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DOI:
10.1111/jnc.13973

Document Version
Accepted author manuscript

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Received Date : 29-Nov-2016

Revised Date : 26-Jan-2017

Accepted Date : 31-Jan-2017

Article type : Original Article

C-REACTIVE PROTEIN IN THE DETECTION OF POST-STROKE INFECTIONS: SYSTEMATIC REVIEW AND INDIVIDUAL PARTICIPANT DATA ANALYSIS

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Running title: CRP for post-stroke infections

Keywords: Stroke; Infections; Systematic Review; Individual Participant Data Meta-analysis; Biomarkers; C-reactive protein.

Abbreviations: AUC: area under the curve; CDC Centers for Disease Control and Prevention; CRP: C-reactive protein; IDI: integrated discrimination improvement; IL: interleukin; IPD: individual participant data; IQR: interquartile range; NIHSS: National Institutes of health Stroke Scale; OCSP: Oxfordshire Classification Stroke Project; OR: odds ratio; PISCES: Pneumonia in Stroke Consensus; ROC: receiver operating characteristic; RTI: respiratory tract infection; TOAST: Trial of Org in Acute Stroke Treatment.

ABSTRACT

We conducted a systematic review and individual participant data meta-analysis to explore the role of C-reactive protein (CRP) in early detection or prediction of post-stroke infections. CRP, an acute-phase reactant binds to the phosphocholine expressed on the surface of dead or dying cells and some bacteria, thereby activating complement and promoting phagocytosis by macrophages. We searched PubMed up to May-2015 for studies measuring CRP in stroke and evaluating post-stroke infections. Individual participants' data were merged into a single database. CRP levels were standardized and divided into quartiles. Factors independently associated with post-stroke infections were determined by logistic regression analysis and the additional predictive value of CRP was assessed by comparing areas under ROC curves and integrated discrimination improvement index (IDI). Data from seven studies including 699 patients were obtained. Standardized CRP levels were higher in patients with post-stroke infections beyond 24 hours. Standardized CRP levels in the fourth quartile were independently associated with infection in two different logistic regression

models, model 1 [stroke severity and dysphagia, OR=9.70(3.10-30.41)] and model 2 [age, sex and stroke severity, OR=3.21(1.93-5.32)]. Addition of CRP improved discrimination in both models [IDI=9.83% (0.89-18.77) and 5.31% (2.83-7.79), respectively], but accuracy was only improved for model 1 (AUC 0.806 to 0.874, p=0.036). In this study, CRP was independently associated with development of post-stroke infections, with the optimal time-window for measurement at 24-48 hours. However, its additional predictive value is moderate over clinical information. Combination with other biomarkers in a panel seems a promising strategy for future studies.

INTRODUCTION

Stroke represents the fifth greatest cause of death and one of the main causes of disability worldwide (Mozaffarian D. et al, 2016). Post-stroke infections have a major effect on stroke outcome, accounting for one third of all deaths and increasing the likelihood of being discharged with requirements for extended care (Westendorp WF. et al, 2011; Heuschmann PU. et al, 2004). Infections after stroke arise from higher microbial exposure derived from patients' immobility, use of medical devices (e.g. urinary catheters) or aspiration associated with dysphagia. Further, immunosuppression is noted after central nervous system insults, and consists mainly of down-regulation of the cellular immune response, manifested by functional deactivation of monocytes, T helper and natural killer T cells (Klehmet J. et al, 2009; Wong CH. et al, 2011).

Two recent clinical trials have failed to demonstrate the benefit of preventive antibiotics in terms of better outcomes, despite reducing post-stroke infections but not pneumonia (Westendorp WF. et al, 2015; Kalra L. et al, 2015). Therefore, improved selection of patients at the highest risk for post-stroke infections is a crucial factor for future trials, by combining clinical variables (Hoffmann S. et al, 2012; Smith CJ. et al, 2015-1) and biological information, such as blood biomarkers of inflammation or immunity. However, a recent review has concluded that there is only limited evidence for a diagnostic or predictive role of blood biomarkers in stroke-associated pneumonia (Smith CJ. et al, 2015-2)

C-reactive protein (CRP) is a widely available biomarker, used in clinical practice as an acute-phase marker. CRP binds to the phosphocholine expressed on the surface of dead or dying cells and some bacteria, thereby activating complement and promoting phagocytosis by macrophages (Pepys MB. et al, 2003). In stroke, CRP elevations have been related to poor functional outcome and mortality (Montaner J. et al, 2006) and also to the occurrence of post-stroke infections (Molnar T. et al, 2010; Worthmann H. et al, 2015). In this study, we aimed to assess whether CRP levels are associated with

an increased risk of post-stroke infections by undertaking a systematic review and individual participant data (IPD) meta-analysis. Secondary aims were to explore the optimal time-window to measure CRP and to evaluate the additional predictive value of CRP over clinical factors associated with infection.

METHODS

The protocol for the systematic review and IPD meta-analysis was previously registered and published in the PROSPERO database (CRD42015023991), and we followed the PRISMA guidelines recommendations for the manuscript preparation.

SEARCH

We searched PubMed up to May 2015 for studies measuring CRP in acute ischemic stroke and assessing post-stroke infections. The list of search terms is available as a supplementary file (supplementary file 1). The search was performed independently by three authors (AB, AV-B, JS-P). Duplicated publications based in the same cohort studies were considered only once. Additional references were searched in the website www.stroke-biomarkers.com and in the reference list from the identified articles.

Inclusion criteria were ischemic stroke diagnosis, measurement of blood CRP levels within the first week after stroke, and assessment of post-stroke infections during the first week of hospitalization. Exclusion criteria were unknown languages, experimental studies with animal models or cell cultures, reviews or abstracts from congresses/conferences, letters, editorials, case reports; studies including just hemorrhagic stroke or transient ischemic attacks; post-stroke infections not recorded; interventional studies or clinical trials.

DATA EXTRACTION AND QUALITY ASSESSMENT

Three different authors (AV-B, SG, JS-P) independently performed data extraction and quality assessment. The quality of the articles was assessed using a 15-point questionnaire for the evaluation of biomarker studies in stroke (García-Berrocoso T. et al, 2013). All articles fulfilling inclusion criteria were included in further analyses, independently of the quality score. Corresponding authors were contacted and asked to complete a pre-defined database (supplementary file 2). Infection was recorded according to the definition used in each published study. Only infections diagnosed within the first week after admission, and not clinically apparent or treated at admission, were considered as post-stroke infections.

STATISTICAL ANALYSIS

All analyses were performed with SPSS v.22 unless stated otherwise.

Data obtained from each study were merged into a single database. As different assay methods were used and differences in CRP levels were present between cohorts (supplementary file 3), CRP values were standardized calculating the Z-score value for each independent cohort, by subtracting the mean and dividing by the standard deviation. As standardized CRP values were not normally distributed (Kolmogorov–Smirnov test), Mann-Whitney U and Kruskal-Wallis tests were applied and data were reported as median and interquartile range (IQR). For multiple comparisons, Bonferroni correction was applied. Pearson Chi-squared test assessed differences among categorical variables. Differences in temporal profiles were assessed with Friedman's test. Post hoc analysis with Wilcoxon signed-rank tests was performed with Bonferroni correction.

Predictive models for post-stroke infections were developed using logistic regression analysis by the forward-stepwise method, including all baseline variables associated with infections in univariate analysis. Standardized CRP levels were analyzed as a dichotomous variable, above and below the 4^{th} quartile. This quartile was chosen for being close to the cut-off with the highest accuracy to predict post-stroke infection. In addition, the predictive value of CRP as a continuous variable, as well as the variation of CRP levels between baseline and 24-48 hours, were explored. Comparisons of areas under the receiver operating characteristic (ROC) curves (AUC) from models, with or without CRP, were performed using DeLong's method with MedCalc software (version 12.4; MedCalc Software, Ostend, Belgium) (DeLong ER. et al, 1988). Integrated discrimination improvement (IDI) index was calculated using R software v.2.15.0 (R Development Core Team 2012; Vienna, Austria; Hmisc and PredictABEL packages). Briefly, the IDI index provides a numerical value for the difference between predictive probabilities from the models with and without the biomarkers (Pencina MJ. et al, 2010).

Where time from stroke onset to infection was available, a subanalysis was performed after excluding patients with early infection, defined as infection diagnosed before the time of CRP determination. CRP levels were compared between those patients with or without further development of infection. To search for factors independently associated with infection in this subgroup, Cox regression analysis was performed including baseline variables associated with infections in univariate analysis and standardized CRP levels above the 4^{th} quartile.

Finally, the same analyses were performed pooling data from the studies that recorded respiratory tract infections (RTI)

RESULTS

SEARCH

The initial PubMed search identified a total of 1,497 studies, and additional search on the website www.stroke-biomarkers.com identified one more potential study. 12 potential studies were identified after applying the full eligibility criteria (Figure 1). Corresponding authors were contacted, and two studies based on the same cohort were removed. Three other authors did not reply or were not able to provide the data. Finally, we collated data from seven studies including 699 patients (Molnar T. et al, 2010; Worthmann H. et al, 2015; Emsley HC. et al, 2003; Waje-Andreassen U. et al, 2005; Topakian R. et al, 2008; Hug A. et al, 2011; Fluri F. et al, 2012). All studies but one (Emsley HC. et al, 2003) excluded patients with preexisting infections. Two patients with pre-stroke infections were excluded from further analyses, giving a final sample size of 697 patients. Characteristics of the included studies and the merged cohort are described in Table 1.

QUALITY ASSESSMENT

Quality of the included articles was moderate [9(8-9) points], ranging from 7 to 10 (supplementary file 4). Most frequently missing points were reporting of blinding (not reported in any study for clinical data collection, or for biomarker measurement), sample size calculation (not reported by any study), and use of previously established cut-offs for the biomarker (just one study).

KINETICS OF CRP AND INFECTION ANALYSIS

All studies performed a first CRP measurement within the first 24 hours after stroke. CRP was also measured in five studies (N=506) between 24-48 hours and in another five (N=447) between 48-72 hours. As median time to infection was 3 days, no further time-windows were explored. The whole temporal profile over the 3 time-points could be explored in just three studies (N=387), showing a rising pattern of CRP concentration (Figure 2A). Median standardized CRP values were higher in patients with post-stroke infections between 24-48 and 48-72 hours, but there were no differences within the first 24 hours (Figure 2B).

LOGISTIC REGRESSION AND ADDITIONAL PREDICTIVE VALUE ANALYSES

Given that no differences were observed with respect to standardized median CRP-values within the first 24 hours and median time to infection was 3 days, the 24-48 hours time-window was chosen to perform further analyses. The univariate analysis for infections is shown in Table 2. Logistic regression analysis included at the first step age, sex, diabetes, atrial fibrillation, NIHSS, dysphagia and stroke etiology (TOAST) as covariates. The best predictive model for infection comprised

baseline stroke severity (National institutes of Health Stroke Scale, NIHSS) and dysphagia (model 1). However, dysphagia status was not evaluated in all studies, and the global sample size of the model was small (116 patients). Therefore, a second predictive model was developed by adjusting for age, sex and baseline NIHSS (model 2). In both models, standardized CRP at 24-48 hours above the 4th quartile was independently associated with infection (OR= 9.70 (3.10-30.41) and 3.21 (1.93-5.32) for models 1 and 2, respectively, both p<0.0001). The addition of CRP improved the discrimination of infection status in both models (IDI=9.83% (0.89-18.77) and 5.31% (2.83-7.79) for models 1 and 2, respectively, both p<0.05). Accuracy was also improved for model 1 (AUC from 0.806 to 0.874, p=0.036) but not for model 2 (AUC from 0.781 to 0.799, p=0.197). Figure 3 and supplementary file 5 show the results of the logistic regression analysis and the additional predictive value. The results were similar when additional analyses were performed, considering standardized CRP as a continuous variable, as well as using the variation of CRP levels from the first determination to 24-48h (data not shown).

SUBANALYSIS AFTER EXCLUSION OF PATIENTS WITH EARLY INFECTION

Time from stroke onset to infection was available in five studies (N=536, 113 infections). CRP remained higher between 24-48 and 48-72 hours in patients who developed further infections, after exclusion of patients with early infection at both time-windows (26 and 38 patients for each time-window, respectively). CRP values in patients with early infections were higher than in patients who developed infections later. However, given the small number of patients with early infections, these differences were not statistically significant. Cox regression models were performed in the subgroup of patients with known time from stroke onset to infection, after removal of patients with early infection at 48 hours. CRP measured at 24-48h was independently associated with infection (HR=2.97 (1.90-4.66), p<0.0001). This subanalysis is detailed in the supplemental data (supplementary file 6).

SUBANALYSIS FOR RESPIRATORY TRACT INFECTIONS (RTI)

RTI were reported in five studies (N=537, 57 RTI). No uniform criteria for diagnosis were applied and just one study used validated criteria for RTI diagnosis. Subanalysis in this cohort revealed that 24-48h standardized CRP was independently associated with RTI (OR=9.09 (1.58-52.49), p=0.014 and 5.99 (2.76-13.01), p<0.0001 for models 1 and 2, respectively). The evaluation of the additional predictive value over clinical models was similar to the whole cohort. This subanalysis is detailed in the supplemental data (supplementary file 7).

DISCUSSION

In the present study, we attempted to address the question of whether CRP could be used in clinical practice for early detection or prediction of post-stroke infections. To investigate the role of CRP levels, a widely available biomarker with good reproducibility and low cost (Pierrakos C. et al, 2010), we conducted this systematic review and IPD meta-analysis, in order to increase sample size and hereby statistical power.

It has been suggested that about a half of the cases of stroke-associated pneumonia occur within the first 48 hours after stroke onset (Finlayson O. et al, 2011). In this study, just 26 cases were diagnosed in this time-window from 113 cases of infection in which time of diagnosis was known (32%), and median time of infection diagnosis was 3 (2-6) days after stroke onset. Given these results, and the fact that we found no differences in median CRP levels measured in the first 24 hours between patients developing or not infections during the first week, the 24-48 hours time-window seems optimal to start CRP measurement in clinical practice. However, considering the rising temporal profile of CRP and given that the differences are even more pronounced with increasing time from onset, it seems that the association improves over time. In this sense, serial measurements might be the most beneficial approach in clinical practice.

Previous studies of CRP and post-stroke infections have described CRP as independently associated with pneumonia, together with age, NIHSS score and interleukin-6 (IL-6) in diabetic stroke patients (Zhang X. et al, 2012). Moreover, when combined with white blood cell count and copeptin, it has shown a high accuracy in the prediction of infection (Fluri F. et al, 2012). However, to our knowledge, whether CRP levels provide additional predictive value over clinical variables alone has not been reported so far. In our study the additional predictive value of CRP for the identification and prediction of infections when compared with clinical variables was only moderate, and not significant in some subanalyses. This fact limits the clinical use of CRP as a single biomarker for the selection of patients at high-risk of developing infection. The inflammatory response that stroke triggers conditions an elevation of systemic inflammatory markers such as CRP (Pepys MB. et al, 2003), but also contributes to the immunosuppressive state that facilitates the development of post-stroke infections (Bustamante A. et al, 2016). Therefore, it seems unlikely that a single biomarker from this cascade could be specifically associated with infections in the setting of acute cerebral ischemia. An alternative approach including other biomarkers reflecting different pathways of the inflammatory and immune response after stroke and the infection itself, such as IL-6 (Bustamante A. et al, 2014), procalcitonin (Xie J. et al, 2011) or mHLA-DR (Hoffmann S. et al, 2016) in a panel might be of interest.

A large sample size, serial measures in most studies, and sub-group analyses according to the time of infection are the main strengths of the present study. Our results point to a rising pattern of CRP concentration starting before the infection is clinically manifest, implying perhaps an intermediate subclinical state where the infection is present but without symptoms. In fact, it has previously been proposed that early elevations of CRP are more related to stroke severity, whilst later elevations are related to post-stroke infections (Molnar T. et al, 2010). In this sense, CRP measurement may not just aid in the diagnosis of suspected stroke-associated infections, but even in selecting high risk patients before clinical diagnosis of infection. Whether prophylactic measures in these patients could avoid the development of a clinically manifested infection would need a prospective study.

The present study was designed for analysis of all infections. With respect to RTI, such a sub-group analysis loses sample size and power. The association of CRP with RTI was similar to the association with infections in the overall cohort, in that CRP was also independently associated also with respiratory tract infections, but lacked additional predictive value. These results should be carefully interpreted, as in addition to a smaller sample size, there was substantial variability in the definition of respiratory tract infection, with only a single study using published societal criteria (Fluri F. et al, 2012) and just one other using predefined diagnostic criteria (Hug A. et al, 2011).

However, our study also has some limitations, most of which relate to the characteristics of the included studies, which contributed to significant heterogeneity in two of the critical factors of the present meta-analysis. First, the methods for determining CRP were quite different across the studies, which required further standardization of the results. Moreover, variable time-point for CRP measurements required us to create wide 24 hour windows to explore serial profiles. Second, and perhaps most important, the absence of a uniform definition of infection reflects the need for standardization of these critical issues for future research. For such future studies, the recommendations of the Pneumonia in Stroke Consensus (PISCES) Group, based on modified CDC (Centers for Disease Control and Prevention) criteria (Smith CJ. et al, 2015-2), could be applied.

In conclusion, this IPD meta-analysis shows that CRP is associated with post-stroke infections, with optimal measurement between 24-48 hours after stroke. A subclinical state in which infection is present but not manifest clinically could explain these results. Serial CRP measurements appear to be the most accurate approach. With respect to effect size, the additional predictive value of CRP was moderate over clinical information alone. These conclusions, however, are limited by the marked heterogeneity of the pooled studies. Evaluation in well-designed prospective studies using standardized methodology, including aligned methodologies for bioassays, sampling time-points and

definition of infection, is needed. Combination of CRP with other biomarkers in a panel also seems a promising strategy for future prospective studies.

Involves human subjects: No
If yes: Informed consent & ethics approval achieved:
=> if yes, please ensure that the info "Informed consent was achieved for all subjects, and the experiments were approved by the local ethics committee." is included in the Methods.

ARRIVE guidelines have been followed:
No
=> if No, skip complete sentence
=> if Yes, insert "All experiments were conducted in compliance with the ARRIVE guidelines."

Conflicts of interest: None
=> if 'none', insert "The authors have no conflict of interest to declare."
=> otherwise insert info unless it is already included

ACKNOWLEDGEMENTS

Neurovascular Research Laboratory takes part in the Spanish stroke research network INVICTUS (RD12/0014/0005).

COMPETING INTERESTS

All authors declare no competing interests.

FUNDING

Neurovascular Research Laboratory is supported on stroke biomarkers research by FIS PI15/354, co-financed by the European Regional Development Fund, (FEDER). A.B. is supported by a Rio Hortega contract CM/00265 from the Instituto de Salud Carlos III.

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FIGURE LEGENDS

FIGURE 1. FLOW CHART

FIGURE 2. CRP TEMPORAL PROFILE

As the three time-points of CRP measurement were not available for every patient, the graphs include only those patients with all 3 determinations (N=387, three studies). Extreme values were removed from the graph but not from the statistical analysis. 2A: boxplots represent standardized CRP values in the merged cohort at the three different time-windows. 2B: light boxplots represent standardized CRP values in the merged cohort at the three time-windows in patients who did not develop any infection during the first seven days after stroke, while dark boxplots represent CRP standardized values in patients who developed infections.

FIGURE 3. EVALUATION OF THE ADDITIONAL PREDICTIVE VALUE OF CRP (MEASURED AT 24-48H) OVER CLINICAL MODELS

The figure represents the comparison between predictive models with and without standardized CRP, dichotomized as above and under the 4th quartile. A and B represent the comparison of the predictive accuracy (area under the ROC curve). The continuous line represents the predictive model constructed just with clinical variables [dysphagia and admission NIHSS for model 1 (A) and age, sex and admission NIHSS for model 2 (B)]. The discontinuous line represents each predictive model constructed with the addition of CRP. C and D represent the integrated discrimination improvement (IDI) index: the bars represent the same models as in A and B (light bars, clinical model and dark bars, the same clinical model plus CRP). The predictive probabilities of infection and no infection for each model are expressed as percentages. The IDI values [9.83% (0.89-18.77), p=0.031 for model 1 and 5.31% (2.83-7.79) p<0.0001 for model 2] result from the sum of the differences in predictive probabilities for infection and no infection.

TABLES

TABLE 1. BASELINE CHARACTERISTICS OF EACH STUDY AND THE MERGED COHORT OF THE INDIVIDUAL PARTICIPANT DATA ANALYSIS

	Emsley, 2003	Waje-Andreassen, 2005	Topakian, 2008	Molnar, 2010	Hug, 2011	Fluri, 2012	Worthmann, 2015	All
Sample size	37	11	111	49	50	385	56	697
Blood collection time/s	<24h 24-48h	<24h 24-48h 48-72h	<24h	<24h 24-48h 48-72h	<24h 48-72h	<24h 24-48h 48-72h	<24h 24-48h 48-72h	<24h 24-48h 48-72h
Serum/Plasma	Plasma	Serum	Serum	Serum	Serum	Serum	Serum	-
CRP vs. hsCRP	CRP	hsCRP(<10mg/mL) CRP(>10mg/mL)	CRP	hsCRP	CRP	CRP	hsCRP(<40mg/L) CRP(>40mg/L)	-
Assay	ELISA	ELISA	Immunoturbidimetric	Immunoassay	Standard laboratory assays	Immunoturbidimetric	Nephelometric	-
Age	69 (60-77)	75 (64.5-77.5)	70 (63-78)	68.5 (61.5-77.5)	74 (64-80)	75 (63-81)	74 (62-81)	73 (63-80)
Sex (% female)	35.1%	45.5%	51.4%	49%	68%	42.1%	53.6%	46.5%
Hypertension	64.9%	36.4%	74.8%	72.1%	74%	80%	69.6%	75.8%
Diabetes mellitus	8.1%	0%	19.8%	18.6%	18%	19.2%	28.6%	19.1%
Dyslipidemia	54.1%	36.4%	28.8%	17%	16%	29.2%	35.7%	29.1%
Atrial fibrillation	21.6%	18.2%	31.5%	23.3%	32%	19.3%	30.4%	23.5%
Pre-stroke disability	13.5%	0%	-	-	0%	-	0%	3.3%
Admission NIHSS	13 (10-18)	9 (4.5-19.5)	14 (9-18)	10 (5.5-16.5)	13 (7-17)	5 (2-19)	6.5 (2-16)	8 (4-15)
TOAST LAA	21.6%	0%	-	-	14.6%	16.6%	21.8%	17.0%
CE	21.3%	54.5%	-	-	52.1%	26.8%	36.4%	30.1%
SVO	16.2%	9.1%	-	-	6.3%	19.2%	16.4%	16.9%
SUC	37.8%	36.4%	-	-	27.1%	33.2%	25.5%	30.3%
SOC	2.7%	0%	-	-	0%	4.2%	0%	5.6%
Dysphagia	-	45.5%	-	20.9%	61.2%	-	33.9%	39.6%
Previous infections	5.4%	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded	Excluded
Infection rate	32.4%	45.5%	25.2%	22.4%	50%	17.4%	35.7%	24.1%
Time to infection	4 (1.5-8)	3 (2-4)	-	4 (3.5-5)	-	3 (2-7)	3 (1-3)	3 (2-6)

diagnosis								
RTI rate	18.9%	18.2%	-	-	36%	5.5%	16.1%	10.6%
Time to RTI diagnosis	2 (1-7)	2.5 (2-3)	-	-	-	2.5 (1.5-3)	3 (3-3)	3 (1-3)
RTI diagnostic criteria	Clinical assessment	Not specified	-	-	Self-based criteria	CDC Criteria	Clinical Assessment	-

CRP: C-reactive protein; hsCRP: ultrasensitive C-reactive protein; NIHSS: National Institutes of Health Stroke Scale; TOAST: Trial of Org 10172 in Acute Stroke Treatment classification; LAA: large-artery atherosclerosis; CE: cardioembolic; SVO: small vessel occlusion; SUC: stroke of undetermined cause; SOC: stroke of other cause; RTI: respiratory tract infections; CDC: center for disease classification criteria.

TABLE 2. UNIVARIATE ANALYSIS FOR INFECTIONS

		ALL (N=697)	INFECTION (N=168)	NO INFECTION (N=529)	P value
Age		73 (63-80)	77 (68-83)	71 (60-79)	<0.0001**
Sex (Female)		46.5%	54.8%	43.9%	0.014**
Hypertension		75.8%	81.4%	73.9%	0.050*
Diabetes mellitus		19.1%	21.6%	18.3%	0.354
Dyslipidemia		29.1%	24.8%	30.5%	0.175
Atrial fibrillation		23.5%	46.7%	15.7%	<0.0001**
Previous disability		3.3%	1.6%	4.4%	0.649
NIHSS score		8 (4-15)	14 (9-18.5)	6 (3-12)	<0.0001**
Dysphagia		39.6%	75%	18.2%	<0.0001**
TOAST	**LAA**	17.0%	15.6%	17.5%	<0.0001**
	CE	30.1%	48.4%	24.4%	
	SVO	16.9%	7.8%	19.7%	
	SUC	30.3%	22.7%	32.8%	
	SOC	5.6%	5.5%	5.7%	
CRP<24h		1.63 (1.63-1.80)	1.65 (1.57-1.93)	1.63 (1.63-1.74)	0.222
CRP 24-48h		1.67 (1.63-1.93)	1.94 (1.67-2.49)	1.64 (1.63-1.80)	<0.0001**
CRP 48-72h		1.72 (1.63-2.19)	2.44 (1.90-3.72)	1.65 (1.63-1.86)	<0.0001**
ISAN Score (over 22)		8.5 (5-12)	11 (8-14)	7 (4-9)	<0.0001**
A2DS2 Score (over 10)		5 (3-7)	7 (5-8.5)	4 (1-5)	<0.0001**

*NIHSS: National Institutes of Health Stroke Scale; TOAST: Trial of Org 10172 in Acute Stroke Treatment classification; LAA: large-artery atherosclerosis; CE: cardioembolic; SVO: small vessel occlusion; SUC: stroke of undetermined cause; SOC: stroke of other cause; CRP: standardized levels of C-reactive protein; ISAN: pre-stroke Independence (modified Rankin scale), Sex, Age, National Institutes of Health Stroke Scale; A2DS2: Age, Atrial fibrillation, Dysphagia, male Sex, stroke Severity (National Institutes of Health Stroke Scale).*denotes p<0.1; **p<0.05*