparable to other third-party payer jurisdictions.

Conclusions

From a healthcare payer perspective, treating hospitalized patients with COVID-19 with remdesivir and usual care should be preferred to treating with only prior usual care. Future cost-effectiveness comparisons for hospitalized patients should generally be evaluated on this base-case treatment strategy.

Acknowledgements

E-CATCO was designed by the CATCO Steering Committee and the Canadian Critical Care Trials Group. Special thanks to Drs. David Williamson and Claudio Martin for their reviews of this manuscript. We are grateful for the commitment of all our colleagues (Francois Lamontagne, Lauren Kelly) in participating centers, and staff at the Sunnybrook Research Institute for their expertise.

Funding and Conflicts of Interest

This economic evaluation (E-CATCO) and CATCO was funded by the Canadian Institutes of Health Research, the Vancouver Coastal Health Research Institute, the Northern Alberta Clinical Trials and Research Centre, Covenant Health Research Centre, the St. Joseph's Health Care Foundation, and the London Health Sciences Foundation.

RAF is the H. Barrie Fairley Professor of Critical Care Medicine at the University Health Network and the University of Toronto Interdepartmental Division of Critical Care Medicine. SM is the Innovative Medicines Canada and Health Research Foundation chair in Pandemic Preparedness Research. RZ is the recipient of the Lyonel G Israels Research Chair in Hematology at the University of Manitoba. TCL receives salary support from the Fonds de recherche du Québec - Santé. DHST is supported by a Tier 2 Canada Research Chair in HIV Prevention and STI Research.

No funding for either the trial itself or this economic evaluation was received from the manufacturers of any remdesivir (Gilead), other treatments or sources not listed above.

None of the funders played a role in the conception, design, conduct, oversight, analysis, interpretation, or decision to submit this manuscript for publication or in the preparation, review, or approval of the manuscript.

Oversight

Study methods, operations, and manuscript generation were coordinated by the E-CATCO steering committee (VL, RF, SM, AT, RP).

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Authors Statement

Vincent Lau, Robert Fowler, Ruxandra Pinto, François M. Carrier, Matthew P. Cheng, John Conly, Cecilia T. Costiniuk, Erick Duan, Madeleine Durand, Patricia S. Fontela, George Farjou, Mike Fralick, Anna Geagea, Jennifer Grant, Kosar Khwaja, Nelson Lee, Todd C. Lee, Rachel Lim, Conar R O'Neil, Jesse Papenburg, Makeda Semret, Michael Silverman, Wendy Sligl, Ranjani Somayaji, Darrell H. S. Tan, Jennifer LY Tsang, Jason Weatherald, Cedric Philippe Yansouni, Ryan Zarychanski, Srinivas Murthy all have: (1) made substantial contributions to conception and design, acquisition of data, analysis, and interpretation of data; (2) drafted the submitted article and revised it critically for important intellectual content, and (3) provided final approval of the version to be published.

Conception: Lau, Fowler, Murthy, Pinto

Background: Lau, Fowler, Murthy, Pinto

Data collection: Lau, Fowler, Pinto, Carrier, Cheng, Conly, Costiniuk, Duan, Durand, Fontela, Farjou, Fralick, Geagea, Grant, Khwaja, Lee, Lee, Lim, O'Neil, Papenburg, Semret, Silverman, Sligl, Somayaji, Tan, Tsang, Weatherald, Yansouni, Zarychanski, Murthy
Data analysis: Lau, Fowler, Pinto, Murthy
Drafting the manuscript: Lau, Fowler, Pinto, Carrier, Cheng, Conly, Costiniuk, Duan, Durand, Fontela, Farjou, Fralick, Geagea, Grant, Khwaja, Lee, Lee, Lim, O'Neil, Papenburg, Semret, Silverman, Sligl, Somayaji, Tan, Tsang, Weatherald, Yansouni, Zarychanski, Murthy
Revising the manuscript: Lau, Fowler, Pinto, Carrier, Cheng, Conly, Costiniuk, Duan, Durand, Fontela, Farjou, Fralick, Geagea, Grant, Khwaja, Lee, Lee, Lim, O'Neil, Papenburg, Semret, Silverman, Sligl, Somayaji, Tan, Tsang, Weatherald, Yansouni, Zarychanski, Murthy

Data statement section

E-CATCO cost-effectiveness analysis will be made available in the Supplementary Appendix. Any further data requests can be made to the corresponding author.

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Supplemental Figure 3: Full Tornado Diagram of major cost drivers in E-CATCO

Table 1. Summary of health economic evaluation framework (E-CATCO)

Question:	Is the use of remdesivir as compared to standard care without remdesivir cost-effective for the prevention of mortality and other clinically important outcomes (invasive mechanical ventilation) in adult, hospitalized patients with COVID-19 in CATCO?
Perspective:	Healthcare public payer (in-hospital costs)
Setting:	Adult, hospitalized patients with COVID-19 (52 centers, 6 provinces in Canada: British Columbia, Alberta, Manitoba, Ontario, Quebec, Newfoundland and Labrador)
Comparators:	Remdesivir group: Remdesivir 200 mg intravenous initially and 100 mg on days 1 up to 9 (or until discontinued by treatment team) plus usual care versus Usual care group: usual care without remdesivir
Time Horizon:	From participant randomization to hospital discharge/death (non-fixed time span)
Discount Rate:	No discounting (no long-term follow-up > 1 year)
Clinical Outcomes:	In-hospital mortality, invasive mechanical ventilation (IMV)
Costs:	Direct medical costs associated with treatment and complications (ICU and ward hoteling costs, personnel, medications, laboratory/rad and procedures/surgeries) per jurisdiction Mean unit cost approach (across all jurisdictions) for missing unit costs per jurisdiction
Evaluation:	Primary outcome: Incremental cost-effectiveness ratios (ICERs) per in-hospital mortality averted Secondary outcomes: ICERs for other clinically important outcomes: Incremental cost per invasive mechanical ventilation event averted
Currency (price date):	Canadian Dollars (2020)
Uncertainty:	Non-parametric bootstrapping to produce confidence intervals (probabilistic sensitivity analysis) Cost sampling from publicly available databases (6 jurisdictions) Sensitivity analyses to deal with structural and methodological uncertainty

ARDS = acute respiratory distress syndrome; CATCO = Canadian Treatments for COVID-19; COVID-19 = coronavirus disease-19; E-CATCO = Economic Evaluation alongside CATCO, ICER = incremental cost-efficacy/effectiveness ratio; IMV = invasive mechanical ventilation; mg = milligram(s)

Table 2: Study Resource Utilization and Mean Unit Costs

	Remdesivir (n=634)	Usual Care (n=647)	Difference	Unit Cost	SD	Total Cost
Study-related drugs (Unit cost size, standard/medium dose and duration)						
Remdesivir ($2340 USD per course * 1.25 CAD conversion)[c]	634	0	634	$2,925.00	$0.00	$1,854,450.00
Other medications (Unit cost size, standard/medium dose and duration)						
Ceftriaxone days (1g, 1g IV daily)[a]	2114	2303	-189	$14.83	$4.04	-$2,808.15
Azithromycin IV days (500mg vials, 500mg x 1, then 250mg IV daily)[a]	2500	2632	-133	$0.98	$0.05	-$130.47
Piperacillin-tazobactam days (3.375g vials, 3.375g IV q6h)[a]	5156	6814	-1658	$29.69	$3.67	-$49,217.97
Vancomycin days (500mg vials, 15mg/kg x 85 kg load, then 1g IV q12h)[a]	2141	2044	97	$77.06	$14.89	$7,444.28
Imipenem-cilastin days (500mg vials, 500mg IV q6h)[a]	5746	7929	-2182	$88.33	$10.01	-$192,763.60
Dexamethasone IV doses (10 mg vials)[c]	18207	25564	-7357	$3.99	$0.94	-$17,593.22
Dexamethasone PO doses (4 mg tablets)[c]	25315	29171	-3856	$0.40	$0.17	-$2,292.21
Hydrocortisone IV doses (100 mg vials)[c]	34780	27790	6990	$3.90	$0.90	$54,470.18
Methylprednisolone IV doses (100mg vials)[c]	6007	11410	-5403	$13.43	$0.00	-$7,254.01
Prednisone PO doses (5 mg tablets)[c]	6038	14747	-8710	$0.04	$0.01	-$3,203.93
Micafungin IV days (100mg vial, 200mg IV x 1, then 100mg IV daily)[a]	430	345	85	$196.00	$0.00	$16,660.00
Tocilizumab IV days (400mg vial, 400mg x 1)[c]	29	28	1	$212.01	$28.88	$212.01
Phenytoin IV (100mg vial, 15mg/kg IV load, then 100mg IV q8h)	0	131	-131	$6.32	$0.14	-$2,484.37
Amiodarone IV (200mg vial, 1mg/min x 18hr, then 0.5mg/min x 30hr)	312	351	-39	$0.37	$0.00	-$142.00
Dalteparin VTE (DVT/PE) IV (125 units/kg x 85kg)	3	10	-7	$52.47	$37.67	-$367.27
Dobutamine IV days (2.5mcg/kg/min IV)[a]	45	17	28	$3.42	$0.29	$117.04
Norepinephrine IV days (4mg vials, 0.05 mcg/kg/min)[a]	399	448	-49	$4.11	$0.36	-$201.49
Norepinephrine IV days (4mg vials, 0.15 mcg/kg/min)[a]	191	323	-132	$12.34	$0.36	-$1,628.34
Propofol IV days (200mg vials, 50mcg/kg/min)[a]	1410	1985	-575	$356.92	$0.00	-$205,228.08
Midazolam IV days (5 mg vials, 5mg/hr)[a]	1410	1985	-575	$100.37	$0.12	-$57,711.60
Hydromorphone IV days (2mg vials, 2mg/hr)[a]	1410	1985	-575	$45.29	$0.25	-$26,039.51
Rocuronium IV days (50mg vial, 10mcg/kg/min)[a]	399	477	-78	$374.32	$0.76	-$29,196.94
Labs/Investigations/Radiology (per test)						
Complete blood count[a]	7747	7823	-76	$7.81	$5.99	-$593.67
Arterial blood gas[a]	4680	6090	-1410	$63.21	$90.59	-$89,133.10
Creatinine[a]	7747	7823	-76	$5.98	$6.72	-$454.49
Chest radiograph[a]	994	1019	-25	$28.05	$18.72	-$701.29
COVID Naso-pharyngeal/nasal swab[c]	730	750	-20	$125.00	$0.00	-$2,500.00
COVID Throat swab[c]	67	92	-25	$125.00	$0.00	-$3,125.00
Sputum microbiology[c]	664	675	-11	$18.02	$11.03	-$198.24
Bronchoalveolar lavage culture[c]	6	4	2	$18.54	$10.53	$37.08
Viral nucleic acid test[c]	969	986	-17	$87.50	$0.00	-$1,487.50
CT chest[a]	3	10	-7	$135.86	$68.87	-$951.05
CT head[a]	8	4	4	$124.32	$61.40	$497.27
Electroencephalogram[c]	0	2	-2	$201.14	$65.96	-$402.28
Transthoracic echocardiogram[c]	0	0	0	$160.37	$52.32	$0.00
Personnel						
ICU physician (per day)[c]	2340	3045	-705	$254.70	$128.22	-$179,562.98
Ward physician (per day)[c]	5388	4773	615	$48.73	$16.30	$29,966.92
ICU nurse (1:1 nurse/patient ratio, per day)[c]	2340	3045	-705	$975.70	$5.63	$11,005,876.15
Ward nurse (1:4 nurse/patient ratio, per day)[c]	5388	4773	615	$228.72	$4.69	$675,193.72
Pharmacist (per hour per day)[a]	2340	3045	-705	$46.18	$2.44	-$32,559.09
Respiratory therapist (per hour)[a]	2340	3045	-705	$34.93	$6.45	-$24,626.71
Physical therapist (per hour)[a]	2340	3045	-705	$37.37	$5.12	-$26,349.26
Social work (per hour)[a]	2340	3045	-705	$37.09	$5.63	-$26,147.48
Dietician (per hour)[a]	2340	3045	-705	$38.38	$5.09	-$27,059.45
Unit clerk (per hour)[a]	2340	3045	-705	$28.64	$5.63	-$20,194.58
Procedures/Surgeries						
Non-invasive ventilation days[c]	234	327	-93	$111.58	$55.62	-$10,376.72
Invasive mechanical ventilation (IMV) days[c]	1410	1985	-575	$116.03	$55.02	-$66,718.32
Intubations[c]	104	143	-39	$73.23	$57.66	-$2,855.92
Tracheostomies[a]	18	29	-11	$289.42	$94.08	-$3,183.58
Proning days[c]	906	1282	-376	$64.80	$0.00	-$24,364.80
Arterial catheterization[a]	241	262	-21	$37.86	$8.86	-$795.03
Central venous catheterization[a]	104	143	-39	$42.75	$15.19	-$1,667.36

Table 2: Study Resource Utilization and Mean Unit Costs

Chest tube insertions[a]	7	5	2	$105.02	$39.51	$210.05
Extra-corporeal membrane oxygenation days[c]	5	9	-4	$617.14	$439.34	-$2,468.56
Intermittent hemodialysis central venous catheterization[c]	25	22	3	$121.52	$65.72	$364.57
Dialysis days[c]	204	239	-35	$144.41	$72.18	-$5,054.33
Bronchoscopies[c]	6	4	2	$142.18	$55.01	$284.36
Pulmonary vasodilators (iNO) days[c]	18	47	-29	$3,000.00	$0.00	-$87,000.00
Esophageal-gastro-duodenoscopy[a]	6	1	5	$149.07	$68.04	$745.37
Hoteling costs						
ICU days[c]	2340	3045	-705	$3,495.24	$1,438.80	-$2,464,142.61
High dependency unit days[c]	19	5	14	$3,495.24	$1,438.80	$48,933.33
Ward days[c]	5388	4773	615	$1,045.94	$358.91	$643,254.64

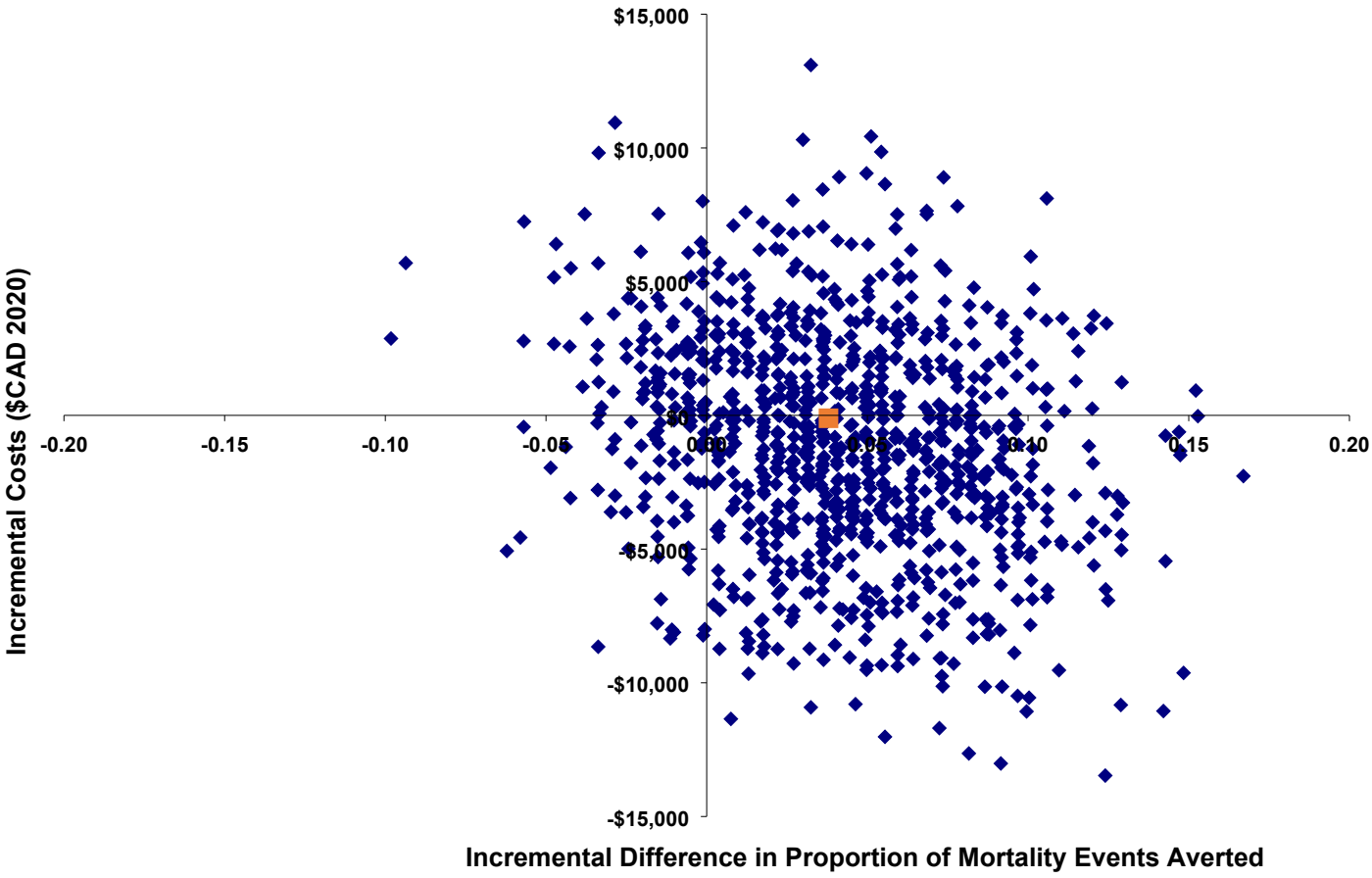
ABG = arterial blood gas; CAD = Canadian Dollar; CBC = complete blood count; COVID-19 = coronavirus disease-19; CRRT = continuous renal replacement therapy; CT = computerized tomography; DVT = deep vein thrombosis; ECMO = extracorporeal membrane oxygenation; EEG = electroencephalogram; EGD = esophageal-gastro-duodenoscopy; hr = hour; ICU = intensive care unit; IHD = intermittent hemodialysis; IMV = invasive mechanical ventilation; iNO = inhaled nitric oxide; IV = intravenous; g = grams; mcg = micrograms; mg = milligrams; mL = milliliter; n = number; NAT = nucleic acid test; NIV = non-invasive ventilation; NP = nasopharyngeal; PE = pulmonary embolism; PO = by mouth; SD = standard deviation; TTE = transthoracic echocardiogram; UF = ultrafiltration; USD = United States Dollar; VTE = venous-thromboembolism
*Sources: provincial (British Columbia, Alberta, Manitoba, Ontario, Quebec, Newfoundland and Labrador) databases (formularies, schedule of benefits), Sunnybrook Hospital/Research Institute
**Standard weight-based dosing assumption (85kg)
[a]Assumption used to estimate resource utilization of line-item
[c]Resource use directly drawn from CATCO case-report form

Table 3. Incremental cost-effectiveness ratios – for primary outcome of mortality and secondary outcome of invasive mechanical ventilation averted (mean cost and effects, per patient) in E-CATCO

Cost-Effectiveness (Mortality)			
	Costs ($, CAD)	Mortality Event Averted	
Remdesivir	$ 37,918.42	0.809	
Placebo	$ 38,026.40	0.771	**ICER**
Incremental difference*	-$107.98	0.038	**Remdesivir dominant**
*cost and effects not adjusted for censoring			($ per mortality averted)
Cost-Effectiveness (Invasive mechanical ventilation)			
	Costs ($, CAD)	IMV Event Averted	
Remdesivir	$ 37,918.42	0.836	
Placebo	$ 38,026.40	0.779	**ICER**
Incremental difference*	-$107.98	0.057	**Remdesivir dominant**
*cost and effects not adjusted for censoring			($ per IMV event averted)

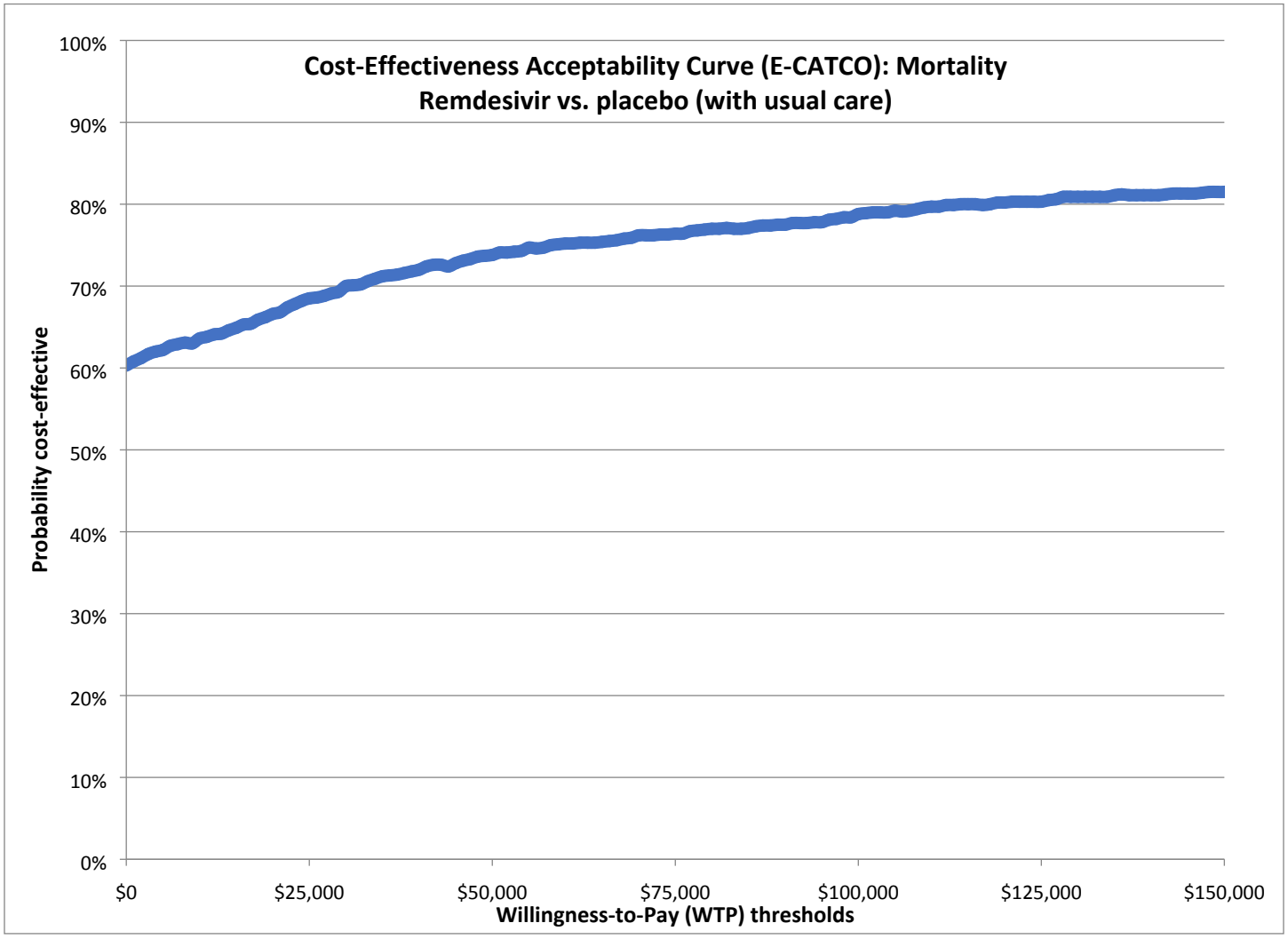
ARDS = acute respiratory distress syndrome; CAD = Canadian Dollar; CATCO = Canadian Treatments of COVID-19; CI = confidence interval; ICER = incremental cost-effectiveness ratio; IMV = invasive mechanical ventilation.

Figure 1: Incremental cost-effectiveness plane for mortality averted (remdesivir vs. placebo - with usual care): point-estimate (red) and non-parametric bootstrapping simulations (blue)



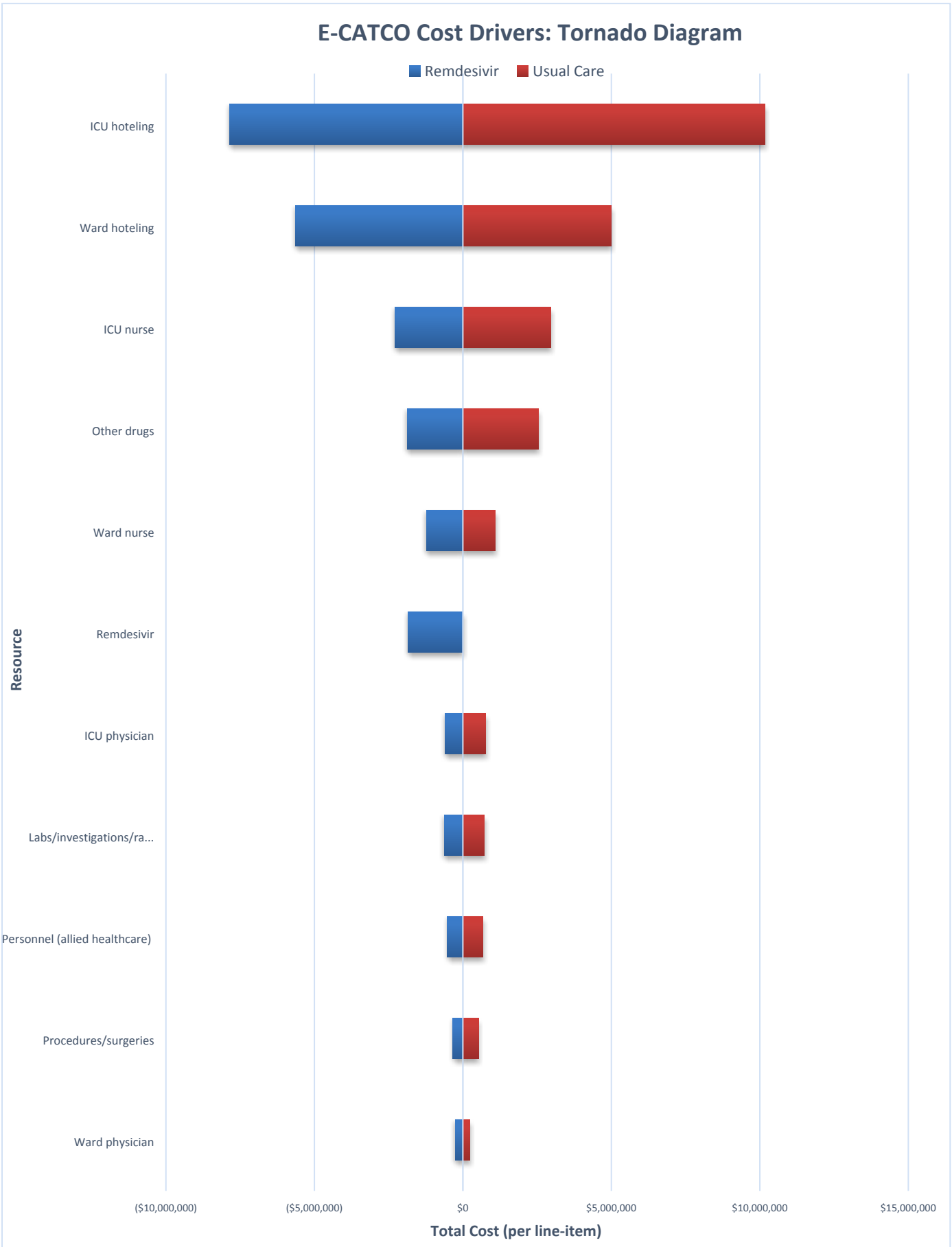
CAD = Canadian Dollar; CATCO = Canadian Treatments of COVID-19; CI = confidence interval; ICER = incremental cost-effectiveness ratio;

Figure 2: Cost-effectiveness acceptability curve for mortality averted (remdesivir vs. placebo - with usual care) for varying WTP thresholds



CAD = Canadian Dollar; CATCO = Canadian Treatments of COVID-19; CI = confidence interval; ICER = incremental cost-effectiveness ratio; WTP = willingness-to-pay threshold

Figure 3: Tornado diagram of major cost drivers in E-CATCO (summarized by major costing categories)



ABG = arterial blood gas; CBC = complete blood count; COVID-19 = coronavirus disease-19; CRRT = continuous renal replacement therapy; CT = computerized tomography; ECMO = extracorporeal membrane oxygenation; EEG = electroencephalogram; hr = hour; HDU = high dependency unit; ICU = intensive care unit; IHD = intermittent

Figure 3: Tornado diagram of major cost drivers in E-CATCO (summarized by major costing categories)

hemodialysis; IMV = invasive mechanical ventilation; iNO = inhaled nitric oxide; IV = intravenous; g = grams; mcg = micrograms; mg = milligrams; mL = milliliter; n = number; NAT = nucleic acid test; NIV = non-invasive ventilation; NP = nasopharyngeal; PO = by mouth; SD = standard deviation; TTE = transthoracic echocardiogram; UF = ultrafiltration; VTE = venous-thromboembolism

Supplemental Table 1. CHEERS checklist

Section/item	Item No	Recommendation	Reported on page No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page 2
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Page 3
		Present the study question and its relevance for health policy or practice decisions.	Page 3
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Page 3-4
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 3-4
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 3-4
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page 3-4
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 3-4
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Page 3-4
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 4-5
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Page 4-6
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Not applicable
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Not applicable
Estimating resources and costs	13°	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative	Page 4-6

Section/item	Item No	Recommendation	Reported on page No
		interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Not applicable
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 4-6
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Not applicable
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Supplemental Table 2
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Page 4-6
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Page 5-6
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Page 5-6
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study	Page 5-6

Section/item	Item No	Recommendation	Reported on page No
		perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Not applicable
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Page 5-6
Discussion			
Study findings, limitations, generalizability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalizability of the findings and how the findings fit with current knowledge.	Page 7-8
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Page 9
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Page 9

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist

Supplemental Table 2: Health economic evaluation assumptions

Assumption	Rationale
Therapeutic remdesivir administration • We assumed the unit cost of remdesivir across all jurisdictions from previously estimated costing in Ontario	Pharmaceutical pricing/costing would likely reflect national/provincial formulary across all jurisdictions
Concurrent co-interventions (e.g. anti-viral, antibiotic, anti-fungal administration, immunomodulators, other medications under investigation for COVID-19, other investigations (labs/radiology)) • We assumed that utilization of various concomitant co-interventions would be low/minor, and hence were excluded from analysis (e.g. osteltamivir, acyclovir, ganiciclovir, lamivudine, valacyclovir, ritonavir, darunavir, efavirenz, convalescent plasma, hydroxychloroquine, baracitinib, sarilumab, anakinra, interferon beta)	In, general, various line-items were excluded (even if measured from CATCO CRF) if the following conditions were met: - Low incidence of resource utilization - Low overall unit cost per line-item - Not plausibly expected to be impacted biologically/clinically by remdesivir administration - Not expected to have incremental differences between remedesivir or placebo groups
Variability in investigations and treatment practice of disease/illness • Based on variability in incidence of disease/illness, we will investigate the incidence of each illness severity, and average resource utilization for a particular illness • We will utilize the mean costs for a particular illness (we will attempt to directly derive this variability from the case report forms) For patients who undergo multiple investigations, treatment (medications/procedures/surgeries) for a particular disease/illness, we will assume the lowest number of potential interventions to treat the disease/illness, as well as mean resource utilization for such events from CATCO	Various clinical diagnoses will have variability in severity, and therefore, variability in the way they are investigated and treated (i.e. *seizures* could be investigated/treated with a range if interventios: e.g. CT head, EEG, anti-epileptic drugs), therefore, we assumed the minimum amount of investigations/treatments for each specific illness
Investigation/interventions of other outcomes • Certain assumptions will need to be made for healthcare resource utilization for certain services, investigations, procedures/surgeries, as they may not be explicitly captured in CATCO, but can be gleaned indirectly from the case report forms: o broncho-alveolar lavage (BAL) cultures were assumed to have a bronchoscopy procedure to perform them o other viral etiologies were assumed to have a viral NAT swab sent	There are certain investigations or interventions that would be expected to be associated with various disease state suspicions (and given correct circumstances, we would assume these would be tested/treated in these ways)

- outcome of pneumothorax was assumed to require a chest tube (even if not formally recorded)
- pulmonary embolism/VTE diagnoses were assumed to have had a CT chest
- seizure diagnoses were assumed to have CT head, EEG and anti-epileptic drug prescription for standard interval (e.g. phenytoin weight based load
- stroke diagnoses were assumed to have CT head
- Congestive heart failure diagnosis would entail a TTE
- Gastrointestinal bleed would entail an EGD
- High dependency unit days were costed using ICU unit costs
- NIV days were costed using IMV unit costs
- UF/CRRT/IHD unit costs were equivalent
- ECMO utilization includes per day cost, alongside cannulation costs (e.g. surgeon, anesthesia, nursing)
- initiation (on the first day) of intermittent hemodialysis or continuous renal replacement therapy would incur a cost of central venous hemodialysis line placement
- all hospital admissions would incur pan-cultures (urine, sputum, blood cultures)
- daily blood work assumed at minimum CBC, Cr, electrolytes
- ICU admission would assume ABGs twice daily, and placement of arterial line
- CXR were assumed to be performed during admission to hospital, admission to ICU and following intubation
- Following intubation and IMV initiation, assumed central line placement also
- Immunmodulator (tocilizumab) dosing: 400mg IV x 1 per patient (given shortage and dose rationing)
- Days of antibiotics were broken down by early antibiotics (e.g. for community acquired pneumomia) and later ventilator-associated pneumonias (or assumed to be VAP)
  - Ceftriaxone 1g IV q24h x 7 days
  - Azithomycin 500mg x 1, then 250mg x 4 days
  - Additional antibiotic courses/days assumed to be:
    - Pipercillin-tazobactam 3.375g IV q6h x 7 days
    - If still on antibiotics past 2

weeks: ○ Imipenem-cilastin 500mg IV q6h x 7 days (for any other additional courses) • If on antibiotics past 3 weeks: ○ At least one week course of Vancomycin (1.5g IV x 1 then, 1g IV q12h x 7 days) ○ Proning was assumed to occur 2x per day (with at least 5 people involved with proning, with their associated personal protective equipment: 1 gown, 1 N95 mask, 1 face-shield, 1 pair of gloves, 1 surgical mask)	
Imputation of missing data (missing resource use or unit costs) • For those patients with missing data from a clinical outcomes perspective, multiple imputation methods will be utilized – including generalized estimating equations (GEEs) • For missing unit costs (which are not attainable from public jurisdiction databases or trial site-specific inquiries), we will utilized a mean-unit cost approach • A mean unit cost approach was used, where the mean unit cost within a particular provinces (e.g. remainder of 6 provinces, if missing) was used to impute the missing jurisdictions unit costs ("mean cost approach")	We will utilize standard multiple imputation methods to handle missing clinical outcome data, or costing-ratio or mean cost approach methodology for missing unit costs
Data collection: hospital time horizon and resource use natural units • Although collected, we only included resource use and outcomes to hospital discharge (as there was no mechanism to ensure accurate resource use collection as an outpatient • Many resource uses were not measured necessarily by dosage on CATCO CRFs (e.g., opiates, vasopressor/inotropes) ○ Therefore, if there was an appropriate "standard dose" for non-titratable medications, it was applied to the resource use in question (usually measured in days on medication, or days intubated, or days in ICU) ▪ Micafungin 200mg IV x 1, then 100mg IV daily x 6 days • No assumption made for possible COVID associated pulmonary aspergillosis (micafungin poses as surrogate for voriconazole)	These various assumptions derived either from main study CATCO methodology, our systematic review of health economic literature from probiotics, or from consultation with the E-CATCO steering committee Higher weight-based dosing (85kg) was assumed given the higher propensity of these patients in hospital compared to historical epochs (normally would assume 70kg)

▪ Phenytoin for seizures was assumed to be 15mg/kg IV load, then 100mg IV q8h x 7 days ▪ Amiodarone for VT/VF/arrhythmia was 1mg/hr x 18 hours, then 0.5mg/hr x 30 hours, then stopped ▪ Dalteparin VTE dosing was assumed to be 125 units/kg for patients with known VTE ▪ Inhaled nitric oxide was assumed to be the cost of the non-disposable circuit x 50ppm (based on per day usage/unit costing) o If there was a clinically appropriate "medium dose" for titratable medications (e.g. vasopressors/inotropes, opiate infusions, sedation infusions) were estimated for various medications ▪ Neuromuscular blockade use days were assumed to be rocuronium, and at a standard dose of 10mcg/kg/min (based on ventilator days) ▪ Propofol use days assumed a medium dose of 50mcg/kg/min (built into ventilator days) ▪ Midazolam use days assumed a 5mg/hour (built into ventilator days) ▪ Hydromorphone use assumed to be 2mg/hour (built into ventilator days) ▪ Illness severity scores (e.g. APACHE) were used to estimate medium doses • Norepinephrine dosing included 0.05mcg/kg/min & 0.15 mcg/kg/min based on illness severity • Dobutamine dosing: 2.5mcg/kg/min • All weight-based dosing was assumed to be for 85kg adult (instead of 70kg) • Base-case analysis patient to nurse ratios assumed to be: 1:1 in ICU, 1.5:1 in high dependency units, and 4:1 on the ward	

ABG = arterial blood gas; APACHE = Acute Physiologic Assessment and Chronic Health Evaluation; BAL = broncho-alveolar lavage; CATCO = Canadian Treatments for COVID-19; CBC = complete blood count; COVID-19 = coronavirus disease-19; Cr = creatinine; CRF = case-report forms; CRRT = continuous renal replacement therapy; CT = computerized tomography; CXR = chest x-ray; E-CATCO = Economic evaluation alongside CATCO; ECMO = extracorporeal membrane oxygenation; EEG = electroencephalogram; g = grams; ICU = intensive care unit; IHD = intermittent hemodialysis; IV = intravenous; kg = kilograms; mcg = micrograms; mg = milligrams; min = minute; TTE = transthoracic echocardiogram; UF =

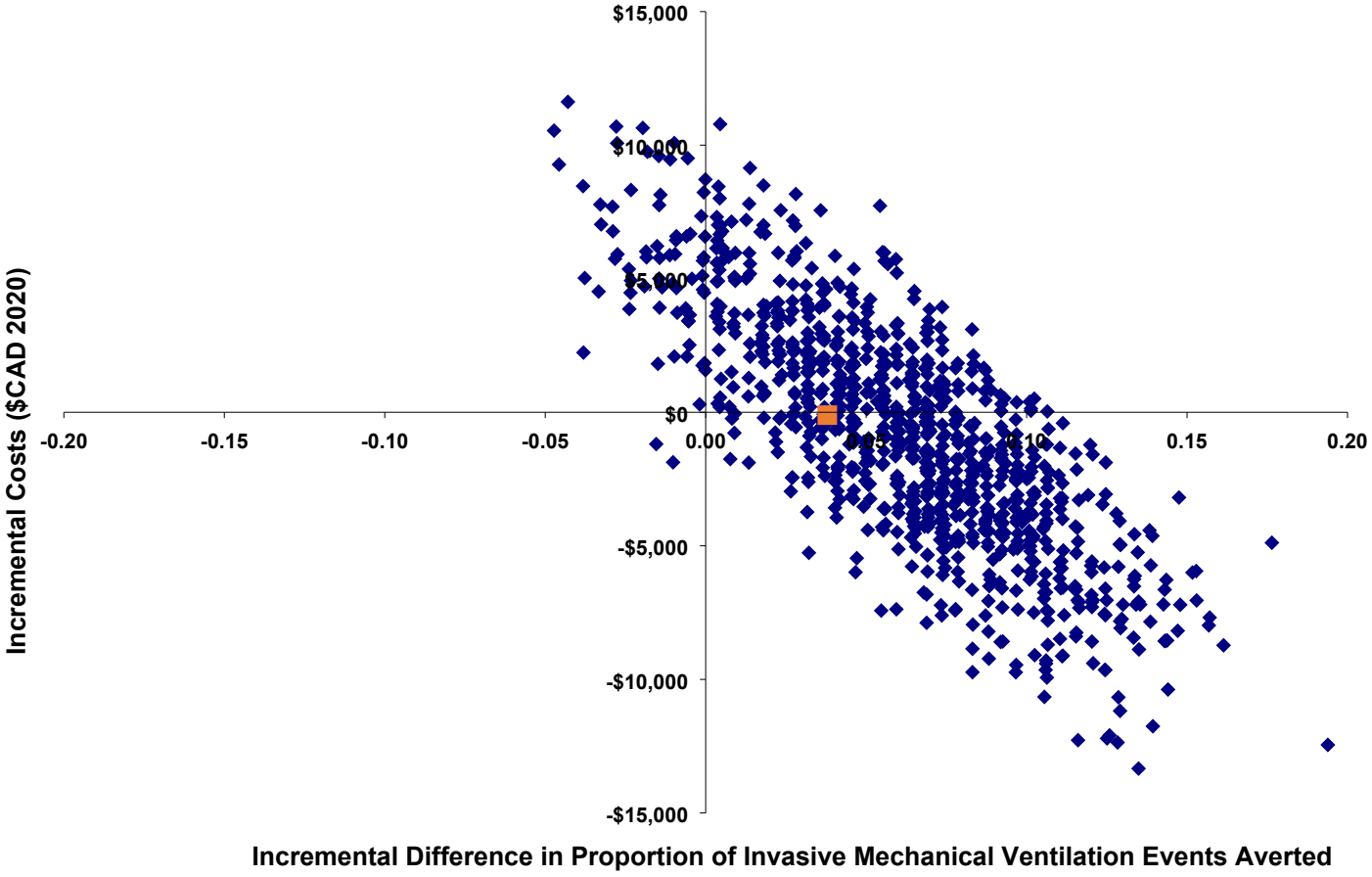
ultrafiltration; VAP = ventilator-associated pneumonia; VF = ventricular fibrillation; VTE = venous-thromboembolism; VT = ventricular tachycardia;

Supplemental Table 3: Subgroup analyses of mean per-patient costs: remdesivir vs. placebo - with usual care (mortality)

	Remdesivir	Usual Care	Mean Difference [Remdesivir – Usual Care]	p-value (interaction)
All patients				
# of patients (n)	634	647		
Cost per patient, mean ± SD, $ (CAD)	$37,918 ± 42,413	$38,026 ± 46,021	-$108 ± 62,584	0.97
Subgroup: *Age*				
<55 years				
# of patients (n)	178	178		
Cost per patient, mean ± SD, $ (CAD)	$33,667 ± 38,825	$31,552 ± 43,266	$2,115 ± 58,132	0.63
>55 years				
# of patients (n)	456	469		
Cost per patient, mean ± SD, $ (CAD)	$38,491 ± 40,513	$39,974 ± 45,671	-$1,481 ± 61,050	0.60
Subgroup: *Sex*				
Female				
# of patients (n)	260	255		
Cost per patient, mean ± SD, $ (CAD)	$32,654 ± 36,091	$36,333 ± 42,548	-$3,679 ± 55,793	0.29
Male				
# of patients (n)	374	391		
Cost per patient, mean ± SD, $ (CAD)	$40,454 ± 42,393	$38,589 ± 46,831	$1,665 ± 63,169	0.61
Subgroup: *Ordinal scale score*				
Mechanical ventilation with PF <150 AND vasopressors/dialysis or ECMO (Score:9)				
# of patients (n)	4	1		
Cost per patient, mean ± SD, $ (CAD)	$148,563 ± 51,574	$163,059 ± 0	-$14,496 ± 51,574	0.82
Mechanical ventilation with PF <150 OR SF ratio <200 OR vasopressors (Score: 8)				
# of patients (n)	11	8		
Cost per patient, mean ± SD, $ (CAD)	$77,306 ± 49,652	$103,102 ± 50,861	-$25,796 ± 71,078	0.29
Mechanical ventilation with PF >150 OR SF >200 (Score: 7)				
# of patients (n)	13	7		
Cost per patient, mean ± SD, $ (CAD)	$80,951 ± 43,266	$97,783 ± 57,814	-$16,832 ± 72,211	0.51
HFNC or NIV (Score: 6)				
# of patients (n)	56	67		
Cost per patient, mean ± SD, $ (CAD)	$43,746 ± 35,102	$56,731 ± 56,676	-$12,986 ± 66,666	0.12
O_2 by mask/prongs (Score: 5)				
# of patients (n)	287	329		
Cost per patient, mean ± SD, $ (CAD)	$31,663 ± 34,748	$31,310 ± 39,737	$353 ± 52,787	0.91
No O_2 therapy (Score: 4)				
# of patients (n)	263	235		
Cost per patient, mean ± SD, $ (CAD)	$40,254 ± 42,393	$38,589 ± 46,831	-$388 ± 59,647	0.92

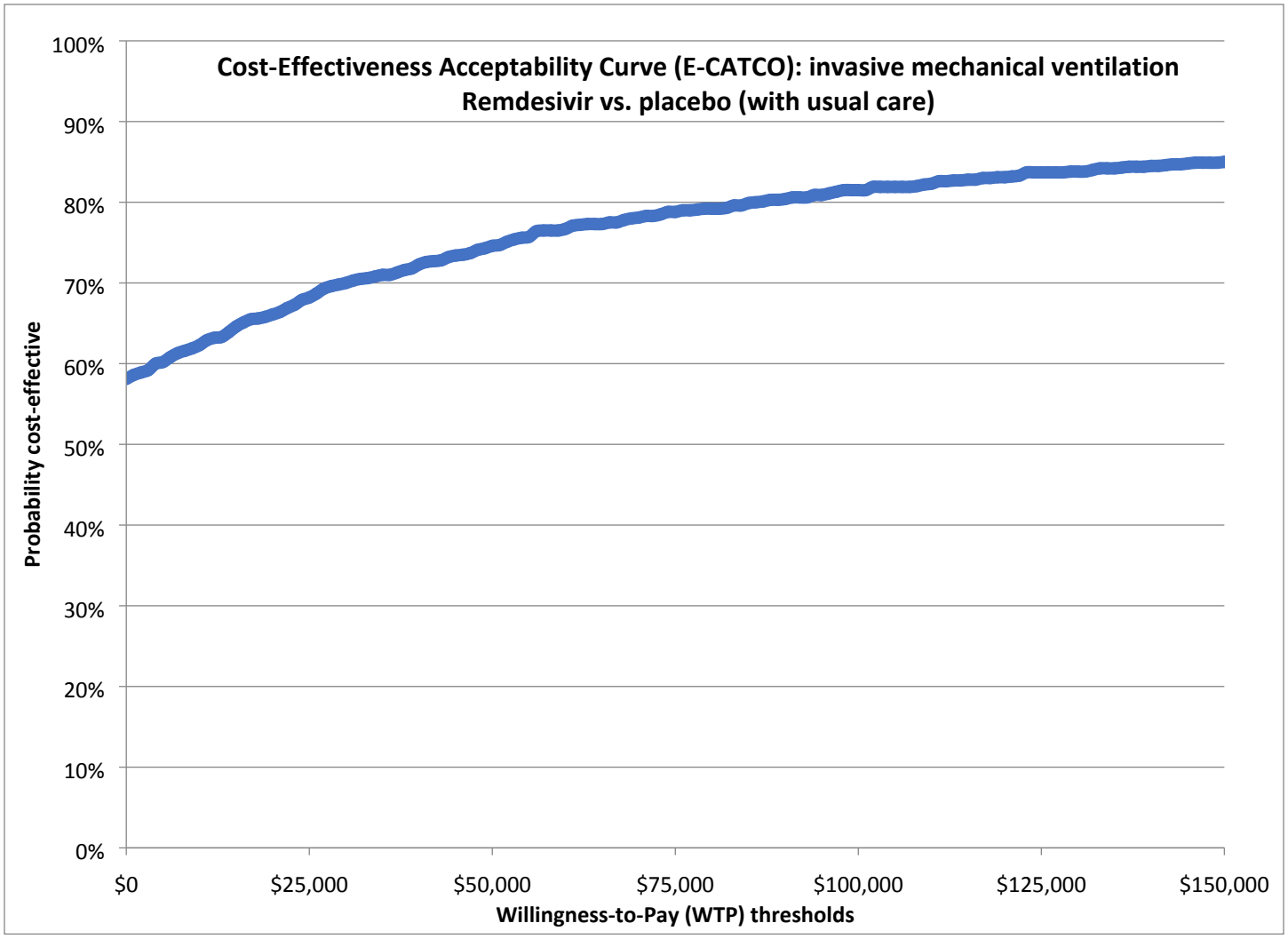
CAD = Canadian Dollar; CATCO = Canadian Treatments for COVID-19; CI = confidence interval; ECMO = extracorporeal membrane oxygenation; HFNC = high flow nasal canulae; ICER = incremental cost-effectiveness ratio; ICU = intensive care unit; NIV = non-invasive ventilation; SD = standard deviation; PF = PaO2/FiO2; n = number; SF = SpO2/FiO2;

Supplemental Figure 1: Incremental cost-effectiveness plane for invasive mechanical ventilation averted (remdesivir vs. placebo - with care): point-estimate (red) and non-parametric bootstrapping simulations (blue)



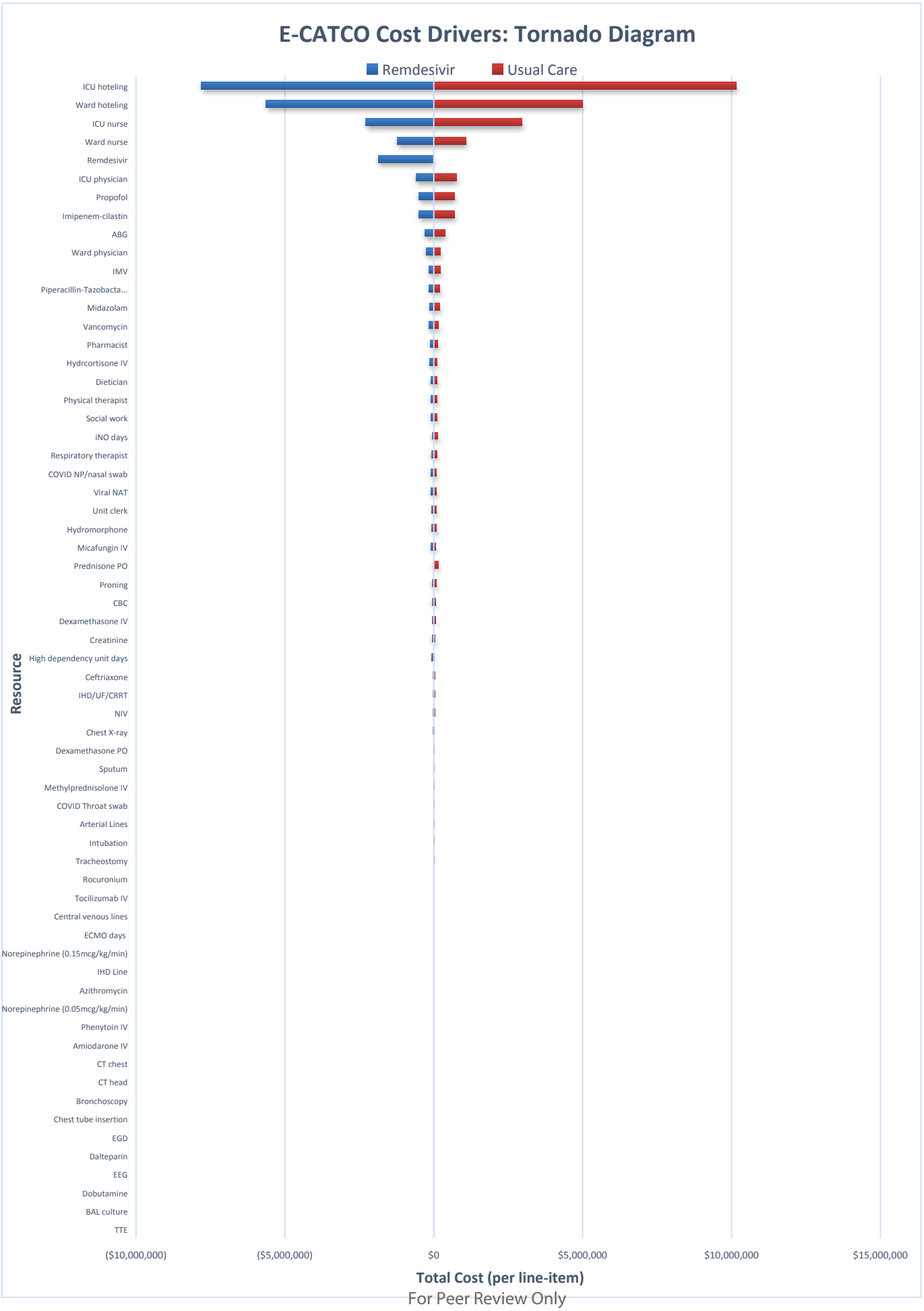
CAD = Canadian Dollar; CATCO = Canadian Treatments of COVID-19; CI = confidence interval; ICER = incremental cost-effectiveness ratio; IMV = invasive mechanical ventilation

Supplemental Figure 2: Cost-effectiveness acceptability curve for invasive mechanical ventilation averted (remdesivir vs. placebo - with usual care) for varying WTP thresholds



CAD = Canadian Dollar; CATCO = Canadian Treatments of COVID-19; CI = confidence interval; ICER = incremental cost-effectiveness ratio; IMV = invasive mechanical ventilation; WTP = willingness-to-pay

Supplemental Figure 3: Full Tornado Diagram of major cost drivers in E-CATCO



ABG = arterial blood gas; CBC = complete blood count; COVID-19 = coronavirus disease-19; CRRT = continuous renal replacement therapy; CT = computerized tomography; ECMO = extracorporeal membrane oxygenation; EEG = electroencephalogram; hr = hour; ICU = intensive care unit; IHD = intermittent hemodialysis; IMV = invasive mechanical ventilation; iNO = inhaled nitric oxide; IV = intravenous; g = grams; mcg = micrograms; mg = milligrams; mL = milliliter; n = number; NAT = nucleic acid test; NIV = non-invasive ventilation; NP = nasopharyngeal; PO = by mouth; SD = standard deviation; TTE = transthoracic echocardiogram; UF = ultrafiltration; VTE = venous-thromboembolism