Ability of serum C-reactive protein and white blood cell count in predicting acute ischemic stroke: A short-term follow-up study

Abstract

Background: Stroke is one of the leading causes of mortality and long-term morbidity. The aim of the present study was to determine the ability of baseline serum C-reactive protein (CRP) and white blood cell count (WBC) values in predicting the outcome of acute ischemic stroke (AIS).

Methods: This study consisted of patients with first AIS referred to Poursina Hospital, Rasht, Iran. Severity of stroke was determined according to the National Institute of Health (NIH) Stroke Scale at the time of admission. Serum CRP levels and WBC count were measured at the time of admission. All patients were followed-up for 90 days after discharge and the severity of stroke was assessed using modified Rankin Scale (mRS). Receiver operating characteristic curve analysis was used for calculating the most appropriate cutoff point of CRP and WBC count for differentiating patients with and without poor outcome at the end of the study period.

Results: A total of 53 out of 102 (52%) patients had poor outcome. The most appropriate cutoff value for CRP in differentiating patients with and without poor outcome was 8.5 mg/L (sensitivity: 73.1%, specificity: 69.4%) and for WBC, the difference did not reach to a significant level. The cutoff point of CRP > 10.5 mg/ml yielded a predictive ability at sensitivity: 75%, specificity: 63.8% whereas predictive ability of WBC for mortality was at a borderline level.

Conclusion: These findings indicate that high levels of serum CRP in AIS at the time of admission is associated with poor prognosis. However, this study found no ability for WBC in predicting AIS outcome.

Keywords: C reactive protein, White blood cell count, Ischemic Stroke, Prognosis.

Citation:
Bakhshayesh-Eghbali B, Roudbary SA, Basir Jafari S, Ability of serum C-reactive protein and white blood cell count in predicting acute ischemic stroke. A short-term follow-up study. Caspian J Intern Med 2016; 7(3): 206-210.
CRP, the most important inflammatory biomarker may play a role in progression of cerebrovascular pathologies (7, 8). There is conflicting evidence regarding the exact role of CRP as a prognostic biomarker in ischemic stroke outcome (9, 10). Similarly, the white blood cell count (WBC) has been also shown to predict the risk of first-time myocardial infarction and ischemic stroke (11, 12).

It is well known that the prediction of outcome after ischemic stroke is important in clinical settings. However, identification of an independent prognostic marker in patients with stroke is still a matter of controversy. To our knowledge, the data regarding the predicting ability of serum CRP and WBC counts in patients with stroke are scarce. Thus, the aim of the present study was to determine the ability of serum CRP and WBC values assessed at the time of admission in predicting the outcome of acute ischemic stroke.

Methods
Patient selection and data collection: Patients with first-ever acute ischemic stroke who were referred to Poursina Hospital, Rasht, Iran in a one year period (2013-2014) were consecutively recruited in this cross-sectional study. The inclusion criteria were: onset of symptoms less than 24 hours and evidence of ischemic stroke on computed tomography (CT). Patients with history of previous cerebrovascular accidents (CVA), evidence of hemorrhagic stroke in CT, co-existing malignancy, end-stage liver or renal disease, active infectious diseases and use of anti-inflammatory agents were excluded from the study.

Demographic data and clinical findings including ischemic heart disease (self-reported or use of cardiovascular drugs), hypertension (self-reported or use of anti-hypertensive agents), dyslipidemia (self-reported or use of anti-dyslipidemic agents), diabetes (self-reported or use of anti-diabetic agents) were recorded at the time of admission. Severity of stroke was determined by a neurologist using the National Institute of Health Stroke Scale (NIHSS) at the time of admission.

The severity of stroke was categorized into three group based on NIHSS score (0-4 mild, 5-15 moderate and >16 severe). Serum inflammatory markers including WBC and CRP were measured at the admission time. CRP was measured quantitatively using BIONIK kit (Made in Iran, normal range: 4-6 milligram/liter).

Follow-up: All patients were followed-up for 90 days after discharge from the hospital. The severity of stroke was assessed using mRS. Patients with mRS score lower than 4 were considered as patients with good outcome and those with mRS score of 4 and higher as poor outcome patients.

Statistical Analysis: Statistical analysis was done using SPSS Version 16 (IBI cor, Chicago, USA). Kolmogrov-Smirnov test was used for testing normality in quantitative data. Chi-square test and Fisher’s exact test were used for comparison of qualitative data. Multivariate regression logistic analysis was used to determine the predictors of poor outcome after 90 days of onset of stroke. Receiver operative characteristic (ROC) curve analysis was used for calculating the most appropriate cutoff point of CRP and WBC count to differentiate patients with and without poor outcome and mortality after 90 days.

Results
A total of 102 patients were recruited in this study. There were 43 (42.2%) males and 59 (57.8%) females and the mean age of patients was 69.471±12.125 years (range: 36-88). Table 1 shows the baseline characteristics of the patients. After 90 days of admission, 53 (52%) patients had poor outcome and good outcome in 49 (48%) patients.

The cumulative rate of mortality was 32.4% (33/102). Median white blood cell count (8200±420.651 versus 9000±514.740 per micro liter, P=0.047) and CRP level (25±4.004 versus 5±1.837 milligram per liter, P<0.001) were significantly higher in patients with poor outcome compared to those with good outcome, respectively.

Multivariate logistic regression analysis was performed for controlling the potential confounding effect of age, chronic diseases, GCS and NIHSS at admission. CRP but not WBC count remained an independent predictor for poor outcome in patients with acute ischemic stroke (table 2).

The most appropriate cutoff value for CRP in differentiating the two outcome groups was 8.5 mg/L (sensitivity: 73.1%, specificity: 69.4%) and for WBC was 8.25×10³ per micro liter (sensitivity: 61.5%, specificity: 51%). However, the predictive ability of WBC did not reach to a significant level. Serum CRP > 10.5 mg/L predicted mortality at sensitivity of 75%, specificity of 63.8% whereas WBC did exhibit a borderline predictive ability for mortality (figures 1, 2).
Table 1. Baseline characteristics of patients (n=102)

| Variables              | Good outcome (n=49) | Poor outcome (n=53) | Pvalue |
|------------------------|---------------------|---------------------|--------|
| Age                    | 65.388±11.800       | 73.245±11.261       | 0.001  |
| Gender                 |                     |                     |        |
| Male                   | 23 (46.9)           | 20 (37.7)           | 0.347  |
| Female                 | 26 (53.1)           | 33 (62.3)           |        |
| Smoker                 | 12 (24.5)           | 15 (28.3)           | 0.663  |
| Chronic disease        |                     |                     |        |
| Ischemic heart disease | 7 (14.3)            | 20 (37.7)           | 0.007  |
| Diabetes               | 17 (34.7)           | 26 (49.1)           | 0.142  |
| Hypertension           | 32 (65.3)           | 44 (83)             | 0.040  |
| Dyslipidemia           | 17 (34.7)           | 28 (52.8)           | 0.065  |
| GCS at admission       |                     |                     |        |
| 15                     | 46 (93.9)           | 29 (54.7)           | <0.001 |
| 10-14                  | 2 (4.1)             | 11 (20.8)           |        |
| <10                    | 1 (2)               | 13 (24.5)           |        |
| NIHSS at admission     |                     |                     |        |
| Mild                   | 31 (63.3)           | 16 (30.2)           | 0.003  |
| Moderate               | 5 (10.2)            | 13 (24.5)           |        |
| Severe                 | 13 (26.5)           | 24 (45.3)           |        |
| CRP                    | 9.95±12.85          | 35.90±28.85         | <0.001 |

GCS, Glasgow Coma Score. National Institute of Health Stroke Scale (NIHSS). CRP, C reactive protein

Table 2. Predictors for poor outcome in multiple logistic regression analysis (adjusted for chronic diseases)

| Variable              | Adjusted odd's ratio |
|-----------------------|----------------------|
| WBC count at admission| 1.043 (0.872-1.247)  |
| CRP                   | 1.041 (1.011-1.071)  |
| Age                   | 1.056 (1.009-1.106)  |
| GCS<15 at admission   | 8.007 (1.796-35.704) |
| NIHSS at admission    |                      |
| Mild                  | reference            |
| Moderate              | 2.356 (0.739-7.516)  |
| Severe                | 4.553 (1.074-19.298) |

Discussion

According to the findings of the current study, higher CRP levels not WBC on admission in acute ischemic stroke patients are associated with poor outcome. Ischemic brain injury begins a complex cascade which resulted in a systemic inflammatory response after both ischemic and hemorrhagic stroke (13). Different cytokines are involved in various aspects of stroke (14). Several studies have reported...
that higher levels of inflammatory markers such as CRP are associated with worse outcome after ischemic stroke (3, 15-16). According to pathophysiologic mechanisms of stroke, these findings may indicate different patterns of immune-inflammatory activation (17). For example, a recent study has indicated that CRP levels can predict the risk of recurrent strokes among lacunar stroke patients (18). It was documented that CRP level has a moderate prognostic factor to identify carotid stenosis (19). The results of this study are in agreement with previous studies (20-22) who demonstrated increased levels of serum CRP at admission was associated with worse outcome in patients with acute ischemic stroke. There are data that suggest immune response following stroke occurs in a time-dependent period with the fact that the innate immune response occurring in the first 24 hours following ischemic injury and theorized that the CRP is not sensitive enough for predicting beyond 24 hours and thus may not represent inflammatory status (23). Results from a population-based cohort in prediction of a 90-day subacute recurrent stroke revealed a weak significant association for C-reactive protein (24). We also report the appropriate cutoff of CRP for adverse consequences of stroke including poor outcome and mortality. There are limited studies calculating the appropriate cutoff of based on ROC curve analysis. Ghabae et al. for the first time reported the cutoff of CRP value of 2.2 mg/l as the optimal cutoff value for the prediction of mortality within 7 days (sensitivity: 0.81, specificity: 0.80) (25). While in another similar study, CRP cutoff of 1.5 mg/dl was determined as the optimum sensitivity and specificity for adverse clinical outcome (26). Our study revealed higher amount of CRP as an appropriate cutoff point with an acceptable sensitivity and specificity. The difference between our measures and previous studies may be attributed to longer follow-up duration (e.g. 90 days). On the other hand, there are conflicting ideas against considering CRP as prognostic biomarker for ischemic stroke outcome. Because a large body of literatures are based on the studies conducting the relationship between CRP and ischemic stroke outcome by determination of mortality as an outcome measure. It is well-known that there are moderate to severe functional impairments in more than 50 percent of stroke patients (23). Therefore we tried to utilize the NIHSS score beside the mortality outcome. Another factor that is suggested as a prognostic marker for outcome among patients with myocardial infarction and ischemic stroke is WBC count. Increasing the number of leukocytes could be a predisposing factor in high risk patients for ischemic stroke (27-28). The findings of the present study regarding predicting ability of WBC are in contrast with the study by Sahan et al. (29). Nerdi et al. have investigated the association of elevated WBC count at early stage (72 hours) of cerebral ischemia and found it a significant independent predictor of poor clinical outcome, and discharge disability (30). Although blood biomarkers may provide valuable information regarding prediction of outcome in acute ischemic stroke but the ability of other acute phase reactant are different and this issue requires further prospective studies. In conclusion this study indicates that high serum CRP at the time of admission of acute stroke is predictive of poor outcome and serum levels greater than 10.5 mg/dl is predictive of mortality.

Acknowledgments
We would like to thank all the individuals who in one way or another helped in the realization of this study.

Funding: This study is a medical thesis of Seddigheh Basir Jafari funded by the Vice-Chancellorry for Research of Guilan University of Medical Sciences.

Conflict of Interest: Authors declared no conflict of interest.

References
1. Rothstein L, Jickling GC. Ischemic stroke biomarkers in blood. Biomark Med 2013; 7: 37-47.
2. Krishnamurthi RV, Feigin VL, Forouzanfar MH, et al. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet Glob Health 2013; 1: e259-81.
3. Kara H, Akinci M, Degirmenci S, et al. High-sensitivity C-reactive protein, lipoprotein-related phospholipase A2, and acute ischemic stroke. Neuropsychiatr Dis Treat 2014; 10: 1451-7.
4. Vila N, Castillo J, Davalos A, Chamorro A. Proinflammatory cytokines and early neurological worsening in ischemic stroke. Stroke 2000; 31: 2325-9.
5. Serpero LD, Bellissima V, Colivicchi M, et al. Next generation biomarkers for brain injury. J Matern Fetal Neonatal Med 2013; 26: 44-9.
6. Moreno VP, Subira D, Meseguer E, Llamas P. IL-6 as a biomarker of ischemic cerebrovascular disease. Biomark Med 2008; 2: 125-36.
7. Curb JD, Abbott RD, Rodriguez BL, et al. C-reactive protein and the future risk of thromboembolic stroke in healthy men. Circulation 2003; 107: 2016-20.
8. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Plasma concentration of C-reactive protein and risk of developing peripheral vascular disease. Circulation 1998; 97: 425-8.
9. Wilson PW, Nam BH, Pencina M, et al. C-reactive protein level is not an independent predictor of future risk of thromboembolic stroke in patients with ischemic stroke. Cerebrovasc Dis 2018; 45: 707-15.

10. Bos MJ, Schipper CM, Koudstaal PJ, et al. High serum C-reactive protein level is not an independent predictor for stroke: the Rotterdam Study. Circulation 2006; 114: 1591-8.
11. Ernst E, Hammerschmidt DE, Bagge U, Matrai A, Dormandy JA. Leukocytes and the risk of ischemic diseases. JAMA 1987; 257: 2318-24.
12. Koren-Morag N, Tanne D, Goldbourt U. White blood cell count and the incidence of ischemic stroke in coronary heart disease patients. Am J Med 2005; 118: 1004-9.
13. Tuttolomondo A, Di Raimondo D, Pecoraro R, et al. Inflammation in ischemic stroke subtypes. Curr Pharm Des 2012; 18: 4289-310.
14. Tuttolomondo A, Di Raimondo D, Di Sciacca R, Pinto A, Licata G. Inflammatory cytokines in acute ischemic stroke. Curr Pharm Des 2008; 14: 3574-89.
15. Liu Y, Wang J, Zhang L, et al. Relationship between C-reactive protein and stroke: a large prospective community based study. PLoS One 2014; 9: e107017.
16. Ormstad H, Aass HC, Lund-Sorensen N, Amthor KF, Sandvik L. Serum levels of cytokines and C-reactive protein in acute ischemic stroke patients, and their relationship to stroke lateralization, type, and infarct volume. J Neurol 2011; 258: 677-85.
17. Oto J, Suzue A, Inui D, et al. Plasma proinflammatory and anti-inflammatory cytokine and catecholamine concentrations as predictors of neurological outcome in acute stroke patients. J Anesth 2008; 22: 207-12.
18. Elkind MS, Luna JM, McClure LA, et al. C-reactive protein as a prognostic marker after lacunar stroke: levels of inflammatory markers in the treatment of stroke study. Stroke 2014; 45: 707-16.
19. Mullenix PS, Steele SR, Martin MJ, Starnes BW, Andersen CA. C-reactive protein level and traditional vascular risk factors in the prediction of carotid stenosis. Arch Surg 2007; 142: 1066-71.
20. Welsh P, Barber M, Langhorne P, et al. Associations of inflammatory and haemostatic biomarkers with poor outcome in acute ischaemic stroke. Cerebrovasc Dis 2009; 27: 247-53.
21. Abubakar SA, Okubadejo NU, Ojo OO, et al. Relationship between admission serum C-reactive protein and short term outcome following acute ischaemic stroke at a tertiary health institution in Nigeria. Niger J Clin Pract 2013; 16: 320-4.
22. Di Napoli M, Schwaninger M, Cappelli R, et al. Evaluation of C-reactive protein measurement for assessing the risk and prognosis in ischemic stroke: a statement for health care professionals from the CRP Pooling Project members. Stroke 2005; 36: 1316-29.
23. VanGilder RL, Davidov DM, Stonehart KR, et al. C-reactive protein and long-term ischemic stroke prognosis. J Clin Neurosci 2014; 21: 547-53.
24. Segal HC, Burgess AI, Poole DL, et al. Population-based study of blood biomarkers in prediction of subacute recurrent stroke. Stroke 2014; 45: 2912-7.
25. Ghabae M, Zandieh A, Mohebbi S, et al. Predictive ability of C-reactive protein for early mortality after ischemic stroke: comparison with NIHSS score. Acta Neurol Belg 2014; 114: 41-5.
26. Di Napoli M, Papa F, Boccola V. C-reactive protein in ischemic stroke: an independent prognostic factor. Stroke 2001; 32: 917-24.
27. Grau AJ, Boddy AW, Dukovic DA, et al. Leukocyte count as an independent predictor of recurrent ischemic events. Stroke 2004; 35: 1147-52.
28. Elkind MS, Sciacca RR, Boden-Albala B, et al. Relative elevation in baseline leukocyte count predicts first cerebral infarction. Neurology 2005; 64: 2121-5.
29. Sahan M, Sebe A, Acikalin A, et al. Acute-phase reactants and cytokines in ischemic stroke: do they have any relationship with short-term mortality? Eur Rev Med Pharmacol Sci 2013; 17: 2773-7.
30. Nardi K, Milia P, Eusebi P, et al. Admission leukocytosis in acute cerebral ischemia: influence on early outcome. J Stroke Cerebrovasc Dis 2012; 21: 819-24.