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ORIGINAL COMMUNICATION

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Prognostic value of admission C-reactive protein in stroke patients undergoing IV thrombolysis

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Abstract *Objective* To test the hypothesis that pre-treatment C-reactive protein (CRP) predicts outcome in stroke patients undergoing intravenous thrombolysis (IVT) treatment. *Methods* We analyzed the data of 111 consecutive patients with IVT within 6 hours of stroke onset for stroke involving the middle cerebral artery territory and admission CRP ≤6 mg/dl. *Results* CRP levels were consistently, yet non-significantly lower in patients with unfavourable outcome definitions. Median (range) CRP levels were 0.3 (0–5.9) mg/dl vs. 0.4 (0–5.7) mg/dl (p = 0.13) in patients dependent or dead after 3 months (modified Rankin Scale score > 2; n = 59) vs. independent patients (n = 52); 0.2 (0.1–1.5) mg/dl vs. 0.4 (0–5.9) mg/dl (p = 0.28) in patients dead after 3 months (n = 14) versus survivors (n = 97); and 0.2 (0.1–0.7) mg/dl vs. 0.4 (0–5.9) mg/dl (p = 0.09) in patients with significant neurological deterioration within 24 hours (increase in ≥4 points on National Institute of Health Stroke scale; n = 9) vs. patients without early deterioration (n = 102). Independent predictors of dependency/death after 3 months, identified by multivariate logistic regression analyses, were baseline NIHSS score (OR = 1.31, 95 % CI 1.16–1.48, p < 0.001), time from onset to treatment (OR = 1.01, 95 % CI 1.0–1.02, p = 0.024), and presence of diabetes (OR = 8.16, 95 % CI 1.18–56.5, p = 0.033). *Conclusion* Pre-treatment CRP clearly failed to predict outcome in stroke patients treated with IVT. Our findings contradict previously published work and highlight the need for further research on this topic.

Key words stroke · thrombolysis · outcome · C-reactive protein · inflammation

Introduction

Intravenous thrombolysis (IVT) treatment improves outcomes in acute ischemic stroke, when recombinant tissue plasminogen activator (rt-PA) is administered within 3 hours of symptom onset [22]. Pooled analysis of randomised placebo-controlled trials suggested a potential benefit of IV rt-PA even beyond the time window of 3 hours [23]. However, this potential may come with risks and has not been approved by regulatory authorities [10].

Identification of reliable outcome predictors could support decision-making at the point-of care and also guide management after IVT treatment. Multiple clinical factors and patient characteristics influence outcome in patients undergoing IVT. Unfavourable outcome is associated with high initial stroke severity, a long symptom onset to treatment time, advanced age, male sex, history of previous stroke, diabetes, and high systolic blood pressure [9, 21].

The heterogeneity in treatment benefit, especially in patients receiving IVT beyond the 3-hour time window,

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has led to the search for biomarkers as potential predictors of outcome. A recent study claimed pre-treatment C-reactive protein (CRP) to be a powerful prognostic tool in stroke patients treated with IVT [12]. This finding still lacks confirmation by other groups. However, several pieces of evidence make this issue worth further investigation.

Acute stroke triggers a systemic inflammatory response that might exacerbate tissue damage by promoting the conversion of the ischemic penumbra into infarcted area [14]. There is also accumulating evidence that CRP decreases tissue plasminogen activator activity and acts as a procoagulant [18, 26]. Several studies have linked CRP levels to mid- and long-term prognosis after ischemic stroke [6, 13, 28]. Increased CRP, measured within 24 to 72 hours of admission, is an independent predictor of survival after ischemic stroke [13]. Early neurological worsening may also be related to the extent of the acute phase response after stroke [27]. Experimental and clinical data suggest that post-stroke inflammatory responses are complex cascade phenomena, which may have detrimental or sometimes even beneficial effects [17]. However, if there was clear evidence that high CRP levels adversely affect outcome and exacerbate tissue damage, potential future drugs specifically blocking CRP effects could improve outcome in stroke and acute cardiovascular disease [15].

We therefore tested the hypothesis that pre-treatment CRP levels predict outcome in a single-centre cohort of stroke patients treated with IVT, using three outcome definitions.

Patients and methods

From January 2003 to June 2006, 129 patients underwent IVT for acute ischemic stroke at the Academic Teaching Hospital Wagner-Jauregg, Linz, Austria. A total of 111 patients were valid for analyses after exclusion of individuals with stroke involving a territory other than the middle cerebral artery, those with known inflammatory or malignant diseases, and those probably infected (admission CRP > 6 mg/dl). A detailed history of vascular risk factors was obtained from all patients. All patient data were collected in the prospective local stroke thrombolysis registry. Blood samples were drawn from all patients before start of rt-PA administration. CRP was measured by a particle-enhanced immunoturbidimetry assay (Cobas Integra C-reactive Protein Latex, Roche Diagnostics, Basel, Switzerland) with a range from 0.0085 mg/dl to 160 mg/dl (normal ≤ 0.5 mg/dl). Urine status was checked in all patients. Chest X-rays were performed when pneumonia was suspected clinically. Data on body temperature was not recorded systematically in our prospective registry.

IVT was carried out in 72 patients according to the Safe Implementation of Thrombolysis in Stroke – MOnitoring STudy (SITS-MOST) protocol [19]. 39 patients received IVT in spite of contraindications to the SITS-MOST protocol (age > 80 years in 18 patients; start of IVT between 3 and 6 hours after stroke onset in 21 patients). Prior to IVT start within 3 hours of stroke onset, patients underwent computed tomography, magnetic resonance imaging (MRI), or both. After 3 hours, a standardized MRI protocol was used to select candidates for IVT within an expanded time window of up to 6 hours. IVT between 3 and 6 hours of stroke onset was performed as an individual decision based on clinical and MRI findings with informed consent from patients or relatives. MRI was performed on a 1.5-T unit (Magnetom Symphony; Siemens) with a standard head coil. Imaging included diffusion-weighted spin-echo echo planar imaging, fluid-attenuated inversion recovery, 3D-time-of-flight MR angiography, and dynamic susceptibility contrast perfusion imaging using a gradient-echo echo planar imaging sequence. For perfusion MRI, Gadovist (Schering) was applied with a dosage of 0.2 mL/kg body weight through an automated injector (Ohio Tandem; Ulrich) at a flow rate of 5 mL/s. All sequences were applied in transverse orientation; total scanning time was < 15 minutes. For the decision whether to treat or not, perfusion/diffusion mismatch was assessed visually by the neuroradiologist and neurologist on duty without routine post-processing. In general, rt-PA was not given to patients with large DWI lesions (exceeding 50 % of the middle cerebral artery territory) and those without a relevant amount of perfusion/diffusion mismatch. Patients and/or relatives were informed of potential benefits and harms of IVT. Treatment was started after informed consent.

Clinical assessment and outcome definitions

Severity of neurological deficit was assessed immediately before the start of IVT, 2 hours after the start of IVT, and after 24 hours using the National Institutes of Health Stroke Scale (NIHSS) [3]. The 3-month outcome was assessed in the Vascular Outpatients Department of the Academic Teaching Hospital Wagner-Jauregg or by telephone interview using the modified Rankin Scale (mRS) [25]. Unfavourable outcome in terms of dependency or death after 3 months was defined by a mRS score > 2, while independency at 3 months corresponded to a mRS score ≤ 2. Early neurological deterioration was defined by an increase of ≥ 4 points on the NIHSS within 24 hours of IVT start.

Statistical analysis

Categorical variables are reported as percentages. Continuous variables with normal distribution are expressed as means (± SD) and skewed data are presented as medians (range). For univariate analyses of categorical variables, we used two-tailed Fisher's Exact test. For continuous variables, intergroup differences were assessed by two-tailed independent samples t test (data with normal distribution) and Mann-Whitney-U-test (skewed data). To control the risk of type 1 errors due to multiple testing, we used a Bonferroni correction setting the alpha value more stringent to $p < 0.0025$. We used nonparametric Spearman's rank correlation to investigate the association between CRP levels and continuous variables such as white blood cell count and fibrinogen.

Multivariate logistic regression analyses, considering the data of the whole cohort and including all variables tested in univariate analyses, were performed to identify independent predictors of mortality after 3 months, dependency or death after 3 months, and neurological deterioration within 24 hours. Admission CRP was included in the models as a dichotomized variable using the cut-point defining the highest quartile for both the whole cohort and the subgroup treated per SITS-MOST protocol (> 0.7 mg/dl). Results are presented with p values, odds ratios (OR), and 95 % confidence intervals (CI). All analyses were carried out with SPSS software (Version 14.0, SPSS Inc., Chicago, IL, USA).

Results

The mean age was 68.9 ± 12.2 years in the whole cohort (n = 111) and 67.0 ± 10.0 years in the subgroup treated per SITS-MOST protocol (n = 72). Median NIHSS score

was 14 both in the whole cohort (range 4–25) and in the subgroup treated per SITS-MOST protocol (range 4–24). Median time from onset to treatment was 157 minutes (range 50–360 minutes) for the whole cohort and 140 minutes (range 60–180 minutes) for the patients treated per SITS-MOST protocol.

Univariate associations of baseline characteristics with outcome measurements are given in Tables 1–3, with separate calculations for the whole cohort and the subgroup treated per SITS-MOST protocol within each table. We compared baseline characteristics of patients according to survival vs. mortality after 3 months (Table 1), independency vs. dependency or death after 3 months (Table 2), and occurrence vs. absence of significant neurological deterioration within 24 hours (Table 3).

Mortality at 3 months was 12.6 % in the whole cohort and 11.1 % in the subgroup treated per SITS-MOST protocol. 46.8 % of all patients and 56.9 % of patients of the SITS-MOST subgroup were independent at 3 months. Significant neurological deterioration within 24 hours was observed in 8.1 % of all patients and in 9.7 % of patients treated per SITS-MOST protocol.

For both the whole cohort and the subgroup treated according to SITS-MOST protocol, CRP levels > 0.7 mg/dl defined the highest quartile. During the stay in our hospital, 28 of 111 (25.2 %) patients were diagnosed with infection. Of these, 14 had urinary tract infection (UTI), 10 had pneumonia, and 4 acquired both UTI and pneumonia. Admission CRP levels (median; range) did not differ significantly between patients later diagnosed with infection (0.5; 0–5.7) and patients free of infection (0.3; 0–5.9, $p = 0.56$).

Admission CRP levels significantly correlated with fibrinogen levels ($r = 0.57$, $p < 0.01$) and white blood count ($r = 0.37$, $p < 0.01$). There were no significant correlations with other baseline variables. Median admission CRP levels were consistently lower in patients with unfavourable outcome endpoints regardless whether patients were treated per SITS-MOST protocol or not, but associations with outcome were not significant (Tables 1–3).

In univariate analyses, baseline NIHSS score was the only variable significantly associated with independency (mRS ≤ 2) vs. dependency/death (mRS > 2) after 3 months (Table 1). This was true for the whole cohort ($p < 0.001$) as well as for the subgroup treated per SITS-MOST protocol ($p = 0.001$). All other associations of baseline variables with outcome definitions did not reach the level of significance.

Table 1 Association of baseline characteristics with mortality at 3 months

	All patients (n = 111)			IVT per SITS-MOST (n = 72)		
	Survival (n = 97)	Mortality (n = 14)	p	Survival (n = 64)	Mortality (n = 8)	p
Age, years	69.0 (± 11.9)	68.2 (± 14.3)	0.82	67.3 (± 9.7)	64.8 (± 12.9)	0.50
Male	45 (46)	9 (64)	0.26	35 (55)	6 (75)	0.45
Hypertension	74 (76)	9 (64)	0.34	48 (75)	7 (88)	0.67
Diabetes	20 (21)	2 (14)	0.73	14 (22)	2 (25)	1.0
Dyslipidemia	28 (29)	4 (29)	1.0	21 (33)	2 (25)	1.0
Current smoker	20 (21)	5 (36)	0.3	13 (20)	3 (38)	0.36
Prior stroke	18 (19)	1 (7)	0.46	8 (13)	0	0.59
AF	28 (29)	7 (50)	0.13	18 (28)	4 (50)	0.24
CHF	12 (12)	3 (21)	0.4	8 (13)	3 (38)	0.1
Statin therapy	7 (7)	1 (7)	1.0	5 (8)	1 (13)	0.52
Antiplatelets	40 (41)	5 (36)	0.78	27 (42)	4 (50)	0.72
Baseline MRI	73 (75)	7 (50)	0.06	49 (77)	4 (50)	0.2
SBP, mmHg	155 (± 19)	159 (± 21)	0.48	153 (± 19)	157 (± 22)	0.62
DBP, mmHg	87 (± 13)	91 (± 9)	0.2	86 (± 13)	94 (1± 0)	0.12
Glucose, mg/dl	117 (76–330)	125 (88–316)	0.5	116 (80–330)	125 (97–316)	0.27
NIHSS score	13 (4–25)	16.5 (8–25)	0.03	13 (4–24)	17 (8–23)	0.11
IVT delay, min	150 (50–356)	168 (84–360)	0.26	140 (60–180)	168 (98–180)	0.05
WBC, 10^9/L	8.1 (± 2.5)	8.0 (± 2.1)	0.81	8.1 (± 2.6)	8.2 (± 2.2)	0.91
Fibrinogen, g/l	371 (± 87)	338 (± 70)	0.18	367 (± 90)	343 (± 65)	0.47
CRP, mg/dl	0.4 (0–5.9)	0.2 (0.1–1.5)	0.28	0.4 (0–5.7)	0.3 (0.1–1.5)	0.33

Values are mean (± SD), median (range), and number (percentage), as applicable.
IVT intravenous thrombolysis; *SITS-MOST* Safe Implementation of Thrombolysis in Stroke-MOnitoring Study; *AF* atrial fibrillation; *CHF* congestive heart failure; *MRI* magnetic resonance imaging; *SBP* systolic blood pressure; *DBP* diastolic blood pressure; *NIHSS* National Institute of Health Stroke Scale; *IVT* delay time from stroke onset to start of intravenous thrombolysis treatment; *WBC* white blood cell count; *CRP* C-reactive protein

Table 2 Association of baseline characteristics with functional outcome at 3 months

	All patients (n = 111)			IVT per SITS-MOST (n = 72)		
	mRS 0–2 (n = 52)	mRS 3–6 (n = 59)	p	mRS 0–2 (n = 41)	mRS 3–6 (n = 31)	p
Age, years	67.8 (± 12.9)	69.9 (± 11.5)	0.36	67.7 (± 10.6)	66.1 (± 9.3)	0.52
Male	28 (54)	26 (44)	0.35	23 (56)	18 (58)	1.0
Hypertension	36 (69)	47 (80)	0.27	27 (66)	28 (90)	0.02
Diabetes	8 (15)	14 (24)	0.34	7 (17)	9 (29)	0.26
Dyslipidemia	17 (33)	15 (25)	0.41	13 (32)	10 (32)	1.0
Current smoker	14 (27)	11 (19)	0.37	9 (22)	7 (23)	1.0
Prior stroke	7 (14)	12 (20)	0.45	5 (12)	3 (10)	1.0
AF	13 (25)	22 (37)	0.22	11 (27)	11 (36)	0.45
CHF	7 (14)	8 (14)	1.0	4 (10)	7 (23)	0.19
Statin therapy	3 (6)	5 (9)	0.72	3 (7)	3 (10)	1.0
Antiplatelets	22 (42)	23 (39)	0.85	17 (42)	14 (45)	0.81
Baseline MRI	42 (81)	38 (64)	0.06	34 (83)	19 (61)	0.06
SBP, mmHg	154 (± 18)	156 (± 21)	0.65	153 (± 19)	155 (± 20)	0.66
DBP, mmHg	87 (± 13)	87 (± 12)	0.99	87 (± 14)	87 (± 12)	0.87
Glucose, mg/dl	116 (76–330)	118 (88–316)	0.29	116 (80–330)	116 (95–316)	0.58
NIHSS score	10 (4–22)	16 (6–25)	0.001	10 (4–22)	16 (7–24)	0.001
IVT delay, min	151 (60–356)	162 (50–360)	0.14	140 (60–180)	150 (85–180)	0.33
WBC, 10^9/L	8.1 (± 2.7)	8.1 (± 2.3)	0.97	8.1 (± 2.8)	8.1 (± 2.2)	0.99
Fibrinogen, g/l	371 (± 91)	364 (± 80)	0.66	374 (± 99)	352 (± 69)	0.3
CRP, mg/dl	0.4 (0–5.7)	0.3 (0–5.9)	0.13	0.4 (0–5.7)	0.3 (0–1.8)	0.18

Values are mean (± SD), median (range), and number (percentage), as applicable.
mRS modified Rankin Scale score; *mRS 0–2* defines independency; *mRS 3–6* defines dependency or death; *IVT* intravenous thrombolysis; *SITS-MOST* Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy; *AF* atrial fibrillation; *CHF* congestive heart failure; *MRI* magnetic resonance imaging; *SBP* systolic blood pressure; *DBP* diastolic blood pressure; *NIHSS* National Institute of Health Stroke Scale; *IVT* delay time from stroke onset to start of intravenous thrombolysis treatment; *WBC* white blood cell count; *CRP* C-reactive protein

Multivariate logistic regression analyses, considering the data of the whole cohort and including all variables tested in univariate analyses, identified baseline NIHSS score as the only independent predictor of mortality after 3 months (OR = 1.17, 95 % CI 1.01–1.35, p = 0.038). The endpoint "death or dependency" was predicted by the baseline NIHSS score (OR = 1.31, 95 % CI 1.16–1.48, p < 0.001), time from stroke onset to treatment (OR = 1.01, 95 % CI 1.00–1.02, p = 0.024), and presence of diabetes (OR = 8.16, 95 % CI 1.18–56.5, p = 0.033). Independent predictors of early neurological deterioration could not be identified.

Discussion

The findings of this study suggest that pre-treatment CRP levels are not useful in predicting outcome in stroke patients undergoing IVT. The absence of a prognostic value of admission CRP was consistently found for all three analyzed outcome definitions and across both the whole cohort and the subgroup treated per SITS-MOST protocol.

Our results contradict the findings of Montaner et al. [12] who claimed admission CRP to be a powerful prognostic tool among candidates for IVT. In their cohort of 143 patients treated with IVT within 3 hours of stroke onset, logistic regression analysis identified admission CRP as a predictor of mortality after 3 months.

Both studies raise several methodological and clinical questions. Patients with admission CRP > 6 mg/dl were excluded because of probable infection before stroke. This clearly is an arbitrary cut-point that we also used for better comparability of our results with those of Montaner et al. [12]. Lower CRP cut-points may still be indicative of subclinical infection. Di Napoli and Papa recommended that no value should be discharged as too high, as some patients may have very high CRP levels even in the first few hours after acute stroke because of constitutional hyperresponsiveness [5]. Reanalyzing our data without using a CRP cut-point as exclusion criterion meant there were only two patients' data to add to the cohort, which had no effect on our findings (data not shown). Using a high sensitivity CRP (hs-CRP) assay, Montaner et al. [12] found that mortality rates were especially elevated for those patients at the highest quartile (> 0.77 mg/dl). This cut-point level was also selected for inclusion in their multivariate analysis. Interestingly,

Table 3 Baseline characteristics and neurological deterioration within 24 hours

	Early neurological deterioration					
	All patients (n = 111)			IVT per SITS-MOST (n = 72)		
	No (n = 102)	Yes (n = 9)	p	No (n = 65)	Yes (n = 7)	p
Age, years	69.7 (± 11.5)	60.0 (± 16.6)	0.12	67.7 (± 9.0)	60.0 (± 15.7)	0.24
Male	50 (49)	4 (44)	1.0	37 (57)	4 (57)	1.0
Hypertension	76 (75)	7 (78)	1.0	49 (75)	6 (86)	1.0
Diabetes	19 (19)	3 (33)	0.38	14 (22)	2 (29)	0.65
Dyslipidemia	30 (29)	2 (22)	1.0	22 (34)	1 (14)	0.42
Current smoker	23 (23)	2 (22)	1.0	14 (22)	2 (29)	0.65
Prior stroke	19 (19)	0	0.35	8 (12)	0	1.0
AF	34 (33)	1 (11)	0.27	21 (32)	1 (14)	0.43
CHF	14 (13)	1 (11)	1.0	10 (15)	1 (14)	1.0
Statin therapy	8 (8)	0	1.0	6 (9)	0	1.0
Antiplatelets	43 (42)	2 (22)	0.31	29 (45)	2 (29)	0.69
Baseline MRI	74 (73)	6 (67)	0.71	48 (74)	5 (71)	1.0
SBP, mmHg	155 (± 18)	156 (± 31)	0.94	153 (± 19)	160 (± 27)	0.38
DBP, mmHg	87 (± 12)	93 (± 12)	0.17	86 (± 13)	95 (± 11)	0.08
Glucose, mg/dl	118 (76–330)	116 (84–265)	0.46	116 (80–330)	116 (84–265)	0.72
NIHSS score	14 (4–25)	13 (7–19)	0.67	14 (4–24)	13 (9–19)	0.91
IVT delay, min	150 (50–360)	160 (60–220)	0.71	145 (70–180)	140 (60–180)	0.95
WBC, 10^9/L	8.2 (± 2.5)	7.2 (± 2.3)	0.23	8.3 (± 2.5)	6.9 (± 2.4)	0.19
Fibrinogen, g/l	369 (± 87)	346 (± 60)	0.44	366 (± 91)	354 (± 55)	0.73
CRP, mg/dl	0.4 (0–5.9)	0.2 (0.1–0.7)	0.09	0.4 (0–5.7)	0.2 (0.1–0.7)	0.11

Values are mean (± SD), median (range), and number (percentage), as applicable.
IVT intravenous thrombolysis; *SITS-MOST* Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy; *CHF* congestive heart failure; *MRI* magnetic resonance imaging; *SBP* systolic blood pressure; *DBP* diastolic blood pressure; *NIHSS* National Institute of Health Stroke Scale; *IVT* delay time from stroke onset to start of intravenous thrombolysis treatment; *WBC* white blood cell count; *CRP* C-reactive protein

our cohort, tested with a conventional CRP assay, had a similar CRP cut-point for the highest quartile (> 0.7 mg/dl). However, both cut-points are clearly beyond the "high-sensitivity range", the forte of modern hs-CRP assays. Hence, it is unlikely that use of an hs-CRP assay would have substantially changed our results.

A major limitation of our study is the relatively low number of patients potentially leading to a type II errors for single endpoints investigated. However, based on post-hoc power analyses, we estimated about 85 % statistical power to detect a difference in CRP levels using the endpoint "functional outcome at 3 months". Data on some potential confounders of CRP levels such as CRP gene polymorphisms or body temperature were not collected systematically. Furthermore, our study focussed on pre-treatment CRP levels only. Serial post-treatment CRP measurement over several days might have shed light on the predictive value of later CRP levels and on the relationship of admission levels with later levels. In 43 stroke patients treated with IVT, Audebert et al. found [1] that successful thrombolysis, defined by an improvement on the NIHSS of at least 4 points within 24 hours, was associated with subsequently lower CRP levels. However, CRP at admission failed to discriminate improvement from unfavourable IVT outcome [1].

We are not aware of further publications on the predictive value of admission CRP in stroke patients undergoing IVT. Considering the enthusiasm for potential biomarkers in the stroke community and the nearly ubiquitous availability of CRP assays, the lack of publications on this topic is remarkable. A possible explanation for this is publication bias, with non-significant or "negative" results not being submitted or published.

After ischemic stroke, levels of CRP and many other inflammatory markers peak after several days [14]. CRP measured at considerably later time points than in our study may better reflect the magnitude of the inflammatory response after stroke and correlate with initial stroke severity and long-term outcome [1, 6, 11, 20, 28]. In one study, CRP levels measured between 12 and 24 hours, but not within the first 12 hours after stroke, predicted an unfavourable long-term outcome [28]. CRP levels at discharge may even better correlate with long-term prognosis than CRP measured within 24 hours after stroke onset [6].

The lack of correlation between baseline stroke se-

verity and CRP levels in our and Montaner's study [12] is probably due to the very early measurement of CRP. We did not evaluate associations of admission CRP levels with final lesion size on brain imaging, the occurrence of hemorrhagic transformation, or vessel recanalization. However, investigation of these surrogate markers of outcome is of secondary importance compared to the question whether admission CRP in stroke patients undergoing IVT can predict survival vs. mortality or even functional outcome.

In patients with ischemic stroke, increased CRP levels may reflect the (pre-existing) degree of atherosclerosis or vulnerability of plaques, the presence of risk factors such as smoking or obesity, the severity of the stroke itself, early complicating infections, or a combination of these factors [4, 20]. Furthermore, CRP levels are influenced by genetic factors [2] and the use of medication such as statins [7]. Hence, when associations of CRP levels with stroke outcome are evaluated, use of appropriate statistical analysis with adjustment for potential confounders and established predictors of outcome is obligatory. Unfortunately, this is not common practice. Recently, admission CRP was claimed to be an "independent" predictor of in-hospital mortality without reporting on baseline stroke severity [16].

Our study identified three independent predictors of unfavourable outcome defined by a mRS score > 2 after 3 months: higher initial stroke severity as assessed by the NIHSS, longer time delay from stroke onset to IVT start, and the presence of diabetes. These baseline variables have already been reported as predictors of IVT outcome [9, 21, 23].

We used multimodal MRI to select candidates for IVT within the expanded time window of 3–6 hours after stroke onset. In a recent multicenter study, this very same approach was shown to be a safe and effective tool for selecting patients for IVT [24]. However, the mismatch concept remains controversially debated, with standardised criteria still to be defined [8].

In conclusion, our findings suggest that admission CRP is not useful for predicting outcome in stroke patients with IVT. Because of conflicting evidence on this issue, larger studies with serial CRP measurement at prefixed time points and appropriate statistical analyses with adjustment for major outcome determinants and confounding variables are needed.

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