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ORIGINAL RESEARCH

Infection, Inflammation, and Poststroke Cognitive Impairment

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BACKGROUND: Infection and inflammation are dementia risk factors in population-based cohorts; however, studies in stroke are scarce. We determined the prevalence of infection after stroke and routinely measured inflammatory biomarkers during hospitalization and their associations with acute and 6-month cognitive impairment.

METHODS AND RESULTS: A prospective stroke cohort completed the Oxford Cognitive Screen at ≤2 weeks and 6 months after stroke. Infection, inflammatory markers (C-reactive protein, white cell count, and neutrophil/lymphocyte ratio), and systemic inflammatory response syndrome were ascertained throughout admission with electronic patient records supplemented by hand searches. Associations with acute and 6-month global and domain-specific cognitive impairment were analyzed using multivariable regression, adjusting for demographic/vascular factors and stroke severity. Among 255 patients (mean age, 73.9 [SD, 12.6] years; 46.3% women; mean education, 12.6 [SD, 3.7] years; median National Institutes of Health Stroke Scale score 5 [range, minimum-maximum, 0–30]), infection was present in 90 patients (35.3%) at mean 4.4 (SD, 6.9) days after stroke, consisting predominantly of pneumonia (47/90; 52%) and urinary tract infection (39/90; 43%). Admission white cell count was elevated in 25.1% (n=64; mean, 9.5×10^9/L [SD, 3.2×10^9/L]), C-reactive protein in 41.2% (n=105; mean, 27.5 [SD, 50.9 mg/L]), neutrophil/lymphocyte ratio in 55.7% (n=97; mean, 5.5 [SD, 4.5]), and systemic inflammatory response syndrome in 26.6% (n=53 [45.2%] positive during hospitalization). Infection was associated with acute and 6-month poststroke cognitive impairment ($P<0.05_{adj}$) with stronger associations acutely for severe infection (infection+systemic inflammatory response syndrome; $P=0.03_{adj}$). Acute language, executive function and attention domain impairments, and 6-month number processing impairment were associated with infection ($P<0.05_{adj}$). No significant relationships were found for any biomarker and cognitive impairment.

CONCLUSIONS: Infection and elevations in routinely measured inflammatory biomarkers are common following stroke; however, only infection is associated with poststroke cognitive impairment, suggesting that increases in these biomarkers may be nonspecific. Infection may present a tractable target for reducing poststroke cognitive impairment.

Key Words: cognition ■ cognitive dysfunction ■ infection ■ inflammation ■ stroke

Despite modest improvement in stroke outcomes,[1] poststroke cognitive impairment (PSCI) and dementia remain highly prevalent and often disabling.[2,3] PSCI risk is mediated in part by preexisting brain susceptibility[4] and the impact of the stroke lesion. However, these factors do not explain all the variance in risk.[2,5] Within nonstroke populations, there is emerging evidence linking infection to future development of all-cause dementia and, in particular, vascular dementia[6,7] with a dose–response effect, and preliminary data suggest that infection may also be important in PSCI.[8,9]

Infection is the most frequent complication of stroke, affecting ≈30% of patients, with pneumonia and urinary tract infections (UTIs) being most common.[10] Infections are associated with increased stroke morbidity and death.[11] Stroke unit care may result in better outcomes in

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CLINICAL PERSPECTIVE

What Is New?

- Infection and elevations in routinely measured inflammatory biomarkers are common following stroke. However, only infection, particularly severe infection and pneumonia, was associated with acute and 6-month poststroke cognitive impairment, suggesting that increases in routinely measured inflammatory biomarkers are nonspecific and do not mediate the risk of cognitive impairment associated with infection.
- The pattern of cognitive domain impairment found to be associated with infection is suggestive of a vascular profile consistent with findings from nonstroke studies of a preferential risk of vascular versus Alzheimer' dementia after infection.

What Are the Clinical Implications?

- Infection prevention and rapid treatment may help reduce risk of cognitive impairment and dementia after stroke and likely explains some of the effect of organized stroke unit care on improved stroke outcomes.
- An improved understanding of the mechanisms underpinning the links between the systemic response to infection and cognitive impairment is needed to inform development of new treatments to prevent cognitive decline after stroke.

Nonstandard Abbreviations and Acronyms

NIHSS	National Institutes of Health Stroke Scale
NLR	neutrophil/lymphocyte ratio
OCS	Oxford Cognitive Screen
PSCI	poststroke cognitive impairment
WCC	white cell count

part through preventing such complications[12]; however, there are few data specifically on cognitive function. In 1 big data study, infection after stroke including during the follow-up period after discharge was associated with a >40% increase in the risk of early dementia with greater impact of more severe (hospital) infection (3–12 months after stroke).[8] However, dementia was identified solely through administrative diagnostic coding, which is known to have poor sensitivity.[13,14] Infections may act through systemic inflammatory pathways to trigger a disordered microglial response in the aging brain, resulting in progression of Alzheimer disease[15] and small-vessel disease via vascular inflammation, endothelial dysfunction, and blood–brain barrier disruption.[16]

Stroke-associated biomarkers of inflammation may also be associated with PSCI,[17–19] including C-reactive protein (CRP),[19] neutrophil/lymphocyte ratio (NLR),[17] erythrocyte sedimentation rate,[20] terminal C5b-9 complement complex, interleukin-6, and macrophage inflammatory protein-1α.[21] Ischemia leads to the induction of proteases and free radicals, blood–brain barrier opening, and, ultimately, myelin breakdown and oligodendrocyte death.[22] A more proinflammatory immune signature in peripheral blood at 2 days after stroke has been linked to PSCI within the first year,[23] and acute inflammation appears more predictive than chronic inflammation for poststroke cognitive outcome at 36 months.[21]

However, there are few studies that have examined both stroke-associated infection and biomarkers of inflammation in relation to PSCI despite inflammation being expected to co-occur with infection. It is important for understanding both mechanisms and risk prediction whether infection or acute inflammation, from whichever cause (or both), increases the risk of PSCI and to what extent these are independent of confounding factors. Additionally, given that infection appears to predispose individuals predominantly to vascular dementia, a greater impact on those with a vascular cognitive profile would be expected,[24] though there are few data particularly in relation to PSCI.

Therefore, this study in acute stroke patients sought to determine (1) the prevalence, subtype, and severity of infection and the prevalence of elevated routinely collected markers of inflammation during hospitalization, as well as (2) the relationship between acute infection, inflammatory markers, and global and domain-specific cognitive function acutely and at 6-month follow-up.

METHODS

A consecutive sample of patients with acute stroke (n=866) was recruited through the Oxford Cognitive Screening (OCS) program[25] (2012–2019, National Research Ethics Committee–REC 14/LO/0648; 18/SC/0550) based within the regional acute stroke unit, John Radcliffe Hospital, United Kingdom. Manually collected research data were supplemented by routinely acquired electronic patient record data through linkage to the Oxford Cognitive Comorbidity, Frailty, and Aging Research database (REC reference 18/SC/0184). For the present study, consecutive patients recruited from January 2015 to September 2019 with both acute and 6-month follow-up data were included, as electronic patient record, and therefore Oxford and Reading Cognitive, Comorbidity, Frailty, and Aging Research Database, commenced in 2015 (Figure 1). Patients with acute stroke were included if aged ≥18 years, able to concentrate for ≈20 minutes

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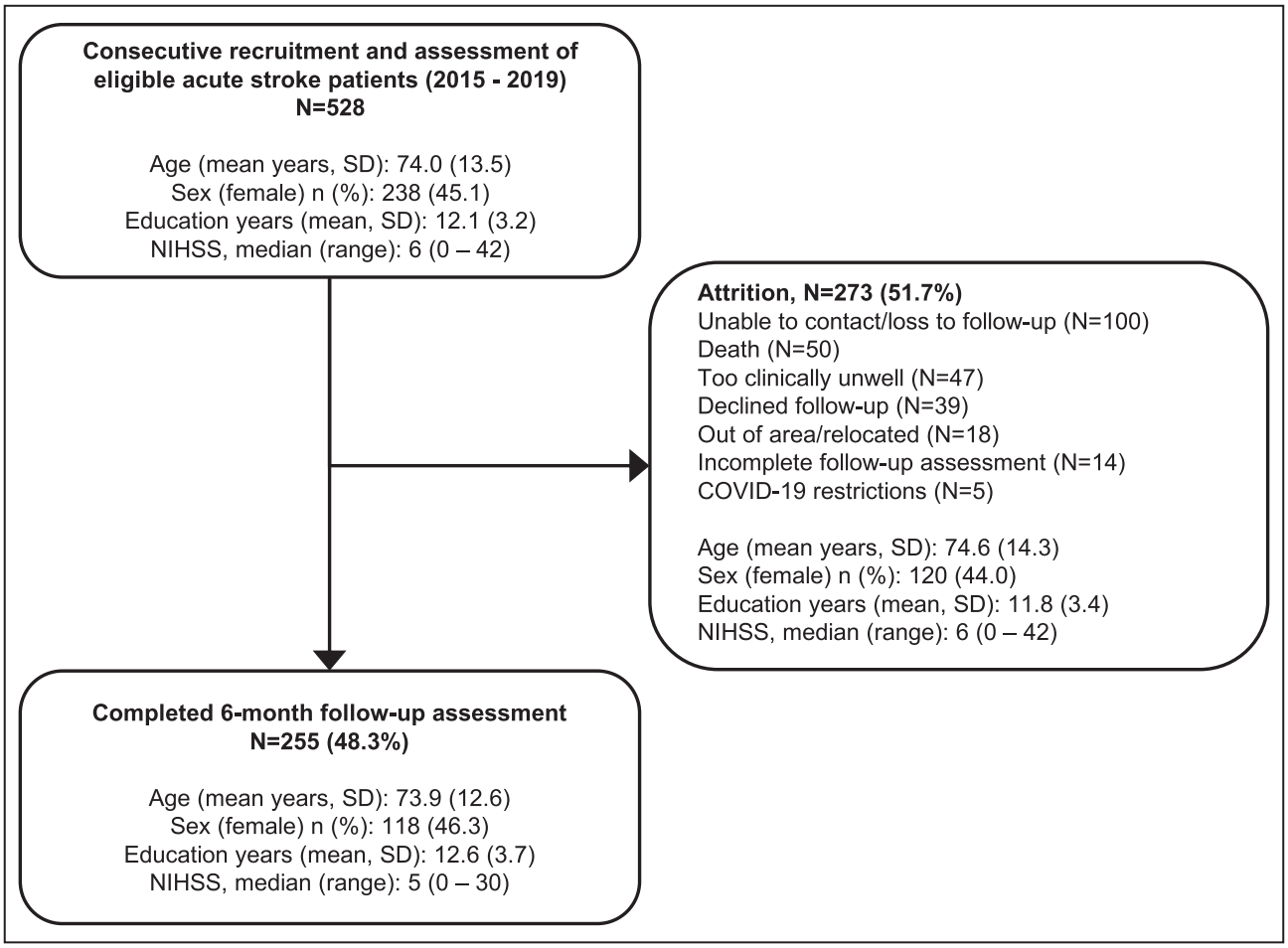

Figure 1. Flowchart of study cohort.
NIHSS indicates National Institutes of Health Stroke Scale.

as judged by the multidisciplinary team, and had sufficient English language comprehension to understand assessment instructions. All participants included provided written or witnessed informed consent, and Strengthening the Reporting of Observational Studies in Epidemiology reporting guidance for cohort studies was followed.

Participants

All included participants received cognitive screening with the OCS within 2 weeks of stroke and again at 6-month follow-up. Data collection also included patient demographics, comorbidities, vascular risk factors, and stroke characteristics, including stroke severity evaluated using the National Institutes of Health Stroke Scale (NIHSS).[26] Diagnosis of infection, routinely acquired laboratory test results, Charlson comorbidity index (Table S1),[27] and secondary events (eg, hydrocephalus) were obtained through linkage to Oxford and Reading Cognitive, Comorbidity, Frailty, and Aging Research Database and hand searching of electronic patient records.[28]

Infections and Inflammatory Markers

Infections were categorized into UTI, pneumonia, other respiratory, gastrointestinal, hepatitis, soft tissue, central nervous system, blood, and other (eg, sinusitis, esophageal candidiasis). Suspected UTI was defined as symptomatic with positive dipstick for leukocyte esterase or nitrite, and received treatment, while confirmed UTI required symptoms and a positive culture and received appropriate therapy.[29] Pneumonia was binarized as suspected (symptoms, clinical diagnosis, treated) or confirmed (chest radiograph). All remaining infections were confirmed with positive signs/symptoms and laboratory tests (eg, positive culture or antigen detection). The presence of a hospital discharge *International Classification of Diseases, Tenth Revision* (*ICD-10*) diagnosis of sepsis was recorded.[30]

Severity of infection inflammatory response was defined by the systemic inflammatory response syndrome (SIRS) criteria[31] (≥2 of the following: heart rate >90/min; respiratory rate >20/min; temperature <36°C or >38°C; or white cell count [WCC] $<4\times10^9$/L or $>12\times10^9$/L). Total days (consecutive or nonconsecutive)

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SIRS-positive during the admission period was calculated. Routinely acquired inflammatory markers, including CRP, WCC, lymphocyte count, and neutrophil count, were recorded from admission, and any repeat sampling during admission was reviewed to identify peak values of CRP and WCC. Admission neutrophil count divided by the lymphocyte count yielded the NLR with normal reference range for adults of 0.78 to 3.53.[32] Reference intervals employed were derived from the patient recruitment site (John Radcliffe Hospital, Oxford University Hospitals Natonal Health Service Foundation Trust).

Cognitive Assessment

Cognition was assessed within 2 weeks after stroke and at 6 months using the OCS.[25] The OCS covers a broad range of cognitive domains and was designed specifically for use in acute stroke, being as inclusive as possible for patients with aphasia and neglect (Demeyere et al[25]) taking 15–20 minutes to complete. All 12 subtest scores were categorized into 6 cognitive domains: language (picture naming, semantic understanding, sentence reading), attention (egocentric attention/sustained attention, allocentric attention), executive function (trail-making), memory (orientation, verbal memory, episodic memory), praxis (gesture imitation), and number processing (calculation and number writing). Subtests were binarized into impaired or unimpaired on the basis of normative scores for each subtest (cutoffs were set at fifth centile).[25] Severity of global cognitive impairment was characterized by the proportion of subtests impaired across all domains (ie, *n* subtests impaired divided by the total 12 subtests). Domain-specific impairment was defined as at least 1 subtest impaired within a domain, and multidomain impairment was characterized by at least 1 subtest impaired in >1 domain. The OCS was administered by trained psychologists and occupational therapists at the bedside acutely and at in-person follow-up. Supplementary information regarding the OCS is described in Data S1.

Statistical Analysis

Descriptive statistics (mean±SD, n [%], median [range; minimum-maximum]) were used to summarize sample demographics, clinical characteristics and the prevalence of poststroke infection, SIRS, and elevated inflammatory markers (aim 1). Differences in clinical characteristics and cognitive function between patients with and without infection were determined using the *t* test and Fisher's exact test as appropriate.

To address aim 2, we employed generalized linear models to assess associations between stroke-associated infection, SIRS, and inflammatory markers (CRP, NLR, WCC) and severity of global cognitive impairment acutely and at 6 months. Initially, univariable generalized linear model analyses were conducted to explore the relationships between the infection/inflammation variables and cognitive outcomes. Subsequently, if a significant univariable relationship was identified, multivariable generalized linear model regression was performed. The models were adjusted for covariates known to be associated with cognitive impairment following stroke, including age, sex, years of education, stroke severity (NIHSS), previous stroke, atrial fibrillation, hypertension, diabetes, and smoking.[16,33,34] Multivariable regression was also conducted to examine the relationship between severe infection (infection+SIRS) and cognitive impairment acutely and at 6 months. Finally, logistic regression models were also applied to investigate the relationship between poststroke infection/inflammation and binarized domain-specific cognitive function (impaired/unimpaired) acutely and at 6 months. Each of these models again adjusted for demographics and stroke-related and vascular risk factors. Missing data were addressed through multiple imputation. Sensitivity analyses were undertaken restricted to participants with complete NIHSS data (findings were broadly similar; see Data S2). For all analyses, *P* values <0.05 were considered statistically significant. Unstandardized β, SE for the unstandardized β, the *t* statistic, and the *P* value were reported for all regression analyses. Odds ratios and 95% CIs were presented for logistic regression analyses. All analyses were carried out in R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria).[35] The data that support the reported findings are available from the corresponding author upon reasonable request.

RESULTS

Among 255 stroke survivors, (mean age, 73.9 [SD,12.6] years; 118 (46.3%) women, mean years of education, 12.6 [SD, 3.7]; 120 [47.1%] with NIHSS >5) cognitive assessment was completed at a mean of 3.6 (SD, 3.8) days after stroke, with a mean follow-up interval of 6.7 (SD, 1.1) months (Figure 1; Table 1). Acutely, 213 (83.5%) were impaired on at least 1 subtest in a cognitive domain, with multidomain impairments being most common (n=166 [65.1%]). At 6 months, 192 (75.3%) were impaired, and 175 (49.8%) demonstrated multidomain impairments. Domain-specific impairments ranged from 26.9% in praxis to 44.9% in attention acutely, and 17.9% in number processing to 35.9% in attention at follow-up (Table S2). Group differences between the follow-up and attrition groups are outlined in Table S3.

Prevalence of Infections Acutely After Stroke

Of the 255 participants, 90 (35.3%) experienced ≥1 infection during hospitalization at a mean 4.4 (SD,

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Table 1. Cohort Characteristics

	All patients N=255	No infection N=165	Infection (≥1) N=90	*P* value
Age, y, mean (SD)	73.9 (12.6)	72.7 (13.2)	76.3 (11.0)	0.03
Sex, female, n (%)	118 (46.3)	74 (44.9)	44 (48.9)	0.54
Education, y, mean (SD)	12.6 (3.7)	12.79 (3.7)	12.2 (3.6)	0.25
Stroke subtype, n (%)				
Ischemic	211 (82.8)	138 (83.6)	73 (81.1)	0.61
Hemorrhagic	42 (16.5)	25 (15.2)	17 (18.9)	0.48
Mixed	2 (78.4)	2 (1.2)	0 (0.0)	0.54
First-ever stroke, n (%)	178 (69.8)	117 (70.9)	61 (67.8)	0.67
NIHSS score (admission),* median (range; min-max)	5 (0–30)	4 (0–24)	6 (0–30)	0.16
NIHSS score <5, n (%)	95 (44.2)	73 (51.0)	22 (15.4)	<0.01
NIHSS score ≥5, n (%)	120 (55.8)	70 (49.0)	50 (69.4)	
Independent at admission,† n (%)	232 (91.0)	158 (95.8)	74 (82.2)	<0.01
CCI score, median (range; min-max)	1 (0–6)	1 (0–6)	1 (0–5)	0.11
Atrial fibrillation, n (%)	61 (23.9)	36 (21.8)	25 (27.8)	0.28
Hypertension, n (%)	146 (57.3)	89 (53.9)	57 (63.3)	0.19
Diabetes, n (%)	46 (18.0)	31 (18.8)	15 (16.7)	0.74
Smoking, n (%)				
Current	20 (7.8)	14 (8.5)	6 (6.7)	0.81
Past	26 (10.2)	15 (9.1)	11 (12.2)	0.52
Never	209 (82.0)	136 (82.4)	73 (81.1)	0.87
Hospital stay, d, mean (SD)	11.2 (10.4)	8.0 (6.7)	17.0 (13.1)	<0.01
T1 assessment after stroke, d, mean (SD)	3.6 (3.8)	3.2 (3.3)	4.4 (4.6)	0.02
Acute cognitive impairment (OCS), n (%)	213 (83.5)	129 (78.2)	84 (93.3)	<0.01
Single-domain impairment, n (%)	47 (18.4)	33 (20.0)	14 (15.6)	0.40
Multi-domain impairment, n (%)	166 (65.1)	96 (58.2)	70 (77.8)	<0.01
T2 assessment after stroke, mo, mean (SD)	6.7 (1.1)	6.7 (1.0)	6.8 (1.3)	0.59
6-mo cognitive impairment (OCS)	201 (78.8)	124 (75.2)	77 (85.6)	0.06
Single-domain impairment, n (%)	64 (25.1)	46 (37.1)	18 (20.0)	0.18
Multi-domain impairment, n (%)	137 (53.7)	78 (47.3)	59 (65.6)	<0.01

CCI indicates Charlson comorbidity index; NIHSS, National Institute of Health Stroke Scale; OCS, Oxford Cognitive Screen; and T1/T2, time point 1, time point 2.

*Admission NIHSS data available for n=215 (84.3%); n=143 no infection, n=72 infection.

†Independence was categorized by not receiving any support (required family or carer).

6.9) days after stroke (Table 2). The majority (n=68 [75.6%]) were single infections (multiple in n=22 [24.4%]). Compared with no infection, the group with ≥1 infection was older in age (*P*=0.029), less likely to have more minor stroke (NIHSS score <5; *P*=0.006), were less functionally independent (*P*=0.001), had longer admissions (*P*<0.0001), and experienced more multidomain cognitive impairments at both acute assessment (*P*=0.002) and follow-up (*P*=0.006) (Table 1). Pneumonia was most common, affecting 47 (18.4%) patients followed by UTI (39 [15.3%]). Pneumonia was more common in those with dysphagia (n=29 [61.7%]; *P*=0.002) and nasogastric tube (n=17 [36.2%]; *P*<0.001), and UTI was more common in women (n=26 [66.7%]; *P*=0.008) and those catheterized (n=14 [35.9%]; *P*<0.001). Among those with UTI, *Escherichia coli* was the most common causative culture-positive organism (n=13/39 [33.3%]), followed by mixed growth (n=10/39 [25.6%]). Causative organisms (UTIs, soft tissue, septicemia) are displayed in Table S4.

Prevalence of Elevated Inflammatory Markers and SIRS Acutely After Stroke

On admission, the most frequently elevated biomarker was NLR in 142 (55.7%) patients, followed by CRP in 105 (41.2%), and WCC in 64 (25.1%) (Table 3). Peak CRP (mean, 52.0 [SD, 74.7] mg/L) occurred most often on day 3 (median; range [minimum-maximum], 0–52) and was elevated at some point in the majority (n=137 [72.1%]). SIRS-positive on admission occurred in 53 of 199 (26.6%, SIRS was unavailable in 56 patients) (Table 2), and 90 (45.2%) were SIRS-positive at least once during hospitalization (with a mean of

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Table 2. Prevalence of Poststroke Infections, Secondary Events, and Clinical Features Among All Patients During Admission Period

	n (%)	Days poststroke confirmed	
		Mean/SD	Median (range; min–max)
Any infection	90 (35.3)	4.4/6.9	1.5 (0–49)
Single infection	68 (26.7)		
Multiple infections (>1)	22 (8.6)		
Pneumonia*	47 (18.4)	5.8/10.0	1.5 (0–49)
UTI†	39 (15.3)	6.8/7.8	5 (0–42)
Soft tissue	9 (3.5)	6.6/7.4	1 (0–17)
Other respiratory	8 (3.1)	2.5/3.6	0.5 (0–9)
Blood	8 (3.1)	8.4/16.3	1.5 (0–48)
Other infection‡	5 (2.0)	3.4/3.7	4 (0–9)
Gastrointestinal	3 (1.2)	21.0/23.8	12 (3–48)
Hepatitis (B)	1 (0.4)	8.0/NA	8 (NA)
Sepsis	8 (3.1)	2.6/3.7	1 (0–9)
SIRS§ positive on admission	53/199 (26.6)		
SIRS positive anytime during admission	90/199 (45.2)		
Total nonconsecutive days positive		2.7/3.3	2 (1–26)
Oromotor/speech dysfunction			
Dysphagia	103 (40.4)		
Dysarthria/anarthria	115 (45.1)		
Nasogastric tube fed	43 (16.9)		
Urinary dysfunction			
Catheterization	22 (8.6)		
Incontinence	27 (10.6)		

Days poststroke refers to first confirmed infection in instances of multiple.
SIRS indicates systemic inflammatory response syndrome; and UTI, urinary tract infection.
*Pneumonia confirmed: n=43 (16.9%); suspected (clinical diagnosis, treated): n=4 (0.4%).
†UTI confirmed: n=38 (14.9%); suspected (clinical diagnosis, treated): n=1 (1.6%).
‡Other infection (1 each): conjunctivitis, esophageal candidiasis, oral candidiasis, pyrexia of unknown origin, sinusitis.
§SIRS data available for n=199 of 255 patients.

2.7 [SD, 3.3] days; range [minimum-maximum], 1–26) days. Sepsis was identified in 8 (3.1%) patients during hospitalization.

Infection and Severity of Cognitive Impairment

The presence of any infection during hospitalization was associated with increased severity of global cognitive impairment acutely (P=0.005) and at 6 months (P<0.001), including after adjustment for confounders (P=0.032$_{adj}$ and P=0.006$_{adj}$) (Table 4, Figure S1, Table S5). Regarding different subtypes of infection, associations were seen for pneumonia both acutely (P=0.029$_{adj}$) and at 6 months (P=0.027$_{adj}$) but not for UTI (Table 4, Table S6). Severe infection (SIRS-positive) was associated with acute cognitive impairment (P=0.014$_{unadj}$, P=0.033$_{adj}$),m but associations at 6 months attenuated after adjustment (P=0.011$_{unadj}$, P=0.051$_{adj}$) (Table 4). Conversely, infection with a SIRS-negative status was not associated with severity of cognitive impairment at either time point (Table 4, Table S7).

Inflammatory Biomarkers and Severity of Cognitive Impairment

Univariable analyses showed no significant relationships between any inflammatory biomarker (CRP, WCC, or NLR) and cognitive impairment acutely or at 6 months (Table 4). In contrast, SIRS positivity on admission was associated with cognitive impairment acutely (P=0.033), including after adjustment (P=0.025$_{adj}$; Table 4; Table S8) but not at 6 months (P=0.452$_{adj}$).

Infection and Domain-Specific Cognitive Impairment

Stroke-associated infection was associated with domain-specific impairments in language (adjusted odds ratio, 1.725 [95% CI, 1.002–2.971]; P<0.05), executive function (adjusted odds ratio, 1.881 [95% CI, 1.050–3.367]; P<0.05), and attention (adjusted odds ratio, 2.006 [95% CI, 1.142–3.522]; P<0.05), and number processing (adjusted odds ratio, 2.137 [95% CI, 1.073–4.254]; P<0.05) at 6 months (Figure 2, Figure S2).

DISCUSSION

Just over one-third of this sample of patients with acute stroke had at least 1 infection during hospitalization, with pneumonia being most common, followed by UTI. Infection was associated with severity of cognitive impairment acutely and at 6-month follow-up independent of demographic factors and other confounders, including stroke severity. Infection was also associated with acute deficits in language, executive function, and attention domains, as well as 6-month deficits in number processing. Although inflammatory biomarkers, including NLR, CRP and WCC, were frequently elevated on admission, none were associated with cognitive impairment.

To our knowledge, there are only 2 previous studies of infection and cognitive outcome in a stroke cohort. One hospital-based study found an increased dementia risk in those with hypoxic-ischemic episodes, defined as composite of secondary insults, including cardiac and thromboembolic events and infection; however, numbers with infection were too small (pneumonia, 2; sepsis, 1) to allow separate analyses.[9] The subsequent

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Table 3. Poststroke Inflammatory Biomarkers During Hospital Admission

Inflammatory biomarker	Mean (SD)	Median (range; min–max)	Outside reference interval, n (%)
WCC (on admission), $\times 10^9$/L	9.5 (3.2)	9.0 (4.2–20.6)	64 (25.1)
WCC (peak), $\times 10^9$/L	10.8 (4.1)	10.0 (4.2–38.0)	101 (39.6)
Day of peak WCC	2.5 (5.1)	0 (0–33)	
CRP* (on admission), mg/L	28.5 (50.9)	7.6 (0.4–282.9)	105 (41.2)
CRP* (peak), mg/L	52.0 (74.7)	18.4 (0.5–461.5)	137 (72.1)
Day of peak CRP	5.1 (7.3)	3 (0–52)	
Lymphocyte count (on admission), $\times 10^9$/L	1.7 (0.9)	1.5 (0.3–7.6)	5 (2.0)
Neutrophil count (on admission), $\times 10^9$/L	6.9 (3.1)	6.1 (2.1–17.3)	97 (38.0)
NLR (on admission)	5.5 (4.5)	3.8 (0.7–27.1)	142 (55.7)

Reference intervals: WCC (4.0–11.0×10^9/L); CRP (0–5 mg/L); lymphocyte count, 1.0–4.0×10^9/L; neutrophil count (2.0–7.0×10^9/L); NLR (0.78–3.53).
CRP indicates C-reactive protein, plasma; NLR, neutrophil/lymphocyte ratio; and WCC, white cell count.
*CRP data were available for 177 of 255 patients (69.4%) on admission and 190 of 255 patients (74.5%) throughout hospitalization.

big data population-based study[8] of administrative primary care data (>60 000 stroke survivors) found early dementia (3–12 months after stroke) risk was elevated, particularly after hospitalization-associated infection, which also increased the risk of late dementia.[6,36] However, the study design was retrospective and did not allow adjustment for stroke severity. Our study extends these previous findings by ascertaining cognitive

Table 4. Associations Between Poststroke Infection, Inflammatory Biomarkers, and Severity of Cognitive Impairment Acutely and at 6 Months

	Severity of cognitive impairment							
	Acute (≤2 wk)				6 mo			
	β	SE	*t*	*P*	β	SE	*t*	*P*
Unadjusted models								
Infection (any)	8.68	3.08	2.82	0.005	7.87	2.16	3.64	<0.001
Pneumonia	12.27	3.78	3.25	0.001	8.25	2.68	3.07	0.002
UTI	5.92	4.14	1.43	0.153	5.10	2.93	1.74	0.082
SIRS (admission)	7.62	3.55	2.15	0.033	1.31	2.48	0.53	0.600
SIRS (any time)	4.67	3.17	1.47	0.142	2.26	2.20	1.03	0.305
Infection, SIRS-negative	5.26	4.91	1.07	0.286	6.72	4.12	1.63	0.105
Infection, SIRS-positive	9.28	3.74	2.48	0.014	7.02	2.73	2.57	0.011
CRP (admission)	−0.02	0.04	−0.45	0.651	0.01	0.03	0.29	0.770
CRP (peak)	0.01	0.02	0.50	0.619	−0.01	0.02	−0.89	0.375
WCC (admission)	−0.18	0.47	−0.37	0.710	−0.32	0.33	−0.97	0.334
WCC (peak)	0.63	0.37	1.73	0.085	−0.04	0.26	−0.15	0.877
NLR (admission)	−0.53	0.33	−1.60	0.111	−0.27	0.23	−1.17	0.243
Adjusted models								
Infection (any)	6.33	2.94	2.15	0.032	5.70	2.07	2.75	0.006
Pneumonia	8.03	3.65	2.20	0.029	5.77	2.59	2.23	0.027
UTI	3.53	3.98	0.89	0.376	3.05	2.82	1.08	0.281
SIRS (admission)	7.88	3.50	2.25	0.025	1.80	2.38	0.75	0.452
Infection, SIRS-negative	3.95	4.81	0.82	0.412	3.90	3.24	1.21	0.229
Infection, SIRS-positive	7.97	3.71	2.15	0.033	4.90	2.50	1.96	0.051

Adjusted models included variables significant in univariable analyses as well as demographics and vascular risk factors (age, sex, education, stroke severity, previous stroke, atrial fibrillation, hypertension, diabetes, and smoking). Severity of cognitive impairment was defined by proportion of Oxford Cognitive Screen tasks impaired acutely and at 6 months. SIRS-positive or -negative refers to any time during the admission period. The potential impact of the natural log transformation on CRP values was explored, considering its nonnormal distribution. The transformation was considered, and despite this adjustment, peak CRP did not exhibit a significant association with poststroke cognitive impairment (results shown in Figure S1). CRP indicates C-reactive protein; NLR, neutrophil/lymphocyte ratio; SIRS, systemic inflammatory response syndrome; UTI, urinary tract infection; and WCC, white cell count.
Significance $P<0.05$.

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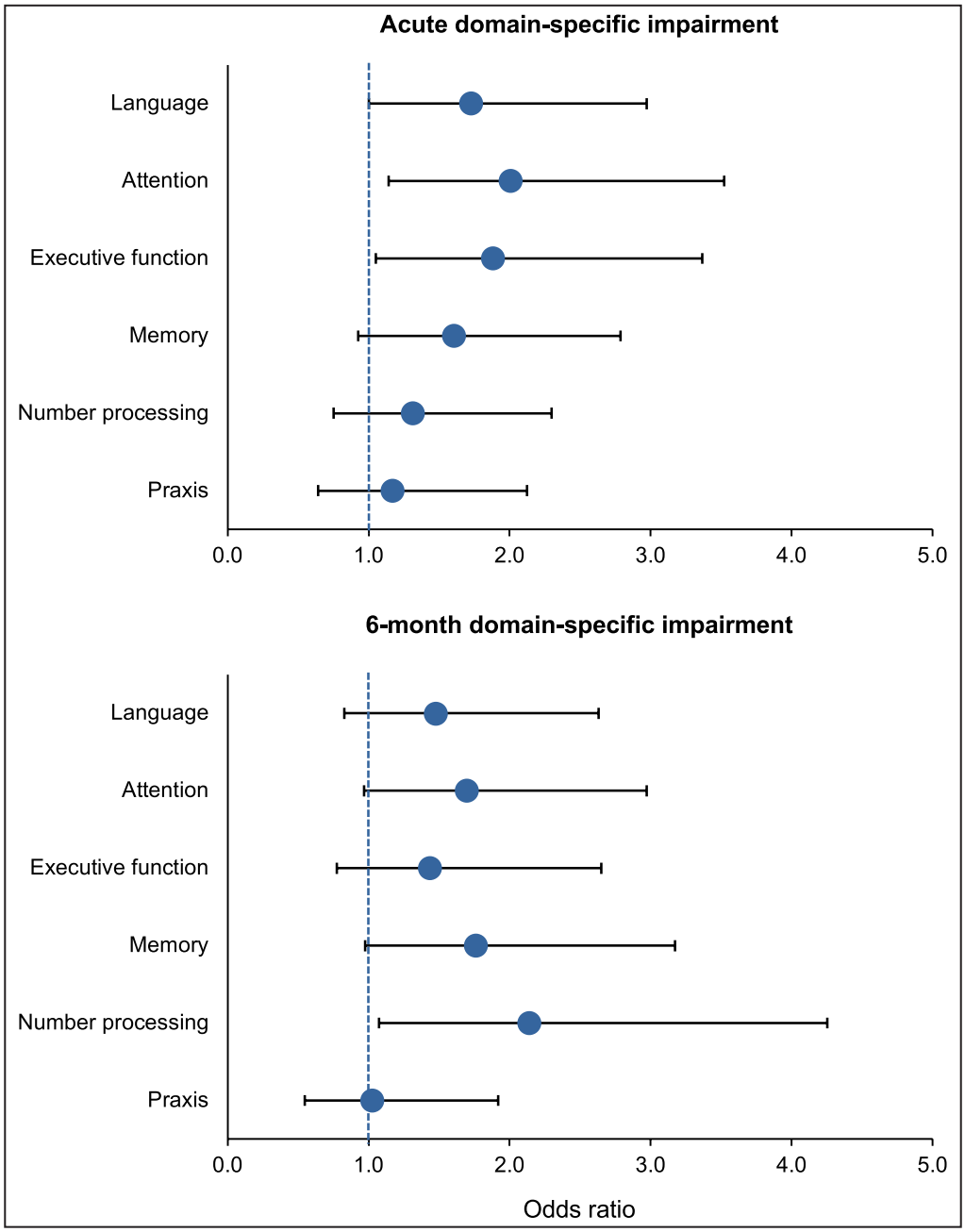

Figure 2. Odds ratios for the effect of acute poststroke infection on domain-specific impairments acutely and at 6 months.
Acute assessment with the Oxford Cognitive Screen occurred at a mean of 3.63 (SD, 3.83) days after stroke. Circles denote the odds ratios, and bars indicate 95% CIs. Each model was corrected for demographics, stroke severity, and vascular risk factors (see Figure S2).

impairment through prospective participant assessment, measuring infection severity directly using SIRS, and performing robust adjustment for a number of covariates.

Existing research suggests a biphasic inflammatory response to stroke, where an early activation phase is followed by systemic immunosuppression,[37,38] which increases susceptibility to infection.[37] The prevalence of infection in our study (35% occurring on average around 4 days after stroke) is consistent with the pooled prevalence in meta-analyses (30%), which also report older age, more severe stroke, dependency, and longer hospital admissions as risk factors.[10,39] We also recorded more pneumonia in dysphagic and nasogastric-fed patients,[39] and UTI in older female patients, which is consistent with previous studies.[40]

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Infection may also precipitate stroke; stroke risk increases immediately following onset of acute respiratory infections or UTI,[41] and we cannot exclude the possibility that some infections were present before the stroke, particularly since a fifth were identified on day of admission, of which a third were SIRS positive.

Previous studies have shown that WCC, CRP, and NLR are elevated in acute stroke, particularly with greater stroke severity, larger lesion volume, poor functional outcome, and recurrent stroke,[42,43] and the few data available suggest that similar factors are associated with the presence of SIRS.[44,45] The reported prevalence of SIRS following stroke ranges from 14% to 36% on admission[44–48] and 22% to 53% during admission,[48] similar to the rates observed in our study (27% on admission, 45% during admission). Elevated inflammatory markers in acute stroke may also occur from chronic comorbidities, such as diabetes, hypertension, and smoking,[49] though in our study, smoking and diabetes rates were relatively uncommon. Comorbid load may also enhance the risk of SIRS[50]; however, the median Charlson comorbidity index score in our sample was relatively low.

Despite the prevalence of elevated inflammatory markers, we found no associations between CRP, WCC, or NLR and severity of cognitive impairment acutely or at 6 months. There are few previous studies on routinely available inflammatory biomarkers and poststroke cognition, and findings are conflicting. Both positive and null associations with PSCI acutely and at 6 months have been reported for CRP[18,19] and WCC.[51,52] Elevated NLR has been shown to be associated with global impairment at 3 months and visuospatial and memory domain impairment (NLR ≥3.80)[17] and executive dysfunction (Montreal Cognitive Assessment) (NLR ≥4.05).[53] However, the sample characteristics and type/timing of cognitive assessment differed among studies. Taken together with our findings, the relationship between these individual inflammatory markers and poststroke cognition remains uncertain. A recent study of an extensive panel of inflammatory biomarkers obtained using a research protocol (including terminal C5b-9 complement complex, interleukins, macrophage inflammatory protein-1α, and tumor necrosis factor) found associations with baseline (but not chronic) biomarkers and cognitive impairment at up to 36 months' follow-up, suggesting that more sensitive/specific measures may detect inflammation relevant to cognitive outcomes. We found SIRS (a composite measure of the inflammatory response using routinely measured markers) was linked to global cognitive impairment acutely but not at follow-up, in line with a previous study of SIRS and functional outcome at 3 to 6 months after stroke.[44]

Regarding specific cognitive domains, infection was associated with impairments in language, attention, and executive function acutely, and number processing at 6 months after adjustment for confounders. The pattern of impairments is consistent with that generally seen in cerebrovascular/small-vessel disease with relatively prominent deficits in frontal/executive domains.[24,54,55] However, deficits, particularly in attention, may be seen in delirium, which may co-occur with infection and could have contributed to the acute findings, although the requirement for informed consent will have excluded many/most with delirium.[56] Future research efforts could potentially benefit from more comprehensive and specialized assessments to differentiate between acute poststroke delirium and cognitive impairment as although these overlap, they may nevertheless be differently associated with infection and with future cognitive decline. The lower number of frontal/executive domain associations at 6 months could have resulted from a reduction in power, as fewer individuals showed impairments across all domains at this time point. The lack of a relationship with memory deficits is consistent with a recent UK Biobank study of infection and visual/verbal memory function, although it should be noted that our study may have been underpowered.[7] Our findings are also supported by a recent multicohort study[55] in which hospitalization-associated infection was linked to a greater risk of vascular dementia versus Alzheimer's disease, suggesting greater cerebral susceptibility to infection in those with cerebrovascular disease.

Our study has some strengths. We addressed a key knowledge gap on the association of infection and routinely available inflammatory biomarkers with cognitive function in a representative sample of patients with acute stroke (average age, 74 years; 56% with NIHSS score ≥5; 29% aphasic). We used a longitudinal study design and stroke-specific cognitive screen, with careful ascertainment of infection, inflammation biomarkers, and measures of infection/inflammation severity through linkage to detailed hospital electronic patient record data, supplemented by hand searching of patient records. However, our study also has limitations, such as inflammatory biomarkers and SIRS data were not available for each day of admission as these were acquired as part of routine care, and underascertainment of peak values is possible, although patients with acute stroke are usually comprehensively assessed and monitored. Additionally, attrition could have led to underestimation of the measured infection rate since we included only patients with both baseline and follow-up data (we did not have data on infection in patients lost to follow-up), and this might also have impacted the observed associations between infection and cognition. Further, our study was designed and set up before delirium screening in acute stroke was well established and we were therefore unable to identify delirium in the acute phase. However, lack of data on delirium does

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not invalidate the observed association between infection and baseline cognitive impairment (and patients with delirium were likely included in the cognitively impaired group). Baseline cognitive impairment,[2] as well as delirium,[57] has been shown to predict future dementia. We could not adjust for stroke location, which is a known associate of cognitive function after stroke; therefore, this should be considered in future studies. Finally, we could not exclude patients with prestroke infection or cognitive decline, and consequently some of the association between infection and cognition could be driven by existing infection or increased susceptibility to infection in those with undiagnosed prestroke dementia. While the requirement for informed consent may exclude certain patients with more severe dementia, individuals with prestroke cognitive decline may still have been able to provide consent.

Our findings require replication in larger cohorts but have potential implications for the prevention of poststroke dementia. Infection is thought to increase the risk of dementia through inflammatory mediators acting on the brain.[6,7,58] Patients with stroke may be particularly vulnerable to the effects of infection because of increased permeability of the blood–brain barrier and coexistent small-vessel disease.[57] The pattern of cognitive domain impairment linked to infection is suggestive of a vascular profile and supports the findings from nonstroke studies of a preferential risk of vascular versus Alzheimer's dementia after infection. Infection prevention and rapid treatment of infection may therefore help reduce dementia risk after stroke and likely explains some of the effect of organized stroke unit care on improved outcomes.[12,44] It may also present a tractable target for trials.

Conclusions

Infection is prevalent in hospital patients with stroke and is associated with cognitive impairment acutely and at 6-month follow-up with strong associations for pneumonia and severe infection. In contrast, despite the frequent elevation in routinely measured inflammatory biomarkers (CRP, WCC, and NLR) indicating an acute inflammatory response, individual biomarkers were not associated with cognitive impairment. Future research should aim to determine the underlying mechanisms linking infection to PSCI, including the use of detailed inflammatory biomarker panels, and the relationship to cognitive outcomes in the longer term.

ARTICLE INFORMATION

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Disclosures

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Supplemental Material

Data S1–S2
Tables S1–S8
Figures S1–S2

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