Relation of Concomitant Heart Failure to Outcomes in Patients Hospitalized With Influenza

Muhammad Siyab Panhwar, MD[a], Ankur Kalra, MD[b], Tanush Gupta, MD[c], Dhaval Kolte, MD, PhD[d], Sahil Khera, MD, MPH[e], Deepak Bhatt, MD, MPH[f], and Mahazarin Ginwalla, MD, MS[g,*]

Influenza is a major public health challenge. Patients hospitalized with influenza who also have heart failure (HF) may be at risk for worse outcomes compared with patients without HF. There is a lack of large studies examining this issue. We queried the 2013 to 2014 National Inpatient Sample for all adult patients (aged ≥ 18 years) admitted with influenza with and without concomitant HF. Using propensity score matching, patients were matched across demographics, discharge weights, and comorbidities. Outcomes included in-hospital mortality, complications, length of stay, and average hospital costs. Of 218,540 influenza hospitalizations, 45,460 (20.8%) had concomitant HF. Patients with HF had higher in-hospital mortality (6.1% vs 3.8%, adjusted odds ratio [aOR] 1.66 [95% confidence interval [CI] 1.44 to 1.91]; p <0.001), acute kidney injury (29.5% vs 22.2%, aOR 1.47 [95% CI 1.37 to 1.57]; p <0.001), acute kidney injury requiring dialysis (2.0% vs 1.0%, aOR 2.08 [1.62 to 2.67], acute respiratory failure (36.2% vs 23.5%, aOR 1.85 [1.73 to 1.97]; p <0.001), and acute respiratory failure requiring mechanical ventilation (17.1% vs 9.3%, OR 2.01 [1.84 to 2.21]; p <0.001), longer length of stay (5.70 ± 0.02 days vs 4.60 ± 0.01 days, p <0.001) and higher average hospital costs ($11,609 ± $52 vs $9,003 ± $38, p <0.001). In conclusion, in patients hospitalized with influenza, HF is associated with increased risk of in-hospital mortality and complications. Our results highlight a need for early recognition and aggressive treatment of HF in these patients to try to improve outcomes. **(Am J Cardiol 2019;123:1478−1480)**

Influenza poses a major challenge to public health in the United States.[1] We recently showed that in patients hospitalized with heart failure (HF), influenza was associated with adverse outcomes.[2] There are no large studies, to our knowledge, assessing the impact of HF on patients hospitalized with influenza. Therefore, we aimed to examine this using a large inpatient administrative database.

Methods

We queried the 2013 to 2014 National Inpatient Sample using recommended analysis methods[3] to identify adult patients aged ≥18 hospitalized with influenza, using International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) codes 487.0, 487.1, 487.8, and 488.XX. HF was identified using ICD-9-CM codes 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, and 428. Comorbidities were identified using their respective ICD-9-CM codes. We performed propensity score matching across age, race, gender, discharge weights, insurance status, hospital characteristics, and comorbidities. Our outcomes were in-hospital mortality, in-hospital complications, costs, and length of stay. Uni- and multivariable regression analyses were performed as appropriate on matched and unmatched data to assess for the effect of HF on outcomes. Propensity score matching was conducted using the MatchIt package in RStudio (RStudio version 1.1), while SPSS version 25 (IBM, Armonk, New York) was used for all other analyses. All reported results are weighted.

Results

Of 218,540 weighted influenza hospitalizations, 45,460 (20.8%) had concomitant HF. Patients with HF were older (73.6 ± 14.1 years vs 62.4 ± 19.0 years, p <0.001), and more likely to be male (45.6% vs 43.2%, p <0.001) and white (73.1% vs 69.9%, p <0.001). Propensity score matching resulted in 44,345 patients in each cohort, with well-balanced characteristics. In the matched population, patients with HF had higher incidence of in-hospital mortality and in-hospital complications, along with longer length of stay and higher average hospital costs (Table 1 and Figure 1). The results were similar in the unmatched population (Table 1).

[a]Department of Medicine, Harrington Heart & Vascular Institute, University Hospitals Cleveland Medical Center, Case Western Reserve University School of Medicine, Cleveland, Ohio; [b]Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, Ohio; [c]Montefiore Medical Center, Albert Einstein College of Medicine, New York, New York; [d]Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; [e]New York-Presbyterian Hospital, Columbia University Medical Center, New York, New York; [f]Brigham & Women's Hospital Heart & Vascular Center, Harvard Medical School, Boston, Massachusetts; and [g]Division of Cardiovascular Medicine, Harrington Heart & Vascular Institute, University Hospitals Cleveland Medical Center, Case Western Reserve University School of Medicine, Cleveland, Ohio. Manuscript received December 22, 2018; revised manuscript received and accepted January 25, 2019.

See page 1480 for disclosure information.

*Corresponding author: Tel. +1 414-418-9683.

E-mail address: Mahazarin.Ginwalla@UHhospitals.org (M. Ginwalla).

0002-9149/
https://doi.org/10.1016/j.amjcard.2019.01.046

Table 1
In-hospital outcomes, with heart failure as predictor variable

Outcomes	Before matching			After matching		
	No heart failure	Heart failure	p Value	No heart failure	Heart failure	p Value
In-hospital mortality						
Incidence	2.8%	6.2%	-	3.8%	6.1%	-
Unadjusted OR (95% CI)	Ref	2.29 [2.05−2.55]	<0.001	Ref	1.66 [1.44−1.91]	<0.001
Adjusted OR* (95% CI)	Ref	1.87 [1.65−2.12]	<0.001	-	-	-
Acute kidney injury						
Incidence	15.6%	30.0%	-	22.2%	29.5%	
Unadjusted OR (95% CI)	Ref	2.32 [2.20−2.45]	<0.001	Ref	1.47 [1.37−1.57]	<0.001
Adjusted OR* (95% CI)	Ref	1.63 [1.53−1.74]	<0.001	-	-	
Acute kidney injury requiring dialysis						
Incidence	0.9%	2.1%	-	1.0%	2.0%	-
Unadjusted OR (95% CI)	Ref	2.48 [2.07−2.98]	<0.001	Ref	2.08 [1.62−2.67]	<0.001
Adjusted OR* (95% CI)	Ref	2.01 [1.61−2.51]	<0.001	-	-	-
Acute respiratory failure						
Incidence	21.3%	36.5%	-	23.5%	36.2%	
Unadjusted OR (95% CI)	Ref	2.12 [2.01−2.23]	<0.001	Ref	1.85 [1.73−1.97]	<0.001
Adjusted OR* (95% CI)	Ref	1.91 [1.80−2.03]	<0.001	-	-	-
Acute respiratory failure requiring mechanical ventilation						
Incidence	8.8%	17.4%	-	9.3%	17.1%	
Unadjusted OR (95% CI)	Ref	2.19 [2.05−2.34]	<0.001	Ref	2.01 [1.84−2.21]	<0.001
Adjusted OR* (95% CI)	Ref	2.19 [2.03−2.38]	<0.001	-	-	-
Length of stay						
Mean ± SE (days)	4.24 ± 0.01	5.79 ± 0.02	<0.001	4.60 ± 0.01	5.70 ± 0.02	<0.001
Unadjusted parameter estimate (95% CI)	Ref	1.36 [1.33 − 1.39]	<0.001	Ref	1.09 [1.08−0.11	<0.001
Adjusted parameter estimate* (95% CI)	Ref	1.23 [1.21−1.26]	<0.001	-	-	-
Hospital costs						
Mean ± SE ($)	8,218 ± 19	11,692 ± 51	<0.001	9,003 ± 38	11,609 ± 52	<0.001
Unadjusted parameter estimate (95% CI)	Ref	1.42 [1.39−1.46]	<0.001	Ref	1.12 [1.11−1.13]	<0.001
Adjusted parameter estimate* (95% CI)	Ref	1.28 [1.26−1.32]	<0.001	-	-	-

Key: OR = odds rartio; SE = standard error.
* Adjusted for age, race, sex, insurance status, and comorbidities.

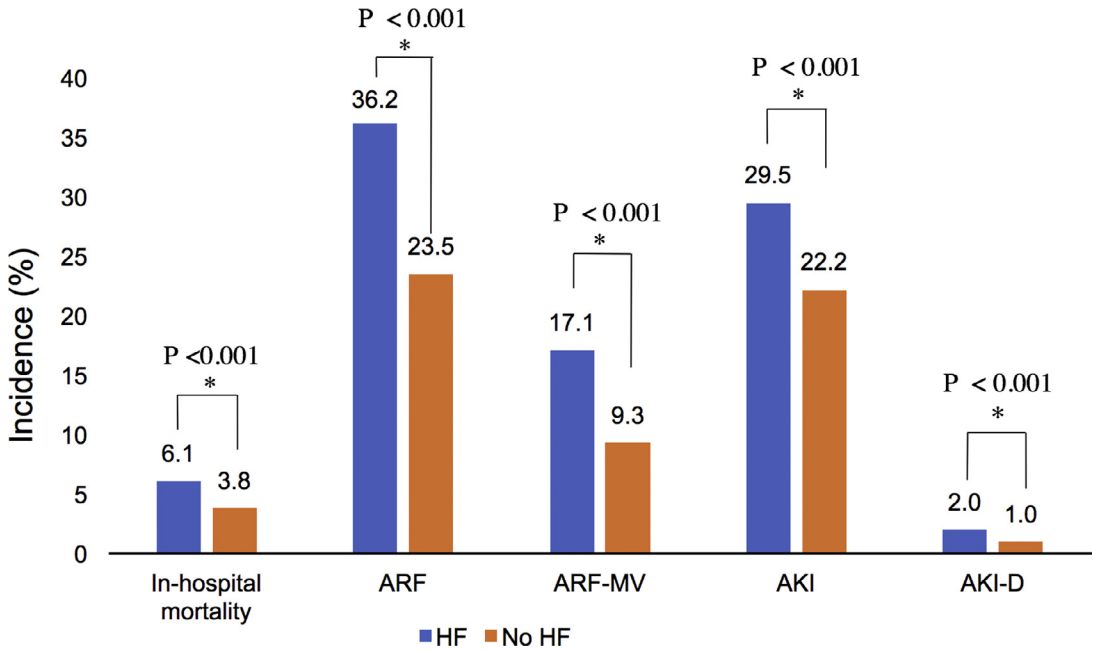

Figure 1. Incidence of outcomes by HF status. * indicates statistical significance. ARF = acute respiratory failure; ARF-MV = acute respiratory failure requiring mechanical ventilation; AKI = acute kidney injury; AKI-D = acute kidney injury requiring dialysis; HF = heart failure.

Discussion

In this large, national, propensity score-matched analysis of over 80,000 influenza hospitalizations, HF was associated with worse outcomes, including mortality, in influenza patients. Influenza can cause significant morbidity in patients with HF.[4] We recently also showed that influenza is associated with increased mortality and in-hospital complications in HF patients.[2] Patients with HF may have reduced baseline cardiopulmonary and renal function, increasing the risk of respiratory and renal failure due to influenza infection.

Our results highlight a need for early and aggressive treatment of patients with influenza and HF to try to improve outcomes in these patients. While reducing HF admissions remains challenging, influenza admissions can be prevented through vaccination,[1] which has been shown to be protective in HF patients.[5,6] A strength of our study is that it is a propensity score-matched analysis of over 80,000 influenza cases nationwide. However, it is reliant on ICD-9 codes, and prone to erroneous coding. Further, our study demonstrates only an association, and further work is needed to identify the causative mechanisms behind adverse outcomes of HF in patients with influenza.

Disclosures

Dr. Deepak Bhatt discloses the following relationships − Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic, Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, PhaseBio, Pfizer, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Novo Nordisk, PLx Pharma, Takeda. Dr. Kalra is a consultant to Medtronic and Philips. Dr. Ginwalla is site principal investigator for GALACTIC-HF (Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure) study and is a consultant for Xact Labs.

1. Estimated Influenza Illnesses, Medical visitsVisits, and Hospitalizations Averted by Vaccination in the United States; https://www.cdc.gov/flu/about/disease/2016-17.htm; Accessed on January 15, 2019.
2. Panhwar MS, Kalra A, Gupta T, et al. Effect of Influenza on Outcomes in Patients with Heart Failure. *JACC Heart Fail* 2019;7:112-117.
3. Khera R, Angraal S, Couch T, Welsh JW, Nallamothu BK, Girotra S, Chan PS, Krumholz HM. Adherence to methodological standards in research using the national inpatient sample. *JAMA* 2017;318:2011–2018.
4. Udell JA, Zawi R, Bhatt DL, Keshtkar-Jahromi M, Gaughran F, Phrommintikul A, Ciszewski A, Vakili H, Hoffman EB, Farkouh ME, Cannon CP. Association between influenza vaccination and cardiovascular outcomes in high-risk patients: a meta-analysis. *JAMA* 2013;310:1711–1720.
5. Vardeny O, Udell JA, Joseph J, Farkouh ME, Hernandez AF, McGeer AJ, Talbot HK, Bhatt DL, Cannon CP, Goodman SG, Anand I, DeMets DL, Temte J, Wittes J, Nichol K, Yancy CW, Gaziano JM, Cooper LS, Kim K, Solomon SD. High-dose influenza vaccine to reduce clinical outcomes in high-risk cardiovascular patients: rationale and design of the INVESTED trial. *Am Heart J* 2018;202:97–103.
6. Clar C, Oseni Z, Flowers N, Keshtkar-jahromi M, Rees K. Influenza vaccines for preventing cardiovascular disease. *Cochrane Database Syst Rev* 2015:CD005050. https://doi:10.1002/14651858.CD005050.pub3.