University of Louisville Journal of Respiratory Infections

ORIGINAL RESEARCH

Clinical Outcomes for Patients with Community-Acquired Pneumonia are Worse in Those with a History of Stroke

Pradeepthi Badugu[1], MD; Dilip KC[1], MD; Safoora Fatima[1], MD; Murali Kolikonda, MD; Bibodh Karki, MD; Mahder A. Tella, MPH; Vidyulata Salunkhe, MD MPH*

[1]Division of Infectious Diseases, School of Medicine, University of Louisville, Louisville, KY, USA

*pradeepthi.badugu@gmail.com

Recommended Citation: Badugu P, KC D, Fatima S, et al. Clinical outcomes for patients with community-acquired pneumonia are worse in those with a history of stroke. Univ Louisville J Respir Infect **2022**; 6(1):Article 4. doi: 10.18297/jri/vol6/iss/1/4.

Abstract

Background: Stroke is one of the most prevalent neurological diseases in the United States. Community-acquired pneumonia (CAP) is the leading cause of infections in survivors of stroke. There is limited research evaluating the clinical outcomes of CAP in patients with stroke. The objective of this study was to evaluate the clinical characteristics and outcomes of hospitalized patients with CAP and a history of stroke.

Methods: This was a secondary analysis of the University of Louisville Pneumonia Study database. Patients were divided into two groups based on the presence or absence of a history of stroke. Clinical outcomes were length of stay, time to clinical stability, and one-year mortality, which were assessed via stratified Cox proportional hazards regression. Differences in risk of clinical outcomes were reported as adjusted hazard ratios.

Results: We found no significant differences in time to clinical stability between the two groups. The median length of stay for patients with a history of stroke hospitalized with CAP was six days and for patients without stroke was five days (P=0.01). We observed a 16% higher risk of mortality in stroke patients with CAP than in the non-stroke population (P=0.001).

Conclusions: This study indicates that hospitalized patients with CAP have a longer hospital stay and higher mortality than those without stroke.

Introduction

Stroke is the fifth leading cause of death in the United States.[1] Its prevalence is approximately 3% in adults, affecting approximately 7 million individuals nationwide.[2] It is among the ten leading causes of chronic disability.[3, 4] Surviving patients experience a wide range of complications that may require subsequent hospital admissions. The most frequent causes of readmission to the hospital within five years of the initial stroke are recurrent stroke, infection, and cardiac events.[5] Cerebral ischemia and damage to the central nervous system can significantly increase a patient's susceptibility to systemic infections.[6]

Researchers have studied various infections in patients during the acute phase of stroke, among which pneumonia remains the most common cause of infection-related short-term and long-term hospital readmission.[5, 7-9] General functional decline and dysphagia after stroke put patients at significant risk of severe lung infection.[10] Patients may present with non-specific signs and symptoms of community-acquired pneumonia (CAP), such as altered mental status due to an impaired cough reflex. Furthermore, antiplatelet and anti-inflammatory drug therapy can mask pyrexia and acute inflammatory markers.[11] Katzan *et al.* observed a three-fold higher 30-day mortality rate in patients who experienced pneumonia after an acute stoke.[12]

Researchers have extensively studied the risk factors and clinical outcomes of aspiration- and stroke-associated pneumonia. However, there are few studies that investigate the clinical outcomes of CAP in patients with a history of stroke. The aim of our study was to assess the clinical characteristics, incidence, and outcomes of CAP in patients with a history of stroke.

Methods

Study design and study population

This was a secondary analysis of the University of Louisville Pneumonia Study database, which was a prospective, observational cohort study of adult patients hospitalized with CAP in the city of Louisville, Kentucky, from June 1, 2014, to May 31, 2016, and from October 1, 2016, to March 31, 2017.[13] Data from all hospitalized patients with CAP in Louisville from the nine adult hospitals were reviewed and included in the database. Institutional Review Board approval was obtained (IRB number: 11.0613). The study was exempt from informed consent. Data operations were conducted by the study coordinating center located at the University Of Louisville Division Of Infectious Diseases.

Inclusion criteria

The inclusion criteria have been described previously.[13] The diagnosis of CAP required the presence of three criteria: (1) new pulmonary infiltrate on imaging (computed tomography [CT] scan or chest X-ray) at the time of hospital admission; (2) the presence of at least one of the following signs and symptoms of CAP: new or increased cough, fever >100 °F or hypothermia 96 °F, leukocytosis >11,000 cells/mm^3, left shift >10% band forms/mL, or leukopenia <4,000 cells/mL; and (3) no alternative diagnosis at the time of hospital discharge to explain the first two criteria.

The term "stroke" referred to a medical history of ischemic stroke, hemorrhagic stroke, or transient ischemic attack (TIA) as documented in medical records or imaging. Patients were categorized into one of two groups. The stroke group consisted of patients with CAP and a documented history of stroke. The non-stroke group consisted of patients with CAP but without a documented history of stroke.

Study variables

We collected demographics, vital signs (temperature, blood pressure, heart rate, and respiratory rate), laboratory tests on admission, and comorbidities. The following comorbidities were reviewed: neoplastic disease, congestive heart failure (CHF), renal disease, liver disease, diabetes mellitus, chronic obstructive pulmonary disease (COPD), coronary artery disease, essential arterial hypertension, hyperlipidemia, obesity, and current smoking status.

Study outcomes

Time to clinical stability was evaluated daily within the first seven days of hospitalization to determine the day on which patients reached clinical stability. A patient was considered clinically stable when the following four criteria were met: (1) improved cough and shortness of breath, (2) lack of fever for at least 8 hours, (3) improving leukocytosis (decreased at least 10% from the previous day), and (4) tolerating oral intake. Length of stay (LOS) was defined as the number of days between admission and discharge. Patients hospitalized for more than 14 days were censored at 14 days to capture LOS data related only to bacterial CAP. Mortality was defined as death by any cause at any time within one year of the day of hospitalization. Verification of death was obtained from the Kentucky Department of Vital Statistics.

Statistical analysis

Descriptive statistics were reported. Categorical data were summarized as frequencies and percentages, and continuous data were summarized as medians and interquartile ranges (IQR) or means and standard deviations (SD). Chi-squared tests of independence were performed to test baseline descriptive statistics between groups for categorical data. Mann-Whitney U tests were performed to test between groups for continuous data. Clinical outcomes were assessed via stratified Cox proportional hazards regression, adjusting for CURB-65 score, age of 65 years or more, sex, race, and histories of chronic obstructive pulmonary disease, chronic heart failure, coronary artery disease, hypertension, and diabetes. Kaplan–Meier curves were produced. Differences in risk of clinical outcomes were reported as adjusted hazard ratios (aHR).

Results

During our study period, there were 10,101 adults hospitalized with CAP. Among them, 1,337 had a history of stroke. Clinical characteristics and laboratory values for the two groups are described in **Table 1**. The patients in the stroke group were older than those in non-stroke group (71.32±14.47 *vs.* 65.87±16.79 years; $P<0.001$) and more frequently had a medical history of CHF, renal disease, diabetes, coronary artery disease with or without a myocardial infarction, hyperlipidemia, or hypertension; $P<0.001$ for each. Stroke patients also more frequently had a family history of coronary artery disease or a prior coronary intervention (percutaneous transluminal coronary angioplasty or coronary artery bypass grafting [PTCA/CABG]); $P<0.001$ for each. A greater proportion of patients in the stroke group had altered mental status or suspicion of aspiration at the time of admission; $P<0.001$. They were also more frequently nursing home residents or hospitalized for a period of more than two days within the 90 days prior to admission for CAP. A greater proportion of patients in the stroke group were taking aspirin, statins, or antiplatelet drugs as home medications prior to hospital admission; $P<0.001$ for each. The me-

Table 1. Clinical characteristics of the study population, including demographics, social and medical history, indicators of severity of disease, vital signs, and laboratory values at the time of admission.

	Stroke* (*n*=1,337)	Non-stroke* (*n*=8,764)	*P*
Demographics			
Age, mean±SD	71.32±14.47	65.87±16.79	<0.001
Male	609 (46)	4064 (46)	0.595
Black	269 (20)	1677 (19)	0.416
Nursing home resident	322 (24)	950 (11)	<0.001
Social and medical history			
Essential arterial hypertension	1126 (84)	5928 (68)	<0.001
Hyperlipidemia	809 (61)	3684 (42)	<0.001
Congestive heart failure	538 (40)	2448 (28)	<0.001
Diabetes	551 (41)	2756 (31)	<0.001
Coronary artery disease	573 (43)	2527 (29)	<0.001
Prior myocardial infarction	293 (22)	1043 (12)	<0.001
Prior PTCA/CABG	322 (24)	1401 (16)	<0.001
Family history of coronary artery disease	404 (30)	2214 (25)	<0.001
Chronic obstructive pulmonary disease	632 (47)	4229 (48)	0.521
Renal disease	473 (35)	2391 (27)	<0.001
Current smoker	322 (24)	2821 (32)	<0.001
Obesity (BMI>30)	415 (31)	3101 (35)	0.002
Neoplastic disease	161 (14)	1083(14)	>0.999
Liver disease	80 (6)	633 (7)	0.112
Hospitalized >2 days in the prior 90 days	504 (38)	2426 (28)	<0.001
Number of comorbidities, mean±SD	4.26±1.90	3.62±1.94	<0.001
≥4 comorbid conditions	872 (65)	4413 (50)	<0.001
Severity			
PSI, median [IQR]	122 [98, 146]	98 [72, 127]	<0.001
Altered mental status	365 (27)	1486 (17)	<0.001
Ventilatory support	181 (14)	1190 (14)	0.996
Vasopressors	44 (3)	250 (3)	0.424
Suspicion of aspiration	247 (19)	939 (11)	<0.001
Vitals, mean±SD			
Temperature (℃)	37.37±0.88	37.41±0.96	0.15
Respiratory rate (breaths/minute)	24.20±7.00	24.30±7.07	0.639
Systolic blood Pressure (mmHg)	118.45±27.98	117.87±26.56	0.463
Diastolic blood pressure (mmHg)	56.90±16.53	59.42±17.19	<0.001
Heart Rate (beats/minute)	102.92±23.78	106.20±22.63	<0.001
Laboratory values, mean±SD			
Hematocrit	34.67±6.12	35.62±6.39	<0.001
Blood urea nitrogen (mg/dL)	27.71±19.47	23.53±17.36	<0.001
Serum glucose (mg/dL)	179.10±99.86	170.41±91.41	0.001
Serum sodium (mEq/L)	137.87±5.67	138.27±122.99	0.905
Serum potassium (mEq/L)	4.10±0.73	4.09±2.24	0.872
Bicarbonate (mEq/L)	25.65±5.77	26.33±7.23	0.033
pH	7.39±0.08	7.38±0.10	0.039
Hemoglobin (g/dL)	11.20±2.09	11.65±3.04	<0.001
White blood cell count×1,000/μL	13.36±7.59	13.36±7.65	0.974
Cholesterol (mg/dL)	135.46±47.23	139.73±45.48	0.094
Triglycerides (mg/dL)	119.44±75.04	121.15±119.80	0.785
Medications			
Aspirin	650 (49)	2879 (33)	<0.001
Antiplatelet	202 (15)	532 (6)	<0.001
Statins	705 (53)	2937 (34)	<0.001

Abbreviations: BMI, body mass index; IQR, interquartile range; PSI, Pneumonia Severity Index; PTCA/CABG, percutaneous transluminal coronary angioplasty/coronary artery bypass graft; SD, standard deviation.

* *n* (%) except where otherwise specified.

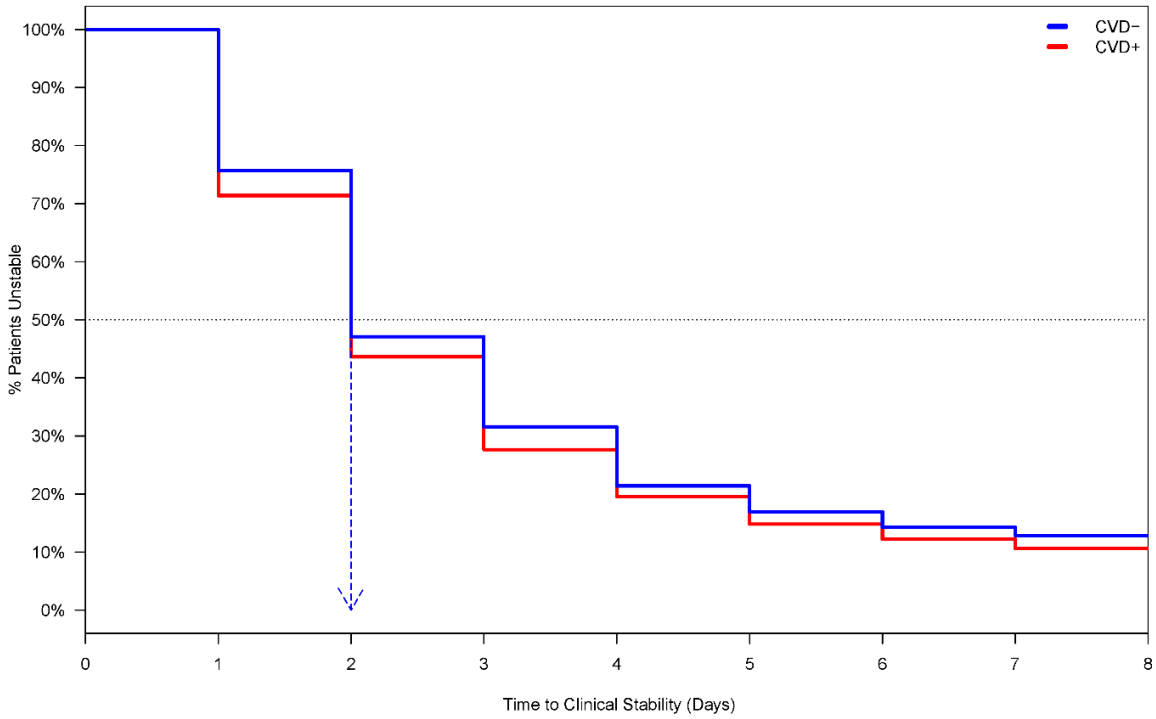

Figure 1. Kaplan–Meier curves for time to clinical stability for study population. **Abbreviations:** CVD+, stroke; CVD-, non-stroke.

dian Pneumonia Severity Index score was 122 in the stroke population *versus* 98 in the non-stroke population; $P<0.001$. Diastolic blood pressure and heart rate within the first 24 hours after admission were significantly lower in the stroke population; $P<0.001$ for each. Temperature, respiratory rate, and systolic blood pressure during the same period were not significantly different between groups. We observed no significant differences in cholesterol and triglyceride levels between the two groups. There was no significant difference in the proportion of men or African American persons between the groups. A higher proportion of patients in the non-stroke group smoked (32% *vs.* 24%; $P<0.001$) or were obese (35% *vs.* 31%; $P<0.001$) than in the stroke group.

Time to clinical stability

The median time to clinical stability for patients in both groups was 2 days (stroke IQR 1, 4; non-stroke IQR 1, 3; **Figure 1**). After adjusting for confounding variables, no significant differences were detected in time to clinical stability between the two groups (aHR for attaining stability 0.94 [95% confidence interval (CI) 0.88–1.00]; $P=0.084$).

Length of stay

The median LOS for the stroke group was 6 days (IQR 4, 9). For the non-stroke group, LOS was 5 days (IQR 3, 8). The Kaplan–Meier curve for length of stay can be seen in **Figure 2**. After adjustment for confounding variables, we found significant differences in length of stay (aHR for discharge 0.92 [95% CI 0.86–0.98]; $P=0.01$).

Mortality

The patients with a history of stroke had a 16% higher risk of death compared to the non-stroke population by the end of one year (**Figure 3**). The observed aHR for death was 1.16 (95% CI 1.04–1.29); $P=0.001$.

Discussion

This study demonstrated that adults hospitalized for CAP with a history of stroke had longer hospital stays and higher mortality within one year than those admitted for CAP without a history of stroke. Time to clinical stability, another short-term outcome of the study, was not significantly different between groups. The differences in length of stay and mortality were present after adjusting for age and common comorbidities.

It is possible that pathophysiological processes played a role in the increased mortality and length of stay in the stroke population admitted with CAP. One pathophysiological mechanism that could have contributed to these differences is immune dysregulation following

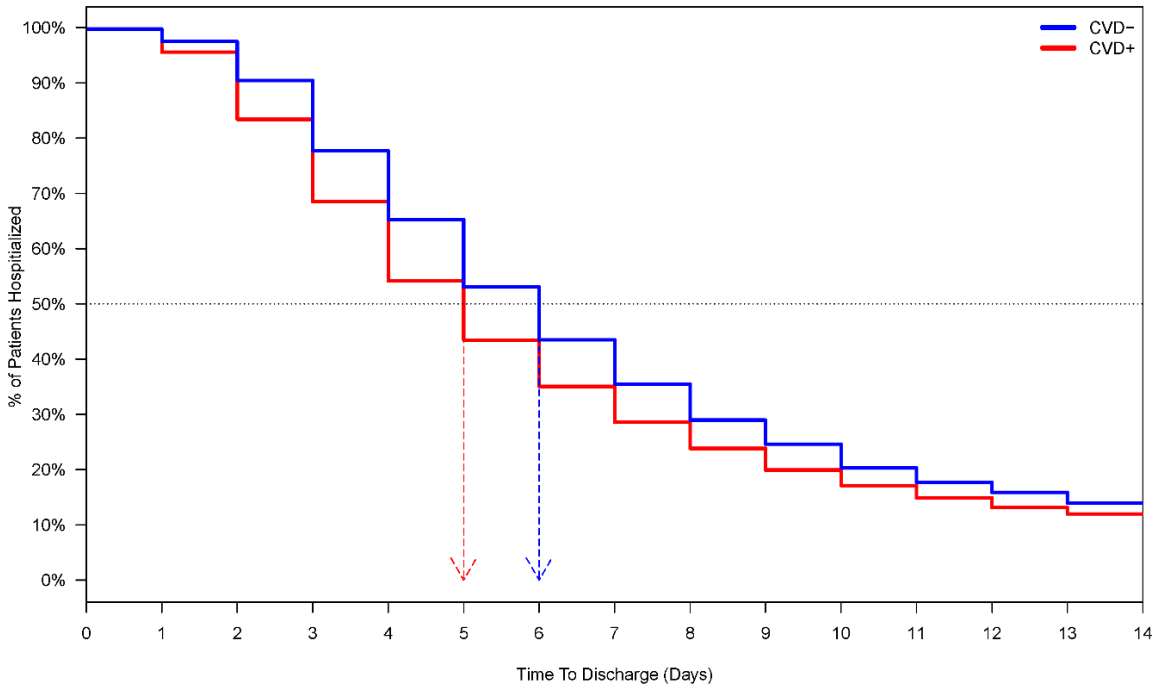

Figure 2. Kaplan–Meier curves for length of stay for study population.

severe brain injury associated with stroke.[14] Offner *et al.* identified a series of events in post-stroke experimental animal models that can lead to the loss of peripheral immune competence.[15] Additionally, they observed reduced T cell activation and profound loss of immune T and B cells in the spleen and thymus.[15] In another study, all experimental mice developed spontaneous septicemia and pneumonia after three days of focal cerebral ischemia.[16] Part of this immune depression serves as a protective mechanism to counteract the effects of blood-brain barrier disruption and limit further tissue destruction.[6] Thus, brain inflammation following stroke can cause systemic immunosuppression, resulting in increased susceptibility to infection.[15, 17] Further research is needed to understand immune dysregulation and its clinical significance.

A recent study by Bordon *et al.* documented a statistically significant association between need for hospitalization and mortality in patients with CAP independent of comorbidities.[18] It was hypothesized that CAP can cause an acute increase in cytokine expression. This acute systemic inflammation may destabilize atherosclerotic plaques and trigger events. CAP can also produce a chronic inflammatory response. A persistent, chronic inflammation would accelerate the natural history of disease, explaining decreased patient survival after CAP.

Increased length of stay can increase the probability of hospital-acquired infections in those who have had a stroke, thus contributing to increased mortality. Additionally, patients with a history of stroke may be more deconditioned and require more physical therapy after an infection, particularly one serious enough to necessitate hospitalization; this may also contribute to delayed discharge. Other factors, such as stroke-facilitated aspiration and general functional decline, can increase risk of infection as well as severity of disease.[6, 10] Krabbe *et al.* found that a chronic state of systemic inflammation and immune senescence in older patients can contribute to increased susceptibility to infection and worse clinical outcomes.[19] We observed that a higher proportion of patients with stroke who were admitted for CAP had mental status changes and suspicion of aspiration than those admitted for CAP without a history of stroke.

A systematic review found that over the last two decades, several studies were conducted to examine the role of prophylactic antibiotics after an acute stroke.[20] Multiple randomized controlled trials tested the administration of different antibiotics, including minocycline, moxifloxacin, levofloxacin, ceftriaxone, and mezlocillin plus sulbactam, in stroke patients. Meta-analysis of a portion of these studies, involving 506 patients, concluded that prophylactic antibiotic therapy contributed to a decrease in the incidence of infection in patients with acute stroke compared to patients on a placebo (22% *vs.* 36%; relative risk [RR] 0.58 [95% CI 0.43–0.79]). However, the rate of mortality was not significantly different between the two

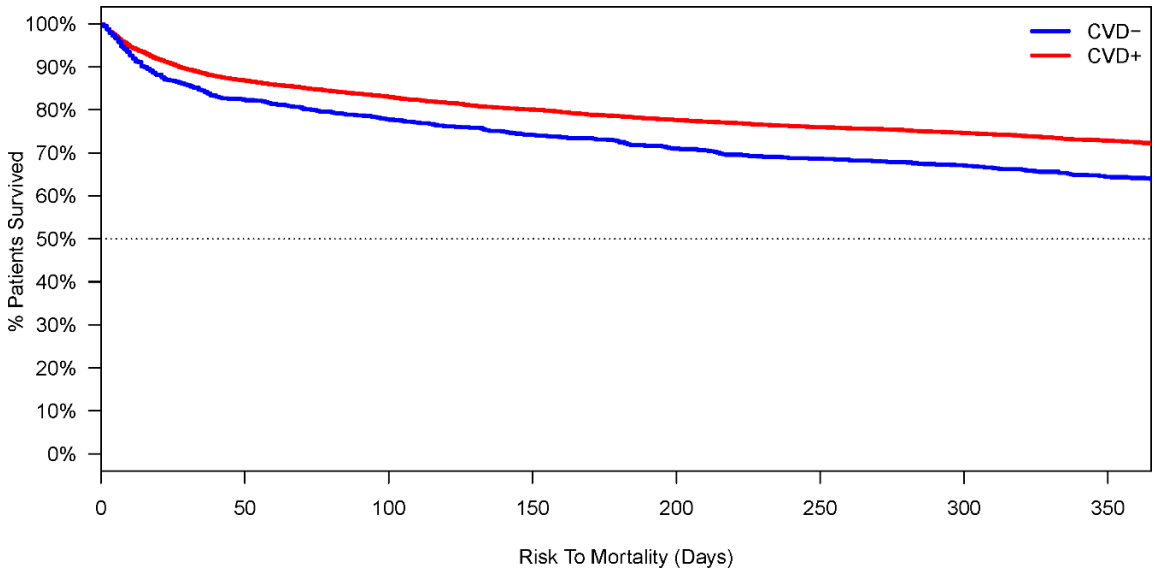

Figure 3. Survival graph for the study population.

groups (13% *vs.* 15%; RR 0.85 [95% CI 0.47–1.51]).[20, 21] The growing burden of antimicrobial resistance should be considered when treating individual patients with prophylactic antibiotics. Researchers also studied immunotherapeutic and immune-stimulatory approaches to counteract immune depression after stroke in animals.[16, 21] Scientists have tested the administration of T cells, natural killer cells, interferon-gamma and beta-blockers in mouse models. However, the clinical relevance of these studies is yet to be determined.[16, 21] Thus, future studies, including randomized controlled trials, are warranted to assess pharmacological and non-pharmacological approaches, such as oral care, head elevation, swallowing rehabilitation, and vaccination against pneumonia among stroke patients to prevent CAP. Clinicians also recommend post-discharge stratification of mortality risk that may help to identify patients at greater risk of CAP.

We identified a few weaknesses for our study. Clinical characteristic data were dependent on the accuracy of the electronic medical records. The duration between the occurrences of stroke and the onset of CAP was not assessed; thus, the documented stroke may have occurred at any time in the patient's medical history. Also, which patients had serious sequelae and which did not is not clarified in the study. Some patients may have recovered almost completely years after a stroke while recent stroke patients with serious sequelae may have much greater predisposition to developing CAP. Another limitation is that TIA patients were included, but they actually may be at equivalent risk to a non-stroke patient if their cardiovascular risk factors were corrected.

Our study had several strengths. At least three factors gave the present study increased generalizability: the population varied in age, including adults above 18 years, with a large sample size; the study population was broadly representative, with 46% identifying as men and 20% identifying as black; and the study evaluated all adult patients hospitalized for CAP with a previous history of stroke in Louisville during the study period. Other strengths were that patients were identified using social security numbers rather than the medical record numbers and that CAP was defined using clinical criteria rather than billing information.

In conclusion, patients hospitalized for CAP with a history of stroke are likely to experience longer lengths of stay and higher mortality than those without a history of stroke.

Acknowledgements: The authors acknowledge the efforts of University of Louisville Pneumonia Study Group, Louisville, Kentucky and Riley Sumner MLIS, ULH Hospital Librarian.

Received: June 1, 2020

Accepted: January 30, 2022

Published: February 11, 2022

Funding Source: The author(s) received no specific funding for this work.

Conflict of Interest: All authors declared no conflict of interest in relation to the main objective of this work.

References

1. Kochanek KD, Xu J, Arias E. Mortality in the United States, 2019. NCHS Data Brief. Hyattsville, MD: National Center for Health Statistics, **2020**. Report No.: 395.

2. Ovbiagele B, Nguyen-Huynh MN. Stroke epidemiology: advancing our understanding of disease mechanism and therapy. Neurotherapeutics **2011**; 8(3):319-29. doi: 10.1007/s13311-011-0053-1. PMID: 21691873.

3. Centers for Disease Control and Prevention (CDC). Prevalence of stroke–United States, 2006-2010. MMWR Morb Mortal Wkly Rep **2012**; 61(20):379-82. PMID: 22622094.

4. Centers for Disease Control and Prevention (CDC). Prevalence and most common causes of disability among adults–United States, 2005. MMWR Morb Mortal Wkly Rep **2009**; 58(16):421-6. PMID: 19407734.

5. Rao A, Barrow E, Vuik S, Darzi A, Aylin P. Systematic Review of Hospital Readmissions in Stroke Patients. Stroke Res Treat **2016**; 2016:9325368-. doi: 10.1155/2016/9325368. PMID: 27668120.

6. Dirnagl U, Klehmet J, Braun JS, et al. Stroke-induced immunodepression: experimental evidence and clinical relevance. Stroke **2007**; 38(2 Suppl):770-3. doi: 10.1161/01.STR.0000251441.89665.bc. PMID: 17261736.

7. Westendorp WF, Nederkoorn PJ, Vermeij J-D, Dijkgraaf MG, van de Beek D. Post-stroke infection: a systematic review and meta-analysis. BMC Neurol **2011**; 11:110-. doi: 10.1186/1471-2377-11-110. PMID: 21933425.

8. Lichtman JH, Leifheit-Limson EC, Jones SB, Wang Y, Goldstein LB. Preventable readmissions within 30 days of ischemic stroke among Medicare beneficiaries. Stroke **2013**; 44(12):3429-35. doi: 10.1161/STROKEAHA.113.003165. PMID: 24172581.

9. Ottenbacher KJ, Karmarkar A, Graham JE, et al. Thirty-day hospital readmission following discharge from postacute rehabilitation in fee-for-service Medicare patients. Jama **2014**; 311(6):604-14. doi: 10.1001/jama.2014.8. PMID: 24519300.

10. Yuan MZ, Li F, Tian X, et al. Risk factors for lung infection in stroke patients: a meta-analysis of observational studies. Expert Rev Anti Infect Ther **2015**; 13(10):1289-98. doi: 10.1586/14787210.2015.1085302. PMID: 26359533.

11. Kishore AK, Vail A, Chamorro A, et al. How is pneumonia diagnosed in clinical stroke research? A systematic review and meta-analysis. Stroke **2015**; 46(5):1202-9. doi: 10.1161/strokeaha.114.007843. PMID: 25858238.

12. Katzan IL, Cebul RD, Husak SH, Dawson NV, Baker DW. The effect of pneumonia on mortality among patients hospitalized for acute stroke. Neurology **2003**; 60(4):620-5. doi: 10.1212/01.wnl.0000046586.38284.60. PMID: 12601102.

13. Ramirez JA, Wiemken TL, Peyrani P, et al. Adults Hospitalized With Pneumonia in the United States: Incidence, Epidemiology, and Mortality. Clin Infect Dis **2017**; 65(11):1806-12. doi: 10.1093/cid/cix647. PMID: 29020164.

14. Kamel H, Iadecola C. Brain-immune interactions and ischemic stroke: clinical implications. Arch Neurol **2012**; 69(5):576-81. doi: 10.1001/archneurol.2011.3590. PMID: 22782509.

15. Offner H, Vandenbark AA, Hurn PD. Effect of experimental stroke on peripheral immunity: CNS ischemia induces profound immunosuppression. Neuroscience **2009**; 158(3):1098-111. doi: 10.1016/j.neuroscience.2008.05.033. PMID: 18597949.

16. Prass K, Meisel C, Höflich C, et al. Stroke-induced immunodeficiency promotes spontaneous bacterial infections and is mediated by sympathetic activation reversal by poststroke T helper cell type 1-like immunostimulation. J Exp Med **2003**; 198(5):725-36. doi: 10.1084/jem.20021098. PMID: 12939340.

17. Santos Samary C, Pelosi P, Leme Silva P, Rieken Macedo Rocco P. Immunomodulation after ischemic stroke: potential mechanisms and implications for therapy. Crit Care **2016**; 20(1):391-. doi: 10.1186/s13054-016-1573-1. PMID: 27923376.

18. Bordon J, Wiemken T, Peyrani P, et al. Decrease in long-term survival for hospitalized patients with community-acquired pneumonia. Chest **2010**; 138(2):279-83. doi: 10.1378/chest.09-2702. PMID: 20382718.

19. Krabbe KS, Pedersen M, Bruunsgaard H. Inflammatory mediators in the elderly. Experimental gerontology **2004**; 39(5):687-99. doi: 10.1016/j.exger.2004.01.009. PMID: 15130663.

20. van de Beek D, Wijdicks EF, Vermeij FH, et al. Preventive antibiotics for infections in acute stroke: a systematic review and meta-analysis. Arch Neurol **2009**; 66(9):1076-81. doi: 10.1001/archneurol.2009.176. PMID: 19752296.

21. Shi K, Wood K, Shi F-D, Wang X, Liu Q. Stroke-induced immunosuppression and poststroke infection. Stroke Vasc Neurol **2018**; 3(1):34-41. doi: 10.1136/svn-2017-000123. PMID: 29600006.