Persistent Functional Decline Following Hospitalization with Influenza or Acute Respiratory Illness

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BACKGROUND/OBJECTIVES: Influenza is associated with significant morbidity and mortality, particularly for older adults. Persistent functional decline following hospitalization has important impacts on older adults' wellbeing and independence, but has been under-studied in relation to influenza. We aimed to investigate persistent functional change in older adults admitted to hospital with influenza and other acute respiratory illness (ARI).

DESIGN: Protective observational cohort study.

SETTING: Canadian Immunization Research Network Serious Outcomes Surveillance Network 2011 to 2012 influenza season.

PARTICIPANTS: A total of 925 patients aged 65 and older admitted to hospital with influenza and other ARI.

MEASUREMENTS: Influenza was laboratory-confirmed. Frailty was measured using a Frailty index (FI). Functional status was measured using the Barthel index (BI); moderate persistent functional decline was defined as a clinically meaningful loss of ≥10 to <20 points on the 100-point BI. Catastrophic disability (CD) was defined as a loss of ≥20 points, equivalent to full loss of independence in two basic activities of daily living.

RESULTS: Five hundred and nineteen (56.1%) were women; mean age was 79.4 (standard deviation=8.4) years. Three hundred and forty-six (37.4%) had laboratory-confirmed influenza. Influenza cases had lower baseline function (BI = 77.0 vs 86.9, $P < .001$) and higher frailty (FI = 0.23 vs 0.20, $P < .001$) than those with other ARI. A total of 8.4% died, 8.2% experienced persistent moderate functional decline, and 9.9% experienced CD. Higher baseline frailty was associated with increased odds of experiencing functional decline, CD, and death. The experience of functional decline and CD, and its association with frailty, was the same for influenza and other ARI.

CONCLUSION: Functional loss in hospital is common among older adults; for some this functional loss is persistent and catastrophic. This highlights the importance of prevention and optimal management of acute declines in health, including influenza, to avoid hospitalization. In the case of influenza, for which vaccines exist, this raises the potential of vaccine preventable disability. **J Am Geriatr Soc 69:696-703, 2021.**

Keywords: activities of daily living; aged; frail elderly; hospitalization; influenza

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INTRODUCTION

The health impact of influenza is traditionally thought of in terms of morbidity and mortality over short time horizons. Even so, health impacts may be long lasting, particularly for older adults who suffer functional declines following acute illness. Hospitals are places intended to

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improve health and wellbeing, but hospital admission can also lead to harm for vulnerable older adults—either harms associated with the condition that led to admission, or with iatrogenic factors such as deconditioning, delirium, or nosocomial infection.[1] There is a robust existing literature on the functional impact of hospitalization in general among older adults, with studies showing that one-third of older adults will be discharged with a new disability.[2,3] Prognosis for subsequent functional recovery is poor over the following year, with only 30% of individuals recovering to their pre-admission level of function in self-care activities of daily living (ADLs) 1 year post-discharge.[4] This functional decline is associated with greater reliance on formal and informal care supports in the community, with increased risk of requiring long-term care facility (LTCF) admission,[5] and with increased risk of mortality.[6]

As populations age, it is increasingly important to understand and prevent functional decline and losses in independence. In the present study, we aimed to investigate functional change in older adults admitted to Canadian hospitals with influenza and other acute respiratory illnesses (ARIs). Our objectives were as follows:

1. To assess the prevalence of functional decline and catastrophic disability (CD) in adults aged 65 years and older who are admitted to hospital for influenza and other ARI.
2. To assess whether the risk of functional decline is different for influenza cases versus ARI.
3. To examine whether baseline frailty is associated with functional decline and CD.
4. To examine whether the relationship between frailty and CD varies based on influenza status.

METHODS

The present study includes patients aged 65 and older who were enrolled in the Canadian Immunization Research Network (CIRN) Serious Outcomes Surveillance (SOS) Network during the 2011 to 2012 influenza season. In this season, the SOS Network included 40 hospitals across 7 Canadian provinces, representing approximately 9,000 adult acute care beds, and detailed data on functional trajectories (baseline, on admission, 30 days after discharge) were collected.[7]

As previously described, active surveillance was performed to identify patients with influenza. Nasopharyngeal (NP) swabs were obtained within 7 days of symptom onset and 5 days of admission for those with the following admission diagnoses: respiratory infection or symptom, exacerbation of chronic obstructive pulmonary disease (COPD)/asthma, community acquired pneumonia, unexplained sepsis, or cardiac/respiratory diagnosis with fever ≥37.5°C. All NP swabs were tested for influenza A and B by reverse transcriptase polymerase chain reaction or viral culture.[8]

In the context of active influenza surveillance in the SOS Network (where calculation of vaccine effectiveness is an important focus, requiring inclusion of influenza "cases" and test-negative "controls"), patients with laboratory-confirmed influenza (LCI), whose admission was attributable to influenza or a complication of influenza, were considered to be cases. "Other ARI" patients were those who met inclusion criteria outlined above but had a negative NP swab, matched on age (greater or less than 65) and admission date ±2 weeks. This "other ARI" group thus included many diagnoses such exacerbations of asthma, COPD, or heart failure, myocardial infarction, thromboembolism, and other infectious illnesses (e.g., respiratory viruses, pneumonia, sepsis). The present analysis included only patients aged 65 and older.

Measures

Demographic data included age in years (continuous variable), sex (female/male), and baseline place of residence (community or LTCF). All clinical data (including function and frailty) were gathered by on-site research monitors using the best available source, including chart review and interviews with the patient and/or a collateral informant. Baseline status was determined by asking about health and function 2 weeks before the current illness to provide a strong time anchor and minimize recall bias.[9] Follow-up interviews were conducted in person or by telephone. Notably, the telephone Barthel index (BI) has been found to have robust reliability and validity.[10,11]

Function was assessed using the BI.[12] The BI considers independence in 10 ADLs: feeding, toilet use, bowel and bladder control, grooming, dressing, bathing, mobility, stair climbing, and transfers (from bed to chair and back). For each item, a score of 10 indicates independence, 5 indicates need for assistance, and 0 indicates complete dependence. Item scores are summed to produce a final score between 0 and 100 for the individual. As such, a score of 100 indicates complete independence, with decreasing score values indicating a graduated increase in disability or dependence.[12] The BI has been shown to be a valid functional measure, and it has good test-retest reliability.[13] The BI was assessed pre-admission (retrospectively) to reflect function 2 weeks before the onset of the current illness, on admission, and 30 days post-discharge. Change in the BI was calculated by subtracting pre-admission BI score from the 30 days post-discharge score. Participants who were not alive at 30 days post-discharge were omitted from analyses with change in the BI as an outcome.

We defined functional decline and CD using decline in the BI at 30 days post-discharge. A change in BI of 1.85 or more points on a 0 to 20 point version of the BI has been found to be clinically meaningful, which would equate with 9.25 points on the 0 to 100 point version used here.[14] This is reported as the change in BI that is perceived by patients as clinically important and sufficiently beyond measurement error.[14] Here we defined a return to baseline function as a loss of less than 10 points on the BI. We considered a loss of 10 to less than 20 points as clinically meaningful persistent moderate functional decline and a loss of 20 or more points (full loss of function in two domains, or new need for assistance in four domains) to represent a more rigorous definition of CD. An aggregate of CD and death was considered to represent catastrophic outcome.

Frailty was measured using a previously validated Frailty index (FI).[15,16] The FI was based on a Comprehensive Geriatric Assessment and included cognition, mood, sensorium, mobility, nutrition, function, skin, continence, and comorbidities.[17] Binary items such as vision and hearing were scored as 1 (deficit present) or 0 (deficit absent);

items with graded response categories were assigned intermediate scores (e.g., transfers being independent, assisted, or dependent). The FI was calculated by summing the participant's deficit scores and dividing by total possible deficits (here 39). Frailty was categorized based on previously validated cutoffs: FI 0 to 0.1, nonfrail; >0.1 to 0.21, prefrail; >0.21 to 0.45, frail; >0.45, most frail.[18] Frailty was assessed pre-admission (retrospectively), on admission, and 30 days post-discharge. Here, we were primarily interested in pre-admission "baseline" frailty, but were able to use the other time points in the imputation model for missing data.

We also assessed whether patients were vaccinated for influenza, were admitted to ICU, and their length of stay (LOS) in days.

Statistical Analysis

We used independent samples *t* test to compare the influenza and other ARI groups on continuous variables and chi-square test of independence for categorical variables. We used linear regression to examine the relationship between pre-admission frailty and decline in the BI while controlling for age, sex, influenza status, vaccination status, ICU admission, pre-admission BI, and on-admission BI. In Model 2, we added an interaction term between influenza status and frailty to test whether the relationship between frailty and BI decline varied depending on influenza status. To examine the association between pre-admission frailty and catastrophic outcome, CD, and functional decline, we used a similar procedure as outlined above except we used logistic regression. In both the linear and logistic regressions, we multiplied the FI by 10 so that coefficients could be interpreted in relation to a 0.1 change in the FI.

Given the challenges of data collection on frailty and function in hospitalized patients, some data points were missing. Listwise deletion would have resulted in a loss of 427 (46.2%) and 394 (46.5%) cases in the catastrophic outcome and functional decline regressions, respectively. The FI and the BI contained the most missing data. To manage these missing data, we used multiple imputations. Multiple imputations is a state-of-the-art method for handling missing data that results in more power and less bias than listwise deletion.[19-21] Specifically, we conducted multiple imputation by chained equations using predictive mean matching for continuous variables and logistic regression for dichotomous variables. In addition to all analysis variables and the interaction between frailty and influenza status, we included two auxiliary variables in our imputation model to improve the imputations: on admission FI, and FI at 30 days post-discharge. Analyses were conducted for each of 100 multiply imputed datasets and the results were pooled following the rules outlined by Rubin.[19,22] Analyses using listwise deletion are available in Supplementary - Tables S1 to S4. Multiple imputations were created using the Multivariate Imputation by Chained Equations (mice)[23] package in R[24] and analyses were conducted using SPSS version 25 and R version 3.6.3.

Ethics

The Research Ethics Boards (REB) of participating institutions approved the protocol. Patients provided informed written

Table 1. Descriptive Statistics (Mean (SD) for Continuous Variables and Frequency (Percent) for Categorical Variables) for Patients with Laboratory Confirmed Influenza and Other Acute Respiratory Illnesses (ARI)

Variable	Laboratory-Confirmed Influenza (N = 346)	Other ARI (N = 579)	*P*
Age	80.6 (9.00)	78.7 (7.9)	<.01
Female, sex	190 (54.9)	329 (56.8%)	.57
Frailty index (pre-admission), mean (SD)	0.23 (0.12)	.20 (0.11)	<.001
Barthel (pre-admission), mean (SD)	77.0 (31.6)	86.9 (22.8)	<.001
Barthel (admission), mean (SD)	55.7 (32.9)	63.5 (31.1)	<.01
Barthel admission: pre-admission Barthel	−21.3 (27.1)	−23.4 (25.5)	.33
Received influenza vaccine, N (%)	207 (59.8%)	420 (72.5%)	<.001
Length of stay, mean days (SD)	11.7 (12.5)	11.9 (12.5)	.81
Admitted from LTC, N (%)	52 (15.0%)	36 (6.2%)	<.001
ICU, N (%)	39 (11.3%)	81 (14.0%)	.23
30 days post-discharge mortality, N (%)	42 (12.1%)	36 (6.2%)	<.01
Catastrophic outcome, N (%)	80 (23.1%)	90 (15.5%)	<.01
Alive at 30 days post-discharge	**Influenza (N = 304)**	**Other ARI (N = 543)**	
Barthel (30 days post-discharge), mean (SD)	78.0 (27.2)	85.5 (23.2)	<.001
Barthel post-discharge: pre-admission Barthel, mean (SD)	−2.2 (18.9)	−2.5 (16.4)	.86
Functional decline, N (%) (Barthel decline by 10 + points)	70 (23.0%)	98 (18.0%)	.15
Catastrophic disability, N (%) (Barthel decline by 20+ points)	38 (12.5%)	54 (9.9%)	.35

Note: P-values were based on independent samples-test for continuous variables and chi-square tests of independence for categorical variables. Median length of stay is 8 days for both cases and controls. Percentages for functional and catastrophic decline are based on surviving participants. Bold text indicates a heading for subsequent rows, where functional outcomes are reported for survivors only.

consent for data collection and medical record access in accordance with the local REB requirements.

RESULTS

A total of 926 patients aged 65 years and older were enrolled in the 2011/2012 influenza season. One participant who was missing data for all study and auxiliary imputation variables except age, sex, and influenza status was not included in the analyses, leaving a final sample size of 925. Of these, mean age was 79.4 (standard deviation (SD) = 8.4) years, 519 (56.1%) were women, 346 (37.4%) had influenza, and 88 (9.5%) were admitted from a long-term care facility. With their acute illness presentation, both groups had experienced a similar functional loss from baseline to admission (−21.3 vs −23.4 points on the BI, $P = .33$). Patient characteristics for the influenza and other ARI groups are described in Table 1.

Outcomes are illustrated in Figure 1. Of the sample as a whole, 78 (8.4%) died (12.1% of those with influenza vs 6.2% of those with other ARI; $P < .01$). Those with lower baseline function were more likely to die: mean pre-admission BI was 85.19 (SD = 25.15) for those who lived and 61.89, (SD = 34.56) for those who died ($P < .001$). Persistent functional decline (BI decline ≥ 10 points) was experienced by 168 (19.8%) of surviving participants, of whom 76 (8.2%) experienced moderate functional decline and 92 (9.9%) experienced CD (Figure 1).

The percent of participants who experience CD increased across frailty groups: 4.7%, 9.4%, 15.6%, 8.0% for nonfrailty, prefrail, frailty, and most frail, respectively (see Table 2).

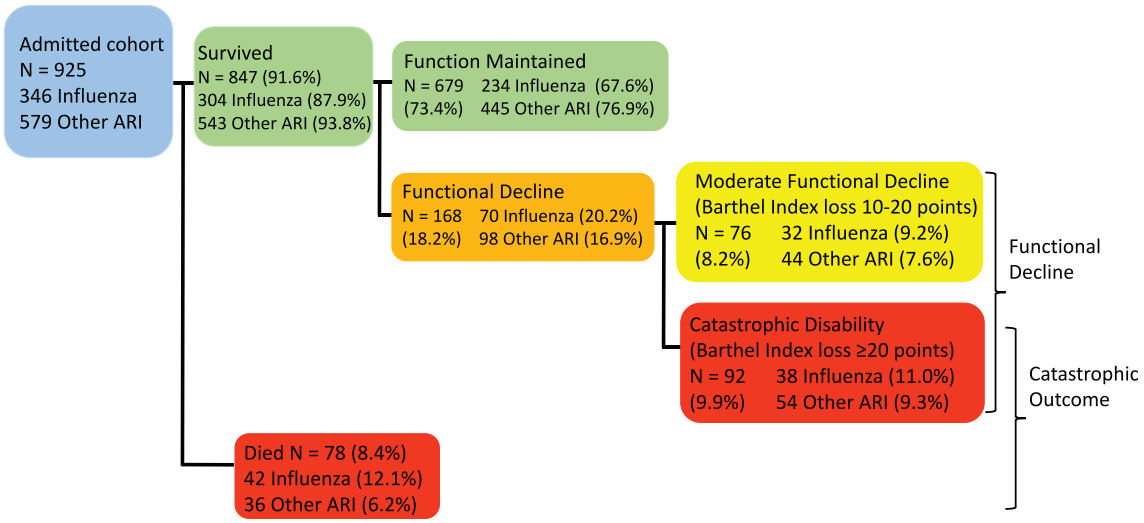

Figure 1. Patient outcomes, subdivided by laboratory-confirmed influenza versus other influenza acute respiratory illness (ARI). Percentages are presented for the overall cohort and within the influenza and other ARI groups.

Table 2. Means (SD) and Frequency (%) for Barthel and Decline by Frailty

	Nonfrail FI ≤ 0.1 (N = 136)	Prefrail 0.1 < FI ≤ 0.21 (N = 399)	Frail 0.21 < FI ≤ 0.45 (N = 356)	Most Frail FI > 0.45 (N = 34)	*P*-value
Barthel prior	99.1 (2.9)	95.8 (9.7)	69.2 (29.3)	19.1 (22.0)	<.001
Barthel on admission	77.7 (28.4)	71.9 (27.2)	46.3 (28.4)	10.2 (13.1)	<.001
Barthel admission: Barthel prior	−21.4 (28.0)	−23.9 (26.3)	−23.0 (25.5)	−8.9 (18.3)	<.05
Catastrophic outcome	12 (8.8%)	51 (12.8%)	96 (27.0%)	11 (32.4%)	<.001
Mortality	6 (4.4%)	15 (3.8%)	48 (13.5%)	10 (29.4%)	<.001
Alive at 30 days post-discharge	**N = 129**	**N = 385**	**N = 308**	**N = 25**	
Barthel 30 days post-discharge	96.7 (10.8)	92.8 (13.2)	69.5 (26.7)	20.5 (23.0)	<.001
Barthel post-discharge: Barthel prior	−2.4 (10.3)	−3.2 (13.9)	−1.7 (22.8)	2.2 (15.3)	.63
Functional decline, N (%) (Barthel decline by 10 + points)	12 (9.3%)	67 (17.4%)	85 (27.6%)	4 (16.0%)	<.001
Catastrophic disability, N (%) (Barthel decline by 20+ points)	6 (4.7%)	36 (9.4%)	48 (15.6%)	2 (8.0%)	<.05

Note: *P*-values based on ANOVA for continuous variables and chi-square for categorical variables. Bold text indicates a heading for subsequent rows, where functional outcomes are reported for survivors only.

The mean baseline frailty score for individuals who experienced CD was 0.24 (SD = 0.10) and 0.20 (SD = 0.11) for those who did not experience CD ($P < .01$). On average, participants declined by −2.38 (SD = 17.4) points on the BI.

The distribution of functional change was similar for the influenza and ARI groups (Supplementary Figure S1); decline in function as part of the acute illness presentation was common to both. The absolute functional loss from baseline to admission was similar for nonfrail, prefrail, and frail patients (−21.4, −23.9, and −23.0 BI points, respectively). For the most frail, whose baseline BI was already less than 20, the absolute further functional loss was less at −8.9 points (Table 2). Considered in relative terms, the mean function level declined 21.6% for nonfrail patients, 24.9% for prefrail, 33% for frail, and 46.6% for the most frail.

Function at all three time points was inversely associated with frailty, whereas the proportions experiencing CD and death increased with frailty (all $P < .001$) (Table 2). Nonfrail, prefrail, and frail patients all lost between 1.7 and 3.2 BI points from baseline to post-discharge, although the most frail had a mean improvement of 2.2 points ($P = .63$). New CD was less commonly observed in the most frail compared with the frail patients (8.0 vs 15.6%) (Table 2). All of the adverse outcomes increased in a step-wise fashion

Table 3. Outcomes by Length of Stay (LOS) Quartiles. Mean (SD) for Continuous Outcomes and Frequency (%) for Categorical Outcomes

	LOS 0–5 days N = 262	LOS 6–8 days N = 230	LOS 9–13 days N = 206	LOS >13 days N = 227	*P*
Catastrophic outcome	30 (11.5%)	31 (13.5%)	41 (19.9%)	69 (30.4%)	<.001
Mortality	16 (6.1%)	11 (4.8%)	19 (9.2%)	32 (14.1%)	<.01
Alive 30 days post-discharge	**N = 246**	**N = 219**	**N = 187**	**N = 195**	
Barthel post-discharge: Barthel baseline	0.42 (14.3)	−2.9 (16.6)	−2.8 (17.3)	−5.0 (21.0)	<.05
Functional decline	27 (11.0%)	40 (18.3%)	40 (21.4%)	62 (31.8%)	<.001
Catastrophic decline	14 (5.7%)	20 (9.1%)	22 (11.8%)	36 (18.5%)	<.01

Note: Bold text indicates a heading for subsequent rows, where functional outcomes are reported for survivors only.

Table 4. Regression Coefficients and Odds Ratios for the Linear and Logistic Regression Models

Variable	Change in Barthel Index (N = 847)		Catastrophic Outcome (N = 925)		Catastrophic Decline (N = 847)		Functional Decline (N = 847)	
	Linear Regression		Logistic Regression		Logistic Regression		Logistic Regression	
Model 1	***b***	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Pre-admission FI	−5.87**	−7.71, −4.03	1.65**	1.22, 2.22	2.26***	1.53, 3.34	2.20***	1.62, 2.99
Age	−0.23**	−0.37, −0.08	1.04**	1.01, 1.06	1.04*	1.01, 1.08	1.05**	1.02, 1.08
Female, sex	−1.02	−3.34, 1.31	0.94	0.63, 1.41	1.13	0.65, 1.95	1.31	0.85, 2.02
Influenza status	−0.77	−3.36, 1.82	1.38	0.91, 2.08	1.17	0.65, 2.09	1.30	0.81, 2.09
Influenza vaccination status	2.97*	0.37, 5.57	0.76	0.49, 1.19	0.73	0.40, 1.33	0.81	0.50, 1.30
Pre-admission Barthel	−0.43***	−0.52, −0.33	1.00	0.99, 1.02	1.04**	1.01, 1.06	1.03***	1.02, 1.05
Barthel prior: Barthel admission	0.11***	0.06, 0.17	0.98***	0.97, 0.99	0.98***	0.97, 0.99	0.98***	0.97, 0.99
Model 2	***b***	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Pre-admission FI	−6.09***	−7.99, −4.18	1.68**	1.23, 2.28	2.46***	1.62, 3.74	2.52***	1.80, 3.52
Age	−0.23**	−0.38, −0.08	1.04**	1.01, 1.06	1.05*	1.01, 1.08	1.05**	1.02, 1.08
Female, sex	−1.05	−3.38, 1.29	0.95	0.63, 1.42	1.14	0.66, 1.97	1.34	0.87, 2.06
Influenza status	−2.33	−7.30, 2.63	1.58	0.62, 4.02	2.11	0.58, 7.61	3.22*	1.19, 8.70
Influenza Vaccination status	2.93*	0.33, 5.53	0.76	0.49, 1.19	0.74	0.40, 1.35	0.82	0.51, 1.33
Pre-admission Barthel	−0.42***	−0.52, −0.32	1.00	0.99, 1.02	1.04**	1.01, 1.06	1.03***	1.02, 1.05
Barthel admission: Barthel prior	0.11***	0.06, 0.17	0.98***	0.97, 0.99	0.98***	0.97, 0.99	0.98***	0.97, 0.99
FI by influenza status	0.75	−1.45, 2.94	0.95	0.68, 1.32	0.77	0.46, 1.29	0.67*	0.45, 1.00

Note: Significant interaction between frailty and influenza status for functional decline. Coefficients for frailty: influenza OR = 1.68* (1.11, 2.54) and other ARI OR = 2.52*** (1.80, 3.52).

*$P < .05$.

**$P < .01$.

***$P < .001$.

with increasing LOS (Table 3); for example the experience of functional decline was 11.0% in patients with LOS ≤5 days, 18.3% for LOS 6 to 8 days, 21.4% for LOS 9 to 13 days, and 31.8% in those with LOS >13 days ($P < .001$).

Functional Decline from Pre-Admission to 30 Days Post-Discharge

On average, participants who were still alive at 30 days post-discharge experienced a drop of 2.38 points on the BI. In the adjusted analysis, each 0.1 increase in baseline frailty was associated with a 5.87 point decline on the BI ($P < .01$). Worse baseline function was associated with attenuation in the absolute further decreases in BI score during admission. Greater functional loss with the acute presenting illness (baseline to admission) was also independently predictive of worse functional outcomes after hospital discharge: for each point lost on the BI from baseline to admission, the odds of functional decline increased by 2% ($P < .001$). Influenza status did not significantly moderate the relationship between pre-admission frailty and BI decline, indicating that average change in BI was similar between influenza and other ARI groups; however, a statistically significant interaction was observed for functional decline (decline in BI by ≥10 points), such that higher frailty was associated with a higher odds of functional decline for other ARI than influenza. See Table 4 for coefficients for Models 1 and 2.

Catastrophic Disability

A total of 170 (18.4%) patients experienced a catastrophic outcome. Each 0.1 increase on the FI was associated with a 65% increase in the odds of a catastrophic outcome and, among survivors, a doubling in the odds of experiencing CD. Greater functional loss with the acute presenting illness (baseline to admission) was also independently predictive of both CD and death, with the odds of each outcome increasing by 2% for each point of BI decline from baseline to admission. More patients with influenza than other ARI experienced a catastrophic outcome (23.1 vs 15.5%, $P < .01$) but this was not statistically significant in the final adjusted model, where influenza status did not significantly moderate the relationship between frailty and CD. See Table 4 for coefficients for Model 1 and 2.

DISCUSSION

Among older Canadians admitted to CIRN SOS network hospitals during the 2011/2012 influenza season, both influenza and other ARI groups experienced a loss of function. Although a large proportion returned to their baseline, 18.2% experienced a clinically meaningful loss of function at 30 days post-discharge, of whom half had CD.

Some patients experienced functional improvement. This may have been attributable to treatment of chronic health conditions, availability of physiotherapy/rehabilitation services, and access to multidisciplinary teams. Additionally, a survivor effect may be at play as the most functionally impaired patients were more likely to die. Indeed, we found that baseline BI was lower for those who died, and the mean change in BI for the most frail was positive.

Functional decline from baseline to admission, representing the functional loss associated with acute presentation of influenza and other ARI, was an important factor. The degree of functional decline at presentation was independently associated with all outcomes (functional decline, CD, and death). This is highly clinically relevant, as functional decline may be the best indication that an older adult is sick. When viewed in absolute terms, the mean 21 to 23 point BI loss experienced by the nonfrail, prefrail, and frail patients represents complete loss of two basic ADLs. Interestingly, although the absolute loss of function appeared to be less in the most frail group (at 8.9 points), when we consider that this group had a mean baseline BI of only 19.1 points, the relative loss of 46.6% of baseline function is striking. Although LOS is most commonly considered as an outcome rather than a risk factor,[25-27] our finding that longer LOS was associated with step-wise increases in all adverse outcomes is consistent with prior literature.[4]

Both influenza and ARI patients experienced loss of function while in hospital. It is notable that patients admitted with influenza had worse function and higher frailty at baseline than those with ARI. This association of lower functional status and higher frailty may mean these individuals are more susceptible to influenza infection requiring hospitalization than their less frail, less functionally impaired peers. Admissions following LTCF outbreaks may also have led to inclusion of more frail and functionally impaired patients in the influenza group; indeed we did find that influenza cases were more likely to have been admitted from LTCF. In our linear regression model examining associations with absolute change in BI, we found that influenza vaccination was associated with better BI scores (a 2.97 point increase vs unvaccinated patients). Although this statistically significant effect could be due to differences in unmeasured characteristics between those who were vaccinated and those who were not, we did control for a number of variables, including frailty.[15] The nonsignificant effect of influenza vaccination in the logistic regression models predicting the dichotomized outcomes of functional decline and CD in this hospitalized population may be due to a loss of sensitivity from dichotomization versus use of continuous functional change. In sum, although vaccination status significantly predicts how much the BI changes from pre-admission to 30 days post-discharge, it is not a significant predictor of who will decline more than 10 or more than 20 points. The major role for influenza vaccination remains to prevent the need for hospital admission in the first place. As we have previously reported, influenza vaccination was 58% effective in preventing influenza hospital admission among older adults in the 2011/2012 season.[15]

Counter to the commonly held view that influenza is an acute self-limited illness, patients admitted with influenza were no less likely than patients with other ARI to experience functional declines. This functional loss has implications in terms of the individual's living situation, as loss of ADL independence would require increased care, and would be expected to lead to lasting need for increased reliance on informal (family and friend) and/or formal (paid) caregivers, and/or incident LTCF placement. These poor

functional outcomes thus have a great impact on both older adults and their families. Indeed, many older adults fear functional dependence and being a burden on their families more than death itself.[28] Stratification by frailty revealed an expected pattern of increasing functional with frailty, however it is important to note that persistent functional declines were not limited to the frail; nonfrail and prefrail individuals also experienced measurable functional declines that persisted after hospital discharge.

To the best of our knowledge, this is the first study to specifically report on functional declines following hospitalization for influenza, although it builds on a robust existing literature demonstrating the impact of hospitalization on function in general patient populations. For example, a study of 2,293 older inpatients (ages 70+) found that 35% had declined in ADL function from baseline to hospital discharge.[2] For older adults who are discharged from hospital with new or increased functional impairment, prognosis for functional recovery is generally poor.[4] With regard to respiratory infectious causes of admission, a Barcelona study reported that 23% of 93 survivors of a hospital admission for pneumonia had experienced functional decline.[29] An American study reported that of 301 consecutive patients aged 65 and older admitted to hospital with pneumonia, 36% had functional decline in basic ADL at hospital discharge and this persisted in 11% after 3 months.[30] An analysis of the Health and Retirement Study cohort found that survivors of a hospital admission for pneumonia had experienced one new impairment in a basic or instrumental ADL, and that pneumonia survivors reported more numerous persistent impairments in functional activities versus survivors of myocardial infarction.[31]

Our study is not without limitations. As has been discussed in a prior publication on frailty from the SOS Network,[15] missing data is a limitation. There were more missing data in influenza cases compared to patients with other ARI. This may reflect the degree of difficulty of data collection in studies of vulnerable older adults. Indeed, as previously discussed in the literature, this may have underestimated the degree of frailty among cases, as frailty tends to be higher in those with missing data due to various factors including the challenges of data collection.[32] We addressed this limitation by using multiply imputed data to ensure as many participants as possible were included. We report analyses based on the 2011/2012 influenza season. SOS Network surveillance has continued in the years since, though not with collection of detailed functional data. As such, this season presents us with the best opportunity to study the impact of admission for influenza and other acute respiratory conditions in what remains a large and well characterized sample.

CONCLUSIONS

Functional loss in hospital is a common occurrence for older adults, and for a smaller but significant subset within this group, functional loss is persistent and catastrophic. This highlights the importance of disease prevention and management to avoid hospitalization from any cause. We found that older adults with LCI had functional losses equivalent to their peers with other ARIs. Preventing hospitalization, including through interventions such as influenza and pneumococcal vaccination, is important in the prevention of functional decline and CD.

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Author Contributions: MKA, SM, and JG conceived the study. SM wrote the initial draft which was updated by MKA. JG performed the statistical analyses. JB and TFH contributed interpretation of influenza testing in the SOS Network's central laboratory. JEM, WB, KK, AM, MS were site investigators in the SOS Network, of which MKA and SAM were co-PIs. All authors contributed to interpretation of results and manuscript revisions.

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REFERENCES

1. Dharmarajan K, Swami S, Gou RY, Jones RN, Inouye SK. Pathway from delirium to death: potential in-hospital mediators of excess mortality. J Am Geriatr Soc. 2017;65(5):1026-1033.
2. Covinsky KE, Palmer RM, Fortinsky RH, et al. Loss of independence in activities of daily living in older adults hospitalized with medical illnesses: increased vulnerability with age. J Am Geriatr Soc. 2003;51(4):451-458.

3. Sager MA, Franke T, Inouye SK, et al. Functional outcomes of acute medical illness and hospitalization in older persons. Arch Intern Med. 1996;156(6):645-652.
4. Boyd CM, Landefeld CS, Counsell SR, et al. Recovery of activities of daily living in older adults after hospitalization for acute medical illness. J Am Geriatr Soc. 2008;56(12):2171-2179.
5. Fortinsky RH, Covinsky KE, Palmer RM, Landefeld CS. Effects of functional status changes before and during hospitalization on nursing home admission of older adults. J Gerontol A Biol Sci Med Sci. 1999;54(10):M521-M526.
6. Sleiman I, Rozzini R, Barbisoni P, et al. Functional trajectories during hospitalization: a prognostic sign for elderly patients. J Gerontol A Biol Sci Med Sci. 2009;64(6):659-663.
7. Andrew MK, Shinde V, Hatchette T, et al. Influenza vaccine effectiveness against influenza-related hospitalization during a season with mixed outbreaks of four influenza viruses: a test-negative case-control study in adults in Canada. BMC Infect Dis. 2017;17(1):805.
8. Nichols MK, Andrew MK, Hatchette TF, et al. Influenza vaccine effectiveness to prevent influenza-related hospitalizations and serious outcomes in Canadian adults over the 2011/12 through 2013/14 influenza seasons: a pooled analysis from the Canadian Immunization Research Network (CIRN) Serious Outcomes Surveillance (SOS Network). Vaccine. 2018;36(16):2166-2175.
9. Hatheway OL, Mitnitski A, Rockwood K. Frailty affects the initial treatment response and time to recovery of mobility in acutely ill older adults admitted to hospital. Age Ageing. 2017;46(6):920-925.
10. Chen XW, Shafei MN, Abdullah JM, Musa KI. Reliability of telephone interview for assessment of long-term stroke outcomes: evidence from inter-rater analysis. Neuroepidemiology. 2019;52(3–4):214-219.
11. Prasad K, Kumar A, Misra S, et al. Reliability and validity of telephonic Barthel index: an experience from multi-centric randomized control study. Acta Neurol Belg. 2018;118(1):53-59.
12. Mahoney FI, Barthel DW. Functional evaluation: the Barthel index. Md State Med J. 1965;14:61-65.
13. Richards SH, Peters TJ, Coast J, Gunnell DJ, Darlow MA, Pounsford J. Inter-rater reliability of the Barthel ADL index: how does a researcher compare to a nurse? Clin Rehabil. 2000;14(1):72-78.
14. Hsieh YW, Wang CH, Wu SC, Chen PC, Sheu CF, Hsieh CL. Establishing the minimal clinically important difference of the Barthel index in stroke patients. Neurorehabil Neural Repair. 2007;21(3):233-238.
15. Andrew MK, Shinde V, Ye L, et al. The importance of frailty in the assessment of Influenza vaccine effectiveness against influenza-related hospitalization in elderly people. J Infect Dis. 2017;216(4):405-414.
16. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. BMC Geriatr. 2008;8:24.
17. Jones DM, Song X, Rockwood K. Operationalizing a frailty index from a standardized comprehensive geriatric assessment. J Am Geriatr Soc. 2004;52(11):1929-1933.
18. Hoover M, Rotermann M, Sanmartin C, Bernier J. Validation of an index to estimate the prevalence of frailty among community-dwelling seniors. Health Rep. 2013;24(9):10-17.
19. Enders CK. Applied Missing Data Analysis. New York: Guilford Press; 2010.
20. Faris PD, Ghali WA, Brant R, et al. Multiple imputation versus data enhancement for dealing with missing data in observational health care outcome analyses. J Clin Epidemiol. 2002;55(2):184-191.
21. Schafer JL, Graham JW. Missing data: our view of the state of the art. Psychol Methods. 2002;7(2):147-177.
22. Rubin DB. Multiple Imputation for Nonresponse in Surveys. Hoboken, NJ: Wiley; 1987.
23. van Buuren S, Groothuis-Ousdhoorn K. mice: multivariate imputation by chained equations in R. J Stat Softw. 2011;45(3):1-67.
24. *R: A Language and Environment for Statistical Computing*; 2014. http://www.r-project.org/. Accessed November 28, 2014.
25. Bindawas SM, Vennu V, Moftah E. Improved functions and reduced length of stay after inpatient rehabilitation programs in older adults with stroke: a systematic review and meta-analysis of randomized controlled trials. Neuro-Rehabilitation. 2017;40(3):369-390.
26. Evans SJ, Sayers M, Mitnitski A, Rockwood K. The risk of adverse outcomes in hospitalized older patients in relation to a frailty index based on a comprehensive geriatric assessment. Age Ageing. 2014;43(1):127-132.
27. Jorgensen R, Brabrand M. Screening of the frail patient in the emergency department: a systematic review. Eur J Intern Med. 2017;45:71-73.
28. *Losing independence is a bigger ageing worry than dying*; 2009. http://www.dlf.org.uk/blog/losing-independence-bigger-ageing-worry-dying. Accessed November 19, 2019.
29. Torres OH, Munoz J, Ruiz D, et al. Outcome predictors of pneumonia in elderly patients: importance of functional assessment. J Am Geriatr Soc. 2004;52(10):1603-1609.
30. El Solh A, Pineda L, Bouquin P, Mankowski C. Determinants of short and long term functional recovery after hospitalization for community-acquired pneumonia in the elderly: role of inflammatory markers. BMC Geriatr. 2006;6:12.
31. Davydow DS, Hough CL, Levine DA, Langa KM, Iwashyna TJ. Functional disability, cognitive impairment, and depression after hospitalization for pneumonia. Am J Med. 2013;126(7):615-624. e615.
32. Andrew MK. Social vulnerability in old age. In: Fillit HM, Rockwood K, Young J, eds. Brocklehurst's Textbook of Geriatric Medicine and Gerontology. 8th ed. Philadelphia: Elsevier; 2016:185-192.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Supplementary Figure S1: Distribution of change in Barthel Index for influenza cases and other acute respiratory infection (ARI).

Supplementary Table S1: Descriptive statistics (mean (SD for continuous variables and frequency (percent) for categorical variables) for cases (influenza positives) and controls (influenza negative) (Listwise deletion).

Supplementary Table S2: Means (SD) and frequency (%) for Barthel and decline by baseline frailty (Listwise deletion).

Supplementary Table S3: Outcomes by length of stay quartiles. Mean (SD) for continuous outcomes and frequency (%) for categorical outcomes (Listwise deletion).

Supplementary Table S4: Regression coefficients and odds ratios for the linear and logistic regression models (Listwise deletion).