GLOBAL HEART

Heart Failure after Laboratory Confirmed Influenza Infection (FLU-HF)

ORIGINAL RESEARCH

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ABSTRACT

Background: Influenza has been shown to exacerbate heart failure (HF). Importantly, no study to date has examined the relationship between HF hospitalizations (HFH) with laboratory confirmed influenza infections. This study evaluated the association between laboratory confirmed influenza infection and HFH in the two largest hospitals in Saskatchewan, Canada.

Methods: We used a retrospective self-controlled case series design to evaluate the association between laboratory-confirmed influenza infection and HFH. We compared the incidence ratio for HFH during the influenza risk interval with the control interval. We defined the influenza risk interval as the seven days after a laboratory confirmed influenza result and the control interval as one year before and after the risk interval.

Results: We identified 114 HFH that occurred within one year before and after a positive test result for influenza between April 1, 2010, and April 30, 2018. Of these, 28 (28 admissions per week) occurred during the risk interval and 86 (0.853 admissions per week) occurred during the control interval. The incidence ratio of a HFH during the risk interval as compared with the control interval was 33.53 (95% confidence interval [CI], 21.89 to 51.36). A decline in incidence was observed after day seven; between days 8 to 14 and 14 to 28 incidence ratios was 0.91 (95% CI, 0.13 to 6.52) and 0.91 (95% CI, 0.22 to 3.68) respectively.

Conclusion: We have observed a significant association between acute influenza infection and HFH. However, further research with a larger sample size and involving a multicenter setting is warranted.

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This study was funded by the University of Saskatchewan College of Medicine Research Award 2018. It was reviewed and approved on ethical grounds by the research ethics board of the former Regina Qu'Appelle Health Region, Regina, SK, Canada (REB/18-70). For this study, it was impracticable for informed consent to be obtained. As such, a waiver of informed consent was granted by the research ethics board. The study was performed in accordance with the relevant guidelines and regulations as outlined by the former Regina Research Ethics Board, Saskatchewan Health Authority, Regina, SK, Canada.

STUDY DESIGN

We screened all subjects with positive influenza respiratory specimens between April 1, 2010 and April 30, 2018 from the Roy Romanow Provincial Laboratory in Saskatchewan, Canada. Of these cases, we identified those that were hospitalized with HF as the primary diagnosis at discharge ascertained from administrative data from Saskatchewan Health Authority health records. We used the following International Classification of Diseases 10 diagnostic codes: I50.0 (Congestive heart failure), I50.1 (Left ventricular failure) and I50.9 (Heart failure, unspecified). Based on the average influenza viral shedding period, we defined the influenza risk interval as the seven days after a respiratory specimen was confirmed by the laboratory to be positive for influenza [2, 9]. We defined the influenza control interval as the 52 weeks before and 51 weeks after the risk interval (Figure 1) [2]. Further stratification allowed patients admitted with HF during the influenza risk interval to be compared with patients admitted with HF during the influenza control interval (Figure 2). Eligibility requirements at screening included an age of 18 years or older, and a HFH that occurred within 52 weeks before and after a positive influenza test between April 1, 2010, and April 30, 2018. Exclusion criteria included HFHs with acute coronary syndrome as a concurrent diagnosis, if the presence of HF could not be objectively determined using the above inclusion criteria, or if hospital records were incomplete. We restricted the analysis to the first event in an episode of care by excluding admissions within 30 days after a previous hospital discharge for HF for the same patient.

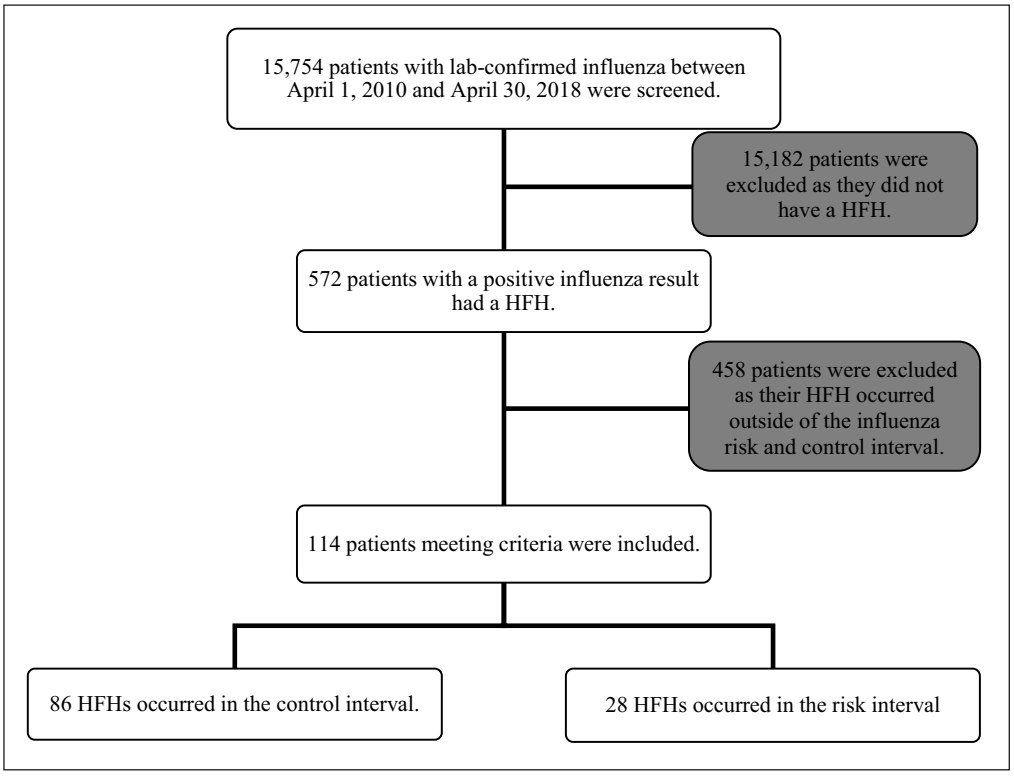

Figure 2 Flow of Study Participants. Influenza positive patients stratified based on their heart failure hospitalization (HFH) during the influenza risk interval compared to the control interval.

STUDY PROCEDURES

Data about respiratory specimens were obtained from the Roy Romanow Provincial Laboratory. Consistent high-specificity laboratory methods (reverse-transcriptase polymerase chain reaction (PCR; monoplex or multiplex assays), viral culture, direct fluorescent antibody staining, and enzyme immunoassays) confirmed influenza infection. The following viruses

were of interest to our study: Influenza A and Influenza B. Data collection including subject demographic information, comorbidities, medications, laboratory tests, and diagnostic imaging reports were conducted by an investigator familiar with the study protocol. The subject record documented the subject's study identification, demographic information meeting the inclusion and exclusion criteria, discharge diagnostic codes and supporting clinical information. Pertinent clinical information was also included: echocardiogram showing ejection fraction (EF), current medications, comorbid conditions, elevated plasma B-type natriuretic peptide (BNP) level of at least 150 pg per milliliter or an N-terminal pro-BNP (NT-pro BNP) level ≥ 600 pg per milliliter [1, 7].

STATISTICAL ANALYSIS

Incidence ratios were estimated with the use of a fixed-effects conditional Poisson regression model. In terms of sample size calculation, Musonda et al. (2006) described a formula where 97 participants would be needed to achieve 80% power [10]. Statistical analysis was performed using SPSS Statistics software (Version 22.0. Armonk, NY: IBM Corporation). The incidence ratio for HFHs during the influenza risk interval as compared to the control interval was determined using the ratio of the incidence rate in the risk interval group divided by the incidence rate in the control interval group [2]. The incidence rate was ascertained by dividing the number of HFHs by the number of weeks in that interval; for the risk interval, it would be one week and for the control interval, it would be 103 weeks. In addition to the primary analysis that defined the influenza risk interval as day one to seven after the index date, we also considered narrower risk intervals (day one to three) and alternative intervals (day eight to 14 and day 15 to 28). Chi-square test was used as a test of significance to compare differences between groups for categorical data. We performed analyses in subgroups defined according to age (≤65 years vs. >65 years), gender, virus type (influenza A [all subtypes] vs. B), history of ischemic heart disease and diabetes (yes vs. no). We evaluated the presence of interactions in these subgroups. Statistical significance would be set at $p < 0.05$.

RESULTS

We identified 15,754 subjects with positive influenza respiratory specimens between April 1, 2010 and April 30, 2018; 8188 were from the city of Regina and 7566 from Saskatoon. Of these, 572 patients (396 from Regina and 176 from Saskatoon) were admitted to hospital with HF as the primary diagnosis at discharge. We excluded 458 patients as their HFH occurred 52 weeks after their positive influenza result (Figure 2). Therefore, in this retrospective population-based analysis, 114 HFHs occurred within 52 weeks before and after a positive test result for influenza. The characteristics of the patients at baseline were balanced between the risk interval and control interval groups (Table 1). The mean age of the study population was 82.6 years (standard deviation 12.9) and 42.1% of the patients were female, of which 79.8% (n = 91) were from Regina and 20.2% (n = 23) were from Saskatoon. The mean EF was 46.11% ± 14.5 and mean BMI was 29.8 kg/m^2 ± 9.2. The median BNP was 700.50 pg/mL. Majority of infections (83.3%) were due to influenza A which is consistent with Canadian epidemiologic data from that time period [4].

Table 1 Baseline Characteristics.

	TOTAL N = 114	RISK INTERVAL N = 28	CONTROL INTERVAL N = 86	P-VALUE
Gender, n (%)				0.16
Male	66 (57.9)	13 (46.4)	53 (61.6)	
Female	48 (42.1)	15 (53.6)	33 (38.4)	
Coronary Artery Disease, n (%)				0.51
No	79 (69.3)	18 (64.3)	61 (70.9)	
Yes	35 (30.7)	10 (35.7)	25 (29.1)	

(Contd.)

	TOTAL N = 114	RISK INTERVAL N = 28	CONTROL INTERVAL N = 86	P-VALUE
Hypertension, n (%)				0.14
No	22 (19.3)	3 (10.7)	19 (22.1)	
Yes	92 (81.7)	25 (89.3)	67 (77.9)	
Diabetes, n (%)				0.28
No	63 (55.3)	13 (46.4)	50 (58.1)	
Yes	51 (44.7)	15 (53.6)	36 (41.9)	
Dyslipidemia, n (%)				0.26
No	90 (78.9)	20 (71.4)	70 (81.4)	
Yes	24 (21.1)	8 (28.6)	16 (18.6)	
Cerebrovascular Disease, n (%)				0.12
No	96 (84.2)	26 (92.9)	70 (81.4)	
Yes	18 (15.8)	2 (7.1)	16 (18.6)	
Smoking, n (%)				0.42
No	84 (73.7)	19 (67.9)	65 (75.6)	
Yes	30 (26.3)	9 (32.1)	21 (24.4)	
Peripheral Vascular Disease, n (%)				0.61
No	105 (92.1)	26 (92.9)	79 (91.9)	
Yes	9 (7.9)	2 (7.1)	7 (8.1)	
Mean BMI (kg/m²) ± SD	29.82 ± 9.2	27.74 ± 8.2	30.35 ± 9.5	0.35
Mean EF (%) ± SD	46.1 ± 14.5	47.2 ± 13.9	45.6 ± 14.9	0.72
Median BNP (pg/mL) (IQR)	700.50 (922)	729.69 (1135)	657 (773)	0.58

Twenty-eight HFHs occurred during the influenza risk interval and 86 HFHs occurred during the control interval. Specifically, there were 28 HFHs in the one week after a patient's respiratory specimen was positive for influenza and only 0.835 HFHs occurred per week in the 52 weeks before and 51 weeks after the risk interval. Therefore, the incidence rate of the influenza risk interval was 28 because 28 HFHs occurred in one week, and the incidence rate in the control interval was 0.835 because 86 HFHs occurred in 103 weeks (Table 2).

Table 2 Incidence Rate and Ratio Sample Calculation.

INFLUENZA TIME INTERVAL	INCIDENCE RATE	INCIDENCE RATIO
Risk Interval	$\frac{28 HFHs}{1 week} = 28 HFH/week$	$\frac{28 HFHs/week}{0.835 HFHs/week} = 33.53$
Control Interval	$\frac{(54+32) HFHs}{(52+51) weeks} = 0.835 HFHs/week$	

Consequently, the incidence ratio of HFH during the risk interval as compared with the control interval was 33.53 (95% CI, 21.89 to 51.36). In looking at the first three days of the risk interval, the incidence ratio for HFHs is even higher at 55.23 (95% CI, 35.21 – 86.64) (Figure 3). Evidently, the first few days following a positive influenza result is the driving factor behind the increased incidence ratio for HFHs during the influenza risk interval. A decline in incidence was observed after day seven; between day's eight to 14 and 14 to 28 incidence ratios was 0.91 (95% CI, 0.13 to 6.52) and 0.91 (95% CI, 0.22 to 3.68) respectively (Figure 3).

In the subgroup analyses, an elevated incidence of HFHs after influenza infection was observed among adults older than 65 years of age but not for younger adults. However, the difference was not statistically significant (p = 0.23). The incidence ratios were higher for influenza B than