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Relationship Between Frailty and Respiratory Syncytial Virus Infection in Hospitalized Older Adults

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Background. This study aimed to evaluate the impact of frailty on clinical outcomes and disease severity of respiratory syncytial virus (RSV) infection in older adults using data from the CIRN SOS Network (Serious Outcomes Surveillance Network; Canadian Immunization Research Network).

Methods. This cohort study used data from the CIRN SOS Network collected during the 2012–2013, 2013–2014, and 2014–2015 influenza seasons. Patients aged ≥50 years who were hospitalized for acute respiratory illness were tested for RSV by multiplex reverse transcription–polymerase chain reaction. The analysis focused on frailty to assess its association with RSV disease severity and clinical outcomes. Frailty was categorized as *nonfrail*, *prefrail*, and *frail* according to validated cutoffs based on baseline frailty index.

Results. Among 365 older adults hospitalized for RSV-related acute respiratory infections, most were classified as frail (61.1%), with fewer classified as prefrail (28.5%) or nonfrail (10.4%). Frailty was significantly associated with severe RSV outcomes, such as prolonged hospitalization and increased oxygen therapy requirements. Specifically, frail patients experienced longer hospitalizations and higher intensive care unit admission rates, with an odds ratio of 3.48 (95% CI, 1.30–9.12) for the association between frailty and severe disease. While RSV types A and B showed no significant differences in clinical outcomes, chronic obstructive pulmonary disease and chronic kidney disease emerged as factors associated with disease severity, alongside frailty.

Conclusions. Frailty is an important predictor of RSV severity in older adults and is associated with longer hospital stays and increased health care needs. This highlights the need to consider frailty in RSV vaccine and therapeutic trials and suggests the potential benefits of interventions and public health and programmatic messaging tailored to older adults living with frailty.

Keywords. frailty; major clinical events; older adults; respiratory syncytial virus.

Respiratory syncytial virus (RSV) is a respiratory virus that typically causes mild symptoms in the upper respiratory system of adults during certain seasons. However, RSV infections can become more severe in older adults, leading to significant respiratory issues, hospitalization, and mortality [1]. The recent development and approval of vaccines targeting adult RSV present a unique opportunity to prevent severe infections caused by this virus. Vaccination against RSV is particularly important for at-risk populations, such as frail individuals and those with underlying health conditions.

Despite advancements in vaccination, decision making regarding the use of these vaccines in recommended programs and clinical settings is complicated by insufficient data on how RSV affects older adults, particularly in subgroups categorized by age, frailty level, and health conditions [2, 3]. The literature indicates that the annual prevalence of RSV among older adults residing in communities ranges from 2% to 10% in the United States, with slightly higher rates of 5% to 10% observed in group residential settings [4]. A 2015 study estimated 1.5 million RSV-linked infections annually in developed nations, with approximately 14.5% resulting in hospitalization and contributing to approximately 14 000 deaths within hospital settings [5]. Nonetheless, there remains a lack of detailed understanding of how different levels of frailty among older adults affect the outcomes of RSV infections. This study aimed to address this gap.

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Current studies highlight the importance of recognizing RSV as a threat to older adults, especially in nations with an aging population [4]. As people age, different components of the innate and adaptive immune systems undergo changes, with some being upregulated and others downregulated, leading to an overall dysregulated response to the pathogens [6]. However, the capacity to fight infections varies significantly within the same age group, making frailty a key determinant. Frailty, a multidimensional syndrome characterized by decreased reserve and diminished resistance to stressors, is an important predictor of adverse health outcomes in older adults [7, 8]. Frail individuals often experience compromised immune responses, making them more vulnerable to infections and hindering their capacity to recover from acute respiratory illnesses (ARIs), including influenza and RSV [9–11]. Despite this, frailty has not been extensively studied in relation to RSV infection. One study explored the impact of frailty on the health outcomes of older adults with RSV infections and found no association between frailty (as measured by the Groningen Frailty Index) age, or comorbidities with the occurrence or severity of RSV infections or related respiratory issues [12]. The findings of this study were restricted due to the small number of patients diagnosed with RSV infection through polymerase chain reaction testing (n = 36), of whom only 2 were classified as being frail.

A previous study by our research group examined the overall burden of RSV infection in hospitalized adults [13]. To further investigate this topic and address existing knowledge gaps, in the analysis reported here we focused on evaluating the burden of RSV infection among older adults, with emphasis on elucidating the relationship between disease severity and frailty levels. This study had 2 objectives: first, to assess how frailty affects clinical outcomes in older adults diagnosed with RSV; second, to determine the association between varying degrees of frailty and overall RSV disease severity.

METHODS

Data Source: CIRN SOS Network

The data source for this study was the Serious Outcomes Surveillance (SOS) Network of the Canadian Immunization Research Network (CIRN). Data were collected during the 3 influenza seasons from 2012 to 2015 and encompassed active surveillance for broadly defined ARIs. Surveillance activities were conducted in 5 Canadian provinces: British Columbia, Ontario, Quebec, New Brunswick, and Nova Scotia [13].

Network nurses screened all hospitalized patients aged ≥16 years who presented with ARI during the influenza season in Canada (generally November–May). ARI was broadly defined as any respiratory condition that may or may not include symptoms such as fever, cough, or unexplained fever. Nasopharyngeal swabs were collected from these patients as part of routine clinical practice. These samples were initially tested for the presence of influenza A and B viruses by reverse transcription–polymerase chain reaction (RT-PCR). Furthermore, during the study period, nasopharyngeal swabs from individuals aged ≥50 years who met the ARI criteria underwent additional analysis by multiplex RT-PCR to detect RSV and other common respiratory viruses. All nasopharyngeal swab processing was performed at the CIRN SOS Reference Laboratory within the Canadian Center for Vaccinology in Halifax, Nova Scotia, Canada, with the Seeplex RV15 One-Step ACE Detection multiplex RT-PCR assay (Seegene Inc) [14].

Study Design and Participants

This cohort study utilized epidemiologic surveillance data from the CIRN SOS Network. Participants were categorized by disease severity (nonsevere and severe) and frailty degree (nonfrail, prefrail, and frail). The eligibility criteria for inclusion in the study required individuals to (1) have a positive result for RSV from multiplex RT-PCR testing of a nasopharyngeal swab, (2) have available data on sociodemographic and clinical information with details on health outcomes, and (3) be aged ≥50 years.

Exclusion criteria were applied to individuals who tested negative for RT-PCR screening. Cases of RSV coinfection with influenza or other respiratory viruses were included in all the analyses.

The study protocol, which encompassed data collection, sample acquisition, and medical record screening, was approved by the research ethics board at each participating site. This study was registered at ClinicalTrials.gov (NCT01517191). Detailed information, including the number of participating sites and any additional locations beyond Halifax, can be found in Ethics Approval and Participation Consent in the Notes section.

Data Collection

The CIRN SOS Network adheres to a standardized data collection protocol that encompasses detailed patient demographic and clinical outcomes [11]. In this study, we retrieved data on various demographic and health-related factors. Specifically, information was collected on the patients' sex, age, and residential situation before hospital admission. Additionally, health-related data were gathered: smoking status, presence of comorbidities (any cardiopathy, congestive heart failure, chronic obstructive pulmonary disease [COPD], asthma, diabetes mellitus, neoplasms, chronic kidney disease [CKD], and immunosuppression or immunocompromised status), need for regular support in activities of daily living, and influenza vaccination status. Influenza vaccination status was classified as vaccinated in the current season, vaccinated in a prior season only, or never vaccinated and was based on the participants' immunization records at the time of enrollment. Notably, no RSV vaccines

Table 1. Sociodemographic and Clinical Characteristics of the Study Population (N = 365)

Variable	Median (IQR) or No. (%)
Age, y	76 (65–85)
50–64	85 (23.3)
65–74	83 (22.7)
75–84	101 (27.7)
≥85	96 (26.3)
Sex	
Female	233 (63.8)
Male	132 (36.2)
Baseline living	
Community private house	296 (81.1)
Assisted living/long-term care facility	64 (17.5)
Community group home	4 (1.1)
Unknown	1 (0.3)
Smoking status	
Never smoked	166 (45.5)
Former smoker	156 (42.7)
Current smoker	39 (10.7)
Unknown	4 (1.1)
Comorbidity	
Any cardiac illness	203 (55.6)
Congestive heart failure	68 (18.6)
Chronic obstructive pulmonary disease	114 (31.2)
Asthma	57 (15.6)
Diabetes mellitus	114 (31.2)
Neoplasm	89 (24.4)
Chronic kidney disease	59 (16.2)
Immunosuppressed or immunocompromised	33 (9.0)
No. of comorbidities	
0	27 (7.4)
1 or 2	225 (61.6)
≥3	113 (31)
Baseline: required regular support for activities of daily living	206 (56.4)
Season of enrollment	
2012–2013	109 (29.9)
2013–2014	139 (38.1)
2014–2015	117 (32.1)
Coinfection	
RSV/influenza	33 (9.0)
RSV/hMPV	2 (0.5)
Influenza vaccination status	
Never vaccinated	74 (20.3)
Current season vaccination	259 (71.0)
Vaccination in prior seasons only	32 (8.8)
Frailty assessment	
Frailty index	0.24 (0.14–0.36)
Cutoff	
Nonfrail, <0.08	38 (10.4)
Prefrail, ≥0.08 and <0.21	104 (28.5)
Frail, ≥0.21	223 (61.1)

Abbreviations: hMPV, human metapneumovirus; RSV, respiratory syncytial virus.

were available for older adults during the data collection period.

Frailty Assessment

Frailty was evaluated by the deficit accumulation method. Consistent with earlier studies from the CIRN SOS Network [15], we developed a frailty index (FI) by accumulating age-related deficits, which yielded a total deficit score. This score was subsequently converted into an FI ranging from 0 to 1: FI = total deficits/n, where n represents the number of components derived from age-related health issues, functional limitations, and abilities. Frailty levels were classified into 3 categories according to well-established cutoffs: nonfrail ($FI < 0.08$), prefrail ($0.08 \leq FI < 0.21$), and frail ($FI \geq 0.21$) [16]. These thresholds were chosen because of their robust validation in previous studies, which demonstrated their effectiveness in stratifying patients according to frailty-related health outcomes and risks [17, 18].

Definition of Disease Severity

All participants underwent an assessment of their disease severity. Chest radiography or computed tomography scans conducted within the first 72 hours of hospital admission were evaluated by the treating physician. The evaluating physician could have been an emergency department physician, radiologist, infectious disease specialist, or internal medicine practitioner. These medical professionals were tasked with determining whether the imaging findings indicated pneumonia.

Our study focused on the outcome of lower respiratory tract infections (LRTIs), defined as the presence of ≥3 symptoms or signs, as used in studies on the RSVPreF vaccine [2, 3, 19]. We used a composite scoring system combining symptoms and radiologic findings to classify LRTI cases. Specifically, LRTI was defined as the presence of ≥3 of the following symptoms: cough, wheezing, sputum production, dyspnea, and pneumonia confirmed through chest radiography.

Severe RSV infection was defined as the presence of at least 1 of the following conditions: LRTI, need for supplemental oxygen during hospitalization, admission to the intensive care unit (ICU), need for mechanical ventilation, or mortality from any cause within 30 days of hospital admission. Cases that did not meet these criteria were classified as "nonsevere."

Hospital Outcomes

Patient data were collected from hospital admission to discharge or death. The outcomes examined included 30-day in-hospital mortality, length of hospital stay, and potential complications, including the requirement for supplemental oxygen therapy, mechanical ventilation, and ICU admission. These outcomes were analyzed with a specific focus on stratifying patients according to their frailty levels to elucidate the association between frailty and severity of RSV infection.

Table 2. Clinical Characteristics According to Disease Severity

Variable	No. (%) or Median (IQR)			*P* Value
	Overall (N = 365)	Nonsevere (n = 55)	Severe (n = 310)	
Age, y				
50–64	85 (23.3)	16 (29.1)	69 (22.3)	.452
65–74	83 (22.7)	13 (23.6)	70 (22.6)	
75–84	101 (27.7)	16 (29.1)	85 (27.4)	
≥85	96 (26.3)	10 (18.2)	86 (27.7)	
Sex				
Female	233 (63.8)	33 (60.0)	200 (64.5)	.624
Male	132 (36.2)	22 (40.0)	110 (35.5)	
Smoking status				
Never smoked	166 (45.5)	31 (56.4)	135 (43.5)	.293
Former smoker	156 (42.7)	19 (34.5)	137 (44.2)	
Current smoker	39 (10.7)	4 (7.3)	35 (11.3)	
Unknown	4 (1.1)	1 (1.8)	3 (1.0)	
Comorbidity				
Any cardiac illness	203 (55.6)	28 (50.9)	175 (56.5)	.538
Congestive heart failure	68 (18.6)	8 (14.5)	60 (19.4)	.511
Chronic obstructive pulmonary disease	114 (31.2)	5 (9.1)	109 (35.2)	<.001
Asthma	57 (15.6)	9 (16.4)	48 (15.5)	>.99
Diabetes mellitus	114 (31.2)	18 (32.7)	96 (31.0)	.919
Neoplasm	89 (24.4)	13 (23.6)	76 (24.5)	>.99
Chronic kidney disease	59 (16.2)	4 (7.3)	55 (17.7)	.080
Immunosuppressed or immunocompromised	33 (9.0)	8 (14.5)	25 (8.1)	.197
Influenza vaccination status				
Unvaccinated in the current season	106 (29.0)	25 (45.5)	81 (26.1)	<.001
Current season vaccination	259 (71.0)	30 (54.5)	229 (73.9)	
Frailty assessment				
Frailty index	0.24 (0.14–0.36)	0.19 (0.09–0.29)	0.26 (0.15–0.37)	.002
Cutoff				.016
Nonfrail, <0.08	38 (10.4)	11 (20.0)	27 (8.7)	
Prefrail, ≥0.08 and <0.21	104 (28.5)	18 (32.7)	86 (27.7)	
Frail, ≥0.21	223 (61.1)	26 (47.3)	197 (63.5)	
RSV infection status				
RSV monoinfection	330 (90.4)	48 (87.3)	282 (91.0)	.496
RSV/hMPV coinfection	2 (0.5)	0 (0.0)	2 (0.6)	
RSV/influenza coinfection	33 (9.0)	7 (12.7)	26 (8.4)	
Chest x-ray/CT scan				
Normal	37 (10.1)	14 (25.5)	23 (7.4)	<.001
Altered				
No pneumonia	277 (75.9)	40 (72.7)	237 (76.5)	
Pneumonia	49 (13.4)	1 (1.8)	48 (15.5)	
Not available	2 (0.5)	0 (0.0)	2 (0.6)	
Symptom				
Cough	319 (87.4)	42 (76.4)	277 (89.4)	.014
Wheezing	114 (31.2)	6 (10.9)	108 (34.8)	<.001
Sputum production	194 (53.2)	14 (25.5)	180 (58.1)	<.001
Shortness of breath	285 (78.1)	16 (29.1)	269 (86.8)	<.001

Abbreviations: CT, computed tomography; hMPV, human metapneumovirus; RSV, respiratory syncytial virus.

Statistical Analysis

Quantitative data are expressed as median (IQR), followed by an assessment of normality with the Shapiro-Wilk test. Categorical data are presented as absolute numbers, accompanied by their relative frequencies in parentheses. The Brown-Mood median test was used to compare quantitative data, whereas the Pearson χ^2 test was used to compare categorical data.

We employed ridge regression modeling to identify the factors associated with severe RSV infection. This method was selected over nonpenalized regression to address potential multicollinearity among predictor variables and to enhance the

Table 3. Clinical Outcomes According to Frailty Status

Parameter	No. (%) or Median (IQR)			*P* Value
	Overall (N = 365)	Nonfrail,[a] <0.21 (n = 142)	Frail, ≥0.21 (n = 223)	
Disease severity				
Nonsevere	55 (15.1)	29 (20.4)	26 (11.7)	.033
Severe	310 (84.9)	113 (79.6)	197 (88.3)	
Comorbidity				
Any cardiac illness	203 (55.6)	44 (31.0)	159 (71.3)	<.001
Congestive heart failure	68 (18.6)	7 (4.9)	61 (27.4)	<.001
Chronic obstructive pulmonary disease	114 (31.2)	30 (21.1)	84 (37.7)	.001
Asthma	57 (15.6)	37 (26.1)	20 (9.0)	<.001
Diabetes mellitus	114 (31.2)	24 (16.9)	90 (40.4)	<.001
Neoplasm	89 (24.4)	36 (25.4)	53 (23.8)	.827
Chronic kidney disease	59 (16.2)	4 (2.8)	55 (24.7)	<.001
Immunosuppressed or immunocompromised	33 (9.0)	19 (13.4)	14 (6.3)	.034
Chest x-ray/CT scan				.039
Normal	37 (10.1)	19 (13.4)	18 (8.1)	
Altered				
No pneumonia	277 (75.9)	98 (69.0)	179 (80.3)	
Pneumonia	49 (13.4)	23 (16.2)	26 (11.7)	
Not available	2 (0.5)	2 (1.4)	0 (0.0)	
In-hospital mortality				
7 d	5 (1.4)	0 (0.0)	5 (2.2)	.181
30 d	12 (3.3)	1 (0.7)	11 (4.9)	.056
Length of hospitalization, d	7 (4–11)	4 (3–7.75)	8 (5–13)	<.001
Complication				
Oxygen therapy during admission	279 (76.4)	94 (66.2)	185 (83.0)	<.001
Mechanical ventilation	26 (7.1)	7 (4.9)	19 (8.5)	.275
Admission to the intensive care unit				
7 d	46 (12.6)	11 (7.7)	35 (15.7)	.038
30 d	49 (13.4)	12 (8.5)	37 (16.6)	.038

Abbreviation: CT, computed tomography.

[a]Nonfrail includes nonfrail (<0.08) and prefrail (≥0.08, ≤0.21) cutoffs.

stability and predictive accuracy of the model, acknowledging that clinical data sets often contain complex interrelationships and varying degrees of correlation between the variables [20]. The dependent variable in our analysis was disease severity, and the independent variables were those identified in the literature as predictors of poorer clinical outcomes in RSV infections. These included demographic factors such as age and sex and health conditions such as cardiopathies, congestive heart failure, COPD, asthma, diabetes mellitus, neoplasms, CKD, and immunosuppression or immunocompromised status [1, 21, 22]. Frailty was introduced as an additional variable of interest to assess its association with disease severity. Ridge regression was used to estimate the odds ratio and 95% CI for each predictor, enabling a robust quantification of its association with disease severity. Odds ratios were derived by exponentiating the model coefficients, and 95% CIs were approximated via bootstrapping (5000 resamples).

Statistical significance was assessed by a 2-sided *P* value <.05. All analyses were performed with R version 4.4.0 (Puppy Cup release) and RStudio IDE version 2024.12.0+467 (Kousa Dogwood release).

Sensitivity Analysis

Sensitivity analysis was conducted to investigate whether there were statistically significant differences in the clinical presentation or outcomes between patients infected with RSV A and RSV B (as identified during the initial multiplex RT-PCR testing).

RESULTS

Study Population

This study examined 365 older adults who were hospitalized for RSV-related acute respiratory infections. Table 1 outlines the participants' sociodemographic and clinical characteristics. The median age was 76 years (IQR, 65–85), 27.7% were aged 75 to 84 years, and 26.3% were aged ≥85 years. The majority (63.8%) were women, and 81.1% resided in private community houses. Among the participants, 45.5% had never smoked, and

Table 4. Ridge Regression Model Results Identifying Factors Associated With Disease Severity

Parameter	Odds Ratio (95% CI)
Age, y	1.00 (.99–1.02)
Sex	
Female	1 [Reference]
Male	0.87 (.62–1.22)
Frailty index	**3.48 (1.30–9.12)**
Comorbidity	
Any cardiac illness	1.00 (.73–1.37)
Congestive heart failure	1.03 (.71–1.54)
Chronic obstructive pulmonary disease	**2.07 (1.54–2.67)**
Asthma	1.11 (.71–1.73)
Diabetes mellitus	0.87 (.62–1.20)
Neoplasm	1.13 (.79–1.62)
Chronic kidney disease	**1.54 (1.05–2.20)**
Immunosuppressed or immunocompromised	0.72 (.42–1.28)

Values in bold indicate those that demonstrated statistical significance.

42.7% were former smokers. In terms of comorbidities, 55.6% of the participants had preexisting cardiac illnesses. COPD and diabetes mellitus were preexisting conditions in 31.2% of the participants. Additionally, 24.4% had cancer, 18.6% had congestive heart failure, and 15.6% had asthma. Regarding the need for support in activities of daily living, 56.4% of the patients required regular assistance. Frailty status was evaluated by the FI, with a median 0.24 (IQR, 0.14–0.36), indicating that 61.1% were classified as frail, 28.5% as prefrail, and 10.4% as nonfrail. Of 365 patients, RSV-influenza coinfections were detected in 33 (9.0%), whereas 2 (0.5%) had RSV/human metapneumovirus.

Disease Severity

Several differences were identified between the nonsevere and severe disease groups (Table 2). Severe cases were more prevalent in the age groups of 75 to 84 years (27.4%) and ≥85 years (27.7%) than in the 50- to 74-year age group. However, this difference was not statistically significant ($P = .45$).

COPD was significantly more prevalent in the severe group (35.2% vs 9.1%, $P < .001$). The median FI was significantly higher in severe cases (0.26; IQR, 0.15–0.37) than nonsevere cases (0.19; IQR, 0.09–0.29; $P = .002$). Notably, frail patients were overrepresented in the severe group (63%) as compared with the nonsevere group (47.3%, $P = .016$). Radiologic results indicated that 15.5% of patients with severe illness showed signs of pneumonia on imaging, as opposed to 1.8% in the nonsevere group. Furthermore, patients with severe disease had higher rates of cough (89.4% vs 76.4%, $P = .014$), wheezing (34.8% vs 10.9%, $P < .001$), and sputum production (58.1% vs 25.5%, $P < .001$), highlighting the symptomatic differences between the groups.

Clinical Outcomes

Table 3 presents the clinical outcomes of the study cohort stratified according to frailty status. The data indicated that 84.9% of patients were classified as having severe disease, with a higher proportion observed in frail individuals (88.3%) than in their nonfrail counterparts (79.6%, $P = .033$). Radiologic evaluations revealed that 75.9% of patients had abnormal findings without pneumonia, whereas 13.4% were diagnosed with pneumonia. The prevalence of pneumonia was marginally lower in frail patients (11.7%) than in nonfrail individuals (16.2%).

The 7-day in-hospital mortality rate was 1.4%, with all deaths occurring among frail patients (2.2%) and none occurring in the nonfrail group ($P = .18$). For 30-day in-hospital mortality, frail patients accounted for 4.9%, as compared with 0.7% in the nonfrail group, although this difference was not statistically significant ($P = .056$). Regarding hospitalization duration, frail patients exhibited a significantly longer median length of stay of 8 days (IQR, 5–13), as opposed to 4 days for nonfrail patients (IQR, 3–7.75; $P < .001$). Oxygen therapy was more frequently required by frail patients (83.0%) than by nonfrail patients (66.2%, $P < .001$). Mechanical ventilation was required in 7.1% of the cases overall, with no significant difference between the frail and nonfrail groups. ICU admission rates were higher among frail patients for the 7-day period (15.7% vs 7.7%, $P = .038$) and 30-day period (16.6% vs 8.5%, $P = .038$).

Factors Associated With Severe RSV Infection

As shown in Table 4, frailty, COPD, and CKD were significantly associated with RSV infection severity in older adults, according to the ridge regression model. The odds ratio was 3.48 (95% CI, 1.30–9.12) for frailty, 2.07 (95% CI, 1.54–2.67) for COPD, and 1.54 (95% CI, 1.05–2.20) for CKD. Other variables in the model, including age, sex, cardiopathies, congestive heart failure, asthma, diabetes mellitus, cancer, and immunosuppression, did not demonstrate statistically significant associations.

Sensitivity Analysis

Supplementary Table 1 presents the sensitivity analysis of the clinical outcomes associated with RSV types A and B in 365 patients (169 with RSV-A and 196 with RSV-B). The analysis revealed no statistically significant differences in comorbidities, frailty, or disease severity between the groups. Mortality rates, hospitalization durations, and complications (eg, oxygen therapy, mechanical ventilation, and ICU admission) were also comparable.

DISCUSSION

Our analysis underscores the key role of frailty in influencing clinical outcomes, such as disease severity and hospitalization characteristics, in older adults diagnosed with RSV. Frailty was associated with longer hospital stays and a higher need

for oxygen therapy, emphasizing its impact on treatment intensity and recovery duration. Moreover, frail patients exhibited a greater likelihood of severe disease presentation than their nonfrail counterparts, effectively illustrating the association between increased frailty and heightened disease severity. Although mortality rates within 7 and 30 days showed no statistically significant differences between the frail and nonfrail groups, the pronounced severity of symptoms and extended length of hospital stay among frail patients highlight the burden of frailty on clinical outcomes. Additionally, while our analysis did not find statistically significant variations in outcomes between RSV subtypes A and B, it affirms the substantial threat that RSV poses to older adults, irrespective of the subtype.

RSV infection is associated with significant morbidity and mortality in individuals aged ≥65 years [1, 4, 23, 24]. Previous findings indicate that when compared with influenza, RSV can lead to longer hospital stays (≥7 days), secondary bacterial pneumonia, ICU admissions, exacerbated COPD, and increased mortality within 1 year of admission [25]. Comparing RSV and influenza outcomes in hospitalized adults with ARIs showed a higher prevalence of conditions such as congestive heart failure or COPD in those with RSV, as well as longer hospital stays and a greater need for mechanical ventilation [23, 24]. As seen with influenza, evidence highlights the severe impact of RSV in older adults, particularly those with existing health conditions [13]. Importantly, hospitalization for ARI, especially lengthy stays, often results in functional decline [26], increased frailty [10], and risk of institutionalization [27]. This aligns with our findings, emphasizing the role of frailty in worsening clinical outcomes in patients with RSV.

While the CIRN SOS Network recently described the burden of RSV in adults aged ≥50 years [13], the present study focused on assessing the relationship between disease severity and frailty levels. Our investigation demonstrated that frailty is a significant factor influencing adverse outcomes in older adults hospitalized with RSV infection. In a broader academic context, frailty is recognized as an important condition associated with increased vulnerability to various illnesses, including respiratory disease. Frailty affects immune function, reducing the body's ability to combat infections effectively, which leads to severe consequences when infected with viruses such as RSV [28]. Existing research has primarily focused on influenza, demonstrating that frailty predicts severe disease progression and increases health care utilization. However, specific studies directly linking frailty to RSV outcomes in older adults are limited. This gap presents an opportunity for our findings to contribute substantially to the literature by confirming the impact of frailty. Our findings emphasize the importance of frailty assessment in the management of RSV, supporting the implementation of health care strategies that incorporate frailty screening and targeted interventions to mitigate the disease burden in frail older adults.

Frailty, COPD, and CKD were the most significant factors associated with RSV infection severity in our cohort. Among adults residing in community settings, the presence of a symptomatic chronic cardiac or respiratory disease and residence in a long-term care facility were associated with an increased probability of hospitalization and utilization of outpatient medical services during RSV infection [1]. Moreover, COPD has been extensively documented as a risk factor for respiratory infections due to compromised lung function, which affects disease progression and severity [29]. Similarly, CKD is associated with immune system dysfunction, increased vulnerability to infections, and complicated clinical outcomes [30]. While individual studies have emphasized these conditions as general infection risks, detailed studies focusing on their role in RSV infection severity in older adults are scarce. Our findings shed light on the compounded risk of these comorbidities in the aging population with RSV infection, reinforcing the need for comprehensive health management strategies that consider chronic conditions alongside acute viral infections. This study integrates and extends previous knowledge, aligning with calls for personalized medical approaches catering to individual health profiles, particularly in older adults.

Our analysis revealed that frail patients with RSV required significantly longer hospitalizations than their nonfrail counterparts. Academic consensus reinforces that frailty is associated with prolonged hospital stays, attributed to reduced physiologic reserves, which exacerbate recovery periods and elevate the risk of complications [31]. Research on health services has repeatedly shown that frail individuals not only stay longer but also require more intensive and expensive care [32]. Comparatively, findings in influenza cases revealed similar patterns, highlighting how frailty magnifies recovery challenges [33]. A longer hospital stay is an important metric, as it also predisposes patients to deconditioning, incomplete mobility and functional recovery, and the need for increased caregiver support from sources both informal (family and friend) and formal (home care and nursing home admission) [34, 35]. While previous research did not yield RSV-specific insights [36], our investigation established clear parallels in patients admitted with RSV infection, emphasizing that frailty predisposes patients to extended care requirements, irrespective of the respiratory virus involved.

Our sensitivity analysis revealed no statistically significant differences in disease severity or clinical outcomes between RSV-A and RSV-B. This observation contributes to the understanding that preventive and therapeutic interventions for RSV infections in older adults may not require subtype-specific modifications, while emphasizing the importance of broad-spectrum strategies.

Our study is timely, given that advancements in RSV prevention are poised to alter public health strategies. Until now, RSV control has primarily relied on infection control measures

and hygiene maintenance. The recent approval of the first vaccine for adults aged ≥60 years by the US Food and Drug Administration in May 2023 marks an important development in RSV management [37]. Despite these advancements, current RSV management remains centered on supportive care owing to the lack of a broadly effective antiviral treatment for older adults. Ribavirin, an antiviral drug, is seldom used because of insufficient evidence supporting its effectiveness in this context [38]. This ongoing challenge is reflected in the literature, which outlines the substantial risks of RSV and the need for expanded treatment options. Existing management strategies, as noted in various studies, focus on maintaining patient stability through supportive care rather than directly treating the virus itself. Although antiviral protocols have been established for influenza to shorten the duration of illness, RSV management lags behind, highlighting the urgent need for new therapeutic solutions.

Although our study effectively explored the relationship between frailty and RSV outcomes, it has several limitations. Although the sample sizes of the frail and nonfrail patients were comparable, subtle differences were observed between the cohorts. These findings highlight the significance of frailty in influencing disease severity and clinical outcomes. However, the initial data collection focused on influenza rather than RSV, which may have affected the recruitment process for a wider range of frailty categories in this study. The literature suggests that targeted recruitment based on frailty may enhance our understanding of its role in RSV infection.

Our use of RV15 multiplex testing to identify RSV, instead of the more sensitive real-time RT-PCR, may have limited the detection of coinfections. Nevertheless, our audit revealed no inconsistencies in the testing methods employed. Another limitation is that the CIRN SOS surveillance testing was performed with nasopharyngeal swabs, potentially missing severe cases if the virus was localized in the lower respiratory tract. This limitation is well documented in the adult RSV testing literature, highlighting the need for more comprehensive testing approaches to ensure a detailed assessment of the extent of infection in hospitalized patients [39]. The SOS Network was designed for influenza surveillance; as such, data collection was conducted during the influenza seasons. RSV and influenza seasonality tended to be similar but not identical; therefore, we may have missed RSV circulation outside the surveillance window. In another recent CIRN SOS Network study focusing primarily on RSV disease burden and prevalence, the limitations were similar to those of the present study [13].

These challenges are consistent with the broader literature, highlighting the difficulties posed by seasonal and operational limitations in the accurate diagnosis of RSV infections. Furthermore, our findings may have underestimated the true impact of frailty on RSV-related outcomes in adults. It is possible that some frail individuals had limitations in the use of mechanical respiratory support due to preexisting do-not-resuscitate or do-not-intubate directives, which could have influenced the observed differences in disease severity between the groups. This underscores the complexity of RSV management in older adults and highlights the need for future studies that incorporate end-of-life care decisions into their analyses.

CONCLUSIONS

This study highlights the significant impact of frailty on the severity and clinical outcomes of RSV infections in older adults. The notable distinction between frail and nonfrail patients underscores the need for targeted health care strategies, particularly in hospitalized populations, where frailty may contribute to prolonged hospital stays, higher resource utilization, and increased risk of complications. Although the recent approval of RSV vaccines for older adults offers hope for reducing infection rates, the management of RSV remains challenging, given the limited availability of effective antiviral treatments. Our findings suggest that including frail populations in vaccine trials is necessary to ensure efficacy across diverse patient groups. Frailty could also be specifically considered among high-risk groups, particularly those recommended to receive RSV vaccination in the National Immunization Technical Advisory Group's advice and public immunization programs. Despite certain limitations, such as influenza-focused initial data collection and potential underdiagnosis due to seasonal constraints, our research provides meaningful insights into the impact of RSV in older adults, particularly those living with frailty. Future efforts should focus on refining diagnostic tests, enhancing preventive measures, and developing comprehensive care strategies to address the complexities of RSV and its associated comorbidities. Implementing these strategies is essential to ease the clinical and logistical challenges posed by RSV in health care systems, especially as the demographic trend toward an aging population continues to grow.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Author contributions. HP: conceptualization, methodology, software, validation, formal analysis, and writing. JM: conceptualization, methodology, and writing. MKA: conceptualization, investigation, supervision, overall project administration, and writing. SAM: conceptualization, investigation, supervision, overall project administration, and writing. JL: investigation, resources, and writing. TFH: investigation, resources, and writing. ME: investigation, resources, and writing. All authors provided

key insights into the interpretation of the analyses and contributed to manuscript revisions. All authors approved the final manuscript.

Availability of data and materials. The data sets generated and/or analyzed during the current study are not publicly available because of confidential patient data; however, the data sets are available from the corresponding author upon reasonable request.

Disclaimer. The authors are solely responsible for the final content and interpretation of the manuscript. None of the funders were involved in the analyses, interpretation of the findings, or manuscript writing.

Ethics approval and participation consent. This study adhered to the ethical standards established by the local research ethics boards (REBs). Prior to supplemental testing and secondary use of data from the CIRN SOS Network, approval was granted by the REBs at IWK (REB 1024817) and Nova Scotia Health (REB 1024818). The research protocol conformed to ethical guidelines across all participating institutions and received approval from their REBs, including those at Nova Scotia Health (Halifax site), Mount Sinai Hospital (Mount Sinai and Toronto Invasive Bacterial Diseases Network sites), Hamilton Health Sciences/McMaster Health Sciences (Hamilton site), University of British Columbia Clinical (Vancouver site), Ottawa Health Science Network (Ottawa site), Comité d'éthique de la recherche du Centre hospitalier universitaire de Québec (Québec City site), Comité d'éthique de la recherche sur l'humain du Centre Hospitalier Universitaire de Sherbrooke (Sherbrooke site), Horizon Health Network (Saint John site), Montreal General Hospital (Montreal site), North York General (North York site), Toronto East General Hospital (Toronto East site), William Osler Health System (William Osler site), and Health Sciences North (Sudbury site).

In compliance with local REB requirements, written consent was obtained from the patients at the time of their enrollment. For specific seasons, when no additional study involvement or biological sample collection beyond routine influenza testing was necessary, the REBs permitted a waiver of consent for the collection of anonymized public health surveillance data because of the critical role of the study in producing unbiased surveillance data. This protocol, registered under ClinicalTrials.gov (NCT01517191), meets the standards required for ethical research and reflects the requisite approval from the ethics committees.

Data collection, sharing, and management were conducted in compliance with ethical standards and privacy regulations, including the memorandum of understanding among the principal investigators, Dalhousie University, and the Public Health Agency of Canada. The data were securely entered into the DACIMA web-based data capture system, in which personally identifiable information was coded and removed to ensure confidentiality of the data.

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