Association of Extracorporeal Membrane Oxygenation With New Mental Health Diagnoses in Adult Survivors of Critical Illness

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IMPORTANCE Extracorporeal membrane oxygenation (ECMO) is used as temporary cardiorespiratory support in critically ill patients, but little is known regarding long-term psychiatric sequelae among survivors after ECMO.

OBJECTIVE To investigate the association between ECMO survivorship and postdischarge mental health diagnoses among adult survivors of critical illness.

DESIGN, SETTING, AND PARTICIPANTS Population-based retrospective cohort study in Ontario, Canada, from April 1, 2010, through March 31, 2020. Adult patients (N=4462; age ≥18 years) admitted to the intensive care unit (ICU), and surviving to hospital discharge were included.

EXPOSURES Receipt of ECMO.

MAIN OUTCOMES AND MEASURES The primary outcome was a new mental health diagnosis (a composite of mood disorders, anxiety disorders, posttraumatic stress disorder; schizophrenia, other psychotic disorders; other mental health disorders; and social problems) following discharge. There were 8 secondary outcomes including incidence of substance misuse, deliberate self-harm, death by suicide, and individual components of the composite primary outcome. Patients were compared with ICU survivors not receiving ECMO using overlap propensity score-weighted cause-specific proportional hazard models.

RESULTS Among 642 survivors who received ECMO (mean age, 50.7 years; 40.7% female), median length of follow-up was 730 days; among 3820 matched ICU survivors who did not receive ECMO (mean age, 51.0 years; 40.0% female), median length of follow-up was 1390 days. Incidence of new mental health conditions among survivors who received ECMO was 22.1 per 100-person years (95% confidence interval [CI] 19.5-25.1), and 14.5 per 100-person years (95% CI, 13.8-15.2) among non-ECMO ICU survivors (absolute rate difference of 7.6 per 100-person years [95% CI, 4.7-10.5]). Following propensity weighting, ECMO survivorship was significantly associated with an increased risk of new mental health diagnosis (hazard ratio [HR] 1.24 [95% CI, 1.01-1.52]). There were no significant differences between survivors who received ECMO vs ICU survivors who did not receive ECMO in substance misuse (1.6 [95% CI, 1.1 to 2.4] per 100 person-years vs 1.4 [95% CI, 1.2 to 1.6] per 100 person-years; absolute rate difference, 0.2 per 100 person-years [95% CI, −0.4 to 0.8]; HR, 0.86 [95% CI, 0.48 to 1.53]) or deliberate self-harm (0.4 [95% CI, 0.2 to 0.9] per 100 person-years vs 0.3 [95% CI, 0.2 to 0.3] per 100 person-years; absolute rate difference, 0.1 per 100 person-years [95% CI, −0.2 to 0.4]; HR, 0.68 [95% CI, 0.21 to 2.23]). There were fewer than 5 total cases of death by suicide in the entire cohort.

CONCLUSIONS AND RELEVANCE Among adult survivors of critical illness, receipt of ECMO, compared with ICU hospitalization without ECMO, was significantly associated with a modestly increased risk of new mental health diagnosis or social problem diagnosis after discharge. Further research is necessary to elucidate the potential mechanisms underlying this relationship.
Extracorporeal membrane oxygenation (ECMO) provides temporary respiratory and/or cardiac support to critically ill patients and is often considered when initial conventional treatment has failed. Existing observational and randomized evidence have supported the use of ECMO in reducing short-term mortality in refractory respiratory failure, cardiogenic shock, and cardiac arrest. Furthermore, while ECMO is associated with substantial inpatient resources and costs, a significant number of survivors after ECMO are alive up to 5 years postdischarge, with relatively minimal resource utilization. The use of ECMO has grown worldwide, particularly in the context of the COVID-19 pandemic, where ECMO has been used for refractory respiratory failure in cases of severe COVID-19.

Despite collective public optimism surrounding the use of ECMO in refractory cases of critical illness, much less is understood about the long-term morbidity associated with this therapy, particularly as it pertains to mental health outcomes. Survivors of critical illness are known to have substantial physical morbidity, and existing data demonstrate that these patients are at risk of downstream psychiatric morbidity, including higher incidence of mental health diagnoses, psychoactive medication use, substance misuse, self-harm, and suicide. Given the severity of illness found among patients receiving ECMO, its invasive nature, as well as the prolonged duration of therapy and recovery that is often required among those who survive, it was hypothesized that survivors after ECMO may be at even greater risk of downstream mental health morbidity than other survivors of critical illness. This study investigated the incidence of long-term mental health morbidity associated with ECMO survivorship, using population-based data from Ontario, Canada, and compared this with non-ECMO ICU survivorship.

Methods

Data Sources and Setting
We conducted a population-level cohort study using health administrative databases from Ontario, Canada (population 14.6 million). Within Ontario’s single-payer health care system, all publicly funded health care services, and physician, hospital, and demographic information for residents are recorded in administrative databases (ICES). Studies conducted at ICES using administrative data fall under section 45 of the Personal Health Information Protection Act of Ontario and do not require research ethics board approval. Data are collected without a requirement for individual patient consent. We linked 10 databases at ICES (eTable 1 in the Supplement) at the individual patient level, from April 1, 2010, through March 31, 2020 (inclusive). Patients are linked across provincial databases using their Ontario Health Insurance Plan (OHIP) number, which is unique to each citizen in Ontario. Data contained in ICES are full and complete, with the exception of emigration from Ontario, which represents approximately 0.5% of patients per year.

We registered our protocol with the Center for Open Science (https://osf.io/vn5bg).

Outcomes
The primary outcome was incidence of any new mental health diagnosis postdischarge, occurring prior to the end of the study period, the patient’s death, or emigration from Ontario. New mental health diagnoses were determined using the ICES Mental Health and Addictions Scorecard, as used previously, and include any of the following: mood or anxiety disorders (eg, depression, anxiety), posttraumatic stress disorder (PTSD), schizophrenia or psychotic disorders, other mental health diagnoses (including adjustment reaction, reactive depression, anxiety neurosis, hysteria, neurasthenia, obsessive-compulsive neurosis, personality disorders, sexual deviations, and psychosomatic illness), or social problems (including economic problems, marital difficulties, family disruption or divorce, parent-child problems, problems with aged parents, educational problems, social maladjustment, occupational problems, and legal problems). Diagnoses could be noted from either inpatient hospital admissions or outpatient encounters (including primary care or emergency department visits).

Key Points

**Question** Is the use of extracorporeal membrane oxygenation (ECMO) associated with postdischarge psychiatric morbidity among adult survivors of critical illness?

**Findings** In this population-based retrospective cohort study of 4462 participants, exposure to ECMO, compared with intensive care unit hospitalization without ECMO, was significantly associated with a modestly increased risk of new mental health diagnoses or social problems after discharge (hazard ratio, 1.24).

**Meaning** Among adult survivors of critical illness, receipt of ECMO was significantly associated with a modestly increased risk of new mental health diagnoses or social problems, but further research on the mechanisms underlying this relationship is needed.

**Patients** We included consecutive adult patients (≥18 years of age), with an index intensive care unit (ICU) discharge in Ontario from April 1, 2010, through March 31, 2020 (inclusive), who received ECMO and who survived to hospital discharge. We identified ECMO use by the presence of an inpatient ECMO intervention code in the Discharge Abstract Database and a billing code for ECMO in the OHIP Claims Database, as performed previously (eTable 2 in the Supplement). We matched these patients with those admitted to an ICU setting during the study period but who never received ECMO and survived to hospital discharge. For control participants with multiple ICU admissions, we randomly selected one for inclusion as the index admission. We excluded patients admitted to the ICU due to deliberate self-harm, as these patients are at high risk for future self-harm and suicide. We captured history of preexisting mental health diagnoses in the 5 years prior to the index admission through the use of International Statistical Classification of Diseases, Tenth Revision (ICD-10) codes and any outpatient mental health visits with a primary care physician or psychiatrist in the previous year.
Secondary outcomes included substance misuse (secondary to alcohol or drug dependence), the composite of any new mental health diagnosis or substance misuse, death by suicide, and hospital visit for deliberate self-harm.\textsuperscript{15} We also separately evaluated each of the 4 components of the primary outcome (mood disorder/anxiety disorder/PTSD; schizophrenia/psychotic disorder; other mental health diagnoses; and social problems) as secondary outcomes. As per ICES regulations, cell sizes with 5 patients or less were suppressed to protect patient confidentiality.

**Statistical Analyses**
We present data as mean (SD) or median (IQR) values. Since ECMO is used only in select institutions in Ontario, and there are relatively stringent selection criteria for receiving ECMO, we created an initial matched cohort of 6 non-ECMO ICU controls for every single ECMO case. We performed greedy matching using the index admission institution, age (5-year groups), and the Charlson Comorbidity Index (CCI).\textsuperscript{18} To compare crude mental health outcome rates, we reported the incidence proportion and rate per 100 person-years with accompanying 95% CIs.

To estimate the association between ECMO survivorship and postdischarge mental health diagnoses, suicide, and self-harm, we followed existing recommendations for causal inference in critical care\textsuperscript{19,20} and analyzed ECMO survivorship and non-ECMO ICU survivorship using overlap propensity-score weighting.\textsuperscript{15} The overlap weights technique was used to assign less weight to those with outlier propensity scores and more weight to those with propensity scores close to 0.5. This technique improves covariate balance and overlap of probabilities in creating propensity scores, as compared with other approaches.\textsuperscript{21} Overlap weighting does not exclude any potential study participants and is not affected by extreme outliers dominating the analyses, which can occur with traditional propensity-score matching or inverse probability-treatment weighting.

As recommended, we identified covariates a priori, based on 2 factors: (1) existing literature and hypotheses about potential for confounding; and (2) their ability to influence the provision or timing of ECMO (as determined in existing randomized trials).\textsuperscript{4,7} We included the following preadmission confounders: age, sex, number of encounters (hospital admissions, outpatient psychiatry visits, outpatient physician visits) in the past year, previous outpatient mental health or substance misuse visits to primary care clinicians, income quintile, rural residency, CCI score, specific comorbidities that might influence ECMO candidacy (ie, malignancy, chronic kidney disease, chronic obstructive pulmonary disease, preexisting mental health disorders, and previous history of self-harm). We also included confounders arising during admission: year of admission, institution, severity of illness (assessed using the Multiple Organ Dysfunction Score [MODS]) at the time of ICU admission, use of invasive mechanical ventilation, kidney replacement therapy, tracheostomy, ICU length of stay, hospital length of stay, and discharge disposition. Based on previous work, we anticipated less than 1% of neighborhood income quintile and rurality, and less than 3% of MODS and ICU length of stay to be missing at random. For the former, we imputed the mode, and for the latter, we imputed the age and index ECMO status group mean.

We compared cohorts before and after overlap weights for balance by using weighted standardized differences. We fit an overlap-weighted cause-specific Cox proportional hazards model with robust standard errors to examine ECMO survivorship vs non-ECMO ICU survivorship with the study outcomes, while accounting for mortality as a competing risk. We tested the proportionality assumption by including a statistical interaction between ECMO survivorship status and follow-up time as a linear term. The Wald $\chi^2$ tests yielded a $P$ value of greater than 0.1. We interpreted this as evidence of minimal violation of the proportionality assumption and did not carry forward the statistical interaction and compute time-dependent hazard ratios (HRs). Patients were censored from the analysis at the first instance of any of the following: death, loss of Ontario health insurance status, or the end of the study period (March 31, 2020). We used overlap-weighted cumulative incidence function (CIF) curves to plot the weighted CIF of new mental health diagnoses in the follow-up, and used the CIF equality test to see if the curves were statistically different. To estimate potential bias related to unmeasured confounders, we computed an $E$ value.\textsuperscript{22}

To identify prognostic factors associated with new post-critical illness mental health outcomes, we generated separate cause-specific Cox proportional hazards regression models using the ECMO survivor cohort. We followed the PROGRESS guidelines\textsuperscript{23,24} and recommendations for development of prognostic models in critical care.\textsuperscript{25} These guidelines recommend a clinically hypothesis-driven approach for a priori selection of all model variables, as opposed to bivariant association testing methods.

**Sensitivity Analyses**
We preplanned sensitivity analyses to further evaluate potential confounding of our causal inference analyses by specific variables.

First, we hypothesized that access to in-person clinical visits with physicians (including primary care physicians and psychiatrists) would be strongly affected by restrictions instituted during the COVID-19 pandemic, and this had the potential to influence our primary outcome (new mental health diagnosis). As such, we conducted a sensitivity analysis excluding survivors after ECMO from our cohort who were discharged from hospital on January 1, 2020, or later, and we terminated the follow-up window on December 31, 2019. Second, while the ICES databases have strong validity in identifying new mental health diagnoses, they may not as easily identify worsening or uncompensated mental illness among patients with preexisting mental health diagnoses. Further, patients with preexisting mental health follow-up may be more likely to be diagnosed with new mental illness after ICU admission, and this could represent a source of bias. Therefore, we conducted a sensitivity analysis following exclusion of patients with any mental health diagnoses in the previous 5 years. In addition, despite the use of overlap weights, we thought that the non-ECMO ICU cohort might include those with lower severity of illness, and so we performed a post hoc sensitivity
analysis excluding control patients who did not receive invasive mechanical ventilation. We conducted all statistical analyses using SAS Enterprise Guide 7.1 (SAS Institute Inc). A P value of less than .05 (2-sided) was deemed to be statistically significant. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory.

### Results

#### Cohort Construction and Categorization

A total of 1054 adult patients received ECMO in Ontario during the study period. Of these, 412 were excluded (406 [38.5%] died prior to hospital discharge, and 6 of those who survived died prior to hospital discharge, and 6 of those who survived...
Received ECMO due to deliberate self-harm), and 642 patients were included in the analyses. These patients were initially matched 1:6 to 3830 non-ECMO ICU survivors on the basis of institution, age, and CCI score. Median duration of follow-up was 730 days (IQR, 289-1437) among survivors after ECMO, and 1390 days (IQR, 572-2408) among non-ECMO ICU survivors.

Baseline Characteristics and ICU Interventions

Baseline characteristics of survivors after ECMO, along with matched controls (prior and after overlap weight application) are shown in Table 1. Among ECMO patients, the mean (SD) age was 50.7 (14.8) years, 40.7% were women, and 467 (72.7%) had a CCI of 2 or less. Among non-ECMO ICU survivors, the mean age was 51.0 (15.0) years, 39.9% were women, and 2798 (73.1%) had a CCI of 2 or less. In terms of preexisting psychiatric history, 300 (46.7%) survivors after ECMO, and 1850 (48.3%) of non-ECMO ICU survivors had at least 1 primary care or psychiatry visit for mental health in the preceding 5 years.

Index admission characteristics of survivors after ECMO, along with matched controls (prior and after overlap weight application) are depicted in Table 2. The primary indication for ECMO was respiratory failure, occurring in 400 patients (62.3%). The mean MODS was 5.6 (SD, 3.3), with 152 patients (23.7%) receiving kidney replacement therapy, and 221 (34.4%) receiving tracheostomy. Median hospital length of stay was 41 days (IQR, 23-70), and 210 patients (32.7%) were discharged to a long-term care facility after their acute care hospitalization. Categorization by year of admission is shown in eTable 3 in the Supplement.

Association of ECMO With Mental Health Outcomes

Balance after overlap weighting between ICU survivors who were and were not exposed to ECMO are shown in Table 1, Table 2. Index Admission Characteristics of Survivors After ECMO Compared With Control Non-ECMO ICU Survivors, and Comparison of Covariate Differences After Applying Overlap Weights

<table>
<thead>
<tr>
<th>Variable</th>
<th>Prior to overlap weights</th>
<th>After application of overlap weights, %a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year of admissionb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010-2011</td>
<td>7 (1.1)</td>
<td>373 (9.7)</td>
</tr>
<tr>
<td>2011-2012</td>
<td>9 (1.4)</td>
<td>308 (8.0)</td>
</tr>
<tr>
<td>2012-2013</td>
<td>26 (4.0)</td>
<td>355 (9.3)</td>
</tr>
<tr>
<td>2013-2014</td>
<td>45 (7.0)</td>
<td>415 (10.8)</td>
</tr>
<tr>
<td>2014-2015</td>
<td>57 (8.9)</td>
<td>345 (9.0)</td>
</tr>
<tr>
<td>2015-2016</td>
<td>58 (9.0)</td>
<td>388 (10.1)</td>
</tr>
<tr>
<td>2016-2017</td>
<td>74 (11.5)</td>
<td>383 (10.0)</td>
</tr>
<tr>
<td>2017-2018</td>
<td>108 (16.8)</td>
<td>416 (10.9)</td>
</tr>
<tr>
<td>2018-2019</td>
<td>114 (17.8)</td>
<td>385 (10.1)</td>
</tr>
<tr>
<td>2019-2020</td>
<td>144 (22.4)</td>
<td>462 (12.1)</td>
</tr>
<tr>
<td>Indication for ECMOc</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>400 (62.3)</td>
<td></td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>114 (17.8)</td>
<td></td>
</tr>
<tr>
<td>Unknownd</td>
<td>128 (19.9)</td>
<td></td>
</tr>
<tr>
<td>Multiple Organ Dysfunction Score, mean (SD)</td>
<td>5.6 (3.3)</td>
<td>2.5 (2.7)</td>
</tr>
<tr>
<td>Invasive mechanical ventilation</td>
<td>627 (97.7)</td>
<td>1513 (39.5)</td>
</tr>
<tr>
<td>Kidney replacement therapy</td>
<td>152 (23.7)</td>
<td>219 (5.7)</td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>221 (34.4)</td>
<td>116 (3.0)</td>
</tr>
<tr>
<td>ICU length of stay, mean (SD), d</td>
<td>11.4 (18.1)</td>
<td>4.1 (5.3)</td>
</tr>
<tr>
<td>Hospital length of stay, mean (SD), d</td>
<td>55.5 (49.9)</td>
<td>15.3 (25.4)</td>
</tr>
<tr>
<td>Hospital length of stay, median (IQR), d</td>
<td>41 (23-70)</td>
<td>6 (6-14)</td>
</tr>
<tr>
<td>Hospital length of stay, d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7</td>
<td>1286 (33.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>7-14</td>
<td>1520 (39.7)</td>
<td>44 (6.9)</td>
</tr>
<tr>
<td>&gt;14</td>
<td>1024 (26.7)</td>
<td>598 (93.1)</td>
</tr>
<tr>
<td>Discharge disposition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home, without home care</td>
<td>192 (29.9)</td>
<td>2412 (63.0)</td>
</tr>
<tr>
<td>Home, with home care</td>
<td>240 (37.4)</td>
<td>1039 (27.1)</td>
</tr>
<tr>
<td>Long-term care facility</td>
<td>210 (32.7)</td>
<td>379 (9.9)</td>
</tr>
<tr>
<td>Duration of follow-up, median (IQR), d *</td>
<td>730 (289-1437)</td>
<td>1390 (572-2408)</td>
</tr>
</tbody>
</table>

Abbreviations: ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.

a Weighted absolute standard difference was 0.00 for all variables; therefore, values for each variable were the same for the survivors after ECMO group and the non-ECMO ICU survivors group.
b Start and end points for each year are April 1 of the earlier year through March 31 of the later year.
c Variable not used in overlap weighting.
d Refers to ECMO cases where indication could not be determined through diagnostic coding.

* Patients were censored at the time of death, loss of Ontario health insurance status, or March 31, 2020, (whichever came first).
Table 3. Incidence Rates, Absolute Rate Differences, and Weighted Hazard Ratios Comparing Mental Health Outcomes Among Survivors After ECMO With Matched Non-ECMO Intensive Care Unit Survivors

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cases per 100 person-years (95% CI)</th>
<th>Incidence rate difference*</th>
<th>Weighted hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Survivors after ECMO (n=642)</td>
<td>Non-ECMO ICU survivors (n=3830)</td>
<td></td>
</tr>
<tr>
<td>Any mental health condition</td>
<td>22.1 (19.5 to 25.1)</td>
<td>14.5 (13.8 to 15.2)</td>
<td>7.6 (4.7 to 10.5)</td>
</tr>
<tr>
<td>Any mental health or substance misuse condition</td>
<td>23.6 (20.8 to 26.7)</td>
<td>15.4 (14.6 to 16.2)</td>
<td>8.2 (5.2 to 11.2)</td>
</tr>
<tr>
<td>Mood disorder or anxiety disorder or PTSD</td>
<td>18.0 (15.7 to 20.7)</td>
<td>12.1 (11.5 to 12.7)</td>
<td>5.9 (3.3 to 8.5)</td>
</tr>
<tr>
<td>Schizophrenia or psychotic disorder</td>
<td>0.4 (0.2 to 0.9)</td>
<td>0.5 (0.4 to 0.6)</td>
<td>−0.1 (−0.4 to 0.6)</td>
</tr>
<tr>
<td>Other mental health diagnosesb</td>
<td>4.7 (3.7 to 5.9)</td>
<td>2.7 (2.4 to 2.9)</td>
<td>2.0 (0.9 to 3.1)</td>
</tr>
<tr>
<td>Social problemsc</td>
<td>0.8 (0.5 to 1.4)</td>
<td>0.7 (0.6 to 0.9)</td>
<td>0.1 (−0.4 to 0.6)</td>
</tr>
<tr>
<td>Substance misuse</td>
<td>1.6 (1.1 to 2.4)</td>
<td>1.4 (1.2 to 1.6)</td>
<td>0.2 (−0.4 to 0.8)</td>
</tr>
<tr>
<td>Deliberate self-harm</td>
<td>0.4 (0.2 to 0.9)</td>
<td>0.3 (0.2 to 0.3)</td>
<td>0.1 (−0.2 to 0.4)</td>
</tr>
</tbody>
</table>

Abbreviations: ECMO, extracorporeal membrane oxygenation; PTSD, posttraumatic stress disorder.
* Incidence rates are not adjusted.
** Includes adjustment reaction, reactive depression, anxiety neurosis, hysteria, neurasthenia, obsessive-compulsive neurosis, personality disorders, sexual deviations, and psychosomatic illness.
* Includes economic problems, marital difficulties, family disruption/divorce, parent-child problems, problems with aged parents, educational problems, social maladjustment, occupational problems, and legal problems.

Table 2, and eFigure in the Supplement. Weighted standard difference across all covariables was 0.00. Incidence rates and adjusted HRs showing the association between ECMO survivorship and the outcomes of interest (using non-ECMO ICU survivors as the reference) and accounting for competing risk of death are shown in Table 3, with weighted CIF curves displayed in the Figure. Raw counts of the outcomes prior to overlap weights are shown in eTable 4 in the Supplement.

Primary Outcome
With regard to the primary outcome, 236 (36.8%) survivors after ECMO, and 1565 (40.9%) of non-ECMO ICU survivors were diagnosed with a new mental health condition following discharge. The incidence rate was 22.1 per 100 person-years (95% CI, 19.5-25.1) among survivors after ECMO, compared with 14.5 per 100 person-years (95% CI, 13.8 to 15.2) among non-ECMO ICU survivors (absolute rate difference, 7.6 per 100-person-years [95% CI, 4.7 to 10.5]). Following propensity score weighting, survivors after ECMO had significantly higher associations than non-ECMO ICU survivors (absolute rate difference, 7.6 per 100-person-years [95% CI, 13.8 to 15.2] among survivors after ECMO, compared with 15.65 per 100 person-years [95% CI, 19.5-25.1] among non-ECMO ICU survivors, p<0.05).

Secondary Outcomes
Findings for individual components of the primary composite outcome are presented in Table 3. Additionally, ECMO survivorship was not significantly associated with postdischarge substance misuse (HR, 0.86 [95% CI, 0.48 to 1.53]; absolute rate difference, 0.2 per 100-person years [95% CI, −0.4 to 0.8]) or deliberate self-harm (HR, 0.68 [95% CI, 0.21 to 2.23]; absolute rate difference of 0.1 per 100-person years [95% CI, −0.2 to 0.4]). There were less than 5 cases of suicide total across the entire cohort.

Factors Associated With New Mental Health Diagnoses Among Survivors After ECMO
Among the 642 ECMO patients who survived to discharge, prognostic factors associated with incidence of new mental health diagnoses are presented in Table 4. The only 2 prognostic factors found to be significantly associated with new mental health diagnoses were preexisting mental health diagnoses (HR, 2.39 [95% CI, 1.78 to 3.20]) and having had an outpatient psychiatry visit in the year prior to the index admission (1.82 [95% CI, 1.25 to 2.65]).

Discussion
Among adult survivors of critical illness, receipt of ECMO, compared with ICU hospitalization without ECMO, was significantly associated with a modestly increased risk of new mental health diagnosis or social problem diagnosis after discharge. However, the mechanisms underlying this relationship are unclear.

Key stakeholders in ECMO research have identified long-term sequelae associated with ECMO survivorship to be a priority, but to date, little evidence exists. To that end, the results of this current study show that diagnoses of new mental health conditions were common among survivors after ECMO. The most frequent diagnoses were related to depression, anxiety, and traumatic disorders, which was unsurprising given the invasive nature of critical care. Such diagnoses are the most common among all adult survivors of critical illness. In addition, this work found that ECMO survivorship was significantly associated with an increased risk of postdischarge mental health diagnoses. This relationship appears to be potentially greater than what is seen among non-ECMO ICU survivors, a population that has been quite vulnerable to psychiatric morbidity. Particularly in the context of the ongoing COVID-19 pandemic and an associated increase in the use of ECMO worldwide, this work provides important information for clinicians with regard to psychological support for survivors following discharge. That said, while there was an
association between ECMO survivorship and downstream psychiatric morbidity, the results suggest that the associated increased risk was likely modest. It was also found that there was no association with substance misuse or deliberate self-harm, and suicide was rare. These relatively small absolute differences must be considered in the context of randomized evidence suggesting improved survival among patients receiving ECMO for refractory respiratory and cardiac failure.\textsuperscript{4,5,7} As such, while the findings of this current study should not preclude selection of patients for receipt of ECMO, they serve to identify a potential group of vulnerable patients that may more commonly experience psychiatric morbidity, and thus require additional downstream support.

While the present study draws attention to a potential relationship, further research is needed to provide insights into the mechanisms that may potentially link ECMO survivorship with psychiatric morbidity. In the prognostic model, the only 2 factors that were found to be associated with future mental health diagnoses were preexisting mental health diagnoses and previous outpatient psychiatric visits. However, the prognostic association of these factors may be related to confounding, as such patients are more likely to

All P values were calculated using the cumulative incidence function equality test. ECMO indicates extracorporeal membrane oxygenation; ICU, intensive care unit.
have existing contact with a mental health clinician and thus receive a mental health diagnosis. There are a number of theoretical associations between ECMO survivorship and downstream mental health morbidity. Although data are limited, existing work on functional capacity and health-related quality of life among survivors after ECMO shows that these patients experience substantial physical limitations following discharge, similar to studies of non-ECMO adult survivors of critical illness.30 Furthermore, existing data have linked severity and course of ICU admission with mental health morbidity.15,27,28 This relationship is the most generalizable to all populations.

**Limitations**

This study has several limitations. First, this work is observational, and thus cannot confirm a causal relationship between ECMO provision and downstream mental health morbidity. Despite statistical adjustment, the possibility of residual confounding remains. Second, while many covariates were measured, the granularity of the available data was limited (eg, ECMO indications and configurations), suggesting the possible influence of unmeasured confounding. There was also imprecision in the findings. To that end, multiple sensitivity analyses were performed, and an $E$ value was calculated to provide insights into the reliability of our findings. Third, the outcomes were limited only to mental health diagnoses identified in visits with clinicians remunerated through the provincial health care system. Services privately paid for by patients would not have been captured. Similarly, the outcome of self-harm was only limited to events that would have required hospital attention. Fourth, while the included patients came from multiple centers, they exist within the same province and health care system, and thus these findings may not be generalizable to all populations.

**Conclusions**

Among adult survivors of critical illness, receipt of ECMO, compared with ICU hospitalization without ECMO, was significantly associated with a modestly increased risk of new mental health diagnosis or social problem diagnosis after discharge. Further research is necessary to elucidate the potential mechanisms underlying this relationship.
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Other - content expertise on intensive care unit (ICU) outcomes/mental health outcomes: Herridge.

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