The clinical and cost effectiveness of PAV+ mode for mechanical ventilation

Short-title: PAV+ for mechanical ventilation in the ICU

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Abstract

Background

Mechanical ventilation is a cornerstone of the intensive care unit (ICU) and has been vital during the coronavirus pandemic, but it adds expense to what is already one of the highest cost care settings. As hospitals expand ICU capacity during the pandemic, optimizing provision of MV could provide patient and cost benefits, whilst also alleviating pressure on hospital capacity. Here, the cost-effectiveness of proportional-assist ventilation with load adjustable gain factors (PAV+ mode) versus pressure-support ventilation (PSV), is evaluated.

Methods

A published Markov model of the care pathway for mechanically ventilated ICU patients was adapted to the Canadian public-payer perspective. Outcomes of interest were the cost of care in year one, and the cost-effectiveness of PAV+ mode versus PSV after 20 years. Clinical and cost model inputs (2017 CAD [$]) were informed by a structured literature review of PubMed. In an update to the published model, comparative effectiveness of PAV+ mode versus PSV was determined via pragmatic meta-analysis.

Results

PAV+ mode was considered likely to be cost-effective compared to PSV, having a cost per quality-adjusted life year gained of $6,575 after 20 years. Over 20 years, higher care costs were driven by increased patient survival, and in cost-effectiveness acceptability analysis, 95% of simulations would be cost-effective at a willingness-to-pay threshold of $14,729. Over one year, use of PAV+ mode reduced care costs ($53,898 versus $60,271).

Interpretation

Use of PAV+ mode is expected to benefit patient care in the ICU and be a cost-saving or cost-effective alternative to PSV.

Keywords

Critical Care; Respiration, Artificial; Economics, Medical; Health Care Costs; Hospital Costs

Introduction

Mechanical ventilation (MV) is an important component of patient critical care. A report on intensive care unit (ICU) usage in Canada suggests 33% of ICU patients in 2013–14 needed invasive ventilation,[1] and MV is increasingly being used in patients admitted to the ICU.[2] Awareness of MV has increased in the current global coronavirus disease 2019 (COVID-19) health crisis, where ventilator support has become an essential component of care for patients suffering hypoxia and acute respiratory distress syndrome that often accompanies the disease.[3] A review of published studies from around the world found 29%–90% of patients with COVID-19 admitted to ICUs received invasive MV.[4] With COVID-19 disrupting the availability of critical care resources,[6] including MV, and straining hospital finances due to cancellation of elective surgeries,[7] there is increasing need for strategies to optimize use of

critical care resources. Even pre-COVID-19, Ontario alone saw ~125,000 patients requiring MV in ICUs, accounting for around 570,000 days of ventilation, from 2009–2012.[5]

Ventilation support can be delivered via a variety of modes, such as those which target a preset volume or constant pressure of inspired air. Constant pressure ventilation, in the form of pressure support ventilation (PSV), is the most common mode of ventilator support used worldwide after the initial acute phase of critical illness.[5] It works by delivering airflow until a target pressure is reached, and held constant for a duration that is influenced by the patient's respiratory system mechanics. While this method is effective at overcoming the resistive and elastic forces limiting the patient's capacity to sustain the work of breathing independently, clinicians cannot know the work performed by the patient's respiratory muscles. Patient-ventilator interaction can therefore be suboptimal, with risk of promoting diaphragm atrophy or inducing a form of muscle strain injury.[8,9] Asynchrony between patient breathing and ventilator delivery is also a potential problem of PSV,[10] and it has been associated with increased requirements for tracheostomy,[11] longer time on MV,[12] and higher ICU mortality.[12,13]

To improve the patient-ventilator interaction, adaptive modes of ventilation were developed, whereby the volume or pressure of air is modulated within each breath.[14] One such adaptive mode is proportional-assist ventilation with load-adjustable gain factors (PAV+ mode) in which respiratory system capacity is measured to help offload the respiratory muscle work in a relationship proportional to patient effort. This allows for measurement and control of the level of respiratory muscle work to ensure it remains in an optimal range,[15–17] and helps improve the coupling of patient and ventilator inspiratory and expiratory times.[18]

Multiple studies suggest a clinical benefit of PAV+ mode over PSV,[18–20] however it is unknown if increasing use of PAV+ mode in Canadian ICUs would result in resource use savings and be cost effective. In this study we synthesize available evidence to explore the utility and cost-effectiveness of PAV+ mode in the Canadian setting.

Methods

Ventilation patient care pathway and model development

The published Markov cohort cost-utility model[21] considered patient care from the point of initiating invasive MV (**Figure 1**). While on MV, patients could be synchronous or asynchronous with the ventilator. Synchronous patients had a higher probability of being stable during a spontaneous breathing trial (SBT) and progressing to extubation (being removed from the ventilator).[22] After successful weaning, patients were in the ICU without MV before transfer to the general ward (GW) and subsequent discharge. The model has daily cycles, such that a patient can move between health states (e.g. from asynchronous to synchronous MV, or from ICU to GW) once per day. At any stage of the pathway, patient mortality was possible. Adverse events (AEs) considered during care were tracheostomy, ventilator-associated pneumonia (VAP), other nosocomial infection, and reintubation.

The published model contained a single health state for "weaning", depicted by an SBT and extubation occurring as one step.[21] For the Canadian setting, an additional health state of liberation was included after the SBT to formalize the weaning process and liberation from the ventilator (Figure 1). Patients failing the SBT remain on the ventilator until their next

SBT, while those passing are assessed for extubation. During the liberation phase, patients are extubated and then monitored closely to ascertain whether they can breathe unaided and clear secretions sufficiently without the need for an artificial airway (endotracheal tube). The outcomes of this state are remaining in the liberation phase (being in the ICU without MV), returning to MV in the ICU, or progression to the GW without MV.

Model outputs

Outcomes of interest in this health-economic model were total costs of care and patient quality of life (QoL). Cost-effectiveness was reported as an incremental cost-effectiveness ratio (ICER), measured as the cost per quality-adjusted life year (QALY) gained.

Model inputs

A structured literature review (see Appendix) was conducted to identify relevant data. As multiple efficacy data sources for PAV+ mode versus PSV were identified, to best summarize PAV+ mode efficacy, a pragmatic meta-analysis was performed to prevent introduction of bias from arbitrary selection of a single study (see Appendix). Additional inputs for MV that can impact on costs and patient QoL considered were initial one-off cost of PAV+ mode, time on MV, time in the ICU, time in hospital, ICU mortality, hospital mortality, occurrence of AEs, and outpatient mortality. Cost inputs from the public payer perspective, were sourced from the literature review where available and otherwise identified through reports from Canadian authorities and the Canadian Management Information Systems Database. All costs are reported in 2017 CAD ($), with costs from earlier years inflated to 2017 using the Canadian consumer price index for healthcare (Statistics Canada, Table 326-0021). Half-cycle correction was applied to both costs and QoL.

Time horizon and discounting

The model considers short-term (1 year) and long-term (20 years) time horizons. The former is to assess the immediate impact of a change in ventilation mode (a patient stay in ICU is often less than one month, and so all relevant clinical outcomes are realized within one year) and the latter to cover the assumed lifespan of a patient, given the base case mean age of 67 years. Costs and QoL utilities (measured using the EuroQoL 5 dimensions survey [EQ-5D]) incurred after the first year are discounted at 1.5% per annum in line with guidelines from the Canadian Agency for Drugs and Technologies in Health.[23] The full list of model parameters is provided in **Table 1**.

Statistical analysis

The robustness of the base case results was assessed through probabilistic sensitivity analysis (PSA), whereby the model is run repeatedly (2,000 times) and for each iteration, each input parameter is sampled from a distribution around the base case (default) value. The distribution is defined by the uncertainty (standard deviation, interquartile range, or 95% confidence interval) provided in the source publication. The distribution is normal for most inputs but is log-normal for odds ratios. The results of these analyses are presented as median (95% credible interval [CrI]) and as a cost-effectiveness scatter plot. The willingness-to-pay (WTP) threshold was set at $50,000 per QALY gained, in the suggested $20,000 to $100,000 range.[24] Scenario analyses were additionally conducted.

Ethics approval

The study is an economic model informed by aggregate data from published literature. The study was deemed exempt from ethics commission review (independent assessments by the clinical author and the data protection officer of Coreva Scientific) as no human patients are treated or face risk of harm in the performance of this work.

Results

Seven clinical studies comparing PAV+ mode with PSV[18–20,22,25–27] were identified from studies known to the clinical author (KJB) and identified in systematic reviews.[28,29] As these systematic reviews[28,29] did not report on all outcomes required for our model, and no individual study among those identified in the literature review presented robust clinical data on the required model inputs, comparative efficacy of PAV+ mode versus PSV was determined via a pragmatic meta-analysis (see Appendix). For dichotomous endpoints, PAV+ mode was associated with improved, although not always statistically significant, outcomes. PAV+ mode was associated with a significant reduction in ICU length of stay and time on MV (see Appendix). All findings were included as model inputs (**Table 1**).

Cost-effectiveness of PAV+ mode versus PSV

Base case cost-effectiveness results are shown in **Table 2**. Over one year, the cost of care per patient was $6,373 less costly with PAV+ mode ($53,898) compared with PSV ($60,271). In the PSA, there was a 95.8% chance of PAV+ mode being cost saving at one year (Figure 2), with the median (95% CrI) saving being $6,667 (-$1,208 to $14,782). Over one year, use of PAV+ mode resulted in 0.04 extra QALYs (0.29 vs. 0.25). The increase in QALYs occurred in 100% of simulations in the PSA, and there was a 99.6% likelihood of PAV+ mode being cost effective at the WTP threshold of $50,000 per QALY gained.

Over 20 years, the cost of care per patient with PAV+ mode ($144,041) was $6,065 higher than with PSV ($137,976). With PAV+ mode, patients lived on average 1.44 years longer and accumulated an additional 0.92 QALYs. In the base case, the cost per QALY gained at 20 years was $6,575 (**Table 2**). In the PSA, at 20 years there was a 19.9% chance of PAV+ mode being cost saving and all simulations led to increased QALYs. The likelihood of PAV+ mode being cost effective at a WTP threshold of $50,000 was 100% with a 20-year time horizon (Figure 2).

Varying the WTP threshold influenced whether the use of PAV+ mode versus PSV mode would be considered cost-effective (**Figure 3**). With a time horizon of 1 year, most PSA simulations were dominant. Over a 20-year time horizon, the WTP threshold at which 95% of simulations would be considered cost-effective was found to be $14,729.

Scenario analyses were performed to understand if certain model parameters were driving the results and how PAV+ mode performed in different conditions. The meta-analysis performed here determined that PAV+ mode was associated with significantly shorter time on MV and in hospital, but differences in most AEs did not reach significance. Running the model with only significant differences included did reduce the cost and QALY benefit of PAV+ mode but did not change overall outcomes (**Table 3**). At 20-years, cost and QALY outcomes for PAV+ mode versus PSV were +$425 and +0.53, respectively, giving an ICER of $802 per QALY gained. A younger or more female patient population had little impact on either

absolute or relative results (**Table 3**). The same was true if PSV had a purchase cost or if the difference in asynchrony between PAV+ mode and PSV was eliminated. Including costs per day for ICU and GWs from the Canadian Institute for Health Information rather than from published literature increased the saving with PAV+ mode at one year by 27.7% (**Table 3**). The most notable change to the base case came from use of Canadian data instead of meta-analysis data. In this scenario, PAV+ mode was cost saving at both 1 year (-$8,268) and 20 years (-$5,857), with QoL being equal (1-year) or improved (20-year) with use of PAV+ mode.

Interpretation

Clinicians have a medical and fiscal responsibility to choose wisely in spending healthcare dollars, and to optimize patient access to hospital resources and flow through the hospital from admission to discharge. This requires discerning which treatments are most likely to be clinically effective and most cost-effective for patient-important outcomes. As hospitals look to increase ICU capacity during the COVID-19 pandemic, health-economic models provide a means of modelling the economic and clinical impact of a change in intervention before committing to implementation.

This analysis sought to synthesize available data regarding mode of MV (PAV+ mode versus PSV) on patient outcomes and corresponding costs from a Canadian perspective. The pragmatic meta-analysis aimed to provide an objective assessment of the clinical effectiveness of the PAV+ mode versus PSV. Significant reductions were observed in patient-ventilator asynchrony and in-patient time on MV, time in the ICU, and time in hospital.

Applying these data to our health-economic model, we found use of PAV+ mode relative to PSV reduced costs to payers in year one, but increased costs over a longer time horizon. The cost per QALY gained over the 20-year time horizon was found to be $6,572. Acceptability analysis found that PAV+ mode would be cost-effective in 95% of cases if the WTP was $14,729 per QALY gained. From these results, use of PAV+ mode has a high likelihood to be considered cost effective in Canada.[24] The increased costs observed align with previous analyses in the United States and United Kingdom, where higher patient survival with PAV+ mode resulted in higher costs of care (the survival paradox).[21] Key drivers of cost in the current model were time on MV and in the ICU. The reasons for PAV+ mode resulting in shorter time on MV and in the ICU in this model can only be surmised and may well be multifactorial. For example, the algorithms underlying PAV+ mode may help maintain the patient's respiratory muscles allowing for earlier success in SBTs and/or earlier readiness for liberation. Alternatively, or additionally, reduced incidence of tracheostomy may play a role as time to tracheostomy has been previously associated with time on MV and in the ICU.[30] Results of a large, multi-centre clinical trial [ClinicalTrials.gov Identifier: NCT02447692] are pending, but may help to answer these questions definitively.

There are two published meta-analyses of PAV+ mode.[28,29] As in our analysis, these studies converted data reported as a median and (interquartile) range to means and standard deviations for analysis using the methods of Wan et al.[31] (used by Kataoka et al. [29]) or Hozo et al.[32](used by Vijayaraghavan et al.[28] via personal communication). Our results are more

aligned to those of Kataoka et al.[29] Potential reasons for this may be the consensus use of the methodology presented by Wan et al.[31] or the greater overlap in included studies.

Limitations

This study uses a pragmatic meta-analysis to determine the comparative effectiveness of PAV+ mode compared with PSV. As no systematic review was undertaken, there remains the potential that data relevant to the analysis were not captured. All data identified in previous meta-analyses,[28,29] were included, plus a prospective, observational case-control study.[26] The use of a computational model allowed for cost and outcomes data to be extrapolated to 20 years, but no model can fully reproduce clinical practice. Results should be treated as estimates and interpreted with respect to their uncertainty and the readers' clinical judgment. Sensitivity and scenario analyses across a range of clinical parameters suggest that results are robust, but confirmation in a real-world analysis on patients is recommended.

Conclusions

Based on available evidence to date, PAV+ mode is likely to be cost effective in the Canadian setting. Costs of care in the year of admission to ICU are expected to be reduced, though over a 20-year time period would increase due to longer patient life expectancy.

Data-sharing statement

Data relating to results presented will be made available on reasonable request.

Contributions

RS and KB contributed substantially to conception and design, acquisition of data, and analysis and interpretation of data. JD contributed substantially to acquisition, analysis, and interpretation of data. RS and JD drafted the manuscript, KB revised it critically for important intellectual content. RS, JD, and KB all gave final approval of the version to be published and agreed to act as guarantor of the work.

List of abbreviations

AE, adverse event; CAD, Canadian dollar; COVID-19, coronavirus disease 2019; CrI, credible interval; GW, general ward; ICU, intensive care unit; MD, mean difference; MV, mechanical ventilation; OR, odds ratio; PAV+, proportional-assist ventilation with load adjustable gain factors; PSV, pressure support ventilation; QALY, quality-adjusted life year; QoL, quality of life; SBT, spontaneous breathing trial; VAP, ventilator-associated pneumonia; WTP, willingness-to-pay.

References

1. Canadian Institute for Health Information. *Care in Canadian ICUs*.; 2016. https://secure.cihi.ca/free_products/ICU_Report_EN.pdf.

2. Hill AD, Fowler RA, Burns KEA, Rose L, Pinto RL, Scales DC. Long-Term Outcomes and Health Care Utilization after Prolonged Mechanical Ventilation. *Ann*

Am Thorac Soc. 2017;14(3):355-362. doi:10.1513/AnnalsATS.201610-792OC

3. Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Med*. 2020;46(5):854-887. doi:10.1007/s00134-020-06022-5

4. Wunsch H. Mechanical Ventilation in COVID-19: Interpreting the Current Epidemiology. *Am J Respir Crit Care Med*. 2020;202(1):1-4. doi:10.1164/rccm.202004-1385ED

5. Critical Care Services Ontario. Long-Term Mechanical Ventilation: Toolkit for Adult Acute Care Providers. 2013;(November). https://www.criticalcareontario.ca/EN/Toolbox/Toolkits/Long-Term Mechanical Ventilation Toolkit for Adult Acute Care Providers.pdf.

6. Barrett K, Khan YA, Mac S, Ximenes R, Naimark DMJ, Sander B. Estimation of COVID-19-induced depletion of hospital resources in Ontario, Canada. *CMAJ*. 2020;192(24):E640-E646. doi:10.1503/cmaj.200715

7. Wiseman SM, Crump RT, Sutherland JM. Surgical wait list management in Canada during a pandemic: many challenges ahead. *Can J Surg*. 2020;63(3):E226-E228. doi:10.1503/cjs.006620

8. Goligher EC, Dres M, Fan E, et al. Mechanical ventilation-induced diaphragm atrophy strongly impacts clinical outcomes. *Am J Respir Crit Care Med*. 2018;197(2):204-213. doi:10.1164/rccm.201703-0536OC

9. Brochard L, Telias I. Bedside Detection of Overassistance During Pressure Support Ventilation. *Crit Care Med*. 2018;46(3):488-490. doi:10.1097/CCM.0000000000002913

10. Epstein SK. How often does patient-ventilator asynchrony occur and what are the consequences? *Respir Care*. 2011;56(1):25-38. http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=21235836&retmode=ref&cmd=prlinks.

11. Thille AW, Rodriguez P, Cabello B, Lellouche F, Brochard L. Patient-ventilator asynchrony during assisted mechanical ventilation. *Intensive Care Med*. 2006;32(10):1515-1522. doi:10.1007/s00134-006-0301-8

12. De Wit M, Miller KB, Green DA, Ostman HE, Gennings C, Epstein SK. Ineffective triggering predicts increased duration of mechanical ventilation*. *Crit Care Med*. 2009;37(10):2740-2745. doi:10.1097/CCM.0b013e3181a98a05

13. Blanch L, Villagra A, Sales B, et al. Asynchronies during mechanical ventilation are associated with mortality. *Intensive Care Med*. 2015;41(4):633-641. doi:10.1007/s00134-015-3692-6

14. Schmidt M, Kindler F, Cecchini J, et al. Neurally adjusted ventilatory assist and proportional assist ventilation both improve patient-ventilator interaction. *Crit Care*. 2015;19(1):56. doi:10.1186/s13054-015-0763-6

15. Ranieri VM, Grasso S, Mascia L, et al. Effects of proportional assist ventilation on inspiratory muscle effort in patients with chronic obstructive pulmonary disease and

acute respiratory failure. *Anesthesiology*. 1997;86(1):79-91. doi:10.1097/00000542-199701000-00012

16. Wysocki M, Meshaka P, Richard J-C, Similowski T. Proportional-assist ventilation compared with pressure-support ventilation during exercise in volunteers with external thoracic restriction. *Crit Care Med*. 2004;32(2):409-414. doi:10.1097/01.CCM.0000108869.12426.51

17. Younes M. Proportional Assist Ventilation, a New Approach to Ventilatory Support: Theory. *Am Rev Respir Dis*. 1992;145(1):114-120. doi:10.1164/ajrccm/145.1.114

18. Bosma KJ, Read BA, Bahrgard Nikoo MJ, Jones PM, Priestap FA, Lewis JF. A Pilot Randomized Trial Comparing Weaning From Mechanical Ventilation on Pressure Support Versus Proportional Assist Ventilation. *Crit Care Med*. 2016;44(2):1-11. doi:10.1097/CCM.0000000000001600

19. Botha J, Green C, Carney I, Haji K, Gupta S, Tiruvoipati R. Proportional assist ventilation versus pressure support ventilation in weaning ventilation: a pilot randomised controlled trial. *Crit Care Resusc*. 2018;20(1):33-40. http://www.ncbi.nlm.nih.gov/pubmed/29458319. Accessed June 5, 2019.

20. Elganady AA, Beshey BN, Abdelaziz AAH. Proportional assist ventilation versus pressure support ventilation in the weaning of patients with acute exacerbation of chronic obstructive pulmonary disease. *Egypt J Chest Dis Tuberc*. 2014;63(3):643-650. doi:10.1016/j.ejcdt.2014.04.001

21. Saunders R, Geogopoulos D. Evaluating the Cost-Effectiveness of Proportional-Assist Ventilation Plus vs . Pressure Support Ventilation in the Intensive Care Unit in Two Countries. *Front public Heal*. 2018;6(June):1-8. doi:10.3389/fpubh.2018.00168

22. Xirouchaki N, Kondili E, Vaporidi K, et al. Proportional assist ventilation with load-adjustable gain factors in critically ill patients: Comparison with pressure support. *Intensive Care Med*. 2008;34(11):2026-2034. doi:10.1007/s00134-008-1209-2

23. Canadian Agency for Drugs and Technologies in Health. Guidelines for the Economic Evaluation of Health Technologies: Canada. 2017;(March):1-76. https://www.cadth.ca/sites/default/files/pdf/guidelines_for_the_economic_evaluation_of_health_technologies_canada_4th_ed.pdf.

24. Cape J, Beca JM, Hoch JS, Ontario CC. Health policy and economics introduction to cost-effectiveness analysis for clinicians. *Univ Toronto Med J*. 2013;90(3):103-105.

25. Sasikumar S, Shanbhag V, Shenoy A, Unnikirshanan R. Comparison of pressure support and proportional assist ventilation plus for weaning from mechanical ventilation in critically ill patients. *Indian J Crit Care Med*. 2013;17(May 2016):34. http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L71239402%5Cnhttp://rd8hp6du2b.search.serialssolutions.com?sid=EMBASE&issn=09725229&id=doi:&atitle=Comparison+of+pressure+support+and+proportional+assist+ventilation+plus+for+weaning.

26. Aguirre-Bermeo H, Bottiroli M, Italiano S, et al. Ventilación con presión de soporte y ventilación proporcional asistida durante la retirada de la ventilación mecánica. *Med Intensiva*. 2014;38(6):363-370. doi:10.1016/j.medin.2013.08.003

27. Teixeira SN, Osaku EF, Lima de Macedo Costa CR, et al. Comparison of Proportional Assist Ventilation Plus, T-Tube Ventilation, and Pressure Support Ventilation as Spontaneous Breathing Trials for Extubation: A Randomized Study. *Respir Care*. 2015;60(11):1527-1535. doi:10.4187/respcare.03915

28. Tirupakuzhi Vijayaraghavan BK, Hamed S, Jain A, et al. Evidence Supporting Clinical Use of Proportional Assist Ventilation: A Systematic Review and Meta-Analysis of Clinical Trials. *J Intensive Care Med*. January 2018:885066618769021. doi:10.1177/0885066618769021

29. Care I, Kataoka J, Kuriyama A, Norisue Y, Fujitani S. Proportional modes versus pressure support ventilation : a systematic review and meta ‐ analysis. *Ann Intensive Care*. 2018. doi:10.1186/s13613-018-0470-y

30. Arabi YM, Alhashemi J, Tamim H, et al. The impact of time to tracheostomy on mechanical ventilation duration, length of stay, and mortality in intensive care unit patients. *J Crit Care*. 2009;24(3):435-440. doi:10.1016/j.jcrc.2008.07.001

31. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14:135. doi:10.1186/1471-2288-14-135

32. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median , range , and the size of a sample. 2005;10:1-10. doi:10.1186/1471-2288-5-13

33. KJ B, BA R, MJ BN, PM J, FA P. A Pilot Randomized Trial Comparing Weaning From Mechanical Ventilation on Pressure Support Versus Proportional Assist Ventilation. *Crit Care Med*. 2016;44(6):1098-1108. doi:10.1097/CCM.0000000000001600

34. Vaporidi K, Babalis D, Chytas A, et al. Clusters of ineffective efforts during mechanical ventilation: impact on outcome: Supplementary material. *Intensive Care Medicine*. 2016:1-8.

35. Sinuff T, Muscedere J, Cook DJ, et al. Implementation of clinical practice guidelines for ventilator-associated pneumonia: A multicenter prospective study. *Crit Care Med*. 2013;41(1):15-23. doi:10.1097/CCM.0b013e318265e874

36. Miltiades AN, Gershengorn HB, Hua M, Kramer AA, Li G, Wunsch H. Cumulative Probability and Time to Reintubation in U.S. ICUs. *Crit Care Med*. 2017;45(5):835-842. doi:10.1097/CCM.0000000000002327

37. Bouadma L, Sonneville R, Garrouste-Orgeas M, et al. Ventilator-Associated Events: Prevalence, Outcome, and Relationship With Ventilator-Associated Pneumonia. *Crit Care Med*. 2015;43(9):1798-1806. doi:10.1097/CCM.0000000000001091

38. Brinkman S, de Jonge E, Abu-Hanna A, Arbous MS, de Lange DW, de Keizer NF. Mortality after hospital discharge in ICU patients. *Crit Care Med*. 2013;41(5):1229-1236. doi:10.1097/CCM.0b013e31827ca4e1

39. Evans J, Kobewka D, Thavorn K, D'Egidio G, Rosenberg E, Kyeremanteng K. The impact of reducing intensive care unit length of stay on hospital costs: evidence from a tertiary care hospital in Canada. *Can J Anesth*. 2018;65(6):627-635. doi:10.1007/s12630-018-1087-1

40. Lachaine J, Beauchemin C. Economic evaluation of dexmedetomidine relative to midazolam for sedation in the intensive care unit. *Can J Hosp Pharm*. 2012;65(2):103-110. doi:10.4212/cjhp.v65i2.1116

41. Liu CC, Rudmik L. A Cost-effectiveness Analysis of Early vs Late Tracheostomy. *JAMA Otolaryngol Neck Surg*. 2016;142(10):981. doi:10.1001/jamaoto.2016.1829

42. Lee SJ. Cost-Utility Analysis of Oral Antiseptic Chlorhexidine in decreasing Ventilator-Associated Pneumonia in Intensive Care Units. 2016.

43. Muscedere JG, Day A, Heyland DK. Mortality, Attributable Mortality, and Clinical Events as End Points for Clinical Trials of Ventilator-Associated Pneumonia and Hospital-Acquired Pneumonia. *Clin Infect Dis*. 2010;51(S1):S120-S125. doi:10.1086/653060

44. Cooper K, Frampton G, Harris P, et al. Are educational interventions to prevent catheter-related bloodstream infections in intensive care unit cost-effective? *J Hosp Infect*. 2014;86(1):47-52. doi:10.1016/j.jhin.2013.09.004

Tables

Table 1 Model parameters

Grouping	Parameter	Base case [reference]
Patient cohort demographics	Age, mean years (SD)	67 (12) [33]
	Gender, % female (SE)	39.7 (0.13) [2]
Reference efficacy Standard of care (PSV)	Asynchrony >10% at MV initiation, % (range)	4.2% (0.7, 14.1) [34]
	Time on MV, mean days (95% CI)	8.1 (4.5, 28.3) [35]
	Time in ICU, mean days (95% CI)	12.6 (7.4, 33.3) [35]
	Time in hospital, mean days (95% CI)	43.5 (18.6, 68.4) [35]
	Spontaneous breathing trial success, % (95% CI)	77.9 (73.8, 82.1) [22]
	Liberation success, % (95% CI)	85.3 (85.1, 85.6) [36]
AE rates	Tracheostomy, % (95% CI)	26 (8.1, 44.0) [33]
	VAP, % (95% CI)	8.8 (5.7, 11.9) [35]
	Nosocomial infection, % (95% CI)	0.85 (0.66, 1.04) [37]
	ICU mortality (95% CI)	25.4 (20.7, 30.1) [35]
	Hospital mortality (95% CI)	30.3 (25.3, 35.3) [35]
	Post-discharge mortality, % (95% CI)	Year 1: 12.5 (12.4, 12.6) [38] Year 2: 19.3 (19.2, 19.5) [38] Year 3: 27.5 (27.3, 27.7) [38] Year 4+: life tables
Comparative effectiveness PAV+ vs. PSV	Total time MV, mean days (95% CI)	-1.53 (-2.24, -0.83) †
	ICU length of stay, mean days (95% CI)	-1.54 (-2.19, -0.90) †
	Hospital length of stay, mean days (95% CI)	-1.83 (-2.51, -1.16) †
	Successful weaning/liberation, OR (95% CI)	1.49 (0.59, 3.79) †
	ICU mortality, OR (95% CI)	0.70 (0.41, 1.20) †
	Hospital mortality, OR (95% CI)	0.70 (0.40, 1.22) †
	Tracheostomy, OR (95% CI)	0.76 (0.44, 1.31) †
	Extubation failure/re-intubation, OR (95% CI)	0.52 (0.25, 1.08) †
	Asynchrony index >= 10 (95% CI)	0.13 (0.07, 0.23) †
Costs	ICU, $ per day (95% CI)	2,765 (2,354, 3,690) [39]
	GW, $ per day (95% CI)	1,019 (717, 1,400) [39]
	MV initiation, $ per event (95% CI)	139 (125, 153) [40]
	MV maintenance, $ per day (95% CI)	851 (766, 936) [40]
	Tracheostomy, $ per event (95% CI)	4,193 (3,908, 4,477) [41]
	VAP, $ per day (95% CI)	58 (30, 73) [42,43]
	VAP, additional length of stay (95% CI)	9.5 (8.8, 10.1) ‡
	Other nosocomial infection, $ per event (95% CI)	870 (783, 956) [44]
	PSV, $ purchase cost	0 (assumption)
	PAV+, $ one-off purchase cost	27,000 ⁑

Grouping	Parameter	Base case [reference]
	Post-discharge, $ annual cost (95% CI)	13,707 (6,241, 37,631)[2]
Health state utility	Baseline (95% CI)	0.776 (0.677, 0.899)[21]
	Annual disutility (95% CI)	0.003 (0.003, 0.004)[21]
	MV (95% CI)	-0.390 (-0.590, 0.090)[21]
	ICU (95% CI)	0.402 (0.362, 0.442)[21]
	Hospital (95% CI)	0.520 (0.450, 0.590)[21]
	Post-discharge to 1 year (95% CI)	0.550 (0.480, 0.610)[21]

†Present study, determined from meta-analysis (see Appendix). ‡Canadian MIS Database, F2010/11 - F2014/15. ⁑ Personal communication fromMedtronic. Probabilistic model inputs (used for the PSA) were based on input variance, calculated from reported confidence intervals.
AE, adverse event; CI, confidence interval; GW, general ward; ICU, intensive care unit; MV, mechanical ventilation; OR, odds ratio; PAV+, proportional-assist ventilation with adjustable gain parameters; PSV, pressure support ventilation; SD, standard deviation; SE, standard error; VAP, ventilator-associated pneumonia.

Table 2 Base case cost and quality-adjusted life year outcomes

Time horizon	Mode/result	Costs	QALY	ICER
1 year	PAV+	$53,898	0.29	
	PSV	$60,271	0.25	
	Difference	-$6,373	+0.04	Dominant
20 years	PAV+	$144,041	6.79	
	PSV	$137,976	5.86	
	Difference	$6,065	+0.92	$6,592

Results for the base case analysis with total costs and total QALYs, the difference (PAV+ minus PSV), and the associated ICER. In the 1-year time horizon, where PAV+ was associated with savings for the QALYs gained, the ICER is considered dominant as there is no additional cost associated with a QALY gain.
ICER, incremental cost-effectiveness ratio; PAV+, proportional-assist ventilation with adjustable gain parameters; PSV, pressure support ventilation; QALY, quality-adjusted life year.

Table 3 Scenario analyses

Scenario	1 year		20 years	
	Difference	ICER	Difference	ICER
Base case (default values)	-$6,373 +0.04	Dominant	$6,065 0.92	$6,592
Only significant differences in comparative effectiveness included	-$6,767 +0.02	Dominant	+$425 +0.53	$802
Younger population (50 years)	-$6,373 +0.04	Dominant	+$8,281 +1.08	$7,668
Population 70% female	-$6,373 +0.04	Dominant	+$6,345 +0.94	$6,750
No difference in asynchrony between PAV+ mode and PSV	-$5,477 +0.03	Dominant	+$6,319 +0.87	$7,263
PSV also has a purchase cost ($27,000)	-$6,550 +0.04	Dominant	+$5,888 +0.92	$6,400

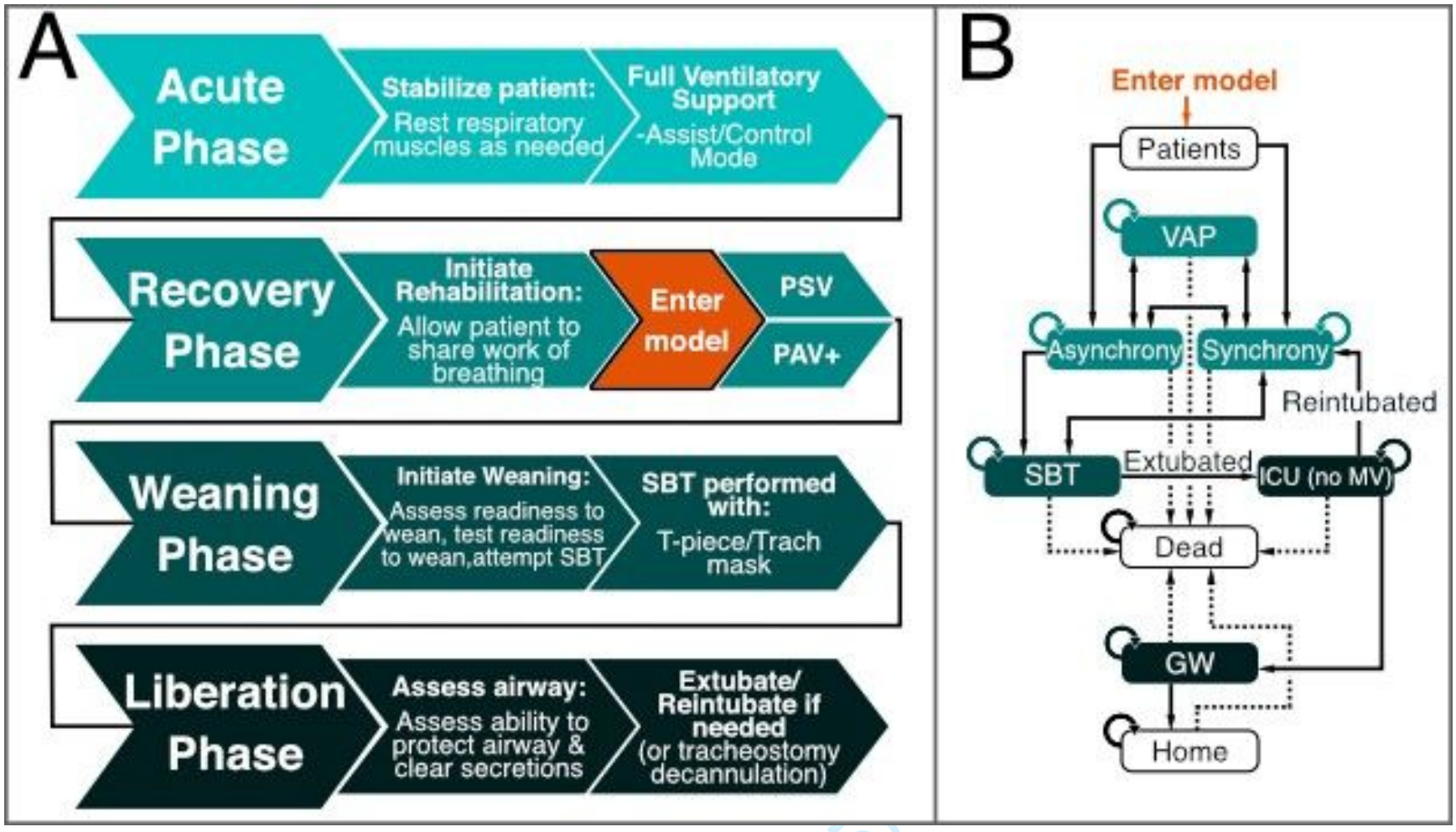
Per day hospital costs taken from CIHI data.[1] ICU $3,592; GW $1,135	-$8,138 +0.04	Dominant	+$4,320 +0.92	$4,696
Canadian efficacy data only[33]	-$8,268 0.0	Cost saving	-$5,857 +0.17	Dominant

Results are presented as PAV+ versus standard care PSV with difference in costs over difference in QALYs. The associated ICER is shown; in cases where costs decrease and QALYs increase, the ICER is taken as dominant. Care in Canadian ICU1: Data Tables, Table 13 Average daily cost for stay in ICU and GW by hospital type, 2013–2014. https://www.cihi.ca/sites/default/files/document/icu_datatables_en.xlsx

CIHI, Canadian Institute for Health Information; GW, general ward; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; PAV+, proportional-assist ventilation with adjustable gain parameters; PSV, pressure support ventilation.

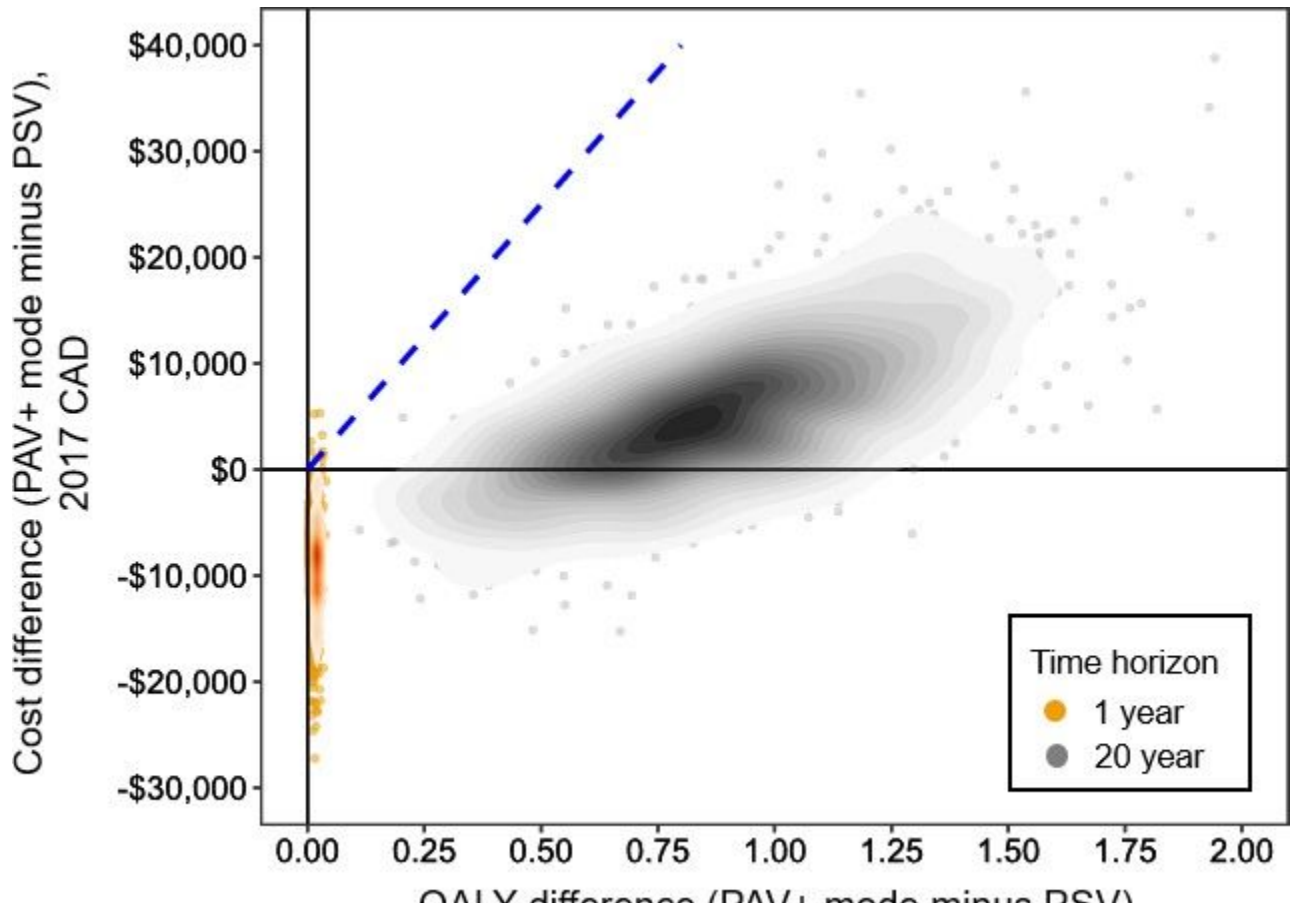
Figures and captions

Figure 1 Model structure



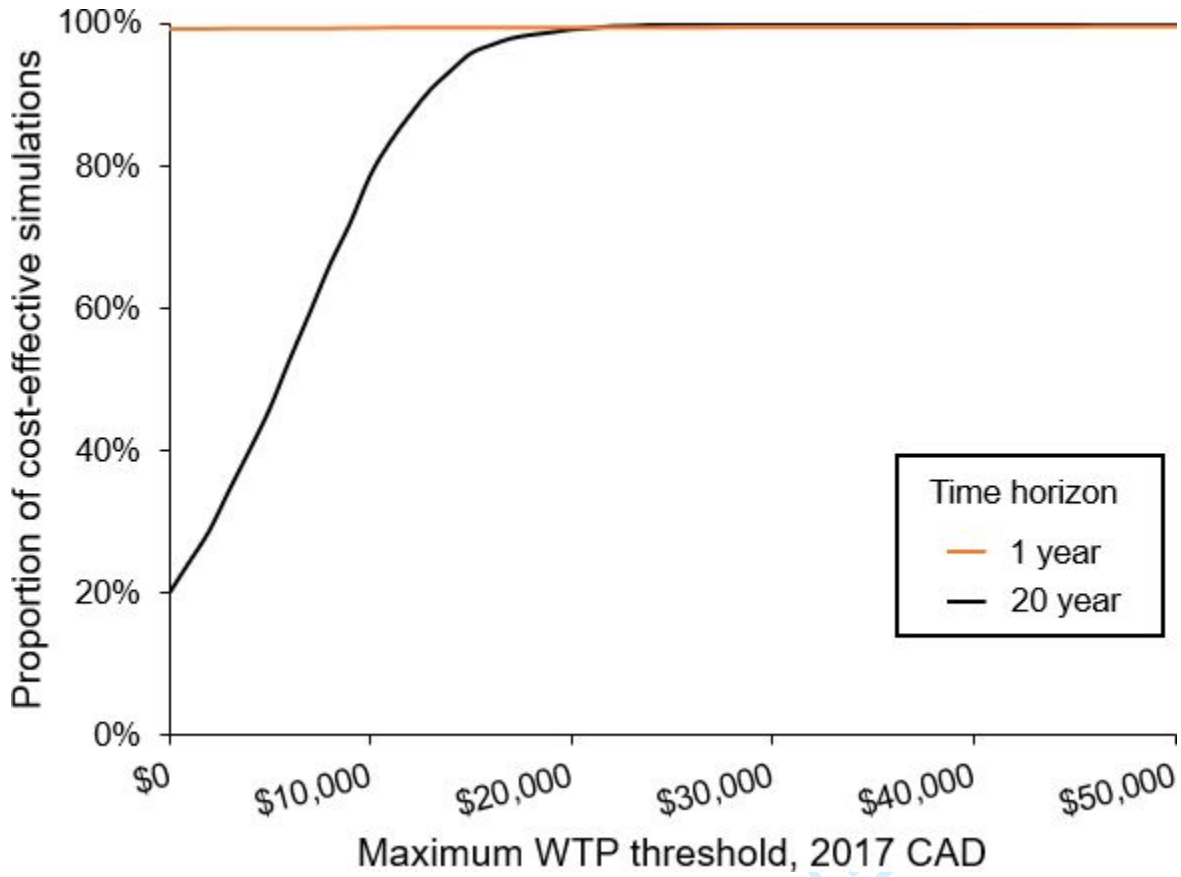
The clinical stages of MV are shown in A. The model beings once the patient is out of the acute phase and enters the Recovery phase. The model is shown in B. Patients on MV are either synchronous or asynchronous with the ventilator. Synchronous patients can become asynchronous and vice versa. Patients on MV are at risk of ventilator-associated pneumonia. From MV, patients undergo a spontaneous breathing trial, which if successful results in liberation (extubation and removal from invasive MV). After successful liberation. the patient is transferred to lower-acuity care (GW) and later discharged home. If there is patient compromise after extubation (extubation failure) the patient will be reintubated and placed back on MV. At any stage patients may die.
GW, general ward; MV, mechanical ventilation; PAV+, proportional-assist ventilation with adjustable gain parameters; PSV, pressure support ventilation; SBT, spontaneous breathing trial; VAP, ventilator-associated pneumonia.

Figure 2 Cost-effectiveness plane at two time horizons for PAV+ mode versus PSV



A sensitivity analysis of 2,000 replicates was performed for cost-effectiveness time horizons of 1 year and 20 years. The blue reference line indicates a willingness-to-pay threshold of $50,000 per QALY gained. Points underneath this line are considered cost-effective. Simulations in the lower right quadrant (increase in QALY, decrease in cost) are considered dominant. Density of individual probabilistic simulation results for each time horizon is represented by highlighted areas of the cost-effectiveness plane.
CAD, Canadian dollar; PAV+, proportional-assist ventilation with adjustable gain parameters; PSV, pressure support ventilation; QALY, quality-adjusted life year.

Figure 3 ***Cost-effectiveness acceptability curve at two time horizons for PAV+ mode versus PSV***



The proportion of simulations is shown according to varying thresholds of cost effectiveness. Cases where the result was dominant (a decrease in costs accompanied by an increase in QALY) are counted among the cost-effective scenarios, hence the curves' indicating non-zero proportions of simulations as cost-effective even at a willingness to pay threshold of $0.
PAV+, proportional-assist ventilation with adjustable gain parameters; CAD, Canadian dollar; PSV, pressure support ventilation; QALY, quality-adjusted life year; WTP, willingness to pay (threshold).

Appendix - The clinical and cost effectiveness of PAV+ mode for mechanical ventilation

Short-title: PAV+ for mechanical ventilation in the ICU

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Appendix

Identifying relevant literature

The aim of the literature searches was to supplement data identified from the original model publication,[1] by identifying recent literature reporting on efficacy, safety, and costs associated with MV in Canada. In combining data from the previous study with that from the Canadian setting, the aim was to provide a holistic view of data on PAV+ mode. As the focus of the publication is an economic model, the intent of the searches was to obtain a representative assessment of additional data available on outcomes in the Canadian setting, thus they were performed pragmatically rather than systematically.

To inform the model design and data analysis, a structured literature search of PubMed was performed using search terms detailed in **Table 1**. These were supplemented by hand searches of Google Scholar to identify relevant, non-PubMed-indexed clinical studies. The supplementary materials of included studies were also reviewed for relevant data.

Table 1 Structures searched in PubMed to identify relevant cost data

#	Aim	Search string	Hits
1	Country specific	canada[ad] OR "Canada"[tw] OR "Canadian"[tw] OR "Canadians"[tw] OR "Canada"[Mesh] OR "Alberta"[tw] OR "British Columbia"[tw] OR "Manitoba"[tw] OR "New Brunswick"[tw] OR "Newfoundland and Labrador"[tw] OR "Northwest Territories"[tw] OR "Nova Scotia"[tw] OR "Nunavut"[tw] OR "Ontario"[tw] OR "Prince Edward Island"[tw] OR "Quebec"[tw] OR "Saskatchewan"[tw] OR "Yukon Territory"[tw] OR "Toronto"[tw] OR "Ottawa"[tw] OR "Winnipeg"[tw] OR "Regina"[tw] OR "Edmonton"[tw] OR "Vancouver"[tw] OR "Montreal"[tw] OR "Saint John"[tw] OR "Halifax"[tw] OR "St John's"[tw] OR "Charlottetown"[tw] OR "Alberta"[ad] OR "British Columbia"[ad] OR "Manitoba"[ad] OR "New Brunswick"[ad] OR "Newfoundland and Labrador"[ad] OR "Northwest Territories"[ad] OR "Nova Scotia"[ad] OR "Nunavut"[ad] OR "Ontario"[ad] OR "Prince Edward Island"[ad] OR "Quebec"[ad] OR "Saskatchewan"[ad] OR "Yukon Territory"[ad] OR "Toronto"[ad] OR "Ottawa"[ad] OR "Winnipeg"[ad] OR "Regina"[ad] OR "Edmonton"[ad] OR "Vancouver"[ad] OR "Montreal"[ad] OR "Saint John"[ad] OR "Halifax"[ad] OR "St John's"[ad] OR "Charlottetown"[ad] OR "CADTH"[tw]	216,400
2	All cost studies	"Costs and Cost Analysis"[Mesh] OR "Cost-Benefit Analysis"[Mesh] OR "Cost of Illness"[Mesh] OR "Health Care Costs"[Mesh] OR "Cost Sharing"[Mesh] OR "Cost Savings"[Mesh] OR "Technology, High-Cost"[Mesh] OR "Cost Control"[Mesh] OR "Cost Allocation"[Mesh] OR "Direct Service Costs"[Mesh] OR "Hospital Costs"[Mesh] OR "Employer Health Costs"[Mesh] OR "Drug Costs"[Mesh] OR "Health Expenditures"[Mesh] OR "Health Resources/economics"[Mesh] OR "Economics, Hospital"[Mesh] OR "Economics, Medical"[Mesh] OR "Economics, Pharmaceutical"[Mesh] OR "Economics, Nursing"[Mesh] OR "Managed Care Programs"[Mesh] OR "Insurance, Physician Services"[Mesh] OR "Budgets"[Mesh] OR "Economics"[Mesh] OR "Commerce"[Mesh] OR Cost[tw] OR economic[tw] OR "Length of Stay/economics"[Mesh] OR "Length of Stay/statistics and numerical data"[Mesh] OR "Financial Management, Hospital"[Mesh] OR "Hospital Charges/statistics and numerical data"[Mesh] OR "Hospital Costs"[Mesh] OR "Economics, Hospital"[Mesh] OR "LOS"[tiab] OR ((USD[tw] OR CAD[tw] OR dollar[tw] OR dollars[tw]) AND (Cost[tw] OR price[tw] or expense[tw] OR burden[tw] OR "pricing"[tw] OR "prices"[tw])) OR (("Cost"[tw] OR spending[tw] OR "economic"[tiab] OR "Costs"[tw] OR "economics"[tiab]) AND ("Healthcare"[tiab] OR "health care"[tiab] or	1,013,476

#	Aim	Search string	Hits
		"medical"[tiab] OR treatment[tiab] OR hospital[tiab] OR hospitalization[tw] OR hospitalisation[tw] OR "health service"[tiab]))	
3	Studies since 2012	"2012/01/01"[PDAT]:"2018/05/01"[PDAT]	6,589,304
4	Recent cost studies	#1 AND #2 AND #3	6,942
5	Adverse events (AE) of interest	"Tracheotomy"[Mesh] OR "Tracheotomy"[tw] OR "Tracheostomy"[tw] OR "Pneumonia, Ventilator-Associated"[Mesh] OR VAP[tw] OR "ventilator-associated pneumonia"[tw] OR "Respiration, Artificial/adverse effects"[Mesh] OR "Respiration, Artificial/complications"[Mesh] OR "Respiration, Artificial/economics"[Mesh] OR "Respiration, Artificial/mortality"[Mesh] OR "Respiration, Artificial/statistics and numerical data"[Mesh] OR "Length of Stay/economics"[Mesh] OR synchrony[tw] OR synchronous[tw] OR asynchrony[tw] OR asynchronous[tw] OR ((LOS[tw] OR stay[tw]) AND (ICU[tw] OR "intensive care"[tw])) OR ((mortality[tw] OR death[tw] OR surviving[tw] OR survival[tw]) AND (ICU[tw] OR "intensive care"[tw] or "critically ill"[tw]))	160,942
6	Those reporting on assisted ventilation	"Respiration, Artificial"[Mesh] OR "High-Frequency Ventilation"[Mesh] OR "Interactive Ventilatory Support"[Mesh] OR "mechanical ventilation"[tw] OR "assisted ventilation"[tw] OR "proportional assist"[tw] OR "proportional-assist"[tw] OR PAV[tw] OR "PAV+"[tw] OR NAVA[tw] OR PSV[tw] OR "neurally adjusted"[tw] OR "artificial respiration"[tw] OR "artificial ventilation"[tw]	92,907
7	AEs and assisted ventilation	#5 AND #6	26,126
8	Cost of assisted ventilation	#4 AND #7	36

Literature search results

Regarding clinical effectiveness outcomes, the literature review identified seven clinical studies comparing PAV+ mode with PSV.[2–8] Of these, four covered the recovery phase of critical care, [2,3,5,7] three the weaning phase,[4,6,8] two were Canadian,[2,3] and one was not randomized.[7] A total of 271 patients were managed with PAV+ mode and 253 with PSV. Clinical and safety data of interest from these studies were extracted and used for meta-analysis.

Pragmatic meta-analysis

Methods

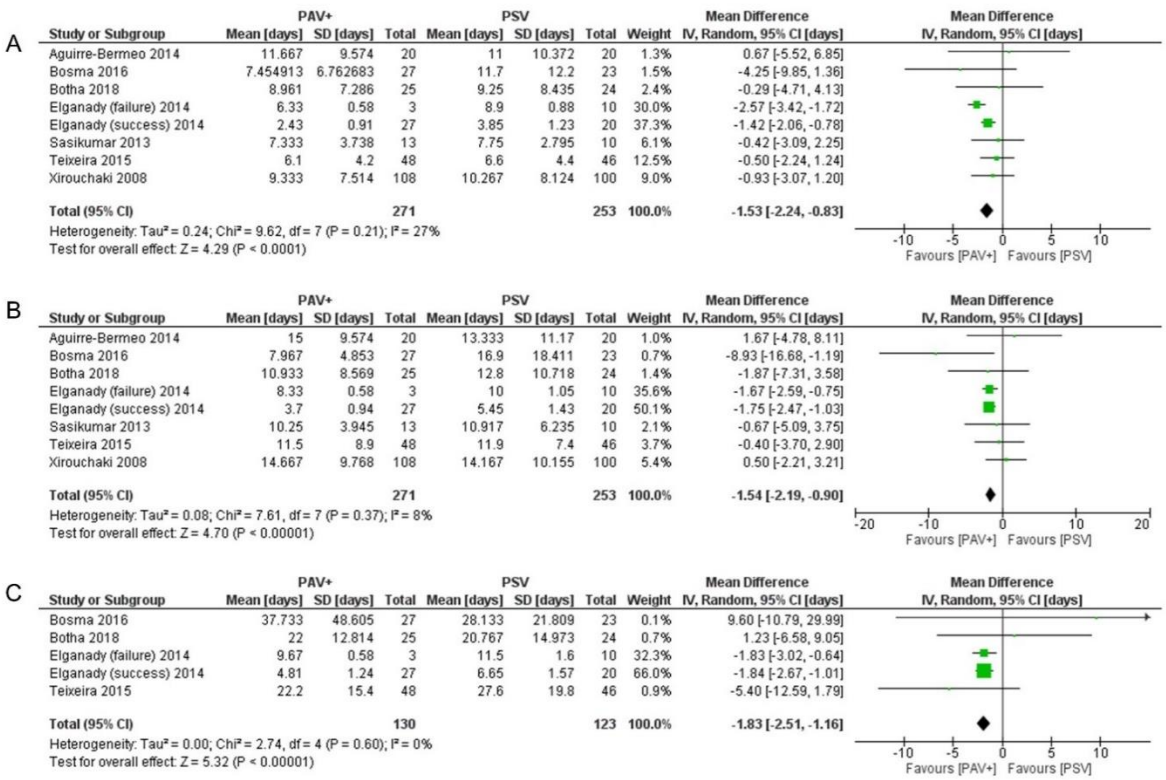
No individual study among those identified in the literature review presented robust clinical data on the required model inputs for the Canadian setting. In their absence, a pragmatic meta-analysis of results was conducted. Included studies were reviewed independently by both RS and KJB, with data extraction also performed independently by both authors. Where there was disagreement between included data, this was resolved by discussion. Unless already in the correct form for analysis, extracted data were converted to means and standard deviations according the method of Wan et al.[9] Data conversion (using R) and meta-analysis (using RevMan v5.3) were performed by JD and outcomes checked by RS and KJB. In the meta-analysis, a random-effects model was used to account for low powered studies and potential differences in clinical practice between countries. Dichotomous outcomes were calculated as odds ratios or as Peto odds ratios for rare outcomes or where numerous groups had zero events.

Results

Data extraction resulted in sufficient data to assess all required endpoints for hospital time: total time on MV, ICU length of stay, and hospital length of stay. Total patient numbers were 524 for time on MV and in the ICU, and 253 for hospital length of stay. For each endpoint, heterogeneity was low ($I^2 \leq 24\%$) and PAV+ mode was associated with a significant reduction in time in each care setting. Meta-analysis results for these endpoints are shown in Figure 1.

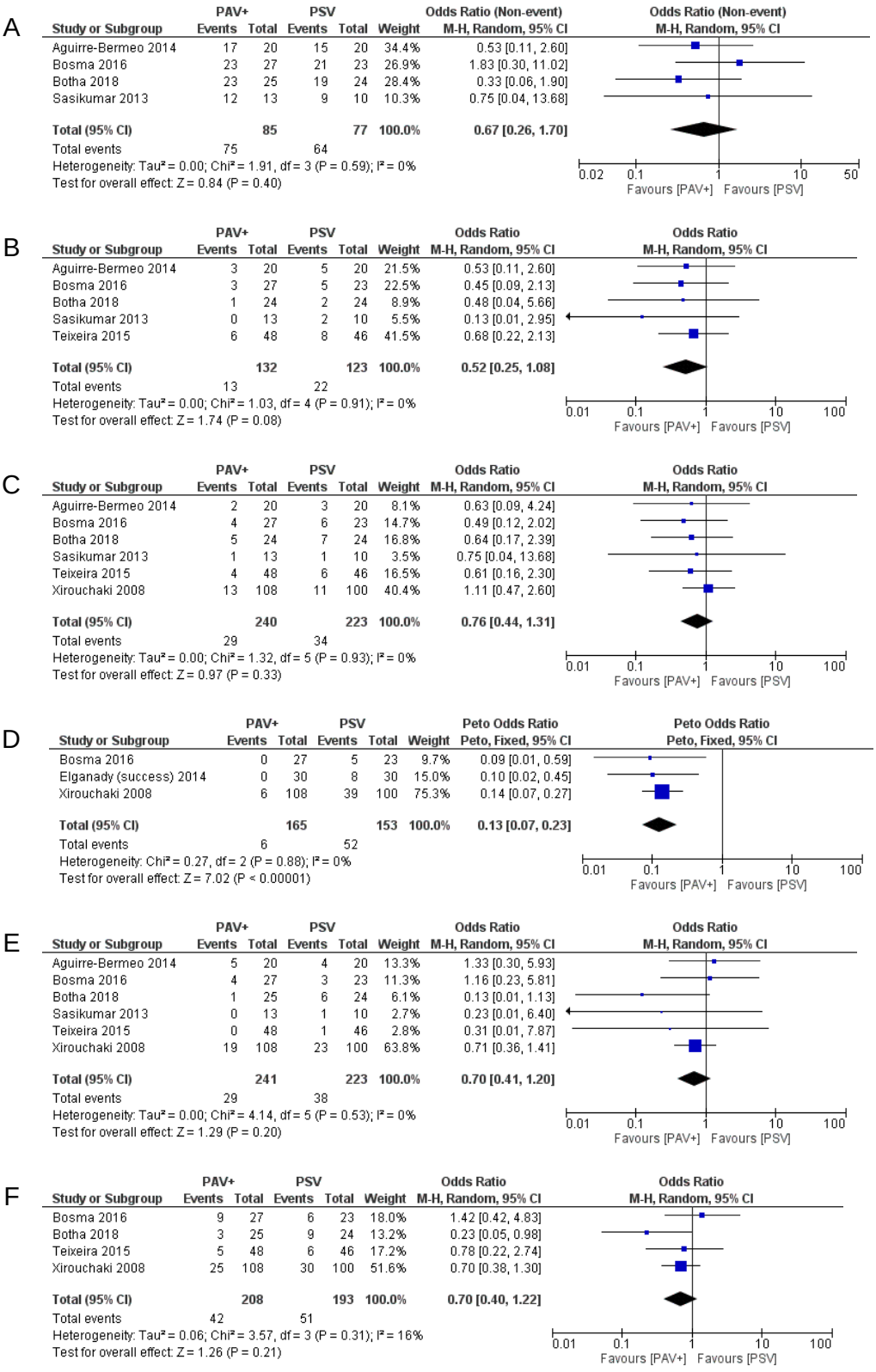
For dichotomous endpoints, six events had three or more studies reporting on the outcome: weaning success, extubation/liberation failure, need for tracheostomy, ICU mortality, hospital mortality, and asynchrony index ≥ 10. For all outcomes, heterogeneity of reported data was low ($I^2 \leq 16\%$). PAV+ mode was generally associated with improved outcomes, although not statistically significant (**Figure 2**), with the exception of asynchrony index ≥ 10, where PAV+ mode was significantly associated with decreased odds of asynchrony (OR 0.13, 0.07-0.23). The meta-analysis results represent the base-case inputs for our health-economic analysis and are summarized in **Table 2**.

Figure 1 Meta-analysis results for continuous outcomes



Results for time on MV (A), length of stay in the ICU (B) and length of stay in hospital (C) are shown. CI, confidence interval; IV, inverse variance; PAV+, proportional-assist ventilation with adjustable gain parameters; PSV, pressure support ventilation; SD, standard deviation.

Figure 2 ***Meta-analysis results for dichotomous outcomes***



Results for weaning success (A), extubation/liberation failure (B), need for tracheostomy (C), asynchrony index ≥ 10 (D), ICU mortality (E) and overall hospital mortality (F) are shown. All are presented as odds ratios with random-effects models, except for odds of asynchrony index ≥ 10, calculated as Peto odds ratios since 2 of 3 PAV+ had zero events.

CI, confidence interval; M-H, Mantel-Haenszel; PAV+, proportional-assist ventilation with adjustable gain parameters; PSV, pressure support ventilation; SD, standard deviation.

Table 2 Meta-analysis summary results

Outcome	PAV+		PSV		
Continuous	Mean (SD)	N	Mean (SD)	N	MD
Total time MV (days)	5.33 (0.96)	271	6.87 (1.08)	253	-1.53 [-2.24, -0.83]
ICU length of stay (days)	6.61 (0.83)	271	8.16 (1.05)	253	-1.54 [-2.19, -0.90]
Hospital length of stay (days)	6.69 (0.86)	130	8.53 (1.18)	123	-1.83 [-2.51, -1.16]
Dichotomous	Events	Total	Events	Total	OR
Successful weaning/liberation	75	85	64	77	1.49 [0.59, 3.79]
ICU mortality	29	241	38	223	0.70 [0.41, 1.20]
Hospital mortality	42	208	51	193	0.70 [0.40, 1.22]
Tracheostomy	29	240	34	223	0.76 [0.44, 1.31]
Extubation failure/re-intubation	13	132	22	123	0.52 [0.25, 1.08]
Asynchrony index >= 10	6	165	52	153	0.13 [0.07, 0.23]

Summary of inputs, after conversion to means and standard deviations where necessary, and results from the pragmatic meta-analysis. Results (MD or OR) are shown with 95% CIs. Mean (SD) values are weighted means, where the weight for each study is taken from the RevMan 5.3 output.
ICU, intensive care unit; MD, mean difference (PAV+ mode – PSV); MV, mechanical ventilation; OR, odds ratio (PAV+ mode relative to PSV); PAV+, proportional-assist ventilation with adjustable gain parameters; PSV, pressure support ventilation; SD, standard deviation.

References

1. Saunders R, Geogopoulos D. Evaluating the Cost-Effectiveness of Proportional-Assist Ventilation Plus vs . Pressure Support Ventilation in the Intensive Care Unit in Two Countries. *Front public Heal*. 2018;6(June):1-8. doi:10.3389/fpubh.2018.00168

2. Bosma KJ, Read BA, Bahrgard Nikoo MJ, Jones PM, Priestap FA, Lewis JF. A Pilot Randomized Trial Comparing Weaning From Mechanical Ventilation on Pressure Support Versus Proportional Assist Ventilation. *Crit Care Med*. 2016;44(2):1-11. doi:10.1097/CCM.0000000000001600

3. Botha J, Green C, Carney I, Haji K, Gupta S, Tiruvoipati R. Proportional assist ventilation versus pressure support ventilation in weaning ventilation: a pilot randomised controlled trial. *Crit Care Resusc*. 2018;20(1):33-40. http://www.ncbi.nlm.nih.gov/pubmed/29458319. Accessed June 5, 2019.

4. Elganady AA, Beshey BN, Abdelaziz AAH. Proportional assist ventilation versus pressure support ventilation in the weaning of patients with acute exacerbation of chronic obstructive

pulmonary disease. *Egypt J Chest Dis Tuberc*. 2014;63(3):643-650. doi:10.1016/j.ejcdt.2014.04.001

5. Xirouchaki N, Kondili E, Vaporidi K, et al. Proportional assist ventilation with load-adjustable gain factors in critically ill patients: Comparison with pressure support. *Intensive Care Med*. 2008;34(11):2026-2034. doi:10.1007/s00134-008-1209-2

6. Sasikumar S, Shanbhag V, Shenoy A, Unnikirshanan R. Comparison of pressure support and proportional assist ventilation plus for weaning from mechanical ventilation in critically ill patients. *Indian J Crit Care Med*. 2013;17(May 2016):34. http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L71239402%5Cnhttp://rd8hp6du2b.search.serialssolutions.com?sid=EMBASE&issn=09725229&id=doi:&atitle=Comparison+of+pressure+support+and+proportional+assist+ventilation+plus+for+weaning.

7. Aguirre-Bermeo H, Bottiroli M, Italiano S, et al. Ventilación con presión de soporte y ventilación proporcional asistida durante la retirada de la ventilación mecánica. *Med Intensiva*. 2014;38(6):363-370. doi:10.1016/j.medin.2013.08.003

8. Teixeira SN, Osaku EF, Lima de Macedo Costa CR, et al. Comparison of Proportional Assist Ventilation Plus, T-Tube Ventilation, and Pressure Support Ventilation as Spontaneous Breathing Trials for Extubation: A Randomized Study. *Respir Care*. 2015;60(11):1527-1535. doi:10.4187/respcare.03915

9. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14:135. doi:10.1186/1471-2288-14-135