

A population-based cohort study of readmissions following hypoxic ischemic brain injury

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12 designed the study. David Stock formulated the methodology and carried out the statistical
13 analyses. Vincy Chan and Binu Jacob drafted the manuscript, and all authors had significant
14 input into the editing and interpretation of data, and read and approved the final manuscript.
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3 **1 ABSTRACT**
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6 **2 Background:** Readmission to acute care is common and associated with indicators of
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8 **3** suboptimal care and health system inefficiencies. The objective of this study was to identify
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10 **4** independent predictors of readmission following survival of hypoxic-ischemic brain injury (HIBI).
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15 **6 Methods:** A population-based retrospective cohort study was conducted using Ontario's
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17 administrative health data. HIBI survivors age 20 years or older discharged from acute care
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19 between fiscal years 2002/03 and 2010/11 (N=593) were included. Multivariable negative
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21 binomial regression was used to identify independent predictors of both number of
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23 **9** readmissions and cumulative readmission duration during one-year post index discharge.
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30 **12 Results:** Almost 40% of HIBI patients were readmitted within one-year of index acute care
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32 discharge. Number of readmissions was associated with age (35-49 vs. 65-79 years RR: 0.57;
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34 95% CI: 0.38-0.85 and ≥80 vs. 65-79 years RR: 0.58; 95% CI: 0.34-0.97) and higher comorbidity
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36 score (ADG score >30 vs. < 10 RR: 1.60; 95% CI: 1.11-2.31). Duration of readmission was
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38 associated with increased index hospital length of stay (31-90 vs. ≥ 90 days RR: 4.17; 95% CI:
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40 1.38-12.64), prior health services use (minimal vs. very high RR: 0.15; 95% CI: 0.05-0.49), and
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42 discharge disposition (home vs. continuing care RR: 0.44; 95% CI: 0.21-0.91).
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45 **18**
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48 **19**
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50 **20 Interpretation:** This is the first population-wide study examining risk factors for readmission
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52 following HIBI. Findings indicate a high readmission rate in the first year, reflecting care gaps
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1 and system inefficiencies. This suggests that bolstered discharge and home care planning and
2 support are needed to address the specific needs of those living with HIBI.

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1 Introduction

2 Hypoxic ischemic brain injury (HIBI) is a non-traumatic brain injury (nTBI) that results from
3 sustained oxygen deprivation arising from ischemic (i.e., restricted blood flow) or
4 anoxic/hypoxic (i.e., no/low oxygen irrespective of ischemia) origins.^{1,2} The common causes of
5 HIBI are cardiac or respiratory arrest, near drowning, carbon monoxide poisoning, and
6 asphyxia.^{3,4} Previous research has shown that patients with HIBI place considerable burden on
7 the health system, with approximately one in two patients experiencing at least one alternate
8 level of care (ALC) day,⁵ a negative system level outcome that is costly for the health system
9 and patients waiting for appropriate care.

10 Readmission is an equally negative system level outcome that is costly to both the
11 patient and the health system.^{6,7} Between 2010-2011, 8.5% of Canadian patients were re-
12 hospitalized within 30-days, resulting in an estimated \$1.8 billion associated cost to the
13 healthcare system.⁸ Data on the brain injury population show that readmission rates among
14 patients with a traumatic brain injury (TBI) range from 16% to 29%,⁹⁻¹³ with acute care costs
15 accounting for 46% to 65% of care expenditures during the year post injury.¹⁴ The aggregate
16 first-year medical costs of TBI and nTBI patients were estimated at \$120.7 million and \$368.7
17 million respectively, within the Ontario-wide population discharged between 2004 and 2007.¹⁴
18 Factors associated with re-hospitalization among patients with TBI were age, injury severity,
19 injury while on active duty, more comorbidities, previous acute care stays, inpatient
20 rehabilitation length of stay (LOS), and acute care discharge functional status.^{13, 15-18} Discharge
21 to extended care facilities and inpatient rehabilitation facilities were also associated with 30-
22 day readmission rates in older trauma patients.¹⁹

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3 1 Most research on readmissions for brain injury-related events have focused on the TBI
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6 2 population, with many best-practice guidelines for the HIBI population modeled after those set
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8 3 for TBI. This is problematic, as the HIBI population is distinct and differs significantly in terms of
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10 4 their demographic, clinical and environmental profile.²⁰ Moreover, patients with HIBI
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12 5 experience less functional improvement^{21, 22} and greater psychosocial problems²² in the long
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14 6 term. It is currently unknown whether readmission rates and factors associated with
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16 7 readmission identified among the TBI population are common to those with HIBI. As such,
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18 8 planning and prevention of readmissions for HIBI using these data is vague and there is need for
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20 9 evidence on HIBI-specific predictors of acute care readmission.
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25 10 The objective of this study was to address this gap by identifying factors that predict the
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27 11 number, and cumulative duration, of acute care readmissions among survivors of HIBI.
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29 12 Understanding which factors predict readmissions can inform policy aimed at minimizing
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31 13 avoidable readmissions, and thereby support effective HIBI-specific health planning for
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33 14 Canadian survivors of these injuries.
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1 **Methods**

2 Study Design

3 A retrospective cohort study was conducted to analyze re-hospitalization rates among patients
4 with HIBI within one year of acute care discharge. Population-based administrative data on
5 acute care were extracted from the Canadian Institute of Health Information Discharge Abstract
6 Database (DAD), which contains demographic and clinical information on all hospital discharges
7 and deaths from all publicly funded hospitals in Ontario, Canada. Data in the DAD were
8 obtained through the Ontario Cancer Data Linkage Program (cd-link). The cd-link is an initiative
9 of the Ontario Institute for Cancer Research/Cancer Care Ontario Health Services Research
10 Program, whereby risk reduced coded data from the Institute for Clinical Evaluative Sciences
11 are provided directly to researchers with the protection of a comprehensive data use
12 agreement.

14 Setting and Patients

15 Patients with HIBI who were 20 years or older and discharged from acute care between
16 fiscal years 2002/03 and 2010/11 were identified from the DAD. Patients with HIBI were
17 identified using International Classification of Diseases Version 10 (ICD-10) diagnostic codes
18 G93.1 (anoxic brain damage) as the most responsible diagnosis for the acute care stay (MRDx)
19 or I46.0 (cardiac arrest with successful resuscitation), R09.0 (asphyxia), R09.2 (respiratory
20 arrest), T71 (asphyxiation), T75.1 (drowning and nonfatal submersion), G92 (toxic
21 encephalopathy), T58 (toxic effect of carbon monoxide), and T70.2 (other and unspecified
22 effects of high altitude) as the MRDx with G93.1 in any secondary diagnostic field.

1 *Outcomes*

2 The outcomes of interest were 1) number of acute care readmissions post index HIBI
3 acute care discharge and 2) cumulative readmission duration, within one-year of index acute
4 care discharge, defined as between 4 and 365 days (inclusive).

5 *Potential Predictors*

6 Potential demographic, clinical and health services predictors of readmissions within
7 one year were assessed. The demographic variables included age at admission, sex,
8 neighborhood income quintile and rurality, the latter two aggregated to the level of
9 dissemination area, the smallest divisible geographical Canadian census unit. The clinical and
10 acute care episode characteristics included fiscal year of acute care admission, special care
11 hours, index acute care LOS, index acute care number of alternate level of care (ALC) days –
12 days in which acute medical care is no longer required yet the patient still occupies an acute
13 care bed²³, presence of one or more psychological/behavioural conditions identified by a
14 Chapter 5 ICD-10 code in any of the index admission diagnostic fields, and discharge disposition
15 from index acute care admission. Comorbidity index was derived from a weighted sum of Johns
16 Hopkins Aggregated Diagnosis Groups (ADGs)²⁴ accumulated over the two years prior to
17 admission to the HIBI acute care episode. Healthcare utilization was measured using Adjusted
18 Clinical Groups (ACG) Resource Utilization Band (RUB) score.^{25, 26}

19 *Analyses*

20 Negative binomial count regression models were used to determine the independent
21 relative effects of predictors on 1) the number of readmissions and 2) the duration of
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1 readmissions. Due to over-dispersion (Pearson's chi-square test), a Poisson distribution was not
2 used. Visual inspection of predicted versus relative outcome frequencies indicated negligibly
3 improved fit with a zero-inflated model. Multiple individual models comprised of each potential
4 predictor and the outcome variable, were examined. Forward selection was used, where each
5 potential predictor was entered from order of most significant (based on the likelihood ratio
6 test from bivariable models) to least significant. Age and sex were forced into all models.
7 Potential predictors were not retained if the p-value was > 0.1 . Due to a high proportion of
8 patients who died after the index acute care event, an offset variable was used to adjust
9 person-time contribution.

11 Results

12 Between fiscal years 2002/03 and 2010/11, there were more than 2000 patients with a HIBI-
13 related acute care visit (76% with ICD-10 code G93.1 as an MRDx). Among patients who
14 survived their index acute care episode (N=593), 39.2% (n=233) were re-hospitalized within one
15 year of discharge, some of whom were readmitted more than once (average readmissions=
16 1.79 ± 1.31), resulting in 417 readmissions. Of the index acute care episode survivors, 29.3% died
17 within one year of discharge. The majority of readmissions had anoxic brain damage coded as
18 the MRDx (66.2%), followed by cardiac arrest (16.1%), contributing to 4,758 inpatient hospital
19 days (average duration of readmission stay= 20.42 ± 39.21 days) within 1-year of index acute care
20 discharge. Hospitalizations with an anoxic brain damage and "awaiting admission to adequate
21 facility elsewhere" (ICD-10:Z75.1) as the MRDx accounted for 13.6% and 8.20% of readmission
22 days, respectively. Of those readmitted at least once, 46.4% were 65 years or older, 69.1%

1 were males, 88.8% had moderate to very high ACG RUB, 27.0% had more than 30 ADG
2 comorbidities, 73.3% had an index acute care stay of 10 to 90 days, and 27% were discharged
3 home post-index acute care event (Table 1).

4 Relative effects of potential predictors on the number of readmissions (Table 2, left) and
5 duration of readmissions (Table 2, right), within 1-year of index HIBI-related acute care
6 discharge are presented in Table 2. Data show that the rate of readmissions among patients 35
7 to 49 years (RR: 0.57; 95% CI: 0.38-0.85) and 80 years or older (RR: 0.58; 95% CI: 0.34-0.97) was
8 more than 40% lower than for patients 65 to 74 years; a reduced readmission rate was
9 observed for patients 50 to 65 years (RR: 0.72; 95% CI: 0.52-1.00), though this was of borderline
10 statistical significance. An index acute care episode ADG score of more than 30 was associated
11 with a 60% (RR: 1.60; 95% CI: 1.11-2.31) increased rate of acute care readmission within 1-year,
12 relative to those who have an ADG score of less than 10. There was suggestion of an increased
13 likelihood of readmission with increasing amount of time spent in the special care unit, being
14 free of a psychological/behavioural diagnosis, or having been discharged home or to inpatient
15 rehabilitation instead of continuing/long-term care, though the point estimates were not
16 statistically significant.

17 Compared to those whose index HIBI acute care episode was 90 days or more, patients
18 with an index HIBI acute care episode of 10 to 30 and 31 to 90 days were likely to spend 2.88
19 (RR: 2.88; 95% CI: 1.28-6.52) and 4.17 (RR: 4.17; 95% CI: 1.38-12.64) more days in hospital
20 within a year following discharge for HIBI, respectively. Those that used minimal health services
21 within the prior two years (ACG RUB healthy/none) were likely to spend 0.15-fold fewer days
22 (RR: 0.15; 95% CI: 0.05-0.49) in the hospital during the year post index HIBI acute care episode

1 discharge relative to HIBI patients whose prior utilization of services was very high. Compared
2 to patients discharged to complex continuing care/long-term care, those discharged home from
3 their index acute care HIBI episode were likely to spend fewer days (RR: 0.44; 95% CI: 0.21-0.91)
4 in an acute care bed during the following year. The interaction between age and sex was not
5 significant in both models.

6 7 **Interpretation**

8 This is the first study to investigate predictors of re-hospitalizations specific to the HIBI
9 population. Our findings suggest that the proportion of patients readmitted (39.2%) within one
10 year of acute care discharge were higher than that for patients with TBI (16% - 29%).¹¹⁻¹³
11 Observed predictors of fewer readmissions are both older and younger age relative to patients
12 65 to 79 years, while prior comorbidity is associated with more readmissions. Observed
13 predictors of cumulative duration of readmissions are having more than minimal prior contact
14 with the healthcare system, an index episode LOS between 10 and 90 days, and being
15 discharged to continuing/long-term care after the index acute episode instead of home.

16 These findings are similar to those identified for TBI, medical and surgical patients, and
17 all-cause readmissions.²⁷ It is plausible that patients between 35 and 64 years are less likely to
18 have readmissions following survival of an acute care stay for HIBI because they are less frail
19 than the 65 to 79 years of age reference group. The oldest patients who survive their HIBI acute
20 care episode may be less likely to have acute care readmissions chiefly due to having less
21 severe HIBI injuries, contributing to their survival of index acute care episode when almost 80%

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3 1 of HIBI patients admitted to acute care die in hospital.⁵ Socioeconomic status indicators such as
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6 2 neighborhood income quintile and rurality were not associated with readmission in this study, a
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8 3 finding consistent with the all-cause readmission by Canadian Institute for Health Information.⁸
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11 4 Discharge to home, instead of continuing/long-term care, from the index acute care
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14 5 episode is associated with a greater number of readmissions, but fewer days in acute care over
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16 6 the year. Studies have shown that discharge destination other than home is independently
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18 7 associated with increased rate of readmission in TBI and other trauma populations^{19, 27} and is
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21 8 likely an indicator of medical complexity and injury severity. Re-hospitalization among patients
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24 9 with TBI has been suggested to arise from post discharge care that is ill-equipped to resolve
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26 10 sudden complications and prevention protocols planning for such events have been
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28 11 recommended.²⁸ Our finding also suggests that this group of HIBI acute care survivors may, on
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31 12 average, be lacking caregiver support at home, and thus, may experience a greater number of
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34 13 readmissions. However, overall, they may be less complex medically due to a less severe HIBI or
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36 14 comorbidity profile, and therefore, spending fewer days in the acute care when readmitted.
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38 15 There is growing evidence that care of complex patients can benefit substantially from
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41 16 interdisciplinary team-based models. These can facilitate more optimal management of
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44 17 comorbid health conditions during acute care as well as improved coordination of discharge
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46 18 planning to ensure the necessary formal and informal supports are in place.²⁹ Strategies
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48 19 including the introduction of new sub-acute care facilities, auxiliary nurses to support specialist
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51 20 nursing staff, and patient-held summaries of specialist consultations may prevent inappropriate
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53 21 admissions or reduce LOS³⁰, avoiding the decline into frailty characteristic of patients who linger
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56 22 unnecessarily in hospital.³¹ Adequate planning and support services during the transition from
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1 inpatient/rehabilitation to home and afterwards is crucial in preventing the exacerbation of
2 care needs, manageable in the current setting, into those requiring readmission. Transition
3 supports emphasizing a more holistic approach to patient care both pre and post discharge and
4 available homecare have been demonstrated to maximize functional independence, overall
5 health and directly prevent readmissions.^{32, 33} Health professionals and service organizations
6 should factor in individual need in context of available family and social supports, as well as be
7 aware of ongoing healthcare and rehabilitation needs to facilitate access to required services.
8 These processes require co-ordination between multiple healthcare, social and community
9 support systems.

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11 **Strengths and Limitations**

12 Limitations associated with the use of health administrative data are recognized. Many factors
13 that contribute to readmission such as injury severity, social support and availability of private
14 insurance were not available. There is currently no consensus on the case definition for HIBI
15 and milder cases of HIBI may be missed in health administrative data, resulting in an
16 underreported number of patients with HIBI. This was addressed by including patients with an
17 anoxic brain damage ICD-10 code as a secondary acute care diagnosis, with MRDx consistent
18 with causes of HIBI.

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20 Nonetheless, this is the first study to report readmissions among patients with a HIBI-related
21 acute care event at a population level in a publicly funded health system. Furthermore, a
22 quality assessment of DAD indicated near-perfect agreement for non-clinical variables and

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3 1 moderate to substantial agreement for the most responsible diagnosis.³⁴ Finally, findings from
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5 2 this Ontario-wide study represent a substantial proportion (39%) of the Canadian population
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8 3 and may be generalizable to jurisdictions with comparable acute care health systems and post-
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10 4 acute care formal and informal support structures.

6 **Conclusion**

7 This study suggests that between fiscal years 2002/03 and 2010/11, more than 1 in 3 patients
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9 8 with a HIBI-related acute care admission were readmitted within 1-year of discharge. Findings
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11 9 support literature on other brain-injured populations that interdisciplinary teams in the
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13 10 inpatient setting for patients with HIBI would be beneficial, and highlight an unmet need for
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15 11 appropriate and adequate support in the transition from inpatient to home. This includes the
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17 12 provision of homecare services to ensure that patients are adequately cared for post discharge.
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19 13 This study also highlights the need for HIBI-specific research to support evidence-based best
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21 14 practice in meeting the needs of these unique patients. Findings from this study will help
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23 15 inform health service planning for this understudied population, thereby preventing avoidable
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25 16 care gaps and health system inefficiencies of which readmission rates are an indicator.
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Table 1: Characteristics of patients with hypoxic ischemic brain injury (HIBI) in the acute care setting and readmission within 1-year of acute care discharge, Ontario, Canada, 2002/03 – 2010/11

Characteristics	HIBI Discharges (N=593)	Readmission within 1yr (n=233)
	N (%)	N (%)
Age at admission (years)		
20 - 34	54 (9.1)	20 (8.5)
35 - 49	107 (18.0)	35 (15.0)
50 - 64	189 (31.9)	70 (30.0)
65 - 79	188 (31.7)	85 (36.5)
80+	55 (9.3)	23 (9.9)
Sex		
Females	204 (34.4)	72 (30.9)
Males	389 (65.6)	161 (69.1)
Income Quintiles		
Quintile 1 (lowest)	165 (27.8)	62 (26.6)
Quintile 2	126 (21.2)	52 (22.3)
Quintile 3	105 (17.7)	42 (18.0)
Quintile 4	123 (20.7)	52 (22.3)
Quintile 5 (highest)	74 (12.5)	25 (10.7)
Rurality		
Rural	58 (9.8)	23 (9.9)
Urban	535 (90.2)	210 (90.1)
ACG RUB		
None or healthy	34 (5.7)	13 (5.6)
Low	35 (5.9)	13 (5.6)
Moderate	198 (33.4)	75 (32.2)
High	152 (25.6)	56 (24.0)
Very high	174 (29.3)	76 (32.6)
ADG Comorbidity Index		
<10	187 (31.5)	69 (29.6)
10-30	265 (44.7)	101 (43.4)
>30	141 (23.8)	63 (27.0)
Fiscal Year		
2002-2003	137 (23.1)	50 (21.5)
2004-2005	123 (20.7)	51 (21.9)
2006-2007	131 (22.1)	50 (21.5)
2008-2009	138 (23.3)	56 (24.0)
2010	64 (10.8)	26 (11.2)
Special Care hours		
None	86 (14.5)	31 (13.3)
1-499	333 (56.2)	127 (54.5)
500-999	95 (16.0)	40 (17.2)
1000+	79 (13.3)	35 (15.0)
Index DAD LOS (days)		
<10	119 (20.1)	37 (15.9)
10 - 30	203 (34.2)	77 (33.0)
31 - 90	210 (35.4)	94 (40.3)
>90	61 (10.3)	25 (10.7)
DAD ALC (days)		
0	354 (59.7)	131 (56.2)
1-14	100 (16.9)	44 (18.9)
>14	139 (23.4)	58 (24.9)
Psychological/Behavioral		

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Absent	452 (76.2)	185 (79.4)
Present	141 (23.8)	48 (20.6)
Discharge Disposition		
Home	130 (21.9)	63 (27.0)
Rehabilitation	122 (20.6)	54 (23.2)
Continued Care	181 (30.5)	62 (26.6)
Other	160 (27.0)	54 (23.2)

Note: ACG= Adjusted Clinical Group, ADG= Aggregated Diagnostic Group, RUB= Resource Utilization Band, SCU= Special Care Unit, ALC= Alternate Level of Care.

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Table 2: Rate ratios (RR) and 95% confidence intervals (CI) for predictors of number of readmissions (left), and cumulative duration of readmission (right), within 1-year of acute care discharge, Ontario, Canada, 2002/03 – 2010/11, (N=593).

Potential Predictors	Number of Readmissions RR (95% CI)	Cumulative Duration of Readmission (Days) RR (95% CI)
Age at admission (years)		
20-34	0.93 (0.57-1.51)	0.64 (0.25-1.67)
35-49	0.57 (0.38-0.85)	0.51 (0.23-1.09)
50-64	0.72 (0.52-1.00)	0.71 (0.37-1.39)
65-79	1.00	1.00
80+	0.58 (0.34-0.97)	0.70 (0.27-1.80)
Sex		
Females	1.06 (0.80-1.40)	1.03 (0.57-1.86)
Males	1.00	1.00
ACG RUB	NR	
None or healthy		0.15 (0.05-0.49)
Low		0.85 (0.24-3.02)
Moderate		0.68 (0.36-1.28)
High		0.71 (0.37-1.40)
Very high		1.00
ADG Comorbidity Index		NR
<10	1.00	
10-30	1.19 (0.85-1.65)	
>30	1.60 (1.11-2.31)	
Length of Index Episode (days)	NR	
<10		1.67 (0.78-3.59)
10-30		2.88 (1.28-6.52)
31-90		4.17 (1.38-12.64)
>90		1.00
Special Care Hours		NR
None	0.88 (0.58-1.33)	
1-499	1.00	
500-999	1.22 (0.85-1.77)	
1000+	1.47 (0.98-2.19)	
Psychological Behavior		NR
Absent	1.00	
Present	0.73 (0.52-1.01)	
Discharge Disposition		
Home	1.41 (0.97-2.06)	0.44 (0.21-0.91)
Rehabilitation	1.43 (0.97-2.09)	1.25 (0.60-2.63)
Continued Care	1.00	1.00
Other	1.09 (0.74-1.60)	1.73 (0.74-4.06)

Note: ACG= Adjusted Clinical Group, ADG=Aggregated Diagnostic Group, RUB= Resource Utilization Band, NR=not retained in the model

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract – Page 1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found – Page 3
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Page 5
Objectives	3	State specific objectives, including any prespecified hypotheses - Page 6
Methods		
Study design	4	Present key elements of study design early in the paper – Page 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection - Page 7
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up - Page 7 <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Page 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group - Page 8
Bias	9	Describe any efforts to address potential sources of bias – Page 9
Study size	10	Explain how the study size was arrived at – Page 7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why - Page 8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding - Page 8 & 9 (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses

Continued on next page

Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed – Page 9 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders - Page 15 (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time – Page 9 <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included – Page 9 & 10 (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses -

Discussion

Key results	18	Summarise key results with reference to study objectives – Page 11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias - Page 13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence – Page 11,12,13, 14
Generalisability	21	Discuss the generalisability (external validity) of the study results – Page 14

Other information

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based – Page 1
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*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.