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The Association between Major Depressive Disorder and Outcomes in Older Veterans Hospitalized with Pneumonia

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Abstract

Background—Major depressive disorder (“depression”) has been identified as an independent risk factor for mortality for many comorbid conditions, including heart failure, cancer and stroke. Major depressive disorder has also been linked to immune suppression by generating a chronic inflammatory state. However, the association between major depression and pneumonia has not been examined. The aim of this study was to examine the association between depression and outcomes, including mortality and ICU admission, in Veterans hospitalized with pneumonia.

Methods—We conducted a retrospective national study using administrative data of patients hospitalized at any Veterans Administration acute care hospital. We included patients >65 years old hospitalized with pneumonia from 2002–2012. Depressed patients were further analyzed based on whether they were receiving medications to treat depression. We used generalized linear mixed

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effect models to examine the association of depression with the outcomes of interest after controlling for potential confounders.

Results—Patients with depression had a significantly higher 90-day mortality (odds ratio 1.12, 95% confidence interval 1.07–1.17) compared to patients without depression. Patients with untreated depression had a significantly higher 30-day (1.11, 1.04–1.20) and 90-day (1.20, 1.13–1.28) mortality, as well as significantly higher ICU admission rates (1.12, 1.03–1.21), compared to patients with treated depression.

Conclusion—For older veterans hospitalized with pneumonia, a concurrent diagnosis of major depressive disorder, and especially untreated depression, was associated with higher mortality. This highlights that untreated major depressive disorder is an independent risk factor for mortality for patients with pneumonia.

Keywords

mortality; major depressive disorder; pneumonia

INTRODUCTION

Approximately 35 million people in the United States will be diagnosed with major depressive disorder in their lifetime [1], making it one of the most prevalent mental health diseases. The Centers for Disease Control and Prevention state that major depressive disorder is responsible for eight million ambulatory care visits a year [2]. This significant health and economic burden of depression has necessitated a better understanding of the disease and its role as a significant risk factor in many other common medical conditions. Depression has already been shown to be an independent risk factor for mortality in heart failure, stroke and cancer [3–5]. In addition, depression has been shown to cause immune dysregulation and suppression, which is believed to be one possible mechanism of depression's associated risk [6]. However, despite those facts, there is limited data on the relationship between depression and acute infections, such as pneumonia.

Pneumonia and influenza are the leading infectious cause of death in the United States [7]. Pneumonia is responsible for approximately 1.2 million hospital discharges a year [8]. A recent study found that there was an increased independent association between depression and the odds of hospitalization for pneumonia [9]. However to our knowledge, there are no previous studies on whether depression may worsen clinical outcomes in patients hospitalized with pneumonia.

The aim of this study is to determine the association between major depressive disorder and outcomes, namely 30- and 90-day mortality and ICU admission, in patients >65 years of age who are hospitalized with pneumonia after adjusting for potential confounders. Given that depression has been linked to immune dysregulation, our a priori hypothesis was that a diagnosis of depression would be associated with increased mortality for older patients hospitalized with pneumonia.

METHODS

We conducted a retrospective cohort study using clinical and administrative databases of the Department of Veterans Affairs (VA) Health Care System. These databases are the repositories of clinical data from all VA hospitals and outpatient clinics [10]. The Institutional Review Board of the VA North Texas Health Care System approved this study. A more detailed discussion of the methods of this study have been previously published [10].

Inclusion Criteria

Inclusion criteria included:

- a. Hospitalization between October 1, 2001 and September 30th, 2012.
- b. 65 years or older on the date of admission.
- c. Discharged with a diagnosis of pneumonia defined as either a primary diagnosis of pneumonia (ICD-9 codes 480.0–483.99 or 485.0–487.0) or a secondary diagnosis of pneumonia with a primary diagnosis of respiratory failure (ICD-9 code 518.81) or sepsis (ICD-9 code 0.38xx).
- d. Had at least one dose of antimicrobial therapy within the first 48 hours of admission.
- e. Present at three or more VA outpatient clinic visits in the year preceding admission.

For patients who were admitted more than once during the study period, only their first hospitalization was included.

Data Sources and Definitions

The inpatient and outpatient demographic, utilization, pharmacy and comorbidity data from the VA Corporate Data Warehouse were used.

Major Depressive Disorder was identified using ICD-9 codes 296.2, 296.3, or 311 listed in the 12 months prior to admission. Treated depression was defined as having an outpatient prescription filled for a selective serotonin reuptake inhibitor, serotonin-norepinephrine reuptake inhibitor or tricyclic antidepressant in the 90 days prior to admission. The specific medications included in the definition were: Bupropion, Citalopram, Fluoxetine, Mirtazapine, Paroxetine, Sertraline, Trazodone, Venlafaxine, Amitriptyline, Clomipramine, Desipramine, Doxepin, Imipramine, and Nortriptyline. Anxiolytics and antipsychotic medications were excluded from the definition of treated depression due to their frequent use in treating conditions other than depression.

The date of death identified by the VA Vital Status file was used to determine mortality, which has approximately a 98% accuracy in reporting mortality [11].

Race and ethnicity categories included white, black, Hispanic, and other/unknown. Tobacco use and/or smoking cessation efforts were identified using ICD-9 codes for tobacco use

(305.1, V15.82), smoking cessation clinic use, and/or use of medications for the treatment of nicotine dependence (bupropion, nicotine replacement, or varenicline). Alcohol abuse was defined using ICD-9 codes 291, 303, 305.0, and illicit drug use by ICD-9 codes 292, 304, 305 (excluding 305.0–.1). Mental health conditions, including bipolar disorder, schizophrenia, and post-traumatic stress disorder, were defined using the Selim method, which includes a patient-reported mental health survey validated in the elderly Veterans Affairs patient population [12, 13]. We used the Charlson-Deyo comorbidity methodology to classify other preexisting comorbid conditions [14]. Priority status was used as a proxy for socioeconomic status [15].

To further control for potential confounding by medications, a count of unique drugs in each of the following classes was calculated for outpatient prescriptions filled within 90-days prior to presentation: statins, beta blockers, calcium channel blockers, anxiolytics, antipsychotics, oral antidiabetic agents, insulin, other antihypertensive agents, inhaled beta agonists, other bronchodilators, theophylline, and oral corticosteroids. In addition, dichotomous variables were created to identify those with corticosteroid use or outpatient use of any antibiotics within 90-days prior to admission.

Outcomes

Primary outcomes were 30-day and 90-day mortality. While 30-day mortality has largely been shown to be associated with pneumonia-related mortality, 90-day mortality has been shown to be comorbidity-related [16]. Therefore, both were used as primary outcomes. A secondary outcome was ICU admission rate, which was chosen as a proxy for severity of illness while hospitalized.

Statistical Analysis

Bivariate statistics were used to test the association of socio-demographic and clinical characteristics with all-cause 30-day and 90-day mortality as well as our secondary outcome. Categorical variables were analyzed using the chi-square test and continuous variables were analyzed using Student's t-test or Wilcoxon rank-sum test where appropriate.

We used generalized linear mixed effect models to examine the association of major depressive disorder with the outcomes of interest after controlling for potential confounders, including sociodemographics (age, race, gender, marital status, and priority status), comorbid conditions based on a Charlson comorbidity score (such as heart failure, cirrhosis), mental health conditions (such as bipolar disorder, alcohol abuse) identified using the Selim method, prior outpatient health care utilization in the 12 months prior to admission, severity of illness, and the admitting hospital. The model was then adjusted to examine the association between treated depression, as defined above, with the outcomes of interest, as opposed to the association between untreated depression with the outcomes of interest.

Statistical significance was defined as a two-tailed p-value of < 0.05 . STATA 14 (College Station, Texas) were used for all analyses.

RESULTS

Baseline Characteristics

Of the 103,997 patients who met the inclusion criteria, 19.7% carried a diagnosis of major depressive disorder. Only 12.6% of patients with a known diagnosis of depression were being actively treated for their depression. The general characteristics of the entire cohort (n= 103,997) was 98% men, 82.9% white, with a mean age of 77.8 years (standard deviation of 7.4) and a mean Charlson comorbidity score of 3.2 (standard deviation of 2.6).

Univariate results

Table 1 shows the key characteristics of the cohort by diagnosis, and treatment status, of depression. Among patients with depression, there was a significantly higher proportion ($p < 0.001$) of other psychiatric conditions present, particularly bipolar disorder and post-traumatic stress disorder. Patients with depression also had a significantly higher proportion ($p < 0.001$) of alcohol abuse. This is consistent with the literature which has consistently demonstrated the comorbidity between depression and other psychiatric conditions, as well as alcohol abuse [17–20].

In the unadjusted models, patients with depression had a higher 30-day (15.0% versus 14.1%, $p = 0.002$) and 90-day (24.5% versus 22.9%, $p < 0.001$) mortality than patients without a diagnosis of depression. Also, patients with untreated depression had a higher 30-day (16.5% versus 14.1%, $p < 0.001$) and 90-day (27.3% versus 22.9%, $p < 0.001$) mortality as compared to patients with treated depression. Figure 1 and 2 demonstrates that those with depression (vs. no depression) or untreated (vs. treated depression) has significantly higher mortality ($p < 0.001$).

Results of Multilevel Regression Models

The same trend of increased mortality in patients with depression, particularly untreated depression, remained after adjusting for potential confounders. For patients with depression there was an increased 90-day mortality (OR 1.12, CI 95% 1.07–1.17) as opposed to patients without depression. Both 30-day (OR 1.11, CI 95% 1.04–1.20) and 90-day mortality (OR 1.20, CI 95% 1.13–1.28) was significantly higher in patients with untreated depression as opposed to those with treated depression. There was also a significantly increased risk of admission to the ICU (OR 1.12, CI 95% 1.03–1.21) in patients with untreated depression.

DISCUSSION

Major depressive disorder was associated with increased mortality in this national cohort study of veterans hospitalized with pneumonia. Upon analysis of the smaller depression cohort, we demonstrated that untreated depression was associated with significantly increased mortality as compared to those receiving treatment. To our knowledge, this is the first study to demonstrate an increased mortality risk for patients hospitalized with pneumonia and with depression. These results suggest that depression, especially untreated depression, is an independent risk factor for mortality in patients hospitalized with

pneumonia. It also suggests that untreated depressed patients have increased rates of admission to the intensive care unit.

Our result supports recent data from Davydow et. al [9] which showed that depression was associated with increased hospitalization (OR 1.28, 95% CI 1.08–1.53) for patients diagnosed with pneumonia. In that study, there was no subgroup analysis performed between treated versus untreated depression due to limitations of the database that was used. Therefore, it was not possible to examine whether untreated depression was associated with increased hospitalization. Nevertheless, the increased rate of hospitalization seen among patients with a diagnosis of depression in that study did remain elevated even after adjustment for confounders, such as functional impairments, just as the mortality rate remained elevated in the depressed population in our study even after adjustment for confounders.

Taken together, these results raise an interesting question: should hospitalized patients be routinely screened for depression given its emerging role as an independent risk factor in common conditions seen in the hospital, such as heart failure, cancer, stroke and now, pneumonia? The United States Preventative Services Task Force guidelines state that patients in “primary care settings” should be screened for depression if support is available to provide treatment and follow-up [21]. However, they recommend against screening if ability to provide support, including ability to provide follow-up, is not present [21]. It can be surmised that the inability to provide follow-up in the hospital setting is part of why national recommendations for screening hospitalized patients for depression has not been implemented. However, at least one organization has implemented screening in the hospitalized population. In order to obtain Joint Commission-sponsored certification as a Comprehensive Stroke Center, depression screening is required [22]. A recent study demonstrated that it was feasible to perform depression screening, using a modification of the PHQ-9, and that the screening could be justified by a high prevalence of depression, 35% discovered in their cohort [22]. In fact, there is an elevated mean prevalence of 29% for depression in the older hospitalized population in general [23, 24].

We also had a high prevalence of depression in our cohort, approximately 20%. While it is certainly possible the higher prevalence is related to the older, hospitalized population, it is possible this is because the study was performed in a VA cohort. The VA population has been recognized to have a higher prevalence of depression than the general population [15]; of note, however, the younger population in the VA usually demonstrates the exceptionally higher prevalence of depression, not the elderly population [15].

Regardless of the cause of the elevated prevalence of depression, the combination of elevated prevalence and depression’s role as an independent risk factor in many conditions cannot be ignored. This study provides additional impetus for considering whether depression screening may be beneficial for health outcomes in hospitalized patients. More research will be necessary to determine whether identification of depression in hospitalized patients can lead to improved health outcomes.

There were several limitations to this study. The study was limited to patients older than 65 and the VA population, which has a limited female component. Therefore, that may affect the generalizability of the results. Also, the study relied heavily on ICD-9 codes, which may not detect the true prevalence of depression in the population. The definition of treated depression was limited as well to the filling of an outpatient prescription in the 90 days prior to admission, which does not necessarily guarantee that the patient was actively taking their medication at the time of their admission nor does it identify patients who may have been receiving non-pharmacologic treatment. In addition, we were also unable to stratify our results based on the severity of the pneumonia, due to the fact that our database did not include laboratory results necessary to calculate scores such as the Pneumonia Severity Index or CURB-65. The severity of pneumonia could have acted as an additional confounder on our results. Finally, there is always the possibility of additional confounders that we were not able to account for, though we feel the combination of comorbidities, sociodemographics, severity of illness and medication use that we compiled is a robust compilation of confounders.

CONCLUSION

For older veterans hospitalized with pneumonia, a concurrent diagnosis of major depressive disorder, especially untreated depression, was associated with higher mortality. This study highlights that untreated major depressive disorder is noted to be an independent risk factor for mortality in a common infectious condition, pneumonia. Further research is necessary to determine whether screening hospitalized patients for depression may be beneficial to help identify this risk factor.

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Figure 1.
Kaplan-Meier graph of depression versus no depression

Figure 2.
Kaplan-Meier graph of treated versus untreated depression

Table 1

Comparison of diagnosis depression vs. no depression in patients hospitalized with pneumonia

Variables	Treated Depression, n = 13,073 (12.57%)	Not Treated Depression, n = 7,466 (7.18%)	Not Depressed, n = 83,458	p-value Depressed versus Not Depressed
Age, mean (SD), y	76.7 (7.5)	77.7 (7.5)	78.0 (7.3)	$P < 0.001$
Men	12,740 (97.5%)	7292 (97.7%)	82,159 (98.4%)	$P < 0.001$
Race				
White	11,316 (86.6%)	6,235 (83.5%)	66,821 (80.1%)	$P < 0.001$
Black	917 (7.0%)	693 (9.3%)	10,131 (12.1%)	$P < 0.001$
Hispanic	857 (6.6%)	467 (6.3%)	5,289 (6.3%)	$P = 0.566$
Married	7012 (53.6%)	3523 (47.2%)	43,209 (51.8%)	$P = 0.2$
Nursing Home Residence	392 (3.0%)	220 (2.9%)	1,123 (1.3%)	$P < 0.001$
Socioeconomic Proxy				
VA Priority group1	3,889 (29.7%)	2,124 (28.4%)	15,941 (19.1%)	$P < 0.001$
VA Priority group2–6	8,158 (62.4%)	4,724 (63.3%)	58,694 (70.3%)	$P < 0.001$
VA Priority Group7–8	1,026 (7.8%)	618 (8.3%)	8,823 (10.6%)	$P < 0.001$
ICU Admission	2,199 (16.8%)	1,417 (19.0%)	14,324 (17.2%)	$P = 0.1$
Mechanical Ventilation	2,422 (18.5%)	1,381 (18.5%)	15,153 (18.2%)	$P = 0.6$
Noninvasive mechanical ventilation	663 (5.1%)	369 (4.9%)	3,718 (4.5%)	$P < 0.001$
Vasopressor Use	635 (4.9%)	414 (5.5%)	4,338 (5.2%)	$P = 0.6$
Number of emergency department visits in prior 12 months	11,681	6092	61,631	$P < 0.001$
Number of primary care visits in prior 12 months	87,997	43,444	443,929	$P = 0.4$
Number of psychiatry visits in prior 12 visits	58,359	23,423	67,565	$P < 0.001$
Comorbid conditions				
HIV and/or AIDS	45 (0.3%)	36 (0.5%)	283 (0.3%)	$P = 0.2$
Cerebral vascular accident	3,053 (23.4%)	1,857 (24.9%)	18,526 (22.2%)	$P < 0.001$
Chronic obstructive pulmonary disease	7,635 (58.4%)	3,957 (53.0%)	43,111 (51.7%)	$P < 0.001$
Dementia	1116 (8.5%)	689 (9.2%)	3,554 (4.3%)	$P < 0.001$
Diabetes	5,145 (39.4%)	2,675 (35.8%)	28,525 (34.2)	$P < 0.001$
Diabetes with complication	1,865 (14.3%)	972 (13.0%)	8,703 (10.4%)	$P < 0.001$
Heart Failure	3,938 (30.1%)	2,164 (29.0%)	21,411 (25.7%)	$P < 0.001$
Myocardial Infarction	1,239 (9.5%)	658 (8.8%)	5,935 (7.1%)	$P < 0.001$
Mild Liver Disease	165 (1.3%)	105 (1.4%)	764 (0.9%)	$P < 0.001$
Moderate Liver Disease	2,383 (18.2%)	1,341 (18.0%)	13,893 (16.6%)	$P < 0.001$
Peripheral Vascular Disease	2,502 (19.1%)	1,431 (19.2%)	13,652 (16.4%)	$P < 0.001$
Renal Disease	2,448 (18.7%)	1,379 (18.5%)	14,189 (17.0%)	$P < 0.001$
Any prior malignancy	3,340 (25.5%)	1,917 (25.7%)	21,239 (25.4%)	$P = 0.666$
Hematologic malignancy	328 (2.5%)	160 (2.1%)	2,234 (2.7%)	$P < 0.02$

Variables	Treated Depression, n = 13,073 (12.57%)	Not Treated Depression, n = 7,466 (7.18%)	Not Depressed, n = 83,458	p-value Depressed versus Not Depressed
Metastatic solid tumor	570 (4.4%)	346 (4.6%)	3,739 (4.5%)	$P = 0.9$
Rheumatologic Disease	444 (3.4%)	221 (3.0%)	2,380 (2.9%)	$P = 0.003$
Tobacco Use	6,128 (46.9%)	3,292 (44.1%)	34,371 (41.2%)	$P < 0.001$
Alcohol Abuse	828 (6.3%)	445 (6.0%)	1,967 (2.4%)	$P < 0.001$
IV Drug Use	483 (3.7%)	278 (3.7%)	799 (1.0%)	$P < 0.001$
Bipolar Disorder	696 (5.3%)	382 (5.1%)	1,382 (1.7%)	$P < 0.001$
Post-traumatic stress disorder	2,035 (15.6%)	822 (11.0%)	2,452 (2.9%)	$P < 0.001$
Schizophrenia	446 (3.4%)	309 (4.1%)	2,135 (2.6%)	$P < 0.001$
Medication Use				
Anticonvulsants	2,978 (22.8%)	916 (12.3%)	9,210 (11.0%)	$P < 0.001$
Beta-agonists	9,135 (69.9%)	4,753 (63.7%)	52,975 (63.5%)	$P < 0.001$
Beta-blockers	6,814 (52.1%)	3,688 (49.4%)	40,404 (48.4%)	$P < 0.001$
Calcium channel blockers	4,966 (38.0%)	3,018 (40.4%)	32,886 (39.4%)	$P < 0.001$
Corticosteroids	9,291 (71.1%)	4,862 (65.1%)	53,396 (64.0%)	$P < 0.001$
Guideline concordant antibiotics	10,608 (81.1%)	5,748 (77.0%)	67,605 (81.0%)	$P < 0.001$
Insulin	1,927 (14.7%)	704 (9.4%)	8,676 (10.4%)	$P < 0.001$
Oral antidiabetic medications	2,495 (19.1%)	911 (12.2%)	13,949 (16.7%)	$P = 0.7$
Other antihypertensive medications	3,295 (25.2%)	1,221 (16.4%)	17,804 (21.3%)	$P < 0.05$
Other bronchodilators	5,289 (40.5%)	1,963 (26.3%)	27,351 (32.8%)	$P < 0.001$
Statins	5,718 (43.7%)	1,897 (25.4%)	29,500 (35.3%)	$P < 0.001$
Theophylline	371 (2.8%)	143 (1.9%)	2,395 (2.9%)	$P = 0.004$