Impact of Influenza Vaccination on In-Hospital Outcomes Among Patients with Pre-existing Heart Failure Hospitalized for Acute Respiratory Illness

NIS Analysis for the RCOP Match Mentorship Program

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## Preamble:

* **Reference Studies:**
  + [Udell et al., 2013](https://pubmed.ncbi.nlm.nih.gov/24150467/)
  + [Hashem et al., 2023](https://pubmed.ncbi.nlm.nih.gov/37350092/)
* **Study Objective:** To assess the association between inpatient influenza immunization and adverse hospital outcomes among adult patients with pre-existing heart failure (HF) admitted for acute respiratory illness. The study evaluates the impact of immunization on mortality, clinical complications, and healthcare resource use during the U.S. influenza seasons from 2018 to 2020.
* **Data Source:** Retrospective cross-sectional analysis using the National Inpatient Sample (NIS) from 2018 to 2020. The NIS is part of the Healthcare Cost and Utilization Project (HCUP) and provides a stratified, nationally representative sample of U.S. inpatient hospitalizations across all payers and geographic regions.
* **Cohort Definition:** Hospitalizations were included if they met all of the following criteria
  + Adults aged ≥18 years
  + Admission occurred during the influenza season (October through May)
  + Primary diagnosis of acute respiratory illness, defined by ICD-10-CM codes for:
    - Influenza: J09.x, J10.x, J11.x
    - Pneumonia: J12.x–J18.x
    - Acute bronchitis/bronchiolitis: J20.x, J21.x
  + Secondary diagnosis of heart failure, defined by: I50.x, I0981, I110, I130, I132, I97130, I97131, O29121–O29129, Z95811, Z95812
  + Influenza immunization recorded during the hospitalization, identified by ICD-10-CM code Z23.\* (used as a proxy for receipt of influenza vaccination or immunization-related care during admission)
* **Outcomes of Interest:**
  + **Primary Outcome:**
    - In-hospital mortality
  + **Secondary Outcomes:**
    - Length of stay (LOS), in days
    - Inflation-adjusted total hospital charges (2020 USD)
    - Use of mechanical ventilation
    - Diagnosis of sepsis
* **Outcome definitions:**
  + Mechanical Ventilation: ICD-10-PCS codes 5A09B5K, 5A09C5K, 5A09D5K, 5A1935Z, 5A1945Z, 5A1955Z
  + Sepsis: ICD-10-CM codes A40., A41., R6520, R6521, plus select pregnancy-, neonatal-, and device-related septicemia codes
* **Covariates for Adjustment:** All multivariable models included the following covariates
  + **Demographic Factors:** Age, sex, race/ethnicity
  + **Socioeconomic Factors:** ZIP code-based income quartile, primary insurance payer
  + **Clinical Factors:** Presence of confirmed influenza diagnosis (J09.x–J11.x), Elixhauser comorbidity index (aggregate score)
  + **Hospital-Level Factors:** Geographic region, bed size, and urban/teaching hospital status
* **Statistical Methods:**
  + **Univariable Analysis:**
    - Categorical variables: Compared using Pearson’s chi-square test with Rao & Scott adjustment
    - Continuous variables: Analyzed using the design-based Kruskal–Wallis test, a non-parametric alternative suitable for survey-weighted data
  + **Multivariable Analysis:**
    - Binary outcomes (e.g., mortality, mechanical ventilation, sepsis): Modeled using survey-weighted logistic regression with the quasibinomial family
    - Continuous outcomes (e.g., LOS, total charges): Modeled using survey-weighted linear regression with the gaussian family
    - All estimates were reported as adjusted odds ratios (aORs) or beta coefficients, with 95% confidence intervals
* **Software:** All statistical analyses were performed using the R Statistical Language (Version 4.5.0; R Foundation for Statistical Computing, Vienna, Austria), incorporating survey-weighted procedures via the *survey* package to account for the complex sampling design of NIS.

## Baseline Table:

| **Characteristic** | **Overall** N = 491,210*1* | **No** N = 476,435*1* | **Yes** N = 14,775*1* | **p-value***2* |
| --- | --- | --- | --- | --- |
| Age, y | 74 (13) | 74 (13) | 72 (14) | <0.001 |
| Sex |  |  |  | 0.2 |
| Female | 261,120 (53%) | 253,425 (53%) | 7,695 (52%) |  |
| Male | 230,080 (47%) | 223,000 (47%) | 7,080 (48%) |  |
| Race |  |  |  | <0.001 |
| Asian or Pacific Islander | 8,955 (1.9%) | 8,620 (1.8%) | 335 (2.3%) |  |
| Black | 65,350 (14%) | 63,110 (14%) | 2,240 (15%) |  |
| Hispanic | 34,550 (7.2%) | 33,185 (7.1%) | 1,365 (9.4%) |  |
| Other | 12,850 (2.7%) | 12,385 (2.7%) | 465 (3.2%) |  |
| White | 359,090 (75%) | 348,970 (75%) | 10,120 (70%) |  |
| Confirmed influenza | 78,030 (16%) | 76,130 (16%) | 1,900 (13%) | <0.001 |
| Income quartile |  |  |  | 0.048 |
| $1 - $51,999 | 161,030 (33%) | 156,000 (33%) | 5,030 (35%) |  |
| $52,000 - $65,999 | 139,075 (29%) | 134,720 (29%) | 4,355 (30%) |  |
| $66,000 - $87,999 | 107,195 (22%) | 104,105 (22%) | 3,090 (21%) |  |
| $88,000 or more | 76,720 (16%) | 74,640 (16%) | 2,080 (14%) |  |
| Insurance payer |  |  |  | <0.001 |
| Medicaid | 34,935 (7.1%) | 33,460 (7.0%) | 1,475 (10.0%) |  |
| Medicare | 395,335 (81%) | 384,415 (81%) | 10,920 (74%) |  |
| Other | 15,400 (3.1%) | 14,675 (3.1%) | 725 (4.9%) |  |
| Private | 45,050 (9.2%) | 43,415 (9.1%) | 1,635 (11%) |  |
| Hospital region |  |  |  | <0.001 |
| Midwest | 129,785 (26%) | 125,460 (26%) | 4,325 (29%) |  |
| Northeast | 83,880 (17%) | 82,305 (17%) | 1,575 (11%) |  |
| South | 202,650 (41%) | 196,295 (41%) | 6,355 (43%) |  |
| West | 74,895 (15%) | 72,375 (15%) | 2,520 (17%) |  |
| Hospital bedsize |  |  |  | <0.001 |
| Large | 208,725 (42%) | 201,985 (42%) | 6,740 (46%) |  |
| Medium | 146,795 (30%) | 142,295 (30%) | 4,500 (30%) |  |
| Small | 135,690 (28%) | 132,155 (28%) | 3,535 (24%) |  |
| Hospital location/teaching status |  |  |  | <0.001 |
| Rural | 84,275 (17%) | 82,210 (17%) | 2,065 (14%) |  |
| Urban, non-teaching | 111,105 (23%) | 107,485 (23%) | 3,620 (25%) |  |
| Urban, teaching | 295,830 (60%) | 286,740 (60%) | 9,090 (62%) |  |
| No. of comorbidities |  |  |  | 0.024 |
| No comorbidities | 5 (<0.1%) | 5 (<0.1%) | 0 (0%) |  |
| One comorbidity | 37,655 (7.7%) | 36,330 (7.6%) | 1,325 (9.0%) |  |
| Two or more comorbidities | 453,550 (92%) | 440,100 (92%) | 13,450 (91%) |  |
| *1*Mean (SD); n (%) | | | | |
| *2*Design-based KruskalWallis test; Pearson's X^2: Rao & Scott adjustment | | | | |

## Univariable Analysis:

| **Characteristic** | **Overall** N = 491,210*1* | **No** N = 476,435*1* | **Yes** N = 14,775*1* | **p-value***2* |
| --- | --- | --- | --- | --- |
| In-hospital mortality | 18,410 (3.7%) | 18,245 (3.8%) | 165 (1.1%) | <0.001 |
| Length of stay (days) | 4.0 (3.0, 7.0) | 4.0 (3.0, 7.0) | 4.0 (3.0, 7.0) | 0.6 |
| Inflation-adjusted total charge ($) | 34,183 (20,287, 60,412) | 34,107 (20,212, 60,421) | 36,204 (22,599, 60,181) | <0.001 |
| Mechanical ventilation | 21,925 (4.5%) | 21,450 (4.5%) | 475 (3.2%) | 0.001 |
| Septicemia | 10,075 (2.1%) | 9,880 (2.1%) | 195 (1.3%) | 0.005 |
| *1*n (%); Median (Q1, Q3) | | | | |
| *2*Pearson's X^2: Rao & Scott adjustment; Design-based KruskalWallis test | | | | |

## Multivariable Logistic Regression:

### In-hospital Mortality:

| **Characteristic** | **OR** | **95% CI** | **p-value** |
| --- | --- | --- | --- |
| Immunization encounter |  |  |  |
| No | — | — |  |
| Yes | 0.32 | 0.23, 0.46 | <0.001 |
| Age, y | 1.04 | 1.03, 1.04 | <0.001 |
| Sex |  |  |  |
| Female | — | — |  |
| Male | 1.19 | 1.11, 1.27 | <0.001 |
| Race |  |  |  |
| Asian or Pacific Islander | — | — |  |
| Black | 0.89 | 0.69, 1.16 | 0.4 |
| Hispanic | 0.77 | 0.59, 1.00 | 0.051 |
| Other | 1.09 | 0.81, 1.48 | 0.6 |
| White | 0.83 | 0.65, 1.05 | 0.12 |
| Confirmed influenza |  |  |  |
| No | — | — |  |
| Yes | 0.74 | 0.66, 0.82 | <0.001 |
| Income quartile |  |  |  |
| $1 - $51,999 | — | — |  |
| $52,000 - $65,999 | 0.95 | 0.86, 1.03 | 0.2 |
| $66,000 - $87,999 | 0.85 | 0.77, 0.94 | 0.002 |
| $88,000 or more | 0.88 | 0.79, 0.99 | 0.031 |
| Insurance payer |  |  |  |
| Medicaid | — | — |  |
| Medicare | 0.86 | 0.73, 1.02 | 0.092 |
| Other | 1.59 | 1.25, 2.03 | <0.001 |
| Private | 1.03 | 0.85, 1.26 | 0.8 |
| Hospital region |  |  |  |
| Midwest | — | — |  |
| Northeast | 1.35 | 1.21, 1.52 | <0.001 |
| South | 1.05 | 0.95, 1.15 | 0.4 |
| West | 1.27 | 1.13, 1.43 | <0.001 |
| Hospital bedsize |  |  |  |
| Large | — | — |  |
| Medium | 0.90 | 0.83, 0.99 | 0.023 |
| Small | 0.88 | 0.80, 0.96 | 0.004 |
| Hospital location/teaching status |  |  |  |
| Rural | — | — |  |
| Urban, non-teaching | 1.00 | 0.88, 1.13 | >0.9 |
| Urban, teaching | 1.14 | 1.03, 1.27 | 0.015 |
| Elixhauser comorbidity index | 1.18 | 1.16, 1.20 | <0.001 |
| Abbreviations: CI = Confidence Interval, OR = Odds Ratio | | | |

### Mechanical Ventilation:

| **Characteristic** | **OR** | **95% CI** | **p-value** |
| --- | --- | --- | --- |
| Immunization encounter |  |  |  |
| No | — | — |  |
| Yes | 0.67 | 0.54, 0.83 | <0.001 |
| Age, y | 0.97 | 0.97, 0.98 | <0.001 |
| Sex |  |  |  |
| Female | — | — |  |
| Male | 1.13 | 1.06, 1.20 | <0.001 |
| Race |  |  |  |
| Asian or Pacific Islander | — | — |  |
| Black | 0.84 | 0.67, 1.06 | 0.14 |
| Hispanic | 0.87 | 0.69, 1.10 | 0.2 |
| Other | 1.08 | 0.83, 1.41 | 0.6 |
| White | 0.81 | 0.65, 1.00 | 0.050 |
| Confirmed influenza |  |  |  |
| No | — | — |  |
| Yes | 0.88 | 0.80, 0.96 | 0.006 |
| Income quartile |  |  |  |
| $1 - $51,999 | — | — |  |
| $52,000 - $65,999 | 0.92 | 0.85, 1.00 | 0.044 |
| $66,000 - $87,999 | 0.81 | 0.74, 0.89 | <0.001 |
| $88,000 or more | 0.80 | 0.72, 0.90 | <0.001 |
| Insurance payer |  |  |  |
| Medicaid | — | — |  |
| Medicare | 1.12 | 0.99, 1.26 | 0.076 |
| Other | 1.31 | 1.08, 1.58 | 0.005 |
| Private | 1.22 | 1.06, 1.40 | 0.006 |
| Hospital region |  |  |  |
| Midwest | — | — |  |
| Northeast | 1.42 | 1.27, 1.58 | <0.001 |
| South | 1.20 | 1.10, 1.31 | <0.001 |
| West | 1.18 | 1.05, 1.32 | 0.005 |
| Hospital bedsize |  |  |  |
| Large | — | — |  |
| Medium | 0.88 | 0.82, 0.95 | 0.001 |
| Small | 0.77 | 0.70, 0.83 | <0.001 |
| Hospital location/teaching status |  |  |  |
| Rural | — | — |  |
| Urban, non-teaching | 1.51 | 1.33, 1.72 | <0.001 |
| Urban, teaching | 1.95 | 1.74, 2.19 | <0.001 |
| Elixhauser comorbidity index | 1.28 | 1.26, 1.30 | <0.001 |
| Abbreviations: CI = Confidence Interval, OR = Odds Ratio | | | |

### Sepsis:

| **Characteristic** | **OR** | **95% CI** | **p-value** |
| --- | --- | --- | --- |
| Immunization encounter |  |  |  |
| No | — | — |  |
| Yes | 0.63 | 0.45, 0.88 | 0.006 |
| Age, y | 0.99 | 0.99, 0.99 | <0.001 |
| Sex |  |  |  |
| Female | — | — |  |
| Male | 1.14 | 1.04, 1.25 | 0.004 |
| Race |  |  |  |
| Asian or Pacific Islander | — | — |  |
| Black | 0.83 | 0.60, 1.16 | 0.3 |
| Hispanic | 0.93 | 0.67, 1.31 | 0.7 |
| Other | 0.97 | 0.64, 1.46 | 0.9 |
| White | 0.80 | 0.58, 1.09 | 0.2 |
| Confirmed influenza |  |  |  |
| No | — | — |  |
| Yes | 1.13 | 1.00, 1.27 | 0.056 |
| Income quartile |  |  |  |
| $1 - $51,999 | — | — |  |
| $52,000 - $65,999 | 1.01 | 0.89, 1.14 | >0.9 |
| $66,000 - $87,999 | 0.97 | 0.85, 1.12 | 0.7 |
| $88,000 or more | 1.08 | 0.92, 1.26 | 0.3 |
| Insurance payer |  |  |  |
| Medicaid | — | — |  |
| Medicare | 1.04 | 0.86, 1.25 | 0.7 |
| Other | 1.31 | 0.98, 1.74 | 0.065 |
| Private | 1.02 | 0.82, 1.27 | 0.9 |
| Hospital region |  |  |  |
| Midwest | — | — |  |
| Northeast | 1.03 | 0.88, 1.20 | 0.7 |
| South | 1.00 | 0.89, 1.13 | >0.9 |
| West | 1.08 | 0.92, 1.26 | 0.4 |
| Hospital bedsize |  |  |  |
| Large | — | — |  |
| Medium | 0.99 | 0.88, 1.11 | 0.9 |
| Small | 1.04 | 0.92, 1.17 | 0.5 |
| Hospital location/teaching status |  |  |  |
| Rural | — | — |  |
| Urban, non-teaching | 0.84 | 0.71, 0.98 | 0.026 |
| Urban, teaching | 0.89 | 0.77, 1.02 | 0.084 |
| Elixhauser comorbidity index | 1.19 | 1.16, 1.22 | <0.001 |
| Abbreviations: CI = Confidence Interval, OR = Odds Ratio | | | |

## Multivariable Linear Regression:

### Length of Stay:

| **Characteristic** | **Beta** | **95% CI** | **p-value** |
| --- | --- | --- | --- |
| Immunization encounter |  |  |  |
| No | — | — |  |
| Yes | -0.05 | -0.21, 0.12 | 0.6 |
| Age, y | 0.01 | 0.00, 0.01 | <0.001 |
| Sex |  |  |  |
| Female | — | — |  |
| Male | -0.17 | -0.24, -0.10 | <0.001 |
| Race |  |  |  |
| Asian or Pacific Islander | — | — |  |
| Black | -0.32 | -0.64, 0.01 | 0.058 |
| Hispanic | -0.34 | -0.67, -0.01 | 0.041 |
| Other | -0.12 | -0.54, 0.31 | 0.6 |
| White | -0.31 | -0.62, -0.01 | 0.045 |
| Confirmed influenza |  |  |  |
| No | — | — |  |
| Yes | -0.22 | -0.31, -0.12 | <0.001 |
| Income quartile |  |  |  |
| $1 - $51,999 | — | — |  |
| $52,000 - $65,999 | -0.16 | -0.25, -0.07 | <0.001 |
| $66,000 - $87,999 | -0.25 | -0.35, -0.14 | <0.001 |
| $88,000 or more | -0.17 | -0.29, -0.05 | 0.005 |
| Insurance payer |  |  |  |
| Medicaid | — | — |  |
| Medicare | -0.32 | -0.53, -0.11 | 0.003 |
| Other | -0.45 | -0.74, -0.16 | 0.002 |
| Private | -0.20 | -0.44, 0.04 | 0.11 |
| Hospital region |  |  |  |
| Midwest | — | — |  |
| Northeast | 0.83 | 0.71, 0.95 | <0.001 |
| South | 0.48 | 0.38, 0.58 | <0.001 |
| West | -0.15 | -0.28, -0.03 | 0.014 |
| Hospital bedsize |  |  |  |
| Large | — | — |  |
| Medium | -0.34 | -0.44, -0.23 | <0.001 |
| Small | -0.55 | -0.65, -0.45 | <0.001 |
| Hospital location/teaching status |  |  |  |
| Rural | — | — |  |
| Urban, non-teaching | 0.52 | 0.42, 0.63 | <0.001 |
| Urban, teaching | 0.84 | 0.74, 0.94 | <0.001 |
| Elixhauser comorbidity index | 0.48 | 0.46, 0.50 | <0.001 |
| Abbreviation: CI = Confidence Interval | | | |

### Inflation-adjusted Total Charge:

| **Characteristic** | **Beta** | **95% CI** | **p-value** |
| --- | --- | --- | --- |
| Immunization encounter |  |  |  |
| No | — | — |  |
| Yes | -3,181 | -5,264, -1,098 | 0.003 |
| Age, y | -275 | -319, -231 | <0.001 |
| Sex |  |  |  |
| Female | — | — |  |
| Male | 891 | -76, 1,857 | 0.071 |
| Race |  |  |  |
| Asian or Pacific Islander | — | — |  |
| Black | -11,672 | -17,599, -5,744 | <0.001 |
| Hispanic | -199 | -6,307, 5,908 | >0.9 |
| Other | -3,502 | -11,412, 4,408 | 0.4 |
| White | -14,521 | -20,154, -8,888 | <0.001 |
| Confirmed influenza |  |  |  |
| No | — | — |  |
| Yes | -4,336 | -5,674, -2,997 | <0.001 |
| Income quartile |  |  |  |
| $1 - $51,999 | — | — |  |
| $52,000 - $65,999 | -927 | -2,306, 452 | 0.2 |
| $66,000 - $87,999 | -1,158 | -2,785, 469 | 0.2 |
| $88,000 or more | 3,997 | 1,664, 6,331 | <0.001 |
| Insurance payer |  |  |  |
| Medicaid | — | — |  |
| Medicare | -1,548 | -4,799, 1,703 | 0.4 |
| Other | -3,491 | -7,482, 500 | 0.086 |
| Private | -47 | -3,654, 3,559 | >0.9 |
| Hospital region |  |  |  |
| Midwest | — | — |  |
| Northeast | 15,454 | 12,928, 17,979 | <0.001 |
| South | 10,909 | 9,496, 12,322 | <0.001 |
| West | 27,083 | 24,581, 29,585 | <0.001 |
| Hospital bedsize |  |  |  |
| Large | — | — |  |
| Medium | -3,536 | -5,472, -1,600 | <0.001 |
| Small | -8,694 | -10,387, -7,001 | <0.001 |
| Hospital location/teaching status |  |  |  |
| Rural | — | — |  |
| Urban, non-teaching | 16,951 | 15,283, 18,619 | <0.001 |
| Urban, teaching | 19,235 | 17,812, 20,658 | <0.001 |
| Elixhauser comorbidity index | 6,166 | 5,841, 6,490 | <0.001 |
| Abbreviation: CI = Confidence Interval | | | |