HHS Public Access

Author manuscript

J Stroke Cerebrovasc Dis. Author manuscript; available in PMC 2022 April 01.

Published in final edited form as:

J Stroke Cerebrovasc Dis. 2021 April ; 30(4): 105605. doi:10.1016/j.jstrokecerebrovasdis.2021.105605.

Association Between Chronic Inflammatory Diseases and Stroke-Associated Pneumonia – an Epidemiological Study

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Abstract

Background: Pneumonia, the most common post-acute ischemic stroke (AIS) infection, accounts for up to 30% of deaths after a stroke. Multiple chronic inflammatory diseases, such as rheumatoid arthritis, psoriasis, and inflammatory bowel disease, are associated with increased risk of stroke and stroke morbidity. This study assessed the relationship between chronic inflammatory diseases and stroke-associated pneumonia (SAP).

Methods: Using data from the 2015-2017 National Inpatient Sample, we classified hospital discharges with a diagnosis of AIS as having ulcerative colitis, Crohn's disease, rheumatoid arthritis, psoriasis, systemic lupus erythematosus, other chronic inflammatory diseases, multiple chronic inflammatory diseases, or none. With multivariable logistic regression, we assessed for associations between chronic inflammatory disease and in-hospital SAP or death.

Results: Among AIS discharges, there was a decreased risk of SAP among those with psoriasis or other chronic inflammatory diseases (adjusted odds ratio (aOR) 0.70, 95%CI 0.63-0.99; aOR 0.64, 95%CI, 0.46-0.89, respectively), compared to those without psoriasis and without other chronic inflammatory disease, respectively. Rheumatoid arthritis, psoriasis, and other chronic inflammatory diseases were associated with reduced in-hospital mortality (aOR 0.89, 95%CI 0.78-1.00; aOR 0.77, 95%CI 0.59-1.00; aOR 0.69, 95%CI 0.50-0.94, respectively).

Conclusions: The risk of SAP and in-hospital mortality varies by chronic inflammatory disease - psoriasis and other chronic inflammatory diseases are associate with reduced rates of SAP, whereas rheumatoid arthritis, psoriasis and other chronic inflammatory disease were associated

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with reduced in-hospital mortality. Further investigations are needed to determine a relationship between the potential role of immunomodulation and the reduction in SAP and mortality in chronic inflammatory diseases.

Keywords

Acute Ischemic Stroke; Cerebrovascular infarction; Stroke; Stroke complications; Stroke-associated Pneumonia

Background:

Stroke is a leading cause of worldwide morbidity and mortality. The initial acute ischemic insult results in cell death and brain damage that is an early driver of mortality. However, further damage also occurs through neuroinflammation and stroke-induced immunosuppression. A number of pro-inflammatory cytokines, including interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α, recruit peripheral immune cells to help clear cellular debris from the ischemic insult and initiate repair of the damaged brain tissue (1). However, this inflammatory response also leads to an impaired innate and adaptive immune response (2–4). This immunosuppression contributes to stroke-associated infections, the most common being pneumonia, which account for up to 30% of deaths after an acute ischemic stroke (5). In addition to increased mortality, stroke-associated pneumonia (SAP) is also associated with up to nine times risk of neurological deterioration, over thirty times increase in likelihood of having a poor functional outcome as measured by a modified Rankin scale, and prolonged hospitalizations (6–9).

In addition to immunosuppression, numerous factors have been associated with SAP. The biggest risk factor for SAP is dysphagia, but other risks include increased age, low baseline functional independence, more severe strokes, bilateral stroke lesions, COPD, and coronary artery disease (10–12). Additionally, increased levels of IL-6 in stroke patients correlate with increased risk of SAP and further suggest a role of inflammation in post-stroke infections.

Patients with baseline high inflammatory states secondary of chronic inflammatory diseases, such as rheumatoid arthritis, psoriasis, and inflammatory bowel diseases, have been associated with increased risk of stroke and increased morbidity and mortality from stroke (13, 14). This risk varies with the specific inflammatory disease and may be reduced with improved disease control. For example, the risk of stroke in psoriasis patients correlated with disease severity and was attenuated among those treated with TNF-α inhibitors compared to traditional therapies like methotrexate (15, 16). Thus, the decreased risk of stroke among those treated with TNF-α inhibitors may be partly explained by a reduction in inflammation among these patients. However, patients with rheumatoid arthritis are at up to 60% increased risk of stroke, with the greatest risk among rheumatoid arthritis patients on glucocorticoids (17). It remains unclear if the increased risk among those on glucocorticoids is related to changes in patients inflammatory state, immunosuppression, and/or secondary effects of glucocorticoids like metabolic resistance. However, overall, among patients with rheumatoid arthritis, improved disease control via the use of any disease modifying antirheumatic agent,

including both TNF-α inhibitors and glucocorticoids, reduced the risk of stroke among rheumatoid arthritis patients compared to those not on a disease modifying agent (18,19).

While it is clear that the presence of a chronic inflammatory state is associated with increased risk of stroke, the relationship between chronic inflammatory diseases and post-stroke infections has been poorly studied. Only one study has specifically looked at post-stroke complications among rheumatoid arthritis patients in the Taiwan Longitudinal Health Insurance Database and did not find an association (20). However, in general, patients with chronic inflammatory diseases are at increased risk of developing pneumonia and the use of some biological agents like TNF-α inhibitors may further increase this risk (21–25).

Our study is the first to specifically evaluate the relationship between common chronic inflammatory diseases (inflammatory bowel disease, rheumatoid arthritis, psoriasis, systemic lupus erythematosus, ankylosis spondylitis, and polymyalgia rheumatica) and the risk of SAP. Given the association between inflammation, immunosuppression and stroke, we hypothesized that these associations would also translate to a greater risk of SAP and in-hospital mortality among stroke patients with chronic inflammatory disease.

Methods:

Sample Population:

This is a secondary analysis of the 2015-2017 National Inpatient Sample (NIS) database. The NIS is a publicly available database developed for the Healthcare Cost and Utilization Project. It includes de-identified data from all-payer unique inpatient hospitalizations and readmissions in non-federal hospitals in the United States (26). This study was approved by the Colorado Multiple Institutional Review board as “not human subjects” research.

Cohort Identification:

Using ICD-9 or ICD-10 discharge diagnosis codes, we classified hospitalizations for adults age ≥18 years with acute ischemic stroke into mutually exclusive groups with a given chronic inflammatory disease (ulcerative colitis, Crohn’s disease, rheumatoid arthritis, psoriasis, systemic lupus erythematosus, other [ankylosing spondylitis, polymyalgia rheumatica], multiple chronic inflammatory diseases, or no chronic inflammatory disease. Hospitalizations classified as elective admission or transfers from an outside hospital were excluded. See appendix table 1 for ICD-9 and ICD-10 codes for each diagnosis. ICD codes were identified from https://www.icd10data.com/ and https://www.icd9data.com/ were consistent with prior studies (27, 28).

Statistical Analysis:

We characterized the cohort using descriptive statistics. Appropriate trend weights obtained from the Agency for Healthcare Research and Quality were used to generate national estimates of discharge characteristics (29). A survey-weighted logistic regression modeling approach (adjusting for age, gender, race and ethnicity, comorbidities or conditions associated with SAP [diabetes mellitus, hypertension, obesity, chronic obstructive pulmonary disorder, congestive heart failure, end stage renal disease, cirrhosis], and year of

survey sample) was used to estimate the odds ratios and 95% confidence intervals for the association between each chronic inflammatory disease and SAP and between each chronic inflammatory disease and in-hospital mortality. A separate model was fitted to the data for each inflammatory condition considered; we did not adjust for multiple comparisons in this exploratory analysis. Incomplete records were excluded from multivariable analysis. All analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC). We considered a two-tailed $p<0.05$ as statistically significant.

Results:

A total of 310,615 discharges from 2015-2017 were identified to have a diagnosis of acute ischemic stroke representing a weighted total of 1,553,074 discharges. The proportion of discharges with a given chronic inflammatory disease ranged from 0.13% of acute ischemic stroke discharges with multiple chronic inflammatory disease to 1.63% with rheumatoid arthritis (Table 1). The majority of discharges were aged 60 years or older with exception of discharges with a co-diagnosis of systemic lupus erythematosus, where 50.7% of discharges were aged 18-59 years. In terms of gender, there was a female predominance among acute ischemic stroke discharges with a diagnosis of rheumatoid arthritis, systemic lupus erythematosus, and those with multiple chronic inflammatory diseases (73.1%, 84.6%, and 78.9%, respectively).

Controlling for year of sample, age, gender, race, comorbidities (hypertension, diabetes mellitus, obesity) and conditions that might contribute to the risk of SAP (alcohol abuse, end-stage renal disease, congestive heart failure, chronic obstructive pulmonary disease), the effect of a given chronic inflammatory disease on the risk of SAP varied with each individual disease (Table 2). Discharges with acute ischemic stroke with a co-diagnosis of psoriasis and other chronic inflammatory diseases were associated with decreased odds of SAP compared to those without psoriasis or other chronic inflammatory diseases (adjusted OR (aOR)-0.70, 95% CI 0.63-0.99; aOR-0.64, 05% CI 0.46-0.89, respectively). Neither, ulcerative colitis, Crohn’s disease, rheumatoid arthritis, systemic lupus erythematosus, nor multiple chronic inflammatory diseases were associated with altered risk of stroke-associated disease.

Using multivariable logistic regression to control for year of sample, age, sex, race, comorbidities and conditions altering SAP risk, there was also a significantly reduced risk of in-hospital death among discharges with either rheumatoid arthritis, psoriasis or other chronic inflammatory diseases when compared to those without each (aOR-0.89, 95% CI 0.78-1.00; aOR 0.77, 95% CI 0.59-1.00; aOR 0.69, 95% CI 0.05-0.94, respectively) (Table 3).

Discussion:

The results presented here suggest that there exists a complex interplay between chronic inflammatory states associated with diseases like inflammatory bowel disease, rheumatoid arthritis, and psoriasis, and SAP. While prior data suggest that patients with chronic inflammatory conditions have a higher incidence of acute ischemic stroke, our data indicate

that psoriasis and the combined group of ankylosing spondylitis and polymyalgia rheumatica patients were found to be at altered risk of SAP, and, surprisingly, at lower risk than those without these conditions. These, in addition to rheumatoid arthritis, were also associated with a slight decreased risk of in-hospital mortality. However, neither Crohn's disease, ulcerative colitis, nor systemic lupus erythematosus were associated with altered risk of SAP or in-hospital mortality.

Within minutes of ischemic infarction, microglial cells are activated and are capable of phagocytosis, antigen presentation, and cytokine release to stimulate an inflammatory response and disruption of the blood brain barrier (30). These pro-inflammatory cytokines recruit peripheral immune cells that are important for recovery (1). However, this acute inflammatory response may also lead to impaired innate and adaptive immunity, predisposing stroke patients to infections. This includes reduced lymphoid organ size, reduced T-lymphocyte counts and responses, and impaired neutrophil and monocyte responses (2–4). In the PREDICT study, stroke-induced immunosuppression was an independent predictor of stroke-associated pneumonia, with up to 10% of those patients in the highest serum IL-6 quartile developing SAP and none in the lowest quartile developing SAP (11). IL-6 elevations play a key role in the pathophysiology of numerous chronic inflammatory diseases (Crohn's disease, rheumatoid arthritis, systemic lupus erythematosus, and psoriasis) (31). Thus, it is possible that chronic inflammatory disease might also correlate with stroke-associated pneumonia.

Among patients with inflammatory bowel disease, previous studies have suggested that the risk of stroke is more than five times higher in patients with more severe disease and during periods of acute exacerbations (32). However, the risk of stroke among severe inflammatory bowel disease and psoriasis patients was attenuated by those on TNF-α inhibitors (13,15,32). Prior studies have not directly addressed the potential translation of these protective effects to the risk of SAP. In the data presented here, there was no increased risk of SAP among most groups of chronic inflammatory disease.

Notable exceptions included the groups of with other chronic inflammatory diseases, psoriasis, and rheumatoid arthritis, which appeared to be inversely correlated with SAP and/or in-hospital mortality. This is congruent with one of the few previous studies that have looked at the impact of a chronic inflammatory disease on stroke-associated pneumonia. In a longitudinal Taiwanese study of rheumatoid arthritis patients from 2001 to 2013 hospitalized for an acute stroke, rheumatoid arthritis patients were not at increased risk of SAP or in-hospital mortality compared to matched controls[20].

From a biological perspective, these data may not be surprising. Given the importance of pro-inflammatory cytokines in rheumatoid arthritis, psoriasis, and ankylosing spondylitis pathophysiology, there has been increased use of monoclonal antibodies to target pro-inflammatory cytokine cascades – both TNF-α inhibitors, starting in the early 2000's, and IL-6 receptor inhibitors, starting in 2012. Between 30-85% of rheumatoid arthritis patients were treated with a TNF-α inhibitor between 2001 – 2006 with rates increasing overtime (35–37). The rates of TNF-α inhibitor use in other chronic inflammatory diseases are lower and more variable – only 17% of Crohn's disease, 4% of ulcerative colitis and 2% of

psoriasis patients were treated with a TNF-α inhibitor or other biological agent (38, 39). However, in these patients there was a significantly higher rate of corticosteroid use. These therapies, and their varied use depending on chronic inflammatory disease, may also affect the pro-inflammatory cytokine storm contributing to stroke-associated infections (33,34). Further studies are needed to assess the exact role of immunomodulatory therapy in modification of the risk of post-stroke infections.

This study is limited by the retrospective nature of the analysis, which relies heavily on discharge medical diagnosis coding. In this respect, there is the potential for misclassification of discharges, including the possibility that some patients may have also had concurrent pneumonia at the time of presentation with their acute ischemic stroke. It is also impossible to determine the disease severity and/or the use of immunomodulators, which not only affect the risk of stroke among these patients but also have the potential to influence a subject's outcome in terms of both in-hospital mortality and the development of stroke-associated pneumonia. Additionally, these or other unmeasured confounders may account for some of the differences in SAP risk identified in this study, as it is not possible to differentiate discharges for an initial stroke from those with a recurrent stroke and there is a potential for misclassification. A final caveat with this observational data is the issue of multiple comparison which can limit the interpretation of these results in terms of their statistical significance. Despite these limitations, the strength of this study is derived from the use of a large, national inpatient sample that includes all-payer unique inpatient hospitalizations across the United States. This allows analysis of relatively uncommon conditions not possible in many other stroke databases.

In conclusion, this study identifies a variable association between individual chronic inflammatory diseases and stroke-associated pneumonia. Specifically, psoriasis and other inflammatory spondyloarthropathies (ankylosing spondylitis, polymyalgia rheumatica) may be protective from stroke-associated pneumonia, whereas, these in addition to rheumatoid arthritis may be associated with decreased risk of in-hospital mortality. Taken together, the findings presented here lay the foundation for deeper analysis of the effects of immunomodulators and anti-inflammatory medications on the risk of stroke-associated pneumonia and in-hospital mortality among subjects with chronic inflammatory diseases.

Acknowledgments

Grant Support: NIH Building Interdisciplinary Research Careers in Women's Health K12-HD057022

Appendix Table 1:: ICD-9 (2010-2015) and ICD-10 (2015-2017) diagnosis codes

Diagnosis	ICD-9	ICD-10
Acute Ischemic Stroke	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.11, 434.91, 434.0, 436.0	I63.x
Pneumonia	480.x, 481, 482.x, 483, 484, 485	A40.3, J12.x, J13, J14 J15.x, J16.x, J17, J18

Diagnosis	ICD-9	ICD-10
Ulcerative Colitis	556.x	K51.x
Crohn's Disease	555.x	K50.x
Rheumatoid Arthritis	714.0, 714.2	M05.1x, M05.2x, M05.3x, M05.4x, M05.5x, M05.6x, M05.7x, M05.8x, M05.9x, M06.0x
Psoriasis	696.1, 696.8	L40.0, L40.1, L40.2, L401.4, L40.5, L40.8, L40.9, L40.51, L40.52, L40.53, L40.54, L40.59, M07.1, M07.2, M07.3
Systemic Lupus Erythematosus	710.0	M32.10, M32.11, M32.12, M32.13, M32.14, M32.15, M32.19, M32.8, M32.9
Ankylosing Spondylitis	720.0	M45.0, M45.1, M45.2, M45.9
Polymyalgia Rheumatica	725.0	M31.5, M31.3

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Table 1:

NIS acute ischemic stroke discharge demographics and outcomes

Chronic Inflammatory Disease		Ulcerative Colitis	Crohn's Disease	Rheumatoid Arthritis	Psoriasis	SLE	Other	Multiple	None
Raw (Weighted) Counts		703 (3,515)	799 (3,995)	5,069 (25,345)	1,298 (6,490)	1,378 (6,890)	839 (4,195)	408 (2,040)	300,121 (1,500,605)
Weighted % total NIS		0.22%	0.26%	1.63%	0.42%	0.44%	0.27%	0.13%	96.62%
Age Group (%)	18-59yr	19%	28%	14%	25%	51%	5%	28%	23%
	60-69yr	22%	27%	22%	27%	23%	10%	24%	23%
	70-79yr	30%	25%	30%	28%	17%	26%	25%	24%
	80-89yr	24%	18%	27%	16%	8%	41%	19%	22%
	90+yr	5%	2%	7%	4%	1%	18%	4%	8%
Gender	Female	53%	54%	73%	43%	85%	64%	79%	50%
	Male	47%	46%	27%	57%	15%	36%	21%	50%
Race	Non-Hispanic white	84%	82%	74%	81%	49%	91%	71%	67%
	Non-Hispanic black	8%	12%	15%	8%	34%	4%	17%	18%
	Hispanic	4%	3%	7%	6%	11%	3%	9%	9%
	Other	4%	3%	4%	5%	6%	2%	3%	6%
Comorbidity	HTN	74%	73%	83%	83%	77%	84%	82%	83%
	DM	31%	28%	32%	39%	29%	29%	27%	39%
	ESRD	7%	6%	5%	5%	12%	3%	5%	61%
	Alcohol Abuse	2%	3%	2%	5%	1%	0.6%	1%	2%
	Cirrhosis	3%	2%	2%	3%	2%	0.2%	2%	1%
	CHF	12%	14%	15%	12%	13%	15%	11%	14%
	COPD	14%	18%	20%	18%	14%	13%	18%	13%
	Obesity	11%	10%	11%	20%	16%	9%	12%	13%
Disposition *	Home	34%	34%	28%	37%	38%	28%	32%	34%
	Short-term Hospital/ Rehab	4%	4%	3%	4%	4%	2%	5%	3%
	SNF/ Hospice	42%	40%	45%	40%	36%	49%	40%	42%
	Home Health	13%	15%	18%	14%	16%	17%	18%	14%
	AMA	0.6%	0.4%	0.5%	0.7%	0.9%	0.4%	0.5%	1%
	Died	6%	6%	6%	4%	6%	4%	5%	6%
	Unknown	0%	0%	0%	0.1%	0.1%	0%	0%	0%
In-hospital Pneumonia		10%	9%	9%	7%	10%	4%	6%	8%

Values represent the weighted % of the sample.

Abbreviations: AMA (against medical advice), CHF (congestive heart failure), COPD (chronic obstructive pulmonary disease), DM (diabetes mellitus), ESRD (End-stage renal disease), HTN (hypertension), SNF (skilled nursing facility), SLE (systemic lupus erythematosus)

*Discharge Disposition (26): The categories include the following 1) Short-term Hospital/Rehab (short term general hospital with inpatient acute care or rehabilitation services); 2) SNF/Hospice (SNR, intermediate care facility, long term acute care hospital psychiatric hospitals, hospice services), Home Health (home with additional health care services provided, home intravenous access provided, home hospices services), AMA (left against medical advice)

Table 2:

Effects of a given chronic inflammatory disease on diagnosis of stroke-associated pneumonia

Chronic Inflammatory Disease	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Ulcerative Colitis	1.30 (1.03-1.64)	1.18 (0.92-1.51)
Crohn's Disease	1.16 (0.93-1.46)	1.10 (0.87-1.38)
Rheumatoid Arthritis	1.10 (1.00-1.21)	1.05 (0.95-1.16)
Psoriasis	0.77 (0.62-0.96)	0.70 (0.63-0.99)
Systemic lupus Erythematosus	1.16 (0.98-1.37)	0.98 (0.76-1.27)
Other	0.50 (0.36-0.68)	0.64 (0.46-0.89)
Multiple	0.75 (0.50-1.13)	0.80 (0.53-1.21)

Adjusted OR -Multivariable logistic regression modeling for a dependent variable of diagnosis of pneumonia, independent variable is a given chronic inflammatory disease(s), adjusting for age, sex, race, comorbidity, year of survey sample.

Table 3:

Effects of a given chronic inflammatory disease on in-hospital mortality

Chronic Inflammatory Disease	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Ulcerative Colitis	1.06 (0.78-1.44)	0.95 (0.69-1.31)
Crohn's Disease	1.06 (0.80-1.40)	1.05 (0.79-1.39)
Rheumatoid Arthritis	0.96 (0.85-1.08)	0.89 (0.78-1.00)
Psoriasis	0.72 (0.56-0.94)	0.77 (0.59-1.00)
Systemic lupus Erythematosus	0.94 (0.76-1.17)	1.07 (0.86-1.34)
Other	0.79 (0.58-1.07)	0.69 (0.50-0.94)
Multiple	0.81 (0.51-1.27)	0.84 (0.53-1.35)

Adjusted OR - Multivariable logistic regression modeling for a dependent variable of in-hospital mortality, independent variable is a given chronic inflammatory disease(s), adjusting for age, sex, race, comorbidity, year of survey sample.