

Procalcitonin as a prognostic marker in patients with acute ischemic stroke

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Abstract

Background: Information about the degree of disability and death after an acute ischemic stroke remains lacking. This study's objectives were to examine the prognostic value of procalcitonin (PCT) serum levels in acute ischemic stroke (AIS). **Methods:** This research was a follow-up cohort study done on 70 patients referred to the neuropsychiatry department at Benha University Hospital who met the inclusion criteria for ischemic stroke. Multiple laboratory tests are performed on each patient, including (CBC, liver function tests, renal function tests, thyroid function tests, Procalcitonin (PCT) measurement within 72 hours of symptom start, CRP), CT brain (first and follow-up after 48 hs) or MRI brain with diffusion, ECG. After one month from the beginning of acute ischemic stroke, the Modified Rankin Scale (mRS) is used to assess the degree of impairment. The procalcitonin levels of acute ischemic stroke patients who died within 30 days were considerably greater than those who survived. Increasing PCT levels were shown to be linked with higher mRS scores ($p=0.001$). A greater procalcitonin concentration was substantially related with a worse result ($p=0.001$, respectively). Comparing the AUCs of PCT and CRP, PCT's AUC (ability to predict bad result) was considerably superior ($p=0.028$). In univariable analysis, older age, hypertension, higher CRP, TLC, and PCT were related with an increased likelihood of a bad outcome. In a multivariate analysis, however, the presence of hypertension, a higher CRP, and a PCT were identified as risk factors for a poor outcome among the investigated patients. PCT is a strong predictor of poor prognosis in instances with AIS, according to the findings. PCT is an important indicator of severity and mortality after AIS.

Keywords: acute ischemic stroke, Procalcitonin, Crp, predictors of poor outcome.

1. Introduction

Stroke is the second leading cause of death globally, after only ischemic heart disease [1]. Each year, the World Stroke Organization receives reports of about 13.7 million stroke occurrences, of which 60 percent involve persons under the age of 70. [1]. People over 25 years old have a 24.9% lifetime chance of experiencing a stroke [2].

Thromboembolism related with atherosclerosis of big arteries or cardiac disorders such as atrial fibrillation are the most prevalent causes [9].

Large vascular occlusions (LVO), also known as internal carotid artery (ICA), M1 or M2 section of the middle cerebral artery (MCA), or vertebro basilar arteries occlusions, occur for between 11 and 29 percent of all instances of acute ischemic stroke (AIS) [3].

Cerebral tissue often dies permanently due to a lack of blood flow as a consequence of brain hypoperfusion caused by an LVO, which produces the core infarction.

The penumbra, which surrounds the core and includes hypoperfused brain tissue, may be spared if the blood supply is restored swiftly [1]. Endovascular treatment (EVT) has so successfully recanalized an LVO [5].

Diverse stroke field triage assessments have been developed for rapid diagnosis and triage. Validated for clinical usage, these ratings allow rapid identification of individuals who may be undergoing an acute ischemic stroke [8].

As additional acute ischemic stroke biomarkers, several inflammatory biomarkers, including procalcitonin (PCT) and C-reactive protein (CRP), have been identified [9].

The C-cells of the thyroid gland produce PCT, a prohormone of calcitonin. PCT seemed to be a more accurate biomarker for the diagnosis of infection in previous studies [11]. Recent studies suggest that it may be a greater predictive factor for ischemic stroke than CRP [14].

2. Patients and methods

This is a follow up cohort study that was conducted on 70 patients with acute ischemic stroke from the neuropsychiatry department of Benha university hospitals From July 2022 to September 2022. All patients fulfilling criteria of Acute ischemic stroke defined according to the World Health Organization criteria (16) within less than 72 hours after symptom onset were include. while the Exclusion criteria included intracerebral hemorrhage, subarachnoid hemorrhage, systemic infections, transient ischemic attack, patient received TPA, patient with thyroid dysfunction, and patient with serum calcium disturbance.

Tools:

All patients was subjected to the following:

- 1-Medical history.
- 2-Physical examinations& neurological examination.
- 3-Electrocardiogram.
- 4-Laboratory:

- Procalcitonin (PCT) measurement within less than 72 hours after symptom onset (For PCT measurement, the blood sample was collected by venipuncture within 48 hours after hospital admission. Blood samples were centrifuged at 2264 g for 10 minutes. The serum was measured within 2 hours after sample collected)
- Cbc (complete blood count).
- Total bilirubin and direct bilirubin.

- aspartate aminotransferase (AST) and alanine transaminase (ALT)
- serum urea&creat.
- Triglycerides .
- CRP (C-reactive protein)
- thyroid function test (free t3&free t4&TSH)
- serum electrolytes (Na,K&Ca total and ionized)

5-Radiological: CT brain (initial and follow up after 48 hs) or MRI brain with diffusion.

6-The Modified Rankin Scale (mRS) after one month from onset of acute ischemic stroke. (mRS) is used to measure the degree of disability in patients who have had a stroke.

Ethical consideration:

An informed written consent was obtained from patients before participation, it included data about aim of the work, study design ,site ,time ,subject, tools,

confidentiality and their acceptance for publication of anonymous data was obtained .An approval from Research Ethics Committee in Benha faculty of medicine was obtained.

Statistical analysis:

The collected data was tabulated and analyzed using the Statistical Package for Social Science (SPSS) .Categorical data was expressed as number and percentage using "chi square" or Fisher's exact test for analyzing them. Continuous variables was presented as mean and standard deviation if normally distributed using "Student t" test for analyzing them. Or median and interquartile range (IQR) If non parametric, with Mann Whitney as a significant test. Other suitable tests of significance was used if indicated according to the situation. The accepted level of significance in this work was 0.05, (P<0.05 will be considered significant).

3. Results

Table (1) Demographic data in patients with AIS.

		AIS N=70	
		No.	%
Gender	Male	24	34.3
	Female	46	65.7
Age (years)			
Mean ± SD.		63.30 ± 11.37	
Median (Min. – Max.)		62.0 (42.0 – 85.0)	

SD, standard deviation.

The present study was conducted on 70 AIS cases. Their mean age was 63.3 years, ranged from 42 to 85 years. They were 24 (34.3%) males and 46 (65.7%) females.

Table (2) Risk factors in patients with AIS.

Risk factor	AIS N=70	
	No.	%
Hypertension	39	55.7%
DM (Diabetes mellitus)	37	52.9%
IHD (ischemic heart disease)	26	37.1%
Mitral valve replacement (MVR)	3	4.3%
Smoking		
No	64	91.4%
Yes	6	8.6%
ECG		
NSR	60	85.7%
AF	10	14.3%

Risk factors was assessed thoroughly for all studied cases, 39 cases (55.7%) had hypertension, 37 cases (52.9%) had DM, 26 cases (37.1%) had IHD, 3 cases (4.3%) had MVR, 6 cases (8.6%) were smokers, while 64 cases (91.4%) were non smokers. All studied cases were subjected to ECG, 10 cases (14.3%) had AF, while 60 cases (85.7%) had NSR.

Table (3) The outcome in patients with AIS.

Outcome	AIS N=70	
	No.	%
Survived	63	90.0
Not survived	5	7.1
Missed follow up	2	2.9

Among the entire period of the study, 5 cases (7.1%) died, while 2 cases (2.9%) missed follow up, and 63 cases (90%) survived.

Table (4) Modified Rankin Scale among AIS cases (n = 68).

MRS	AIS N=68	
	No.	%
No significant disability	22	32.4
Slight disability	28	41.2
Moderate disability	5	7.4
Moderately severe disability	8	11.8
Died	5	7.4
Good outcome (≤ 2)	50	73.5
Poor outcome (> 2)	18	26.5

Modified Rankin Scale was calculated for cases who had follow up (n=68), 22 cases (32.4%) had No significant disability, 28 cases (41.2%) had Slight disability, 5 cases (7.4%) had Moderate disability, 8 caess (11.8%) had Moderately severe disability and 5 cases (7.4%) died.

All patients were grouped as two levels: good outcome group (mRS scores ≤ 2) and poor outcome group (mRS scores ≥ 3) (Pan et al., 2020). Good outcome was achieved in 50 cases (73.5%) while poor outcome was present in 18 cases (26.5%).

Table (5) Association between survival with PCT in AIS patients.

	PCT (ng/mL)				Man Whitney test (U)	p
	Mean±SE	Median	Minimum-Maximum			
Survival						
Survived	0.23 0.01	0.19	0.11 0.44		185	0.041
Not survived	0.41 0.10	0.53	0.11 0.60			

Higher PCT level was significantly associated with non survived cases (p=0.041).

Table (6) Association between MRS grades with PCT in AIS patients.

MRS grades	Mean±SE	PCT (ng/mL)		Test (p)
		Median	Minimum-Maximum	
No significant disability	0.124±0.002	0.13	0.11-0.14	Kruskal-Wallis H=57.8 P<0.001*
Slight disability	0.221±0.012	0.21	0.15-0.35	
Moderate disability	0.384±0.010	0.40	0.36-0.40	
Moderately severe disability	0.428±0.004	0.43	0.41-0.44	
Died	0.567±0.020	0.57	0.53-0.60	
Good outcome (n=50)	0.178 ± 0.01	0.15	(0.11 – 0.35)	Mann-Whitney= 841.0 p<0.001*
Poor outcome (n=18)	0.41 ± 0.026	0.42	(0.11 – 0.60)	

Ascending level of PCT was noticed to be associated with increased mRS grades (p<0.001). Poor outcome was significantly associated with higher procalcitonine concentration (p <0.001 respectively).

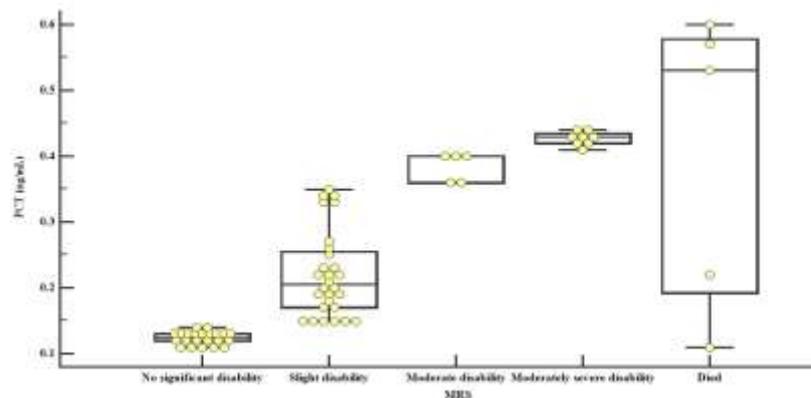


Fig. (1) PCT levels among MRS grades in AIS patients.

Table (7) Validity of Procalcitonin in differentiating poor outcome from good outcome among AIS patients

	Procalcitonin	CRP
AUC	0.934	0.801
95% CI	0.832 – 1	0.686 -0.888
P1	<0.001*	<0.001*
Cut off	>0.215	>21
Sensitivity (%)	94.4	66.7
Specificity (%)	74	80
PPV (%)	56.67	54.6
NPV (%)	97.37	87.0
Accuracy	79.41	76.5
P2		0.028*

, positive predictive value; NPV, negative predictive value. *: Significant ≤ 0.05

P1, probability of AUC; p2, comparison between AUCs of CRP and PCT.

ROC curve of PCT and CRP was conducted for prediction of poor outcome. Regarding PCT, high accuracy AUC was found (AUC=0.934). At best cut off value (=0.215 ng/mL), sensitivity was 94.4%, specificity was 74%, PPV was 56.7%, NPV was 97.4%, accuracy was 79.4%.

While, CRP showed moderate accuracy AUC was found (AUC=0.801). At best cut off value (>21mg/L), sensitivity was 66.7%, specificity was 80%, PPV was 54.6%, NPV was 87%, accuracy was 76.5%.

On comparing both AUCs, PCT showed significantly better AUC (better ability to predict poor outcome) (p=0.028).

Table (8) Logistic Regression analysis for prediction of poor outcome.

	Univariable			Multivariable		
	p	OR	95% C.I	p	OR	95% C.I
Sex	0.083	2.333	0.853 – 3.021			
Age	0.047*	1.053	1.001 – 1.108	0.617	1.180	0.618 – 2.253
Smoking	0.468	0.923	0.742-1.147			
Hypertension	0.011*	2.870	1.509 – 32.838	0.003*	2.700	1.269 – 6.961
DM	0.910	1.065	0.360 – 3.146			
IHD	0.839	0.889	0.285 – 2.772			
AF	0.757	0.768	0.144 – 4.091			
Total cholesterol	0.156	1.011	0.991 – 1.023			
HDL	0.125	1.281	0.924 – 1.441			
LDL	0.308	1.007	0.994 – 1.019			
Total bilirubin	0.289	1.449	0.730 – 2.876			
Direct bilirubin	0.122	0.002	0.000 – 5.485			
ALT	0.125	0.866	0.763 – 1.182			
AST	0.104	0.936	0.863 – 1.014			
Urea	0.065	1.031	0.998 – 1.065			
Creatinine	0.277	0.401	0.077 – 2.084			
Triglycerides	0.160	1.006	0.998 – 1.015			
CRP	<0.001*	1.048	1.028-1.068	0.004*	1.060	1.019-1.102
Free T3	0.178	0.493	0.176 – 1.381			
Free T4	0.270	3.942	0.345 – 44.984			
TSH	0.717	0.897	0.497 – 1.617			
Na	0.850	0.985	0.838 – 1.157			
K	0.137	2.102	0.993 – 5.401			
Total Ca	0.212	3.881	0.848 – 11.173			
Ionized Ca	0.241	3.219	0.952 – 6.275			
TLC	0.003*	1.227	1.073-1.404	0.149	1.226	0.930-1.615
Neutrophils	0.239	1.036	0.977 – 1.098			
Procalcitonin	<0.001*	1.247	1.126 – 1.381	0.016*	1.911	1.131-3.228

OR, odds ratio; CI, confidence interval. *: Significant ≤ 0.05

Regression analysis was conducted for prediction of poor outcome using age, gender, comorbidities, laboratory data, and PCT as confounders. Older age, presence of hypertension, higher CRP, TLC, PCT were associated with risk of poor outcome in univariable analysis. However, in multivariable analysis, presence of hypertension, higher CRP, PCT were considered risk predictors of poor outcome among studied cases.

4. Discussion

Abrupt stroke is sometimes referred to as a cerebrovascular accident, which is the acute development of localised neurological symptoms in a vascular region due to underlying cerebrovascular illness. Every year, there are 800,000 new strokes in the United States. Every 40 seconds, a fresh stroke is performed. The fifth greatest cause of mortality and the leading cause of disability is stroke. There are two primary stroke kinds. The most prevalent form is an ischemic stroke, which occurs when blood supply to a particular region of the brain is interrupted [18].

Ischemic stroke is caused by a thrombotic or embolic event that restricts blood flow to the brain. In a thrombotic event, the blood flow to the brain is impeded inside the blood artery owing to malfunction within the vessel itself, which is often the result of atherosclerosis, arterial dissection, fibromuscular dystrophy, or an inflammatory disorder. In an embolic event, foreign material obstructs blood flow through the afflicted channel [19].

Acute stroke happens rapidly, and the limited early treatment choices at this stage have shown to be effective. Chemical (thrombolysis) or mechanical (thrombectomy) removal of the thrombus are examples of treatments for acute ischemic stroke (AIS) [20].

Significant research efforts are now directed to understanding secondary damage after the original acute injury. Regarding diagnosis, prognosis, and potential treatment targets, recent interest has centred on the study of inflammatory biomarkers related with vascular diseases [21].

Stroke prognosis is not always straightforward to measure and forecast. In affluent nations, the prognosis for ischemic stroke has improved owing to the success of thrombolytic clinical trials and mechanical thrombectomy, specifically the expansion of the treatment window in recent recommendations. This minimises additional brain damage during the acute phase owing to hypoperfusion and may alter inflammatory pathways, hence reducing mortality and morbidity [22].

The detection and measurement of biomarkers implicated in these pathways may provide a more accurate prognosis of ischemic stroke. Theoretically, inflammatory pathways might be therapeutic targets for the secondary harm caused by inflammation following AIS. However, with the exception of vasculitis, the administration of steroids failed to show any advantage in AIS [22].

To discover prospective new treatment targets, it is necessary to unravel inflammatory mechanisms related with AIS. Several inflammatory biomarkers have already been evaluated: brain natriuretic peptide, copeptin, C-reactive protein (CRP), glutamate, glucose, and vitamin D show a substantial connection with stroke patient prognosis [23]. All of these biomarkers are instantly accessible thanks to a quick analysis technique. [14]

Recent research suggests that procalcitonin (PCT) may be a better prognostic inflammatory biomarker for ischemic stroke than CRP. [14]

C-cells of the thyroid gland generate PCT, a prohormone of calcitonin. In prior research, PCT seemed to be a more accurate indicator of infection than other biomarkers. Recent research suggests it may be a better prognostic marker for ischemic stroke than CRP. [14]

The concentration of PCT rose momentarily and seemed related to the degree of tissue damage and hypovolemia after severe trauma (Wang et al., 15). Moreover, PCT independently predicted death in individuals with ischemic stroke [10].

So, the purpose of this research was to examine the predictive value of Procalcitonin (PCT) blood levels in individuals with acute ischemic stroke (AIS).

From July 2022 to September 2022, this cohort research was done on patients with acute ischemic stroke from the neuropsychiatric department at Benha university hospitals. All patients provided their informed consent. The approval of the Benha faculty of medicine's research ethics committee was acquired.

The current investigation included 70 instances with AIS. During the whole trial period, 7.1% of participants died, 2.9% were lost to follow-up, and 90% survived. Their mean age was 63.3 years, with a range of 42 to 85 years and a majority of females. There were 34.3% men and 65.7% women present. Majority of patients were non smokers. Medical history was reviewed comprehensively for all analysed patients, 55.7% had hypertension, 52.9% had DM, 37.1% had IHD, 4.3% had MVR .

All patients evaluated were exposed to ECG; 14.3% exhibited atrial fibrillation, whereas 85.7% had normal sinus rhythm. While Togha et al examined the electrocardiographic records of 361 patients with acute stroke and discovered the most common ECG abnormalities associated with stroke were T-wave abnormalities, prolonged QTc interval, and arrhythmias, which were found in 39.9%, 32.4%, and 27.1% of the stroke patients and 28.9%, 30.0%, and 16.2% of patients with no primary cardiac disease, respectively (Togha et al., 31).

In our study, the average TLC was 9.9X10⁹/L, the average RNC was 67.7%, the average TC was 174 mg/dL, the average TG was 144.4 mg/dL, the average LDL was 101 mg/dL, the average HDL was 44.4 mg/dL, the average bilirubin was 1.1 mg/dL, the average direct bilirubin was 0.2 mg/dL, the average ALT was 18.5 U/

While Alkhaneen et al. found that the fasting serum lipid profile of 114 ischemic stroke patients revealed elevated serum total cholesterol in 23.7% of patients, with a mean serum total cholesterol of 4.3 mmol/L, we found that the proportion of patients with elevated serum total cholesterol was significantly lower. 32 individuals had abnormal triglyceride levels, with a mean of 1.38 0.78. Likewise, serum LDL concentrations were elevated in 27 individuals, with a

mean value of 2.65 1.27 mmol/L. HDL was below the normal reference range in 96.5% of ischemic stroke patients, with a mean value of 1.02 0.27 mmol/L, according to Alkhanee et al.

For patients with follow-up, the Modified Rankin Scale (mRS) revealed that 32.4% had no major impairment, 41.2% had little disability, 7.4% had moderate disability, 11.8% had moderately severe disability, and 7.4% had passed away. All patients were divided into two groups: those with favourable outcomes (mRS scores 2) and those with unfavourable outcomes (mRS scores 3). 73.5 percent of outcomes were positive, whereas 26.5 percent were negative.

Comparing good and poor outcomes, poor outcomes were significantly associated with older age, hypertension, higher TLC, higher TC, lower HDL, higher K, total Ca, ionised Ca concentration, and high CRP, while gender, smoking, diabetes, IHD, and DVT, relative neutrophilic count, ECG, TG and LDL, liver functions, urea, creatinine, thyroid functions, and Na concentration had no significant association.

While Adrian et al. evaluated a total of 93 patients, 47 cases (mean age 65.51 11.73) and 46 controls (mean age 57.78 3.39) were included in the sample.

Those with NIHSS 10 comprised the Control group, whereas those with NIHSS 10 or death comprised the Case group. In an adjusted multivariate analysis, high platelet to lymphocyte ratio (PLR) ($p=0.008$) and high CRP ($p=0.008$) were independent risk factors for poor outcome. In bivariate analysis, the elderly ($p=0.05$), high CRP ($p=0.01$), and embolic stroke type ($p=0.01$), as well as high PLR ($p=0.01$), were identified as significant risk factors for poor outcome in patients with acute ischemic stroke [33]

Additionally, Furlan et al. investigated a total of 8829 AIS cases. Every 1 10(-9) /l rise in TLC was linked with stroke severity on admission ($P=0.0001$), disability at release ($P=0.0005$), and 30-day death ($P=0.0001$). The Kaplan-Meier curves show that enhanced TLC is linked with increased mortality following acute ischemic stroke ($P=0.001$) (Furlan et al., 34), which is consistent with our findings.

While Wang et al. studied 10,299 eligible patients in total, Poor functional outcome utilising mRs was shown to be related with lower levels of potassium and sodium, but there was no significant relationship between calcium and these outcomes, which contradicts our findings. The gap may be attributable to variations in demographic characteristics, as well as the bigger sample size and longer length of follow up in this investigation (Wang et al., 35)

The present research performed a regression analysis for the prediction of a bad result; the presence of hypertension, increased CRP, and PCT were regarded risk predictors of a poor outcome among the patients examined. There was a correlation between increasing PCT levels and higher mRS scores.

This was consistent with the findings of Cho et al, who evaluated a total of 333 individuals. After

controlling for age, sex, medical history, and laboratory findings, the odds ratios for 90-day mortality were as follows: 1.47 for the second quartile (2.2–6.3), 2.54 (95% CI: 0.95–5.91) for the third quartile (6.4–19.6), and 4.10 for the fourth quartile. In AIS patients, a procalcitonin-to-crp ratio (PC ratio) of 2.2 was substantially related with increased mortality Cho et al., [36].

Shi and his colleagues performed a multivariate logistic regression study which revealed a correlation between PCT and AIS severity. PCT was an independent predictor of poor outcome at 3 months. PCT was a reliable diagnostic and predictive indicator for AIS and poor clinical outcomes in individuals with AIS Shi et al., [37].

The current investigation revealed that the median PCT level was 0.2 ng/mL, with a range of 0.1 to 0.6 ng/mL, and that a greater PCT level was strongly linked with patients that did not survive. A greater PCT concentration was strongly related with a worse result.

In accordance with the findings of Yan et al., PCT levels were considerably greater in AIS patients who died within 30 days than in those who survived. PCT was strongly linked with 30-day mortality and was a strong predictor of 30-day total mortality, as shown by regression analysis. Explaining that the elevated PCT level in blood may be the result of an inflammatory response in acute ischemic stroke Yan et al., [38].

The ability of PCT to initiate a systemic cascade of endothelial damage, thrombin formation, and microvascular compromise was attributed by another study to the fact that PCT levels were significantly higher in patients with an unfavourable functional outcome compared to those with a favourable outcome [14].

Cho et al. [36] found that PCT levels in non-survivors tended to be greater than in survivors, but this difference was not statistically significant. This disparity may be due to the study's varied methodology, demographic characteristics, and bigger sample size.

The present investigation demonstrated no significant connection between PCT level and gender, smoking, hypertension, diabetes, ischemic heart disease, or DVT or ECG abnormalities. PCT has a substantial positive association with age, CRP, total Calcium, ionised Calcium, K, urea, TLC, neutrophil, and MRS, as well as a significant negative correlation with direct bilirubin and free T3. Other than that, no significant relationships between PCT and investigated factors were discovered.

PCT in the observation group was substantially greater than in the control group, and PCT in the severe group was significantly higher than in the moderate group, according to a research by Wen et al. PCT in the big cerebral infarction group was more than PCT in the intermediate and small infarction groups, while PCT in the intermediate cerebral infarction group was greater than PCT in the small cerebral infarction group. PCT level was positively linked with both NIHSS and

infarction volume in the observation group. Consequently, the level of PCT in young patients with acute cerebral infarction may be associated with the inflammatory response of the cerebral artery and positively correlated with the amount of cerebral infarction and NIHSS score. PCT concentration may indicate the severity of acute cerebral infarction to some degree [39].

In addition, another research revealed that serum PCT level was an independent risk factor for premature mortality owing to cerebral infarction. They hypothesised that the serum PCT level is not only connected with the occurrence and severity of cerebral infarction, but also plays a role in its pathological course [40].

Comparing the AUCs of PCT and CRP in the current investigation, PCT shown a considerably greater capacity to predict poor outcome. In agreement with previous reports, PCT was a much stronger predictor of pneumonia linked with a stroke (El gazzar et al., 41). Others have observed that PCT is more significantly related with functional results and death after an ischemic stroke than CRP (Wang et al., 15). According to area under the curve (AUC) analysis, the discriminating strength of PCT is larger than that of CRP, as reported by others [42].

Also consistent with Li et al's prospective study of 374 patients with ischemic stroke who were hospitalised within 24 hours of the beginning of symptoms. The blood PCT levels of the 64 non-survivors were considerably ($P < 0.0001$) greater than those of the survivors. Multivariate COX regression analysis revealed that log-transformed PCT and Hs-CRP were independent predictors of death, with adjusted hazard ratios of 4.24 (95% confidence interval [CI], 2.42-6.30) and 15.37 (3.42-41.08), respectively. The area under the receiver operating characteristic curve of PCT and Hs-CRP were 0.89 (95% CI, 0.85-0.93) and 0.68 (95% CI, 0.59-0.77) for mortality, respectively (29). In this investigation, we observed that increasing levels of PCT were linked with higher mRS scores ($p < 0.001$). A greater procalcitonine concentration was substantially related with a worse result ($p < 0.001$, respectively).

After an ischemic insult, resident brain cells and invading immune cells in the ischemic brain upregulate inflammatory mediators, which play a complicated role in the pathogenesis of cerebral ischemia Jin et al., [43]. The proinflammatory cytokines tumour necrosis factor (TNF), interleukin (IL)1, IL6 and IL8 stimulate the PCT-producing CALC-1 gene in adipocytes. Moreover, the amount of calcitonin gene-related peptide (CGRP) rises after ischemia/reperfusion of the brain, which stimulates the formation of CALC-1 and raises serum PCT levels Vijayan et al., [44]

Modulating the production of pro-inflammatory cytokines, PCT influences the immunological response. Additionally, it functions as a chemokine, affecting the migration of monocytes and parenchymal cells to the site of inflammation. PCT may influence the induction

of Inducible nitric oxide synthase (iNOS), an enzyme that generates hazardous quantities of nitric oxide (NO). NO generated by iNOS leads to the pathological development of cerebral ischemia, cerebral inflammation, and neuronal deficit amplification [49]

In addition to being an indicator of inflammation, PCT may be modulated by anti-inflammatory medications such as ibuprofen, suggesting its potential toxicity during inflammation development, according to studies by Preas et al [46].

Different routes, including activation of the Wnt (Wingless-related integration site) pathway, an increase in the formation of reactive oxygen species, and a link with DNA methylation, are among the hypothesised mechanisms that imply PCT may function as a hazardous mediator [47]

Recently, aberrant Wnt signalling activity has been detected in ischemic stroke, which is associated by substantial blood-brain barrier (BBB) rupture, neuronal death, and central nervous system neuroinflammation [48].

After ischemia/reperfusion, excessive reactive oxygen species (ROS) generation leads to acute brain damage Yingze et al., [49]. By activating transcription factors, upregulating adhesion molecules, boosting chemokine synthesis, and attracting inflammatory cells, ROS may stimulate the production of inflammatory cytokines, inducing inflammation and affecting the function of vascular cells Ruan et al., [50]. In the end, cytotoxicity is caused by lipid peroxidation, protein oxidation, and DNA breakage [51]

Emerging research suggested that DNA methylation plays a multifaceted function in several pathogenic processes of cerebral ischemia. One of the causes may be neuronal cell death-promoting effects. Other possible mechanisms include X chromosome inactivation, deficiency of methylenetetrahydrofolate reductase (MTHFR), aberrant homeostasis regulation, increasing oxidative stress, and abnormal modulation of synaptic plasticity [52], so PCT, in a dose-dependent manner, is capable of affecting all qualities of cellular functions, including proliferation, induction of cell death, metabolism, integrity, and thus the degree of disability.

5. Conclusion

PCT is a major indicator of poor prognosis in AIS patients. PCT is an important indicator of severity and mortality after AIS.

6. Limitations

We did not analyse dietary components, which is one of the primary limitations of the current research. Previous research indicates that dietary variables affect all causes of death (53). The second issue is that it did not represent the various subtypes or severity of ischemic stroke based on imaging research data. This is a preliminary novel research using a mix of laboratory tests to evaluate stroke patients for severity. We believe

that a subtype-specific investigation should be included to future prospective validation studies.

The third constraint is that PCT and CRP measures were taken just upon admission, although serial measurements have been demonstrated to be more predictive than single readings (54). However, it is also recognised that PCT at the time of admission is a major predictor of infectious illness present. Nonetheless, we discovered a correlation between a higher initial PCT level and the prognosis of ischemic stroke.

7. Recommendations

For more research, it is suggested THAT Large multicenter studies should be undertaken to corroborate our findings, which include dietary components for analysis, represent the various ischemic stroke subtypes or severity based on imaging study data, and serial measures of PCT and CRP, which may be more predictive than single values.

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Conflicts of interest:

There are no conflicts of interest

References

- [1] BCV.Campbell, DA.De Silva, MR. Macleod, SB.Coutts, LH.Schwamm, SM.Davis, Ischaemic stroke. *Nat Rev Dis Primers*,vol. 5,PP.70, 2019.
- [2] CO.Johnson, M.Nguyen, GA.Roth, E. Nichols, T.Alam, D.Abate, Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*,vol. 18,pp.439–58, 2019.
- [3] AT.Rai, AE.Seldon, S.Boo, PS.Link, JR.Domico, AR.Tarabishy, A population-based incidence of acute large vessel occlusions and thrombectomy eligible patients indicates significant potential for growth of endovascular stroke therapy in the USA. *J Neurointerv Surg*,vol. 9,pp.722, 2017.
- [4] JJ.Heit, ES.Sussman, M.Wintermark, Perfusion computed tomography in acute ischemic stroke. *Radiol Clin North Am*,vol.57,pp.1109–16,2019.
- [5] OA.Berkhemer, PSS.Fransen, D. Beumer, LA. van den Berg, HF. Lingsma, AJ.Yoo, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *New England Journal of Medicine*,vol.372,pp.11–20,2014.
- [6] BC.Campbell, PJ.Mitchell, TJ. Kleinig, HM.Dewey, L.Churilov, N. Yassi, Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med*,vol.372,pp.1009–18,2015.
- [7] GW.Albers, MP.Marks, S.Kemp, S .Christensen, JP.Tsai, S.Ortega-Gutierrez, RA.McTaggart, MT. Torbey, M.Kim-Tenser, T.Leslie-Mazwi, A.Sarraj, SE.Kasner, SA. Ansari, SD.Yeatts, S.Hamilton, M .Mlynash, JJ.Heit, G.Zaharchuk, S. Kim, J.Carrozzella, YY.Palesch, AM. Demchuk, R.Bammer, PW.Lavori, JP. Broderick, MG.Lansberg, DEFUSE 3 Investigators. Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. *N Engl J Med*. Feb 22,vol.378(8),pp.708–718,2018.
- [8] KA.Yaeger, H.Shoirah, CP.Kellner, J. Fifi, J.Mocco, Emerging technologies in optimizing pre-intervention workflow for acute stroke. *Neurosurgery*. (2019) ,vol.85,pp. 9–17.
- [9] JM.Luna, YP.Moon, KM.Liu, High-sensitivity C-reactive protein and interleukin-6- dominant inflammation and ischemic stroke risk: the northern Manhattan study. *Stroke* ,vol.45,pp.979-987,2014.
- [10] D.T ian, S.Zhang, X.He, & H.Liu, Serum procalcitonin as a diagnostic marker in acute ischemic stroke. *Neuroreport*,vol. 26(1),pp. 33–37,2015.
- [11] S.Harbarth, K.Holeckova, C. Froidevaux, D.Pittet, B.Ricou, GE.Grau, Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. *Am J Respir Crit Care Med*. Aug 1. ,vol.164(3),pp.396-402,2001.
- [12] – KS. Massaro, SF.Costa, C.Leone, Procalcitonin (PCT) and C-reactive protein (CRP) as severe systemic infection markers in febrile neutropenic adults. *BMC Infect Dis*,vol.7,pp.137,2007.
- [13] J.Jae-Sik, J.Sung-Mi, Diagnostic value of procalcitonin and CRP in critically ill patients admitted with suspected sepsis. *J Dent Anesth Pain Med*,vol.15,pp.135-140,2015.
- [14] WJ.Deng, RL.Shen, M.Li, Relationship between procalcitonin serum levels and functional outcome in stroke patients. *Cell Mol Neurobiol*,vol.35,pp.355-361,2015.
- [15] – C.Wang, L.Gao, ZG.Zhang, Procalcitonin is a stronger predictor of long-term functional outcome and mortality than high-sensitivity C-reactive protein in patients with ischemic stroke. *Mol Neurobiol*,vol.53,pp.1509-1517,2016.
- [16] – S.Dewilde, L.Annemans, A.Peeters, D.Hemelseoet, Y.Vandermeeren, P. Desfontaines, Modified Rankin scale as a determinant of direct medical costs after stroke. *Int J Stroke*. 2017 Jun,vol.12 (4),pp.392-400.
- [17] H.Pan, M.Fu, W.Ge, C.Z hou, The effects of changes in platelet-to-neutrophil ratios 24 hours after intravenous thrombolysis on prognosis in acute ischemic stroke patients. *Clin Neurol Neurosurg*,vol.190,pp.105739,2020.
- [18] – P.Tadi, F.Lui, Acute Stroke. [Updated 2022 Jun 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing ,vol.14,pp.54-78, 2022.
- [19] G.Ntaios, Embolic Stroke of Undetermined Source: JACC Review Topic of the Week. *J Am Coll Cardiol*. Jan 28,vol.75(3),pp.333-340,2020.

- [20] W.J.Powers, A.A.Rabinstein, T.Ackerson, O.M. Adeoye, N.C. Bambakidis, K.Becker, J.Biller, M.Brown, B.M. Demaerschalk, B.Hoh, Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*,vol. 50, ,pp.344–418, 2019.
- [21] U.U.Tamhane, S.Aneja, D. Montgomery, E.-K.Rogers, K.A.Eagle, H.S.Gurm, Association Between Admission Neutrophil to Lymphocyte Ratio and Outcomes in Patients with Acute Coronary Syndrome. *Am. J. Cardiol.*,vol. 102,pp. 653–657, 2008.
- [22] S.Shekhar, M.W.Cunningham, M.R.Pabbidi, S.Wang, G.W.Booz, F.Fan, Targeting vascular inflammation in ischemic stroke: Recent developments on novel immunomodulatory approaches. *Eur. J. Pharmacol.*,vol. 833,pp. 531–544, 2018.
- [23] W.Whiteley, WL.Chong, A.Sengupta Blood markers for the prognosis of ischemic stroke: a systematic review. *Stroke*,vol. 40,pp.380–389,2009.
- [24] B.Fuentes, J.Castillo, B.San Jose´ ,The prognostic value of capillary glucose levels in acute stroke: the GLyemia in acute stroke (GLIAS) study. *Stroke*,vol. 40,pp.562–568,2009.
- [25] Y.Wang, H.Ji, Y.Tong, Prognostic value of serum 25 – hydroxyl vitamin D in patients with stroke. *Neurochem Res*,vol.39,pp.1332–1337,2014.
- [26] L.Chang, H.Yan, H.Li, N-terminal probrain natriuretic peptide levels as a predictor of functional outcomes in patient with ischemic stroke. *NeuroReport*,vol. 25,pp.985–990,2014.
- [27] XN.Meng, N.Li, DZ.Guo 2014 High plasma glutamate levels are associated with poor functional outcome in acute ischemic stroke. *Cell Mol Neurobiol.* ,vol.45,pp.89-96
- [28] WJ.Tu, X.Dong, SJ.Zhao , Prognostic value of plasma neuroendocrine biomarkers in patients with acute ischaemicstroke. *J Neuroendocrinol* ,vol.25,pp.771–778,2013.
- [29] YM.Li, XY.Liu, Serum levels of procalcitonin and high sensitivity C-reactive protein are associated with long-term mortality in acute ischemic stroke. *J Neurol Sci.* 2015 May 15,vol.352(1-2),pp.68-73,2015.
- [30] M.Katan, YP.Moon, MC.Paik, B. Mueller, A.Huber, RL.Sacco, MS.Elkind, Procalcitonin and Midregional Proatrial Natriuretic Peptide as Markers of Ischemic Stroke: The Northern Manhattan Study. *Stroke*. Jul,vol.47(7),pp.1714-9,2016.
- [31] M.Togha, A.Sharifpour, H.Ashraf, M. Moghadam, MA. Sahraian Electrocardiographic abnormalities in acute cerebrovascular events in patients with/without cardiovascular disease. *Ann Indian Acad Neurol*,vol.21,pp.31-45,2013.
- [32] H.Alkhanee, D.Alsadoun, L.Almojel, (May 31,) Differences of Lipid Profile Among Ischemic and Hemorrhagic Stroke Patients in a Tertiary Hospital in Riyadh, Saudi Arabia: A Retrospective Cohort Study. *Cureus*,vol. 14(5),pp. 25540,2022.
- [33] - F.Adrian, A.Laksmidewi, I.Putra, I.Adnyana, I.Budiarsa, T.Sarongku, C.Tertia, & I.Widyadharma, High platelet to lymphocyte ratio as a risk factor for poor outcome in acute ischemic stroke patient. *Neurology Asia*, ,vol.27(2),pp. 231–237,2022.
- [34] JC.Furlan, MD.Vergouwen, J.Fang, FL.Silver, White blood cell count is an independent predictor of outcomes after acute ischaemic stroke. *Eur J Neurol.* Feb,vol.21(2),pp.215-22,2014.
- [35] A.Wang, X.Tian, H.Gu, Y.Zuo, X. Meng, P.Chen, H.Li, Y.Wang, Electrolytes and clinical outcomes in patients with acute ischemic stroke or transient ischemic attack. *Ann Transl Med.* Jul,vol.9(13),pp.1069,2021.
- [36] J.Cho, S.Jeong, JH.Lee, Procalcitonin to C-reactive protein ratio is associated with short-term mortality in ischemic stroke patients: preliminary report. *Arch Med Sci.* Oct 23,vol.18(2),pp.344-352,2020.
- [37] G.Shi, “Procalcitonin related to stroke-associated pneumonia and clinical outcomes of acute ischemic stroke after IV RT-Pa treatment,” *Cellular and Molecular Neurobiology*, ,vol.42(5), pp. 1419–1427,2021.
- [38] L.Yan, S.Wang, L.Xu, Z. Zhang, Liao P.Procalcitonin as a prognostic marker of patients with acute ischemic stroke. *J Clin Lab Anal*,vol.34,pp.23301,2020.
- [39] H.Wen, M.Lv, Correlation analysis between serum procalcitonin and infarct volume in young patients with acute cerebral infarction. *Neurol Sci.* Aug,vol.42(8),pp.3189-3196,2021.
- [40] Y.Zhang, G.Liu, Y.Wang, Procalcitonin as a Biomarker for Malignant Cerebral Edema in Massive Cerebral Infarction. *Sci Rep*,vol. 8,pp. 993 ,2018.
- [41] AEM. Elgazzar, TH. Elkhateeb, H. Hosny, AY.Ffouda, Procalcitonin and clinical pulmonary infection score as predictors of stroke-associated pneumonia: a prospective observational study,vol.68:3,pp. 363-370,2019.
- [42] S.Hangai, Y.Nannya, M. Kurokawa, Role of procalcitonin and C-reactive protein for discrimination between tumor fever and infection in patients with hematological diseases. *Leuk Lymphoma*,vol.56,pp.910–4,2015.
- [43] R.Jin, L.Liu, S.Zhang, A.Nanda, G.Li, Role of inflammation and its mediators in acute

- ischemic stroke. *J Cardiovasc Transl Res. Oct*,vol.6(5),pp.834-51,2013.
- [44] A.L.Vijayan, Vanimaya, S.Ravindran, Procalcitonin: a promising diagnostic marker for sepsis and antibiotic therapy. *j intensive care*,vol. 5,pp.51 ,2017.
- [45] T.Li, T.Xu, J.Zhao, H.Gao, W.Xie, Depletion of iNOS-positive inflammatory cells decelerates neuronal degeneration and alleviates cerebral ischemic damage by suppressing the inflammatory response. *Free Radic Biol Med. Mar*,vol.181,pp.209-220,2022.
- [46] HL.Preas, ES.Nylen, RH.Snider, Effects of anti-inflammatory agents on serum levels of calcitonin precursors during human experimental endotoxemia. *J Infect Dis.*,vol.184(3),pp.373–376,2001.
- [47] B.Durnaś, M.Wątek, T.Wollny, K. Niemirowicz, M.Marzec, R.Bucki, Gózdź S. Utility of blood procalcitonin concentration in the management of cancer patients with infections. *Onco Targets Ther. Jan 22*,vol.9,pp.469-75,2016.
- [48] Z.Mo, Z.Zeng, Y.Liu, L.Zeng, J.Fang, Y.Ma, Activation of Wnt/Beta-Catenin Signaling Pathway as a Promising Therapeutic Candidate for Cerebral Ischemia/Reperfusion Injury. *Front Pharmacol. May 20*,vol.13,pp.914537,2022.
- [49] Y.Yingze, J.Zhihong, J.Tong, L.Yina, Z.Zhi, Z.Xu, X.Xiaoxing, G. Lijuan, NOX2-mediated reactive oxygen species are double-edged swords in focal cerebral ischemia in mice. *J Neuroinflammation. Jul 14*,vol.19(1),pp.184,2022.
- [50] Y.Ruan, S.Jiang, A.Musayeva, A.Gericke, Oxidative stress and vascular dysfunction in the retina: therapeutic strategies. *Antioxidants* ,vol.9(8),pp.14-74, 2020.
- [51] I.Olmez, & H.Ozyurt, Reactive oxygen species and ischemic cerebrovascular disease. *Neurochemistry International*,vol. 60(2),pp. 208–212,2012.
- [52] M.Zeng, J.Zhen, X.Zheng, H.Qiu, X.Xu, J.Wu, Z.Lin, & J.Hu, The Role of DNA Methylation in Ischemic Stroke: A Systematic Review. *Frontiers in Neurology*,vol. 11, pp.566124,2020.
- [53] M.Mazidi, N.Katsiki, DP.Mikhailidis, D.Pella, Banach M.Potato consumption is associated with total and cause specific mortality: a population-based cohort study and pooling of prospective studies with 98,569 participants. *Arch Med Sci*,vol.16,pp. 260-72,2020.
- [54] P.Schuetz, I.Suter-Widmer, A. Chaudri, M.Christ-Crain, W. Zimmerli, Mueller B. Prognostic value of procalcitonin in community-acquired pneumonia. *Eur Respir J*,vol.37,pp. 384-92,2011.
- [55] A.Zhydkov, M.Christ-Crain, R. Thomann, Utility of procalcitonin, C-reactive protein and white blood cells alone and in combination for the prediction of clinical outcomes in community-acquired pneumonia. *Clin Chem Lab Med*,vol.53,pp.559-66,2015.