People's Democratic Republic of Algeria
Higher Education Ministry And Scientific Research
University of El-Chahid Hamma Lakhdar El-Oued
Faculty of Natural Sciences and Life
Department of Cellular and Molecular Biology

Master's Memory

In order to obtain a diploma of an Academic Master

In Biological Sciences

Specialty: Applied Biochemistry

Theme

Epidemiological and risk factor study, evaluation of biochemical and hematological parameters and Receiver Operating Characteristic Curves analysis of some oxidative stress markers in man and women stroke Patients of Touggourt region

Presented by:

- **Legmairi Maroua**
- **Salem Saadia**

***June 14th*, 2020**

President : Mme. Mahboub Nasma	**(MCB)**	**EL-Oued University**
Examiner : Mme. Bouras Beya	**(MAB)**	**EL-Oued University**
Supervisor : Dr. Derouiche Samir	**(MCA)**	**EL-Oued University**

2019/2020

الإهداء

إلى من تحملت يداه قسوة الحياة لننعم نحن برغد العيش, إلى من مشيت أول خطواتي و أنا أمسك بيده, إلى ذلك الرجل العظيم " أبي " .

إلى من تيسرت دروبي بطهر دعواتها , إلى من احنوت و طمأنت و تفانت في العطاء و شجعت , إلى من تستحق كل نجاحاتي , إلى أعظم امرأة في حياتي " أمي " .

إلى جدران روحي الأربعة , إلى الذين كل ما جار علينا الزمان جادوا , إلى إخوتي عمار , نور الدين , سليم والعربي .

إلى من شددن أزري كلما وهنت , إلى من لهن فضل عظيم في وصولي إلى هذه المرحلة , إلى أخواتي كل واحدة باسمها وأخص بالذكر وردة وفاطمة .

إلى كل أفراد عائلتي من صغيرها وصولا لكبيرها .

إلى من ساهم في تعليمي و لو حرف واحد من معلمي الابتدائي إلى الأساتذة و الدكاترة الجامعيين.

إلى من زرع فينا حب الاطلاع و الايمان بأن لا شيء مستحيل إذا سعينا نجد و اجتهاد , إلى القدوة " الدكتور درويش سمير " .

إلى جميع أصدقائي و أخص بالذكر نزيهة , الصالحة ,الزهرة , نور الهدى , أسماء , شيماء و عائشة .

إلى كل من استهواه موضوعنا و أحب الاطلاع على محتوى مذكرتنا المتواضعة .

سعدية

الإهداء

اهدي هذا البحث الى كل طالب يسعى لكسب المعرفة وتزويد رصيده المعرفي العلمي الثقافي .

الى من ساندني في صلاتها ودعائها .....الى من سهرت الليالي تنير دربي

الى أروع امرأة في الوجود :امي الغالية .

الى من علمني ان الدنيا كفاح.....وسلاحها العلم والمعرفة

الى اعظم واعز رجل في الكون: ابي العزيز .

اهداء خاص الى براعم العائلة: عبد النور . ضياء الدين . سندس . ايمان . هداية .

الى صديقات العزيزات: زهيرة . نسرين . اسماء . هالة . نور الهدى وعائشة .

الى جميع عمال مستشفى سليمان عميرات بتقرت .

أتقدم بجزيل الشكر والامتنان العظيم والتقدير العميق الى أستاذي الغالي المشرف الدكتور درويش سمير لما منحه لي من وقت وجهد وتوجيه وارشاد وتشجيع .

مروة

Acknowledgment

Firstly we thank God the exalted the majestic who helped us in completing this scientific research and who secured health wellness and determination praise be to god very much .

we extend our sincere thanks and appreciation to supervisor **Dr . DEROUICHE Samir** for all his information and guidance provided , which contributed to enriching the subject of our study in its various aspects .

We thanks **Mme. MAHBOUB Nasma** , who has given us the honor to accept the presidency of this thesis, respectful tribute .

We thank **Mme. BOURAS Beya**, for having agreed to examine our thesis and the honor for her presence, permit us to express to her our deep respect.

We also thank the members of the Sliman Amirat Hospital Touggourt : **Dr. BAHRI Mouna , Dr. KOUL Abd Elhak** , head of the internal medicine department for men **Mr . BOUSOUFA Abd Ellatif** , and for women **Ms. Abla** , head of the rehabilitation authority **Mr. KDIDI Abd Elrazak** , head of laboratory **Mr . Fateh .**

We would like to thank **Miss GOUBI** Sana responsible of laboratory , our friend **BEDOUI Samah** , **Mr BEN NADJI Belgacem** from Hospital of 8 MAY for helping us and facilities our research.

Finally, we not forget to thank our family , friends and everyone who helps us to complete this thesis .

Abstract

Stroke is one of the important cerebrovascular diseases and it represent leading cause of mortality and disability in the world . The aim of our work is carried out an epidemiological study, evaluation of some risk factors and biological and oxidative stress markers in patients with stroke in Touggourt region .

Our epidemiological study was carried on 605 stroke patients admitted to hospital Sliman Amirat in the period (January 2014 to August 2018) in Touggourt region .Our socioeconomic risk factors study was conducted on 130 voluntary (65 healthy voluntary and 65 stroke patients), with 40 control and stroke persons were used for biological markers study (Hematological , Biochemical, Electrolyte, and oxidative stress markers) for screening and follow-up stroke . The results of epidemiological study, show that 605 cases of stroke recorded 84% of patients were aged more than 50years. On the other hand, 47% of stroke patients are men versus 53% are women. In this study, 60% of the patients had a ischemic stroke whereas 15% of the people were affected by hemorrhagic stroke. Concerning length of stay, the majority cases 80% stay in hospital less to 10 days of a total cases study.

Concerning the risk factors study , our results demonstrated that a strong association between some socioeconomic behaviors and clinical history with stroke . But the high levels of family stress and excess in treatment with anticoagulants are the most dangerous risk factors with (OR = 12,687 , OR=12,310) respectively , in contrast the brush of teeth daily and anemia safety are important protective factors against this disease . For the biological study , our results revealed significant change ($p< 0,05$) of some hematological , biochemical , electrolytes and oxidative stress markers in stroke patients as compared to controls with a simple differences between women and men .

From this study we found that some of oxidative stress markers have a high sensitivity , specificity and AUC values which qualify them to be important marker for diagnosing and predicting stroke in women and men . On one hand this study showed a significant ($p<0,05$) relationship between the changes of some specifics oxidative stress markers with one of the hematological , electrolyte or biochemical markers . on the other hand we found a significant relationship ($p<0,05$) between some oxidative stress markers and risk factors .

In conclusion several socioeconomic and clinical factors contributed to the dispersion and development of the stroke in Touggourt region . in addition A change in hematological , biochemical , electrolyte markers and their relationship with oxidative stress contributes to the development or complication of the disease after stroke. Suggesting that MDA and SOD testing used as systemic marker for screening and followed stroke treatment .

Key Words: Stroke , Risk factors , Oxidative stress , Ischemic , Hemorrhagic

الملخص

السكتة الدماغية هي واحدة من أهم الأمراض الوعائية الدماغية وتمثل السبب الرئيسي للوفيات و الاعاقة في العالم . الهدف من عملنا هو اجراء دراسة وبائية , تقييم بعض عوامل الخطر و تقييم بعض المعايير البيولوجية و معايير الاجهاد التأكسدي لدى مرضى السكتة الدماغية في منطقة تقرت .

أجريت دراستنا الوبائية على 605 مريضا بالسكتة الدماغية تم ادخالهم الى مستشفى سليمان عميرات في الفترة (من جانفي 2014 الى اوت 2019) بمنطقة تقرت . أجريت دراستنا لعوامل الخطر الاجتماعية و الاقتصادية على 130 متطوعا (65 أصحاء و 65 مريضا بالسكتة الدماغية) مع 40 شخص بين أصحاء (كشواهد) و مصابين بالمرض تم استخدامهم لدراسة المؤشرات البيولوجية (مكونات الدم , البيو كيميائية , الشوارد و عوامل الاجهاد التأكسدي) و ذلك لفحص و متابعة السكتة الدماغية . أظهرت نتائج الدراسة الوبائية أن 506 حالة سكتة دماغية تم تسجيلها . 84% من المرضى تزيد أعمارهم عن 50 سنة. من ناحية أخرى , فان 47% من مرضى السكتة الدماغية هم من الرجال مقابل 53% من النساء . في هذه الدراسة أصيب 60% من المرضى بجلطة إفقارية بينما أصيب 15% من الأشخاص بالسكتة النزفية . فيما يتعلق بمدة الإقامة , تبقى غالبية الحالات 80٪ في المستشفى أقل من 10 أيام من إجمالي الحالات المدروسة .

فيما يتعلق بدراسة عوامل الخطر , أظهرت نتائجنا وجود ارتباطا قويا بين السكتة الدماغية و بعض السلوكيات الاجتماعية و الاقتصادية و التاريخ السريري . لكن المستويات العالية من التوتر الأسري و الافراط في العلاج بمضادات التخثر هما العاملان الأكثر خطورة (OR = 12,687,OR=12,310) على التوالي . بالمقابل تنظيف الأسنان يوميا و السلامة من فقر الدم هي عوامل وقائية مهمة ضد هذا المرض . بالنسبة للدراسة البيولوجية , كشفت نتائجنا عن تغير كبير ($p <0,05$) ,في بعض مكونات الدم و المعايير البيو كيميائية والشوارد ومؤشرات الإجهاد التأكسدي في مرضى السكتة الدماغية مقارنة بالشواهد مع وجود اختلافات بسيطة بين النساء والرجال.

في هذه الدراسة وجدنا ان بعض مؤشرات الاجهاد التأكسدي لديهم حساسية و نوعية و قيم AUC عالية تؤهلهم ليصبحوا مؤشرات مهمة للتشخيص و التنبؤ بالسكتة الدماغية لدى النساء و الرجال . من جهة, أظهرت هذه الدراسة وجود ارتباط معنوي ($p<0,05$) بين تغير بعض مؤشرات الاجهاد التأكسدي المحدد مع احدى مكونات الدم , الشوارد أو المعايير البيو كيميائية . من ناحية أخرى وجدنا ارتباطا معنويا ($p<0,05$) بين بعض مؤشرات الاجهاد التأكسدي و عوامل الخطر.

في الختام , ساهمت عدة عوامل اجتماعية , اقتصادية و سريرية في انتشار و تطور السكتة الدماغية في منطقة تقرت . بالإضافة الى تغيير في مكونات الدم , المعايير البيو كيميائية و الشوارد و علاقتها بالإجهاد التأكسدي يساهم في تطور المرض او مضاعفاته بعد السكتة الدماغية . نقترح استعمال معيارMDAو SOD كمؤشرات بيولوجية مهمة من حيث الكشف , فحص و متابعة السكتة الدماغية .

كلمات مفتاحية : السكتة الدماغية , عوامل خطر , اجهاد تأكسدي , إفقاريه , نزفية .

Abbreviation list

ACA : Anterior cerebral artery.

ACha : Anterior choroidal artery.

AComn : Anterior communicating artery.

AF : Atrial fibrillation**.**

AICA : Anterior inferior cerebellar artery**.**

AIS :Acute Ischemic stroke.

ALP : Alkaline phosphatase.

ATP: Adenosine triphosphate.

AUC: Area under curve.

BHT : Butylated hydroxytoluene .

CNII: Optic nerve.

CN III: Coulometer nerve.

CAT: Catalase .

CBC: Complete blood count.

$CI_{95\%}$: Asymptotic 95% Confidence Interval .

CMP : Comprehensive metabolic panel .

CNS: Central nervous system.

CRP :C-reactive protein .

CT: Computed tomography .

Cu SO 4 : Copper sulfate .

DNA: Deoxyribonucleic acid **.**

DTNB :5,5′-Dithiobis(2-nitrobenzoic acid).

EDTA : Ethylene di-amine tetra-acetic acid.

FAA: Free fatty acid.

FDA: Food and Drug Administration

FNS : Hematological analysis.

GPX : Glutathione peroxidase .

GSH: Reduced Glutathion .

HCl : Hydrochloric acid.

HDL: High density lipoprotein

HGB: Hemoglobin.

HgbA1c: Hemoglobin A1c .

H2O2: Hydrogen Peroxyde .

ICA: Internal carotid.

ICH : Intra cerebral hemorrhage .

IL-6: Interleukin 6 .

IS. Ischemic stroke.

IV t-PA : Intravenous alteplase .

KH_2PO 4,K_2HPO 4 : Phosphate-buffered .

LDL : Low density lipoprotein .

LTA4: Leukotriene A4 .

LTC4: Leukotriene C4.

LYM: Lymphocytes.

M1 MCA: : Middle cerebral artery**.**

MDA: Malondialdehyde .

Met : Methionine .

NaCl : Sodium Chloride.

NADPH : Nicotinamide adenine dinucleotide**.**

NBT : Nitroblue tetrazolium.

NEUT: Neutrophil .

OR : Odds Ratio.

OphA : Ophthalmic artery.

ORAC: Oxygen Radical Absorbance Capacity.

OS : Oxidative stress.

P : P values .

PCA : Posterior cerebral artery**.**

PComm : Posterior communicating artery**.**

PICA: Posterior inferior cerebellar artery .

PLT: Platets .

R^2: Person correlation .

RBC: Red blood cell.

RNAs : Ribonucleic Acid Synthesis .

RNS: Reactive Nitrogen Specie .

ROS : Reactive Oxygen Specie .

SCA: Superior cerebellar artery.

SHA : Subarachnoid Hemorrhage**.**

SOD: Superoxide Dismutase**.**

TBA: Thiobarbituric acid .

Tc: Total cholesterol .

TCA : Trichloroacetic acid.

TG: Triglyceride .

TNF-α: Tumor necrosis factor alpha .

TOAST : Trial of ORG10172 in acute stroke .

TSH: Thyroid-stimulating hormone **.**

US : United States **.**

Utox: Urine toxicology**.**

Vit c : Vitamin c .

WBC: White Blood Cell .

WHO: World Health Organization .

Figures list

Tables list

Summary

Introduction

Introduction

Cerebrovascular accident is a disease that affects the system of brain vasculature (Susan et al., 2012). Stroke is one of the most devastating worldwide neurological disorders (Mahmoud et al., 2019), because a gradual increase in the number of people have a stroke worldwide which threatens the general health of society on the economic and medical side (Hui-Chen et al., 2019), in addition stroke causes several neuronal problems such as neurological disability in the long term which causes several deaths worldwide (Rothwell et al., 2004).

The number of stroke patients is gradually increasing worldwide, with an estimated 5.71 million people with stroke in 2004 According to the World Health Organization (WHO), this number is expected to reach 7.8 million in 2030 (Serge et al., 2001). The Magrebia region has reported varied epidemiological transition among the all Arab and North Afreca from 1990 to 2017 , there are 13.008, 01cases of ischemic stroke and 5.184. 36 cases of hemorrhagic stroke in Algeria (Zaidi et al.,2019), according to the last WHO data published in 2017 stroke deaths in Algeria reached 22.917 or 13.19% of total death .

Stroke is diagnostic by radiological examination like nuclear magnetic resonance imaging (Antonio et al.,2002); Stroke (cerebrovascular accident) is classified into two major types; ischemic which presents (85%) and hemorrhagic (15%) (Parisa & Melissa,2019 ; Abdullah et al., 2018).

In addition to gender, age and genetic factors, the rest of stroke risk factors are closely related to people's daily habits and behaviors (Zheng et al., 2020). Lifestyle plays an important role in the etiology of this disease, including diet (Derouiche et al., 2018). Several known risk factors for stroke include cardiovascular disease, obesity, diabetes mellitus, smoking, and dyslipidemia (Daniela et al., 2019).

Identification of inflammatory biomarkers such as TNF-alpha, IL -6 as well as lipid markers including LDL-c and HDL-c, combined with imaging features may identify asymptomatic patients at high risk for stroke (Martinez et al., 2019). Tissue plasminogen activator (t-PA) is the only FDA approved drug for ischemic stroke but has a limited therapeutic time window of 4.5 hours (Chen et al., 2020).

Oxidative stress is an abnormal condition caused by an excess production of oxidants compared to the antioxidant (Djouadi & Derouiche, 2017). It has been considered as the main

cause of several pathologies (Derouiche et al., 2018), including acute ischemic stroke (Žitňanová et al., 2016). The main reason for the aggravation of cerebral ischemia-induced brain injury is the abnormal increase of oxygen free radicals, and the enhancement of oxygen free radical reactions is an important reason for cerebral edema secondary to CH (Zheng et al., 2019).

In light of these data, the aim of our work is based on the realization of two following complementary aspects:

- The first part: is an epidemiological study and evaluation of some risk factors associated with cerebrovascular accident in Touggourt region

- The second part: is an biological study concerns the determination of the variation and signification of some biochemical, hematological and oxidative stress markers in the prognostic and following up of stroke in women and men of Touggourt region.

First part

Bibliographic part

I. Anatomical and physiological aspect of brain

The brain is Despite representing only an extremely energy demanding organ. ˷2% of body mass, it consumes ˷20% of the total energy in a resting state (Jackman et al., 2015). An adequate blood supply is instrumental to normal brain functioning. The brain's vasculature is composed of a complex network of arterioles, capillaries, venules, and veins that regulate cerebral blood flow (CBF) and maintain the integrity of the blood brain barrier (BBB) (Kane et al., 2019).

I.1.vascular supply of the brain

The brain is vascularized by 4 main arteries; internal carotid arteries and arteries right and left vertebral (figure 01). The two carotid arteries form the anterior circulation, the vertebral arteries when they unite in a basilar trunk thus forming the circulation posterior (Scremin et al., 2015 ; Chandra et al., 2017). The internal carotid arteries originating from the common carotid arteries, and the vertebral arteries. They form the Circle of Willis at the base of the brain, from which the main cerebral arteries are advancing and branching at the surface of the brain (Lindauer, 2017).

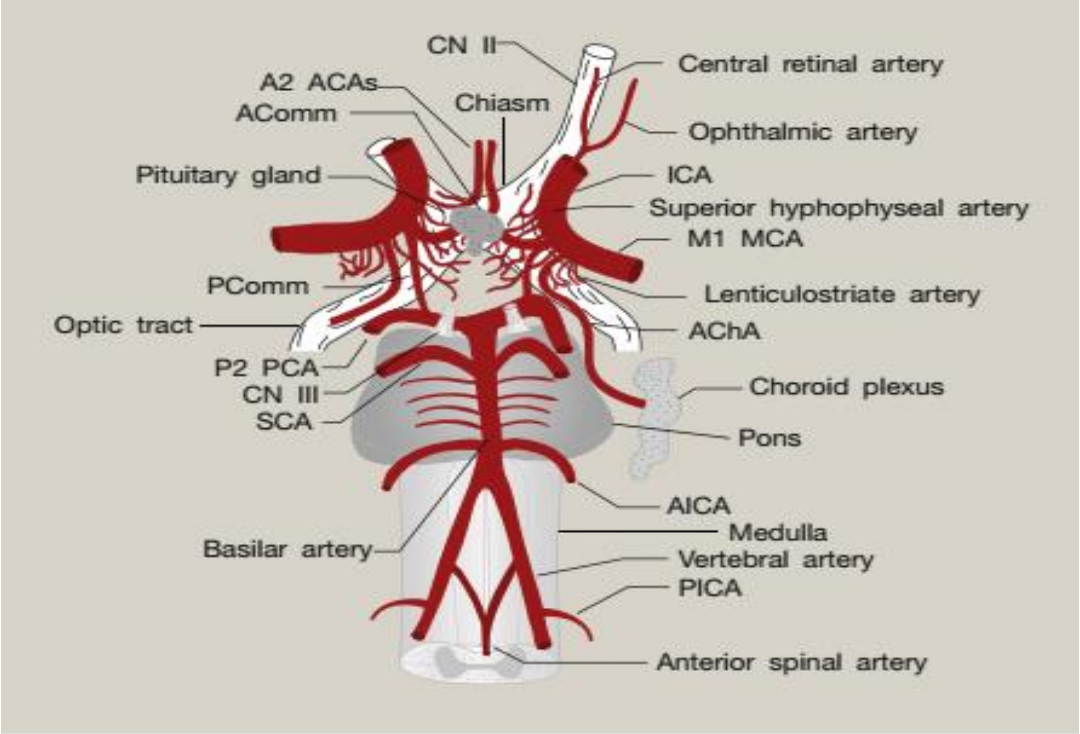


Figure 01: Schematic of the circle of Willis showing anatomical relations (Shah et al., 2018).

I.1.1. Middle Cerebral Artery

The middle cerebral artery (MCA) supplies a large area of the lateral surface of the brain and part of the basal ganglia and the internal capsule via four segments (M1, M2, M3, and M4). The M1 (horizontal) segment supplies the basal ganglia, which is involved in motor control, motor learning, executive function, and emotions. The M2 (Sylvain) segment supplies the insula, superior temporal lobe, parietal lobe, and the infer lateral frontal lobe (Kumral et al., 2002).

I.1.2. Anterior Cerebral Artery

The anterior cerebral artery (ACA) provides blood supply to the frontal, prefrontal, primary motor, primary sensory, and supplemental motor cortices. The sensory and motor cortices receive sensory information and control movement of the contralateral lower extremity. The supplemental motor area contains the Broca area, which is involved in the initiation of speech. The prefrontal cortex is used to organize and plan complex behavior and is thought to influence the personality (Brandt et al., 2000).

I.1.3. Posterior Cerebral Artery

The superficial posterior cerebral artery (PCA) supplies the occipital lobe and the inferior portion of the temporal lobe, while the deep PCA supplies the thalamus and the posterior limb of the internal capsule, as well as other deep structures of the brain. The occipital lobe is the location of the primary and secondary visual areas, where sensory input from the eyes is interpreted. The thalamus relays information between the ascending and descending neurons, while the internal capsule contains the descending fibers of the lateral and ventral cortical spinal tracts (Brandt et al., 2000).

I.1.4. Vertebra basilar

The vertebra basilar region of the brain is supplied by the vertebral arteries and the basilar arteries that originate within the spinal column and terminate at the Circle of Willis. (figure 02). These areas supply the cerebellum and brainstem (Jensen et al., 2005).

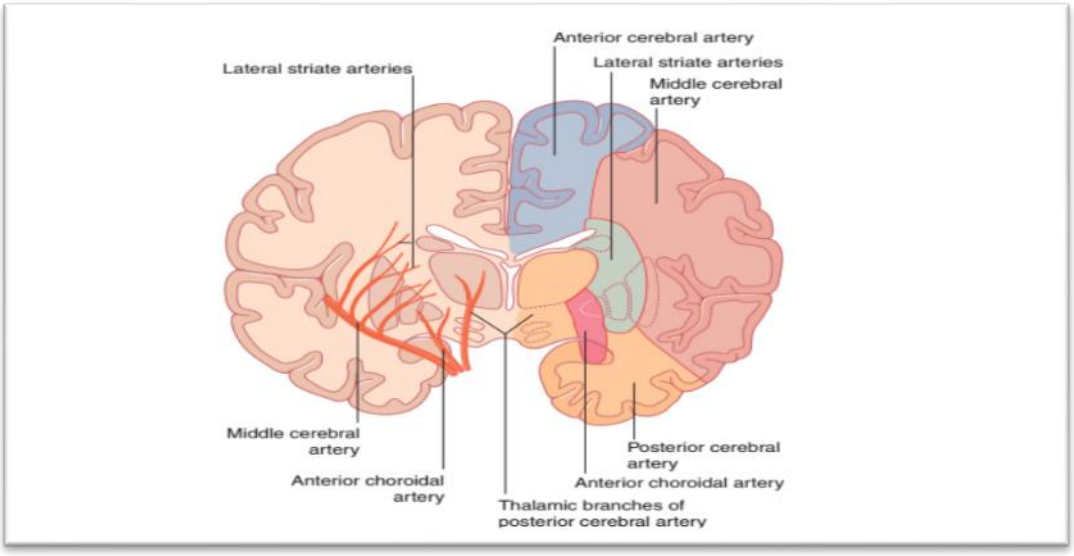


Figure 02: Distribution of perforating branches of the middle cerebral, anterior choroid , and posterior cerebral arteries (Kenna,2019).

I.2. Normal cerebral blood flow

CBF is defined as the blood volume that flows per unit mass per unit time in brain tissue and is typically expressed in units of ml $_{blood}$／(100 g $_{tissue}$ min) . The normal average cerebral blood flow (CBF) in adult humans is about 50 ml／(100 g min) (Fantini et al., 2016).

I.3. Brain diseases

Brain diseases including Alzheimer's, Parkinson's, Huntington's and brain tumors and cerebrovascular accident are globally challenging issues (Jin et al., 2020).

I.3.1.Alzheimer's disease

Is a neurodegenerative disorder characterized by significant cognitive deficits behavioral changes, sleep disorders, and loss of functional autonomy (Lehmann et al., 2016). This neurodegenerative disease process is characterized classically by tow hallmark pathologies: β amyloid plaque deposition and neurofibrillary tangles of hyper phosphorylated tau (Weller et al., 2018). The number of patients suffering from AD is growing rapidly as the population ages worldwide (Lehmann et al., 2016). APOE4 is the human isoform strongest and most highly replicated genetic risk factor for AD (Halliday et al., 2015).

I.3.2.Parkinson's disease

Parkinson's disease (PD) was first described by Dr.James Parkinson in 1817 as a «shaking palsy» (DeManged et al., 2015). It is the most common movement disorder and repress-ents the second most common degenerative disease of the central nervous system (Tysnes & Storstein., 2017), Affecting people mainly in later years of life (Sveinbjornsdottir,2016). Neuropath logically, PD is defined by loss of dopaminergic neurons in the substantial nigra pars compacta of the midbrain (Lill, 2016) which characterized neuropath logically by the presence of α-synuclein-containing Lewy bodies in the substantial nigra of the brain (Tysnes & storstein, 2017).

I.3.3.Huntington's disease

Huntington's disease (HD) is a fully penetrant neurodegenerative disease caused by dominantly inherited CAG tri-nucleotide repeat expansion in the hunting in gene on chromosome 4 (Colgan & Tabrizi, 2017). This progressive neurodegenerative disorder accompanied by symptoms, such as dementia, chorea and depression (Choi et al., 2018). The people affected cannot think, talk, and move properly. Basal ganglia cells get damaged, which controls these capacities (Ghosh et al., 2019).

I.3.4.Brain tumor

Brain tumor is any mass that outcomes from unusual developments of cells in the brain. It might influence any individual at any age (Aswathy et al., 2017). Brain tumors classified to benign or low-grade (grade I and II) and malignant tumors or high-grade (grade III and IV). Benign tumors are non-progressive (non-cancerous) so considered to be less aggressive (Mohsen et al., 2018). Tumors can directly destroy all healthy brain cells. It can also indirectly damage healthy cells by crowding other parts of the brain and causing inflammation, brain swelling and pressure within the skull (Logeswari & Karnan, 2010). Primary tumors start in the brain and do not usually spread to other parts of the body and secondary tumors are formed by cancer cells from a primary tumor originated elsewhere in the body and spread to the brain (Mohsen et al., 2017).

II. Cerebrovascular accident (stroke)

II.1. Definition and classification of stroke

Stroke is a type of cerebrovascular disease that involves the vessels of the central nervous system (Vida, 2004), defined as a clinical picture of vascular origin and a focal neurological deficit (Martin et al., 2011 ; Mevlut et al., 2020) (burst of cerebral arteries , hemorrhage , or occlusion by o thrombus or other particles) leading to cerebral dysfunction (Vida, 2004).This deficit characterized by the rapidity of symptom resolution (within 24 h) , with or without demonstrable new hemorrhage or infraction in the brain (Martin et al., 2011 ; Prakash et al., 2018).

Strokes are sub classified into ischemic and hemorrhagic types, based on the underlying pathogenesis (Fatahzadeh & Glick, 2006).

II.1.1.Ischemic stroke

II.1.1.1.Definition

Ischemic stroke is the most prevalent type of stroke (Pradeep et al., 2012). Defined as neurological event , charactezed by a sudden lack or complete interruption of blood flow in a brain supplying artery (figure 03) by a thrombus or embolus (Ning-Ning et al.,2018 ; Mani et al., 2019 ; Fei et al., 2020) , and reduces oxygen and energy supply to the critical tissues of the brain resulting in rapid cell death and cones ponding loss of neurological function (ahmed et al., 2014). The TOAST classification1 defines 5 IS subtypes based on etiology: 1) large-artery atherosclerosis, 2) cardio embolism, 3) small-artery occlusion, 4) stroke of other determined etiology, and 5) stroke of undetermined etiology (Jackova et al., 2019).

II.1.1.2. Pathophysiology

The event resulting from any subtypes of ischemic stroke result in the loss of blood supply, oxygen , nutrients and elimination of metabolic wastes (French et al., 2016). Neuronal death in ischemia occurs through apoptosis, necrosis, and autophagy after changes obstruct normal neuronal functioning such as ATP depletion and loss of ion exchange function of membrane pumps, terminal depolarization and glutamate mediated calcium excite toxicity, calcium dependent enzyme activation, generation of free radicals, and ultimately degradation of cellular molecules (Gupta et al., 2017).

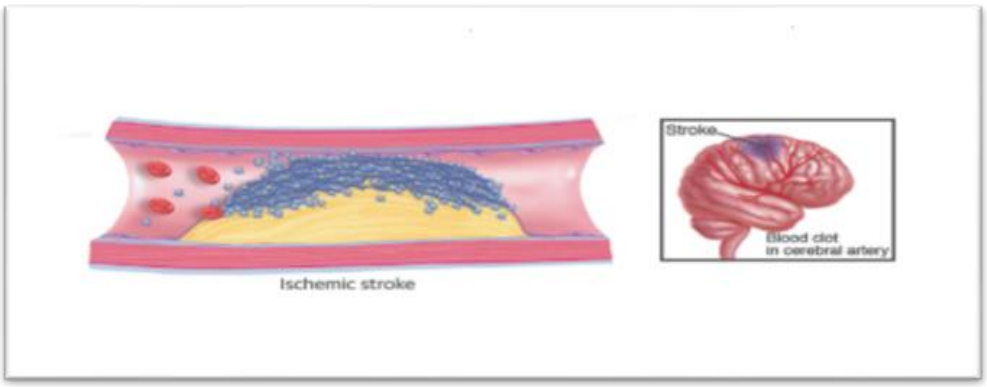


Figure 03: Ischemic stroke (Bonaca M P et al., 2014).

II. 1.2.Hemorragic stroke

II.1.2.1. Definition

Hemorrhagic strokes due to an abnormal vascular structure or the rupture of a blood vessel (figure 04), including two main types intra cerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH) (Li H et al., 2018 ; Shao et al., 2019). ICH refers to bleeding within the brain itself, while SAH refers to bleeding that occurs outside of the brain tissue but still within the skull, precisely between the arachnoid mater and pia mater (Qu et al., 2019).

II.1.2.2. Pathophysiology

Intra hemorrhage (ICH) is usually caused by rupture of small penetrating arteries secondary to hypertensive change or other vascular abnormalities (Qureshi et al., 2001). Its pathophysiology consists of three distinct phases : (1) initial hemorrhage , (2)hematoma expansion and (3) peri hematoma edema (Magistris et al., 2013).The initial injury mechanism in ICH is compressing brain parenchyma by hematoma 's mass effect , resulting in physical disruption of parenchymal architecture (Qureshi et al., 2003) in contrast a secondary mechanism of brain injury is related to clotting cascade after endothelial damage and hemoglobin breakdown (An et al., 2017).

The pathophysiology of SAH is complicated and includes vasospasm (VS), micro-circulatory dysfunction, neuronal apoptosis (Qu et al., 2019).

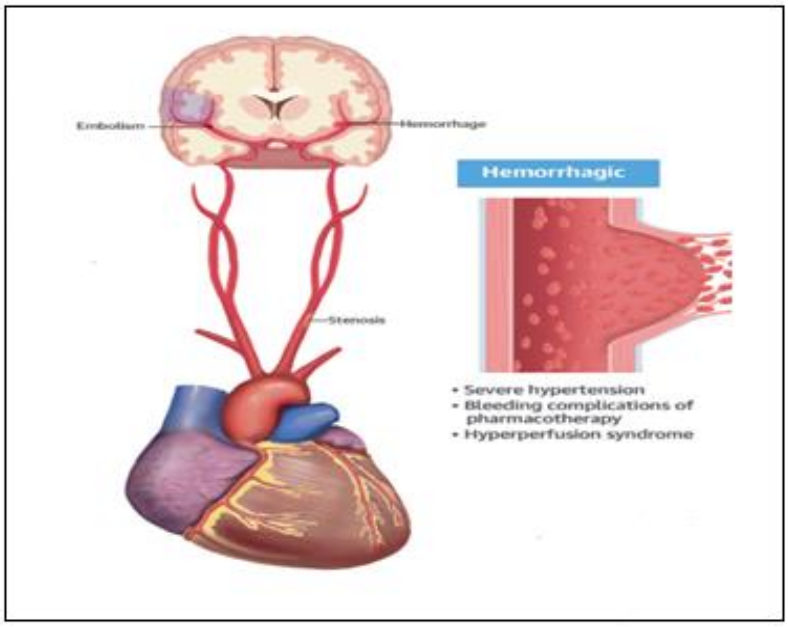


Figure 04: Hemorrhagic stroke (Devgun et al., 2018).

II.2. Burden of stroke

Globally , stroke is a leading cause of mortality and disability and there are substantial economic costs for post stroke (Johnson, 2019).

II.2.1. Epidemiology and mortality

In 2017, stroke was the second leading cause of death worldwide (Jiang et al., 2020) .with 15 million strokes and 5.8 million stroke-related deaths per year (Al-Senani et al., 2019). The absolute number of people with incident strokes has significantly increased by 81% from 1990 to 2017 (Martins et al., 2019). Women are at higher risk of stroke than men, with a lifetime likelihood of 20% versus 17% (Robine & Bernstein, 2015). Ischemic stroke is by far the most common type of stroke, accounting for approximately 70%-90% of all stroke cases (Wang et al., 2017 ; Xu et al., 2013). Ischemic stroke mortality after one year is still at a high concentration (Slot et al., 2008 ; Xu et al., 2020). In 2016, there were 116,4 million of disability-adjusted life-years DALYs du to stroke (Feigin et al., 2016), in other words From the 795,000 new sufferers of stroke (figure 05) , 26% remain disabled in basic activities of daily living (Framingham cohort) and 50% have reduced mobility due to hemiparesis (Katan & Luft, 2018).

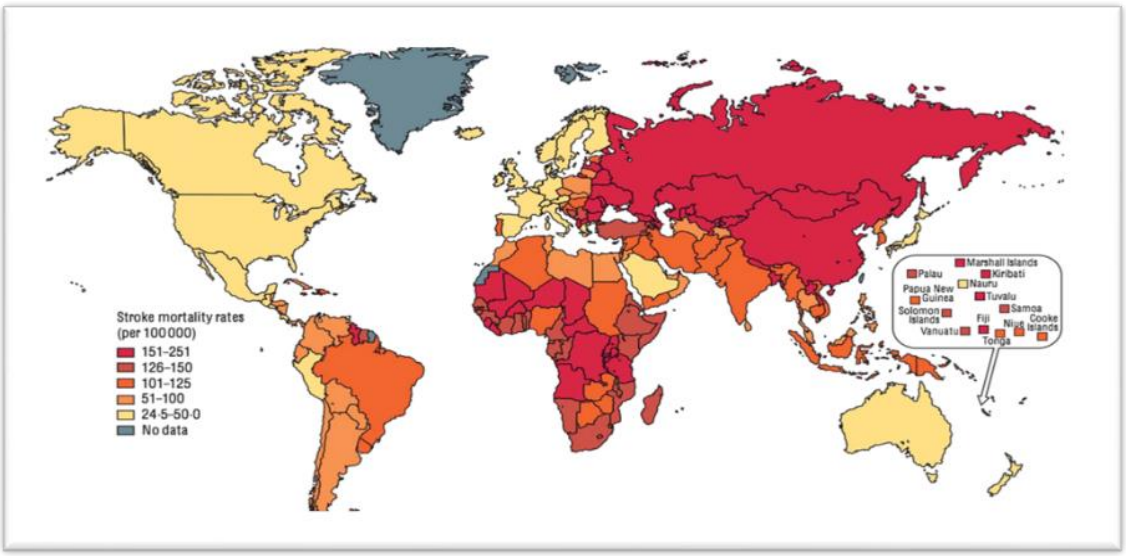


Figure 05: Global variation in stroke burden and mortality (Norrving & Kissela, 2013).

II.2.2. Economic impact of stroke

For the years 2001–2005, the average cost for medication and for outpatient stroke rehabilitation services in the first year after discharge were $11,145 per patient with $7318 spent for rehabilitation services and $3376 for medication (Rajsic et al., 2018).

II.3. Risk factors of stroke

Risk factors are certain characteristic that give an increase likelihood of having stroke (Choudhury et al., 2015). Risk factors for hemorrhagic and ischemic stroke are similar, but there are some notable differences (Boehme et al., 2017) . Risk factors for stroke are usually divided into non modifiable including age , Gender , Race and Heredity and modifiable such as hypertension, Heart disease, Diabetes mellitus, Dyslipidemia, Obesity, Smoking, Excess alcohol consumption (figure 06) (Arboix et al., 2015 ; Choudhury et al., 2015).

II.3.1. Non Modifiable risk factors

II.3.1.1 .Age

For each consecutive decade after 55 years of age, the risk for stroke approximately doubles . The prevalence of stroke for individuals older than 80 years of age is approximately 27%, compared with 13% for individuals 60 to 79 years of age (Grysiewicz et al.,2008).

II.3.1.2.Gender

In general, stroke is more prevalent in men than in women . The incidence of stroke in the young (aged 35–44) is highest in women, however . The increased risk associated with pregnancy is most significant postpartum (Grysiewicz R A et al., 2008).

II.3.1.3.Race

In relation to race/ethnicity, African-Americans and some Hispanic/Latino American groups have a higher incidence and mortality of stroke .Prevalence and severity of risk factors and markers such as hypertension, diabetes, and obesity have been used to explain, at least in part, these disparities in stroke rates. Also, social determinants may play an important role (Farooq & Gorelick, 2017).

II.3.1.4.Heredity

Genetic factors that may be associated with stroke include family history of stroke, a number of inherited autosomal-dominant trait coagulopathies (eg, protein C and S deficiencies) There are many other genetic conditions (eg, inherited metabolic disorders, certain intracranial aneurysm alleles and mutations in the amyloid precursor protein genes causing inherited cerebral amyloid angiopathy syndromes) (Farooq & Gorelick, 2017).

II.3.2. Modifiable risk factors

II.3.2.1.Hypertension

Hypertension is the most important modifiable risk factor for stroke, with a strong, direct, linear, and continuous relationship between blood pressure and stroke risk (Boehme et al., 2017).

II.3.2.2.Heart diseases

Heart diseases such as ; Atrial fibrillation (AF) has long been recognized to be a major risk factor for stroke, and this has only increased with the aging of the US population (Boehme et al., 2017). The Utilization of long-term anticoagulation therapy in the treatment of AF patients significantly increases the risk of future intra cerebral hemorrhage (ICH) (Elkhatib et al., 2020).

II.3.2.3.Diabetes

Diabetes is an independent risk factor for stroke disease Compared with patients without, patients with diabetes have at least twice the risk for stroke, and approximately 20% of patients with diabetes will die from stroke (Assy et al., 2019).

II.3.2.4.Dyslipidemia

The relationship between dyslipidemia and stroke risk is complex, with an increased risk for ischemic stroke with increased total cholesterol, and a decreased risk for ischemic stroke with elevated HDL cholesterol . Total cholesterol, meanwhile, is inversely associated with hemorrhagic stroke, with hemorrhagic stroke risk increasing as total cholesterol decreases (Boehme et al., 2017).

II.3.2.5.Obesity

Obesity is an established risk factor for the development of vascular diseases such as stroke (Oesch et al., 2017). It has classically been associated with disruption of pathways controlling lipid and glucose metabolism, however recent evidence has shown that obesity also has an inflammatory component , which is well established factor in stroke risk and outcome (Haley & Lawrence, 2016).

II.3.2.6.Smoking

Cigarette smoking is a causal risk factor for stroke that is dose- and duration-dependent, biologically plausible ,and interacts synergistically with other factors such as BP and risk of stroke (Towfighi & Hill, 2017).

II.3.2.7.Alcohol Consumption

Heavy alcohol use likely increases the risk of stroke by increasing the risk of hypertension, atrial fibrillation, cardiomyopathy, and diabetes (Towfighi & Hill, 2017).

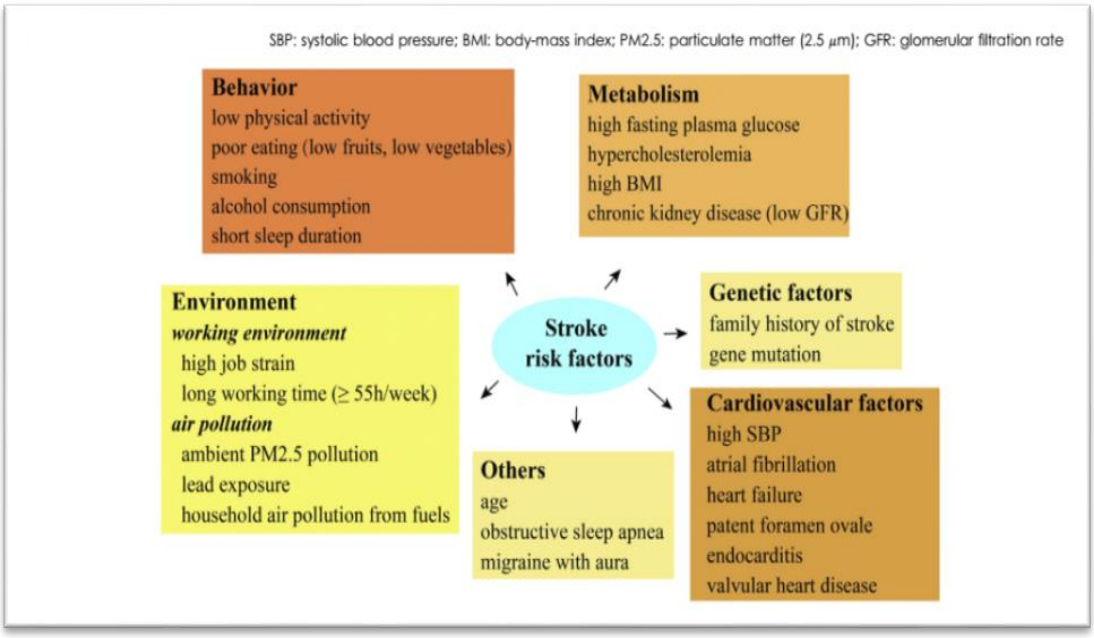


Figure 06 : Risk factors of stroke(Zhang et al., 2019).

II.4. Diagnostic

The initial step in the evaluation of the acute stroke patient is accurate diagnosis (Zweifler, 2017). Acute stroke management in a patient presenting with focal neurologic deficits includes obtaining neuroimaging, most commonly a non-contrast head computed tomography (CT). On the other hand, magnetic resonance imaging (MRI) (Manwani et al., 2018). In addition, the use of a biomarker test (Monbailliu et al., 2017).

II.4.1.Magnetic Resonance Imaging

is an excellent modality for diagnosis of acute stroke with sensitivity of 94% -100% (Manwani et al ., 2018). Multimodal MRI can delineate the presence, size, location, extent and effects of acute brain ischemia, identify the hypo perfused tissue that is at risk of infarction, and show additional features of the cerebrovascular pathology. Magnetic Resonance Imaging (MRI) can also detect or exclude ICH with an accuracy comparable to CT (Merino & Warach, 2010).

II.4.2.Computed Tomography

Multimodal Computed Tomography (CT) , including CT angiography (CTA)and CT perfusion (CTP) (Merino & Warach, 2010).With the limited availability of MRI diagnostics for acute ischemic stroke in routine stroke care, attempts have been made to use CT for determining the time from onset (Audebert & Fiebach, 2015). The major value of acute CT

scanning is in differentiating intra cerebral hemorrhage from ischemic stroke and other pathologic processes such as subdural hematoma, tumor, and abscess (Zweifler, 2017).

II.4.3.Electromagnetic Tomography

Is an emerging imaging modality with significant clinically viable potentials , Electromagnetic Tomography (EMT) may present an effective supplement to current imaging modalities for acute and chronic assessment of perfusion related brain injuries (Semenov S et al., 2015).

II.4.4 .Examples for biomarker

The use of a biomarker test could add important adjunct information to make the diagnosis of AIS and thereby increase the likelihood of administering thrombolytic treatment within the therapeutic window (Monbailliu et al., 2017). Such as :

- MicroRNAs (miRNAs) are a class of small non-coding RNAs .these biomarkers can be used as powerful tools in monitoring different stages of stroke and stroke outcomes (Mirzaei et al., 2017).
- the levels of several inflammatory mediators correlate with stroke severity and outcome. Inflammatory biomarkers such as CRP or several pro inflammatory cytokines, specially IL-6, TNF-α and neutrophil-to-lymphocyte ratio (NLR) among other molecules have been widely associated with stroke diagnostic (Simats et al., 2016; Szegedi et al., 2017).
- Plasma concentrations of the astroglial protein S-100b, a cytosolic calcium-binding protein, have been found to correlate with the extent of tissue damage (infarct volume) and neurologic outcome (Reynolds, 2003).
- Other markers include a lipid panel, HgbA1c, Utox, and TSH (if there is aclinical suspicion for atrial fibrillation) along with the standard CBC and CMP (Stack & Cole, 2017).

II.5. Consequences of stroke

Motor impairment is the most common deficit after stroke, which either happens as a direct consequence of the lack of signal transmission from cerebral cortex or as a slowly accumulating process of the cerebral injuries or muscle atrophy due to learned disuse (Lui & Nguyen, 2018).

II.6. Treatment of stroke

II.6.1. Treatment of ischemic stroke

At present, there is no reparative treatment, and thus, this injury leads to permanent brain dysfunction in the patient. Therefore, we need to reduce the burden of disease in stroke patients and seek to reverse neurological damage by reducing CNS injury and promoting neural regeneration (Xie et al., 2020).

II.6.1.1.Intravenous thrombolysis

Intravenous thrombolysis with Al-teplase, a recombinant tissue plasminogen activator, is the standard medical treatment for acute ischemic stroke within 4.5 hours after the onset of symptoms (Thomalla et al., 2018 ; Mistry et al., 2017).

II.6.1.2.Intra-arterial thrombolysis

Intra-arterial thrombolysis in patients with middle cerebral artery territory strokes and M1 or M2 occlusion within 6 h of symptom onset. The IMS (Interventional Management of Stroke) study explored this latter approach because investigators noted the relative lack of efficacy of IV t-PA on large strokes and patients with major arterial occlusions; there are several ongoing investigations (Marsh & Keyrouz, 2010).

II.6.1.3.Endovascular therapy

Reperfusion therapy remains the only proven treatment for acute ischemic stroke (Rebello et al., 2016) . endovascular thrombectomy ; represented one of the only two Food and Drug Administration (FDA)-approved therapies are currently available to ischemic stroke patients after the tissue plasminogen activator (tPA) (Kaisera, 2020) .

II.6.1.4.Neural stem cells therapy

Neural stem cells are the precursor cells present in the neuro-epithelium along the neur-axis during mammalian fetal development (Zhang et al., 2019).there are many sources of sum an neural stem cells (Kokaia et al., 2018). the transplantation of stem cells induce to an extension of the time window for drug intervention improvement of neurological deficits, reduction of infarct volume, pro-regenerative cerebral reorganization, mitigation of post-stroke neuro-inflammation, and tissue restoration (Sinden et al., 2017).

II.6.1.5.Neuroprotection therapy

The term neuroprotection has also been used to describe the theoretical concept of decreasing additional neuronal injury that occurs upon reperfusion of the ischemic brain(Patel et al., 2017). One of neuroprotection method is the administration of near-infrared laser therapy in which light energy at a wavelength of 808 nm is applied directly to the shaved skull of the patient in an effort to enhance brain recovery through a process called photo bio stimulation (Yip et al., 2008) .

II.6.1.6.Physical therapy

Physical therapy remains the only approved intervention aimed at improving behavioral impairments (Ghuman, 2016).Rehabilitation involves repetitive motor practice to promote use-dependent neuroplasticity and functional recovery, and primarily occurs in the first 6 months after stroke (Ackerley et al., 2016).

II.6.2. Treatment of hemorrhagic stroke

For hemorrhagic stroke, limited treatments are available, which focus on controlling the bleeding and reducing the pressure caused by the bleeding immediately after stroke onset (Corey et al., 2020).

III. Oxidative stress

III.1.Definition

Oxidative stress is broadly referred to as an imbalance between the generation of the Free radicals which are inherently unstable molecules because of balance between the production of reactive species (reactive oxygen specie ROS and reactive nitrogen specie RNS) and their clearance by the anti-oxidant defense system in favor of the former (Stefanovic et al., 2019 ; Betteridge, 2000). Moreover, oxidative stress has been proven to be associated with many diseases, including cancer, diabetes, chronic kidney disease (CKD), cardiovascular diseases (CVDs), neurodegenerative diseases , inflammation ,atherosclerosis and ageing (El Assar et al., 2019 ; Shahidi & Zhong, 2015).

III.2.Free radicals

III.2.1.Definition

A free radical can be defined as an atom or molecule containing one or more unpaired electrons in valency shell or outer orbit and is capable of independent existence. Both ROS and RNS collectively constitute the free radicals and other non-radical reactive species (Phaniendra et al., 2015 ; Kehrer et al., 1993) (table 01 and table 02). These radicals can be produced in cells by losing or accepting a single electron, therefore, behaving as oxidants or reductants (Lobo et al., 2010). The main process of ROS generation in mitochondria could be schematically presented as O2 → O2-• → H2O2 → •OH (Luo et al., 2019).

Table 01 : Reactive oxygen species (Rahman et al., 2012).

Radicals	Non-radicals
Superoxide: O_2^-	Hydrogen peroxide: H_2O_2
Hydroxyl: OH^-	Hypochlorus acid: HOCL
Peroxyl: RO_2^-	Hypobrromus acid: HOBr
Alkoxyl: RO^-	Ozone: O_3
Hydroperoxyl: HO_2^-	Singlet oxygen: Δg

Table 02: Reactive nitrogen species (Rahman et al., 2012).

Radicals	Non-radicals
Nitric oxide: NO^-	Nitrogen dioxide: NO_2
Nitrous acid: HNO_2	Nitrosyl cation: NO
	Nitrosyl anion: NO^- NO^-
	Dinitrogen tetroxide: N_2O_4
	Dinitrogen trioxide : N_2O_3
	Peroxynitrite: $ONOO^-$
	Peroxinitrous acid: ONOOH
	Alkylperoxynitrites: ROONO

III.2.2.Sources of free radicals

Living aerobic organisms stay under the influence of free radicals due to the constant formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) by endogenous and exogenous sources (Kruka et al., 2019).

- **Endogenous sources of ROS**

The endogenous sources of ROS (figure 07) include mitochondria, cytochrome P-450 metabolism, peroxisomes, and inflammatory cell activation (Macrophages and neutrophils contain a group of enzymes called the NADPH oxidase complex, which, upon activation generates superoxide radicals and hydrogen peroxide) (Bhattacharya, 2014).

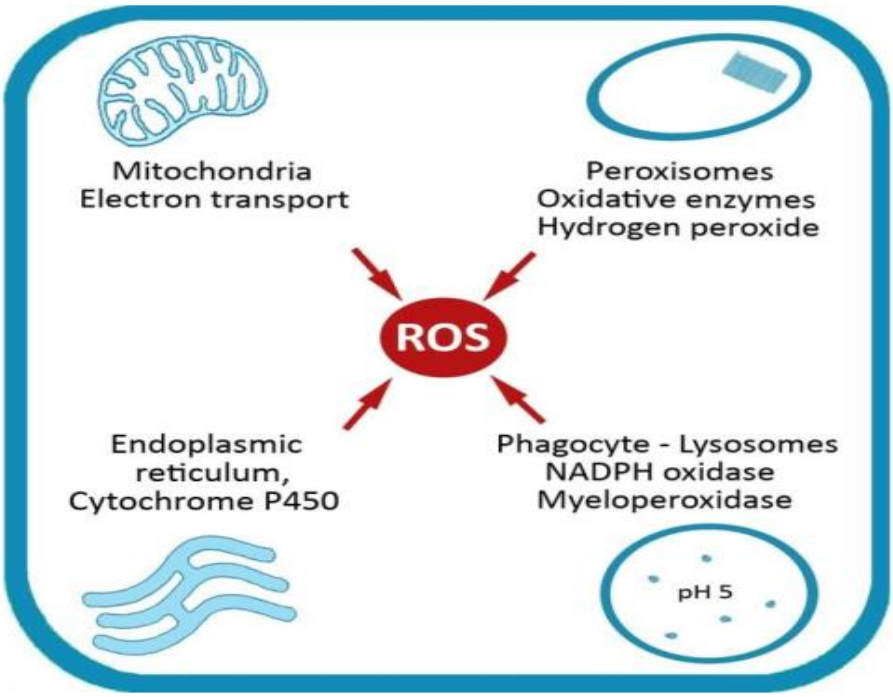


Figure 07 : Endogenous sources of free radicals/ROS (Santo A et al., 2016).

- **Exogenous sources of ROS**

ROS and RNS can also be generated through exposure to external factors such as oral bacteria, ionizing and ultraviolet radiation, food, and air pollution, alcohol, and cigarette smoking, heavy metals and certain chemotherapeutic drugs (Żukowski et al., 2018 ; Santo et al., 2016).

III.3.Antioxidants

Antioxidant state necessary for Natural physiological function. An imbalance in the case of oxidation / antioxidants can cause injury to the tissues of the organism (Vidhya et al., 2018). Antioxidant defense protects biological systems from free radical toxicity and includes both endogenous and exogenous molecules , that function interactively and synergistically to neutralize free radicals,(Krishnamurthy & Wadhwani, 2012 ; Birben et al., 2012). The term 'antioxidant' refers to any molecule stable enough to donate an electron to a rampaging free radical and neutralize it, thus reducing its capacity to damage a target molecule (Li et al., 2016). The antioxidants are present in significant amounts in commonly consumed fruits, vegetables, beverages (juices, tea, coffee), nuts and cereal products (Mirończuk-Chodakowska et al., 2018). In a biological system, antioxidants can be categorized as enzymatic or non-enzymatic (figure 08) (Zhao et al .,2016) .

III.3.1.Endogenous antioxidants

- **Enzymatic antioxidant**

Enzymatic Activities of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX) constitute a first line antioxidant defense system which plays a key and fundamental role in the total defense mechanisms and strategies in biological systems (ghodaro & Akinloye, 2017). SODs are metal-containing proteins that catalyze the removal of superoxide , O_2 is converted by SOD to H_2 O_2 , which is decomposed to water and oxygen by CAT, preventing hydroxyl radicals production (Krishnamurthy & Wadhwani, 2012 ; Liguori et al., 2018). However, catalase is absent in the mitochondria, hence the reduction of H_2O_2 to water and lipid peroxides to their corresponding alcohols is carried out by Glutathione Peroxidase(GPx) (ghodaro & Akinloye, 2017). Additionally, GSH-Px converts peroxides and hydroxyl radicals into nontoxic forms by the oxidation of reduced glutathione (GSH) into glutathione disulfide and then reduced to GSH by glutathione reductase (Birben et al., 2012).

- **Non enzymatic antioxidant**

Non-enzymatic antioxidants include endogenously produced GSH or dietary compounds (Zhao et al., 2016). The endogenous non-enzymatic antioxidants are molecules that inter act with RONS and terminate the free radical chain reac tions: bilirubin, α-tocopherol (vitamin E), and β-carotene are present in blood while albumin and uric acid account for 85% of antioxidant capacity in plasma (Wu JQ, Kosten & Zhang, 2013).

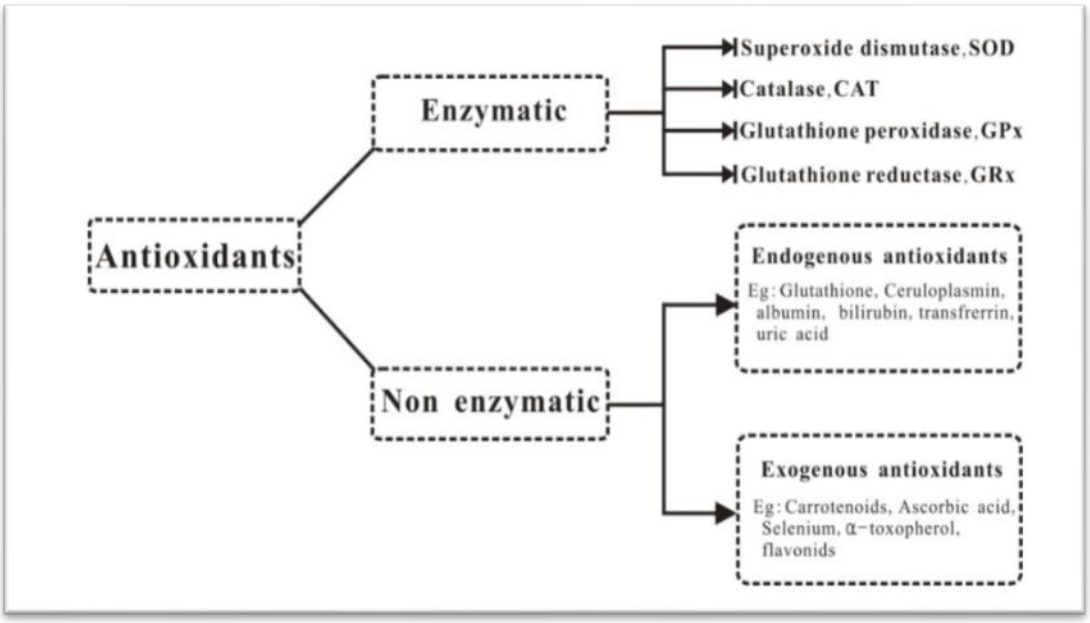


Figure 08 : Enzymatic and non-enzymatic classification of antioxidants

(Li et al., 2016).

III.3.2.Exogenous antioxidants

Dietary antioxidants such as vitamin E, vitamin C, carotenoids, some minerals (e.g. ZnMn, Cu, Se) and polyphenols (flavonoids, phenolic acids, stilbenes, lignans) can affect the activity of endogenous antioxidants. Endo- and exogenous antioxidants may act synergistically to maintain or reestablish redox homeostasis (Mirończuk-Chodakowska et al., 2018).

III.4.Oxidative stress and stroke

Oxidative stress (OS) plays an important role in the pathogenesis of nervous tissue damage in the presence of stroke (Maksimova et al., 2019). Ischaemia would be followed by reperfusion leads to increased production of free radicals (figure 09) (Setyopranoto, 2016).(Chehaibi et al., 2016). Superoxide is one of the most important ROS in the central nervous system [CNS] (Rodrigo et al., 2013). Nitric oxide (NO) plays an important role in vessel dilatation and inflammation (Cheng et al., 2017). The brain is especially prone to free radical damage for several reasons. It is very rich in polyunsaturated fatty acids, which are particularly vulnerable to free radical induced peroxidation, but also has a low content of antioxidant enzymes, such as catalase and glutathione peroxidase (Ozkul et al., 2007).

Histologically, stroke is characterized by an ischemic core [infarct] surrounded by a "penumbra" [peri-infarct] region (Rodrigo et al., 2013), Increased production of superoxide anions, hydroxyl radicals, and peroxy nitrite or nitrogen dioxide has been shown in infiltrating phagocytes, vascular and glial cells in the penumbra (Sidorov et al., 2019). As a result Neurons are killed rapidly within minutes and the tissue in the ischemic core is irreversibly damaged even if blood flow is reestablished (Li et al., 2018). The immune-induced inflammation. Brain ischemia and reperfusion is known to activate the complement system and form complexes such as C5b-9. Circulating dendritic cells, lymphocytes, monocytes, monocyte derived macrophages, and natural killer cells modulate inflammatory responses and thereby facilitate the thrombo-inflammatory response (Yang et al., 2019).

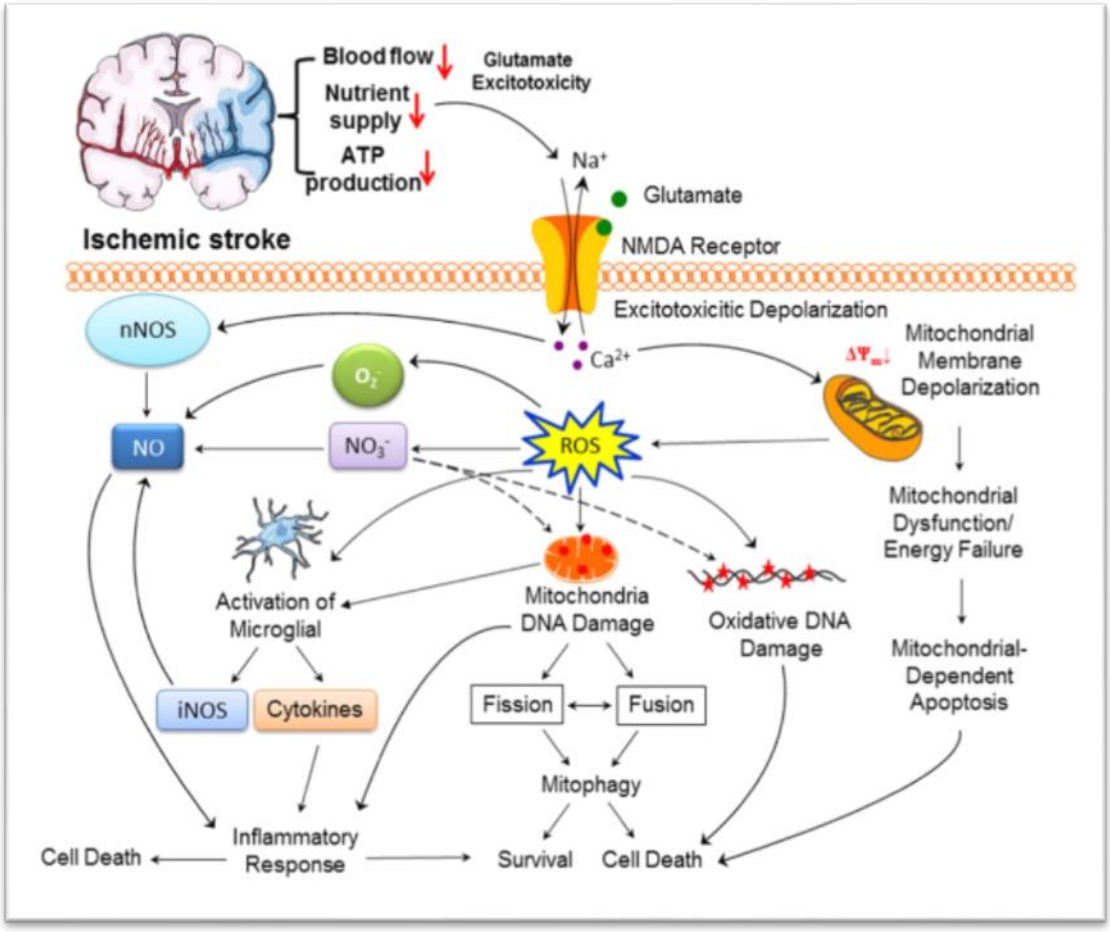


Figure 09: Pathological signaling pathways involved in mitochondrial function and reactive oxygen species(ROS) generation in the cerebral ischemic cascade (Yang, 2018).

Second part

Experimental part

Materials & Methods

I. Materials and Methods

I.1. Patients and reagents

I .1.1. Study period

The period of our study is 6 Months , (from September 2019 to February 2020) at the medicine service and medical analysis laboratory of Sliman Amirat hospital (Touggourt) and at the Faculty of Natural Sciences and Life at the University of Echahid Hamma Lakhdar El-Oued.

I.1.2. Epidemiological and Risk factors study

The stroke reports of 605 patients from hospital of Sliman Amirat in Touggourt were collected and information such as the patient's name, age, sex, type of stroke, region of patients and during of hospitalization was noted. The data was compiled to get the percentage distribution and graphs were drawn for the individual data.

A standard questionnaire was used to obtain the baseline information which Contribute in our study,with face-to-face interviews by us . this questionnaire asked for 130 volunteers divided into 65 healthy group as a control and 65 stroke patients and used for evaluation of some Risk factors of the disease.

I.1.3. Biological study

For biological study, this study is carried out on 40 volunteers ; 10 volunteers women aged between 36-77years, were divided into two groups ; a group of 05 healthy control women aged 54.4±2.11 year, and 05 women has stroke aged 56.20±6.80 years. 30 men volunteers of age between 35-79years , were divided into two groups ; a group of 15 healthy control men aged 56±3.32 year, and 15 men has stroke aged 57.75±4.01 years .

- **Inclusion criteria**

✓ Voluntary live in TOUGGOURT region .

✓ Control group in good health, does not have any pathology.

✓ Voluntary was surfed from stroke .

- **Exclusion criteria**

✓ Persons are suffering from other acute or chronic pathology.

I.1.4.Reagents

Ethylene diamine tetraacetic acid (EDTA), Hydrogen Peroxyde (H2O2) ,Hydrochloricacid (HCl) , Thiobarbituric acid (TBA) , Salicylic acid , Methanol, Tris ,Trichloroacetic acid (TCA) , Copper sulfate (CuSO 4) , Ascorbic acid, DTNB (5,5′-Dithiobis(2-nitrobenzoic acid)), Sodium chloride (NaCl) , Butylated hydroxytoluene (BHT) ,Phosphate-buffered (KH_2PO 4,K_2HPO 4), folin , NBT , Methionin , riboflavin .

I.2. Methods

I.2.1. Collection of data

We used a questionnaire including social and clinical data for each volunteer , after that collecting the risk and protective factors associated with the accident vascular cerebral .

I.2.1.1. Sample collection

About blood sampling for both groups is done morning fasting . It is performed in the vein of the end of the elbow. Blood samples is collected in three tubes . Dry tubes are centrifuged at 3000 rpm for 10 minutes, then obtained the serum to achieve the dosage of oxidative stress (MDA, GSH , vitamin C , SOD ,ORAC and total thiol) parameters .

The anticoagulant tube (EDTA) is mixed well and then assays the hematological and oxidative stress (MDA , GSH) parameters .

The anticoagulant tube (Heparin) are centrifuged at 2000 rpm for 5 minutes , then recover the plasma to realize the dosage of biochemistry parameter: Glucose, triglyceride , HDL , LDL , cholesterol, total bilirubin , alkaline phosphatase activity (ALP) , total protein , albumin , uric acid and electrolyte markers (potassium , sodium , chlorine) .

I.2.2. Method of Hematological analysis

Hematological analysis (FNS) is performed by the hematology Auto analyzer.

I.2.3. Biochemical parameters assay

Glucose, triglyceride, HDL, LDL, cholesterol, total bilirubin , total protein , albumin and uric acid Were determined by Auto analysis (BIOLIS24j) use commercial kits from Spinreact, (Spainref:glucose-20121, triglyceride-20131, HDL-20113, cholesterol- 20111, total bilirubin-20131, total protein-1001291, albumin-1001020,uric acid- 1002011. and enzyme

marker were also measured using commercial kits (Spinreact, ref: alkaline phosphatase-20015).

I.2.4. Method of electrolytes analysis

Determination of the ion gram parameter (potassium , sodium , chlorine) by automatic electrolyte analyzer (Easylute) .

I.2.5. Method of estimating oxidative stress parameters

I.2.5.1. Preparation of erythrocyte homogenate

Blood EDTA tubes contents are centrifuged at 2000 rpm for 10 min and removed the plasma. The cap of EDTA tube was lysis with 50 ml of TBS buffer (EDTA2.92 M;tris 1.21M; pH=7) and incubated 30 min in freezer. After incubation centrifuged at 2500 rpm for 10 min and the obtained supernatant (erythrocyte homogenate) was used for the determination of antioxidant activity (Miller et al., 1988).

I.2.5.2. Separation of leukocyte homogenate

After removing the plasma and separation of erythrocyte, the rest of EDTA tube contents centrifuge at 2000 rpm for 10 min. Wash pellet with lysis buffer and shake incubate in freezer for 30 min. After incubation centrifuged at 2500 rpm for 10 min followed this step by washing with lysis buffer until the Leukocyte pairing and then recovered to make the dosage of stress tests (Miller et al., 1988).

I.2.5.3. Malondialdehyde assay

MDA was measured according to the method described by (Yagi, 1976). Thiobarbituric acid 0.67% (w/v) was added to aliquots of the sample previously precipitated with 10% trichloroacetic acid (w/v). Then the mixture was centrifuged, and the supernatant was heated (100°C) for 15 min in a boiling water bath. Then cool in a cold water bath for 30 minutes, leaving the tubes open to allow evacuation of the gases formed during the reaction and the absorbance was measured at 532 nm using a spectrophotometer. The concentration of TBARS was determined using the molecular extinction coefficient of MDA (a=1.53 105 M-1.Cm-1).

I.2.5.4. Determination of Reduced glutathione level

The determination of the reduced glutathione concentration by measuring the optical density results from the formation of 2-nitro-5-mercocapturic acid from the reduction of

dithio-bis-2-nitrobenzoic acid, which is called reagent of Ellman with SH groupings exist in GSH briefly, 800 µL of homogenate are added to 200 µL of salicylic acid (0.25%) and centrifuge at 1000 rpm for 5 minutes. 500 ml of supernatant are then mixed with 1000 µl of tris buffer (tris 0.4 mol, 0.02 molNaCl pH = 8.9) and 25 µL of DTNB (0.01 mol.L-1). After 5 minutes of incubation, the absorbance is read at 412 nm (Weakbeker& Cory, 1988).

$$GSH\ (nM/mg\ of\ Hb\ ) = \frac{(OD \times 1 \times 1.525)}{(13133 \times 0.8 \times 0.5 \times mg\ of\ pr)}$$

- **13133:**Absorption constant of SH groups at 412 nm.
- **OD :**The absorbance reader by the spectrophotometer.
- **1.525ml :**Total volume of blend.
- **0.5ml:** Volume of solution float.
- **1:**Volume of protein mixture.
- **0.8 ml :**Volume of homogeneous solution without protein exists in 1ml.
- **GSH**: Concentration of glutathione.

I.2.5.5. Determination of superoxide dismutase activity assay

The assay method of SOD activity using the NBT by the superoxide anion (O2 .), is used as a basis for detecting of presence of SOD by measuring the spectrophotometrically absorbance at 560 nm (Beauchamp & Fridovich,1971).

Collect in tubes	**Blank**	**Sample**
EDTA-Met 0.1mM EDTA-13mM Met	1000µL	1000µL
Phosphate buffer (50Mm)	892.2µL	892.2µL
Sample	0	50
Phosphate buffer	1000µL	950µL
NBT (75µM)	85.2µL	85.2µL
Riboflavin (2µM)	22.6µL	22.6µL

Expression of results

$$SOD\ (U\backslash g\ of hb)\frac{(DO\ blanc - DO\ sample)}{(DO\ blanc)}$$

I.2.5.6.Determination of antioxidant power

a. Principle

The total antioxidant power of the serum,its capacity to absorb free oxygen radicals (ORAC: Oxygen Radical Absorbance Capacity), is estimated by the ability of red blood cells to resist free radical-induced hemolysis in vitro in the presence of plasma according to the method of (Oyaizu, 1986). This method is based on the time-dependent monitoring of red blood cell hemolysis induced by a free radical generator.

b. Treatment of red blood cells

- Centrifuge donor blood at 2000 rpm for 10 min and remove plasma.
- Wash gently 1 volume of the pellet with 2 volumes of physiological saline (without lysing the RBCs), then centrifuge again at 2000 rpm for 5 min.

c. Operating mode

✓ **Control tube**

- Add 1 ml of RC: 20 µl of CuSO4 (2 mM), 20 µl of H2O2 (30%) and 2 ml of physiological saline, then stir gently. Incubate for 5 min at room temperature, centrifuge for 5 min at 2000 rpm.
- Read the OD at 450 nm from the supernatant and put it back into the tube and stir gently.
- Repeat this operation every 10 minutes for 1 hour.

✓ **Standard tube**

- To 1 ml of GR are added: 20 µl of CuSO4 (2 mM), 20 µl of H2O2 (30%) and 2 ml of physiological saline, and 20 µl of vitamin C (400 µM) and then stir gently. Incubate for 5 min at room temperature, centrifuge for 5 min at 2000 rpm.
- Read the OD at 450 nm from the supernatant and put it back into the tube and stir gently.
- Repeat this operation every 10 minutes for 1 hour.

✓ **Test tube**

- To 1 ml of RC are added: 20 µl of CuSO4 (2 mM), 20 µl of H2O2 (30%) and 2 ml of physiological saline, and 20 µl of serum (400 µM) and then stir gently. Incubate for 5 min at room temperature, centrifuge for 5 min at 2000 rpm.
- Read the OD at 450 nm from the supernatant and put it back into the tube and stir gently.
- Repeat this operation every 10 min for 1 hour (t0, t10, t20, t30, t40, t50, t60, and average the latter:
- ΣDO = Σ (t0, t10, t20, t30, t40, t50, t60) / 7
- To calculate the total antioxidant power using two methods.

Calculate method

$$ORAC(UI) = \frac{\Sigma(ODcontrol - ODsample)\Delta t}{\Sigma(ODcontrol - ODstandard)\Delta t}$$

I.2.5.7.Determenation of vitamin C concentration

The plasma vitamin c is measured according to the method of Jacota and Dani (1982) using the Folin reagent and a range of ascorbic acid . Brieflt , add ml of plasma to 0.5 mol of the TCA solution (10٪) . Vortex then place the tube in an ice bath for 30 min . centrifuge at 3000rpm for 10 min . take 0.75 ml of the supernatant to which 0.75ml of distilled water and 150µl of Folin (1\10) are added vortex and incubate for 15 min at room temperature . Read the OD using a blank spectrophotometer at 769 nm and determine the vitamin C concentration (µg \ml) (Jago & Dani ,1982).

I.2.5.8.Determenation of total thiol concentration

The serum total thiol was determined according to the method described by Ellman9. Aliquot of the supernatant (50µL) was mixed with 1ml of tris base (0.25M)-EDTA(20mM) buffer and absorbance was taken at 412 nm . this was followed by the addition of 5 ml of 10 mM DTNB , after which another absorbance was taken after 15 min . The absorbance of DTNB blank and sample blank also taken and the total thiol were calculated using the formula

$$Thiol\ (mol\backslash l) = \frac{(A - B - C)\ (4\backslash 0{,}2)}{13.600}$$

Where :

A = Absorbance of supernatant

B=DTNB blank absorbance

C = Sample blank absorbance

Extinction coefficient (13.600 L mol $^{-1}$ cm $^{-1}$)

I.3. Statistical analysis

Statistical analysis is performed by the SPSSV20.0 software results comparisons were carried out by using the Student T test to compare means among the groups, Correlation analysis was carried out using Pearson Correlation test and regression analysis was used for other analysis and statistical data. Differences were considered statically significant at $p < 0.05$.

Results

II .Result

II.1.Epidemiological study of stroke patients

In this study , the number of hospital stroke patient was about 605 patients registered in Touggour .

II.1.1.Distribution of the hospital stroke patients by sex

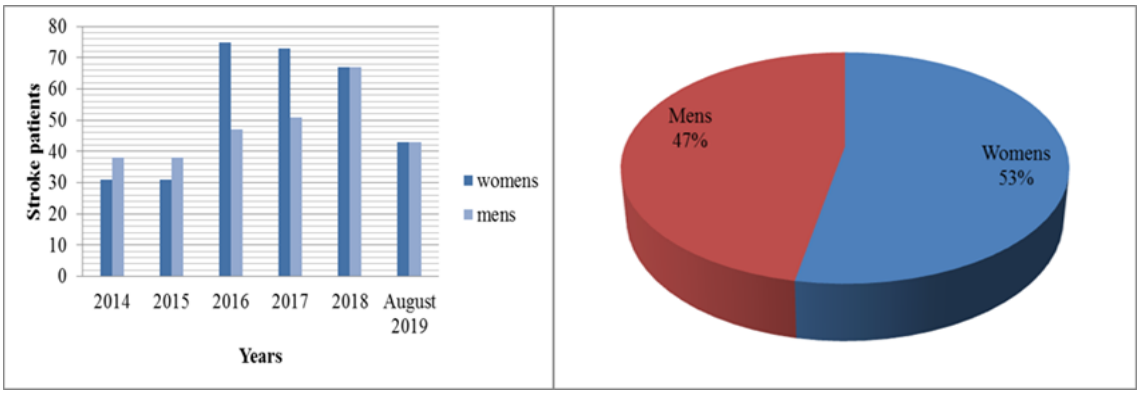


Figure 10 : Distribution of the hospital stroke patients among women's and men's .

In this study it was found that man's accounted for 47% of the stroke population and women's accounted for 53%. In this study, stroke occurs to be most commonly affecting the females when compared to the males (figure10) .

II.1 .2. Distribution of the hospital stroke patients according to the age group

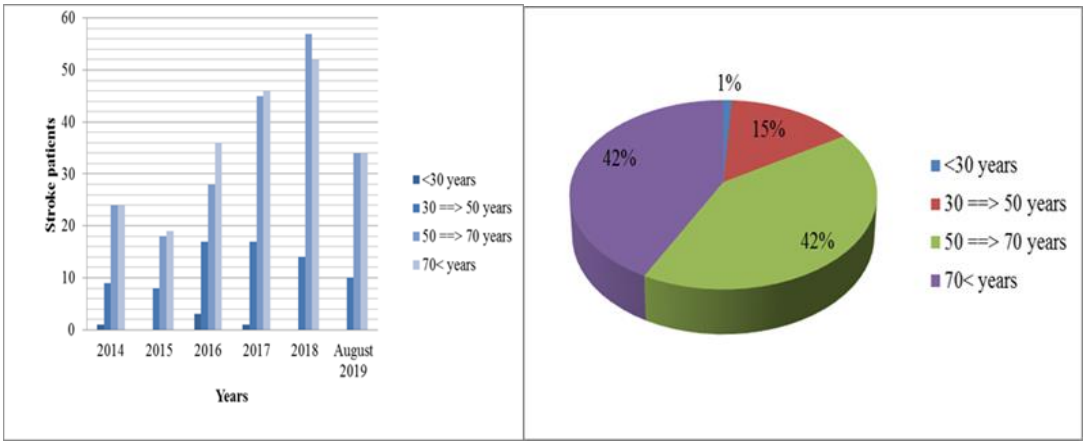


Figure 11: Distribution of the hospital stroke patients according to the age group.

It was found that there were low stroke patients (1%) between the age groups 0-30 years of age. 15 % of the people between 30-50 years, 42 % of the people between ages 50-70

years, 42 % of people have more than 70 years were found to be affected by stroke in Touggourt population (figure 11).

II.1.3.Distribution of the hospital stroke patients according to according to the stroke type

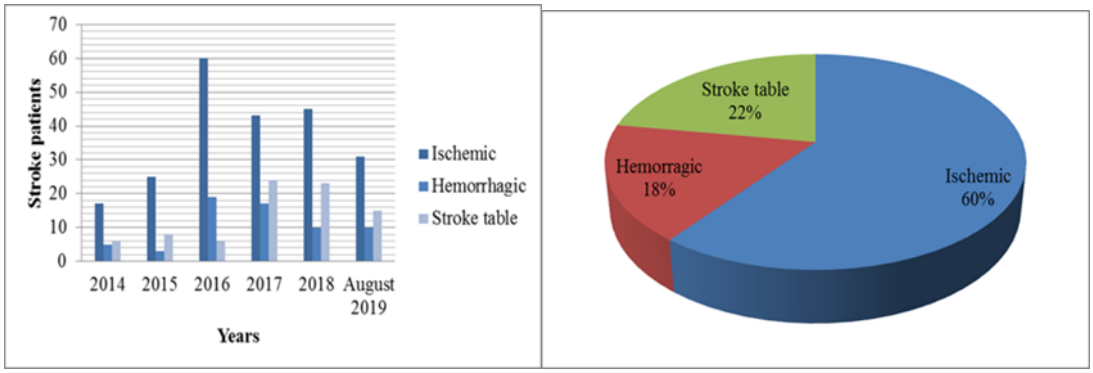


Figure 12: Distribution of the hospital stroke patients according to the stroke type.

The most common type of stroke in this study was found to ischemic stroke type with a distribution of 60% when compared to stroke hemorrhagic with 18% and uncertain type with a percentage distribution of 22% (figure12).

II.1.4.Distribution of the hospital stroke patients according to according to the region

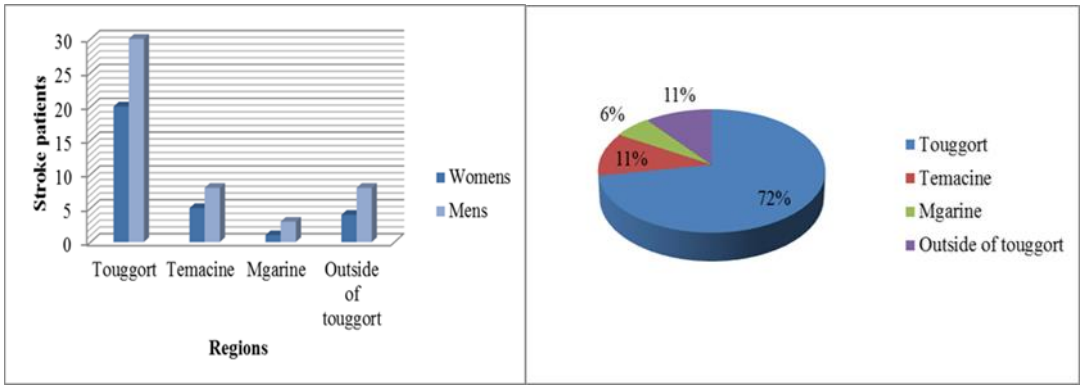


Figure 13: Distribution of the hospital stroke patients according to the region .

In the hospital of Sliman Amirat Touggourt in the period (from January 2014 to August 2019) the majority hospital stroke patients are from Touggourt (72%) represented of a total cases with summit in 2018 (89 patients from Touggourt) , the following stroke patients regions in this hospital are Temacine and Outside of Touggourt represented 11% and 11% of a total cases in the last enumeration patients is the Megarine region represented 6% of total cases (figure13).

II.1.5.Distribution of the hospital stroke patients according to the hospitalization during

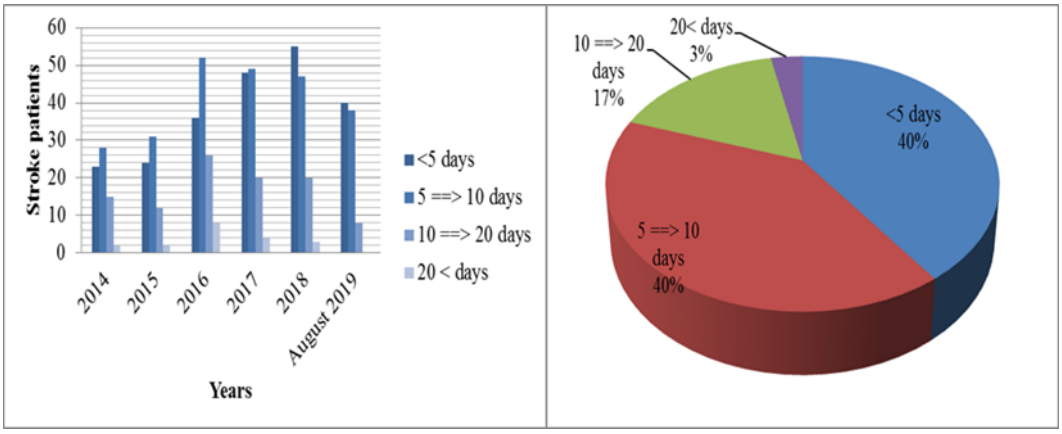


Figure 14: distribution of the hospital stroke patients according to the hospitalization during **.**

The hospitalization period in Sliman Amirat Touggourt of stroke patients is deferent according to the patient from less to 5 days until more than 20 days; the majority cases stay in hospital less to 5 days or between 5 and 10 days represented 40% of a total cases , in second order the patients who are hospitalized between 10 and 20 days represented 17 %, finely with a few number of patients who are hospitalized more than 20 days represented 30% of a total cases.

II.2. Risk factors Study of stroke

II.2.1. Description of study population

Characteristics of the study population are shown in table 03. women and men volunteers for this study from TOUGGOURT region in wilaya of OUARGLA . Our study found of 130 Participants witch divided to 65 control and 65 stroke patients . The general data of socioeconomic characteristics of the two groups of subjects include age, number of children, body weight, mass index, job, educational level, blood group, Blood pressure and social case . The results obtained are homogeneous in both control and stroke patients and do not have any statistically significant differences ($p > 0.05$) . On the other hand Stroke type and season of infection by stroke are specifically for the patients group.

Table 03: Description of study population .

		Control	Stroke patients
Age (ys)		48.75±1.46	50.43±1.54
Number of children		4.308±0.362	4.763±0.314
Body Weight (kg)		75.37±1.83	73.68±1.73
Mass index		28.02±0.698	27.936±0.666
Job	**Worker (%)**	21.54	23.08
	Retired (%)	3.08	7.69
	Hero (%)	25.38	19.23
Educational Level	**Illiterate (%)**	11.54	33.08
	Educated (%)	31.54	16.15
	High school (%)	6.92	0.77
Blood type	**A (%)**	8.62	9.48
	B (%)	15.52	6.90
	AB (%)	3.45	0.86
	O (%)	28.45	26.7
Social case	**Married (%)**	46.15	50
	Single (%)	3.85	00
Stroke type	**Ischemic (%)**		61.54
	Hemorrhagic(%)		16.92
	TIA (%)		21.54
Season of infection by stroke	**Winter (%)**		10.77
	Spring (%)		10.77
	Summer (%)		55.38
	Fall (%)		23.08

II.2.2. Study of socioeconomic and clinic factors

Odds Ratio (OR) values for socioeconomic factors (Table 04) and clinic-pathological factors (Table 05) show that hyper cholesterol , eating of the red meat, diabetes, atrial fibrillation and hypertension are shown to be significant risk factors for the accident vascular cerebral (OR = 2.633; p = 0.045, OR=2.739; p=0.013, OR = 3.765 ; p = 0.006 , OR= 4.636 ; p = 0.004 and OR= 6.682 ; p = 0.000) respectively, in addition smoke, Excess in treatment with

anticoagulants and exposed to high levels of family stress also shown to be significant risk factors for stroke in the study population (OR = 8.071; p = 0.000, OR=12.310; p=0.000 and OR = 12.687 ; p = 0.000) respectively . In contrast brush of teeth daily and Anemia safety are protective factors (OR = 0.337, p = 0.007 ; OR = 0.190, p = 0.026) respectively . Also , Obesity, Heart attack , hereditary , cancer treatments , self-medication , excess of analgesics , migraines, fast food, spicy foods, salt, sugars,vegetables and fruits, soft drinks, excess of water, herds for medication, exercise regularly, exposed to the sun continuously and exposed to work stress are not considered as predictors of stroke in our population since the OR values obtained are not significant.

Table 04: Comparison of the clinic factors of stroke patients and control (N=130).

	Control (%)		Patient (%)		P	OR	CI 95%
	Positive	**negative**	**Positive**	**negative**			
Hypertension	8.46	41.54	27.69	22.31	**0.000**	**6.682**	2.610-17.104
Diabetes	6.92	43.08	19.23	30.77	**0.006**	**3.765**	1.410-10.051
Hyper cholesterol	6.92	43.08	14.62	35.38	**0.045**	**2.633**	0.967-7.170
Atrial fibrillation	5.38	44.62	16.92	33.08	**0.004**	**4.636**	1.553-13.840
Anemia safety	9.23	40.77	2.31	47.96	**0.026**	**0.190**	0.039-0.929
Obesity	10	40	8.46	41.54	0.398	0.762	0.273-2.121
Heart attack	0.77	49.23	0.77	49.23	0.753	1.000	0.061-16.44
family history	5.38	44.62	12.31	37.69	0.054	2.842	0.919-8.790
cancer treatments	0.77	49.23	1.54	48.46	0.500	2.042	0.179-23.366
self-medication	13.85	36.15	6.92	43.08	0.070	0.419	0.153-1.149
Excess in treatment with anticoagulants	3.08	46.92	21.54	28.46	**0.000**	**12.310**	3.375-44.890
Excess of analgesics	20	30	11.54	38.46	0.066	0.474	0.200-1.121
Migraines	5.38	44.62	6.15	43.85	0.500	1.227	0.349-4.316

Table 05: Comparison socioeconomic of the factors of stroke patients and controls (N=130).

	Control (%)		Patient(%)		P	OR	CI 95%
	positive	negative	positive	negative			
Smoke	3.08	46.92	16.92	33.08	**0.000**	**8.071**	2.187-29.780
Fast food	9.23	40.77	8.46	41.54	0.500	0.868	0.305-2.467
Spicy foods	26.92	23.08	30	20	0.343	1.278	0.578-2.825
Salt	5.38	44.62	9.23	40.77	0.194	1.976	0.612-6.380
Sugars	11.54	38.46	10.77	39.23	0.500	0.893	0.352-2.269
Vegetables and fruits	33.08	16.92	31.54	18.46	0.500	0.916	0.403-2.084
Red meat	15.38	34.62	26.92	23.08	**0.013**	**2.739**	1.204-6.230
Soft drinks	16.92	33.08	26.15	23.85	0.053	2.103	0.939-4.710
Excess of Water	37.69	12.31	33.85	16.15	0.252	0.671	0.278-1.618
Herds for medication	17.69	32.31	26.15	23.85	0.079	1.926	0.865-4.290
Exercise regularly	12.31	37.69	5.38	44.62	0.054	0.352	0.114-1.088
Brush your teeth daily	27.69	22.31	15.38	34.62	**0.007**	**0.337**	0.148-0.767
Exposed to the sun continuously	21.54	28.46	15.38	34.62	0.107	0.545	0.239-1.242
Exposed to high levels of family stress	20	30	38.46	11.54	**0.000**	**12.687**	4.902-32.733
Exposed to work stress	15.38	34.62	17.69	32.31	0.335	1.313	0.569-3.029

*** OR > 1** and **P < 0.05** indicate a risk factor. *** OR< 1** and **P < 0.05** indicate a protective factor.

II.3.Study of biological markers and predictive factors

II.3.1.Blood pressure

the results of blood pressure is shown in figure 15 . Result show that there was a no significant change for systolic and diastolic blood pressure in stroke women patient (P > 0.05) compared to control. In contrast concerning a men group we found that a significant increase in systolic blood pressure (P < 0.05) but diastolic blood pressure was shown that no significant differences (P > 0.05).

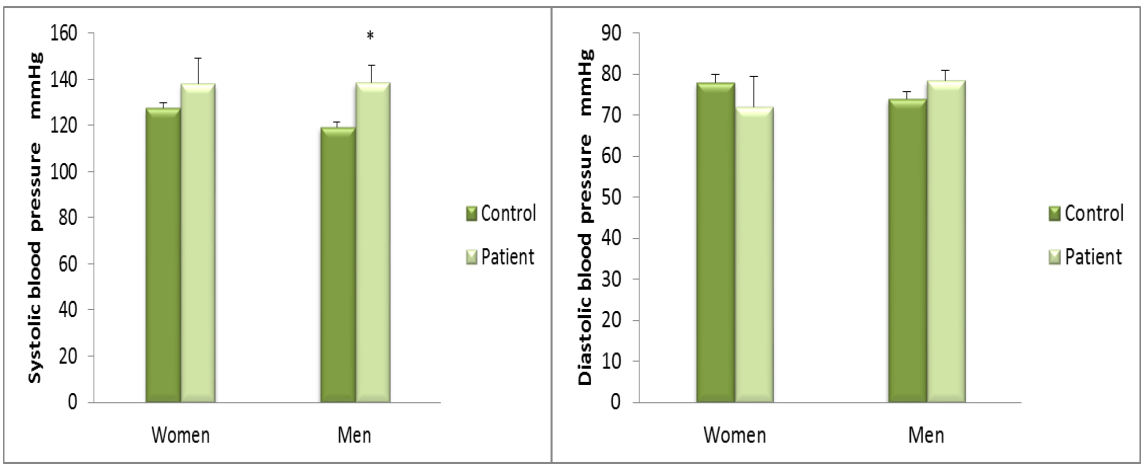


Figure 15 : Blood pressure in control and stroke patient group .

II.3.2.Hematological markers

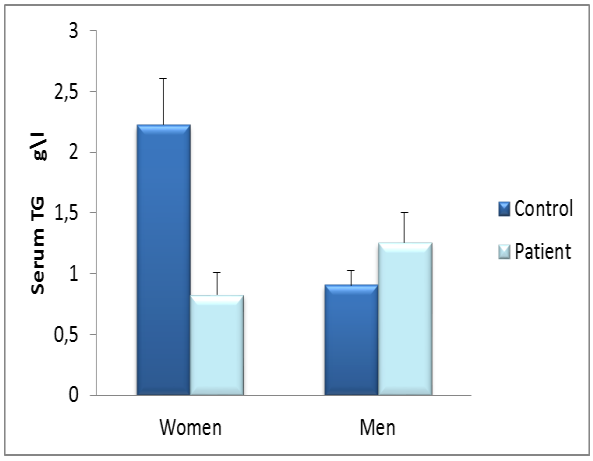
The results of the hematological analysis for control and stroke patient are illustrated in table 06 . the result of women group show that the leukocytes lineage (WBC . NEUT) and PLT are significantly increased ($P < 0.05$ and $P < 0.01$) respectively in the patients group as compared to the control group. Erythrocyte line is significantly decreased (HGB ; $P < 0.01$ and RBC ; $P < 0.001$) in stroke women compared to the women controls . LYM level is shown that no significant differences ($P > 0.05$). Regarding men group, our result show that the leukocytes lineage (WBC, NEUT) is significant increase ($P < 0.001$and $P < 0.01$) respectively in patient group as the control group . Erythrocyte line (HGB, RBC) is significant decrease ($P < 0.001$) in stroke men compared to the women controls . But LYM and PLT are shown that no significant differences($P > 0.05$).

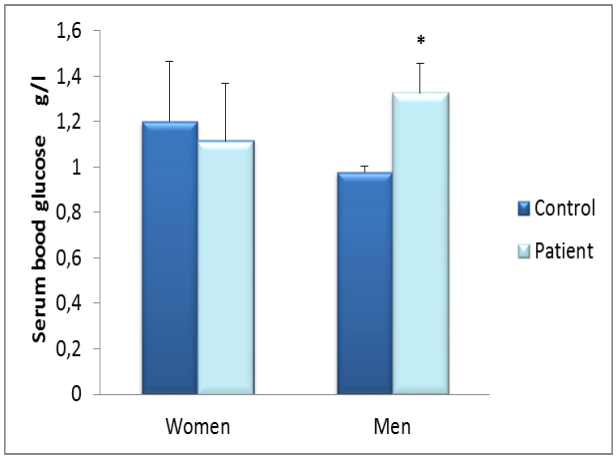
Table 06: Haematological parameters levels in control and stroke patient groups .

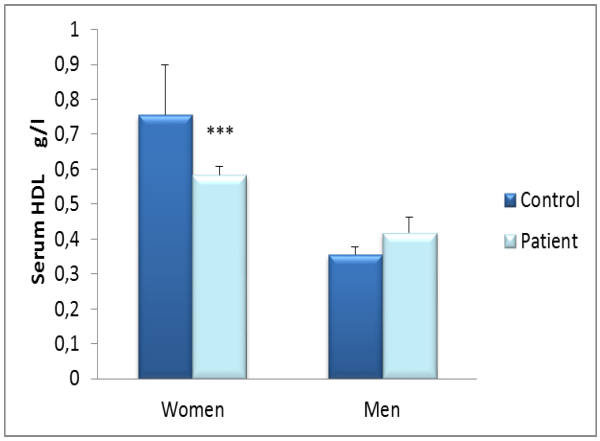
	Women's groups			**Man's groups**		
Parameter	**Control**	**Patient**	**P**	**Control**	**Patient**	**P**
WBC(10*9/L)	5.91±1.39	7.91±1.10	**0.023**	4.87±0.55	9.48±0.78	**0.000**
LYM(10*9/L)	1.92±0.35	2.69±0.56	0.069	1.64±0.17	2.04±0.20	0.081
NEUT(10*9/L)	2.84±1.28	4.80±1.05	**0.021**	2.96±0.46	7.08±0.97	**0.001**
RBC(10*12/L)	5.02±0.31	4.16±0.08	**0.000**	4.90±0.11	3.55±0.23	**0.000**
HGB (g/dL)	14.9±0.88	12.42±0.83	**0.002**	15.14±0.28	10.69±0.69	**0.000**
PLT(10*9/L)	216.8±51.3	313.8±26.3	**0.001**	268±16.6	238.8±22.6	0.198

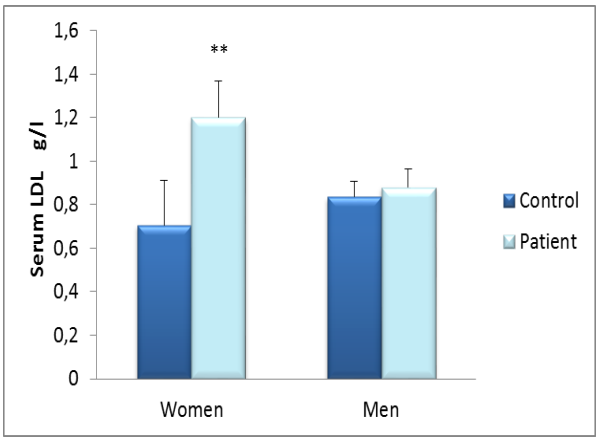
II.3.3.Biochemical markers

Concerning biochemical markers figure 16**,** For women group our result demonstrated that a significant increase ($P < 0.01$) in LDL level and significant decrease in HDL and albumin level ($P < 0.001$ and $P < 0.05$) respectively in women with stroke as compared to controls . But blood glucose, serum TG, cholesterol levels , total bilirubin , total protein and uric acid concentration are no significant differences ($P > 0.05$). In terms of men group , our result revealed that a significant increase in blood glucose level ($P < 0.05$) and significant decrease ($P < 0.001$) in total protein in the patients as compared to the control men . But TG, HDL, LDL, cholesterol, total bilirubin, albumin and uric acid concentration are no significant differences ($P > 0.05$) .









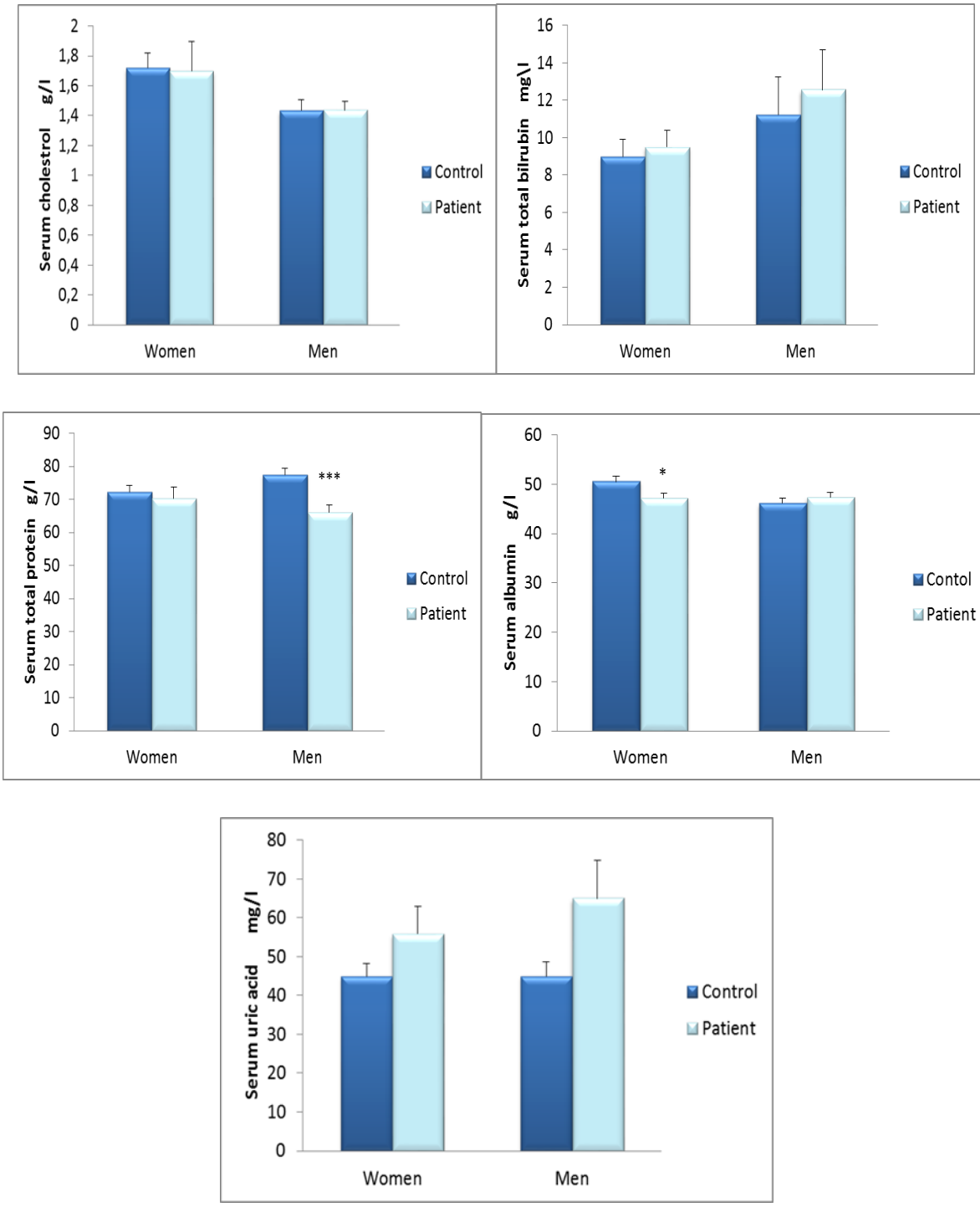


Figure 16: Biochemical parameters in control and stroke patient group.

II.3.4.Enzymatic marker

Seen from figure 17 result of the enzymatic activity .About women , the result obtained show that a very high significant decrease ($P < 0.001$) in alkaline phosphatase activity in women with stroke as compared to controls . In hand of men , we found that a very significant decrease ($P < 0.01$) in alkaline phosphatase activity in the stroke group against the control .

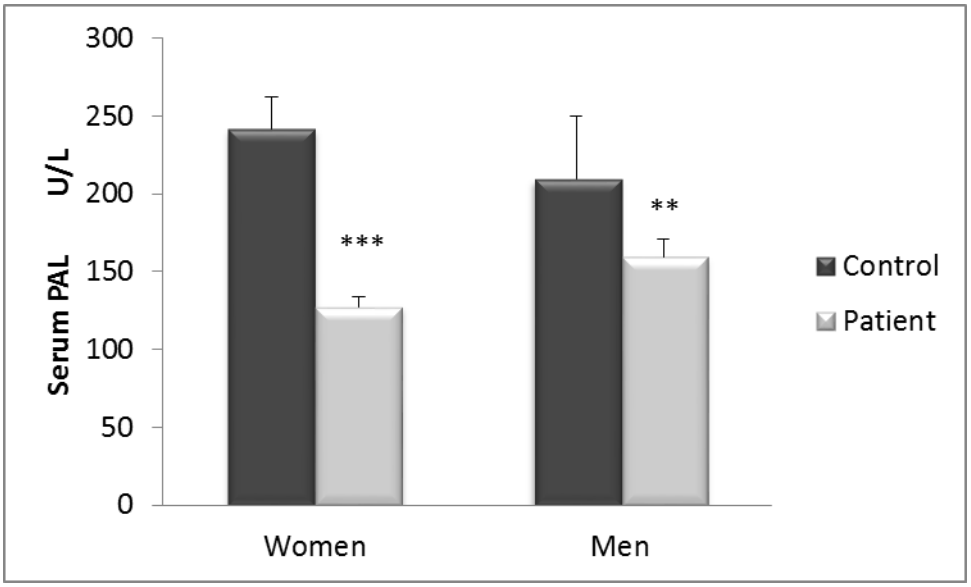
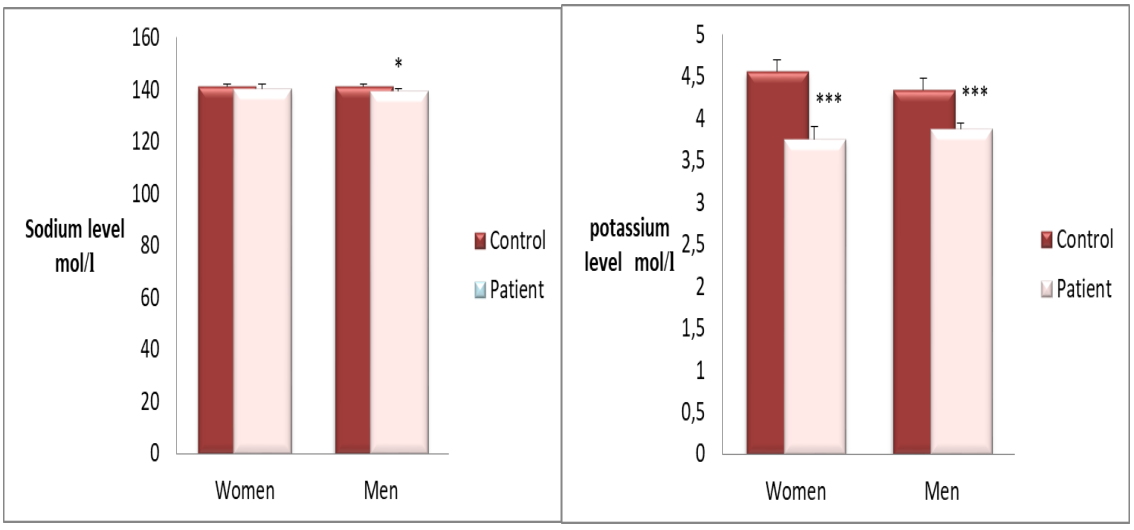


Figure 17: Alkaline phosphatase activity in control and stroke patient group .

II.3.5.Electrolytes level

The result of blood electrolyte analysis (figure 18) shows that potassium concentration was decreased significantly ($P < 0.001$) in the patients women against to the control women. On other hand there were no significant changes ($P > 0.05$) in sodium and chlorine level. Regarding men, we found that a significant decrease in sodium ($P < 0.05$), potassium and chlorine ($P < 0.001$) in the patients as compared to the control group .



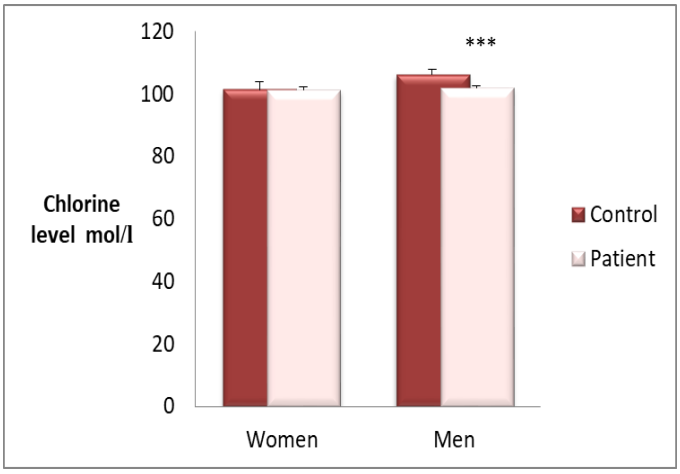


Figure 18: Electrolytes concentration in serum of control and stroke patient .

II.3.6.Oxidative stress markers

The analysis of blood oxidative stress parameters in control and stroke patient are shown in table 07 For women our result explained that a significant increase ($P < 0.05$) of MDA level and SOD activity in leukocytes, erythrocytes and serum ($P < 0.01$) and of ORAC activity ($P < 0.05$), also a significant decrease of GSH ($P < 0.001$) and total thiol ($P < 0.01$) in serum of patient group compared to control group. But there is no significant change ($P>0.05$) in serum MDA , erythrocyte and leukocyte GSH and in serum Vitamin C concentration .

Concerning men group, we revealed that a significant increase of MDA level and SOD activity in erythrocytes ($P < 0.001$), leukocytes ($P < 0.01$) and in serum ($P < 0.05$) and of serum ORAC activity ($P < 0.01$) in patient group compared to men control, in contrast a significant decrease of leukocytes GSH ($P < 0.05$), serum GSH ($P < 0.05$) and total thiol level ($P < 0.01$) of the stroke men compared to the men control . However , our result show that no significant differences in erythrocyte GSH and serum vitamin C level.

Table 07: Oxidative stress parameters in the blood of control and stroke patient .

		Women's groups		Men's groups	
Parameter		Control	Patient	control	patient
MDA (nmol/mg Hb)	Erythrocytes	3.36±0.92	9.59±2.74 *	3.32±0.51	13.55±1.61 ***
	Leukocytes	3.96±1.38	7.78±2.65 *	4.017±0.79	12.25±2.35 **
	Serum	6.46±1.45	8.59±2.40	10.25±0.72	19.16±3.96 *
GSH (µmol/l)	Erythrocytes	0.30±0.07	0.83±0.09	0.30±0.04	0.26±0.02
	Leukocytes	0.13±0.03	0.09±0.03	0.13±0.03	0.09±0.01 *
	Serum	0.21±0.06	0.14±0.01 ***	0.20±0.02	0.14±0.01 *
SOD (U / g Hb)	Leukocytes	13±0.83	14.6±0.92 *	11.84±0.34	18.40±1.57 **
	Serum	11.82±1	14.4±1.12 **	11.72±1.49	17.07±1.68 **
ORAC (U/l)	Serum	0.92±0.06	1.24±0.16 *	1.10±0.02	1.15±0.01**
Vit c (mmol/l)	Serum	6.40±1.59	10.88±8.44	6.08±1.19	9.80±2.80
Thiol (mol /l)	Serum	0.62±0.06	0.23±0.09 **	1.66±0.18	7.28±1.46 **

*** p<0.05, **p<0.01, ***p<0.001**: significantly different from control group.

II.3.7.Predictive factors study

Our result for women explained that Erythrocytes MDA, leukocytes MDA ,leukocytes SOD , serum SOD were a significant predictive factor (P < 0.05) with high percentage of specificity (100 ; 100 ; 100; 100 %) with AUC value (0.78 ; 1 ; 0.89 ; 0.83) and important percentage of sensitivity (33.3; 33.3; 66.7, 66.7) respectively . (Table 08 and figure 19 A) exclusively Serum GSH which was not a significant predictive factor.

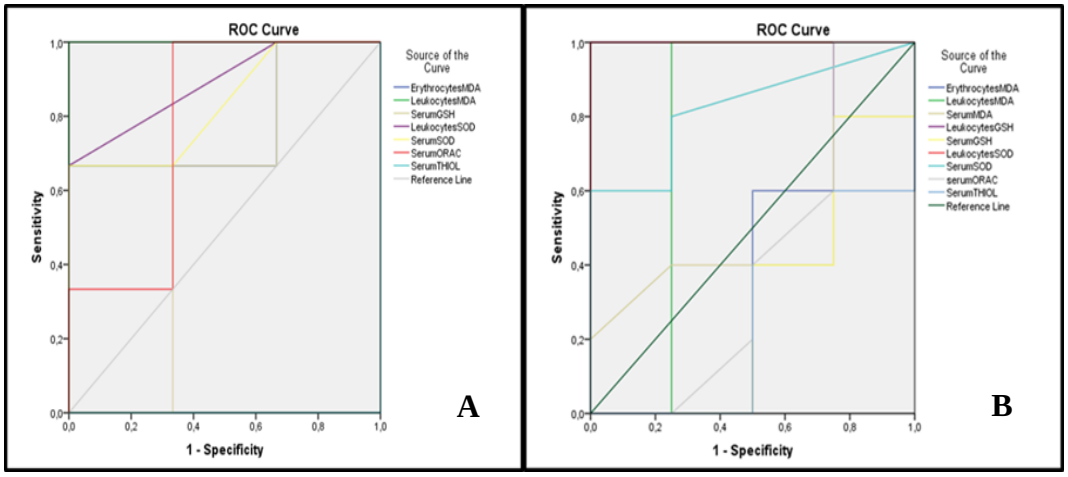


Figure 19: ROC Curve for oxidative stress markers in women **(A)** and men **(B)** .

In contrast about a men group (Table09 and figure 19 B), we found that erythrocytes MDA , leukocytes SOD and serum SOD were a significant predictive factor (P < 0.05) with

high percentage of specificity (100 ;100 ; 100%) with AUC value (1 ; 1 ; 0.83)and important percentage of sensitivity (40; 60 ; 60%) respectively. But serum MDA , Leukocytes GSH and serum SOD were not significant predictive factor (P>0.05).

Table 08: Sensitivity, specificity and AUC values of some oxidative stress markers in women group.

Test Result Variable(s)	Sensitivity %	Specificity %	AUC	*P-value*	$CI_{95\%}$	
					Lower Bound	Upper Bound
Erythrocytes MDA	33.3	100	0.78	0.047	0.543	1.000
Leukocytes MDA	33.3	100	1	0.000	1.000	1.000
Serum GSH	66.7	33.3	0.56	0.691	0.261	0.850
Leukocytes SOD	66.7	100	0.89	0.005	0.736	1.000
Serum SOD	66.7	100	0.83	0.017	0.641	1.000
Serum ORAC	33.3	66.7	0.78	0.047	0,543	1.000
Serum THIOL	66.7	100	0.00	0.000	0.000	0.000

Table 09: Sensitivity, specificity and AUC values of some oxidative stress markers in men group .

Test Result Variable(s)	Sensitivity %	Specificity %	AUC	*P-value*	$CI_{95\%}$	
					Lower Bound	Upper Bound
Erythrocytes MDA	40	100	1	0.014	1.000	1.000
Leukocytes MDA	00	100	0.75	0.221	0.326	1.000
Serum MDA	40	75	0.48	0.903	0.068	0.882
Leukocytes GSH	60	50	0.40	0.624	0.000	0.839
Serum GSH	80	25	0.30	0.327	0.000	0.681
Leukocytes SOD	60	100	1	0.014	1.000	1.000
Serum SOD	60	100	0.83	0.111	0.538	1.000
Serum ORAC	20	50	0.40	0.624	0.000	0.824
Serum THIOL	00	100	0.30	0.327	0.000	0.680

II.3.8 .Correlation between biological markers

In women group

The correlation results between oxidative stress parameters, Hematological parameters, biochemistry markers, enzymatic markers and potassium are shown in the table 10**,** . we learned a positive correlation between (serum total thiol/potassium; P<0. 001) , (serum total thiol/WBC ; P<0. 01), and (serum total thiol /NEUT; P<0. 01). In other hand there was a

negative correlation with P<0. 001 between (erythrocytes MDA / LDL) , (erythrocytes MDA / PAL), (leukocytes MDA / RBC), (Leukocytes SOD /RBC) , (serum SOD / HDL) , (serum total thiol / albumin) . In contrast a negative correlation (P<0.01) between (leukocytes MDA / HGB) (Leukocytes SOD /WBC) , (Leukocytes SOD / HGB) and (serum SOD / PLT). In addition a negative correlation with P<0.05 between (erythrocytes MDA /NEUT), (leukocytes MDA / NEUT), (leukocytes MDA / LDL) , (leukocytes MDA / PAL), (Leukocytes SOD /NEUT) , (Leukocytes SOD /potassium), (serum SOD /LDL) , (serum ORAC / PLT) ,(serum ORAC / HDL), (serum ORAC /LDL) and between (serum thiol / PAL) . There was no correlation (P>0.05) between the rests of correlation test in patients women's groups.

Table 10: Correlation between biological markers for patients women's.

		WBC	NEUT	RBC	HGB	PLT	HDL	LDL	K	ALB	PAL
Erythrocytes MDA	P	0.117	**0.014**	0.587	0.190	0.283	0.074	**0.000**	0.954	0.247	**0.000**
	R	-0.59	-0.81	-0.22	-0.51	-0.40	-0.66	-0.97	-0.02	0.46	-0.97
Leukocytes MDA	P	0.096	**0.040**	**0.000**	**0.007**	0.940	0.366	**0.036**	0.916	0.853	**0.021**
	R	-0.55	-0.65	-0.91	-0.78	0.03	0.32	-0.73	-0.03	-0.06	-0.78
Leukocytes SOD	P	**0.003**	**0.010**	**0.000**	**0.001**	0.156	0.558	0.323	**0.036**	0.748	0.736
	R	-0.83	-0.76	-0.94	-0.87	-0.55	0.21	-0.40	-0.66	0.11	-0.14
Serum SOD	P	0.069	0.623	0.993	0.079	**0.004**	**0.000**	**0.020**	0.380	0.568	0.466
	R	-0.59	-0.17	-0.003	-0.58	-0.87	-0.91	-0.79	-0.31	-0.20	0.30
Serum ORAC	P	0.193	0.563	0.699	0.066	**0.020**	**0.026**	**0.011**	0.692	0.375	0.479
	R	-0.44	-0.20	-0.14	-0.60	-0.78	-0.69	-0.82	0.14	-0.31	-0.29
Serum Thiol	P	**0.006**	**0.006**	0.070	0.146	0.211	0.392	0.352	**0.000**	**0.000**	**0.032**
	R	0.82	0.82	0.62	0.52	0.46	0.32	0.35	0.97	-1.00	-0.70

In men group

The correlation results between oxidative stress parameters, hematological, blood glucose and electrolytes markers are shown in the table 11, we found a negative correlation between (erythrocytes MDA /blood glucose; P<0.05), (leukocytes SOD /RBC; P<0.001) and between (leukocytes SOD /HGB; P<0.001). There was no correlation (P>0.05) between the rests of correlation test in patients men's groups.

Table 11: Correlation between biological markers for patients men's.

		WBC	NEUT	RBC	HGB	GLC	K	NA	CL	Total Protein	PAL
Erythrocytes	P	0.071	0.070	0.686	0.522	**0.026**	0.247	0.418	0.719	0.506	0.833
MDA	R	-0.47	-0.48	0.68	-0.18	-0.67	-0.33	0.22	-0.11	-0.21	0.06

Leukocytes	P	0.151	0.190	**0.000**	**0.000**	0.903	0.978	0.823	0.997	0.533	0.667
SOD	R	-0.39	-0.358	-0.91	-0.93	0.03	-0.008	0.06	-0.001	-0.20	-0.13

II.3.9. Correlation between biological markers and risk factors

The correlation results between oxidative stress parameters, clinical and socioeconomics risk factors are shown in the table 12 and 13.

In women group , There was a significant correlation (P<0.001) between serum thiol and each of hyper cholesterol, Red meat, Diabetes, in addition between serum ORAC and each of Atrial fibrillation, Hypertension, Excess of anticoagulants, high levels of family Stress (P<0.001). we found a significant correlation (P<0.01) between serum SOD and each of Atrial fibrillation , Hypertension, Excess of anticoagulants, high levels of family Stress. There was no correlation (P>0.05) between the rests of correlation test in patients women's groups (table12) . In contrast , all of correlation test was no significant (P>0.05) in patients men's groups (table 13) .

Table 12: Multivariate analysis to multiple predictors (risk factors) and oxidant status in the population study (women).

Independent variable	**Dependent variable**					
	Erythrocytic MDA	Leukocytic MDA	Leukocytic SOD	Serum SOD	Serum ORAC	Serum Thiol
Hyper cholesterol						
P	0.617	0.981	0.461	0.252	0.104	**0.000**
R^2	0.04	0.0001	0.06	0.16	0.29	0.89
Red meat						
P	0.907	0.412	0.282	0.312	0.595	**0.000**
R^2	0.002	0.08	0.14	0.12	0.03	0.89
Diabetes						
P	0.617	0.981	0.461	0.252	0.104	**0.000**
R^2	0.04	0.0001	0.06	0.16	0.29	0.89
Atrial fibrillation						
P	0.076	0.257	0.767	**0.005**	**0.000**	0.624
R^2	0.43	0.15	0.01	0.64	0.99	0.03
Hypertension						
P	0.076	0.257	0.767	**0.005**	**0.000**	0.624
R^2	0.43	0.15	0.01	0.64	0.99	0.03
Excess of anticoagulants						
P	0.076	0.257	0.767	**0.005**	**0.000**	0.624
R^2	0.43	0.15	0.01	0.64	0.99	0.03
Family stress						
P	0.076	0.257	0.767	**0.005**	**0.000**	0.624
R^2	0.43	0.15	0.01	0.64	0.99	0.03

Table 13: Multivariate analysis to multiple predictors (risk factors) and oxidant status in the population study (men)

Independent variable	Dependent variable	
	Erythrocytic MDA	Leukocytic SOD
Hyper cholesterol		
P	0.258	0.963
R^2	0.15	0.0003
Red meat		
P	0.979	0.610
R^2	0.0001	0.03
Diabetes		
P	0.057	0.959
R^2	0.38	0.03
Atrial fibrillation		
P	0.212	0.730
R^2	0.18	0.01
Hypertension		
P	0.579	0.767
R^2	0.04	0.01
Excess of anticoagulants		
P	0.224	0.931
R^2	0.17	0.001
Smoke		
P	0.427	0.369
R^2	0.08	0.10
Family stress		
P	0.574	0.139
R^2	0.04	0.25

Discussion

III. Discussion

III.1.Epidemiological study of stroke in the Touggourt region

In our epidemiological study , we found that a stroke occurs to be most commonly affecting the females when compared to the males . Research conducted until 2004 found a result opposite the rate of the men more than the women, 51% were men and 49% were women (Amytis et al., 2007). Risk factor for stroke is significantly differentiated and imbalanced between women and men in favor of women (Sanne et al., 2016). The sex hormones especially in the reproductive periods, plays an important role in the difference in risk of stroke between women (which present third cause of death) and men (presents the fourth leading cause of death in the world) (Hilda & Louise., 2019 ; Jordan et al., 2018).

Concerning the distribution of stroke according the age group , our study demonstrated that the majority of cerebrovascular accident patients aged between 50-70 years old . which similar with a study conducted in the period 1993 and 2005 on the age of stroke patients showed that the average age of patients with stroke is decreased by 71.2 years to 69.2 years, with 65 years this is the average age of 80% of patients with ischemic stroke (Chengwei et al., 2018 ; Rodney et al., 2018). In addition, no study has shown the relationship between age less than 65 years and the number of mortality among stroke patients but this number is increased with age (Rothwell et al., 2005). This last result deferent of our study because was eliminated the age range between 50 and 60 years , thereafter because it has been reported that immune system dysfunction is associated with aging, especially with respect to T-cell function (Rodney et al., 2018). In fact, recent research results show that the blood-brain barrier is altered by systemic inflammation with no related with the size of the infarct (Shichao et al., 2018).

Our statistical study show that the most common type of stroke was to ischemic stroke type . The results obtained in this study is in concurrence with the study conducted by study of (Shichao et al., 2018), in a study of 21,684 patients, more than 86% of cases of ischemic stroke showed the dominance of this type of stroke (Shichao et al., 2018). In the same study, age is a major risk factor for this type of stroke for more than 80% (Hongxia et al., 2018).

A diagrammatic representation of the hospitalization during of the patients shows that the majority of stroke patients stayed in hospital less to 5 days or between 5 and 10 days . Results of our study is close to results of the study realized in the United States during 2009 to 2011 which indicated that hospitalization is more than 4.2 days for both groups studied

(Judith H et al., 2016) but in author cases the hospitalization during may be 14-day (Amytis et al., 2007) until 30 day of hospitalization which were dominated by cerebrovascular diseases (Merel et al., 2018).

III.2.Study of risk factors for Stroke

Results of our study observed that the hyper cholesterol and the excessive consumption of the red meat are associated with increased risk of stroke . study of (Wang et al.,2017) shown that a significant relationship between the ischemic stroke risk and the serum total cholesterol level for the general population . In other words (Raffaele et al., 2010), explain that a proportionality between the reduction of cholesterol (mostly LDL-C) and the reduction of total stroke with an estimate of 0,8% reduction in TC for a 1% reduction of relative risk of stroke . Our results are in agreement also with study of (Reina et al., 2019) which found that a high consumption of red meat is potential risk for stroke . Red meat contains a large amount of saturated fats that can raise the level of plasma cholesterol, low-density lipoprotein cholesterol, and triglycerides (Kim et al., 2017). While high serum cholesterol levels were associated with stenosis of basal and cortical arteries (Sarti, 2000), a reaction to endothelial inflammation and damage, oxidized lipids from LDL (low-density lipoproteins) particles gather in the endothelial region of the vessel wall (LaRosa, 2006). The oxidation of these particles may be brought about by angiotensin II. Monocyte then infiltrates the arterial wall and differentiates into macrophages, which accumulate oxidized lipids to form foam (Alloubani et al., 2018). In addition red meat is high in heme iron, which can catalyze oxidative reactions in biological systems. Oxidative reactions can damage lipids, proteins, and DNA, increasing the risk of metabolic, neurologic, and cardiovascular diseases (Kim et al., 2017).

In our study the result show that the diabetes mellitus was significantly associate with stroke risk . this result is in agreement with study of (Mohamed et al., 2019). Diabetes can be leads to stroke disease by several possible mechanisms such as vascular endothelial dysfunction, increased early-age arterial stiffness, systemic inflammation , thickening of the capillary basal membrane and very high likelihood of significant comorbid hypertension (Rong et al., 2016 ; Michele et al., 2014). Diabetes mellitus caractezed by insulin resistance with plays a major role in the pathology of cardiovascular disease including stroke. In the context of insulin resistance, increased FFA and defective insulin signaling receptors on the macrophages contribute to macrophage apoptosis and poor clearance of LDL by

phagocytosis. Consequently, necrotic breakdown of advanced lipid-rich plaques occurs, which lead to the progression of clinically relevant atherosclerotic lesions (Tun et al., 2017).

Our study show that the hypertension is widely considered as an important risk factor to having a stroke . which was in accordance with some other studies : study of (Song et al., 2018 ; Jorden et al., 2018) demonstrated that the hypertension is the main risk factor of stroke disease ,with prevalence at around 60% to 70% for all studies (Jacobs et al., 2019). Strokes are strongly associated with hypertension mainly because its strong association with atherosclerosis deposits blocking and narrowing brain arteries , predisposing to local clot formation (John,2003;Song et al., 2018), atheroma and its ischemic consequences may damage cerebral arterioles and the brain tissue they supply (John, 2003).

Our study showed also that the atrial fibrillation (AF) and excess of anticoagulant are risk factors for stroke. study of (Elkhatib et al., 2020) showed that AF constitute an important risk factors for ischemic stroke, also study of (Mohammad et al., 2019) demonstrated that stroke is the most complication of AF. In other hand (Budincevic et al., 2020) said that the oral anticoagulant therapy is a risk factor for hemorrhagic stroke .

Atrial fibrillation is the most arrhythmia in clinical practice (Valeria & Florian, 2019), which increase the risk of stroke 4 to 5 fold because that fibrillation of the atrium produces stasis of blood , which causes thrombus formation and embolism to the brain (Budincevic et al., 2020 ; Kamel et al., 2016). Oral anticoagulant is highly effective therapy which can reduce the risk of AF-related stroke by more than 60 % relative to placebo in high risk patient. However oral anticoagulation use is also associated with an increased risk of bleeding complication including hemorrhagic stroke (Paul, 2013).

Our results showed an association between smoking and stroke disease , which agreement with a study of (Lin et al., 2016).Who stated that a cigarette smoking, an independent modifiable risk factor for cardiovascular disease, doubles the risk of stroke**.** Probable mechanisms by which primary and environmental tobacco smoke exposure can increase the risk of stroke and heart disease are numerous and include car-boxy-hemoglobinemia, increased platelet aggregability, increased fibrinogen levels, reduced HDL-cholesterol, (Shah & Cole, 2010), with most centering on the fact that tobacco smoke contains over 4000 different chemical constituents, including heavy metals and other known toxins. Such chemicals promote the development of free radicals that induce vascular endothelial dysfunction and inflammation, ultimately leading to the development and acceleration of the

atherosclerotic process (John, 2011). Atherosclerosis and arterial damage thus explain how smoking predisposes individuals to large- and small-vessel lacunar stroke. Impaired endogenous fibrinolysis and reduced blood flow in the brain secondary to smoking-induced vasoconstriction may also contribute to lacunar stroke (Shah & Cole, 2010). Ischemic stroke is not the only form of stroke associated with smoking; the risks of intra-cerebral hemorrhage and subarachnoid hemorrhage are also elevated **(**John,2011**)**, Smoking may cause hemorrhagic stroke by damaging the walls of small intra parenchymal arteries, leading to the increased incidence of aneurysms and their rupture (Shah & Cole, 2010).

Our study show that the exposed to high levels of family stress is largely associated with a risk of stroke , which agreement with other studies ; (Jood et al., 2009 ; Poitras et al., 2013). Stress is defined as a process in which environmental demands compromise or exceed an organism's adaptive capacity, resulting in psychological and biological changes **(**Ramírez-Moreno et al., 2019). According to the allosteric load model, the hypothalamic pituitary adrenal (HPA) axis is one of several biological pathways by which perceived stress influences cardiovascular , cerebrovascular and metabolic processes (Lehrer et al., 2019). Stressors activate the sympathetic nervous system, stimulating catecholamine release from the adrenal medulla and adrenergic terminals. The hypothalamic-pituitary-adrenal axis is also activated: the hypothalamus secretes hormones, mainly corticotropin-releasing hormone, which in turn stimulates the anterior pituitary gland. The latter releases adrenocorticotropic hormone, resulting in peripheral release of glucocorticoids (cortisol) and mineralocorticoids (aldosterone). This hormonal response triggers a series of changes (Ramírez-Moreno et al., 2019) vascular inflammation, oxidative stress or immune dysfunction , impact on blood pressure and increases in blood levels of glucose , LDL , total cholesterol and triglyceride which underpinning the pathophysiology of vascular disease including stroke (Booth et al., 2015 ; Lehrer et al., 2019).

Our result showed that anemia safety is protective factor from stroke , according to (Kaiafa et al., 2015) Similarly, alongside smoking, diabetes mellitus, hypertension, and hypercholesterolemia, anemia was characterized as 'the fifth cardiovascular risk factor'. Generally, anemia is considered a hyperkinetic state which disturbs endothelial adhesion molecule genes that may lead to thrombus formation. Furthermore, blood flow augmentation and turbulence may result in the migration of this thrombus, thus producing artery to-artery embolism.(Kaiafa et al., 2016), in order to supply sufficient oxygen to cerebral tissue,

hemoglobin (Hb) and hematocrit (Htc) levels should be kept within normal ranges (Anemia safety) (Akpinar et al., 2017).

In our study population we found that the oral health (brush of teeth daily) is protective factor from stroke , the two most common diseases affecting oral health are dental caries and periodontitis (Dietrich et al., 2017;Choe et al., 2009) found a positive association between periodontal disease and increased risk of ischemic stroke compared with persons with no periodontitis, gingivitis, or tooth loss .

Oral health status including periodontal disease and tooth loss may have an adverse impact on systemic health(Shiga et al., 2019).Periodontal microorganisms have been found in atheroma's . The endotoxin in the microorganisms may damage endothelial cells and induce smooth muscle proliferation (Yoshida et al., 2011). Periodontal disease could increase the production of inflammatory markers and clotting factors, such as C-reactive protein and fibrinogen, and increase platelet aggregation , thus contributing to atherosclerosis and thrombosis (Choe et al., 2009).

A postulated pathway for the association between tooth loss and stroke involves adverse effects of tooth loss on nutrition that, in turn, impacts vascular health. Its leads to a deterioration in chewing ability and the avoidance of certain food groups, such as vegetables and fruits. Which are rich of anti-oxidant vitamins. This vitamins are thought to be responsible for vascular protective effects through the suppression of inflammation which play a significant role in stroke pathology (Iwasaki et al., 2016).

III.3.Biological marker study

Our study showed that the WBC and NEUT are significantly increased in the stroke patients as compared to control both in men and women . Our result are in agreement with the result of (Laridan et al., 2017) that found a neutrophil levels in stroke thrombi are considerably high , because it is the first cell to be recruited after stroke to the injured area and contributes the increased expression of adhesion molecules , cytokines / chemokine, proteases and reactive oxygen species (Liu et al., 2019). This molecules contribute to post ischemic inflammation and endothelium damage and tissue necrosis. (Anrather, 2017;Chen et al., 2016). The increased WBC count during acute stroke may be due to the mobilization of the leukocyte marginal pool as an inflammatory response to the ischemic damage to brain parenchyma (Kazmierski et al., 2004).

Moreover our results illustrated that a significant decrease of RBC and HGB in men and women with stroke when compared with healthy individuals . which agreement with study of (Santos-Silva et al., 2002). During ischemic stroke, erythrocytes undergo oxidative and proteolytic changes which related from the central mechanisms of erythropoiesis regulation.(Pretorius & Lipinski, 2013 ; Ivan et al., 2018). Inflammation can reduce the survival rate of red blood cells (Feng et al., 2017) by WBC activation post-stroke which also led to induce the hemoglobin oxidation and lipid peroxidation, which could, therefore, ultimately lead to hemolysis so decrease erythrocytes count and hemoglobin level. (Bateman et al., 2017).

Concerning the Platelet line , results also show that the level of platelet is significantly increased in stroke women than the women control . The results found were opposite to those observed in study of (Jin et al., 2019) who demonstrated that platelet count (PLT) decreases in the circulatory system of stroke patients.

In our study , women with stroke had significantly high serum LDL-Cholesterol and significantly low HDL-Cholesterol compared to controls . this results are in agreement with a study of (Markaki et al., 2014), who showed that the LDL-C level was significantly higher in survivors of stroke , in other hand (Kim et al., 2012), demonstrated that the patients after stroke had significantly reduced HDL cholesterol level compared to controls . The mechanism which induced to the differences of LDL-C and HDL-C levels in serum women after stroke are unknown yet , but it has been suggested that ischemic attack might lead to the over production of catecholamine secretion which might influence of lipoproteins particles (including LDL and HDL) , also it not ignored the rol of menopause and dysfunction of ovaries which influence of lipid metabolism (Žitňanová et al., 2018).

Our study showed that albumin is significantly decreased in women with stroke as control women . this finding of our study are in agreement with a study by (Behrouz et al., 2016) , which demonstrated that hypo-albuminemia was common in stroke patients , and can occur in up to 45.5% of AIS patients (Wang et al., 2019) . In term of gender (Michaela et al .,2015),explained a strongly association between decreased albumin and depression after stroke , this finding higher observed in women (Pascoe et al., 2015). A potential mechanism of hypo-albuminemia during acute inflammatory states, including acute stroke, involves negative regulation of albumin synthesis by interleukin (IL)-6 and tumor necrosis factor-alpha which have been found to be elevated during acute stroke (Famakin et al., 2010). In other

cases post-stroke decreasing albumin could be a result of malnutrition and/or underlying disease processes e.g. renal or hepatic insufficiency (Butt et al., 2016).

The obtained results show a significant increase in blood glucose level in patient group for men compared to control . This result is in agreement with finding of (Xue et al., 2017). Hyperglycemia is found to be prevalent in acute ischemic stroke (AIS) patients, accounting for 60% of patients at admission . Hyperglycemia in acute stroke is probably the result of multiple factors , including cytokine-induced resistance to insulin action (Garg et al., 2005), and stress which it stimulates the hypothalamus– pituitary–adrenal axis and the sympathetic nervous system leading to release of stress hormones, including cortisol and catecholamine's, which increase glucose levels (Tziomalos et al., 2017). Our study revealed that a decreased total protein in men with stroke compared to healthy men . this result supported the following finding , post stroke hyperglycemia may induce to chronic diabetes which characterized by excess of spices oxygen reactive production , this ROS increasing can caused bio molecular damage including proteins (Sacan et al., 2016 ; Pascoe et al., 2015).

In our experimental study , the result show a significant decrease in Alkaline phosphatase ALP activity in both men and women patients as controls . the result found were opposite to those observed in (Liu et al., 2018) who showed that Alkaline phosphatase ALP activity significantly increased in patients with stroke compared with healthy control.This increasing to be related to inflammation and oxidative stress after stroke (Tan et al., 2017).

Electrolytes are essential for normal cellular function. Electrolytes imbalance is a common phenomenon after stroke (Mohammad et al., 2016).In our study , stroke patients had significantly low serum sodium and chlorine levels compared to control men , on other hand low serum potassium levels in both groups women and men patients than control groups . our result is in correspond with study of (Manaswini et al, 2019) , also (Rejeh et al., 2017) have documented hypothermia 70 % and hypokalemia 41%.

Disorders of sodium and potassium concentration are the commonest electrolyte abnormalities found in cerebral vascular accident (CVA) (Meenakshi et al., 2017). Low sodium after stroke resulting from either the syndrome of inappropriate antidiuretic hormone secretion, inappropriate fluid intake and loss, or high level of brain natriuretic peptides (BNP) (Aqeel & Zahra., 2018) in addition changes in sodium levels can affect a patient’s potassium levels (Inga & Patrick, 2016). concerning a chlorine level our result were opposite to those

observed in (Hajatolla et al., 2016) who showed that no significant differences was observed in the serum chlorine levels between control and patients groups .

III.4.Study of oxidative stress markers

Malondialdehyde (MDA) is currently considered to the most widely used representative of oxidative lipid damage (Liu et al., 2018). In our experimental study , our data show that MDA level is significantly increased in both women and men with stroke compared to controls . This result are in agreement with study of (Antonio et al., 2005), who explained that the MDA showed higher levels in stroke patients than in controls at hospital admission and its levels did not change in the following 7 days.

Stroke is accompanied by increased formation of free radicals (Liu et al., 2017). The brain is particularly sensitive to the oxidative injury because of the high content of polyunsaturated fatty acids (Menon et al., 2020). The increased of MDA level because lipid peroxidation products are a key mediator of apoptosis induced by oxidative stress (Purnima & Sushree, 2009).

In our experimental study , the result show that a significant decrease in glutathione (GSH) and in Total thiol levels (t SH) both in women and men patients as compared with controls . This result are harmony with the finding of (Zimmermann et al., 2004). Who stated that nearly two thirds of patients with stroke showed decreased GSH levels. Glutathione (GSH) is a sulfhydryl (SH) containing tripeptide (Glu-Cys-Gly). It Plays the role of antioxidants and detoxifier (Ozkul et al., 2007 ; An et al., 2009). Ischemic stroke causes brain damage and alterations in GSH redox status (Song et al., 2015) ; firstly by post stroke hypoxic episode which reduced the cysteine uptake and a concomitant decrease in GSH (Pravalika et al., 2018). Secondly in consequence of post stroke inflammation , tissue glutathione (GSH) is rapidly consumed and depleted . As GSH is required for the synthesis of LTC4 from LTA4(leukotriene's type ; pro inflammatory lipids mediators) (Chan et al., 2019).

Concerning t SH , our result are in agreement with the study of (Işık et al.,2017). who showed that a significant decrease in serum total thiol levels in ischemic patients compared to control groups. The subsequent decrease in SH group level in the plasma was previously demonstrated both in an experimental model of cerebral ischemia ,and in clinical studies of acute stroke . Because more than 90% of SH groups in plasma are cysteine containing protein residues such as ; albumins and proteins thiols including GSH (Maksimova et al., 2019 ;

Bektas et al., 2016). So the reduction of GSH level contribute in the reduction of total thiol level.

One of major defenses against RS production is a family of oxido-reductases known as superoxide dismutase (SOD) (Pascotini et al., 2018). Our experimental study demonstrated that a significant increase in SOD activity in patient with stroke (men and women) as compared to controls . The results found were agreement with study realized by (Abdullah et al., 2013) who was observed that during the acute phase, the MDA and SOD levels were increased in the serum of the patients with ischemic stroke .

The antioxidant activity of plasma and erythrocytes may be an important factor providing protection against neurological damage caused by stroke-associated oxidative stress (Milanlioglu et al., 2015). On the other hand, the significance of antioxidant enzyme changes upon conditions of oxidative stress in stroke is strongly under debate, since antioxidant enzymes like SOD and glutathione peroxidase (GPx) might be induced by oxidative stress (and therefore their activity/levels may increase) (Cherubini et al., 2005).

Oxygen radical absorbance capacity (ORAC) method is used to measure antioxidant capacity versus oxygen free radicals (Wesołowski et al., 2016). In our experimental study , Our data revealed that the total antioxidant activity (ORAC) was increased in serum of stroke patient than in controls men and women. studies of (Lorente et al., 2016 ; Guldiken et al., 2009), reported similar results to ours regarding higher levels of total antioxidant capacity in their ischemic stroke patients . The total antioxidant capacity up regulation in patients with AIS might be a compensatory mechanism for higher ROS production in response to ischemia (Lorente et al., 2016 ; Guldiken et al., 2009).

Conclusion & Prospects

Conclusion

Stroke is an important cause of mortality and morbidity in the world. Many international study explained the importance of development in the diagnosis tools for aid in the management of stroke . Many risk factors have been studied to exactly determinate which one is the already responsible involved in cerebrovascular accident .

The results of our study showed that the accident cerebral vascular disease is distributed in the different region of Touggourt with more frequent in women 53% than men . Were the most age group to touch are more than 50 years . We observed that the ischemic stroke is the most common type of stroke with frequency 60% , were the majority cases stay in hospital less to 5 days or between 5 and 10 with frequency 40% .

The results of our study show that that hyper cholesterol, eating of the red meat, diabetes, atrial fibrillation, hypertension, Excess in treatment with anticoagulants and exposed to high levels of family stress are shown to be majors risk factors for stroke , which indicates the importance of social behavior and the clinical factor in causing cerebrovascular accident . In contrast , brush of teeth daily and Anemia safety are protective factors against stroke in Touggourt population.

Through the results of this study, we conclude that this disease leads to a major defect in biochemical parameters such as lipid profile, blood glucose or electrolytes levels and in hematological parameters associated with anemia or inflammation with a great similarity between women and men in most of these parameters, which confirms the importance of these parameters in diagnostic or in Follow-up of stroke disease.

The increase in lipid peroxidation, ORAC levels and SOD activity and low level of GSH and total thiol in different samples, serum erythrocytes and leukocytes, confirms the presence of oxidative stress associated with the stroke disease as a cause or as a development factor for it. Especially what we found a strong relationship between some of these markers with some biochemical and hematological parameters, noting that there is some variation in the results between women and men and also noting the importance of the diversity of samples from serum or White or red blood cells in detecting or determination the causes of the disease. which is exactly what we concluded through the ROC analysis results that MDA, SOD and ORAC are considered to be the most important markers with high sensitivity and important AUC percentage which contributes to their in early detection of the stroke diseases .

High levels of family Stress, hyper cholesterol, Red meat and Diabetes are strongly associated with oxidative stress markers. This confirms that oxidative stress is the pathophysiological mechanism explanation that causes stroke disease through various socio-clinical risk factors.

Prospects:

Given the importance of these results, they open experimental perspectives and other in-depth studies that should allow us to clearly identify to:

- Determine other factors associated with stroke risk .
- Comparative study of risk factors between Touggourt and other region .
- Evaluation of other diagnostic markers of stroke in man and women .
- Determine the genetic polymorphism of stroke disease in Touggourt .
- Evaluation of the effect of antioxidant supplementation as treatment of stroke disease .

Bibliographical references

Bibliographical references

1. **Abdullah A, Ssefer V, Ertugrul U, Osman E, Esref A, Ugur ÇM, Adalet A, Yavuz Y, Faysal E, Nebahat T. (2013).** Evaluation of serum oxidant /antioxidant balance in patients with acute stroke . *J Pak Med Assoc*, 63(5) : 590-592 .

2. **Abdullah S, Serefnur O, Hakan E, Aslıhan S, Sedat A, Ali U. (2018).** Elevated Urinary Methyl malonic Acid/creatinine ratio and Serum Sterol levels in Patients with Acute Ischemic Stroke. *Revista Română de Medicină de Laborator*, 26(1) : 52-57.

3. **Ackerley SJ, Byblow WD, Barber PA, MacDonald H, McIntyre RA, Stinear CM. (2016).**Primed Physical Therapy Enhances Recovery of Upper Limb Function in Chronic Stroke Patients . *journal of Neurorehabilitation andNeural Repair*, (4) : 339–348.

4. **Ahmad S, Elsherbiny NM, Haque R, Khan MB, Ishrat T, Shah ZA, Khan MM, Ali M, Jamal A, Katare DP, Liou GI, Bhatia K. (2014).** Sesamin attenuates neurotoxicity in mouse model of ischemic brain stroke . *Neurotoxicology*, 45 : 100-110 .

5. **Akpinar CK, Gurkas E, Aytac E. (2017).** Moderate to severe anemia is associated with poor functional outcome in acute stroke patients treated with mechanical thrombectomy. *Interventional Neurology*, 7(1-2): 12–18 .

6. **Alloubani A, Saleh A, Abdelhafiz I. (2018).** Hypertension and diabetes mellitus as a predictive risk factors for stroke. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, 12(4) : 577–584 .

7. **Al-Senani F, Al-Johani M, Salawati M, Alhazzani A, Morgenstern LB, Seguel Ravest V, Cuche M, Eggington S. (2019).** An Epidemiological Model for First Stroke in Saudi Arabia. *Journal of Stroke and Cerebrovascular Diseases*, 29 (1): 104465.

8. **Amytis T, Jeffrey L, Rita E, Bruce O. (2007).** A midlife stroke surge among women in the United States. *Neurology*, 69(1898): 1894-1903.

9. **An L, Zhang Y, Thomasson DM, Latour LL, Baker EH, Shen J, Warach S. (2009).** Measurement of glutathione in normal volunteers and stroke patients at 3T using J-difference spectroscopy with minimized subtraction errors. *Journal of Magnetic Resonance Imaging*, 30(2) : 263–270.

10. **An SJ, Kim TJ, Yoon BW. (2017).** Epidemiology, Risk Factors, and Clinical Features of Intracerebral Hemorrhage: An Update. *Journal of Stroke*, 19(1): 3–10.

11. **Anrather J. (2017).** Pathophysiology of the Peripheral Immune response in acute ischemic stroke. *Primer on Cerebrovascular Diseases* , 139–145 .

12. **Antonio Ch, Ruggiero C, Polidori MC, Mecocci P. (2005).** Potential markers of oxidative stress in stroke. *Journal of Free Radical Biology and Medicine*, 39(7) : 841–852.

13. **Antonio M, Michele, Giovanni T, Gabriele D, Sergio C, Marco C, Angela L, Marco P. (2002).** Impact of Aortic Manipulation on Incidence of Cerebrovascular Accidents After Surgical Myocardial Revascularization . *The Society of Thoracic Surgeons*, 4975(02) : 1388-1392.

14. **Aqeel RH, Zahra AA. (2018).** Electrolyte disturbance in hemorrhagic and non-hemorrhagic stroke patients in AL-DIWANIYAH teaching hospital . *Asian J Pharm Clin Res*, 11(11) : 456-459.

15. **Arboix A. (2015).**Cardiovascular risk factors for acute stroke: Risk profles in the different subtypes of ischemic stroke . *world Journal of Clinical Cases*, 3(5) : 418-429.

16. **Aswathy SU, Devadhas G, Kumar SS. (2017).** MRI brain tumor segmentation using genetic algorithm with SVM classifier . IOSR Journal of Electronics and Communication Engineering . *ASPIRE*, 2017 : 22 – 26.

17. **Asy MH, Awd M, Elshabrawy AM, Gharieb M. (2019).** Effect of Ramadan fasting on incidence of Cerebrovascular stroke in Egyptian patients with Type 2 Diabetes Mellitus. *Diabetes Research and Clinical Practice*, 151: 299-304.

18. **Audebert HJ, Fiebach JB. (2015).** Brain Imaging in Acute Ischemic Stroke—MRI or CT? *Current Neurology and Neuroscience Reports*, 15(3) :1-6.

19. **Bateman R, Sharpe M, Singer M, Ellis C. (2017).** The Effect of Sepsis on the Erythrocyte. *International Journal of Molecular Sciences*, 18(9): 1-23 .

20. **Beaucoup C, Fridovich I. (1971).** Superoxide dismutase : Improved assays and an assay applicatuion to acrylamide gels .*Analytical Biochemistry*, 44(1) : 276-287.

21. **Behrouz R, Godoy DA, Topel CH, Birnbaum LA, Caron JL, Grandhi R, Johnson JN, Misra V, Seifi A, Urbansky K, Di Napoli M. (2016).** Early hypoalbuminemia is an independent predictor of Mortality in aneurysmal subarachnoid hemorrhage. *Neurocritical Care*, 25(2) : 230–236.

22. **Bektas H, Vural G, Gumusyayla S, Deniz O, Alisik M, Erel O. (2016).** Dynamic thiol–disulfide homeostasis in acute ischemic stroke patients. *Journal of Acta Neurologica Belgica*, 116(4) : 489–494.

23. **Betteridge DJ. (2000).** What Is Oxidative Stress? *Metabolism*, 49(2) : 3-8 .

24. **Bhattacharya S. (2014).** Reactive Oxygen Species and Cellular Defense System. *Free Radicals in Human Health and Disease*, 18 :17–29.

25. **Birben E, Sahiner UM, Sackesen C, Erzurum S, Kalayci O. (2013).**Oxidative stress and antioxidant defense. *World Allergy Organ J*, 5(1) : 9–19 .

26. **Boehme AK, Esenwa C, Elkind MSV. (2017).** Stroke Risk Factors, Genetics, and Prevention. *Circulation Research*, 120(3) : 472–495.

27. **Bonaca MP, Scirica BM, Braunwald E, Wiviott SD, Goto S, Nilsen DW, Bonarjee V, Murphy SA, Morrow DA. (2014) .** New Ischemic Stroke and Outcomes With Vorapaxar Versus Placebo . *Journal of The American College of Cardiology*, 64(22) : 2319-2326 .

28. **Booth J, Connelly L, Lawrence M, Chalmers C, Joice S, Becker C,Dougall N. (2015).** Evidence of perceived psychosocial stress as a risk factor for stroke in adults: a meta-analysis. *Journal of BMC Neurology*, 15(1) : 1-12 .

29. **Budinčević H, Črnac Žuna P, Saleh C, Lange N, Piechowski JB, Bielen I, Demarin V. (2020).** Antithrombotic therapy in patients with non-traumatic intracerebral haemorrhage and atrial fibrillation: A retrospective study , *Journal of Heliyon*, 6(1) : 2-5 .

30. **Butt A, Rashid AM, Zameer H. (2016).** Frequency of hypoalbuminemia and mortality in acute ischemic stroke .*Original Article*, 10 (01) : 224-225.

31. **Chan SJ, Ng MPE, Zhao H, Ng GJL, De Foo C, Wong PTH, Seet RCS. (2019).** Early and Sustained Increases in Leukotriene B4 Levels Are Associated with Poor Clinical Outcome in Ischemic Stroke Patients. *Journal Neurotherapeutics*, 17: 282–293 .

32. **Chandra A, Ali W, Stone CR, Geng X, Ding Y. (2017).** The cerebral circulation and cerebrovascular disease I: Anatomy . *Brain Circulation*, 3(2) : 45–56.

33. **Chehaibi K, Trabelsi I, Mahdouani K, Slimane MN. (2016).** Correlation of Oxidative Stress Parameters and Inflammatory Markers in Ischemic Stroke Patients. *Journal of Stroke and Cerebrovascular Diseases*, 25(11) : 2585–2593.

34. **Chen H, He Y, Chen S, Qim S, Shen J. (2020).** Therapeutic Targets of Oxidative/Nitrosative Stress and Neuroinflammation in Ischemic Stroke: Applications for Natural Product Efficacy with Omics and Systemic Biology . *Pharmacological research*, 158 :104877.

35. **Chen Z, Huang Y, Li S, Lin J, Liu W, Ding Z, Li X, Chen Y, Pang W, Yang D, Su Z, Li J, Weng Y, Zhang X. (2016).** Platelet-to-white blood cell ratio: a prognostic predictor for 90-day outcomes in ischemic stroke patients with intravenous thrombolysis. *Journal of Stroke and Cerebrovascular Diseases*, 25(10) : 2430–2438.

36. **Cheng YC, Sheen JM, Hu WL, Hung YC. (2017).** Polyphenols and Oxidative Stress in Atherosclerosis-Related Ischemic Heart Disease and Stroke. *Oxidative Medicine and Cellular Longevity*, 2017: 1–16.

37. **Chengwei L, Jonggyu B, Brisa N, Lewis B, Lynda D. (2018).** Temporal trends in age at ischemic stroke onset by ethnicity. *Annals of Epidemiology*, 28(10) : 686–690.

38. **Choe H, Kim YH, Park JW, Kim SY, Lee SY, Jee SH. (2009).** Tooth loss, hypertension and risk for stroke in a Korean population. *Journal of Atherosclerosis*, 203(2) : 550–556.

39. **Choi KA, Choi Y, Hong S. (2018).** Stem cell transplantation for Huntington's diseases. *Methods* , 133 : 104–112.

40. **Choudhury JH, Chowdhury TI, Nayeem A, Jahan WA. (2015).** Modifiable and Non-Modifiable Risk Factors of Stroke: A Review Update . *Journal of National Institute of Neurosciences Bangladesh*, 1(1) : 22-23.

41. **Corey S, Bonsack B, Heyck M, Shear A, Sadanandan N, Zhang H, Borlongan C V. (2020).** Harnessing the anti-inflammatory properties of stem cells for transplant therapy in hemorrhagic stroke. *Brain Hemorrhages*, 1(1) : 24-33 .

42. **Daniela M, Larissa T, Marcus V, Aline G, Luana C, Christina D, Paula L. (2019).** Aerobic Training Efficacy in Inflammation, Neurotrophins, and Function in Chronic Stroke persons: A Randomized Controlled Trial Protocol. *Journal of Stroke and Cerebrovascular Diseases*, 28(2):418-424.

43. **Demaagd G, Pharm D, Philip A. (2015).**Parkinson's disease and its management. *P&T*, 40(8) :504-532.

44. **Derouiche S, Atoussi N, Guediri S. (2018).** The Study of Socioeconomic and Clinic Risk Factors of Breast Cancer in Algerian Women Population. *Frontiers in Biomedical Technologies*, 5(3-4) : 51-57.

45. **Derouiche S, Doudi D, Atia N. (2018).** Study of Oxidative Stress during Pregnancy. *Glob J Pharmaceu Sci*, 4(5): GJPPS.MS.ID.555646.

46. **Devgun JK, Gul S, Mohananey D, Jones BM, Hussain MS, Jobanputra Y, Kumar A, Tuzcu EM, Svensson LG, Kapadia SR. (2018).** Cerebrovascular Events After Cardiovascular Procedures. *Journal of the American College of Cardiology*, 71(17) : 1910–1920.

47. **Dietrich T, Webb I, Stenhouse L, Pattni A, Ready D, Wanyonyi KL, White S,Gallagher JE. (2017).** Evidence summary: the relationship between oral and cardiovascular disease. *British Dental Journal*, 222(5) : 381–385.

48. **Djouadi A, Derouiche S. (2017).** Study of fluoride-induced haematological alterations and liver oxidative stress in rats. *World J. Pharm. Pharm, Sci*. 6(5) : 211-221.

49. **El Assar M, Angulo J, Rodríguez-Mañas L. (2019).** Frailty as a phenotypic manifestation of underlying oxidative stress. *Free Radical Biology and Medicine*, 149 :72-77.

50. **El khatib T, Elsaid A, Al-Molla R, Khamis M, Fahmi R. (2020).** Prevalence and associated risk factors of cerebral microbleeds in Egyptian patients with acute ischemic stroke and atrial fibrillation. *Journal of Stroke and Cerebrovascular Diseases*, 104703.

51. **Elman GL. (1959).** Tissues sulfhydryl group. *Qrch Biochem Biophys*, 82 :70-77.

52. **Famakin B, Weiss P, Hertzberg V, Clellan W, Presley R, Krompf K, Karp H, Frankel MR. (2010).** Hypoalbuminemia predicts acute stroke mortality: paul coverdell georgia stroke registry. *Journal of Stroke and Cerebrovascular Diseases*, 19(1) :17–22.

53. **Fantini S, Sassaroli A, Tgavalekos KT, Kornbluth J. (2016).** Cerebral blood flow and autoregulation: current measurement techniques and prospects for noninvasive optical methods. *Neurophotonics*, 3(3) : 031411.

54. **Farooq MU, Gorelick PB. (2017).** Stroke Risk Factors. *Reference Module in Neuroscience and Biobehavioral Psychology*, doi:10.1016/b978-0-12-809324-5.03844-x

55. **Fatahzadeh M, Glick M. (2006).** Stroke: epidemiology, classification, risk factors, complications, diagnosis, prevention, and medical and dental management. *Journal of Oral Medicine*, 102(2) : 180-190 .

56. **Fei X, Hongbin L, Yanhui L. (2020).** Adult neurogenesis following ischaemic stroke and implications for cell-based therapeutic approaches . *World Neurosurgery*, 138 : 474-480.

57. **Feigin VL, Roth GA, Naghavi M, Parmar P, Krishnamurthi R, Chugh S, Mensah GA, Norrving B, Shiue IY, Marie N, Estep K, Cercy K, Murray CJL, Forouzanfa MH. (2016).** Global burden of stroke and risk factors in 188 countries,during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet Neurology*, 15(9) : 913-924.

58. **Feng GH, Li HP, Li QL, Fu Y, Huang RB. (2017).** Red blood cell distribution width and ischaemic stroke. *Stroke and Vascular Neurology*, 2(3) :172–175.

59. **French BR, Boddepalli RS, Govindarajan R. (2016).** Acute Ischemic Stroke:Current Status and Future Directons . *journal of PMC*, 113(6) : 480–486.

60. **Garg R, Chaudhuri A, Munschauer F, Dandona P. (2005).** Hyperglycemia, insulin, and acute ischemic stroke: a mechanistic justification for a trial of insulin infusion therapy. *journal of Stroke*, 37(1) : 267–273.

61. **Ghodaro OM, Akinloye OA. (2017).** First line defence antioxidants-superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX): Their fundamental role in the entire antioxidant defence grid. *Alexandria Journal of Medicine*, 54(4) : 1-7.

62. **Ghosh D, Samanta S, Chakraborty S. (2019).** Multifractal Study of Parkinson's and Huntington's Diseases with Human Gait Data. *Multifractals and Chronic Diseases of the Central Nervous System*, 117–147 .

63. **Ghuman H, Massensini AR, Donnelly J, Kim SM, Medberry C, Badylak SF, Modo M. (2016).** ECM hydrogel for the treatment of stroke: Characterization of the host cell infiltrate . *Journal of Biomaterials*, 91 : 166-181.

64. **Grysiewicz RA, Thomas K, Pandey DK. (2008).** Epidemiology of Ischemic and Hemorrhagic Stroke: Incidence, Prevalence, Mortality, and Risk Factors. *Neurologic Clinics*, 26(4) : 871–895.

65. **Guldiken B, Demir M, Guldiken S, Guldiken S, Turgut N, Turgut B, Tugrul A. (2009)**. Oxidative stress and total antioxidant capacity in diabetic and nondiabetic acute ischemic stroke patients. *Journal of Clinical and Applied Thrombosis/Hemostasis*, 15(6): 695-700.

66. **Gupta A, Sattur MG, Aoun RJN, Krishna C, Bolton PB, Chong BW, Demaerschalk BM, Lyons MK, McClendon J, Patel N, Sen A, Swanson K, Zimmerman RS, Bendok BR. (2017).** Hemicraniectomy for Ischemic and Hemorrhagic Stroke. *Neurosurgery Clinics of North America*, 28(3) : 349 -360.

67. **Hajatollah M, Durdi Q, Alijan A, Karimollah H, Hadi P. (2016).** Evaluating the serum levels of Calcium , chloride , potassium and sodium in the stroke patient . *International Journal of Medical Laboratory*, 3 (2) : 104-110 .

68. **Haley MJ, Lawrence CB. (2016).** Obesity and stroke: Can we translate from rodents to patients? *Journal of Cerebral Blood Flow & Metabolism*, 36(12) : 2007 -2021.

69. **Halliday MR, Rege SV, Ma Q, Zhao Z, Miller CA, Winkler EA, Zlokovic BV. (2015).** Accelerated pericyte degeneration and blood–brain barrier breakdown in apolipoprotein E4 carriers with Alzheimer's disease. *Journal of Cerebral Blood Flow & Metabolism*, 36(1) :216 -227.

70. **Hilda A, Louise D. (2019).**The impact of sex and age on T cell immunity and ischemic stroke outcomes. *Cellular Immunology*, 8749(19) : 01-18.

71. **Hongxia Z, Siyang L, Xudong Ch, Lei G, Xiaohong Z, Yinuo Z, Kassandra R, Brain W, Kunlin J. (2018).**The effect of age, sex and strains on the performance and outcome in animal models of stroke. *Neurochemistry International*, 168 (18) :03.

72. **Hui-Chen L, Wan-Chen T, Jr-Rung L, Wen-Neng Ch, Chih-Cheng H, Hung-Chen W, Chia-Te K, Chih-Min S, Yu-Jih S, Wei-Che L, Ben-Chung Ch, Cheng-Hsien L, Nai-Wen T. (2019).** Adjunctive statin therapy reduces intracranial hemorrhage and 1-

yearmortality in patients with atrial fibrillation after acute ischemic stroke: Apopulation-based epidemiological study from Taiwan . *Journal of Clinical Neuroscience*, 69 : 224-229 .

73. **Inga Ch, Patrick M. (2016).** Serum potassium and sodium levels after subarachnoid haemorrhage . *British Journal Of Neurosurgery*, 30 (5) : 554 -559 .

74. **Ingrid Ž, Pavol Š, Branislav K. (2016).** Oxidative Stress Markers and Their Dynamic Changes in Patients after Acute Ischemic Stroke,". *Oxidative Medicine and Cellular Longevity*, Article ID 9761697, 2016(7).

75. **Işık M, Beydemir Ş, Yılmaz A, Naldan ME, Aslan HE, Gülçin İ. (2017).** Oxidative stress and mRNA expression of acetylcholinesterase in the leukocytes of ischemic patients. *Journal of Biomedicine & Pharmacotherapy*, 87 : 561 - 567.

76. **Ivan R, Ruslan T, Aleksandr G, Iliya Z, Yana S, Yuliya Z,Ernest V, Galina Reva. (2018).** The role of erythrocyte in cerebral ischemia . *Morphology , Physiology , Pathology*, 8 (1) : 47 – 48 .

77. **Iwasaki M, Sato M, Yoshihara A, Ansai T, Miyazaki H. (2016).** Association between tooth loss and medical costs related to stroke in healthy older adults aged over 75 years in Japan. *Geriatrics & Gerontology International*, 17(2) : 202–210 .

78. **Jackman K, Iadecola C. (2015).** Neurovascular Regulation in the Ischemic Brain. *Antioxidants & Redox Signaling*, 22(2) : 149 -160.

79. **Jackova J, Sedova P, Brown RD, Zvolsky M, Volna M, Baluchova J, Belaskova S, Bednarik J, Mikulik R. (2019).** Risk Factors in Ischemic Stroke Subtypes: A Community-Based Study in Brno, Czech Republic. *Journal of Stroke and Cerebrovascular Diseases*, 29(2) : 104503 .

80. **Jacobs MS, Van HM, Adeoye AM, Tieleman RG, Postma MJ, Owolabi MO. (2019).** Atrial fibrillation in Africa An underreported and unrecognized risk factor for stroke. *Journal of Global Heart*, 14 (3) : 269-279.

81. **Jagota SK, Dani HMA. (1982).** New colorimetric technique for the estimation of vitamin C using Folin phenol reagent. *Anal Biochem*, 127(1) :178-82.

82. **Jensen MB, StLouis EK. (2005).** Management of acute cerebellar stroke . *Neurological Revirw*, 62(4) : 537-544.

83. **Jiang Y, Lu H, Man Q, Liu Z, Wang L, Wang Y, Suo C, Zhang T, Jin L, Dong Q, Cui M, Chen X. (2020).** Stroke burden and mortality attributable to ambient fine particulate matter pollution in 195 countries and territories and trend analysis from 1990 to 2017. *Journal of Environmental Research*, 184 : 109327.

84. **Jin P, Li X, Chen J, Zhang Z, Hu W, Chen L, Xiao WF, Shao B. (2019).** Platelet-to-neutrophil ratio is a prognostic marker for 90-days outcome in acute ischemic stroke. *Journal of Clinical Neuroscience*, 63 : 110–115 .

85. **Jin GZ, Chakraborty A, Lee JH, Knowles JC, Kim HW. (2020).** Targeting with nanoparticles for the therapeutic treatment of brain diseases. *Journal of Tissue Engineering*, 11 : 204173141989746.

86. **John CD. (2003).** Strokes and their relationship to hypertension . *journal of Nephrology and Hypertension*, 12(1) : 91-96.

87. **John WC. (2011).**The relationship between smoking and stroke risk in women: breaking the habit . *journal of Women's Health*, **7**(3) : 261-264 .

88. **Johnson CO. (2019).** Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016 . *Stroke Collaborators*, 18: 439-58 .

89. **Jood K, Redfors P, Rosengren A, Blomstrand C, Jern C. (2009).** Self-perceived psychological stress and ischemic stroke: a case-control study. *Journal of BMC Medicine*, 7(1) : 1-8 .

90. **Jordan G, Leanne B, Sarah K, Lee M, Ervin L, Brice B, Thomas IN. (2018).** In a stroke cohort with incident hypertension; are more women than men likely to be excluded from recombinant tissue-type Plasminogen Activator (rtPA)? *Journal of the Neurological Sciences*, 387 : 139-146 .

91. **Judith H, Erica C, Sara B,Yun W, Larry B. (2016).** Average Temperature, Diurnal Temperature Variation, and Stroke Hospitalizations. *Journal of Stroke and Cerebrovascular Diseases*, 25 (6) : 1489-1494.

92. **Kaiafa G, Savopoulos C, Kanellos I, Mylonas KS, Tsikalakis G, Tegos T, Kakaletsis N, Hatzitolios AI. (2016).** Anemia and stroke: Where do we stand? *Acta Neurologica Scandinavica*, 135(6) : 596–602.

93. **Kaiafa G, Kanellos I, Savopoulos C, Kakaletsis N, Giannakoulas G. Hatzitolios AI. (2015).** Is anemia a new cardiovascular risk factor? . *Int J Cardiol*, 186, 117–124 .

94. **Kaisera EE, Watersa ES, Fagan MM, Scheulin KM, Platt SR, Jeone JH, Fange X, Kinder HA,Shina SK, Duberstein KJ, Parke H, West FD. (2020).** *journal of Brain Research* , 1736 (2020) : 146778 .

95. **Kamel H, Okin P, Elkind SV, Iadecola C. (2016).** Atrial fibrillation and mechanisms of stroke. *Journal of Stroke*, (115) : 012004.

96. **Kane JR. (2019).** The Role of Brain Vasculature in Glioblastoma. Molecular Neurobiology, 56 : 6645–6653 .

97. **Katan M, Luft A. (2018).** Global Burden of Stroke. *journal of Seminars in Neurology, 38(02)* : 208-211.

98. **Kazmierski R, Guzik P, Ambrosius W, Ciesielska A, Moskal J, Kozubski W. (2004).** Predictive value of white blood cell count on admission for in-hospital mortality in acute stroke patients. *Clinical Neurology and Neurosurgery*, 107(1) : 38-43 .

99. **Kehrer JP. (1993).** Free Radicals as Mediators of Tissue Injury and Disease. *Critical Reviews in Toxicology*, 23(1) : 21-48.

100. **Kim K, Hyeon J, Lee SA, Kwon SO, Lee H, Keum N, Lee JK, Park SM (2017).** Role of total, red, processed, and white meat consumption in stroke incidence and mortality: a systematic review and meta-analysis of prospective cohort studies. *Journal of the American Heart Association*, 6(9) : 1-16.

101. **Kim SJ, Park YG, Kim JH, Han YK, Cho HK, Bang OY. (2012).** Plasma fasting and non-fasting triglycerides and high-density lipoprotein cholesterol in atherosclerotic stroke: Different profiles according to low-density lipoprotein cholesterol. *Atherosclerosis*, 223(2) : 463 -467.

102. **Kokaia Z, Darsalia V. (2018).** Human Neural Stem Cells for Ischemic Stroke Treatment. *Human Neural Stem Cells* : 249-263.

103. **Krishnamurthy P, Wadhwani A. (2012).** Antioxidant Enzymes and Human Health, 412.

104. **Kruka J, Aboul-Eneinb HY, Kładnac A, Bowser JE. (2019).** Oxidative stress in biological systems and its relation with pathophysiological functions: the effect of physical activity on cellularredox homeostasis. *Free Radical Research*, 53(5) : 497-521.

105. **Laridan E, Denorme F, Desender L, François O, Andersson T, Deckmyn H, Vanhoorelbeke K, Simon F, De Meyer SF. (2017).** Neutrophil extracellular traps in ischemic stroke thrombi. *Annals of Neurology*, 82(2) : 223-232.

106. **Larosa J, Grundy S, Waters D. (2006) .** Statin therapy after stroke or transient ischemic attack. *New England Journal of Medicine*, 355(22), 2368-2371 .

107. **Lehmann S, Teunissen CE. (2016).**Biomarkers of Alzheimer's disease : the present and the future . *Front Neural*, 7:158.

108. **Lehrer HM , Steinhardt MA, Dubois SK, Laudenslager ML. (2019).** Perceived Stress, Psychological Resilience, Hair Cortisol Concentration, and Metabolic Syndrome Severity: A Moderated Mediation Model. *Journal of Psych neuroendocrinology, 104510.*

109. **Li H, Wu J, Shen H, Yao X, Liu C, Pianta S, Han J, Borlongan CV, Chen G. (2018).** Autophagy in hemorrhagic stroke: Mechanisms and clinical implications. *Progress in Neurobiology*, 163(164) : 79-97.

110. **Li P, Stetler RA, Leak RK, Shi Y, Li Y, Yu W, Bennett MVL, Chen J. (2018).** Oxidative stress and DNA damage after cerebral ischemia: Potential therapeutic targets to repair the genome and improve stroke recovery. Neuropharmacology, 134: 208-217.

111. **Li JK, Liu XD, Shen L, Zeng WM, Qiu GZ. (2016).** Natural plant polyphenols for alleviating oxidative damage in man: Current status and future perspectives . *Tropical Journal of Pharmaceutical Research*, 15 (5): 1089-1098.

112. **Liguori I, Russo G, Curcio F, Bulli G, Aran L, Della-Morte D, Gargiulo G, Testa G, Cacciatore F, Domenico Bonaduce D, Abete P. (2018).** Oxidative stress, aging, and diseases. *Clinical Interventions in Aging*, (13) :757-772.

113. **Lill CM . (2016).** Genetics of Parkinson's disease. *Molecular and Cellular Probes*, 30(6) : 386-396.

114. **Lin MP, Ovbiagele B, Markovic D, Towfighi A. (2016).** Association of secondhand smoke with stroke outcomes. journal of Stroke, 47(11) : 2828-2835.

115. **Lindauer U. (2017).** Physiology of Cerebral Blood Vessels. *Brain Edema*, 3-27.

116. **Liu H, Wang R, Shi J, Zhang Y, Huang Z, You S, Xiao G, Wang D, Cao Y. (2019).** Baseline Neutrophil Counts and Neutrophil Ratio May Predict a Poor Clinical Outcome in Minor Stroke Patients with intravenous Thrombolysis. *Journal of Stroke and Cerebrovascular Diseases*, 28 (11) : 1-7 .

117. **Liu Y, Liang X, Xu X, Dong M, Jia S, Lu C, Wei Y. (2018).** Increased Serum Alkaline Phosphatase in Patients with Acute Ischemic Stroke. *Journal of Stroke and Cerebrovascular Diseases*, 28 (1) : 21-25 .

118. **Liu Z, Cai Y, Zhang X, Zhu Z, He J. (2018).** High serum levels of malondialdehyde and antioxidant enzymes are associated with post-stroke anxiety. *Journal of Neurological Sciences*, 39(6), 999-1007.

119. **Liu Z, Zhu Z, Zhao J, Ren W, Cai Y, Wang Q, Luan X, Zhao K, He J. (2017).** Malondialdehyde: A novel predictive biomarker for post-stroke depression. *Journal of Affective Disorders*, 220(16) : 95-101.

120. **Lobo V, Patil A, Phatak A, Chandra N. (2010).**Free radicals, antioxidants and functional foods: impact on human health. *Pharmacogn Rev*, 4(8) :118-126.

121. **Logeswari T, Karnan M. (2010).** An improved implementation of brain tumor detection using segmentation based on hierarchical self-Organizing Map . *International Journal of Computer Theory and Engineering*, 2(4) : 1793-8201 .

122. **Lorente L, Martín MM, Pérez-Cejas A, Abreu-González P, Ramos L, Argueso M, Cáceres J,Solé-Violán J, Jiménez A. (2016).** Association between total antioxidant capacity and mortality in ischemic stroke patients . *journal of Annals Intensive Care*, 6(39) : 1-6.

123. **Lui SK, Nguyen MH. (2018).** Elderly Stroke Rehabilitation: Overcoming the Complications and Its Associated Challenges. *Current Gerontology and Geriatrics Research*, 2018: 1-9.

124. **Luo J, Mills K, Cessie S, Noordam R, Van Heemst D. (2019).** Ageing, Age-related Diseases and Oxidative Stress: What to Do Next? *Ageing Research Reviews*, 57: 100982.

125. **Magistrism F, Bazak S, Jason M. (2013).** Intracerebral Hemorrhage: Pathophysiology, *Diagnosis and Management. Clinical Review*, 10(1) :15-17.

126. **Mahmoud R, Jennifer L, Amanda G, Luciano A, Negar M, Amin A, Moira K, Nawaf Y, Cecilia B, Subhash K, Suvarna A, Yongchai N, Mariano C, Antonia N, Brian S, David W, Robert S, Richard H, Mayowa O, Bruce O, Vladimir H. (2019).** Age, sex, and setting in the etiology of stroke study (assess):Study design and protocol . *Journal of the Neurological Sciences*, 510 (19): 04-15.

127. **Maksimova MY, Ivanov AV, Virus ED, Alexandrinv VV, Nikiforova KA, Bulgakova PO, Ochtova FR, Suanova ET, Piradov MA, Kubatiev AA. (2019).** Disturbance of thiol/disulfide aminothiols homeostasis in patients with acute ischemic stroke stroke: Preliminary findings. *Clinical Neurology and Neurosurgery*, 183 :105393.

128. **Mana SP, Prati MKS, Man MKM, Alo KKM, Subha SD. (2019).** Altered serum electrolyte status in acute stroke patients in western Odisha , a predictor of syndrome of iInappropriate ADH (SIADH) or cerebral salt aasting syndrome (CSWS) . *Journal of Clinical and Diagnostic Research*, 13(1) : 10-13 .

129. **Mani P, Biruntha MB, Vidhyavathi RM, Sivagurunathan PD, Senthilkumar SR, Durairaj S. (2019) .** Dissecting the role of miR-21 in different types of stroke . *Gene* , 681 : 69-72 .

130. **Manwani B, Rath S, Lee NS, Staff I, Stretz C, Modak J, Finelli PF. (2018).** Early Magnetic Resonance Imaging Decreases Hospital Length of Stay in Patients with Ischemic Stroke. *Journal of Stroke and Cerebrovascular Diseases*, 28(2) : 425-429.

131. **Markaki I, Nilsson U, Kostulas K, Sjöstrand C. (2014).** High Cholesterol Levels Are Associated with Improved Long-term Survival after Acute Ischemic Stroke. *Journal of Stroke and Cerebrovascular Diseases*, 23(1) : 47–53.

132. **Marsh JD, Keyrouz SG. (2010).** Stroke Prevention and Treatment . *Journal of the American College of Cardiology*, 56(9) : 684-691.

133. **Martin B, Leon, Nicolo P, Eugenia N, Eugene H, Blackstone, Donald E,Cutlip, Arie Pieter K, Mitchell W, Krucoff, Michael M, Roxana M, Crai M, Marie-angéle M, John P, Jeffrey JP, Johanna JM, Takkenberg, Alec V,Gerrit-Anne van E, Pascal V, John G, Stephan W, Patrick WS. (2011).** Standardized Endpoint Definitions for Transcatheter Aortic Valve Implantation Clinical Trials . *Journal of the American College of Cardiology*, 57(3) : 253-269 .

134. **Martinez E, Martorell J, Riambau V. (2020).** Review of serum biomarkers in carotid atherosclerosis . *Journal of Vascular Surgery*, 71(1):329-341.

135. **Martins SCO, Sacks C, Hacke W, Brainin M, Figueiredo FA, Pontes-Neto OM, Lavados PM, Marinho MF, Ahoppe A, Mcghie DV, Cruz-Flores S, Ameriso SF, Villarea WMCl, Durán JC . al. (2019).** Priorities to reduce the burden of stroke in Latin American countries . *journal of the Lancet Neurology*, 18 (7) : 674-683 .

136. **Mccolgana P, Tabrizia SJ. (2017).** Huntington's disease: a clinical review . *European Journal of Neurology*, 25 : 24–34.

137. **Mckenna GM. (2019).** Management of the Patient with Malignant Hemispheric Stroke. *Critical Care Nursing Clinics of North America*, 32(1) : 51-66 .

138. **Meena K K, Waleed KN , Kanitkar SA , Abhijit M , Rajdeb S . (2017) .** Electrolyte imbalance in acute stroke . *journal of NJIRM* ,8 (4) : 23-26 .

139. **Menon B, Ramalingam K, Kumar R . (2020).** Evaluating the Role of Oxidative Stress in Acute Ischemic Stroke. *Journal of Neurosciences in Rural Practice*, 11(01) : 156-159 .

140. **Merel S, Esther M, Aneesh B, Kay S, Stephanie D, Anil M, Frank E. (2018) .**Epidemiology, etiology, and management of ischemic stroke in young adults. *Lancet Neurol*, (17) :790-799.

141. **Merino JG, Warach S. (2010).** Imaging of acute stroke. *Nature Reviews Neurology*, 6(10) : 560-571.

142. **Mevlut G, Nazire Belgin A, Ramazan K, Vefa O, Merve G, Muhammed Rasit O . (2020).** A new marker identification of high risk stroke patients: Jugular saturation . *American Journal of Emergency Medicine*, 38(1) :7-11 .

143. **Michael D. (2014).** Stroke and diabetes mellitus . *journal of Diabetes and the Nervous System*, 126(3) : 169-173 .

144. **Milanlioglu A, Aslan M, Ozkol H, Çilingir V, Nuri AM, Karadas S. (2015).** Serum antioxidant enzymes activities and oxidative stress levels in patients with acute ischemic stroke: influence on neurological status and outcome . *journal of Wiener Klinische Wochenschrift*, 128(5-6): 169-174.

145. **Miller S, Dykes D, Polesky H. (1988).**A simple salting out procedure for for extracting DNA from human nucleated cells. *Nucleic Acids Res*, 16(3):1215.

146. **Mirończuk-Chodakowska I, Witkowska AM, Zujko ME. (2018).** Endogenous non-enzymatic antioxidants in the human body. *Advances in Medical Sciences*, 63(1): 68-78.

147. **Mirzaei H, Momeni F, Saadatpour L, Sahebkar A, Goodarzi M, Masoudifar A, Kouhpayeh S, Salehi H, Mirzaei HR, Jaafari MR. (2017).** MicroRNA: Relevance to stroke diagnosis, prognosis, and therapy. *Journal of Cellular Physiology*, 233(2) : 856-865.

148. **Mistry EA, Mistry AM, Nakawah MO, Chitale RV, James RF, Volpi JJ, Fusco MR . (2017).** Mechanical Thrombectomy Outcomes With and Without Intravenous Thrombolysis in Stroke Patients. *Stroke*, 48(9): 2450-2456.

149. **Mohamad A, Paul AF. (2019).** Ischemic stroke risk in patients with non valvular atrial fibrillation . *JACC Review Topic of the Week*, 74(24) :3051 -3064 .

150. **Mohamed H, Mohamed A, Arafa M, Mahmoud G. (2019).** Effect of Ramadan fasting on incidence of cerebrovascular stroke in Egyptian patients with Type 2 Diabetes Mellitus . *Journal of Diabetes Research and Clinical Practice* ,151 : 299-304 .

151. **Mohammad ZH, Soroar H, Satya RS, Basak PM, Islam MN. (2016).** A study of electrolyte imbalance in stroke patients . *journal of TAJ*, 29(1) : 40-42 .

152. **Mohsen H, El-Dahshan EA, El-Horbaty EM, Salem ABM. (2017).** Annals of "Dunarea De JOS" University of Galati– Fascicle II ,1:75-88.

153. **Mohsen H, El-Dahshan ESA, El-Horbaty ESM, Salem ABM, (2018).** Classification using deep learning neural networks for brain tumors. *Future Computing and Informatics Journal*, 3(1) : 68–71.

154. **Monbailliu T, Goossens J, Hachimi-Idrissi S. (2017).** Blood protein biomarkers as diagnostic tool for ischemic stroke: a systematic review . *Journal of future Medicine*, 11(6) :503-509.

155. **Ning-Ning L, Zhi-Ling D, Li-Li H. (2018).** MicroRNA-410 inhibition of the TIMP2-dependent MAPK pathway confers neuroprotection against oxidative stress-induced apoptosis after ischemic stroke in mice . *Brain Research Bulletin*, 143 : 45-57 .

156. **Norrving B, Kissela B. (2013).** The global burden of stroke and need for a continuum of care .*Journal of Neurology*, 80(3):5–12.

157. **Oesch L, Tatlisumak T, Arnold M, Sarikaya H. (2017).**Obesity paradox in stroke – Myth or reality? Asystematic review . *A systematic review*, 12(3) :e0171334 .

158. **Oyaizu M. (1986).**Studies on products of browning reaction : antioxidant activities of products of browning reaction prepared from glucosamine . *Japanese Journal of Nutrition*, 44(6) :307-315.

159. **Ozkul A, Akyol A, Yenise C, Arpaci E, Kiylioglu N, Tataroglu C. (2007).** Oxidative stress in acute ischemic stroke. *Journal of Clinical Neuroscience*, 14(11): 1062-1066.

160. **Parisa P, Melissa Z. (2019).** Cerebrovascular accident in a pediatric patient presenting with influenza . *The Journal of Emergency Medicine*, 57(1) :17-19.

161. **Pascoe MC, Skoog I, Blomstrand C, Linden T. (2015).** Albumin and depression in elderly stroke survivors: An observational cohort study. *Psychiatry Research*, 230(2) : 658-663.

162. **Pascotini ET, Flores AE, Kegler A, Konzen V, Fornari AL, Arend J, Gabbi P, Gobo LA, Bochi GV, Cervi Prado AL, Machado CL, Duarte MMF, Cruz IBM, Moresco RN, Royes LFF, Fighera MR, Fighera MR. (2018).** Brain-derived neurotrophic factor levels are lower in chronic stroke patients: a relation with manganese-dependent superoxide dismutase ALA16VAL single nucleotide polymorphism through tumor necrosis factor-α and caspases pathways. *Journal of Stroke and Cerebrovascular Diseases*, 27 (11) : 3020-3029 .

163. **Patel RAG, McMullen PW. (2017).** Neuroprotection in the Treatment of Acute Ischemic Stroke. *Progress in Cardiovascular Diseases*, 59(6) :542-548.

164. **Paul DZ. (2013).** The temporal relationship between atrial fibrillation and ischemic stroke . *Journal of Atrial Fibrillation* , 5(5) : 72-81 .

165. **Phaniendra A, Babu Jestadi D, Periyasamy L. (2015).** Free Radicals: Properties, Sources, Targets, and Their Implication in Various Diseases . *Ind J Clin Biochem*, 30(1) :11-26.

166. **Poitras VJ, Pyke KE. (2013).** The impact of acute mental stress on vascular endothelial function: Evidence, mechanisms and importance. *International Journal of Psychophysiology*, 88(2): 124-135.

167. **Pradeep H, Diya JB, Shashikumar S, Rajanikant GK. (2012).** Oxidative stress – assassin behind the ischemic stroke. *Folia Neuropathol*, 50(3) : 219–30.

168. **Prakash AP, Saumil P, Jared W, Feinman, Jacob T, Prashanth V, Ronak S, Jay G, Nimesh D, Elizabeth Z, Stuart J, John G. (2018).** Stroke After Transcatheter Aortic Valve

Replacement: Incidence, Definitions, Etiologies and Management Options . *Journal of Cardiothoracic and Vascular Anesthesia*, 32(2) : 968-981 .

169. **Pravalika K, Sarmah D, Kaur H, Vats K, Saraf J, Wanve M, Kalia K, Borah A, Yavagal DR, Dave KR, Bhattacharya P. (2018).** Trigonelline therapy confers neuroprotection by reduced glutathione mediated myeloperoxidase expression in animal model of ischemic stroke. *Journal of Life Sciences*, 216 : 49-58 .

170. **Pretorius E, Lipinski B. (2013).** Thromboembolic ischemic stroke changes red blood cell morphology. *Cardiovascular Pathology*, 22(3) : 241–242.

171. **Purnima DS, Sushree SR. (2009).** A study of serum malondialdehyde levels and paraoxanase activity in ischemic stroke patients. *Journal of Biomedical Research*, 20 (1) : 64-66 .

172. **Qu Y, Zhao L, Guo H. (2019).** Role of Cerebral Venous System in Hemorrhagic Stroke. *Cerebral Venous System in Acute and Chronic Brain Injuries*, 173-178 .

173. **Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo H, Hanley DF. (2001).** Spontaneous Intracerebral Hemorrhage. *New England Journal of Medicine*, 344(19) : 1450-1460.

174. **Qureshi AI, Suri MF, Ostrow PT, Kim SH, Ali Z, Shatla AA, Guterman LR, Hopkins LN. (2003).** Apoptosis as a form of cell death in intracerebral hemorrhage. *Neurosurgery*, 52(5) :1041-1048.

175. **Raffaele DC, Marco S, Rosa MM, Giuseppe L, Francesco P, Alfonso T, Roberto M , Chieti I, Pisa I. (2010).** Cholesterol-lowering interventions and stroke . *Journal of the American College of Cardiology*, 55 (3) : 198-211 .

176. **Rahman T, Hosen I, Islam T, Shekhar HU. (2012).** Oxidative stress and human health. *Advances in Bioscience and Biotechnology*, 3: 997-1019.

177. **Rajesh D, Dhirendra T, Raj S. (2017).** Clinical and biochemical characteristics of exertional heat stroke among paratroopers in Agra, India . *Journal of The Association of Physicians of India*, 65 : 57-61 .

178. **Rajsic S, Gothe H, Borba HH, Sroczynski G, Vujicic J, Toell T, Siebert U. (2018).** Economic burden of stroke: a systematic review on post-stroke care. *The European Journal of Health Economics*, 20 :107-134.

179. **Ramírez-Moreno JM, Muñoz VP, Espada S, Bartolomé AS, Aguirre J, Peral D. (2019).** Association between self-perceived psychological stress and transitory ischaemic attack and minor stroke: a case–control study. *Journal of Neurología (English Edition).*

180. **Rebello LC, Haussen DC, Grossberg JA, Belagaje S, Lima A, Anderson A, Frankel MR, Nogueira RG. (2016).** Early Endovascular Treatment in Intravenous Tissue Plasminogen Activator–Ineligible Patients: Table. *Journal of Stroke*, 47(4) : 1131-1134.

181. **Reina C, Saya T, Kasumi M, Maiko K, Mayumi U, Toshiko T, Junko C, Joji H, Minoru Y,Tomohiro O. (2019).** Factors influencing quality of life in stroke patients: focus on eating habits . *Journal of Stroke and Cerebrovascular Diseases*, 28(6) : 1623 -1628 .

182. **Reynolds MA. (2003).** Early Biomarkers of Stroke. *Clinical Chemistry*, 49(10) : 1733-1739.

183. **Robine J, Bernstein A. (2015).** Dietary Protein and the Risk of Stroke. Foods and Dietary Supplements in the Prevention and Treatment of Disease in Older Adults, 285-296 .

184. **Rodney M, Yun J, Joshua D, Anita R, Anna S, Jeremy M, Nickolas S, Anthony P, Evan R, Diego M, Venugopal R, Julia K, Fudong L, Rajkumar V, Louise D. (2018).** Aging alters the immunological response to ischemic stroke. *Acta Neuropathologica* , 401(18):01-17.

185. **Rodrigo R, Fernández-Gajardo R, Gutiérrez R, Matamala JM, Carrasco R, Miranda-Merchak A, Feuerhake W. (2013).** Oxidative Stress and Pathophysiology of Ischemic Stroke: Novel Therapeutic Opportunities. *CNS & Neurological Disorders - Drug Targets*, 12(2) :1-12 .

186. **Rong C, Bruce O, Wuwei F. (2016).** Diabetes and stroke: epidemiology, pathophysiology, pharmaceuticals and outcomes . *The American Journal Of The Medical Sciences*, 351 (4) : 380-386 .

187. **Rothwell PM, Coull AJ, Silver LE, Fairhead JF, Giles MF, Lovelock CE, Redgrave JNE, Bull LM, Welch SJV, Cuthbertson FC, Binney LE, Gutnikov SA, Anslow P, Banning AP, Mant D, Mehta Z. (2005) .** Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). *Stroke Prevention Research Unit*, 6736(05) :1773-1782.

188. **Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM, Gutnikov SA, Edwards P, Mant D, Sackley CM, Farmer A, Sandercock PAG, Dennis MS, Warlow CP, Bamford JM, Anslow P. (2004).**Change in strok e incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study) . *THE LANCET*, 363:1925-1932.

189. **Sacan O, Turkyilmaz IB, Bayrak BB, Mutlu O, Akev N, Yanardag R. (2016).** Zinc supplementation ameliorates glycoprotein components and oxidative stress changes in the lung of streptozotocin diabetic rats. *journal of BioMetals*, 29(2) : 239-248.

190. **Sanne A, Yankuba S, Diana M, Rachel R, Mark W. (2016).** Total cholesterol as a risk factor for coronary heart disease and stroke in women compared with men: A systematic review and meta-analysis . *Atherosclerosis*, 248 (123) :124-129.

191. **Santo A, Zhu H, Li YR. (2016).** Free Radicals: From Health to Disease .*Reactive oxygen species*, 2(4) :19-29.

192. **Santos SA, Rebelo I, Castro E, Belo L, Catarino C, Monteiro I, Maria DA, Quintanilha A. (2002).** Erythrocyte damage and leukocyte activation in ischemic stroke. *Clinica Chimica Acta*, 320(1-2) : 29-35.

193. **Sarti C, Kaarisalo M,Tuomilehto J. (2000).** The relationship between cholesterol and stroke. *Journal of Drugs & Aging*, 17(1) :33-51.

194. **Scremin OU. (2015).** Cerebral Vascular System. *The Rat Nervous System*, 985-1011.

195. **Semenov S, Planas R, Hopfer M, Hamidipour A, Vasilenko A, Stoegmann E, Auff E. (2015).** Electromagnetic tomography for brain imaging: Initial assessment for stroke detection. *2015 IEEE Biomedical Circuits and Systems Conference (BioCAS)*.

196. **Serge P, Gopal B. (2001).** Voiding and sexual dysfunction after cerebrovascular accidents. *The Journal Of Urology*, 165 (359–370) :359-367.

197. **Setyopranoto I. (2016).** Role of oxidative stress on acute ischaemic stroke. *Indonesian Journal of Medicine and Health*, 7(4):151-160.

198. **Shah RS, Cole JW. (2010).** Smoking and stroke: the more you smoke the more you stroke. *Expert Review of Cardiovascular Therapy*, 8(7): 917–932.

199. **Shah RS, Jeyaretna DS. (2018).** Cerebral vascular anatomy and physiology . *Surgery (Oxford)*, 36(11) : 606-612 .

200. **Shahidi F, Zhong Y. (2015).** Measurement of antioxidant activity. *Journal of Functional Foods*, 18:757-781.

201. **Shao Z, Tu S, Shao A. (2019).** Pathophysiological Mechanisms and Potential Therapeutic Targets in Intracerebral Hemorrhage. *Frontiers in Pharmacology*, 10(1907) : 31607923 .

202. **Shichao S, Yuesong P, Lei B, Xingquan Z, Liping L, Hao L, Yilong W, Li G, Yongjun W. (2018).** GWTG Risk Model for All Stroke Types Predicts In-Hospital and 3-Month Mortality in Chinese Patients with Acute Stroke. *Journal of Stroke and Cerebrovascular Diseases*, 28(3) :800-806.

203. **Shiga Y, Nezu T, Hosomi N, Aoki S, Nishi H, Naito H, Kinoshita1 N, Ueno H, Maruyama H. (2019).** Effect of tooth loss and nutritional status on outcomes after ischemic stroke. *Journal of Nutrition*, 110606.

204. **Sidorov E, Sanghera DK, Vanamala JKP. (2019).** Biomarker for Ischemic Stroke Using Metabolome: A Clinician Perspective. *Journal of Stroke*, 21(1) : 31-41.

205. **Simats A, García-Berrocoso T, Montaner J. (2016).** Neuroinflammatory biomarkers: From stroke diagnosis and prognosis to therapy. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, 1862(3), 411-424.

206. **Sinden OD, Hicks C, Stroemer P, Vishnubhatla I, Corteling R. (2017).** Human Neural Stem Cell Therapy for Chronic Ischemic Stroke: Charting Progress from Laboratory to Patients . *Stem Cells and Development*, 26(13) :933-950.

207. **Slot KB, Berge E, Dorman P, Lewis S, Dennis M, Sandercock P. (2008).** Impact of functional status at six months on long term survival in patients with ischemic stroke: prospective cohort studies .*journal of BMJ*, 336(7640) : 376-379.

208. **Song J, Park J, Oh Y, Lee JE. (2015).** Glutathione Suppresses Cerebral Infarct Volume and Cell Death after Ischemic Injury: Involvement of FOXO3 Inactivation and Bcl2 Expression. *Journal of Oxidative Medicine and Cellular Longevity*,2015 :1-11.

209. **Song Y, Yanping Z, Yuanrui T, Yanchun C, Xianghai Z, Ying L, Hailong Z, Xiaotian C, Lijun Z, Zhengmei F, YingShui Y, Zhibing H, Chong S. (2018).** Common variants of *ROCKs* and the risk of hypertension, and stroke: Two case-control studies and a follow-up study in Chinese Han population . *journal of Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, 1864 (3) : 778-783 .

210. **Stack CA, Cole JW. (2017).** A Diagnostic Approach to Stroke in Young Adults. *Current Treatment Options in Cardiovascular Medicine*, 19(11):84.

211. **Stefanovic V, Andersson S, Vento M. (2019).** Oxidative stress - Related spontaneous preterm delivery challenges in causality determination, prevention and novel strategies in reduction of the sequelae . *Free Radical Biology and Medicine*, 142 :52–60 .

212. **Susan E, Leslie R, Jennifer T, Sarah L, Jane S, Katherine S, Robert J, Jerry H. (2012).** A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data . *pharmacoepidemiology and drug safety*, 21(1):101-122.

213. **Sveinbjornsdottir S. (2016).** The clinical symptoms of Parkinson's disease. *Journal of Neurochemistry*, 139: 318-324.

214. **Szegedi I, Szapáry L, Csécsei P, Csanádi Z, Csiba L. (2017).** Potential Biological Markers of Atrial Fibrillation: A Chance to Prevent Cryptogenic Stroke. *BioMed Research International*, 2017: 1-10.

215. **Tan G, Yuan R, Hao Z, Lei C, Xiong Y, Xu M, Liu M. (2017).** Liver function indicators performed better to eliminate cardio embolic stroke than to identify it from stroke subtypes. *Journal of Stroke and Cerebrovascular Diseases*, 26(1): 230-236.

216. **Thomalla G, Simonsen CZ, Boutitie F, Andersen G, Berthezene Y, Cheng B, Cheripelli B, Cho TH, Fazekas F, Fiehler J, Ford I, Galinovic I, Gellissen S, Golsari A, Gregori J, Günther M, Guibernau J, Häusler KG,Hennerici M, Kemmling A, Marstrand J, Modrau B, Neeb L, Perez F, Puig J, Ringleb P, Roy P, Scheel E, Schonewille W, Serena J, Sunaert S, Villringer K, Wouters A, Thijs V, Ebinger M, Endres M, Fiebach JB, Lemmens R, Muir KW, Nighoghossian N, Pedraza S, Gerloff C. (2018).** MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset. *New England Journal of Medicine*, 379(7) : 611–622.

217. **Towfighi A, Hill V. (2017).** Modifiable Risk Factors for Stroke and Strategies for Stroke Prevention. *Seminars in Neurology*, 37(03): 237–258.

218. **Tun NN, Arunagirinathan G, Munshi SK, Pappachan JM. (2017).** Diabetes mellitus and stroke: A clinical update . *world journal of diabetes*, 8(6) : 235-248.

219. **Tysnes OB, Storstein A. (2017).** Epidemiology of Parkinson's disease. *Journal of Neural Transmission*, 124(8): 901-905.

220. **Tziomalos K, Dimitriou P, Bouziana SD, Spanou M, Kostaki S, Angelopoulou SM, Papadopoulou M, Giampatzis V, Savopoulos CH, Hatzitolios AI. (2017).** Stress hyperglycemia and acute ischemic stroke in-hospital outcome. *Journal of Metabolism*, 67, 99-105.

221. **Valeria C, Florian M. (2019).** A narrative review of nonvitamin K antagonist oral anticoagulant use in secondary stroke prevention . *Journal of Stroke and Cerebrovascular Diseases*, 28 (9) : 2363- 2375.

222. **Vida D. (2004).** Pathophysiology and classification of cerebrovascular disorders. *the journal of the international Federation of Clinical Chemistry And Laboratory Medicine*, 15 (3) :44-46 .

223. **Vidhya R, Rathnakumar K, Balu V, Pugalendi KV. (2018).** Oxidative stress, antioxidant status and lipid profile in pulmonary tuberculosis patients before and after anti-tubercular therapy. *Indian Journal of Tuberculosis*, 66(3) : 375-381.

224. **Wang C, Deng L, Qiu S, Bian H, Wang L, Li Y, Liu M, Wu B. (2019).** Serum albumin is negatively associated with hemorrhagic transformation in acute ischemic stroke patients. *Cerebrovascular Diseases*, (47) :88-94.

225. **Wang IK, Liu CH, Yen TH, Jeng JS, Hsu SP, Chen CH, Lin HJ, Chi HY, Lai TC, Sun Y, Lee SP, Sung SF, Chen PL, Lee JT, Chiang TR, Lin SK, Muo CH, Henry M, Wen CP, Sung FC, Chung YH,Lin HJ. (2017).** Cholesterol levels are associated with 30-day mortality from ischemic stroke in dialysis patients. *Journal of Stroke and Cerebrovascular Diseases*, 26(6): 1349-1356 .

226. **Wang W, Jiang B, Sun H, Ru X, Sun D, Wang L, Wang L, Jiang Y, Li Y, Wang Y, Chen Z, Wu S, Zhang Y, Wang D, Wang Y, Feigin VL. (2017).** Investigators, Prevalence, Incidence, and Mortality of Stroke in China: Results from a Nationwide Population-Based Survey of 480 687 Adults . *journal of Circulation*, 135(8) :759-771.

227. **Weckbeker G, Cory JG. (1988).** Ribonucleotidereductase activity and growth of Glutathoine-depleted mousleikemia L1210 cells in vitro. *Cancer letters*, 40: 257-264.

228. **Weller J, Budson A. (2018).** Current understanding of Alzheimer's disease diagnosis and treatment [version 1; referees: 2 approved]. *F1000Research*, 1161 : 1-9.

229. **Wesołowski P, Zawada K, Wojtowicz A, Struzycka I, Kaminski T. (2016).** Assessment of salivary total antioxidant capacity in patients with primary untreated head and neck squamous cell carcinoma with ORAC . journal of Oral pathology and Medicine, 45(10) : 753-757 .

230. **World Health Organization (WHO). (2017).** Stroke in Algeria . https:// WWW.Worldifeexpectancy.com/Algeria-stroke .

231. **Wu JQ, Kosten TR, Zhang XY. (2013).**Free radicals, antioxidant defense systems, and schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*, 46 :200-206.

232. **Xie F, Liu H, Liu Y. (2020).** Adult neurogenesis following ischaemic stroke and implications for cell-based therapeutic approaches. *World Neurosurgery*, 138 :474-480.

233. **Xu T, Bu X, Li H, Zhang M, Wang A, Tong W, Sun Y, Zhang Y. (2013).** Smoking, heart rate, and ischemic stroke: a population-based prospective cohort study among Inner Mongolians in China. *journal of Stroke*, 44(9) : 2457-2461.

234. **Xu T, Li Y, Su Y, Zuo P, Gao Z, Ke K. (2020).** Serum omentin-1 and risk of one-year mortality in patients with ischemic stroke .*journal Clinical Chemical Acta*, 505: 167-171.

235. **Xue WY, Xu YC, Wu YW, Yang M. (2017).**Observation of elevated fasting blood glucose and functional outcome after ischemic stroke in patients with and without diabetes . *Journal of Oncotarget*, 8 (40) : 67980-67989 .

236. **Yagi K. (1976).**Simple fluorometric assay for lipoperoxyde in blood plasma. *Biochemical Medecine*, 15 : 212-216.

237. **Yang JL, Yang YR, Chen SD. (2019).** The potential of drug repurposing combined with reperfusion therapy in cerebral ischemic stroke: A supplementary strategy to endovascular thrombectomy . *Life Sciences*, 236 : 116889.

238. **Yang JL, Mukda S, Chen SD. (2018).** Diverse roles of mitochondria in ischemic stroke. *Redox Biology*, 16, 263–275.

239. **Yip S, Zivin J. (2008).** Laser therapy in acute stroke treatment. *International Journal of Stroke*, 3 :88-91.

240. **Yoshida M, Akagawa Y. (2011).** The relationship between tooth loss and cerebral stroke. *Japanese Dental Science Review*, 47(2) :157–160.

241. **Zaidi Z, Boussouf K, Benkobbi S, Bitat-Aouati C, Ben Boudiaf S, Fatima Kaddour F, Djelaoudji A. (2019).** Burden of Cardiovascular Diseases in the Maghrebian Region, 1990-2017: Finding from the Global Burden Diseases Study 1990-2017. *Health science journal*, 13(1) : 362.

242. **Zhang G, Li Y, Reuss JL, Liu N, Wu C, Li J, Xu S, Wang F, Hazel TG, Cunningham M, Zhang H, Dai Y, Hong P, Zhang P, He J, Feng H, Lu X, Ulmer JL, Johe KK, Xu R. (2019).** Stable Intracerebral Transplantation of Neural Stem Cells for the Treatment of Paralysis Due to Ischemic Stroke. *STEM CELLS Translational Medicine*.

243. **Zhang S, Zhang W, Zhou G. (2019).** Extended Risk Factors for Stroke Prevention. *Journal of the National Medical Association*, 111(4) : 447-456 .

244. **Zhao J, Wang S, Zhong W, Yang B, Sun L, Zheng Y. (2016).** Oxidative stress in the trabecular meshwork (Review). *International Journal of Molecular Medicine*, 38(4): 995-1002.

245. **Zheng M, Wang X, Yang J, Song M, WEI Y, LIU S. (2019).**Changes of complement and oxidative stress parameters in patients with acute cerebral infarction or cerebral hemorrhage and the clinical significance . *Experimental and Therapeutic Medicine*, 19: 703-709.

246. **Zheng P, Zhang L, Sun R, Peng X. (2020).** Large Population Screening Identified the Main Risk Factors of Stroke in Shashi District of Jingzhou City . *Yangtze Medicine*, 04 (01) : ID:97510,9 pages.

247. **Zimmermann C, Winnefeld K, Streck S, Roskos M, Haberl RL. (2004).** Antioxidant status in acute stroke patients and patients at stroke risk. *Journal of European Neurology* ,51(3) : 157-161.

248. **Žitňanová I, Šiarnik P, Füllöp M, Oravec S, Penesová A, Ďuračková Z, Vaskà E, Turčàni P, Kollár B. (2018).** Gender differences in LDL- and HDL-cholesterol sub fractions

in patients after the acute ischemic stroke and their association with oxidative stress markers. *Journal of Clinical Biochemistry and Nutrition*, 63(2): 144-148.

249. **Żukowski P, Maciejczyk M, Waszkiel D. (2018).** Sources of free radicals and oxidative stress in the oral cavity. *Archives of Oral Biology*, 92: 8–17.

250. **Zweifler RM. (2017).** Initial Assessment and Triage of the Stroke Patient. *Progress in Cardiovascular Diseases*, 59(6): 527-533.

Annexes

Annex 01:

Sex :……

Number of children:…...

Weight :……

Social case:……....

Length :…….

Region :……

Education level:…….

Stroke type :……..

Job:…….

Blood type :……

Season of infection by stroke :……

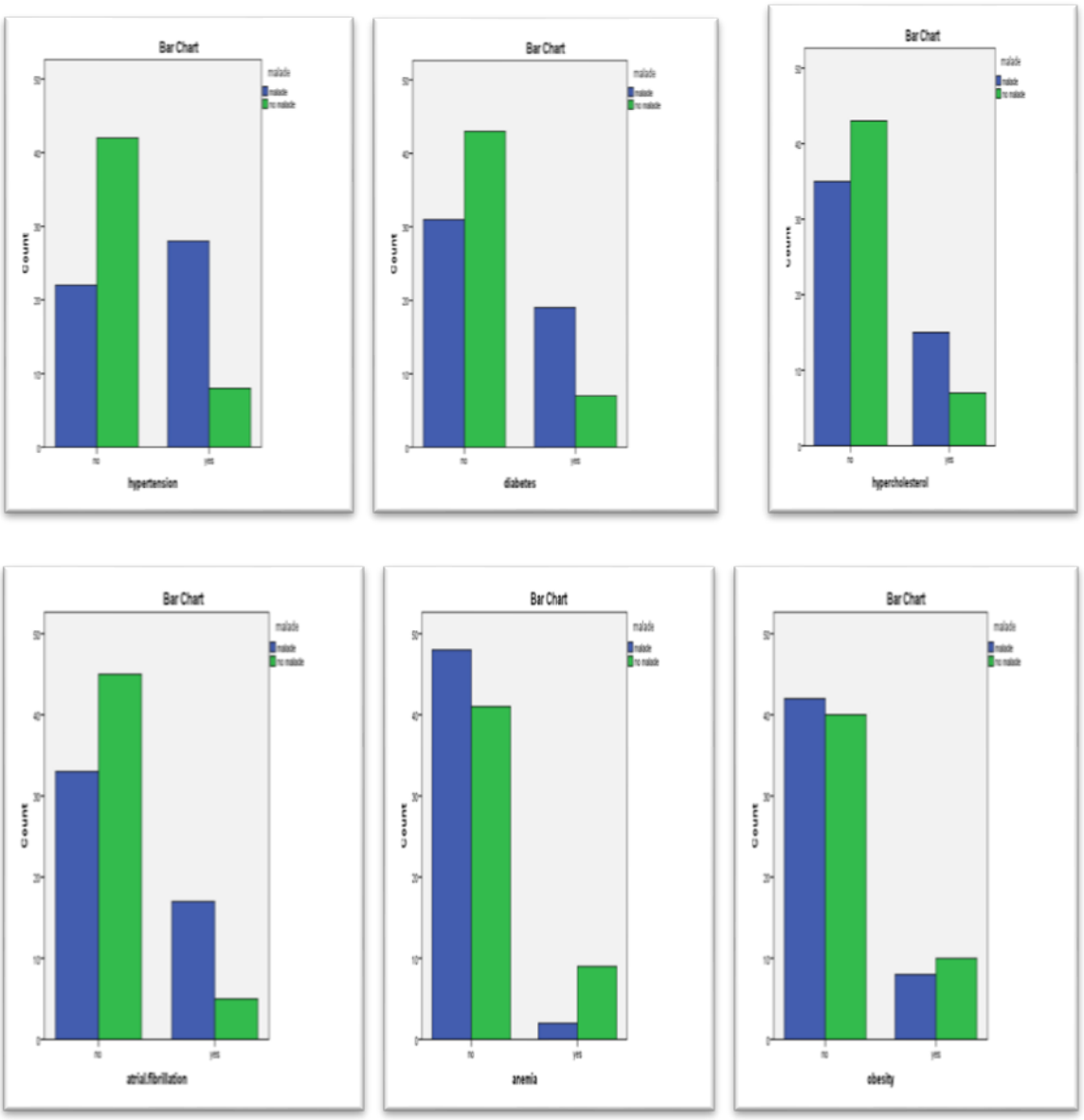
Clinical factors :

N^0	**Questions**	**Yes**	**No**
01	Did you suffer from hypertension ?		
02	Did you suffer from diabetes ?		
03	Did you suffer from hyper cholesterol ?		
04	Did you suffer from atrial fibrillation ?		
05	Did you suffer from anemia safety ?		
06	Did you suffer from obesity ?		
07	Did you suffer from heart attack ?		
08	Did anyone in your family have stroke?		
09	Did you use one of cancer treatments ?		
10	Did you use self-medication ?		
11	Did you use excess of anticoagulants ?		
12	Did you use excess of analgesics ?		
13	Did you suffer from Migraines ?		

Socioeconomic factors:

N^0	**Questions**	**Yes**	**No**
01	Are you addicted to smoke ?		
02	Are you addicted to fast foods ?		
03	Do you eat Spicy foods a lot?		
04	Do you eat a lot of salt ?		
05	Do you eat a lot of sugars ?		
06	Do you eat a lot of vegetables and fruits ?		
07	Do you eat a lot of red meat ?		
08	Are you addicted to soft drinks ?		
09	Do you drink Excess of water?		
10	Do you use Herds for medication ?		
11	Do you practice sports in your daily life?		
12	Do you brush your teeth daily ?		
13	Do you expose to the sun continuously ?		
14	Do you expose to high levels of family stress ?		
15	Do you expose to work stress ?		

Annex 02 :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Bar Chart
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diabetes
Bar Chart
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Count
hypercholesterol
Bar Chart
malade
malade
no malade
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atrial.fibrillation
Bar Chart
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malade
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Count
anemia
Bar Chart
malade
malade
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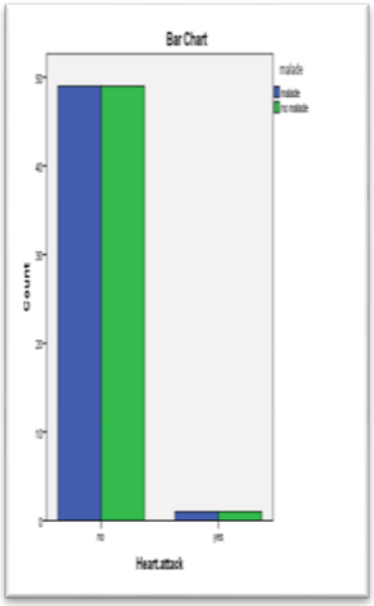
Count
obesity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Count
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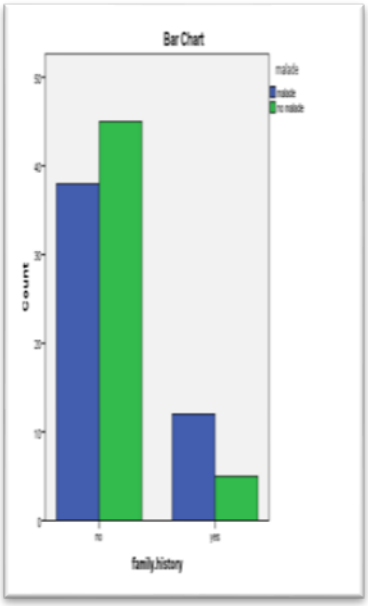
yes
Heart.attack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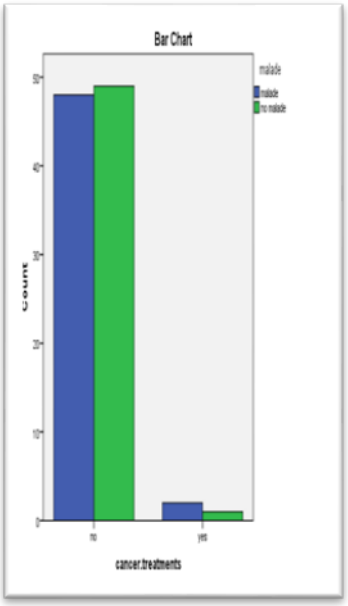
Count
no
yes
family.history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yes
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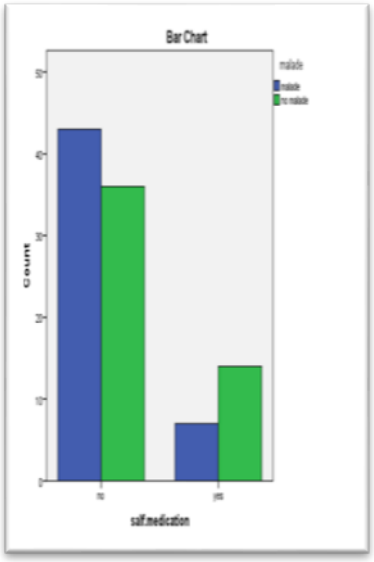
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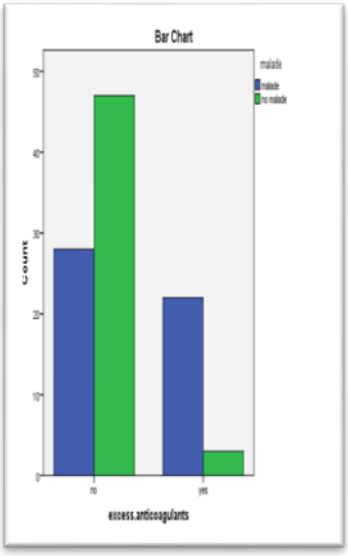
Count
no
yes
self.medication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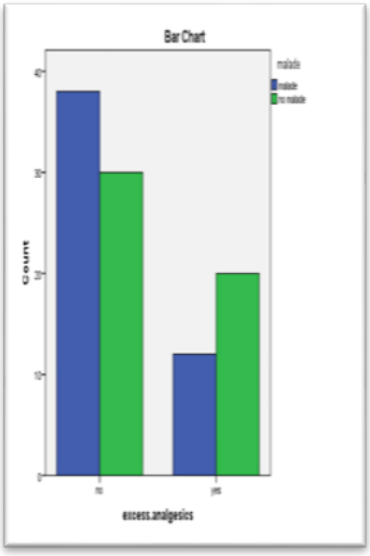
Count
no
yes
excess.anticoagulants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Count
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yes
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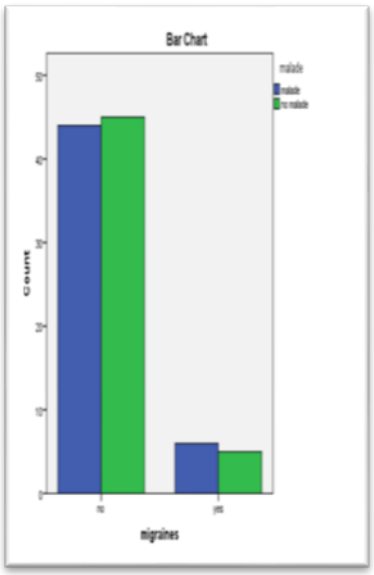
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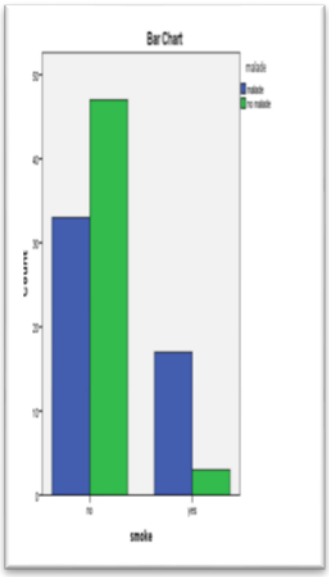
migraines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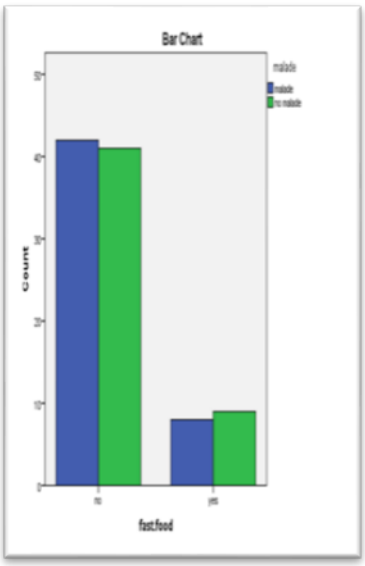
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Count
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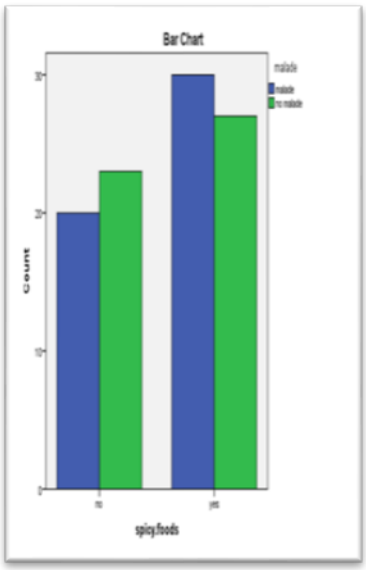
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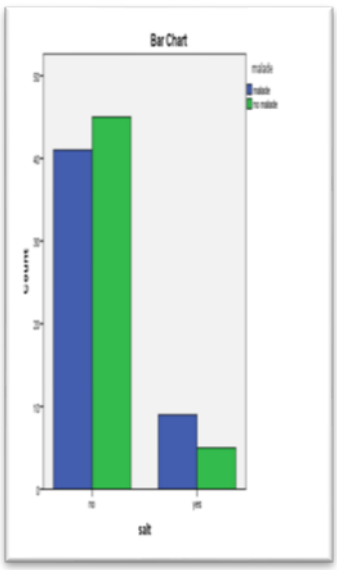
spicy.foods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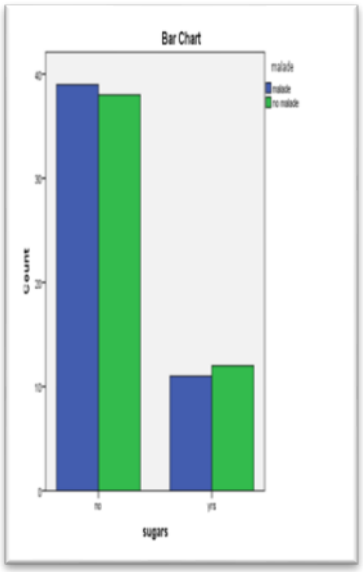
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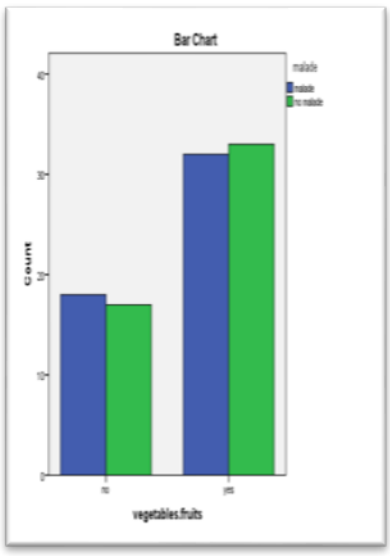
Count
sugars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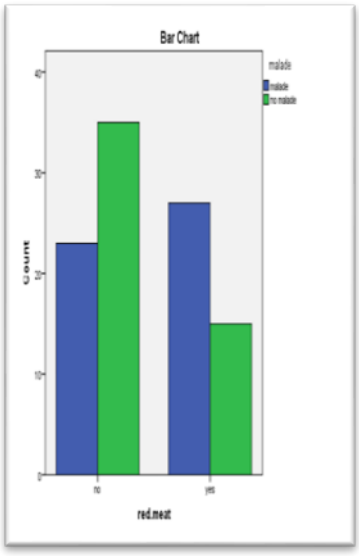
Count
vegetables.fruits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malade
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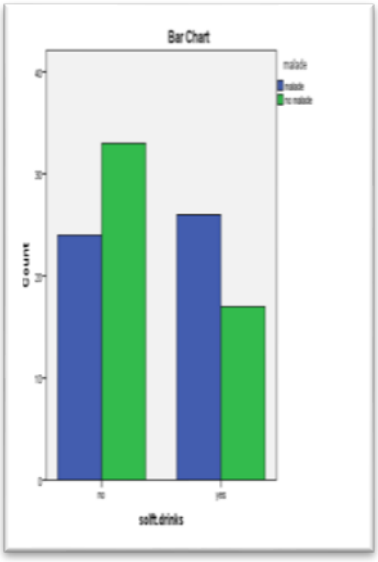
Count
red.meat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Count
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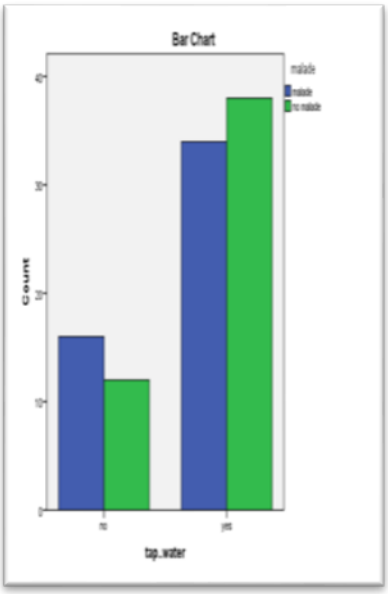
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Count
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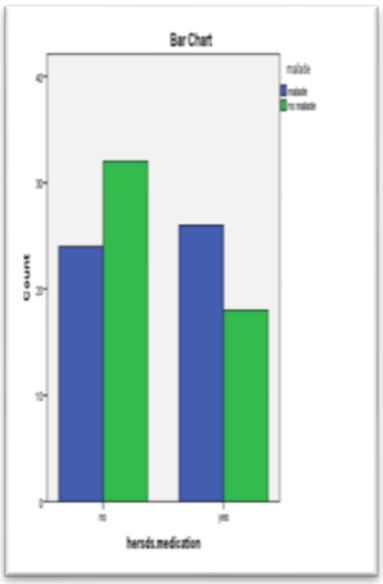
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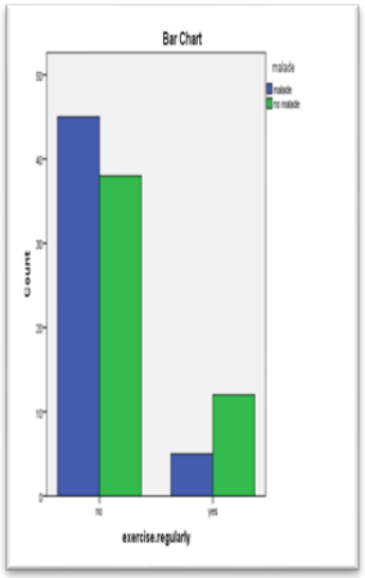
Count
hersds.medication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Count
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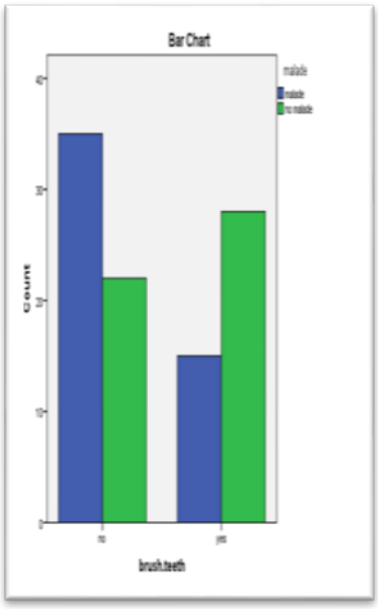
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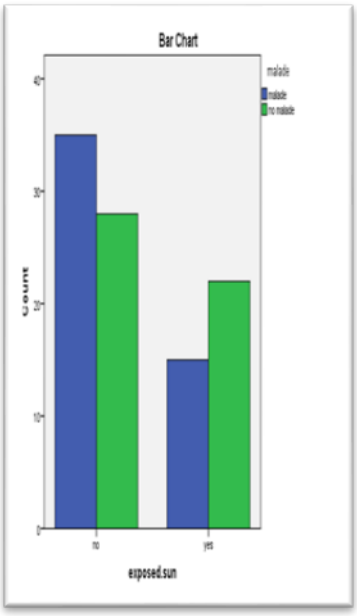
Count
brush.teeth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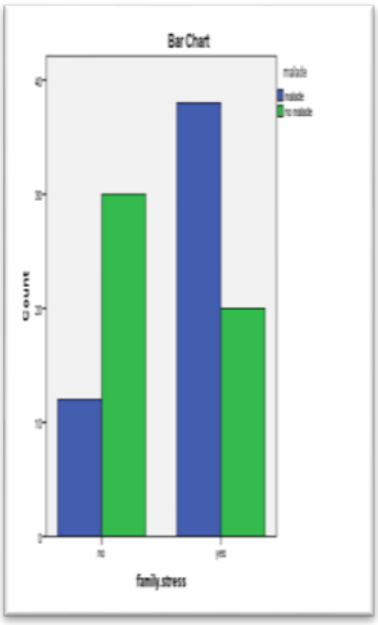
Count
exposed.sun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Count
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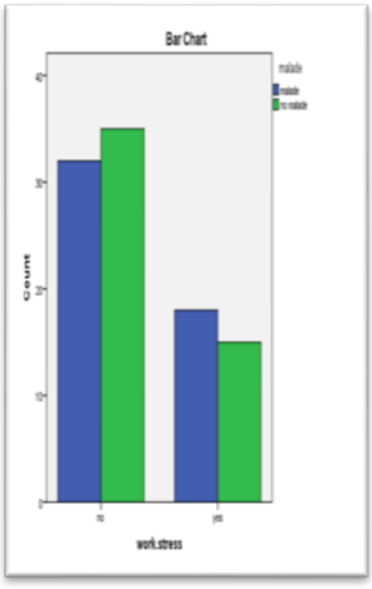
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Annex 03 :

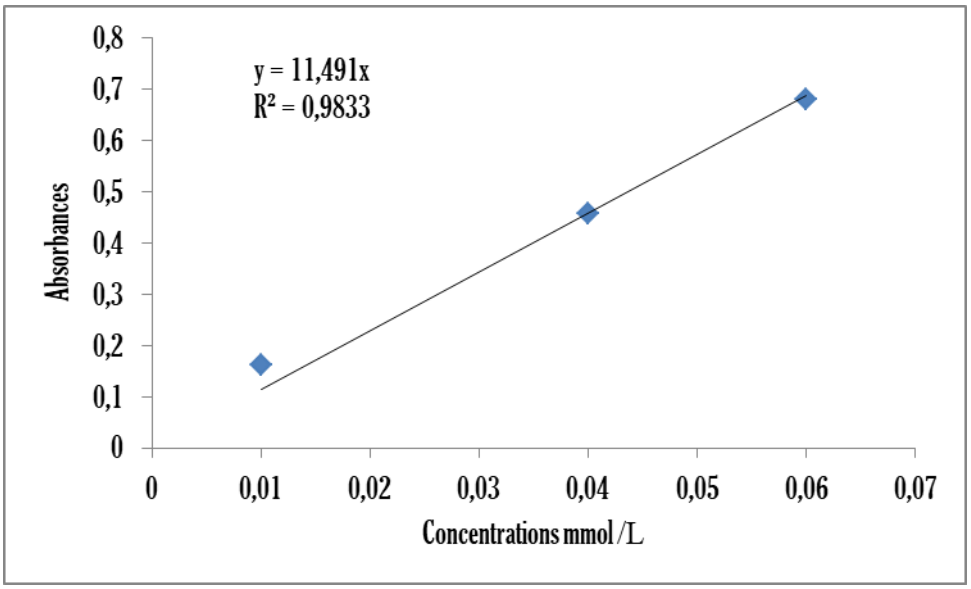

Figure : Calibration curve of ascorbic acid (Vitamin C)