ORIGINAL RESEARCH

Depression is Associated with Decreased Severity and Lower Mortality in Non-Elderly Hospitalized Adults with Influenza in the United States

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Abstract

Background: Depression is associated with risk for chronic disease, though its relationship with infectious diseases is less understood. Depression may modify the clinical outcomes of patients with infectious diseases such as influenza via its association with inflammation. The objective of this study was to evaluate the relationships between depression and clinical outcomes in non-elderly adults with influenza infection.

Methods: This was a secondary analysis of the Nationwide Inpatient Sample database, years 2012–2016. Hospitalized adults aged 18–65 admitted during each influenza season were included. Depression status was documented via ICD-10 codes. The association between depression and clinical outcomes (*e.g.*, disease severity, length of hospital stay, and inpatient all-cause mortality) was evaluated using multivariable regression modeling.

Results: A total of 44,292 patients were included, 12% with depression. After adjustment for confounding, non-elderly influenza patients with depression had a 3.8% decreased risk of a severe disease (95% confidence interval [CI] 1.9–5.7; $P < 0.001$), no difference in length of stay (hazard ratio 0.99, 95% CI 0.96–1.02), and lower all-cause in-hospital mortality *versus* those without depression (odds ratio 0.76 (95% CI 0.59–0.97; $P = 0.028$).

Conclusion: This study suggests that in non-elderly hospitalized patients with influenza, depression is associated with a decreased severity of illness and acute mortality. Chronic inflammation in those with depression may enhance the ability of the immune response to limit influenza infection or reduce pathologic acute inflammation associated with influenza disease.

Introduction

Major depression is a well established risk factor for chronic disease and adverse outcomes in comorbid patients.[1] Among the most studied are the relationships between depression and increased risk for incident cardiovascular disease [1, 2] and type-2 diabetes.[3, 4] In comparison, the literature on depression and infectious diseases is less developed. Depression is associated with a significantly increased acquisition of the common cold [5], *Clostridium (Clostridioides) difficile* infection following total knee replacement surgery [6], bloodstream infection [7], enterovirus infection [8], and is associated with increased risk of infection following elective shoulder arthroplasty.[9] To date, there is limited evidence of the impact of depression on influenza illness and outcomes, though a review of the sparse literature concluded that there is an absence of evi-

dence to support or refute a link between depression and risk for influenza acquisition.[10] There is strong support for an immunologic dysregulation in many patients with depression which could explain some of these increased risks. Depression-related immune dysregulation is also associated with a blunted response to vaccines as well as delayed immunity.[11, 12] Patients with depression have increased pro-inflammatory cytokines (*e.g.*, Interleukin 6, Tumor Necrosis Factor alpha) [13, 14] resulting in release of acute phase proteins, chemokines, and adhesion molecules [15]; immune cell differentiation and recruitment; and a wide array of other impacts on the human body.[16] Given depression is associated with a dysregulated immune state, depressed patients may have a differential disease severity or outcome after infection as well.

Understanding the relationships between depression

and influenza is critical. Nearly 21% of adults in the United States will experience a major depressive episode in their lifetime [17] and depression is now the leading cause of disability worldwide.[18] Further, influenza results in substantial morbidity and mortality globally each year and influenza research is often limited to only the elderly population, leaving a dearth of evidence in non-elderly populations.[19] Further research is warranted to determine if this common mental illness is associated with increased severity of, or poor outcomes in patients with influenza infection. The objective of this study was to evaluate the association between depression and influenza severity and clinical outcomes in non-elderly adult patients hospitalized with influenza in the United States.

Methods

Study Design

This was a secondary analysis of data from the National Inpatient Sample (NIS), Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality. This database contains a 20% stratified sample of approximately 6–8 million hospital discharges per year.[20]

Subjects: Inclusion/Exclusion Criteria

Inpatient stays of individuals aged 18–64 with a discharge diagnosis code (ICD-9 or ICD-10) for influenza, from 2012 through 2016 were included in the analysis. Data were limited to months during the peak months of the typical influenza season in the United States (November through March). Patients without an all patient refined diagnosis related group (APR-DRG) severity or mortality risk subclass were excluded from analysis.

Human Subjects Protection

Because data are de-identified and publicly available this study is considered exempt from IRB approval.

Variable Definitions

Exposure:

Depression: Patients were classified as having depression if they had an ICD-9/10 code for depression diagnoses on discharge (see the Supplementary Appendix for detailed codes).

Outcomes:

Severity: Severity of illness was defined using the all patient refined diagnosis related group (APR-DRG) severity measure as documented in the NIS database.[21] This measure reflects the extent of a pa-

tient's physiologic decompensation or loss of organ system function and is calculated through passing diagnosis and procedure codes through a complex multi-phase algorithm developed by 3M Health Information Systems. The APR-DRG severity was dichotomized into severe (Major or Extreme Loss of Function) versus non severe (Minor or Moderate Loss of Function).

Length of stay: Length of stay was defined as the number of days from admission to discharge or death.

Mortality: Mortality was defined as all-cause inpatient mortality before discharge as documented in the NIS database.

Covariates

The following variables were selected for adjustment in regression modeling due to their potential confounding effects: Age (restricted cubic spline with 4 knots), gender, ICD-9/ICD-10 codes for diagnosis of pneumonia, nicotine dependence, anxiety disorder, and alcohol use disorder (see Appendix for detailed definitions), APR-DRG Severity (for mortality and length of stay models), APR-DRG mortality risk [21], quartile of median household income of patients zip code of residence, and 2017 AHRQ Elixhauser Weighted Comorbidity Index.[22]

Statistical Analysis

Categorical variables were described with frequencies and percentages, while continuous variables were described with means and standard deviations or medians with interquartile ranges, as appropriate. Bivariable comparisons between depressed and non-depressed patients were made using Chi-squared or Fisher's Exact tests, while independent samples t-tests or Mann-Whitney U-tests were used to compare differences in continuous variables.

To define the adjusted impact of depression on disease severity, a multivariable Poisson regression model with a robust error estimator was used.[23] In this model, independent variables included: presence of pneumonia, a restricted cubic spline with 4 knots of the patient's age, nicotine dependence, anxiety disorder, gender, alcohol use disorder, APR-DRG risk of mortality, the quartile of median household income of the patients zip code of primary residence, and the weighted version of the grouped Elixhauser Comorbidity Index using the Agency for Healthcare Research and Quality (AHRQ) algorithm.[22] To assess the adjusted impact of depression on length of hospital stay and account for patients who died before discharge, competing risks regression was used.[24] All variables described above, as well as the severity of illness (APR-DRG Severity) were used for adjustment. To assess the impact of depression on in-hospital mortality, a multivariable logistic regression model was used. The same variables

Table 1. Baseline characteristics of adult, non-elderly inpatients with influenza, November–March, 2012–2016 in the United States.

	Depressed <i>n</i> =4,952	Non-depressed <i>n</i> =37,588	<i>P</i>
Age, mean±SD	50.72±10.69	47.41±12.83	<0.001
Female gender, <i>n</i> (%)	3,286 (66.4)	20,321 (54.1)	<0.001
Pneumonia, <i>n</i> (%)	1,582 (31.9)	11,818 (31.4)	0.481
Nicotine dependence, <i>n</i> (%)	2,045 (41.3)	12,090 (32.2)	<0.001
Alcohol use disorder, <i>n</i> (%)	253 (5.1)	1,536 (4.1)	0.001
Anxiety, <i>n</i> (%)	2,039 (41.2)	3,500 (9.3)	<0.001
APRDRG Severity of Illness, <i>n</i> (%)			<0.001
Minor loss of function	446 (9.0)	4,990 (13.3)	
Moderate loss of function	1,756 (35.5)	14,064 (37.4)	
Major loss of function	1,917 (38.7)	12,370 (32.9)	
Extreme loss of function	833 (16.8)	6,164 (16.4)	
APRDRG Risk of Mortality, <i>n</i> (%)			<0.001
Minor likelihood of death	1,940 (39.2)	16,934 (45.1)	
Moderate likelihood of death	1,260 (25.4)	8,717 (23.2)	
Major likelihood of death	1,233 (24.9)	7,834 (20.8)	
Extreme likelihood of death	519 (10.5)	4,103 (10.9)	
Median household income of residential zip code, <i>n</i> (%)			<0.001
1	1,564 (32.1)	13,104 (35.7)	
2	1,286 (26.4)	9,416 (25.6)	
3	1,176 (24.2)	8,069 (22.0)	
4	842 (17.3)	6,166 (16.8)	
Weighted Elixhauser (AHRQ) Index, <i>n</i> (%)			<0.001
<0	2,000 (40.4)	5,764 (15.3)	
0	195 (3.9)	4,205 (11.2)	
1–4	562 (11.3)	5,713 (15.2)	
≥5	2,195 (44.3)	21,906 (58.3)	

Abbreviations: APRDRG, all patient refined diagnosis related group; AHRQ, Agency for Healthcare Research and Quality; SD, standard deviation.

as documented for the length of stay model were included as covariates. Variance inflation factors, tolerance statistics, and correlation coefficients were used to evaluate the presence of multicollinearity before all regression modeling. R v3.6.1 (R Foundation for Statistical Computing, Vienna Austria) was used for all analyses.

Results

A total of 42,540 hospitalized adult, non-elderly patients with influenza were included in the analysis; 4,952 (12%) with a diagnosis code for depression and 37,588 (88%) without. Baseline socio-demographic and clinical features of patients stratified by the presence or absence of depression diagnosis can be seen in **Table 1**.

Several statistically significant differences in characteristics were identified between depressed and non-depressed hospitalized non-elderly adults with influenza. Depressed patients were slightly older (mean age 50.7 (SD ±10.7) years) compared to patients without depression (mean age 47.4 years (SD ±12.8, *P*<0.001). Patients with depression vs. those without were more likely to be female (66% vs 54%, *P*<0.001), have nicotine dependence (41% vs 32%, *P*<0.001), have alcohol

use disorder (5% vs 4% (*P*=0.001), and an anxiety disorder (41% vs 9%, *p*<0.001). Depressed patients had a decreased unadjusted mortality versus non depressed patients (1.7% vs 2.7%, *P*<0.001).

As depicted in **Table 2**, non-elderly influenza patients with depression were found to have a 3.8% decreased adjusted risk of a major or severe loss of function versus those without depression (95% CI: 1.9%–5.7%; *P*<0.001). **Table 3** reports the results of competing risks regression for evaluation of adjusted associations between depression and length of hospital stay. Non-elderly influenza patients with depression had no change in length of stay (adjusted hazard ratio of discharge 0.99, 95% CI 0.96–1.02). As depicted in **Table 4**, non-elderly influenza patients with depression had lower all-cause in-hospital mortality versus those without depression (adjusted Odds Ratio=0.76; 95% CI 0.59–0.97; *P*=0.028).

Discussion

In a large sample of non-elderly hospitalized patients with influenza infection, those with depression diagnoses had a decreased risk of more severe disease and a lower odds of inpatient mortality, but showed no dif-

Table 2. Results of the multivariable regression model for severity of illness for adult, non-elderly inpatients with influenza, November–March, 2012–2016 in the United States.

Variable	Risk ratio	Lower 95% CI	Upper 95% CI	P
Depression	0.96	0.943	0.981	<0.001
Female gender	1.00	0.991	1.016	0.630
Age, spline 1	1.00	0.994	1.001	0.107
Age, spline 2	1.00	0.992	1.007	0.926
Age, spline 3	0.99	0.946	1.044	0.802
Age, spline 4	1.07	0.914	1.245	0.412
Nicotine dependence	0.98	0.968	0.994	0.005
Anxiety	0.96	0.947	0.981	<0.001
Alcohol use disorder	1.00	0.972	1.023	0.820
Pneumonia	1.19	1.175	1.206	<0.001
APR-DRG mortality risk minor	Reference	-	-	-
APR-DRG mortality risk moderate	4.51	4.303	4.726	<0.001
APR-DRG mortality risk major	6.96	6.651	7.291	<0.001
APR-DRG mortality risk extreme	6.24	5.939	6.552	<0.001
Median household income of ZIP code quartile 1	Reference	-	-	-
Median household income of ZIP code quartile 2	1.00	0.987	1.020	0.704
Median household income of ZIP code quartile 3	1.02	1.004	1.038	0.017
Median household income of ZIP code quartile 4	1.02	0.997	1.035	0.104
Weighted Elixhauser (AHRQ) Index <0	Reference	-	-	-
Weighted Elixhauser (AHRQ) Index 0	0.95	0.927	0.97	<0.001
Weighted Elixhauser (AHRQ) Index 1-4	0.91	0.873	0.954	<0.001
Weighted Elixhauser (AHRQ) Index ≥5	0.97	0.942	1.000	0.048

Abbreviations: APRDRG, all patient refined diagnosis related group; AHRQ, Agency for Healthcare Research and Quality; CI, confidence interval.

ference in length of hospital stay. The relationship between depression and severity of disease was statistically significant, but the magnitude of the association was small and not likely to be clinically meaningful. This limited impact could be due to more severe illness in general regardless of depression status as indicated by the need for hospitalization. This magnitude may be more pronounced in outpatient settings where severity of illness may have a wider distribution. It is also possible that by selecting a younger age cohort, we have selected for more severe hospitalized influenza cases.

While the lower risk of mortality in patients with depression is seemingly paradoxical and is in disagreement with one study in the Veterans Health Administration [25], the results may be consistent with the pathophysiology of influenza mortality. Depression is known to be associated with immune dysregulation, with many individuals suffering from this condition having increased baseline pro-inflammatory cytokines (e.g., Interleukin-6), and other inflammatory markers.[13-15, 26] Since death due to influenza is often associated with an overexuberant inflammatory response to infection rather than an overwhelming disseminated infection [27], patients with an already inflamed state may have negative regulatory networks

activated which protect against excessive increases in inflammation. This negative feedback may prevent severe immunopathologic responses to influenza infection.[28] As an example, patients with lower respiratory tract infections such as pneumonia (a common complication of influenza infection) are at increased risk of myocardial infarction.[29] This is possibly due to the inflammatory response of the acute respiratory infection dislodging atherosclerotic plaques, resulting in infarction. If the inflammatory response post infection is not substantially different from a baseline rate of inflammation, or this cascade is otherwise influenced by the baseline inflammation of a patient with depression, this event may not occur, and in-hospital death rates might be reduced.

Another rationale for our results includes the fact that depression in the NIS database is administratively coded for reimbursement on discharge. This means that the disease was significant for care during hospitalization, or was otherwise coded for a complex case. This may increase the likelihood of therapy for depression with various other medications, some of which could be anti-inflammatory.[30-34] Anti-inflammatory medications may improve the clinical outcomes of these patients similar to the impact of glucocorticoids, macrolide antibiotics, or other

Table 3. Results of the multivariable regression model for all-cause inpatient mortality of adult, non-elderly inpatients with influenza, November–March, 2012–2016 in the United States.

Variable	Hazard ratio	Lower 95% CI	Upper 95% CI	P
Depression	0.99	0.961	1.019	0.47
Female gender	0.97	0.95	0.986	0.001
Age	0.996	0.995	0.996	<0.001
Nicotine dependence	0.75	0.639	0.87	<0.001
Anxiety	1.05	1.029	1.07	0.000
Alcohol use disorder	0.87	0.849	0.897	<0.001
Pneumonia	0.91	0.896	0.932	<0.001
APR-DRG severity of illness, minor	Reference	-	-	-
APR-DRG severity of illness, moderate	0.81	0.782	0.832	<0.001
APR-DRG severity of illness, major	0.56	0.535	0.579	<0.001
APR-DRG severity of illness, extreme	0.27	0.259	0.289	<0.001
APR-DRG mortality risk minor	Reference	-	-	-
APR-DRG mortality risk moderate	0.91	0.882	0.934	<0.001
APR-DRG mortality risk major	0.84	0.807	0.867	<0.001
APR-DRG mortality risk extreme	0.46	0.434	0.483	<0.001
Median household income of ZIP code quartile 1	Reference	-	-	-
Median household income of ZIP code quartile 2	1.05	1.023	1.072	<0.001
Median household income of ZIP code quartile 3	1.04	1.011	1.062	0.004
Median household income of ZIP code quartile 4	1.03	1.003	1.059	0.031
Weighted Elixhauser (AHRQ) Index <0	Reference	-	-	-
Weighted Elixhauser (AHRQ) Index 0	1.01	0.98	1.036	0.59
Weighted Elixhauser (AHRQ) Index 1–4	1.18	1.137	1.229	<0.001
Weighted Elixhauser (AHRQ) Index ≥5	1.1	1.067	1.138	<0.001

Abbreviations: APRDRG, all patient refined diagnosis related group; AHRQ, Agency for Healthcare Research and Quality; CI, confidence interval.

anti-inflammatory medications in patients with severe respiratory infection.[30–33] If depressed patients receive more anti-inflammatory medications than non-depressed patients, inpatient mortality could appear lower. This issue could also inject various confounding biases that were uncontrolled. It is also possible that there is a differential threshold for admitting a patient with depression and our results could be due to unadjusted artifacts of this issue, also similarly described in patients with obesity.[35]

One aspect not evaluated in this study includes the actual risk of influenza acquisition in the presence or absence of depression. The literature on this topic remains inconsistent and is dominated by small samples, with a systematic review concluding the quality of evidence does not support concluding there is an increased risk.[10] However, Segerstrom and colleagues revealed evidence that elderly patients with depression had reduced antibody response to multiple influenza strains compared to those without depression, suggesting a possible increase in risk of influenza acquisition.[12] In a separate study in 70 elderly participants, depression was associated with having significantly more influenza like symptoms, though this was no longer significant in multivariable analysis.[36] Without large prospective studies, this is likely to re-

main an unknown.

This study has several limitations. First, we did not have information on influenza vaccine history. Receipt of the influenza vaccine is thought to, at minimum, a decreased severity of disease even when infected with influenza.[37] Mental illness has also been associated with failure to obtain vaccines, as well as decrease the immune response to some vaccines.[11, 12] Second, we were not able to include information on laboratory values which may be significant in the identification of subgroups affected differently by depressive state (e.g., cytokines and acute phase proteins). We also did not have information on the cause of death for these individuals. Although often difficult to ascertain, this information may assist in identifying subgroups affected differently by depression. Information on the number of days with respiratory symptoms before admission was not available in the NIS database. A delay in hospitalization for or with influenza will delay treatment. Since therapy with oseltamivir is only effective in the initial days of infection, a delay in seeking treatment will result in decreased therapeutic effectiveness resulting in potentially altered clinical outcomes.[38] Therefore, if depressed patients had a shorter duration of symptoms before hospitalization, they may be treated sooner resulting in improved clinical outcomes. Lack

Table 4. Results of the multivariable regression model for all-cause inpatient mortality of adult, non-elderly inpatients with influenza, November–March, 2012–2016 in the United States.

Variable	Odds ratio	Lower 95% CI	Upper 95% CI	P
Depression	0.76	0.594	0.971	0.028
Female gender	1.02	0.892	1.169	0.762
Age, spline 1	1.03	0.993	1.065	0.12
Age, spline 2	0.99	0.91	1.074	0.789
Age, spline 3	1.06	0.618	1.816	0.835
Age, spline 4	0.77	0.146	4.048	0.756
Nicotine dependence	0.75	0.639	0.87	<0.001
Anxiety	0.66	0.525	0.828	<0.001
Alcohol use disorder	1.17	0.9	1.512	0.246
Pneumonia	1.19	1.036	1.368	0.014
APR-DRG severity of illness, minor	Reference	-	-	-
APR-DRG severity of illness, moderate	2.08	1.061	4.072	0.033
APR-DRG severity of illness, major	3.93	1.93	8.021	<0.001
APR-DRG severity of illness, extreme	22.2	10.805	45.627	<0.001
APR-DRG mortality risk minor	Reference	-	-	-
APR-DRG mortality risk moderate	4.85	0.643	36.64	0.126
APR-DRG mortality risk major	7.99	1.021	62.542	0.048
APR-DRG mortality risk extreme	38.7	4.89	306.602	0.001
Median household income of ZIP code quartile 1	Reference	-	-	-
Median household income of ZIP code quartile 2	0.91	0.768	1.087	0.308
Median household income of ZIP code quartile 3	0.91	0.761	1.09	0.308
Median household income of ZIP code quartile 4	0.91	0.746	1.108	0.347
Weighted Elixhauser (AHRQ) Index <0	Reference	-	-	-
Weighted Elixhauser (AHRQ) Index 0	2.02	1.407	2.901	<0.001
Weighted Elixhauser (AHRQ) Index 1–4	1.33	0.737	2.394	0.345
Weighted Elixhauser (AHRQ) Index ≥5	0.99	0.609	1.625	0.983

Abbreviations: APRDRG, all patient refined diagnosis related group; AHRQ, Agency for Healthcare Research and Quality; CI, confidence interval.

of information on anti-inflammatory medications (e.g., statins, steroids, etc) further limits the understanding of the relationship between depression and outcomes if depression is a result of hyperinflammation. Further, we did not have information on depression history and severity, and we lacked data on types of and compliance with treatment received including specific antidepressant medications, anti-psychotics and other psychotropics, some of which have recently been shown to alter feedback loops with depression (and likely inflammation).[39] Given the reliance on discharge ICD-9/10 codes, it is likely patients with depression or other covariates were misclassified. Our study focused on a younger age cohort, one typically not evaluated in studies of influenza and lower respiratory infection. Similar studies may have different results in elderly cohorts. However, defining depression in these older age groups could be challenging in the hospitalized patient. Finally, we did not have information on obesity status. Obesity is associated with nearly a two-fold increased risk for depression [40] and obesity is significantly more prevalent in those with depression.[41] This association could influence our results because

obesity is a known risk factor for severe influenza infection and increased mortality, since the 2009 H1N1 pandemic.[42, 43] Obesity may be an important effect modifier or have substantial interaction effects with depression due to the well-studied immune dysregulation in these patients.[28, 35]

There are many areas of research that are needed in the field of depression and influenza infection. Larger databases with more complete and precise covariates needed for adjustment (e.g., influenza vaccination history, other comorbid conditions, anti-inflammatory medications, obesity) will be necessary to more fully document these potential associations. Although secondary analytics will continue to uncover clues into the relationships between this debilitating disease with risk of and outcomes of infection, prospective studies are needed. For example, understanding the baseline inflammation of individuals prior to infection using novel causal machine learning models [44] may result in targeted approaches to influenza prevention and management. Associations between intestinal or respiratory microbiota, depression, and infection may also

be warranted to define other novel areas for therapy. Recently, changes in the gut microbiota have been documented in patients with depression [45], though the directional impact is still unknown. Regardless, intestinal microbiota dysregulation increases systemic inflammation, and depression is preceded by systemic inflammation in some patients.[46-48] If gut microbiota induced systemic inflammation can trigger mood disorders, modulation of the gut microbiota may play a role in depression therapy and prevention of infec-

tion.[39]

In conclusion, this study suggests that in non-elderly hospitalized patients with influenza, depression is associated with a decreased severity of illness and acute mortality. Depression status may be an important marker of systemic inflammation critical to predicting clinical outcomes in these patients and should be evaluated more closely in more robust databases or prospective studies.

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