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Evaluation of routine laboratory markers as short-term outcome indicators in patients with acute ischemic stroke

Tatyana Popovska[1,2], Rosen Kalpachki[2], Dobrin Svinarov[3], Milena Velizarova[4*]

1. Department of Clinical Laboratory, University Hospital "St. Anna", Sofia, Bulgaria
2. Center for the treatment of strokes, University Hospital "St. Anna", Sofia, Bulgaria
3. Central Clinical Laboratory, University Hospital "Alexandrovska", Sofia, Bulgaria
4. Department of Clinical Laboratory, Medical University, Sofia, Bulgaria

ABSTRACT

Introduction: Stroke is a disease with high mortality and morbidity. Currently, there are no specific laboratory markers that can replace or improve clinical and radiological diagnosis and prognosis. We evaluated the role of C-reactive protein (CRP), fibrinogen and D-dimer in predicting short-term outcomes in acute ischemic stroke.

Methods: We included 118 acute ischemic stroke patients, admitted within 24 h of onset, mean age 72.73±10.08 years. The severity of the stroke was assessed by the National Institutes of Health Stroke Scale (NIHSS), and for poor outcome (PO) we accepted a severe functional deficit at the end of the hospital stay with NIHSS ≥15, and for good outcome (GO) – NIHSS ≤ 14. In all patients, we monitored the dynamics of CRP, fibrinogen and D-dimer and evaluated their predictive value regarding to the PO and GO of the stroke.

Results: D-dimer had the strongest poor predictive value at admission ($p<0.001$). Six hours after admission, CRP, D-dimer or both were higher in PO patients ($p=0.046$, $p=0.022$ and $p=0.006$, respectively). At the 24.h, only CRP could be used to predict PO ($p<0.001$). Elevated CRP, D-dimer or both have been determined as strong indicators of PO with 72 hours of admission ($p<0.001$, $p=0.032$ and $p=0.001$, respectively). Fibrinogen levels were higher 72 hours after admission without a significant relationship with the NIHSS.

Conclusion: Changes in routine biomarkers CRP and D-dimer, but not fibrinogen, can predict short-term stroke prognosis and may be associated with the risk of early neurological deterioration or death during hospital stay.

Keywords: CRP, D-dimer, fibrinogen, ischemic stroke, laboratory markers

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INTRODUCTION

A stroke is a medical emergency, a result of an acute disturbance of cerebral blood circulation, which can lead to death or to severe and irreversible morphological and functional damage to the central nervous system [1]. According to data from the National Statistical Institute of the Republic of Bulgaria, stroke is the second most common cause of death in 2022 (309.7 per 100,000 people) after cardiovascular diseases (403.7 per 100,000 people), the most common cause of severe disability and is constantly increasing [2]. As such, it is especially important to find the factors related to the prognosis of patients with stroke in order to use appropriate treatment regimens and optimize healthcare for these patients.

The diagnosis of acute ischemic stroke (AIS) is made based on a good clinical assessment, laboratory and radiological studies [3]. It was hypothesized that the levels of serum biomarkers such as markers of inflammation (C-reactive protein, CRP), coagulation (fibrinogen) and fibrin degradation (D-dimer), would show independent correlations with both the location and size of cerebral lesions [4-6]. C-reactive protein (CRP) is a commonly studied marker of inflammation involved in all stages of ischemic stroke [6]. Moreoever, its high values are related to the type of stroke (ischemic and hemorrhagic) and to the unfavorable outcome of the disease [7-10]. Some data suggest that elevated CRP levels can be used to predict severity and early outcome in ischemic but not in hemorrhagic stroke [19].

D-dimer is a marker for fibrin formation and degradation [11]. Some studies have shown that plasma levels of D-dimer correlate positively with the volume of the infarcted area in the brain parenchyma [11, 12] and can provide valuable prognostic information regarding stroke severity or risk of death [13-15].

* Corresponding author: Milena Velizarova, Department of Clinical Laboratory, University Hospital "St. Anna", Sofia, Bulgaria. E-mail: milena.velizarova@gmail.com

In contrast to the signficance of CRP and D-dimer, fibrinogen level is not independent prognostic factor in acute stroke [16]. The impact of fibrinogen on enhancing the accuracy of prognostic prediction models would rely on the presence of other risk factors and variables [17]. Here we summarized the changes of CRP, fibrinogen, and D-dimer over time in order to determine their role as indicators for the management of the healing process and short-term prognosis of the disease during the hospital stay.

MATERIALS AND METHODS

This prospective study, conducted in a single center, involved patients presenting with acute neurological deficits admitted from January 2021 to March 2021. Patients with a diagnosis of intracerebral hemorrhage, transient ischemic attack (TIA), epileptic seizure, neoplasms, history of recent surgery or trauma in the previous 3 months, severe renal and/or liver disease, acute coronary event in the last 3 months and COVID-19 and the cases with exitus during hospital stay were excluded from the study. In the study, 118 selected patients were included who did not meet the exclusion criteria. The diagnosis was established based on the clinical assessment, imaging and laboratory diagnostics. All patients included in the statistics have signed informed consent for laboratory analyses, diagnostic procedures and treatment on the day of hospitalization during hospital stay.

We assessed the clinical severity of stroke by the National Institute of Health Stroke Scale (NIHSS) on admition and on discharge. NIHSS is an approved score, used in the standart treatment protocol with fibrinolytics. All patients underwent a CT scan on admission to confirm the presence of cerebral infarction and to rule out hemorrhage or old ischemic events. The CT scans were assessed using the Alberta Stroke Program Early CT Score (ASPECTS), and thrombolytic treatment (29.7%) was performed in patients with ASPECTS≥8 and onset of symptoms within 4.5 hours. Patients with ASPECTS scores below 8 and symptom onset exceeding 4.5 hours (70.3%) received conventional therapy. Laboratory markers fibrinogen, D-dimer, and CRP were monitored in dynamics (on admission, 6-, 24- and 72 hours later) and were related to short-term prognosis of the disease during the hospital stay.

At the end of the hospital stay, the functional score was reassessed by NIHSS and patients were divided into two groups: poor outcome (PO) group with severe functional deficit assessed by NIHSS ≥15; and good outcome (GO) group with NIHSS ≤ 14.

Analytical methods

D-dimer (µg/mL FEU) was measured in a sodium citrate Vacuette tube (Greiner Bio-One, Austria) with an immunoturbidimetric method using Mindray C 3510 (Mindray Global, China). The same Vacuette tube and coagulation analytical platform was used for determination of fibrinogen (g/L) levels with a Claus coagulation method. Serum C-reactive protein (mg/L) was measured in a serum Vacuette tube (Greiner Bio-One, Austria) with a turbidimetry using Dimension EXL 200 (Siemens, Healthineers) platform.

Statistical analysis

Statistical analysis was performed using the SPSS 25.0 software package. The value $p<0.05$ was accepted as a level of significance at which the null hypothesis is rejected. The following methods were applied: descriptive analysis, Fisher's exact test, Kolmogorov-Smirnov and Shapiro-Wilk non-parametric tests, Mauchly's test for multi-normal distribution, Friedman's non-parametric test for several dependent samples, Wilcoxon's paired non-parametric test, Mann-Whitney non-parametric test, analysis of receiver operating characteristic (ROC) curves, validation criteria for screening tests, and Binary Logistic Regression analysis.

RESULTS

Patient characteristics

This study analyzed data from 118 patients diagnosed with acute ischemic stroke, with an average age of 72.73 years (±10.08), comprising 64 (54.2%) males and 54 (45.8%) females. The most common comorbidy was hypertension (in 97.5% of patients), followed by heart disease (47.5%), diabetes mellitus (30.5%), and dyslipidemia (54.2%). Table 1 displays the demographic features, chronic conditions, risk factors, CT findings, therapeutic aproach, and laboratory findings of the patients.

Our study showed that there was no significant correlation between gender (p=0.095), age (p=0.686) and therapeutic (with and without thrombolysis) approach (p=0.653) with the outcome of the treatment, which allowed us to separate patients generally into two groups: with good (GO) and poor short-term outcome (PO) (Table 2).

Laboratory results

In the conducted study, the baseline levels of D-dimer (p=0.001), but not fibrinogen (p=0.229) or CRP (p=0.447) levels, showed a statistically significant relationship with the outcome of the disease.

Table 1. Demographic, clinical, laboratory, and radiological features in all patients diagnosed with ischemic stroke (n=118).

Demographic characteristics	
Age (years), mean±2SD	72.73±10.08
Male, n (%)	64 (54.2%)
Risk factors, n (%)	
Hypertension	115 (97.5%)
Cardiac disease	56 (47.5%)
Diabetes mellitus	36 (30.5%)
Dyslipidemia	64 (54.2%)
Smoking	27 (22.9%)
NIHSS* on admission, median (range)	15 (2-28)
ST findings	
ASPECTS** ≥ 8 points, n (%)	35 (29.66%)
ASPECTS < 8 points, n (%)	83 (70.34%)
Therapeutic approach	
With thrombolysis, n (%)	35 (29.66%)
Without thrombolysis, n (%)	83 (70.34%)
Fibrinogen, mean	
On admission	3.84 g/L
6 hour	3.71 g/L
24 hour	3.89 g/L
72 hour	4.00 g/L
D-dimer, mean	
On admission	1.38 µg/mL
6 hour	1.72 µg/mL
24 hour	1.43 µg/mL
72 hour	1.32 µg/mL
C-reactive protein, mean	
On admission	13.23 mg/L
6 hour	13.74 mg/L
24 hour	28.68 mg/L
72 hour	39.65 mg/L

NIHSS- National Institute of Health Stroke Scale; ASPECT- Alberta stroke program early CT score.

Followed in dynamics, the plasma levels of D-dimer 6 hours from the hospitalization showed a permanent decrease. In patients with a poor outcome, these levels remained elevated compared to those with a good outcome. However, statistical significance in relation to the disease outcome was observed at the 6th hour (p=0.022) and 72nd hour (p=0.032) (Table 2, Fig.1).

Dynamically monitored fibrinogen levels showed an increase after the 6th hour, but there were no significant differences between the patients included in good and poor outcome groups and subsequently fibrinogen could not be useful as a prognostic marker for short-term stroke outcome (Table 2, Fig.2).

Dynamic changes in serum CRP levels were related to a permanent and stable increase in all patients after the 6th hour and had positive correlation with the outcome of the disease at the end of the hospital stay- 6th hour (p=0.046), 24th hour (p<0.001), 72nd hour (p=0.001) (Table 2, Fig. 3).

ROC curve and regression analysis

To determine at what time after the onset of the vascular event CRP, fibrinogen, and D-dimer values were most strongly associated with poor short-term outcome, we applied ROC curve analysis (Table 3).

For D-dimer ≥1.182 µg/mL on admission, the risk of adverse outcome was about 6 times higher (p<0.001). In cases where both threshold values were increased (D-dimer ≥1.182 µg/mL, NIHSS ≥16.5), the risk increased to about 52 times (p<0.001).

Table 2. Comparison of laboratory findings and NIHSS scores between patients with good and poor outcomes.

	Patients with good outcome (n=87)	**Patients with poor outcome (n=31)**	**P value**
Age (years), mean±2SD	72.4 ±10.52	73.65 ±8.86	0.686
Male, n (%)	43 (49.4%)	21 (67.7%)	
Female, n (%)	44 (50.6%)	10 (32.3)	0.095
NIHSS on admission, n	87	31	
NIHSS median ±SD	9.68±5.22	19.29±7.02	**< 0.001**
Therapeutic approach			
with thrombolysis, n (%)	27 (31.0%)	8 (25.8%)	0.653
without thrombolysis, n (%)	60 (69.0%)	23 (74.2%)	
Fibrinogen, n	67	24	
On admission, mean, g/L, x±SD	3.84±1.08	3.68±1.10	0.229
6 hour, mean, g/L, x±SD	3.71±1.11	3.55±1.34	0.393
24 hour, mean, g/L, x±SD	3.89±1.06	3.98±1.40	0.713
72 hour, mean, g/L, x±SD,	4.43±1.15	4.78±1.56	0.221
D-dimer, n	72	26	
On admission, mean, g/L, x±SD	1.38±1.27	2.39±0.67	**0.001**
6 hour, mean, µg/mL, x±SD	1.72±1.62	2.28±1.53	**0.022**
24 hour, mean, µg/mL, x±SD	1.43±1.33	1.71±1.41	0.240
72 hour, mean, µg/mL, x±SD	1.32±1.11	1.54±1.25	**0.032**
C-reactive protein, n	73	27	
On admission, mean, g/L, x±SD	13.23±11.51	18.63±12.40	0.477
6 hour, mean, mg/L, x±SD	13.74±8.59	29.46±18.53	**0.046**
24 hour, mean, mg/L, x±SD	28.68±23.66	60.65±55.41	**< 0.001**
72 hour, mean, mg/L, x±SD	39.65±23.59	83.79±78.79	**0.001**

NIHSS- National Institute of Health Stroke Scale.

Table 3. Findings from the ROC curve analysis, validation criteria for screening tests, and binary logistic regression analysis.

Time (h)	Marker	AUC	Cut-off	Sens.	Spec.	PPV	NPV	OR	95% CI	
									Low limit	High limit
0 h	NIHSS	0.844	≥16.5	81	87	69	93	32.696	9.395	113.795
	D-dimer	0.726	≥1.181	76	65	42	89	5.886	1.683	20.590
	NIHSS+ D-dimer	0.853	≥0.287	83	87	69	94	51.933	13.022	207.123
6 h	CRP	0.623	≥26.85	43	84	50	80	3.892	1.448	10.462
	D-dimer	0.644	≥1.229	72	54	36	85	3.308	1.266	8.645
	CRP + D-dimer	0.672	≥0.245	62	71	43	84	6.930	2.090	22.980
24 h	CRP	0.728	≥18.2	83	63	44	92	8.437	2.938	24.234
72 h	CRP	0.716	≥55.25	66	75	49	86	5.614	2.127	14.821
	D-dimer	0.637	≥0.695	86	43	35	89	4.883	1.453	16.408
	CRP + D-dimer	0.719	≥0.217	71	66	43	87	7.133	2.681	18.975

NIHSS- National Institute of Health Stroke Scale; AUC- Area Under Curve; Sens.- Sensitivity; Spec.- Specificity; PPV- Positive Predictive Value; NPV- Negative Predictive Value; OR- Odd Retio; CI- Confidence Interval.

Patients with CRP values ≥26.85 mg/L exhibited a stronger correlation with an adverse prognosis, with approximately a fourfold higher risk of poor outcome compared to those with lower CRP levels (p=0.046). When D-dimer ≥1.229 µg/ml 6 hours after admission, this risk was about 3.3 times (p=0.022). The risk would be increased to about 7 times (p=0.006) if both DD≥1.229 µg/mL and CRP ≥26.85 mg/L were found.

At 24 hours after admission, there was highly significant predictive role of CRP ≥18.2 mg/L and the risk for PO was 8.4 times increased (p<0.001).

As for the predictive risk role of CRP, D-dimer, and their combination 72 hours after admission, there were highly significant associations: D-dimer ≥0.695 µg/mL showed a 4.8-fold increased risk for poor outcome (p=0.032), while CRP ≥55.25 mg/L was associated with a 5.6-fold increased risk of poor outcome (p<0.001). In cases where both threshold values were exceeded (D-dimer ≥0.695 µg/mL and CRP ≥55.25 mg/L), the risk increased to about 7 times (p=0.001).

DISCUSSION

The sudden cessation of blood flow to the brain in acute ischemic stroke causes tissue hypoxia and triggers an inflammatory cascade that leads to neuronal damage [18, 19]. An understanding of the benefits of timely reperfusion led to the introduction of thrombolytic therapy as the modern treatment of AIS [20]. Currently, there are no laboratory biomarkers with high specificity that can replace clinical and radiological evaluation in making the diagnosis and prognosis [4]. However, it is worthwhile to discuss how to use routine tests to improve laboratory efficiency in decision making, disease monitoring,

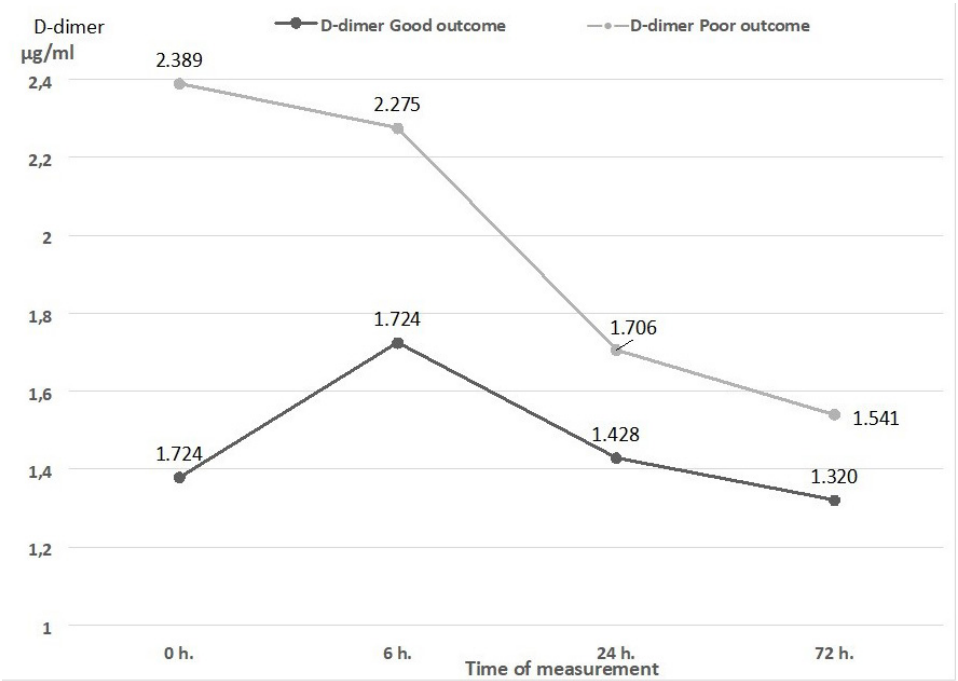

Fig. 1. Monitoring D-dimer levels in patients with good and poor outcome.

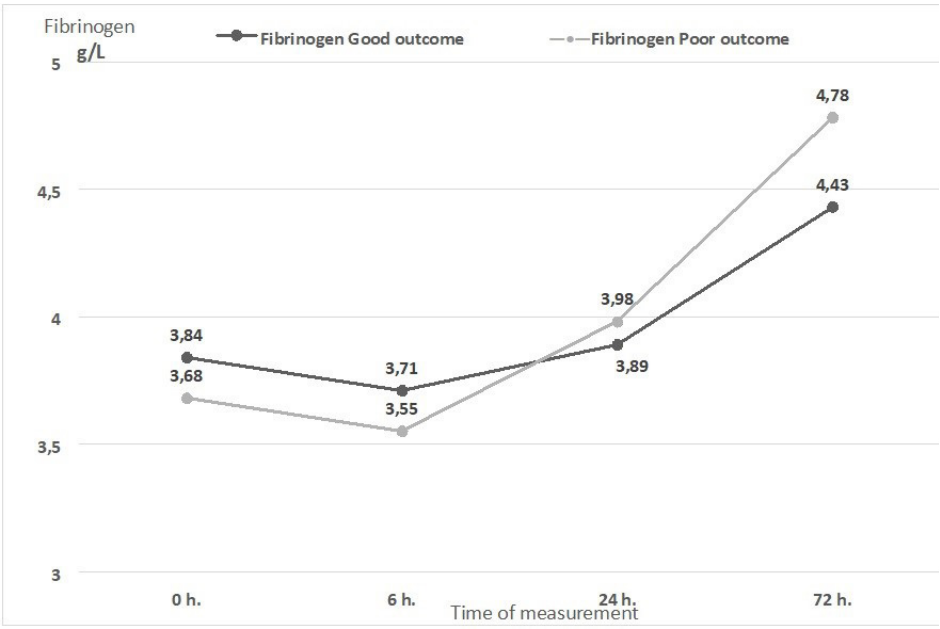

Fig. 2. Monitoring fibrinogen levels in patients with good and poor outcomes.

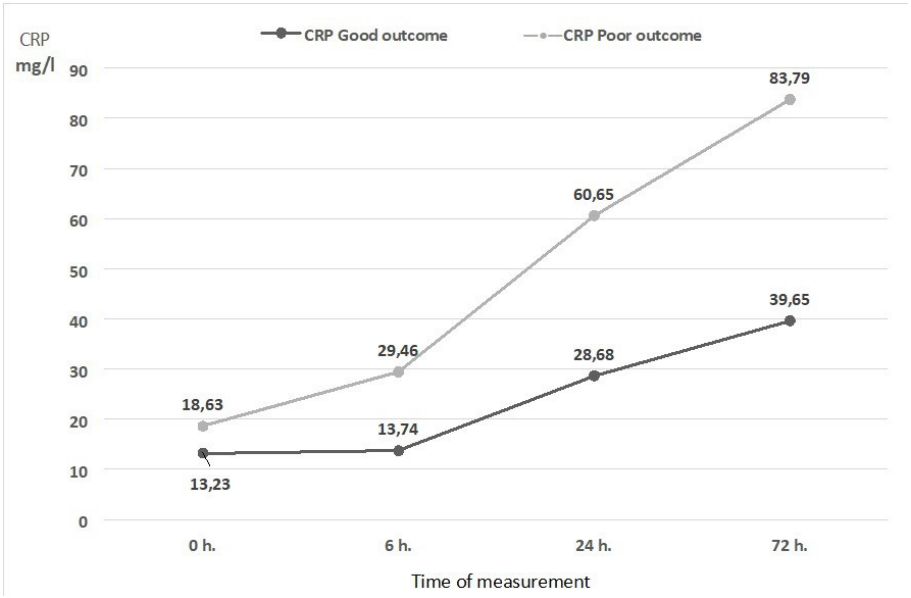

Fig. 3. Monitoring C-reactive protein levels in patients with good and poor outcomes.

and prediction of short-term outcome in thrombotic diseases [5, 6, 21, 22].

In this study, we tracked changes in common laboratory indicators such as CRP, D-dimer, and fibrinogen, assessing their utility in monitoring recovery progress and predicting short-term outcomes in patients with AIS.

Our results showed that NIHSS and D-dimer have the greatest correlation with a poor prognostic outcome on admission, regardless of the therapeutic approach used. Although known for high odds ratio values of NIHSS (OR=32.67) and poor disease outcome, simultaneous interpretation with D-dimer would increase the odds of predicting adverse outcome nearly 52 times (OR=51.93) with specificity 87% and sensitivity 83%. This aligns with the findings of Melake et al. [4], who identified a strong correlation between increased D-dimer levels and both the size of the infarcted region and the severity of clinical symptoms, indicating disease progression and hospital mortality. The results of this study was in contrast to Haapaniemi and Tatlisumak [12] who postulated that D-dimer assessment cannot be used as an acute ischemic stroke marker. We reported that elevated D-dimer levels on admission may be a rapid, economical, and convenient indicator for assessing functional short-term outcome. Our data confirmed the findings of Yao T et al. [15] and Ohara et al. [23] They highlighted the growing importance of measuring D-dimer levels in the assessment and treatment of ischemic stroke. However,

D-dimer should be further investigated and used cautiously as an adjunctive predictive biomarker in an acute cerebrovascular event.

Fibrinogen plays a crucial role in determining the viscosity of blood and serves as a positive protein of acute inflamation reactions. It is reported that fibrinogen level is not an independent prognostic factor in acute stroke [16]. The impact of fibrinogen on enhancing the accuracy of prognostic prediction models would rely on the presence of other risk factors and variables [17]. We found decreased fibrinogen levels in approximately all ischemic patients six hours from the admission and this finding was not related to the applied treatment. We attributed this result either to the natural activation of the fibrinolytic system due to thrombus formation or hyperactivation by the thrombolytic agents in patients treated with Alteplase. These results were consistent with the study by Lu T et al. [24], who found an independent association of changes in fibrinogen levels with the short-term efficacy of thrombolysis performed at the 4th hour—each 20% decrease in fibrinogen levels was associated with a 3.84-fold increase of the probability of improvement. Excessive reduction, however, may be associated with an increased risk of bleeding [25, 26]. Our research team assumed that reduced plasma fibrinogen levels during the first 6 hours of treatment indicated the presence of a reperfusion effect. This suggested the potential role of fibrinogen as a marker of reperfusion processes in patients on thrombolytic therapy.

Conversely, elevated fibrinogen levels serve as an autonomous risk factor for both venous and arterial clotting, correlating with a more intense progression and poorer prognosis [27-30]. According to some authors, hyperfibrinogenemia is positively correlated with the type of infarction and the presence of ischemic lesions in the CT findings of cerebral ischemia [29, 30]. Peycheva et al. [31] discovered that individuals with atherothrombotic stroke exhibited higher average fibrinogen levels (>4.0 g/l) in comparison to those with different stroke subtypes. Additionally, they observed a direct relationship between fibrinogen concentrations and the occurrence of ischemic lesions detected on CT scans. Results from our study presented that fibrinogen level were higher 72 hours after admission without a significant relationship with the NIHSS score and the disease outcome. Our findings contradicted those of Mehta et al. [29] and Peycheva et al. [31], who concluded that fibrinogen independently served as a prognostic factor, influencing neurological deterioration and leading to unfavorable outcomes in patients with acute ischemic stroke.

Neuroinflammation in acute stroke disrupts the integrity of the blood-brain barrier, which leads to the migration of immune cells into the brain parenchyma, releasing interleukins [11, 22]. Of the interleukins, IL-6 has the most powerful stimulating effect, which enhances the synthesis of C-reactive protein (CRP) and provokes the development of an inflammatory process [32]. In this study, CRP showed a notable association with stroke severity and short-term outcomes at 6 hours (p=0.046), 24 hours (p<0.001), and 72 hours (p=0.001) following admission. When we used cut-off values of CRP≥18.2 mg/L, the odds ratio (OR) was OR=8.44, sensitivity and specificity were 83% and 63%, respectively. It seems plausible that inflammatory markers play a pathophysiological role during the early response to cerebrovascular injury [3, 6]. These findings were consistent with findings from other research which demonstrated that elevated CRP levels were linked to an increased likelihood of cerebrovascular, cardiovascular, and peripheral vascular diseases [13, 33], an increased risk of cognitive deterioration in the acute phase of ischemic stroke, and an increased risk of fatal outcome in the first year, regardless of cause [8, 21, 34-36]. Following CRP changes, we reported a stable permanent increase. In the patient group with a good outcome, a significant increase was observed at the 24th hour, while in those with a poor outcome – earlier at the 6th hour.

The results clearly showed the importance of high CRP values as an independent predictor for assessing the risk of early neurological deterioration or poor short-term disease outcome. Our research team advocates for the regular utilization of CRP to assess the risk of adverse functional outcomes or mortality in these patients.

CONCLUSIONS

Our study demonstrates that biomarkers such as CRP, fibrinogen, and D-dimer, either individually or in combination, can serve as valuable tools for diagnosing and monitoring patients with acute ischemic stroke when interpreted within the appropriate clinical context. Nevertheless, it is important to consider the relatively low specificity of a single biomarker (ranging from 63% to 84%), highlighting the necessity of concurrently assessing multiple routine laboratory indicators in clinical practice. Our research team advocates for the routine use of a biomarker panel consisting of CRP, fibrinogen, and D-dimer as a readily accessible and cost-effective means to stratify patients with ischemic stroke and enhance treatment efficacy.

ABBREVIATIONS

AIS – Acute Ischemic Stroke

ASPECT – Alberta Stroke Program Early CT score

AUC – Area Under Curve
CI – confidential interval
CRP – C-reactive protein
CT – computed tomography
GO – good outcome
NIHSS – National Institutes of Health Stroke Scale
NPV – Negative Predictive Value
OR – odd ratio
PO – poor outcome
PPV – Positive Predictive Value
Sens – sensitivity
Spec – specificity
TIA – Transient Ischemic Attack

AUTHORS' CONTRIBUTION

TP- data analysis and interpretation, drafting the manuscript.

RK- conceptualization, investigation, critically reviewing the manuscript.

DS- conceptualization, investigation, critically reviewing the manuscript.

MV- critically reviewing the manuscript.

CONFLICT OF INTEREST

None to declare.

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