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Research title

Frequency of polycythemia in ischemic stroke patients

A THESIS
Submitted to the department of medicine in Al-Nahrain College of Medicine as partial Fulfillment of the requirements for graduation

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Table of Contents

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Dedication

To my beloved parents, who were there for me

With their support and encouragement,

I dedicate this work to all their loving tears and beautiful smiles.

To all my respectable teachers,

Who enlightened me with their knowledge and understanding

To all my fellow students, friends, and colleagues

For their unconditional Support and love.

To all patients out there, hoping this little work will do something to help them more in their sufferings.

ABSTRACT

BACKGROUND:

Stroke is a clinical syndrome characterized by sudden onset of focal rather than global neurological signs that lasts more than 24 hours or leads to death. Polycythemia vera rubra Is a rare myeloproliferative disorder that has a high risk of stroke. The frequency of polycythemia for patients presented with ischemic stroke has been suggested for studying and compare with other researches.

PATIENTS AND METHOD:

A Cross sectional study was conducted with a total of 30 patient with of both gender randomly selected with clinical manifestations of acute ischemic stroke. All interviewed, and history was taken with evaluation of risk factors, smoking history,

RESULTS:

In our study, according to the frequency of PCV levels in all patients, 60% of patient were having normal PCV level, which was the predominant one. Other risk factors were studied as past medical history of patients, where hypertension was the most prevalent medical problem in these patients.

CONCLUSION:

Polycythemia is infrequent in our study among the patients but there is increase in hematocrit level among patients with ischemic stroke that might reflect the extent of ischemia and it is consequences

Chapter one: introduction & aim

Introduction

Stroke

Is a clinical syndrome characterized by sudden onset of focal rather than global neurological signs that lasts more than 24 hours or leads to death and has a presumed vascular cause, which includes both infarction and hemorrhage. [(1)] It is the third leading cause of death worldwide and major cause of adult neurological disability. [(1)] About 80% are caused by primary cerebral ischemia resulting in infarction, on the other hand only 20% are caused by cerebral hemorrhage. [(1)]

Ischemia occurs when there is a decrease in blood flow to less than 20 mL/100 g of brain tissue per minute. Reduction of blood flow to less than 16 mL/100g of brain tissue per minute leads to tissue death within one hour. In the absence of blood flow, death of brain tissue can occur within 4 to 10 minutes [(2).]

Majority of ischemic stroke are duo to local damage to a vessel wall from atherosclerosis and thrombosis. Rests of them are embolic cause and about one-quarter are cardioembolic [(1)].

There are many other rare causes of ischemic stroke. Several hematological disorders and hemostatic defects also increase risk of ischemic stroke. A common feature of these disorders is the creation of a prothrombotic state (hypercoagulable state).

Hematological diseases such as essential thrombocythemia, polycythemia rubra vera (PRV), and thrombotic thrombocytopenic purpura can cause stroke, though it is very rare. They usually produce their own features before development of stroke. [(2)]

Here we report a case who had Ischemic stroke as a presenting feature of Polycythemia rubra vera.

Risk factors: include: modifiable and non-modifiable conditions.

Identification of risk factors in each patient can uncover clues to cause of stroke and the most appropriate treatment & secondary prevention plan.

Non-modifiable risk factors include:
Age, gender, sex, ethnicity, history of migraine headache [3], heredity: family history of stroke or ischemic transient stroke. [4]

Modifiable risk factors include: Hypertension [5], Diabetes mellitus, Cardiac disease, TIAs, Carotids stenosis, Lifestyle issues: Hypercholesterolemia, Excessive alcohol intake, tobacco use [6], physical inactivity, Oral contraceptive use or Hormone use, Sickle cell disease. [5]

Pathophysiology:

1. **Ischemic stroke:**

A. **Thrombotic stroke**: In thrombotic stroke, a thrombus (blood clot) usually forms around atherosclerotic plaques. Since blockage of the artery is gradual, onset of symptomatic thrombotic strokes is slower than that of a hemorrhagic stroke [7]

B. **Embolic stroke**: An embolic stroke refers to an arterial embolism (a blockage of an artery) by an embolus, a traveling particle or debris in the arterial bloodstream originating from elsewhere. Emboli most commonly arise from the heart (especially in atrial fibrillation) but may originate from elsewhere in the arterial tree. In paradoxical embolism, deep venous thrombosis embolizes through an atrial or ventricular septal defect in heart into brain. [8]

2. **Hemorrhagic:** Hemorrhagic strokes are classified based on their underlying pathology. Some causes of hemorrhagic stroke are hypertensive hemorrhage, ruptured aneurysm, ruptured AV fistula, transformation of prior ischemic infarction, and drug induced bleeding. [9]

3. **Hematological abnormality** [10]
   - Thrombocytosis
   - Leukocytosis
   - sickle cell disease
   - Hypercoagulable state

- Polycythemia

Polycythemia Rubra Vera (PRV)

Is a rare myeloproliferative disorder that has a high risk of stroke. PRV is often found after the manifestation of cerebral infarction. An inverse relationship between cerebral blood flow and the packed cell volume has been shown in PRV. [10]

Cerebral blood flow is significantly reduced in polycythemia and predisposes to thrombus formation; it impairs normal uptake of oxygen by tissues and impairs the microcirculation with increase in the plasma red cell volume, the viscosity of the blood increases. Increase in viscosity present as complications of polycythemia including stroke, acute coronary syndrome, pulmonary emboli, deep vein thrombosis and other thrombotic phenomena. [11]

In PRV there is an absolute increase in red cell mass caused by an intrinsic problem in the red cell lineage that increases erythropoiesis. Serum erythropoietin is usually reduced or absent in PRV, but elevated in secondary polycythemia [11]

Secondary polycythemia most often develops as a response to chronic hypoxemia, which triggers increased production of erythropoietin by the kidneys. The most common causes of secondary polycythemia include obstructive sleep apnea, obesity hypoventilation syndrome, and chronic obstructive pulmonary disease (COPD). [12]

Other causes testosterone replacement therapy [13] and heavy cigarette smoking. Erythropoietin-secreting tumors (e.g., hepatocellular carcinoma, renal cell carcinoma, adrenal adenoma) cause some cases.

Secondary polycythemia must be differentiated from primary polycythemia and relative polycythemia (in which RBC numbers are normal but plasma volume is contracted. The reduction in plasma volume may be due to dehydration or to reduced venous compliance;
To the extent that the increased RBCs alleviate tissue hypoxia, secondary polycythemia may in fact be beneficial. [13]

Aim of present study

To review the frequency of polycythemia for patients presented with ischemic stroke

Chapter two: Patients and methods

Design:

Through the period extending from October 2018 to April 2019. Hospital based cross sectional study at medical floor at Imamin Khadimmian city hospital.

*Frequency***:** the number of occurrences of a repeating event per unit of time (14).

*Infrequent***:** occurring along interval is rare.

Method:

A total of [30] patients randomly selected were reviewed with clinical manifestations of acute ischemic stroke that received at medical floor, including: any patients diagnosed clinically with acute ischemic stroke within first 24 hours.

For every patient medical evaluation conducted included: history, evaluation of risk factors, smoking history, venous blood sampling and brain CT or MRI

Considering that normal range of:

Hb……Male (13-18) g/dl
Female (11.5-16.5) g/dl
PCV……. Male (40%-54%)
Female (37%-47%)
Platelet….150000-350000/mm3
WBC……. (4000-11000) mm3

Inclusion criteria:

This study included any patients who had complete acute ischemic stroke within 24 hours.

The following questions were formulated in the questioner:

Frequency of polycythemia in ischemic stroke patients

Research Questionnaire:

Patient name: _____

Gender: ☐ Female ☐ Male

Age: ( ) years old

Past medical history:

Social history: ☐ Active Smoker ☐ Ex-Smoker

No. Of cigarettes:

Family history of stroke: ☐ Yes ☐No

Site of stroke:

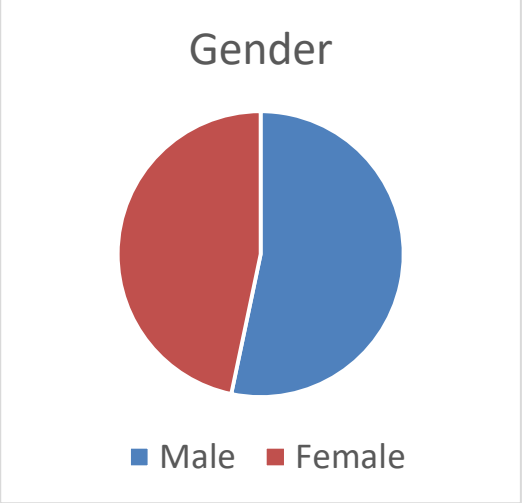
Side of stroke:

Investigations:

Hb	
PCV	
Platelets	
WBC	
ESR	

Chapter three: Results

The present study included many variables, data were analyzed and presented. The total number of collected cases was thirty including 16 patients were and 14 patients were female



Gender		
	Frequency	Percent
Male	16	53.3%
Female	14	46.7%
Total	30	100

Table (1) Gender distribution.

Figure (1) Gender distribution

The range age and mean age according to specific gender as follows:

- Female (34-87) years
- Male (35-72) years
- Concerning the general age ranged from (34-87)

Age Groups		
	Frequency	Percent
30-39 years	2	6.7%
40-49 years	4	13.3%
50-59 years	4	13.3%
60-69 years	8	26.7%
70-79 years	7	23.3%
80-89 years	5	16.7%
Total	30	100

Table (2) Age distribution.

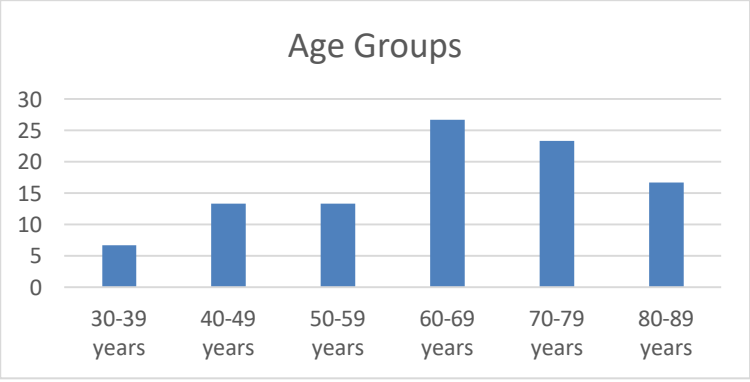


Figure (2) Age distribution.

According to the frequency of risk factors in all patients, Hypertension was the predominant risk in 12 patients and diabetes mellitus 5 patients and patients with hypertension and diabetes mellitus was 12 patients and one patient with no risk factors

Risk factors	Frequency	percentage
NO	1	3.4 %
HT	12	40%
DM	5	16.6%
HT & DM	12	40%

Table (3) Number of risk factors for stroke

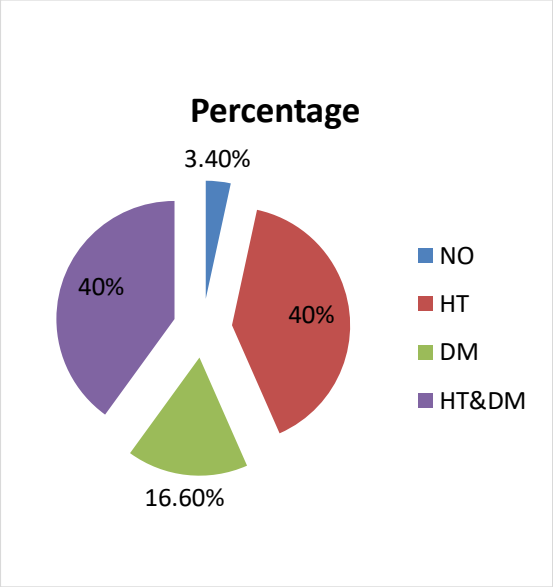


Figure (3) Risk factors frequency

According to smoking status, it is found that (20) patients were active smoker, (8) patients were not smoker and (2) were Ex-smoker. Figure (4) frequency of smoking among patients' ischemic stroke.

Smoking		
	Frequency	Percent
Not smoker	20	66.7%
Active smoker	8	26.7%
Ex-smoker	2	6.7%
Total	30	100

Table (4) prevalence of smoking among patients' ischemic stroke.

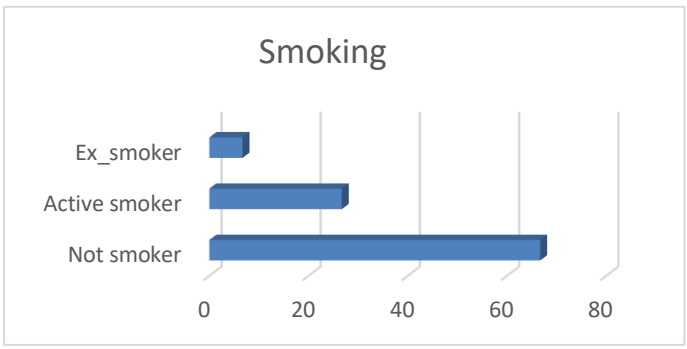


Figure (4) prevalence of smoking among patients' ischemic stroke.

Regarding to blood count finding in Hemoglobin level:

Hemoglobin readings		
	Frequency	**Percent**
Low	5	16.7
Normal	24	80
High	1	3.3
Total	30	100

Table (5) Hemoglobin levels findings

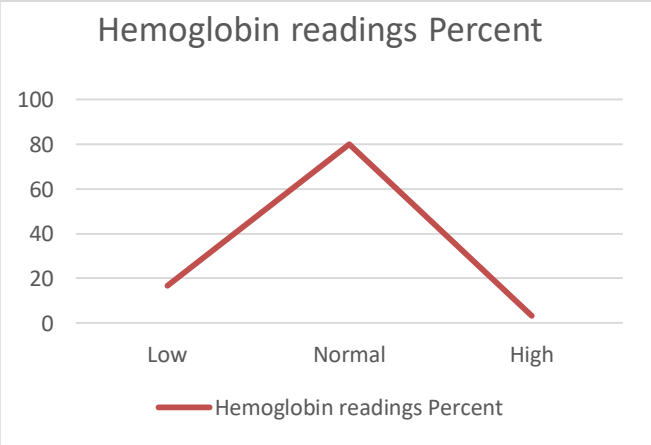


Figure (5) Hemoglobin levels findings

PCV level

PCV Readings		
	Frequency	Percent
Low	9	30%
Normal	18	60%
High	3	10%
Total	30	100

Table (6) PCV levels findings

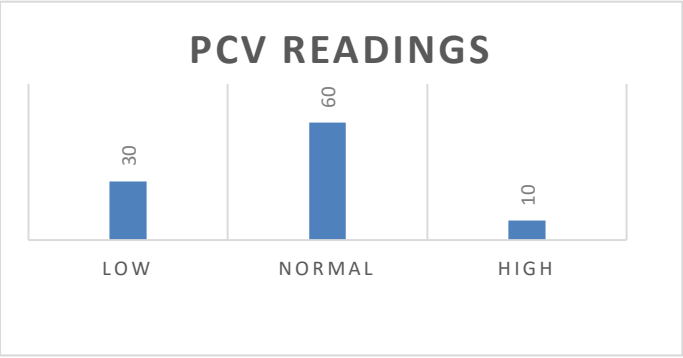


Figure (6) PCV levels findings

Regarding the relationship between PCV and the gender found that

PCV & Gender				
Count				
PCV		Gender		Total
		Male	Female	
	Low	4	5	9
	Normal	11	7	18
	High	1	2	3
Total		16	14	30

Table (7) relationship between PCV and the gender

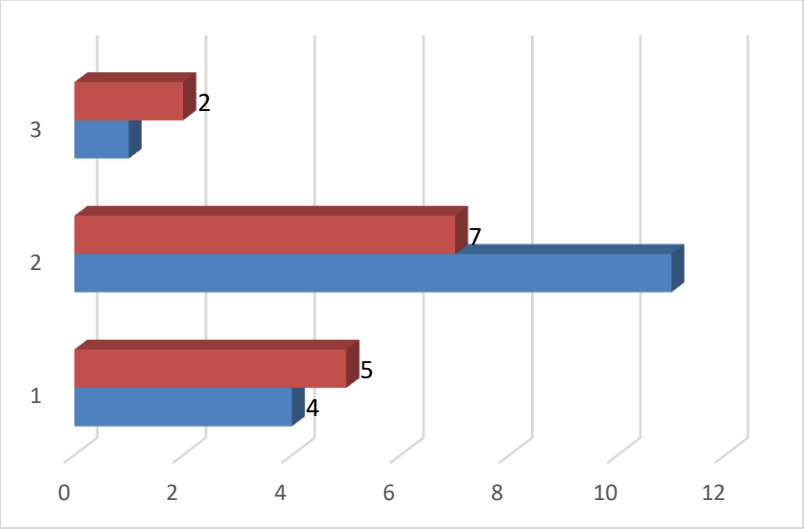


Figure (7) Relationship between PCV and the gender

Regarding relationship between PCV and the past medical history it's found that 1 patient with hypertension and high level PCV also 1 patient had high level PCV and diabetic and 1 patient had the two diseases together

PCV & Past Medical History					
Count					
		Past Medical History			Total
		HTN	DM	HTN & DM	
PCV	Low	4	1	0	9
	Normal	7	3	1	18
	High	1	1	0	3
Total		1	12	5	12

Table (8) Relationship between PCV and the past medical history

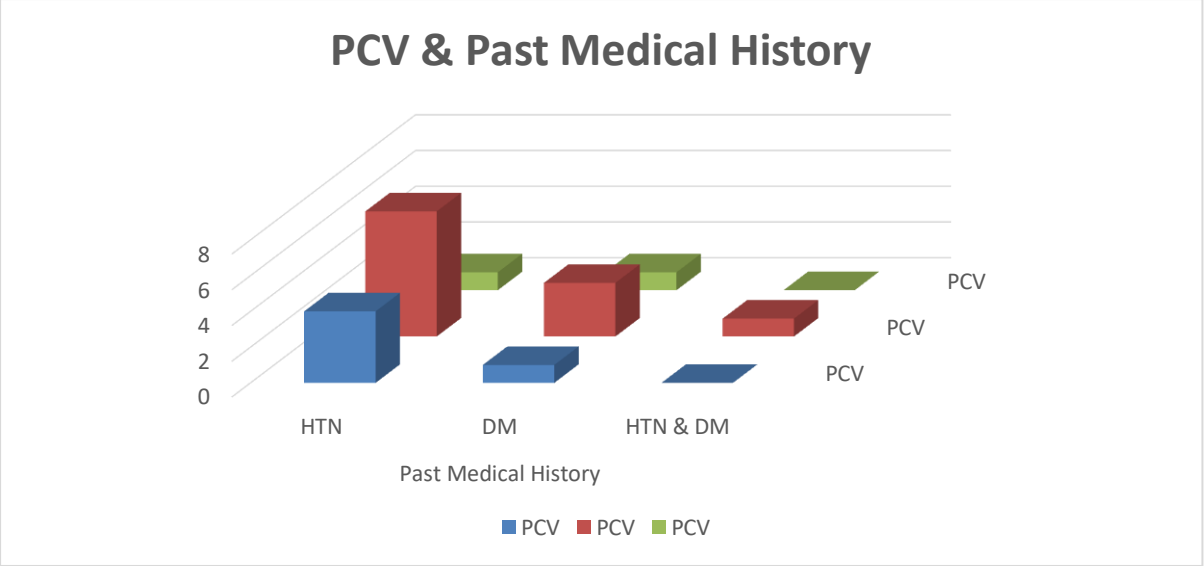


Figure (8) Relationship between PCV and the past medical history

Regarding smoking and PCV level it's found that only 3 patients had high level of PCV and they were not smoker.

PCV & Social History					
Count					
		Social History			Total
		Non-smoker	active smoker	Ex-smoker	
PCV	Low	6	1	2	9
	Normal	11	7	0	18
	High	3	0	0	3
Total		20	8	2	30

Table (9) Relationship between smoking and PCV level

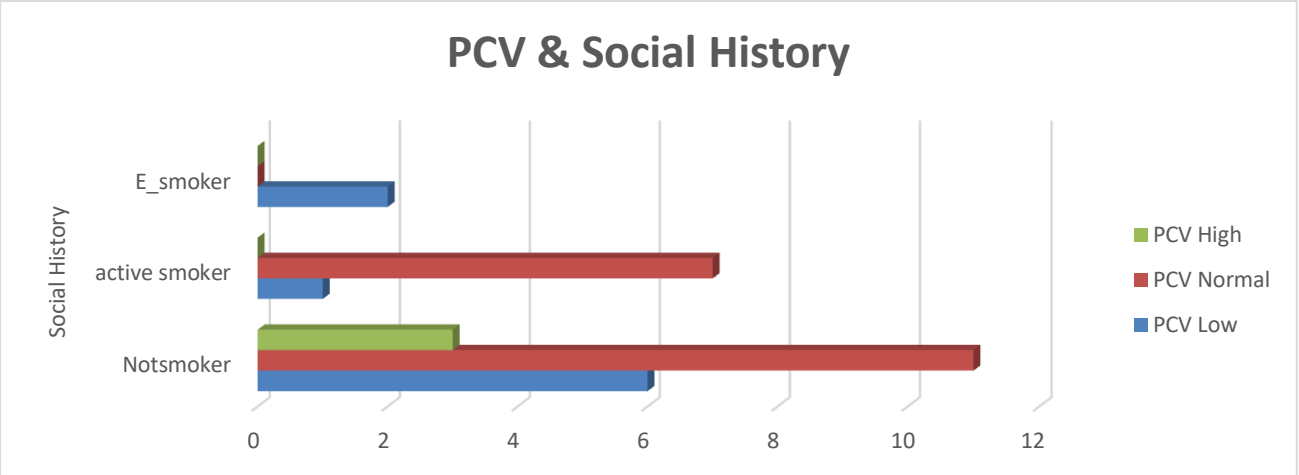


Figure (9) Relationship between smoking and PCV level

Chapter four: discussion:

In all, 30 patients with an acute ischemic stroke, the frequency in male (53.3%) higher than female (46.7%) and this agree with (Eisenblätter, D., Heinemann, L., Classen, E.), who conclude the incidence rate is higher in men than women.

The mean age of patients was (49) with most frequent reported at age (60-69) years and this result of present study in agreement with (National Institutes of Health (NIH) which said that Advanced age is one of the most significant stroke risk factors. 95% of strokes occur in people age 45 and older, and two-thirds of strokes occur in those over the age of 65

Hypertension was the predominant risk in 12 patients. The percentage of acute ischemic stroke in patients had two underlying disease is also higher than single disease and these results of present study agreement with (Whisnant JP) who reported that High blood pressure accounts for 35–50% of stroke risk.

Not smoker patients developed acute ischemic stroke was higher than active smoker and ex-smoker patients in (66.7%) and this result disagree with (Hankey GJ[1].) who said that Up to one quarter of all strokes are directly attributable to cigarette smoking, which independently increases the relative risk of stroke about three-fold.

Hematocrit finding suggested that highest frequency of patients within the normal range (60%) and only (10%) with high level of hematocrit and this result agree with study presented by (Linda LaRue, Milton Alter, Sue Min Lai, Gary Friday, Eugene Sobel, Larry Levitt, Robert McCoy, and Tish Isack) which found that even though patients with stroke usually have a normal hematocrit, those with a high hematocrit may be at increased risk for lacunar infarction opposed to thrombotic or embolic stroke or cerebral hemorrhage.

The highest percentage with high PCV found in female (6.67%) while in male (3.3%) With high percentage of male within the normal (36.7%)

And this disagree with study presented by (Zeng SM[1], Yankowitz J, Widness JA, Strauss RG.) and found that Males have a higher hematocrit (Hct) than females and these results suggest that the variation of Hct level by gender may have a genetic basis.

The high level of PCV is presented in patients with hypertension (6.67%) and this agree with study presented by (Cinar Y[1], Demir G, Paç M, Cinar AB.), found that is Increase in blood viscosity, defined as resistance to flow, is one factor in hypertension and atherosclerosis that contributes to the morbidity and mortality associated with tissue ischemia.

In this research we evaluated the effect of hematocrit on increasing viscosity, and possible related changes in blood pressure, flow rate, and the equivalent physiologic compensation ratios.

The high level of PCV presented in not smoker patients and this result disagree with study presented by (Whitehead TP[1], Robinson D, Allaway SL, Hale AC). () which reported that smoking increases the PCV level and this increase the risk of stroke.

Chapter five: conclusions and recommendations

Conclusions:

Polycythemia is infrequent in our study among the patients that might be explained by our small number of the samples but there is increase in hematocrit level among patients with ischemic stroke that might reflect the extent of ischemia and it is consequences in term of mortality and morbidity but it is.

Recommendation:

Large studies recommended to be performed to assess the relationship between polycythemia and increasing the incidence of ischemic stroke.

Reference

1. Recurrent ischemic stroke unveils polycythemia vera. BMJ Case Rep. 2015 Mar 9;2015. pii: bcr2014207625. doi: 10.1136/bcr-2014-207625.
2. Mechanisms of thrombogenesis in polycythemia vera. Blood Rev. 2015 Jul;29(4):215-21. doi: 10.1016/j.blre.2014.12.002. Epub 2014 Dec 13.
3. Schürks, M; Rist, PM; Bigal, ME; Buring, JE; Lipton, RB; Kurth, T (2009-10-27). "Migraine and cardiovascular disease: systematic review and meta-analysis". *BMJ (Clinical research ed.)*. 339: b3914. doi:10.1136/bmj.b3914. PMC 2768778. PMID 19861375.
4. . *www.nhlbi.nih.gov*. March 26, 2014. Archivedfrom the original on 27 February 2015. Retrieved 27 February 2015.
5. Medical Research Council Working Party (July 1985). "MRC trial of treatment of mild hypertension: principal results". *British Medical Journal*. 291 (6488): 97–104. doi:10.1136/bmj.291.6488.97. PMC 1416260. PMID 2861880.
6. Hankey GJ (August 1999). "Smoking and risk of stroke". *Journal of Cardiovascular Risk*. 6 (4): 207–11. PMID 10501270.
7. "Thrombus". *MedlinePlus*. U.S. National Library of Medicine. Archived from the original on 2016-07-01
8. *Robbins and Cotran Pathologic Basis of Disease, Professional Edition (8th ed.). Philadelphia, Pa: Elsevier. 2009. ISBN 978-1-4377-0792-2.*
9. Anonymous. "Hemorrhagic stroke". National Stroke Association. Archived from the original on 27 June 2016. Retrieved 30 June 2016.
10. Arboix A, Besses C. Cerebrovascular disease as the initial clinical presentation of haematological disorders. Eur Neurol. 1997; 37(4): 207-11
11. Nadeem O, Gui J, Ornstein DL. Prevalence of venous thromboembolism in patients with secondary polycythemia. *Clin Appl Thromb Hemost*. 2013 Jul-Aug. 19
12. Jones SD Jr, Dukovac T, Sangkum P, Yafi FA, Hellstrom WJ. Erythrocytosis and Polycythemia Secondary to Testosterone Replacement Therapy in the Aging Male. *Sex Med Rev*. 2015 Apr. 3 (2):101-112
13. Esparcieux A, Francina A, Vital-Durand D. [Abnormal haemoglobins with high oxygen affinity in the differential diagnostics of polycythemia]. *Rev Med Interne*. 2011 Oct. 32(10):e105-7.
14. http://www.merriam-webster.com/dictionary/frequency