ORIGINAL RESEARCH

Long-Term Outcomes and Health Care Utilization after Prolonged Mechanical Ventilation

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Abstract

Rationale: Limited data are available to characterize the long-term outcomes and associated costs for patients who require prolonged mechanical ventilation (PMV; defined here as mechanical ventilation for longer than 21 d).

Objectives: To examine the association between PMV and mortality, health care utilization, and costs after critical illness.

Methods: Population-based cohort study of adults who received mechanical ventilation in an intensive care unit (ICU) in Ontario, Canada between 2002 and 2013.

Measurement and Main Results: We used linked administrative databases to determine discharge disposition, and ascertain 1-year mortality (primary outcome), readmissions to hospital and ICU, and health care costs for hospital survivors. Overall, 11,594 (5.4%) patients underwent PMV, with 42.4% of patients dying in the hospital (vs. 27.6% of patients who did not undergo prolonged ventilation; $P < 0.0001$). Patients on prolonged ventilation were more frequently discharged to other facilities or home with health care support (84.8 vs. 43.5%, $P < 0.0001$). Among hospital survivors, estimated mortality was higher for patients who underwent PMV: 16.6 versus 11% at 1 year and 42.0 versus 30.4% at 5 years. At 1 year after hospital discharge, patients on prolonged ventilation had higher rates of hospital readmission (47.2 vs. 37.7%; adjusted odds ratio = 1.20; 95% confidence interval = 1.14–1.26), ICU readmission (19.0 vs. 11.6%; adjusted odds ratio = 1.49; 95% confidence interval: 1.39, 1.60), and total health care costs: median (interquartile range) Can $32,526 ($20,821–$56,102) versus Can $13,657 ($5,946–$38,022). Increasing duration of mechanical ventilation was associated with higher mortality and health care utilization.

Conclusions: Critically ill patients who undergo mechanical ventilation in an ICU for longer than 21 days have high in-hospital mortality and greater postdischarge mortality, health care utilization, and health care costs compared with patients who undergo mechanical ventilation for a shorter period of time.

Keywords: critical care; mechanical ventilation; outcome assessment; health care utilization

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Mechanical ventilation is used increasingly for individuals admitted to intensive care units (ICUs) in North America, and is anticipated to increase, due, in large part, to the aging of the population (1, 2). Prior studies have estimated that 3–7% of mechanically ventilated patients require prolonged mechanical ventilation (PMV), variously defined as a duration of more than 96 hours to 21 days of ventilation or longer (3–5). PMV is associated with a disproportionate use of ICU and hospital resources reflecting the number of days spent in an ICU, high in-hospital and postdischarge mortality, decreased functional capacity, and poor quality of life after intensive care (6–10). In the near future, it is anticipated that a substantially higher number of critically ill patients will require PMV, with associated increases in mortality, morbidity, and costs (11–13). Although greater emphasis has been placed on understanding the long-term outcomes of these patients, data are limited to few centers and short follow-up periods (4, 9, 14, 15).

Studies examining long-term outcomes after PMV have typically focused on a more liberally defined group of ventilated patients (i.e., ⩾96 h) due to the use of easily identified codes within existing databases, or had insufficient follow-up to provide meaningful information about long-term prognoses (8, 16). Furthermore, although efforts have been made to understand and identify patients on PMV at increased risk of 1-year mortality (17, 18), only limited data exist to describe the long-term health care needs of these patients.

We sought to examine the association between PMV and mortality, long-term health care utilization, and costs, and to identify factors associated with mortality after PMV.

Methods

Design and Setting

We conducted a population-based cohort study of patients receiving mechanical ventilation in Ontario, a province with 13 million residents, representing approximately one-third of the Canadian population (19).

Data Sources and Patient Population

We used the following health administrative databases: (*1*) the Canadian Institute of Health Information Discharge Abstract Database (DAD), which includes information on all acute care hospital admissions in Ontario; (*2*) the Ontario Health Insurance Plan (OHIP) database, which contains billing claims for physician services; (*3*) the National Ambulatory Care Reporting System database, which includes information on all emergency department (ED) visits; and (*4*) the Ontario Registered Persons Database, which includes demographic and mortality information on all Ontarians. These databases have been previously linked and broadly validated (20, 21), and were analyzed at the Institute for Clinical Evaluative Sciences.

The DAD was used to identify all adults (⩾18 yr) who were admitted to an ICU between April 1, 2002 and March 31, 2013 and received mechanical ventilation. Treatment with mechanical ventilation was identified from physician billing codes using an established approach (22, 23). ICU admission was identified using special care unit codes that distinguish between admissions to general and specialty ICUs, and have been shown to have high validity (24, 25). For each patient, we included only the first hospitalization containing an ICU admission during the study period. For patients with intra- and interfacility transfers between ICUs during the index admission, we created a single ICU episode of care using unique patient identifiers.

We excluded patients whose ICU care involved only an admission to a coronary care unit, cardiac surgery ICU, or a step-down ICU, as these patients have different clinical profiles and outcomes. We also excluded patients with data entry errors (*see* Figure E1 in the online supplement). All remaining patients were linked using unique, encoded identifiers to the OHIP database to identify those patients who received mechanical ventilation during the index ICU admission. The DAD and OHIP databases were also used to characterize the demographic and clinical characteristics and outcomes of patients during the index admission.

Records of patients surviving to hospital discharge were linked to the Registered Persons Database (vital status), the National Ambulatory Care Reporting System (ED visits), and the DAD (readmission to hospital and ICU) databases to identify mortality, health resource use, and health care costs after discharge. Patients were followed until death or until March 31, 2014, whichever occurred first. This study was approved by the institutional review board at Sunnybrook Health Sciences Centre (Toronto, ON, Canada).

Variables

The exposure of interest was PMV, defined as treatment with mechanical ventilation for greater than 21 days (26). A day on mechanical ventilation was identified by the presence of relevant billing codes in the OHIP database. Consequently, any portion of a day on mechanical ventilation represented a full day of ventilator support. We excluded patients for whom total days on mechanical ventilation was two or more days longer than their cumulative days in ICU (n = 2,531, 1.2%), reasoning that these patients may have received mechanical ventilation in non-ICU areas. Patients ventilated for 21 days or less were the comparator group (patients not on PMV).

Covariates

Baseline demographic and clinical data included age, sex, socioeconomic status (neighborhood income quintile), location of residence (urban or rural), most responsible hospital diagnosis (diagnosis contributing most to patient's length of stay in the hospital), Charlson comorbidity index (27, 28) categorized as 0, 1–2, or greater than or equal to 3. We also collected information on hospital procedures (including tracheostomy and percutaneous gastrostomy tube insertion).

Outcomes

Our primary study outcome was mortality during follow-up among patients who survived to hospital discharge. Survival time was defined as time from hospital discharge until death, with censoring at the last available follow-up time (study end date, March 31, 2014).

Secondary outcomes included: discharge disposition at index admission (including hospital mortality and discharge location for survivors); death at 6 months, 1 year, and 5 years after hospital discharge; health care utilization (defined as readmission to hospital, ICU, and ED visits) measured at 6 months, 1year, and during the total follow-up period; and health care costs at 1 year after hospital discharge.

Health care costs were adjusted to 2013 Canadian dollars and represented costs for medically insured services paid by Ontario's single-payer publically funded health

Table 1. Baseline characteristics of patients surviving to hospital discharge according to duration of mechanical ventilation

Characteristics*	Hospital Survivors		
	All (*n* = 152,778)	Ventilated ⩽21 Days (*n* = 146,116)	Ventilated >21 Days (*n* = 6,662)
Female, %	39.7	39.7	41.4
Age, yr, %			
18–24	3.6	3.6	3.9
25–34	5.0	5.0	5.6
35–44	7.9	7.8	9.6
45–54	14.6	14.5	15.7
55–64	21.1	21.1	22.0
65–74	24.2	24.3	23.7
75–84	19.2	19.3	17.3
>85	4.5	4.6	2.2
Most responsible diagnoses during index hospitalization, %			
Circulatory system			
Myocardial infarction and ischemic diseases	20.6	21.3	4.0
Cerebrovascular diseases	3.9	3.8	6.2
Heart failure	1.8	1.9	1.0
Peripheral vascular disease	4.2	4.3	2.6
Other diseases of the circulatory system	7.8	7.9	3.8
Respiratory			
Respiratory failure	2.9	2.5	10.3
Chronic obstructive pulmonary disease	3.4	3.4	3.0
Pneumonia	2.0	1.9	3.9
Other diseases of the respiratory system	3.8	3.5	10.2
Cancer/neoplasm	9.7	9.9	6.4
Trauma	15.3	15.2	17.5
Septicemia	2.5	2.3	6.7
Other infectious disease	1.0	0.9	2.6
Diseases of the digestive system	9.0	8.9	10.3
Other	12.2	12.2	11.7
Charlson score, %			
0	29.4	29.8	22.2
1–2	40.1	40.1	38.2
⩾3	30.5	30.1	39.6
Rural, %	12.9	13.0	11.4
Income quintile, %			
1 (lowest)	23.2	23.2	23.7
2	21.2	21.2	22.3
3	19.2	19.2	19.0
4	18.5	18.5	17.6
5 (highest)	17.4	17.4	17.0
Interventions received, %			
Dialysis	5.5	4.7	22.9
Tracheostomy	7.3	3.7	84.6
Pulmonary artery catheter	28.9	29.4	19.1
Percutaneous/surgical feeding tube	7.9	6.2	45.4
Mechanical ventilation on ICU admission	3.2	3.2	3.9
Days in hospital before ICU admission, mean (SD)	1.8 (5.8)	1.8 (5.8)	2.2 (6.1)
Cumulative days in ICU, %			
0–3 d	39	40.7	—
3–5 d	17.3	18.1	—
5–7 d	11	11.5	—
7–14 d	18.2	19.1	—
14–60 d	13.4	10.5	77.2
60–120 d	0.9	0.1	18.4
120–365 d	0.2	<0.01	4.1
>365 d	0.01	—	0.3
Hospital length of stay, d, median (IQR)	14 (7–26)	14 (8–25)	74 (54–109)
Discharge disposition, %			
Home	54.8	56.6	15.2
Home with support	21.0	21.0	21.1
Rehabilitative care	12.1	11.0	37.6
Complex continuing care	5.0	4.3	18.8

(Continued)

Table 1. (*Continued*)

Characteristics*	Hospital Survivors		
	All (*n* = 152,778)	Ventilated ≤21 Days (*n* = 146,116)	Ventilated >21 Days (*n* = 6,662)
Long-term care	3.2	3.2	3.3
Acute care	1.1	1.0	2.5
Other	2.9	3.0	1.5

Definition of abbreviations: ICU = intensive care unit; IQR = interquartile range.
*$P < 0.05$ for all comparisons.

system (the Ontario Ministry of Health and Long-term Care). Costs categories included total health care costs, and costs associated with the following sectors: in-patient acute care admissions; ED visits; physician visits; and home care. Based on established methods, costs for acute care, ED visits, and home care were calculated using resource intensity weights methodology, by multiplying the resource intensity weight associated with each case for a given episode of care by the provincial average cost per weighted case (29). Costs for physician services were obtained from the OHIP database. Costing data were restricted to the last 9 years of the study to ensure consistency in measured cost categories across time.

Statistical Analyses

We compared demographic and clinical characteristics and outcomes between groups using the chi-square test for categorical variables and Student's *t* test or the Kruskal-Wallis test for continuous variables. Kaplan-Meier survival curves were constructed to describe cumulative mortality after hospital discharge, and differences between patients on PMV and those not on PMV were compared using the log-rank test. Among patients on PMV, we similarly examined differences in posthospital mortality according to the total duration of mechanical ventilation, classified according to the distribution of the data on the number of days ventilated (22–32 d, 33–46 d, 47–64 d, and >64 d).

We used multivariable logistic regression to analyze the association of PMV with health care utilization after discharge from the index hospital admission. To identify risk factors for death among patients on PMV surviving to hospital discharge, we used multivariable Cox proportional hazards regression analysis. Factors considered for both models were age, sex, neighborhood income quintile, area of residence, number of Charlson comorbidities, most responsible diagnosis, and discharge disposition, and, for the Cox proportional hazards model, we also included interventions received during the index admission (dialysis, tracheostomy, insertion of a percutaneous/surgical feeding tube and/or pulmonary artery catheter). All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC), and a *P* value of 0.05 or less was considered statistically significant.

Results

Between April 1, 2002, and March 31, 2013, we identified 213,680 ICU patients who received mechanical ventilation during their index admission, of whom 11,594 (5.4%) required mechanical ventilation for greater than 21 days (patients on PMV).

Patients on PMV received more ICU procedures and experienced significantly higher in-hospital mortality (42.4%) than patients not on PMV (27.6%, $P < 0.001$). Patients who died in hospital tended to be older, have more comorbidities, and required more ICU interventions, a pattern that was consistent for patients on PMV and those not on PMV (Table 1, Table E1). Compared with patients not on PMV, fewer PMV survivors were discharged directly home (15.2 vs. 56.6%, $P < 0.0001$), with the remaining PMV survivors being discharged to in-patient rehabilitation (37.6%), home with supportive care services (21.1%), and 18.8% to complex continuing care (subacute care facility providing specialized and/or complex health services). Among patients on PMV, those with the longest duration of ventilation (>64 d) were least likely to be discharged home, with only 8.3% discharged home without supportive care (Table E2).

Mortality after Discharge

Overall, 50,892 (33.3%) patients died during the postdischarge follow-up period; the median (interquartile range [IQR]) duration of follow-up from hospital discharge was 4.4 (2.0–7.5) years. Kaplan-Meier estimated mortality was higher among patients on PMV compared with patients not on PMV: 11.5% (95% confidence interval [CI] = 10.7–12.3) versus 7.3% (95% CI = 7.2–7.4) at 6 months; 16.6% (95% CI = 15.7–17.5) versus 11.0% (95% CI = 10.9–11.2) at 1 year; 24.9% (95% CI = 23.8–25.9) versus 16.9% (95% CI = 16.8–17.1) at 2 years; and 42.0% (95% CI = 40.7–43.3) versus 30.4% (95% CI = 30.2–30.7) at 5 years after hospital discharge (Figure 1). For the cohort of patients for whom 10-year follow-up was possible (those admitted before 2004), crude 10-year mortality was 57.7% among patients on PMV and 45.6% among patients not on PMV ($P < 0.001$). Among patients on PMV, increasing duration of mechanical ventilation during the index hospitalization was associated with higher mortality rates after discharge (Figure 2).

Health Care Utilization and Cost

Health care utilization, as measured by hospital readmission, ICU readmission, and ED visits, was highest among patients on PMV (Table 2). For example, during the first 6 months after discharge, 36.1% of patients on PMV and 28.7% of patients not on PMV were readmitted to hospital (adjusted odds ratio = 1.19; 95% CI = 1.12–1.25). During the same period, patients on PMV had higher odds of being readmitted to an ICU (adjusted odds ratio = 1.62; 95% CI = 1.50–1.75). These higher rates of health care use by patients on PMV were maintained over the entire follow-up period (Table 2), with health care utilization increasing with increasing

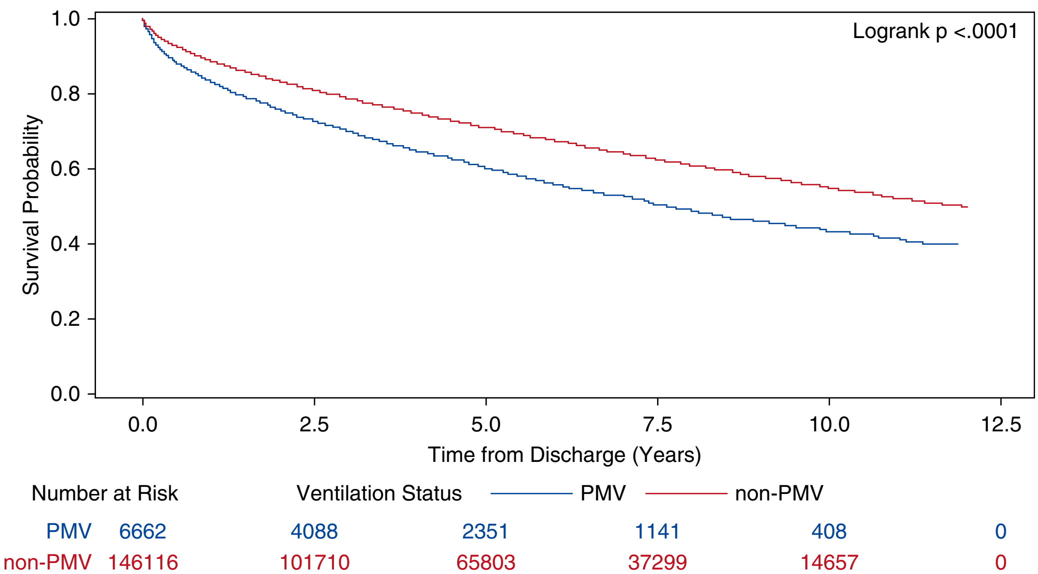

Figure 1. Kaplan-Meier estimates of survival over time after discharge stratified by duration of mechanical ventilation. PMV = prolonged mechanical ventilation. Numbers below the graph indicate the number of individuals at risk at each time point.

duration of mechanical ventilation (Table E3). Among patients on PMV who survived to 1-year after discharge, 43.6% were hospitalized and 15.1% were readmitted to ICU at least once within the 1-year period (Table E4).

Total costs in the year before index admission did not differ meaningfully by PMV status: median (IQR) Can \$8,990 (\$5,493–\$15,686) among PMV survivors and Can \$9,519 (\$5,536–\$16,290) among non-PMV survivors. However, in the year after hospital discharge, median (IQR) costs were Can \$42,784 (\$17,630–\$95,888) among patients on PMV and Can \$13,005 (\$5,922–\$35,705) among patients not on PMV ($P < 0.0001$), with higher costs for patients on PMV across all health care sectors (Table 3). For patients on PMV surviving to hospital discharge, longer duration of ventilation was associated with higher costs during index admission and in the year after hospital discharge (Table E5).

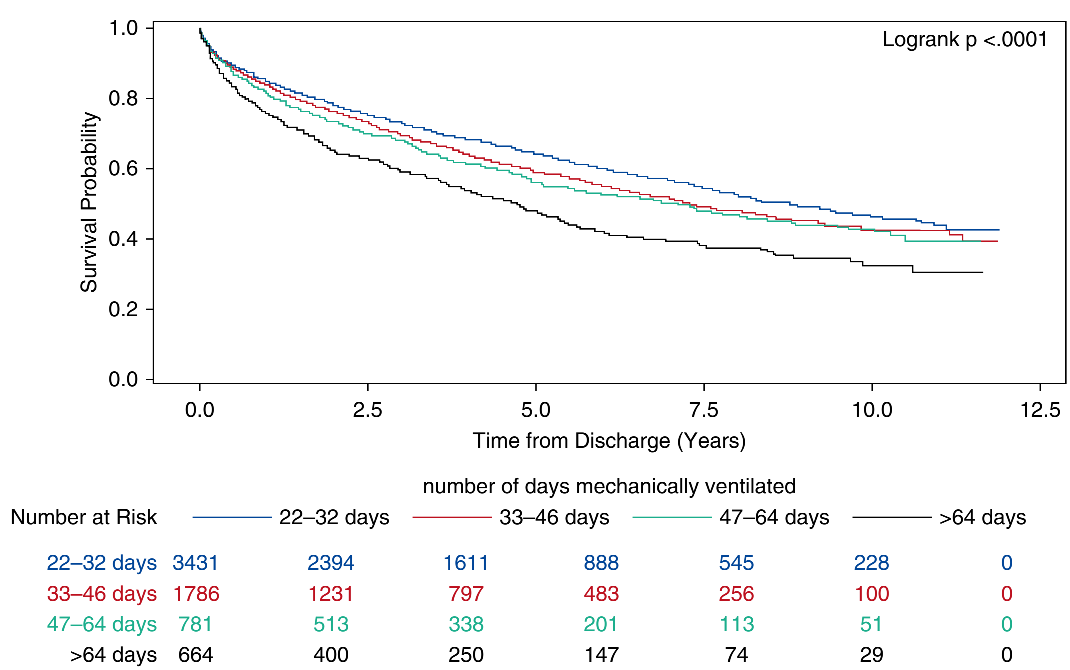

Figure 2. Kaplan-Meier estimates of survival among patients on prolonged mechanical ventilation stratified by duration of mechanical ventilation. Numbers below the graph indicate the number of individuals at risk at each time point.

Table 2. Health care utilization after discharge according to duration of mechanical ventilation

	Ventilated ⩽21 Days % (*n* = *146,116*)	Ventilated >21 Days % (*n* = *6,662*)	Adjusted Odds Ratio* (Non-PMV Reference Group)
Hospital readmission			
6 mo	28.7	36.1	1.19 (1.12–1.25)
1 yr	37.8	47.2	1.20 (1.14–1.26)
Overall	65.0	71.7	1.28 (1.21–1.36)
Days in hospital as a proportion of follow-up†			
Mean (SD)	5.0 (11.2)	7.8 (15.3)	
Median (IQR)	1.3 (0.4–4.1)	2.1 (0.7–6.8)	
Admission to high-level ICU‡			
6 mo	6.3	11.5	1.53 (1.41–1.67)
1 yr	9.0	15.8	1.49 (1.38–1.60)
Overall	20.9	31.3	1.47 (1.39–1.56)
Readmission—any ICU			
6 mo	8.1	14.1	1.58 (1.46–1.70)
1 yr	11.6	19.0	1.49 (1.39–1.60)
Overall	26.6	37.1	1.49 (1.41–1.60)
Emergency department visits			
6 mo	45.4	45.9	1.10 (1.04–1.16)
1 yr	56.7	58.7	1.11 (1.05–1.17)
Overall	83.4	81.4	1.08 (1.01–1.16)

Definition of abbreviations: ICU = intensive care unit; IQR = interquartile range; PMV = prolonged mechanical ventilation.
*All models adjusted for age, sex, Charlson comorbidities, most responsible hospital diagnosis, discharge location, income, and urban/rural area of residence; all odds ratios significant at $P < 0.0001$.
†Restricted to patients who were readmitted to hospital.
‡Excludes ICU stays involving only an admission to coronary care unit, cardiac surgery ICU, or step-down unit.

Factors Associated with Mortality after PMV

We identified age, male sex, residence in a lower-income neighborhood, discharge to a complex continuing care or long-term care facility, higher Charlson comorbidity score, a respiratory- or cancer-related diagnosis, and use of a percutaneous feeding tube during the index admission to be predictors of postdischarge mortality in patients on PMV (Table 4).

Discussion

In this population-based study, we found that patients on PMV comprise only 5% of all mechanically ventilated patients, yet experience higher rates of mortality, hospital and ICU readmission, ED visits, and health care costs in the immediate period and years after hospital discharge, with increasing duration of mechanical ventilation associated with higher mortality rates and health care utilization.

We found that a significant proportion of patients on PMV (67%) died during the 11-year study period, with most (42.5%) dying before hospital discharge. These observations align with prior work (8, 10, 14, 15, 30, 31). Our finding, that a substantial proportion of patients not on PMV also died during follow-up, underscores the vulnerability of patients after an episode of critical illness requiring mechanical ventilation. Coupled with the significantly higher

Table 3. Median health care costs of patients surviving to hospital discharge according to duration of mechanical duration*

Median (IQR) Costs	Ventilated ⩽21 Days (*n* = 78,984)	Ventilated >21 Days (*n* = 3,891)	*P* Value
Total health care cost			
Year before index admission	\$9,519 (\$5,536–\$16,290)	\$8,990 (\$5,493–\$15,686)	0.02
Index admission	\$32,994 (21,308–\$54,736)	\$166,262 (\$118,467–\$246,454)	<0.0001
Year after index admission	\$13,005 (\$5,922–\$35,705)	\$42,784 (\$17,630–\$95,888)	<0.0001
Select heath sector cost (year after index admission)			
In-patient costs	\$2,768 (\$1,579–\$8,047)	\$3,469 (\$1,572–\$13,936)	<0.0001
Physician (fee for service visits)	\$2,078 (\$1,028–\$4,103)	\$3,685 (\$1,856–\$6,949)	<0.0001
Home care	\$690 (\$0–\$2,258)	\$1,519 (\$0–\$5,140)	<0.0001
Emergency department visits	\$183 (\$0–\$822)	\$256 (\$0–\$994)	<0.0001

Definition of abbreviation: IQR = interquartile range.
*Cost data–restricted to patients discharged after 2006.

Table 4. Multivariable analyses of factors associated with death after hospital among the 6,662 patients who received prolonged mechanical ventilation

	Hazard Ratio for Death (95% CI)
Sex (ref: men), women	0.90 (0.83–0.97)
Age (ref: 18–59 yr), yr	
60–69	1.57 (1.41–1.74)
70–79	2.18 (1.97–2.41)
⩾80	2.97 (2.61–3.39)
Comorbidity score (ref: 0)	
1–2	1.58 (1.39–1.80)
⩾3	2.22 (1.94–2.54)
Tracheostomy	1.09 (0.97–1.22)
Percutaneous/surgical feeding tube	1.11 (1.02–1.20)
Pulmonary artery catheter	0.88 (0.79–0.97)
Dialysis	0.87 (0.79–0.96)
Select most responsible diagnoses (ref: myocardial infarction and ischemic diseases)	
Cerebrovascular disease	0.80 (0.63–1.02)
Respiratory failure	1.29 (1.06–1.58)
Chronic obstructive pulmonary disease	1.51 (1.18–1.93)
Pneumonia	1.10 (0.85–1.42)
Other respiratory diseases	1.14 (0.93–1.40)
Trauma	0.69 (0.56–0.86)
Cancer/neoplasm	1.62 (1.31–2.00)
Septicemia	0.91 (0.72–1.15)
Area of residence (ref: urban), rural	1.04 (0.92–1.18)
Income quintile (ref: quintile 5)	
1 (lowest)	1.13 (1.01–1.27)
2	1.01 (0.89–1.14)
3	1.01 (0.89–1.15)
4	1.01 (0.89–1.15)
Discharge disposition (ref: home)	
Home with support	1.02 (0.90–1.16)
Complex continuing care	1.60 (1.41–1.82)
Rehabilitative care	0.96 (0.85–1.09)
Long-term care	1.44 (1.17–1.76)
Acute care	1.74 (1.34–2.26)
Cumulative total ICU days	1.00 (1.00–1.00)
Cumulative number of days mechanically ventilated > 21	1.00 (1.00–1.00)
Hospital length of stay	1.00 (1.00–1.00)

Definition of abbreviations: CI = confidence interval; ICU = intensive care unit.

number of patients on PMV that are discharged to other care settings, these findings also highlight the continuing care needs of this patient population. Moreover, our results should help clinicians explain to patients and their substitute decision makers the implications of PMV on subsequent short- and long-term prognosis, and provide opportunities for targeted interventions and broader stakeholder engagement.

Our study is the first to report on differences in the long-term use of health services after hospital discharge for patients on PMV compared with patients not on PMV. The finding of higher hospital readmission rates among PMV survivors compared with patients not on PMV is consistent with previous follow-up studies of survivors of prolonged critical illness due to sepsis (32) and the acute respiratory distress syndrome (33). Plausible explanations for these higher rates of subsequent health care utilization after prolonged critical illness include overall functional decline and critical illness polyneuropathy, exacerbations of existing diseases, and new onset of chronic comorbidities among survivors of critical illness (34, 35).

We also observed that patients on PMV account for a disproportionate amount of costs associated with care during the index admission compared with patients not on PMV. We extended prior work by demonstrating that PMV continues to be associated with increased total health care costs in the year after discharge, despite similar total health care costs in the year before ICU admission for both cohorts. Although the drivers of higher health care costs among survivors of PMV are not fully understood, these findings suggest that efforts focused on preventing PMV might result not only in improved patient outcomes, but also lower costs to the health system.

Strengths and Limitations

The comprehensive capture of all critically ill patients in the province of Ontario using provincial and national databases over 11 years, and the ability to report on a broad range of outcomes, health care services, and costs during an extensive follow-up period, are strengths of our study.

Our study also has several limitations. Our definition of PMV likely identified the most resource-intensive patients (4). Consequently, our findings may not be generalizable to other practice settings, especially those with more weaning and step-down units. It is also plausible that the associations between PMV and long-term outcomes may result from residual confounding due to unmeasured factors.

Our study lacks data to characterize specific details of health complications after discharge; however, others have identified neurological, functional, and cognitive compromise in patients after critical illness (30, 36). Finally, the potential impact of differences in patient and family preferences for receiving PMV care are unknown, and represent important considerations for future research.

Conclusions

The high mortality and substantial rate of health care utilization associated with PMV underscore the importance of additional research to identify which patients will benefit from this therapy. Our findings should also provide important information to help clinicians discuss the long-term prognosis, benefits, and consequences of PMV with patients and their substitute decision makers. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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