ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

CARDIAC TROPONIN T: A PROGNOSTIC FACTOR IN PATIENTS WITH PRIMARY INTRACEREBRAL HEMORRHAGE.

[1]Arwa Magdi Ragab, [2]Mahmoud Elsaid Alebiary, [3]Wael Mahmoud Elsayed, [4]Mohammed Hanafy Aly Ghonemy

[1,2,3,4,]Neurology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt.

Corresponding author:Arwa Magdi Ragab, Email: arwamagdi@rocketmail.com

Abstract

Background: primary intracerebral hemorrhage is a serious global issue producing marked disability affecting productivity on both national and international levels. Several studies have been directed to predicting functional outcome using variable biomarkers aiming to reduce undesirable outcome. Cardiac Troponin T has proved its role as a prognostic factor in several conditions but its efficacy in predicting outcome in ICH has been infrequently studied. **Aim:** to identify the relationship between cardiac troponin T and functional outcome in patients with primary intracerebral hemorrhage measured by modified Rankin scale (MRS). **Methods:** 60 patients were recruited having primary intracerebral hemorrhage admitted to neurology critical care unit at Zagazig University Hospital during the period between October 2020 and July 2021, studied by a prospective cohort study. Cardiac troponin T was measured upon admission. Functional outcome was assessed after 14 and 30 days by MRS. **Results:** 13 (21.7%) patients had favorable outcome after 14 days compared to 47 (78.3%) patients with unfavorable outcome. Whereas 27 (45%) patients had favorable outcome compared to 33 (55%) patients after 30 days by MRS.**Conclusion:** cardiac troponin T level is a valuable biomarker for predicting functional outcome in patients with primary intracerebral hemorrhage.

Keywords: primary intracerebral hemorrhage, outcome, modified Rankin scale, cardiac Troponin T.

Introduction:

Spontaneous intracerebral hemorrhage (sICH) has been described to be the most fatal form of stroke accounting for nearly 10-15% of all strokes worldwide. The rate of mortality and disability after sICH reflects the pressing need to improve current therapy. Accurate identification of its outcome predictors may help ideal beginning time for immediate intervention and management. Earlier studies have investigated significant associations between clinical, laboratory and radiographic factors on one hand and outcomes in patients with sICH on the other hand **(1)**.

Several markers have been studied to view their association with the outcome of intracerebral hemorrhage to serve as future predictors for functional outcome and disability in those patients. Among those predictors as blood glucose level assessed by **Zheng et al. (2)** and neutrophil to lymphocyte ratio assessed by **(3)**.

Recently, elevation of cardiac troponin has been reported to occur in ICH patients along with only 1.2% of them died of cardiac causes **(4)**.

Hays and Diringer (5) found that the relation between CTnT and hematoma volume expansion and cerebral herniation was inconclusive.

So this study puts more focus on the utility of cardiac troponin T to assess outcome in patients with intracerebral hemorrhage.

Patients and methods:

After considering the ethical rules according to the Code of Ethics of the World Medical Association (Declaration of Helsinki), written informed consent was obtained from all participants, the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. 60 patients were recruited from Neurology intensive care unit and stroke unit during the period from October 2020 till July 2021 fulfilling the following inclusion criteria: age above 18 years, patients with CT brain showing spontaneous ICH admitted within 24 hours after the onset of the qualifying event. The following were considered as exclusion criteria: suspicion or documented history of a bleeding disorder, history of head trauma, receiving anticoagulant drugs before the onset of ICH, a documented and discovered A-V malformation; aneurysm or cerebral neoplasm as the underlying cause of intracerebral hemorrhage, hemorrhagic transformation of cerebral infarct, a recent ischemic heart diseases, defined as previous

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

myocardial infarction (MI) within 2 weeks prior to and up to 3 days after onset of hemorrhagic stroke, symptoms suggestive of acute MI or unstable angina before admission, previous coronary surgery, other heart diseases and debilitating diseases with the possibility of serum cardiac troponin T elevation, such as congestive heart failure, valvular heart disease (VHD) and renal impairment.

All patients were subjected to the following:

(A) Clinical assessment including detailed medical history, full general examination and thorough neurological examination.

The following scales were used to assess the level of consciousness, stroke severity, follow up and short-term outcome of stroke:

❖ Level of consciousness using the Glascow Coma Scale (GCS) classified into mild cases (13-15), moderate cases (9-12) and severe cases (3-8). **(6)**.

❖ Intracerebral hemorrhage score (ICH): is commonly used for risk stratification of outcome in patients with intracerebral hemorrhage depending on 5 main points: GCS, age, size and location of the hemorrhage as well as the presence of intraventricular extension. The end result has a range from 0 to 6 with zero having the best overall 30-days outcome and 6 describing dead patients. **(7)**.

Modified Rankin Scale (mRs): is a commonly used scale for assessing the extent of disability after stroke. We used it to evaluate our patients for short-term outcome (including mortality) after 30 days of stroke onset. The scale consists of 6 grades, from 0 to 5, with the best score 0 corresponding to no symptoms and the worse score 5 corresponding to severe disability. Death can be rated 6 in the mRs. A score on the mRS>2 is defined as unfavourable outcome **(8)**.

(B) Investigations:

I) Laboratory investigations:

❖ Full routine laboratory investigations at admission including complete blood count (CBC), liver function tests (LFT), kidney function tests (KFT), urine analysis, random plasma glucose level on admission followed by fasting and 2 hours post-prandial plasma glucose assessment in diabetes, lipid profile, coagulation profile.

❖ Special laboratory investigations: Serum troponin T level was measured within 12-72 h of stroke with r*eference values:* <100ng/l

II) Radiological investigations:

CT scan of the brain: within the first 24 hours from the onset of symptoms with stressing on the site, size of hematoma, surrounding edema and intraventricular extension.

III) Cardiac investigation: 12-Leads electrocardiogram (ECG): was done to all recent ischemic stroke patients to determineECG changes in patients with unstable angina or recent myocardial infarction.

Statistical analysis:

Statistical analysis was done using Statistical Package for the Social Science (SPSS) software version 25. Data was presented in tables and figures. Quantitative data was presented as mean, median and interquartile range. Qualitative data was presented as frequencies and proportions. Kolmogorov-Smirnov and Levene tests were used to determine the distribution characteristics of variables and variance homogeneity. Pearson's chi square (χ^2) test and fisher's exact test were used to analyze qualitative data as appropriate. Freidman test (F) was used to analyze dependent continuous data.Student t test (T) and Mann Whitney test (MW) was used to analyze continuous data between two groups as appropriate. Kruskal-Wallis H (KW) tests were used to analyze continuous data between more than two groups.Spearman's correlation coefficient (r) was used to test correlation between neutrophil lymphocyte ratio and continuous variables.Binary logistic regression analysis of the predictors of the outcome of ischemic stroke was done to test independent variables and exclude confounders.

P-value of ≤ 0.05 was accepted as statistically significant.

Results:

This prospective cohort study was conducted during the period between October 2020 and July 2021 on 60 patients with first time ever diagnosed primary intracerebral hemorrhage admitted to Neurology department intensive care unit and stroke unit within 24 hours of the onset of the symptoms with performing CT brain, cardiac troponin T level and full routine lab showing that mean age 60.1±9.4 years

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

ranging from 35 to 80 years. Males were 43 (71.7%) and 17(28.3%) were females as shown in tables (1) and (2) as well as figure (1) .

It was also found that 50 of the studied patients were hypertensive either known hypertensive or recently discovered (83.3%), 28 patients were diabetic (46.7%), 22 patients were smokers (36.7%), 20 patients tested positive for HCV (33.3%), 15 patients showed dyslipidemia (25%) and 3 patients were addict (5%) as shown in table (2).

CT findings of the studied patients showed that basal ganglia hematoma came in first position by 25 patients (41.7%) compared to 15 patients with lobar hematoma (25%), 12 patients with thalamic hematoma (20%), 5 patients with cerebellar hematoma (8.3%) and 3 patients with brainstem hematoma (5%). We also found that mean volume of hematoma of the studied patients was 35±20.6 with median 25 and range (5-150), 10 patients showed surrounding edema (16.7%) and 15 patients (25%) showed intraventricular extension as shown table (3).

In our present study, regarding GCS, 58.3% had moderate score (9-12) compared to 25% had mild score (<9) and 16.7% had severe score (≥ 13) with a median value of11 (5-15) as in table (4). There was statistically highly significant ($p< 0.00001$) difference among patients with mild, moderate and severe condition according to GCS regarding mean values of cardiac troponin T by ANOVA test. Also, there was statistically significant increase in mean value of cardiac troponin T in patients with mild ($p<0.0001$) and moderate ($p<0.0001$) cases compared to patients with severe impairment. However, there was no statistically significant ($p> 0.05$) increase in mean value of cardiac troponin T in patients with moderate condition compared to patients with mild condition as in table (6).

Our results regarding ICH score were also studied and it was found that patients with score 2 were the most numerable by 33.3% of the whole sample followed score 3 representing 25% then score 4 representing 16.7% then patients with score 1 showing 15% and patients with score 5 by 6.7% in the last place but no patients had score 6 as in table (4).There was statistically highly significant ($p< 0.00001$) difference among patients with ICH score 0,1,2,3,4,5 regarding mean values of cardiac troponin T by ANOVA test. Also, there was statistically significant increase in mean value of cardiac troponin T in patients with score 0 ($p=0.0027$), score 1, score 2 and score 3 compared those with score 4 and score 5 as in table (6).

The outcome of the condition in our study was assessed by MRS after 14 days and after 30 days with patients with unfavorable outcome (defined as MRS>2) in both groups taking upper hand by 78.3% after 14 days with median 3(1-6) and 55% after 30 days with median 2(0-6) as in table (5). There was highly statistically significant difference between favorable and unfavorable outcome after 30 days but not after 14 day as shown in table (7).

There is highly significant negative correlation between GCS and cardiac troponin T, significant positive correlation between ICH and cardiac troponin T and significant positive correlation between MRS after 30 days and cardiac troponin T as in table (8).

Table (1): demographic criteria of the studied patients:

Variables	Studied patients (n=60)
Age (years):	
Mean ± SD	60.1 ± 9.4
Range	35.0 – 80.0
Sex:	
Male	43 (71.7%)
Female	17 (28.3%)

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

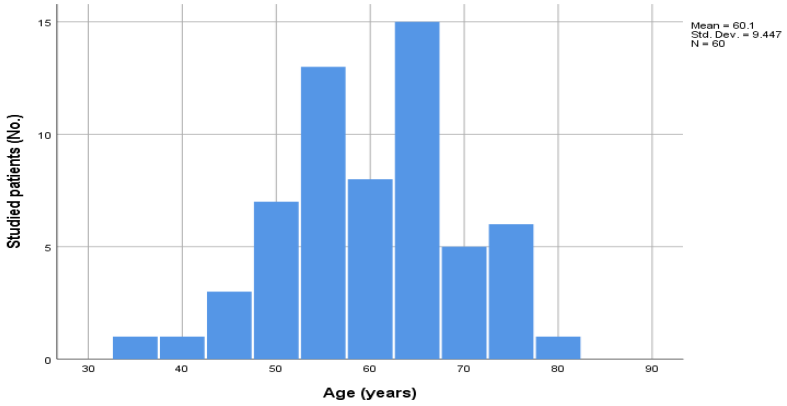

Figure (1): showing age of the studied patients.

Table (2): risk factors of the studied patients:

Variables	Studied patients (n=60)	
	No.	%
Hypertension	60	100%
Diabetes mellitus	28	46.7%
Smoking	22	36.7%
HCV	20	33.3%
Dyslipidemia	15	25%
Addiction	3	5%

Table (3): CT findings of the studied patients:

		Studied patients (n=60)	
		No.	*%*
Side of hematoma	Right	20	33.3%
	Left	40	66.7%
Site of hematoma	Basal ganglia	25	41.7%
	Lobar	15	25%
	Thalamic	12	20%
	Cerebellar	5	8.3%
	Brainstem	3	5%
Surrounding edema		10	16.7%

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

Intraventricular extension	15	25%
Hematoma volume	Mean± SD	35±20.6
	Median (Range)	25(5-150)

Table (4): clinical scales of severity on admission:

Scales	**Studied patients (n=60)**		
	Severity	**No**	**%**
GCS	**Mild (13-15)**	**15**	**25**
	Moderate (9-12)	**35**	**58.3**
	Severe (3-8)	**10**	**16.7**
ICH	**0**	**2**	**3.3**
	1	**9**	**15**
	2	**20**	**33.3**
	3	**15**	**25**
	4	**10**	**16.7**
	5	**4**	**6.7**
	6	**0**	**0**

Table (5): clinical scales of outcome MRS after 14 days and 30 days:

Scales	**Studied patients (n=60)**		
	Score	**No**	**%**
MRS after 14 days	Favorable (0-2)	13	21.7
	Unfavorable (>2)	47	78.3
MRS after 30 days	Favorable (0-2)	27	45.0
	Unfavorable (>2)	33	55.0

Table (6): Relation between clinical scales of severity on admission and cardiac troponin T:

Scales		**Troponin**		**Test of probability**	**P value**
	Severity	**Mean±SD**	**Range**		
GCS	**Mild (13-15)**	37.4**±35.15**	5.0 - 120.0		**<0.00001** HS**
	Moderate (9-12)	44.68**±36.41**a	8.0-155.0		
	Severe (3-8)	101**±21.93**bc	60.0-120.0		
ICH	**0**	11**±8.49**	5.0-17.0	9.332	**<0.00001** HS**
	1	35.78**±36.97**a	5.0-115.0		
	2	37.25**±29.51**bf	9.0-110.0		
	3	50.8**±37.23**cgj	17.0-120.0		
	4	104.7**±32.02**dhkm	60.0-155.0		

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

	5	107.5**±18.93**eilno	80.0-120.0		
	6	11**±8.49**	5.0-17.0		

**: highly significant (p<0.00001)

Regarding GCS:

ap= 0.516, bp<0.0001compared to mild cases.

cp<0.0001 compared to moderate cases.

Regarding ICH:

ap= 0.3883, bp=0.2326, Cp=0.1630, dp=0.0027, ep=0.0028 compared to score 0 cases.

fp=0.9, gp=0.96,hp=0.0004, ip=0.004compared to score 1 cases.

jp=0.238, kp<0.0001, lp=0.0002compared to score 2 cases.

mp=0.001, np=0.001 compared to score 3 cases.

op=0.8744 compared to score 4 cases.

Table (7): relation between cardiac troponin T and MRS after 14 and 30 days:

Scales		**Troponin**		**Test of probability**	**P value**
		Mean**±SD**	Range		
MRS after 14 days	Favorable (0-2)	41.36±45.53	5.0-120.0	1.759	0.19
	Unfavorable (>2)	59.17±42.12	9.0-155.0		
MRS after 30 days	Favorable (0-2)	33.4±31.5	5.0-120.0	13.837	<0.00001** HS
	Unfavorable (>2)	70.65±41.05	8.0-155.0		

Table (8): correlation between cardiac troponin T and MRS

Variables	**Troponin**	
	R	**P**
GCS	-0.5635	**<0.00001(HS)**
ICH	0.4947	**0.000059(HS)**
MRS after 14 days	No significant relation so no correlation	
MRS after 30 days	0.6425	**<0.00001(HS)**

Discussion:

The mean age 60.1±9.4 years ranging from 35 to 80 years. Males were 43 (71.7%) and 17(28.3%) were females which was consistent with **Tveiten et al. (9) as well asRincon et al. (10)** who described that the overall incidence of primary intracerebral hemorrhage was more in men than in women unlike **Nilüfer et al. (11)** and **Ruiz et al. (12)** who stated that there was no difference among male and female in the incidence of primary intracerebral hemorrhage.

During analysis of the included patients, we found that 50 of the studied patients were hypertensive either known hypertensive or recently discovered (83.3%) which was close to the percentage proved by **Brouwers et al. (13)** (82%)**, Safatli et al. (14)** (86.5%)and **Kheder and Ahmed (15)** (80.9%)**.** However the difference in these percentages could be attributed to difference in sample size, socioeconomic levels and health education in the studied groups.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

Also 28 patients (46.7%) were diabetic which was close to the results found by **Zheng et al. (16)** (44.7%) and **Xu et al. (17)** (42%) but way more than **Kremer et al. (18)** (19.4%) and **Melmed et al. (19)** (25%) mostly due to difference in the population and sample size.

22 patients (36.7%) were smokers which was consistent with **Rathor et al. (20)** and **Ren et al. (21)** but more than **Li et al. (22)** (25.5%) and **Xu et al. (17)** (26.5%).

20 patients (33.3%) tested positive for hepatitis C virus and 15 patients (25%) showed dyslipidemia close to **Melmed et al. (21)** (28%) and **Djelilovic-Vranic et al. (23)** (27.38%) but higher than **Ji et al. (24)** (6.4%).

3 patients (5%) were addict either IV drug addicts, pill addicts or alcohol addicts which was lower than most of studies as **Li et al. (22)** (18.4%) and **Ren et al. (21)** mostly due to ethical and religious factors.

CT findings of the studied patients showed that basal ganglia hematoma came in first position by 25 patients (41.7%) compared to 15 patients with lobar hematoma (25%), 12 patients with thalamic hematoma (20%), 5 patients with cerebellar hematoma (8.3%) and 3 patients with brainstem hematoma (5%) which is close to the findings of **Nag et al. (25)** who reported that basal ganglia hematoma was the most common among patients with primary intracerebral hemorrhage studied but far more than the findings found by **Attia et al. (26)** who found lobar hematoma to be the most common one of the patients this could be attributed to difference in studied population regarding their number, age and demographic criteria.

We also found that mean volume of hematoma of the studied patients was 35±20.6 with median 25 and range (5-150) which was close to **Rahmani et al. (27)** but there was a difference regarding intraventricular extension of hematoma and surrounding edema which was less in our study.

Regarding GCS, 58.3% had moderate score (9-12) compared to 25% had mild score (<9) and 16.7% had severe score (≥ 13) with a median value of11 (5-15). This is close to **Han et al. (28)** who reported in a cohort study that their patients GCS of 11.8±2.5 also close to **Wang et al. (29)**.

ICH score was also studied among the patients in our study and it was found that patients with score 2 were the most numerable by 33% of the whole sample followed score 3 representing 25% then score 4 representing 16.7% then patients with score 1 showing 15% and patients with score 5 by 6.7% in the last place but no patients had score 6.

This is close to the results found by **Fernandes et al. (30)** who also reported that patients with score 2 were the most numerous patients found in New Castle but far from what **Suthar et al. (31)** proved that patients with score 0 were the most numerous whereas patients with score 2 came in the place before the last one.

The outcome of the condition in our study was assessed by modified Rankin scale (MRS) after 14 days and after 30 days with patients with unfavorable outcome (defined as MRS>2) in both groups taking upper hand by 78.3% after 14 days with median 3(1-6) and 55% after 30 days with median 2(0-6) which is close to **Trifan et al. (32)** who found MRS with poor outcome in 53.3% of the patients with median 4 (1-6) but completely different from the results found by **Zweifel et al. (33)** who found the absolute contrast of the above mentioned results where patients with favorable outcome in their research represented 55% which could be attributed to various differences in the demographic criteria as well as differences in inclusion and exclusion criteria.

For assessment of functional outcome was modified Rankin scale which was measured after 14 days and 30 days and compared as regarding cardiac Troponin T showing that was highly statistically significant difference between favorable and unfavorable outcome after 30 days but not after 14 days and statistically significant positive correlation ($r=0.6425$ and $p<0.00001$).

The results after 30 days were in agreement with what **He et al. (4)** found ($r=0.350$, $p<0.001$) and **Lioutas et al.2019 (34)** however the difference between these studies and the MRS after 14 days could be attributed to the difference in the period of time after which functional outcome was assessed by MRS where 14 days shall be considered very short time compared to **Lioutas al. (34)** who assessed the outcome after 3 and 12 months while **He et al.**

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

(4) who assessed outcome after 14 days had a much larger population size of 1004 compared to 60 patients in our study.

The mechanisms of elevated cTnI in some of the patients with ICH was complicated and incompletely understood. Cardiac troponins are considered the most sensitive and specific biochemical markers for cardiac injury. **(35)**

Thus, elevation and dynamic changes of serum cTnI levels are indicators of cardiac injury after ICH. The excess of catecholamines was found in patients with ICH, which peaked on the first week and then declined. (**36)**

Given that catecholamine was capable of producing myocardial necrosis, even in the nonischemic heart, the catecholamine surge theory has been reasonable linked to cardiac injury after ICH. **(37).**

In addition, systemic inflammatory responses are activated after ICH and might contribute to myocyte injury and cell death. **(38).**

However the end result of our study is considered to be a combination of the results found are close to **He et al. (4)** who showed that there was statistically positive correlation between cardiac troponin and ICH as well as MRS after 14 days or upon discharge if earlier as well as statistically significant negative correlation with GCS in 1004 patients studied retrospectively however they differ from us that they measured MRS only after 14 days .

On the contrary, **Hjalmarsson et al. (39)** absolutely denies any significant relation between cardiac troponin T and outcome instead they relate prognosis to cardiac changes associated with intracerebral hemorrhage especially prolonged QT interval and they attributed these changes to the stress caused by the central condition causing release of catecholamines into the blood stream.

References:

1- **Dekker SE, Hoffer SA, Selman W, Bambakidis NC.** Spontaneous intracerebral hemorrhage. In Principles of Neurological Surgery Elsevier.2018: 334-342.

2- **Morotti A, BoulouisG, Dowlatshahi D, Li Q, Barras CD, Delcourt C, et al.** Standards for detecting, interpreting, and reporting noncontrast computed tomographic markers of intracerebral hemorrhage expansion. Annals of neurology. (2019): 86(4): 480-492.

3- **Volbers B, Giede-JeppeA, Gerner ST, Sembill J., Kuramatsu JB, Lang S,** et al.Peak perihemorrhagic edema correlates with functional outcome in intracerebral hemorrhage. Neurology 2018: 90(12): e1005-e1012.

4- **He Y, Liu Q, Wang J, Wang DW, Ding H, & Wang W.** Prognostic value of elevated cardiac troponin I in patients with intracerebral hemorrhage. Clinical cardiology. (2020); 43(4): 338–345.

5- **Hays A, Diringer MN.** Elevated troponin levels are associated with higher mortality following intracerebralhemorrhage. Neurology 2006: 66(9): 1330-1334.

6- Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet. 1974;2(7872): 81-4.

7- **Hemphill JC 3rd, Bonovich DC, Besmertis L, Manley GT, Johnston SC.** The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. Stroke. 2001; 32(4): 891-7.

8- **Saposnik G, Di Legge S, Webster F, Hachinski V.** Predictors of major neurologic improvement after thrombolysis inacute stroke. Neurology.2005: 65(8), 1169-1174.

9- **Tveiten A, Ljøstad U, Mygland Å, Thomassen L, Pripp AH, Naess H. Intracerebral** Hemorrhage in Southern Norway – A Hospital-Based Incidence Study. Eur Neurol 2012; 67: 240–5.

10- **Rincon F, Lyden P, Mayer SA**. Relationship between temperature, hematoma growth, and functional outcome after intracerebral hemorrhage. Neurocrit Care. 2013; 18(1): 45-53.

11- **Nilüfer t Y, Koyuncu BA, Çoban O, Tuncay R, Bahar SZ.**Gender differences in acute stroke: Istanbul medical school stroke registry. 2011; 59 (2): 174-179.

12- **Ruiz-Sandoval JL, Chiquete E, Gárate-Carrillo A, Ochoa-Guzmán A, Arauz A, León-Jiménez C, et al.** Spontaneous intracerebral hemorrhage in Mexico: results from a Multicenter Nationwide Hospital-based Registry on Cerebrovascular Disease (RENAMEVASC). Rev Neurol. 2011; 53(12): 705-12.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

13- **Brouwers HB, Chang Y, Falcone GJ, Cai X, Ayres AM, Battey TW, et al.** Predicting hematoma expansion after primary intracerebral hemorrhage. JAMA Neurol. 2014; 71(2): 158-64.
14- **Safatli DA, Günther A, Schlattmann P, Schwarz F, Kalff R, Ewald C.** Predictors of 30-day mortality in patients with spontaneous primary intracerebral hemorrhage. Surg Neurol Int. 2016; 7(Suppl 18): S510-7.
15- **Kheder AH, Ahmed AF.** Prognosis of patients with primary intracerebral haemorrhage in Erbil city: evaluating presentation, location and outcome. Journal of Kurdistan Board of Medical Specialties. 2019; 5 (2).
16- **Zheng Y, Hu Q, Manaenko A, Zhang Y, Peng Y, Xu L, et al.** 17β-Estradiol attenuates hematoma expansion through estrogen receptor α/silent information regulator 1/nuclear factor-kappa b pathway in hyperglycemic intracerebral hemorrhage mice. Stroke 2015; 46(2): 485–491.
17- **Xu XH, Ye XH, Li JW, Cai JS, Gao T, Zhang WJ, et al.** Association between remote diffusion-weighted imaging lesions and cerebral small vessel disease in primary intracerebral hemorrhage. 2019;26(7): 961-968.
18- **Kremer PH, Jolink WM, Kappelle LJ, Algra A, Klijn CJ;** SMART and ESPRIT Study Groups. Risk Factors for Lobar and Non-Lobar Intracerebral Hemorrhage in Patients with Vascular Disease. PLoS One. 2015; 10(11): e0142338.
19- Melmed KR, Cao M, Dogra S, Zhang R, Yaghi S, Lewis A, et al. Risk factors for intracerebral hemorrhage in patients with COVID-19. J Thromb Thrombolysis. 2021; 51(4): 953-960.
20- **Rathor MY, Rani MF, Jamalludin AR, Amran M, Shahrin TC, Shah A.** Prediction of functional outcome in patients with primary intracerebral hemorrhage by clinical-computed tomographic correlations. Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences. (2012); 17(11): 1056–1062.
21- **Ren H, Kong Y, Liu Z, Zang D, Yang X, Wood K, et al.** Selective NLRP3 (Pyrin Domain-Containing Protein 3) Inflammasome Inhibitor Reduces Brain Injury After Intracerebral Hemorrhage. Stroke. 2018; 49(1): 184–192.
22- **Li QQ, Li LJ, Wang XY, Sun YY, Wu J.** Research Progress in Understanding the Relationship Between Heme Oxygenase-1 and Intracerebral Hemorrhage. Frontiers in neurology. (2018); 9: 682.
23- **Djelilovic-Vranic J, Alajbegovic A, Zelija-Asimi V, Niksic M, Tiric-Campara M, Salcic S, et al.** Predilection role diabetes mellitus and dyslipidemia in the onset of ischemic stroke. Med Arch. 2013; 67(2): 120-3.
24- **Ji R, Shen H, Pan Y, Du W, Wang P, Liu G, Wang Y.** China National Stroke Registry investigators. Risk score to predict hospital-acquired pneumonia after spontaneous intracerebral hemorrhage. Stroke. 2014; 45(9): 2620-8.
25- **Nag C, Das K, Ghosh M, Khandakar MR.** Prediction of Clinical Outcome in Acute Hemorrhagic Stroke from a Single CT Scan on Admission. N Am J Med Sci. 2012; 4(10): 463-7.
26- **Attia S, EL Khatib MG, Bilal M, Nassar H**. Spontaneous intracerebral hematoma in young people: Clinical and radiological magnetic resonance imaging features by diffusion-weighted images. Egyptian Journal of Neurology, Psychiatry and Neurosurgery. 2007; 44: 561-576.
27- **Rahmani F, Rikhtegar R, Ala A, Farkhad-Rasooli A, Ebrahimi-Bakhtavar H.** Predicting 30-day mortality in patients with primary intracerebral hemorrhage: Evaluation of the value of intracerebral hemorrhage and modified new intracerebral hemorrhage scores. Iranian journal of neurology. (2018); 17(1): 47–52.
28- **Han J., Lee JM, Koh EJ, Choi HY.**The spot sign predicts hematoma expansion, outcome, and mortality in patients with primary intracerebral hemorrhage. Journal of Korean Neurosurgical Society. 201; 56(4): 303.
29- **Wang G, Li Z, Li S, Ren J, Suresh V, Xu D, et al.** Minocycline preserves the integrity and permeability of BBB by altering the activity of DKK1–Wnt signaling in ICH model. Neuroscience. 2019; 415: 135-146.
30- **Siddique MS, Fernandes HM, Wooldridge TD, Fenwick JD, Slomka P, Mendelow AD.** Reversible ischemia around intracerebral hemorrhage: a single-photon emission computerized tomography study. Journal of neurosurgery. 2002: 96(4): 736-741.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

31- **Suthar NN, Patel KL, Saparia C, Parikh AP.** Study of clinical and radiological profile and outcome in patients of intracranial hemorrhage. Annals of African medicine. 2016; 15(2): 69.

32- **Trifan G, Arshi B, Testai FD.** Intraventricular hemorrhage severity as a predictor of outcome in intracerebral hemorrhage. Frontiers in neurology. 2019; 10: 217.

33- **ZweifelC, Castellani G, Czosnyka M, HelmyA, Manktelow A, Carrera E, et al.** Noninvasive monitoring of cerebrovascular reactivity with near infrared spectroscopy in head-injured patients. Journal of neurotrauma. 2010; 27(11): 1951-1958.

34- **Lioutas VA, Goyal N, Katsanos AH, Krogias C, Zand R, Sharma VK,etal.** Optimization of risk stratification for anticoagulation-associated intracerebral hemorrhage: net risk estimation. Journal of neurology. 2019; 1-10.

35- **Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, et al.** ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). G Ital Cardiol (Rome). 2012; 13(3): 171-228.

36- **Leow MK, Loh KC, KiatKwek T, Ng PY.** Catecholamine and metanephrine excess in intracerebral haemorrhage: revisiting an obscure yet common "pseudophaeochromocytoma". J Clin Pathol. 2007; 60(5): 583-584.

37- **Kuo LT, Chen CM, Li CH, Tsai JC, Chiu HC, Liu LC, et al.** Early endoscope-assisted hematoma evacuation in patients with supratentorial intracerebral hemorrhage: case selection, surgical technique, and long-term results. Neurosurg Focus. 2011; 30(4): E9.

38- **Yang Y, Lv J, Jiang S, Wang D, Hu W, Deng C, et al.** The emerging role of Toll-like receptor 4 in myocardial inflammation. Cell Death Dis 7. 2016; e2234-e2234.

39- **Hjalmarsson C,Bergfeldt L, Bokemark L, Manhem K, Andersson B.** Electrocardiographic Abnormalities and Elevated cTNT at Admission for Intracerebral Hemorrhage: Predictors for Survival.2013; 18(5): 441-449.