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Article

C reactive protein and risk of neurological deficits and disability in patients with acute ischemic stroke

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SUMMARY

Stroke is associated with significant clinical morbidity and mortality. Previous studies have speculated on the role of inflammation in acute ischemic stroke and cardiovascular disorders. Here, we retrospectively assessed the relationship between high sensitivity C reactive protein (hsCRP) levels at stroke onset and neurological and functional morbidity, using different scales like the Barthel Index (BI) for activities of daily living, National Institutes of Health Stroke Scale (NIHSS) for stroke severity, and modified Rankin Scale (mRS) for neurologic disability. We hypothesized that higher hsCRP levels would be significantly associated with the severity of acute ischemic stroke reflected in terms of the above scales. We performed univariate analysis on data from 576 subjects and found that participants with serum hsCRP concentration > 3 mg/L exhibited higher NIHSS score, higher mRS, and lower BI. We also found that subjects with higher hsCRP had significantly increased duration of hospital stay. Logistic binomial regression did not detect statistically increased odds of more severe stroke with higher hsCRP levels. However, our model did suggest increased odds of higher disability with prior history of stroke and in males. In conclusion, higher hsCRP levels in the context of acute ischemic stroke were exhibited in subjects with significant neurological deficits (higher NIHSS scores) and greater disability at onset of stroke (higher mRS scores and BIs). However, these findings did not appear to be causal or increase the odds ratio in our multiple logistic regression model.

INTRODUCTION

Stroke refers to the permanent damage to brain, spinal cord, or retinal tissue due to reduced blood supply or ischemia (1). Stroke can result from occlusion of the blood supply to brain tissue by a clot (ischemic strokes) or bleeding in the brain tissue or between brain and skull leading to injury to the brain (hemorrhagic strokes) (1). Ischemic strokes account for 87% of all strokes (2). Globally, stroke affects approximately 15 million people each year (3,4). Of these, 5 million patients die, and another 5 million are left permanently disabled (3). About 800,000 strokes occur in the United States each year (5). In addition to being a leading cause of mortality, many patients affected by stroke have permanent neurological deficits resulting in significant loss of productivity and increased utilization of healthcare resources (4,6). Many of these patients become dependent on care from other individuals, placing huge economic, physical, and financial burden on the families and healthcare systems (7-9). In one study, at six months after stroke, 35% patients had depression, 30% were unable to ambulate without help, and 26% were dependent on other people for their day-to-day work (5). Estimates suggest direct and indirect costs of stroke amount to 56.1 billion dollars in the United States alone (2).

Stroke incidence doubles after the age of 55 (10). Stroke occurs slightly more often in females compared to males and with disproportionately higher mortality (11). The INTERSTROKE case-control study showed that roughly 90% of strokes could be explained by one of ten risk factors, chiefly including hypertension, diabetes mellitus, cardiac causes, current smoking, abdominal obesity, hyperlipidemia, physical inactivity, and alcohol consumption (12). Many of these factors can be addressed by simple lifestyle changes or preventative medical treatments. A host of non-medical (non-white race, female sex, older age) and medical (prior functional status, history of diabetes and hypertension, severity of neurological deficits, timing of detection and administration of thrombolytic medications or clot removal through angiography) factors can predict mortality and morbidity in ischemic strokes (12,13). Ischemic strokes are more common and can present with wide ranging neurological deficits depending on the regions of the brain that are affected. Common symptoms include one-sided weakness, difficulty in speech and facial droop, etc. (14).

High-sensitivity C reactive protein (hsCRP) is one of the markers of body's acute inflammatory response; higher serum levels are seen in inflammatory conditions (15). Stroke has been linked to the inflammation of blood vessels supplying the central nervous system (16). A past study has also shown an association between high hsCRP levels and the risk of development of acute ischemic stroke (15). There are about 28 different biomarkers, ranging from cardiac enzymes to inflammatory markers in the blood, that have been linked to cardiovascular and cerebrovascular mortality (17,18). However, the data on most of these other biomarkers and their effectiveness at predicting patient outcomes are currently insufficient (17). hsCRP has been considered one of the most studied and suitable biomarkers in cardiovascular and cerebrovascular mortality (19). High levels of hsCRP have been associated with mortality and poor long-term outcomes after the initial stroke (20). The rationale behind this association is that inflammation in the stroke bed may further worsen the tissue damage and lead to worse outcomes (21,22). However, whether high hsCRP levels and

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inflammation do lead to worse neurological deficits or worse functional status at onset of stroke has not been previously studied. Thus, we hypothesized that there is a significant effect of higher hsCRP levels on severity of acute ischemic stroke. If so, we expect the degree of rise of hsCRP levels to exhibit effect on severity of neurological complications and disability at stroke onset, as well. The severity of stroke can be calculated in terms of different scales used to assess neurological deficits, such as National Institutes of Health Stroke Scale (NIHSS), or deficits in functional activity of daily living, which can be measured by Barthel Index (BI) and Modified Rankin Scale (mRS) (23). NIHSS is calculated by doing a clinical exam and assigns a value based on the number and severity of deficits in a neurological exam (23). BI and mRS are functional indices, which calculate ability to do day-to-day activities, and are graded in terms of degree of disability in doing these activities. Specifically, BI is a more detailed score based on capability to do day-to-day activities, while mRS is a simplified scale based on ability to walk (24). In this study, we assessed the relationship between the hsCRP levels in blood and the disability at the time of acute stroke as assessed with above-mentioned scales. We found higher hsCRP levels to correlate with increased neurological deficits and an increased hospital stay duration. This suggests the value of getting serum hsCRP levels routinely at the time of stroke could help predict severity of the stroke-related disability and, therefore, institute appropriate clinical measures directed at increased needs for rehabilitation.

RESULTS

We acquired data from 576 subjects with the diagnosis of acute ischemic stroke from the Louisville Stroke Center patient database between the years 2018 to 2022. The information collected included age and biological sex as well as classical risk factors for stroke, like history of diabetes mellitus, history of smoking, and history of strokes in the past. The studied population ranged in age from 20–97 years and had a male-to-female ratio of 1.49 (**Table 1**). About 35% of patients had diabetes mellitus, 80% had history of hypertension, and 51% had history of smoking (**Table 1**). Additionally, 74% subjects had elevated hsCRP levels greater than 3 mg/L (**Table 1**).

We used ANOVA to determine the effect of increased hsCRP levels on different clinical indices. Participants with higher hsCRP levels (> 3 mg/L) exhibited significantly higher NIHSS scores ($p < 0.001$), higher mRS scores ($p < 0.001$), and lower BI scores ($p = 0.004$) (**Table 2**). Higher hsCRP level subjects also had significantly longer duration of stay in hospital ($p = 0.005$) (**Table 2**). On average, patients with hsCRP > 3 mg/L had 3.1 days of longer stay in the hospital compared to those with hsCRP < 1 mg/L (**Table 2**).

We used multivariate binomial regression to test if patient medical traits could be used to predict an elevated NIHSS score (NIHSS > 4). The results of the regression indicated a low predictability, predicting only 8% of the variation in the results. We found that male patients had lower odds of an elevated NIHSS than female patients with an odds ratio (OR) of 0.516 and $p < 0.001$ (**Table 3**). Patients with a history of stroke had higher odds of elevated NIHSS than those with no such history, (OR = 4.547, p-value < 0.001) (**Table 3**).

We then used multivariate binomial regression to test if patient medical traits could be used to predict an elevated mRS score (mRS > 3). The results of the regression also indicated a low predictability, predicting only 4% of the variation in the results. Male patients had lower odds of an elevated mRS than female patients (OR = 0.592, p-value = 0.007) (**Table 4**). Patients with a history of stroke had higher odds of elevated mRS than those with no such history (OR = 2.496, p-value < 0.001) (**Table 4**).

Finally, we used multivariate binomial regression to test if patient medical traits could be used to predict a lower BI (BI < 90). The results of the regression indicate a low predictability, predicting only 1% of the variation in the results. None of the examined variables, including age, gender, cholesterol level, diabetes mellitus, history of smoking, history of stroke, hypertension, or hsCRP levels, showed a statistically significant association with having a BI score less than 90 (**Table 5**). Presence of hypertension demonstrated the highest odds ratio for BI < 90 (OR = 1.60) but this was not statistically significant ($p = 0.065$) (**Table 5**). Neither moderate (1–3 mg/L) nor high (> 3 mg/L) hsCRP levels had significantly increased odds for lower BI, with ORs of 1.03 (95% CI: 0.50–2.17, $p = 0.94$) and 0.99 (95% CI: 0.53–1.91, $p = 0.98$), respectively (**Table 5**).

CHARACTERISTIC		N (%)
TOTAL N		576
Gender	Female	231 (40.1)
	Male	345 (59.9)
Diabetes mellitus	No	371 (64.6)
	Yes	203 (35.4)
History of smoking	No	282 (49.1)
	Yes	292 (50.9)
History of stroke	No	452 (80.7)
	Yes	108 (19.3)
Hypertension	No	111 (19.8)
	Yes	449 (80.2)

CHARACTERISTIC	MEAN (SD)
Age, years	65.86 (14.11)
hsCRP levels in blood (mg/L)	1.934 (6.961)
Cholesterol (mg/dL)	169.87 (60.89)
HDL (mg/dL)	40.59 (13.91)
NIHSS score	7.06 (7.10)
BI	92.72 (13.76)
mRS upon admission	3.04 (1.47)

Table 1: Subject demographics, medical history, and symptoms. From our study population (n = 576), the majority of subjects were male, and the majority of subjects had been diagnosed with hypertension. About half of subjects had a history of smoking and 19.3% had a history of past stroke or transient ischemic attack (TIA). Additionally, about a third of subjects had received a diagnosis of diabetes mellitus. The mean subject age, blood hsCRP levels, cholesterol, HDL, NIHSS, BI, and mRS upon admission are also reported, here.

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Serum hsCRP levels (mg/L)	< 1	1-3	> 3	*p*-value
Mean NIHSS	4.0	5.7	7.6	<0.001
Mean mRS	2.5	2.6	3.2	<0.001
Mean BI	75.3	72.7	62.8	0.004
Mean hospital stays (days)	3.7	5.4	6.8	0.005

Table 2: Effect of higher hsCRP levels on different functional indices and mean hospital stay in patients with stroke. From the ANOVA results, we found statistically significant relationships between high levels of hsCRP and more severe neurological deficits (in terms of NIHSS), higher degrees of disability (in terms of mRS and BI), and longer hospital stays. NIHSS = NIH Stroke Scale, mRS = modified Rankin Scale, BI = Barthel Index.

DISCUSSION

In the present retrospective cross-sectional study, we examined the effect of high hsCRP levels on functional morbidity and severity of neurological deficits at stroke onset. Our population had relatively high average mRS at admission, which could be related to about 20% of them having had a stroke in the past and therefore having residual disability. The mean NIHSS was seven, which indicated a moderate degree of neurological deficits in our patients at the time of admission. We reported that subjects with higher hsCRP exhibited higher NIHSS scores, higher mRS, and lower BI. Higher hsCRP levels also had a significant effect on mean hospital stay duration, which increases the cost burden on patients and healthcare systems. With our analysis, males and those with a prior history of stroke were associated with increased odds of worse NIHSS, BI and mRS. The increased odds of worse indices with prior history of strokes are expected, as a significant proportion of patients with stroke have residual neurological deficits (higher baseline NIHSS) resulting in disability (higher mRS and BI).

hsCRP is known to be associated with vascular inflammation and, therefore, higher hsCRP levels corresponds with a higher degree of inflammation (25). A prior study has shown inflammation causes prothrombotic effects (26). Inflammation has also been shown to lead to arterial clot formation and embolism in a stenosed internal carotid artery, which is one of the major blood vessels supplying the brain (27). Therefore, it is possible that hsCRP elevation is an effect of inflammation of the vascular supply to the infarcted area. Granular *in vivo* studies supporting the impact of inflammation on clotting of larger blood vessels are lacking (28).

Our ANOVA results suggested a statistically significant effect of higher hsCRP on longer hospital stay as well as with NIHSS and other indices. However, our logistic regression was not consistent this finding. This inconsistency could be due to lack of other predictor variables in the model, such as systolic blood pressure and measures of cholesterol or even other advanced biomarkers, or smaller sample size. Additionally, it is possible that the odds for prediction in this context would be statistically significant if we had used even lower cut offs for NIHSS and mRS and higher cut offs for BI. However, we selected our cut offs based on those that were used by previous stroke studies. The rise in hsCRP levels above these cutoffs did not predict worse neurological deficits or disability at time of acute stroke. Another possible reason that we did not identify a significant effect of higher hsCRP levels on NIHSS or other indices could be that the size or extent of stroke area in brain does not necessarily correlate with the degree of disability or deficits. Other factors such as the location of the lesions are also crucial (29). hsCRP levels in blood, however, depend on the extent of brain tissue that is damaged by stroke (21,22). Further studies can be done to identify whether specific areas of brain injured by stroke lead to worse clinical morbidity.

Parameter	Odds ratio	Lower 95% CI	Upper 95% CI	*p*-value
Age	0.993	0.98	1.007	0.341
Gender (M)	0.516	0.349	0.759	< 0.001
Cholesterol (mg/dL)	0.998	0.994	1.002	0.304
Diabetes Mellitus (Yes)	1.095	0.742	1.615	0.646
History of Smoking (Yes)	1.307	0.893	1.918	0.170
History of Stroke (Yes)	4.547	2.765	7.714	< 0.001
Hypertension (Yes)	1.277	0.8	2.051	0.308
hsCRP (1-3 mg/L)	1.669	0.8	3.529	0.175
hsCRP (> 3 mg/L)	1.195	0.63	2.295	0.588

Table 3: Multivariate binomial regression predicting NIHSS > 4 in subjects with stroke. A history of stroke was the strongest predictor of having another stroke event with NIHSS > 4 (indicating more severe stroke). The effect of gender was also seen; being male was a statistically significant predictor. The other variables did not have a significant effect on the odds ratio. CI = Confidence interval.

Although non-significant, our binomial regression showed similar odds ratio when compared to a previous CHANCE sub-cohort, where they reported an adjusted OR of 1.68 in terms of poor functional outcome on the mRs when hsCRP levels were more than 3 mg/L (28). The CHANCE sub-cohort had 3,044 subjects compared to 576 in our study (30). The CHANCE sub-cohort, which similarly collected data from patients within 24 hours of the stroke event, saw elevated hsCRP in 32% subjects compared to 74% in our cohort (31). CHANCE cohort reported positive association between higher hsCRP and recurrence of stroke as well as higher scores on the functional indices (31). When we compare the CHANCE sub-cohort studies with our data, we have a significantly higher proportion of subjects with elevated hsCRP as well as higher mean NIHSS. This suggests that our cohort may have been imbalanced from the representative stroke population. Due to less proportion of subjects with hsCRP <1mg/L, we might not have sufficient statistical power and wider confidence intervals to detect difference between those with higher hsCRP and those without through binomial regression. The skewness of our data in comparison to normally distributed stroke population likely occured as we are a referral stroke center. Therefore, the data points we gathered are susceptible to referral bias.

Several other studies have also found association between hsCRP and NIHSS. One study included 60 subjects with acute ischemic stroke and found only a moderate correlation coefficient between hsCRP levels and NIHSS (32). In another study, hsCRP was suggested to be crucial in terms of prognostic value in patients with ischemic stroke (33). However, this correlation of hsCRP with increased disability and mortality was modeled in conjunction with other novel inflammatory markers, which are used in research settings (33). Therefore, their model is not fully comparable to our study which lacked these research biomarkers.

Our study has several limitations. Elevated hsCRP levels together with prior history of multiple infarcts has also been shown to increase future risk of strokes and increase risk stratification in a subgroup of the CHANCE cohort (29). Our study did not have follow up data on the subjects, so we could

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Parameter	Odds ratio	Lower 95% CI	Upper 95% CI	*p*-value
Age	0.999	0.986	1.013	0.886
Gender (M)	0.592	0.404	0.863	0.007
Cholesterol (mg/dL)	0.997	0.994	1.001	0.157
Diabetes Mellitus (Yes)	1.126	0.772	1.645	0.537
History of Smoking (Yes)	1.058	0.73	1.535	0.767
History of Stroke (Yes)	2.496	1.555	4.095	< 0.001
Hypertension (Yes)	1.006	0.637	1.583	0.981
hsCRP (1-3 mg/L)	1.876	0.919	3.874	0.086
hsCRP (> 3 mg/L)	1.514	0.816	2.839	0.190

Table 4: Multivariate binomial regression predicting mRS > 3 in subjects with acute ischemic stroke. Multivariate binomial regression predicting mRS > 3 in subjects. mRS > 3 indicates a patient is impaired by neurological disability in activities of daily living. Our analysis did not find any significant predictors of this value in terms of odds ratio. CI = Confidence interval.

Parameter	Odds ratio	Lower 95% CI	Upper 95% CI	*p*-value
Age	1.004	0.991	1.019	0.533
Gender (M)	0.853	0.579	1.261	0.424
Cholesterol (mg/dL)	0.999	0.995	1.003	0.526
Diabetes Mellitus (Yes)	0.986	0.665	1.456	0.945
History of Smoking (Yes)	0.914	0.621	1.344	0.646
History of Stroke (Yes)	0.96	0.593	1.53	0.865
Hypertension (Yes)	1.603	0.982	2.691	0.065
hsCRP (1-3 mg/L)	1.028	0.497	2.169	0.940
hsCRP (> 3 mg/L)	0.99	0.531	1.905	0.976

Table 5: Multivariate binomial regression predicting Barthel Index ≤ 90 in subjects with acute ischemic stroke. Multivariate binomial regression predicting BI ≤ 90 in subjects. BI ≤ 90 indicates a patient is impaired by neurological disability in activities of daily living. Our analysis did not find any significant predictors of this value in terms of odds ratio. CI = Confidence interval.

not do this analysis. hsCRP has also been linked to higher mortality in previous studies, which was not analyzed in our study due to lack of data (34,35). We additionally did not subclassify our subjects according to etiology of their strokes. A previous study has found that higher levels of hsCRP could be associated with not only independent risks of acute ischemic stroke but also more so in cardioembolic and plaque related strokes (15).

The findings of our study are consistent with prior hypotheses that ischemic strokes can be associated with increased pro-inflammatory milieu (29). Inflammatory markers like hsCRP have been studied as a possible biomarker of inflammation that is seen in cardiovascular events and acute ischemic stroke (36). However, we did not identify a statistically significant OR.

Further studies are required to improve our understanding on role of inflammatory markers in diagnoses and severity of acute ischemic strokes and resulting in longer duration of hospital stay. More robust prediction models including non-typical risk factors as well as inflammatory biomarkers could help in further understanding the role of inflammation in acute ischemic stroke. Association of subtypes of ischemic strokes with hsCRP levels will further help to clarify the utility of hsCRP as a biomarker of acute ischemic stroke.

To conclude, patients with higher hsCRP levels in context of acute ischemic stroke may be associated with more significant neurological deficits during their hospital stay (shown by higher NIHSS) and worse performance on measures of daily disability (namely, the mRS and BI) but these alone were not predictive of acute disability in our cohort. Our study did find that higher hsCRP is associated with longer duration of hospital stay. Our findings have clinical utility for continuous monitoring of patient status alongside their lab results and evaluation of their likely future outcomes throughout the recovery process.

METHODS

Deidentified records of 576 patients admitted to the University of Louisville's Stroke Center between the years 2018 to 2022 were reviewed for this study. Whenever a patient with acute ischemic stroke was identified at the hospital, blood samples for hsCRP are collected at the time of diagnosis. Similarly, admission disability scores were calculated in form of NIHSS, mRS, and BI. Besides these factors, demographic data including age, sex, history of stroke, diabetes mellitus, smoking and duration of hospital stay in days were also collected.

The subjects were categorized into cohorts by their serum hsCRP levels with the categories being < 1 mg/L, 1-3 mg/L, and > 3 mg/L, which have been previously stratified as low, intermediate, and high-risk groups (37). NIHSS is a score between 1 and 42 that medical professionals utilize to ascertain the severity of the stroke in terms of neurological deficits. For analysis purposes, NIHSS score was stratified into four categories: minor stroke 1–4; moderate stroke, 5–15, moderate to severe stroke, 16–20; and severe stroke, 21–42 (38). mRS and BI were indicators used to assess the degree of disability in terms of the activity of daily living. mRS varies from 0–6 where 0 meant no disability and 6 referred to death. The BI measures disability level ranging from 100 to 0, where 100 was no apparent disability and a normal capacity to perform everyday tasks. A score of 0 indicated immobility and little to no functional independence.

Statistical analyses were done using the R programming language. ANOVA tests were used to analyze the effect of higher hsCRP levels on NIHSS, mRS and BI. A logistic regression model was fitted using hsCRP as the independent variable while NIHSS, mRS, and BI were used as dependent variables. NIHSS was converted into a bivariate variable with NIHSS < 4 as lower and NIHSS > 4 as higher NIHSS. Similarly, mRS was dichotomized into lower mRS (≤ 3) and higher mRS (> 3). BI was also dichotomized into lower BI (< 90) and higher BI (> 90).

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