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Risk of Developing Alzheimer Disease in Relation to Common Infections

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Keywords
Infections · Alzheimer disease · Meningitis · Urinary tract infections · Pneumonia

Abstract

Introduction: Many studies demonstrate positive associations between infections and Alzheimer disease (AD), suggesting that brain and/or systemic inflammation may impact AD pathogenesis. However, studies of meningitis and AD risk have been limited to animal models or small human cohorts in the USA. The objective of this study was to examine the relationship between incident AD and three different types of infections (meningitis, pneumonia, and urinary tract infections [UTIs]) using a population-based sample of US Medicare beneficiaries. ***Methods:*** We created a case-control dataset by frequency matching 4:1 (control: case) by age group, sex, and month/year of the date of AD diagnosis or control selection date. We identified 52,628 newly diagnosed AD cases and 210,512 population-based controls ≥67 years of age using comprehensive Medicare claims data from 2016 to 2018. We classified infections using ICD-9-CM and ICD-10-CM diagnosis codes. We used logistic regression to calculate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) to evaluate the association between AD and each infection separately. We lagged exposures up to 18 months and examined hospitalization or comorbid sepsis as a proxy for infection severity. Covariates included age, sex, race/ethnicity, and health care utilization. ***Results:*** AD was positively associated with meningitis in individuals hospitalized without superimposed sepsis with a 6-month lag (OR = 2.713, 95% CI: 1.277–5.764), and UTIs without superimposed sepsis with an 18-month lag (OR = 1.231, 95% CI: 1.101–1.376), and with superimposed sepsis with an 18-month lag (OR = 1.388, 95% CI: 1.050–1.835). There was no association between AD and pneumonia in individuals hospitalized with or without superimposed sepsis. When examining infections that occurred in the outpatient setting, the association between AD and UTI remained positive yet attenuated at all time points, however, the association became inverse between AD and pneumonia. ***Conclusion:*** More severe infections, particularly meningitis, may be associated with a higher risk of AD, due to either unmasking of prodromal AD or acceleration of AD pathogenesis in susceptible individuals.

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Introduction

Several studies have proposed a causal association between infections, such as meningitis, and Alzheimer disease (AD) and other dementias [1–4]. Animal models suggest that the meningeal clearance of waste products from the cerebrospinal and interstitial fluids is critical in mechanisms to remove aggregated proteins such as amyloid-β [5]. In a human study, patients with acute bacterial meningitis had low levels of cerebrospinal fluid (CSF) amyloid-β [6], similar to the pattern seen in patients with AD [7, 8]. These findings were confirmed in a study including multiple central nervous system (CNS) infectious agents [9]. Collectively, these studies support the hypothesis that people with a history of meningitis may have a greater risk of AD or an accelerated onset of cognitive impairment. Nevertheless, large population-based epidemiological investigations are needed to confirm the hypothesis that there is a higher risk of AD in relation to meningitis relative to other severe infections. To test this hypothesis, we used a large nationwide population-based sample of Medicare beneficiaries, to examine the association between incident AD and meningitis and other severe infections. We also examined potential indicators of severity such as being hospitalized or having comorbid sepsis.

Methods

Study Design and Eligibility

We constructed a population-based case-control study using the Medicare Master Beneficiary Summary File (MBSF) and inpatient, outpatient, physician/supplier, skilled nursing facility, home health care, and durable medical equipment medical claims data from age-eligible Medicare beneficiaries from 2014 to 2018. We required all cases and controls to be enrolled in Medicare Part A and B without health maintenance organization coverage, alive in the USA, and age-eligible for Medicare for at least 2 years to ensure incident cases. All beneficiaries who met these criteria and who had an International Classification of Diseases, revision 9 or 10, clinical modification (ICD-9-CM and ICD-10-CM) code for AD (331.0, G30.0, G30.1, G30.8, G30.9) in 2016–2018 and no prior year (2014–2017) were included as newly diagnosed AD cases (N = 52,628). We required cases to have an AD-specific code; however, they could have a code for non-AD dementia in 2016–2018 [10]. Controls (N = 210,512) were identified as those without a code for AD or non-AD dementia in 2014–2018 and were frequency matched to cases 4:1 on age group, sex, and month/year of the date of AD diagnosis.

Assessment of Infections and Covariates

We extracted all ICD-9-CM and ICD-10-CM diagnosis codes from all available claims data up to the date of AD diagnosis date in 2016–2018. We created a dichotomous variable for each diagnosis code observed in the years prior (2014–2018) to the AD diagnosis or control reference date. We identified beneficiaries as having an ICD-9-CM or ICD-10-CM diagnosis code (online suppl. Table S1; for all online suppl. material, see https://doi.org/10.1159/000546589) of one of three infections (meningitis, pneumonia, urinary tract infection [UTI]; each separately) prior to being diagnosed with AD, or control selection date. Each infection was examined separately and beneficiaries could have more than one type of infection. However, within each infection type, we included mutually exclusive groups for inpatient and outpatient visits based on infection type (e.g., individuals could not have an outpatient and inpatient visit for the same infection exposure). To determine if severity of the infection impacted AD risk, we compared the odds ratios (ORs) for AD risk in beneficiaries diagnosed with an infection in an outpatient vs. inpatient (hospital) setting, with the latter indicating a more severe infection. Second, for those beneficiaries diagnosed with an infection in the hospital we included codes for sepsis for each of the three infections separately as an indicator of disease severity. Age, sex, and ethnicity were obtained for each beneficiary from the MBSF. We calculated use of medical care in the form of two continuous variables: (1) the sum of unique ICD-9-CM and ICD-10-CM diagnosis codes and (2) sum of unique physician specialty visits, each up to, but not including the date of AD diagnosis.

Statistical Analysis

We performed all analyses using STATA MP version 18 [11]. We used logistic regression, with AD as our outcome variable, to determine the associations between AD and each infection type separately. We reported the OR and respective 95% confidence interval (CI) as an estimate of the relative risk of AD in relation to infection. Covariates included age (continuous), sex, race/ethnicity (in seven categories), and use of care (continuous) [12]. We included a basic model (age, sex, race/ethnicity) and a full model (age, sex, race/ethnicity, and use of care) in our analyses. We repeated all analyses in beneficiaries who were: (1) diagnosed in an inpatient setting (hospital) and (2) diagnosed with sepsis in the hospital. We also

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examined the effect of lagging infection exposure by 6, 12, or 18 months (i.e., excluding all beneficiaries who had an infection that occurred in the 6, 12, or 18 months prior to AD diagnosis/control reference date). Eighteen months was the maximum lag we could apply in our dataset due to sample sizes. In the lagged analyses, we adjusted for use of care for the respective time period rather than the entire period. We did not report any results for cases <11 based on the Centers for Medicare and Medicaid Services (CMS) guidelines. As a sensitivity analysis, we examined whether certain medical conditions, included in other studies examining infections and AD/dementia risk, acted as potential confounders if we observed a 10% change or greater in the OR between exposure of interest and AD [13, 14]. These medical conditions (acute myocardial infarction, asthma, atrial fibrillation, chronic kidney disease, chronic obstructive pulmonary disease, depression, diabetes, congestive heart failure, hyperlipidemia, hypertension, ischemic heart disease, rheumatoid arthritis/osteoarthritis, and stroke/transient ischemic attack) were obtained from the Chronic Conditions Warehouse (CCW) available in the Medicare summary file. To improve diagnostic certainty of AD, we performed another sensitivity analysis in which we included only AD cases who were diagnosed by a neurologist or those cases who had at least two separate AD diagnosis claims codes (separate dates of service).

Results

Cases were less likely to be female (OR = 0.97, 95% CI: 0.95–0.99) and more likely to be black (OR = 1.37, 95% CI: 1.31–1.41) or Hispanic (OR = 1.25, 95% CI: 1.20–1.30) (Table 1).

Meningitis

AD was positively associated with meningitis when examining infections that occurred in the hospital setting at time 0: (OR = 2.555, 95% CI: 1.366–4.780) and with a 6-month exposure lag (OR = 2.713, 95% CI: 1.277–5.764). AD was positively associated with meningitis in the outpatient setting (OR = 1.405, 95% CI: 1.061–1.861), however, with exposure lagging (6, 12, and 18 months), the association was no longer significant (Table 2).

Pneumonia

There was no association between AD and pneumonia that occurred in the hospital setting with or without superimposed sepsis at any time-point (0, 6, 12, and 18 months). We observed a modest inverse association between pneumonia treated in the outpatient setting at time 0: (OR = 0.957, 95% CI: 0.922–0.995) and with exposure lagging of 6 months (OR = 0.909, 95% CI: 0.871–0.948), 12 months: (OR = 0.912, 95% CI: 0.871–0.954), and 18 months: (OR = 0.925, 95% CI: 0.879–0.973) (Table 2).

Urinary Tract Infection

There was a positive association between UTI and AD in the hospital setting with or without sepsis at all time points (0, 6, 12, and 18 months). The OR was slightly attenuated with an 18-month lag for individuals hospitalized only (OR = 1.231, 95% CI: 1.101–1.376) as compared to individuals hospitalized with superimposed sepsis (OR = 1.388, 95% CI: 1.050–1.835). In the outpatient setting, the association between UTIs and AD remained positive at all time-points (0, 6, 12, and 18 months), though it was slightly attenuated as compared to the hospital setting (Table 2).

Sensitivity Analysis

There was no material change to the OR after adjustment of each medical condition assessed, and therefore no variables were determined to be confounders in the relationship between any of the infections and AD (online suppl. Table S2a). Additionally, there was no material change to the OR in our sensitivity analysis that used a more "certain" AD diagnosis (online suppl. Table S2b).

Discussion

In this large population-based study, we observed a positive association between meningitis and AD prior to diagnosis, supporting a potential pathogenic link between meningitis and AD. Prior animal models have found that infections such as meningitis can lead to significant impairment of the glymphatic system and retained proteins and waste products in the CSF compartments [15, 16]. A breakdown within the normally functioning glymphatic system may contribute to the progression of pathological neurodegenerative processes that lead to AD [17]. Notably, we found that those with the most severe meningeal infections requiring hospitalization had the highest risk of AD. A serious infection such as meningitis that requires management in a hospital and intensive care unit (ICU) setting likely has the greatest systemic inflammatory response and an injury to the meningeal lymphatic and glymphatic systems. This, in turn, could impair clearance of toxic AD protein aggregates. There is

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Table 1. Characteristics of incident AD cases and controls, USA, Medicare, 2016–2018

	Cases (N = 52,628), n (%)	Controls (N = 210,512), n (%)	Mutually adjusted OR, OR (95% CI)
Sex			
Male	18,585 (35.3)	74,340 (35.3)	1.00 (Reference)
Female	34,043 (64.7)	136,172 (64.7)	0.97 (0.95–0.99)
Race/ethnicity			
White	43,275 (82.2)	178,075 (84.6)	1.00 (Reference)
Black	4,457 (8.5)	13,834 (6.6)	1.37 (1.31–1.41)
Hispanic	2,986 (5.7)	10,027 (4.8)	1.25 (1.20–1.30)
Asian/Pacific Islander	1,372 (2.6)	1,372 (2.6)	0.92 (0.89–0.98)
Native American	203 (0.4)	843 (0.4)	0.98 (0.84–1.14)
Other	335 (0.6)	1,449 (0.7)	0.99 (0.88–1.12)
Age, years			
Mean (SD)	82.6 (7.6)	82.4 (7.6)	1.002 (1.001–1.003)
Minimum	67	67	
Median	83	83	
Maximum	109	109	
Sum of unique diagnosis codes			
Mean (SD)	78.8 (56.1)	69.9 (49.1)	1.0070 (1.0067–1.0074)
Minimum	0	0	
Median	68	61	
Maximum	543	574	
Sum of unique physician specialties			
Mean (SD)	10.6 (5.8)	10.1 (5.6)	0.962 (0.958–0.965)
Minimum	0	0	
Median	10	10	
Maximum	37	42	

AD, Alzheimer disease; CI, confidence interval; OR, odds ratio; SD, standard deviation.

also evidence suggesting that amyloid β (Aβ) peptides function as antimicrobial proteins (AMPs) within the innate immune system by inactivating infectious pathogens, including *Streptococcus pneumoniae*, the leading cause of bacterial meningitis [18–20]. Alternatively, a more severe CNS infection could also lead to delirium and unmask and/or accelerate prodromal dementia symptoms. Nevertheless, our study provides valuable human data to support a potential pathogenic role for meningitis as a risk factor for AD.

We also demonstrated positive associations between AD and UTIs that required hospitalization. These associations appeared marginally stronger than for UTIs diagnosed in an outpatient setting. There are several potential mechanisms by which systemic UTI infections may contribute to AD risk in patients who require hospitalization. First, we cannot exclude the possibility of enhanced ascertainment of AD diagnoses resulting from use of medical care for management of an infection. However, we did adjust for use of medical care as we have done previously in Medicare-based studies [12]. UTIs may also accelerate the development of clinical AD, albeit more indirectly than meningitis, due to the effects of the most common uropathogen, *Escherichia coli* (*E. coli*), a gram-negative bacteria [21]. Diminution of immune system function with aging, immunosenescence [22], may increase the risk of infections and dementia [23]. Severe systemic infections requiring hospitalization, may either accelerate onset of, or unmask AD in individuals already at high risk for AD or with subclinical prodromal AD. In one study, patients who required ICU level care underperformed healthy control groups at the time of discharge in 11 out of 13 cognitive tests, and these differences were worse for individuals with premorbid cognitive impairment and superimposed delirium. Six percent of individuals without evidence of premorbid cognitive deficits, who required ICU level care, had persistent cognitive deficits at 9-month follow-up [24]. In a more recent study of individuals hospitalized with respiratory failure or shock requiring ICU level care,

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Table 2. Risk of Alzheimer disease in relation to three different infections and severity indicators, USA, Medicare 2016–2018

Exposure Lagging, months	Outpatient				Inpatient				Inpatient + sepsis			
	N	*N*	basic model[a]	full model[b]	*N*	*N*	basic model[a]	full model[b]	*N*	*N*	basic model[a]	full model[b]
	cases	controls	OR (95% CI)	OR (95% CI)	cases	controls	OR (95% CI)	OR (95% CI)	cases	controls	OR (95% CI)	OR (95% CI)
Meningitis												
0	70	174	**1.650** (1.249, 2.180)	**1.405** (1.061–1.861)	18	23	**3.155** (1.699, 5.858)	**2.555** (1.366–4.780)	[c]	[c]	–	–
6	42	143	1.215 (0.860, 1.716)	1.089 (0.770–1.540)	12	16	**3.044** (1.437, 6.447)	**2.713** (1.277–5.764)	[c]	[c]	–	–
12	34	116	1.231 (0.839, 1.806)	1.099 (0.749–1.615)	[c]	[c]	–	–	[c]	[c]	–	–
18	27	88	1.301 (0.844, 2.004)	1.163 (0.754–1.795)	[c]	[c]	–	–	[c]	[c]	–	–
Pneumonia												
0	3,975	14,461	**1.119** (1.079, 1.161)	**0.957** (0.922–0.995)	377	1,177	**1.275** (1.134, 1.433)	1.060 (0.942–1.193)	110	315	**1.400** (1.125, 1.741)	1.098 (0.880–1.369)
6	3,059	12,277	0.996 (0.955, 1.037)	**0.909** (0.871–0.948)	283	962	**1.157** (1.012, 1.322)	1.050 (0.918–1.201)	72	226	1.266 (0.970, 1.653)	1.110 (0.849–1.450)
12	2,559	10,286	0.996 (0.952, 1.041)	**0.912** (0.871–0.954)	236	820	1.134 (0.980, 1.311)	1.035 (0.895–1.199)	60	186	1.282 (0.957, 1.717)	1.139 (0.850–1.528)
18	2,066	8,133	1.017 (0.968, 1.069)	**0.925** (0.879–0.973)	182	644	1.117 (0.946, 1.317)	1.010 (0.856–1.193)	37	139	1.059 (0.736, 1.524)	0.916 (0.635–1.321)
UTI												
0	13,912	49,110	**1.308** (1.278, 1.338)	**1.215** (1.186–1.244)	815	2,140	**1.717** (1.582, 1.864)	**1.533** (1.410–1.666)	142	387	**1.635** (1.347, 1.983)	**1.366** (1.124–1.661)
6	12,325	44,916	**1.180** (1.152, 1.208)	**1.135** (1.107–1.164)	607	1,893	**1.349** (1.230, 1.480)	**1.293** (1.178–1.420)	108	295	**1.541** (1.235, 1.923)	**1.426** (1.142–1.781)
12	10,903	40,020	**1.153** (1.125, 1.181)	**1.106** (1.078–1.135)	533	1,614	**1.371** (1.241, 1.513)	**1.304** (1.180–1.441)	93	247	**1.570** (1.236, 1.995)	**1.451** (1.141–1.845)
18	9,356	34,440	**1.146** (1.117, 1.176)	**1.092** (1.063–1.122)	424	1,323	**1.319** (1.181, 1.473)	**1.231** (1.101–1.376)	69	184	**1.552** (1.175, 2.048)	**1.388** (1.050–1.835)

Bolded numbers represent significant values. CI, confidence interval; OR, odds ratio; UTI, urinary tract infection. [a]Adjusted for age, sex, race/ethnicity. [b]Adjusted for age, sex, race/ethnicity, and use of care. [c]Cases too small to report per CMS guidelines ($N < 11$).

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longer time-periods of delirium were associated with worse cognitive function even at the 12-month follow-up [25]. Nevertheless, it is likely that older adults have less physiological reserve, which includes immunosenescence, needed to counteract allostatic overload [26] in those with prodromal AD, thus increasing the likelihood of diagnosis.

Our findings also support other studies that found a higher risk of dementia after non-CNS related infections, particularly in short-term follow-up [13, 14, 23, 27–32]. However, previous studies provide mixed results with respect to whether CNS-related vs. non-CNS infections contribute to a higher risk of dementia. In one study of Medicare beneficiaries who were hospitalized, the presence of an infection, sepsis, and acute neurological dysfunction (as defined by anoxia, encephalopathy, or delirium) were all associated with a higher risk of being diagnosed with dementia within the 3 years of follow-up [30]. A Danish registry study reported an increased risk of incident dementia after a hospital diagnosed infection; however, these findings did not appear to be specific for infection type or organ system affected [13]. In contrast, in a large European study with exposure lagging >10 years, investigators found that although a hospitalization for any infection type was associated with an increased risk of dementia, the greatest risk for dementia was observed for CNS infections (HR 3.01, 95% CI: 2.07–4.37) compared to non-CNS infections (HR 1.47, 95% CI: 1.36–1.59) [31]. In a UK population-based cohort study, investigators reported the strongest association between infections and risk of dementia in hospital-recorded infections (HR 1.99, 95% CI: 1.94–2.04) as compared to those treated in an outpatient setting in general practice (HR 1.02, 95% CI: 1.00–1.04) [14]. Our findings of a higher risk of AD associated with UTI and meningitis are consistent with this literature. However, unlike many European studies, our maximum time lag was only 18 months given that Medicare claims data are only population-based for individuals ages 65 and older in the USA. As a result, we were only able to examine associations between infections and AD in an 18-month prodromal window. Nevertheless, the ORs for the association between inpatient meningitis in our study remained high at 6 months, which was the longest we could report due to CMS imposed limitations. Future longitudinal studies following younger individuals after serious systemic infections would clarify the role of systemic inflammation and immunosenescence in AD risk if these patients were outside the prodromal AD window.

Interestingly, even less severe, non-meningeal infections, such as UTIs treated in the outpatient setting, were associated with a higher risk of AD, although the association was weaker compared to UTIs treated in hospital settings. UTIs are commonly found in individuals diagnosed with AD/dementia and are frequently due to neurogenic bladder dysfunction [33–35]. A normally functioning urinary tract requires intact central, peripheral, and autonomic nervous systems, all of which may be impaired in neurodegenerative diseases [35]. Older adults with lower urinary tract symptoms have a greater risk of dementia compared to the general population, consistent with UTI as a prodromal AD symptom [34]. In contrast, we acknowledge that our findings demonstrating no association between AD and pneumonia in the inpatient setting are not consistent with other population-based studies, which found a higher risk of AD after all infection types, including with pneumonia [36, 37]. In one US-based study, there was an increased risk of dementia with all infections studied including pneumonia among US veterans [28]. In another study, authors only found an increased risk of dementia with pneumonia in individuals who were identified as pre-frail or frail [38]. It is possible that in our study of Medicare beneficiaries by adjusting for healthcare utilization we may be over-adjusting our models since the importance of health care utilization as a confounder in AD epidemiology studies remains to be determined. When adjusting only for age, sex, and race in our basic model, the association between pneumonia and AD was positive at baseline across all settings. Interestingly, we found that people with pneumonia who did not require hospitalization actually had a slightly lower risk of AD, suggesting that there is something inherently different between UTI and pneumonia with respect to AD risk. One potential explanation for the lower risk of AD in the outpatient setting may be due to the less frail or more physiological robust older adult presenting earlier to the outpatient healthcare provider. These individuals may be more likely to receive yearly vaccinations for influenza [39, 40] and/or participate in other healthy behaviors such as regular exercise not captured in Medicare claims data. Another explanation for the lack of a positive association between pneumonia and AD risk may be due to the fact that the most common pathogens detected in older adults with pneumonia are viruses in contrast to UTIs which are typically due to bacterial pathogens. In a large study of adults with radiographic evidence of pneumonia, only 38% of patients had a pathogen detected (≥1 virus was detected in 23%, ≥1 bacteria detected in 11%, bacterial and viral in 3%, and fungal/mycobacterium in 1%) [41]. In contrast, the most common pathogen reported in both complicated and uncomplicated UTIs was the

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gram-negative bacteria, "uropathogenic *E. coli* (UPEC)" [21]. Interestingly, gram negative bacteria, such as UPEC, contain a lipopolysaccharide, glycolipid membrane [42]. Lipopolysaccharides (LPS) are endotoxins that induce a cascade of cytokines, which may be damaging to neurons. Additionally, AMPs, which may include the Aβ protein, may interact directly with the LPS membrane of bacteria as a line of defense. Studies have reported that LPS "colocalizes" with Aβ protein in the brain [22, 43]. Gram-negative bacterial pathogens common in UTIs, such as *E. coli*, may accelerate AD symptoms in vulnerable individuals in both outpatient and hospital settings.

There are several limitations of the present work. Although Medicare is the only population-based, national health care system in the USA, available to age-eligible citizens or permanent legal residents in the USA, our data only includes individuals ≥67 years old to ensure we had only incident AD cases. We do not have data for beneficiaries prior to age 65 and therefore cannot investigate exposure lagging several decades prior to AD diagnosis. Additionally, we do not have access to laboratory data results and therefore cannot quantify blood or CSF markers of inflammation or effects of systemic infections on other organ systems. Future studies that provide objective measures of inflammation after an infection in the years prior to AD diagnosis could provide additional evidence to support our findings. In our study, sample sizes for meningitis were much smaller with notably wide confidence intervals given that this type of infection is rare compared to UTIs or pneumonia. Additionally, due to limitations in the way hospitals are paid by Medicare for inpatient diagnoses using diagnosis-related groups, Medicare data do not contain specific information on inpatient medications. Medication data could provide insight into whether earlier and/or more aggressive treatment of the infection and reduction of systemic inflammation reduces AD risk as some evidence suggests cognition improves in patients with AD who are treated with antimicrobial/antiviral treatments [19]. Another potential limitation is that some beneficiaries with a code for AD may be misdiagnosed. However, our results were similar in sensitivity analyses in which we required beneficiaries to have been diagnosed with AD by a neurologist or have two separate AD diagnosis codes. Additionally, infectious diseases identified in Medicare require the presence of a diagnostic code, which could be susceptible to misclassification. Due to the nature of Medicare data, we are unable to examine the results of a urinalysis or chest radiograph to confirm the diagnoses of UTI and pneumonia [44]. Despite these limitations, our findings are consistent with prior animal and human studies and provide some evidence from human data supporting the concept that meningitis may contribute to AD pathogenesis.

Statement of Ethics

This study was approved by the Human Research Protection Office/Institutional Review Board at Barrow Neurological Institute/Washington University School of Medicine in St. Louis (IRB ID# 202006145) and by the Centers for Medicare and Medicaid Services. All data were de-identified prior to release. Written informed consent was not obtained as this project was granted a waiver of HIPAA Authorization per section 164.512(i) of the Privacy Rule to allow the research team to use Protected Health Information (PHI) in the context of this research study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.C.S., I.F., N.S., J.A.K., O.J.L.-S., and B.K.: drafted the manuscript. A.C.S. and B.A.R.: study concept and design, obtained funding for the study, oversaw study design and data analysis. A.C.S., I.F., N.S., J.A.K., O.L.S., and B.K.: creation of variables, data acquisition, and analysis. . All authors assisted with interpretation of results, review, critique of the manuscript and tables, and final approval of the manuscript.

Data Availability Statement

The data in this study were obtained from the Centers for Medicare and Medicaid Services (CMS) where data sharing is not allowed under the data use agreement. Further inquiries can be directed to the corresponding author.

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