SAID HUSEIN ISAQ

MALARIA DIAGNOSED IN FOREIGN PATIENTS AT NEU NEAR EAST UNIVERSITY HOSPITAL IN NORTHERN CYPRUS BETWEEN 2016 AND 2023

NEAR EAST UNIVERSITY

INSTITUTE OF GRADUATE STUDIES

DEPARTMENTOFMEDICAL MICROBIOLOGY AND CLINICAL MICROBIOLOGY

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M.Sc. THESIS

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NICOSIA

JANUARY 2024

TURKISH REPUBLIC OF NORTH CYPRUS

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iii

Declaration

Hereby, I declare that this thesis study is my study, I had no unethical behaviors in all stages from the planning of the thesis until writing there, I obtained all the information in this thesis in academic and ethical rules, I provided reference to all of the information and comments which could not be obtained by this thesis study and took these references into the reference list; and, had no behavior of breaching patent rights and copyright infringement during the study and writing of this thesis.

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Acknowledgements

WE PRAISE ALLAH, the Almighty, the Mightiest of All, on whom we depend for nourishment and guidance. I'm grateful to Allah for giving me the chance, determination, and strength to finish my research and thesis. His kindness and mercy sustained me throughout my life, especially during my research.

I would like to express my deepest gratitude to EşrefÇelik, MD Assistant Professor, my thesis Advisor, for spending countless hours reviewing my work and assisting me in bringing this thesis to life. I want to express my gratitude to her for all of the assistance, guidance, and motivation she has provided me throughout my thesis writing process she encouraged me to do my best work.

I would like to extend my appreciation to the entire academic faculty in the department for their invaluable support and assistance throughout my postgraduate studies. Specifically, I am grateful to Associate Professor Dr. EmrahRuh, who serves as the Chairman of the Department of Medical Microbiology and Clinical Microbiology at Near East University, as well as Professor Dr. Kaya Süer.

I would like to extend my appreciation to all those employed in the microbiology laboratory, with a special mention to Dr. EmrahGüler.

Finally, I want to thank my family, who have always been there for me in school and in my personal life and have hoped this success. This piece is for my mother, who is honest and kind, my father, who loves me, and my brothers and sisters. Love for my family fills every breath I take and every drop of blood that flows through my veins. I care about all of you very much.

ÖZET

Said HuseinIsaq: KuzeyKıbrıs'taYakınDoğuÜniversitesiHastanesi'nde 2016-2023 yıllarıarasındayabancıhastalardasıtmatanısıkonuldu.

Danışman: EşrefÇelik, MD Assistant Professor.

Çalışmamızınamacıdünyaçapındahalksağlığıüzerindekietkisigözönünealındığındabüyük önemtaşıyansıtmanınaraştırılmasıdır. Sıtma, çoğunluklatropikalvesubtropikalbölgelerdeözelliklesavunmasızolanpopülasyonlarıetkileyen, hastalıkveölümeönemliölçüdekatkıdabulunanbiretkendir. Hastalığınepidemiyolojisini, bulaşmasınıvetedavisinianlamak, etkilikontrolveönlemestratejilerigeliştirmekiçinçokönemlidir. Ayrıca, ilacadirençlisıtmatürlerininoluşturduğukalıcıtehdit, yenilikçiilaçveaşılarıngeliştirilmesineyönelikaraştırmalarındevametmesinigerektirmektedir. Plasmodium parazitlerininnedenolduğuvedişi Anopheles sivrisinekleritarafındanbulaşansıtma, ateş, başağrısıveciddivakalardakomaveyaölümgibisemptomlargösteriyor.

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KuzeyKıbrıs'takiYakınDoğuÜniversitesiHastanesi'nde 2016-2023 yıllarıarasındateşhisedilenvakalaraodaklananaraştırma, sıtmanınyaşgrupları, cinsiyetlervemilliyetlerarasındadeğişenetkisinivurguluyor. Çalışmanınbulguları, 25 vakanınretrospektifanalizinedayanıyor. Plasmodium falciparum'unözelliklegençyetişkinlerveerkeklerarasındayaygınlığı.

Çalışmaaynızamandakliniksemptomları, laboratuvarsonuçlarınıveçeşitlitedavilerinveteşhisyöntemlerininetkinliğini de inceliyor.

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hakkındadeğerlibilgilersağlıyorvesıtmanınetkisininazaltılmasınayönelikküreselçabalarıil erletiyor.
Anahtar Kelimeler: Sıtma, Serebral, Falciparum, Plasmodium, Teşhis, Kuzey Kıbrıs.

Abstract

Said HuseinIsaq: Malaria diagnosed in foreign patients at Near East University Hospital in Northern Cyprus between 2016 and 2023.

Advisor: EşrefÇelik, MD Assistant Professor.

The aim of our study is to investigate of malaria that is great importance given its worldwide influence on public health. Malaria is a prominent contributor to illness and death, mostly impacting populations that are particularly vulnerable in tropical and subtropical regions. Understanding the epidemiology, transmission, and treatment of the disease is crucial for developing effective control and prevention strategies. Furthermore, the persistent threat presented by drug-resistant strains of malaria necessitates ongoing research to develop innovative drugs and vaccines. Malaria, caused by Plasmodium parasites and transmitted by female Anopheles mosquitoes, presents symptoms like fever, headaches, and in severe cases, coma or death. Its history, stretching back to ancient times, reveals a long-standing battle against this disease, involving traditional medicines like quinine and modern control strategies such as insecticide-treated nets and indoor residual spraying.

The research emphasizes the varying impact of malaria across age groups, genders, and nationalities, with a focus on cases diagnosed at Near East University Hospital in Northern Cyprus between 2016 and 2023. The study's findings are based on a Retrospective analysis of 25 cases, highlighting the prevalence of Plasmodium falciparum, especially among young adults and males. The study also examines the clinical symptoms, laboratory outcomes, and the efficacy of various treatments and diagnostic methods.

The significance of the study lies in its contribution to understanding the epidemiology and treatment of malaria, highlighting the challenges posed by drug-resistant strains and

the need for ongoing research for new medications and vaccines. This research provides valuable insights for public health policies and interventions, especially for travelers and expatriates, and advances global efforts in reducing the impact of malaria.

Keywords: Malaria, Cerebral, Falciparum, plasmodium, diagnosed, northernCyprus.

List of Tables

List of figures

Table of contents

Abbreviations and Symbols

ARF Acute renal failure

ALT Alanine Transaminase

ALP Alkaline Phosphate

AST Aspartate Transaminase

CQ Chloroquine

CM Cerebral Malaria

CRP C-Reactive protein

DDTDichlorodiphenyltrichloroethane

DHF Dihydrofolate

DHPSDihydropteroate Synthase

DHFR Dihydrofolate reductase

GGT Gamma-Glutamyl transferase

HGB Hemoglobin

ITNInsecticide-Treated Nets

IRS Indoor Residual Spraying

PABA Para-Amino Benzoic Acid

PLT Platelets Test

RBM Roll Back Malaria.

RBC Red Blood Cells.

RDT Rapid Diagnostic Test

THF Tetrahydrofolate

UNDPUnited Nations Development Program.

UNICEFUnited Nations Children's Fund

WBC	White Blood Cells
WHO	World health organization.

CHAPTER ONE

INTROODUCTION

1.0 Introduction

Malaria is an infectious disease transmitted by mosquitoes to both humans and other animals(Tuteja, 2007)**.** It is caused by protists, a type of microorganism belonging to the Plasmodium genus, and the infection commences when an infected female mosquito bites, introducing these protists into the bloodstream through its saliva (T. W. Health & Foundation, 2010). Subsequently, they travel to the liver, where they mature and multiply, and therefore, symptoms of the disease commonly encompass fever and headaches, which in severe instances can progress to coma or even prove fatal(Talapko et al., 2019)**.** Malaria is prevalent in tropical and subtropical regions situated in a wide belt around the equator, including extensive areas of Sub-Saharan Africa, Asia, and the Americas(*Malaria Regional Factsheet Malaria Regional Factsheet*, 2021). The term "malaria" originated from "mala aria," a medieval Italian phrase meaning "bad air." Due to its association with marshy and swampy environments, the illness was formerly known as ague or marsh fever(Tuteja, 2007)**.** Although it is no longer native to these locations, malaria was once common over much of Europe and North America. However, isolated instances imported from other places can still be found(Adugna et al., 2022).Malaria has a long history, starting from its ancient origins as a disease transmitted between animals and humans in Africa all the way up to the present day. Malaria, a very prevalent and possibly fatal human infectious illness, was present on every continent except Antarctica at its highest point(Hempelmann, n.d.). The prevention and treatment of this condition have been the focus of scientific and medical research for centuries. Since their discovery, research has mostly focused on the biology of the parasites and the mosquitoes that transmit them(Hempelmann, n.d.).Human behavior, such as population migration and changes in agricultural practices, along with living conditions, are the most crucial determinants in the transmission or elimination of diseases. Accurate statistical data is lacking due to the prevalence of instances in remote rural regions where individuals lack access to healthcare facilities and services. Therefore, most cases are not documented. The disease has historically and continues to

be linked with poverty(Hempelmann, n.d.)References to its distinctive, recurring fevers can be traced back to recorded history, starting around 2700 BC in China. Traditional herbal medicines have been employed for centuries to address malaria. Quinine, derived from the bark of the cinchona tree, was the initial successful remedy for malaria. Following the discovery of the connection between mosquitoes and their parasites in the early 20th century, many methods were implemented to control mosquitoes. These tactics included the extensive application of DDT, draining swamps, covering or oiling open water sources, indoor residual spraying, and the use of insecticide-treated nets. Quinine was prescribed as a preventive measure in locations where malaria is common, along with new medications for treatment (Hempelmann, n.d.).Malaria was still prevalent in over 100 countries across the tropical and subtropical regions, including extensive areas in Central and South America, Hispaniola (Haiti and the Dominican Republic), Africa, the Middle East, the Indian subcontinent, Southeast Asia, and Oceania, as the 20th century ended. The development of resistance in Plasmodium, the parasite causing malaria, to anti-malaria medications, as well as the resilience of mosquitoes to pesticides and the identification of zoonotic varieties of the parasite, have made control methods more challenging(World Health Organization, n.d.) .Malaria in humans probably began in Africa, where it evolved along with the mosquitoes and other species that carry it. The protozoa that cause malaria have split off into different host groups, such as birds, reptiles, humans, and rodents. People are thought to have gotten the Plasmodium falciparum type from gorillas in the first place. People are also infected with P. vivax, which most likely came from African gorillas and chimpanzees. A strain of P. knowlesi that is found in Asian macaque monkeys was recently found to be able to infect people. People are the only ones who can get P. malariae, but there is some proof that it can also infect wild chimpanzees without giving them any symptoms (World Health Organization, n.d.).Recent years have seen a lot of progress in our understanding of where the five human malaria parasites (P. falciparum, P. vivax, P. malariae, P. ovalecurtisi, and Wallikeri) and the monkey parasite P. knowlesi came from in the tropical forests of Southeast Asia. This is because sequencing and molecular genetics have become much more accurate (Nosten et al., 2022).The ancestor of all malaria parasites was possibly an aquatic protozoan invertebrate that had chloroplasts and lived

several hundred million years ago. At an early stage, it reproduced sexually. Later, it changed into the asexual stage (schizogony) that is found in plasmodium today(Nosten et al., 2022).These early parasites infected dipterans, the ancestors of mosquitoes that existed 150 to 200 million years ago. Over the next few periods, some lines of these early parasites changed to feed on blood-feeding insects and created a life cycle with two hosts. This is how the huge variety of parasites we see today came to be. These parasites live on most land animals, like mammals, birds, and reptiles. It is thought that they came from Africa and spread when early hominids moved between continents. P. falciparum is linked to and different from P. reicheinowi, a parasite that lives on chimpanzees. P. vivax, P. malariae, and P. ovale are all in a different clade than the other monkey malaria parasites they share their home with(Nosten et al., 2022).There are several nations where malaria is prevalent; in 2004, there were between 350 and 500 million instances of the disease, according to reports. Worldwide malaria mortality has been estimated to be between 1.1 and 1.3 million per year in World Health Organization (WHO) studies from 1999 to 2004. Approximately two billion people, or more than 40% of the world's population, are at risk of developing malaria(*Malaria Regional Factsheet Malaria Regional Factsheet*, 2021).Malaria can affect almost half of the people in the world. About 247 million people in 85 countries got malaria in 2021 (Savi, 2022). In that same year, the sickness killed about 619 000 people, and there are people who are more likely to get serious malaria than others. People who are pregnant, have HIV/AIDS, or are babies or kids younger than 5 are especially at risk. Some people who are also at risk are migrants, mobile populations, tourists, and people who are going to areas where malaria is common but who haven't been exposed to it for a long time or who aren't taking chemo preventive drugs(Savi, 2022).Certain individuals residing in regions with a high prevalence of malaria may acquire a degree of partial immunity. Although it may not offer total protection, partial immunity can decrease the likelihood of serious disease resulting from malaria infection. Due to this particular factor, a majority of malaria-related fatalities in Africa primarily affect young children, while in regions with lower transmission rates and limited immunity, individuals across all age groups face susceptibility to the disease(Savi, 2022).There is evidence to suggest that how people move and interact with mosquito habitat and environmental factors may

play a role in how malaria spreads. People move between high-risk and low-risk areas over time and space, both on a large (regional or district) and small (community or household) scale. This means that they are exposed to different parasites, mosquito bite patterns, and possibly different living or environmental conditions that may require different safety measures. Previous studies have also shown that having traveled a lot in the past was linked to getting Plasmodium falciparum malaria in refugee camps, coastal areas, cities, and river basins. This highlights the need for more research into how people moving around may be affecting the number of malaria infections (Yukich et al., 2013).Globally, an estimated 247 million cases of malaria were reported in 2021 in 84 malaria-endemic countries (including French Guiana), up from 245 million cases in 2020, and the majority of this rise was attributed to nations in the WHO African Region(Tuteja, 2007).However, North Cyprus remains a country where malaria is extremely rare and eradicated and where there is very little chance of a visitor getting the illness(Güler et al., 2020)**.**

1.2 Statement of problem

Malaria is a leading cause of death worldwide. Young children suffer the most from the disease in regions where it is extremely prevalent(Adugna et al., 2022)**.**An estimated 1 to 2 million children under the age of five perished from malaria last year, with the majority of those deaths occurring in Africa. If malaria were mostly prevalent in industrialized nations, as indicated by the data, there would be a substantially lower margin of error(Talapko et al., 2019). It is a fact that obtaining precise data and deriving significant statistics on malaria is challenging in the world's poorest nations, where the disease is most prevalent(Ladhani et al., 2007).The majority of malaria deaths happen at home without a diagnosis being confirmed, and many people fight, sometimes in vain, to obtain even basic medical treatment while they are ill (Tangpukdee et al., 2009).Significant financial resources are needed to tackle malaria from a scientific standpoint. There hasn't been any progress in the scientific community on creating a vaccine against malaria. While waiting for proper treatment, alternate methods of controlling malaria include educating people about early symptom detection through information campaigns and promoting preventative measures like using insecticide-

treated mosquito nets. To help individuals adopt the proper malaria therapies in this situation, communication strategies created to promote behavioral changes would be crucial(Smith, 1928)**.**A global coalition known as "Roll Back Malaria (RBM)" was founded in recognition of the persistent difficulty this health issue poses, with the goal of halving the malaria load globally by 2010. The World Health Organization (WHO), the United Nations Development Program (UNDP), the United Nations Children's Fund (UNICEF), and the World Bank are among the founding members of this alliance. The goal of RBM is to improve malaria prevention, management, and treatment(WHO, 2015)**.**

1.3Purpose of the Study

To estimate the malaria diagnosed in foreign patients at Near East University Hospital in Northern Cyprus between 2016 and 2023.

1.3.1Specific purposes

1. The specific purpose of this study is to investigate the number of foreign patients' affected malaria parasites in a nearby university hospital between 2016 and 2023.
2. To describe the clinical symptoms and identification of malaria in foreign patients.
3. To examine the outcome association with the malarial-effected foreign patients.

1.4 Research Questions

1. What is the clinical presentation and diagnosis of malarial infection associated with foreign patients at Near East University Hospital?
2. What are the outcomes associated with malarial infection in non-local radiance patients at Near East University Hospital?
3. What are the risk factors for malarial infection related to foreign patients diagnosed at Near East University Hospital?

1.5 Significance of study

The study of malaria holds immense significance due to its global impact on public health. Malaria continues to be a leading cause of disease and mortality, mostly affecting populations that are more susceptible in tropical and subtropical areas. It is essential to comprehend the disease's epidemiology, transmission, and treatment in order to create control and preventive plans that work. In addition, the constant danger posed by drug-resistant types of malaria calls for continued research to provide novel medications and vaccines. It is crucial to look at how malaria affects foreign nationals in order to inform public health policies and interventions, as well as to assist tourists and expatriates. In the end, research on malaria advances efforts worldwide to lessen the impact of the illness and enhance the quality of life for impacted populations.

1.6 Limitation

Size of the sample: Malaria infections aren't very common in Northern Cyprus, so studying them in a single hospital or with a small group of people might not be true to the country or the whole community.Time frame: Between 2016 and 2023, malaria was identified in foreign patients at Near East University Hospital in Northern Cyprus. This number may change over time due to changes in infection control policies, antibiotic use policies, and the types of patients who come to the hospital. Because of this, studies done at different times might not be able to be directly compared.

CHAPTER TWO

LITERETURE REVIEW

2.0 Introduction

Malaria is an illness that affects humans and is caused by four species of Plasmodium parasite, with the most common one being Plasmodium falciparum(CHAPTER 2 LITERATURE REVIEW 2.1 The Malaria Parasites, 2002). There are species such as Plasmodium vivax, ovale, malariae, and P. knowlesi.(T. W. Health & Foundation, 2010). The Plasmodium falciparum parasite functions in the environments of its host and uses tactics to evade the host's defenses(Daily, 2017).The World Health Organization says that 207 million cases of malaria were reported around the world in 2012, and 627,000 people died from it. (Thomas, 2014). The majority of these cases, 90%, occurred in Africa. Unfortunately, children are the most vulnerable to and affected by this disease. However, it is worth mentioning that since the year 2000, there has been a decrease of 54% in mortality rates among young children. Figure 1 shows how the proven cases are spread out around the world. India and sub-Saharan Africa have the most confirmed cases. Most cases of malaria in the US are attributed to tourists who got the disease while visiting a country where it is common.(Thomas, 2014).

*Figure 2. 1*Map of global Malaria

Figure 2.1 shows a map from the World Health Organization that shows how many official cases of malaria were reported in 2010. (Thomas, 2014).

2.1 Life cycle and Pathogenesis

The most vital species in this phylum is Apicomplexa, which belongs to the class Sporozoea, and this class of organisms includes coccidians and Plasmodium, which in turn cause a wide range of diseases in both humans and domestic animals(Thomas, 2014). The life cycle of the eukaryotic Plasmodium parasite is extremely intricate and is partly spent in the vertebrate (human) host and partly in the female Anopheles mosquito. Therefore, this section provides a detailed discussion of the several phases of life that the Plasmodium parasite goes through(Thomas, 2014).The Plasmodium parasite's life cycle begins with human infection through plasmodial sporozoites, which are delivered into the human bloodstream when a female Anopheles mosquito feeds on blood and injects saliva containing these sporozoites. Although the human immune system, mainly through antibodies, can kill some sporozoites, the majority of them still invade the liver. This stage is alternatively known as the pre-erythrocytic or exoerythrocytic phase (Cowman et al., 2016).After traveling to the liver via the circulation, sporozoites multiply and proliferate there until finally becoming schizonts (Stephen et al., 2017). Following this, the schizont divides to produce merozoites, which are several smaller cells. These merozoites become circulatory after departing from the liver. The Plasmodium schizont produces approximately thirty-two merozoites; this developmental stage might take one to two weeks, depending on the species. (Stephen et al., 2017).Hypnozoites, a dormant stage that can linger in the liver for months or even years before turning into schizonts, are shared by P. vivax and P. ovale. This is often associated with the recurrence of malaria episodes, which might happen years after the original infection. (Stephen et al., 2017).After the hepatocytes degrade, the infection of human red blood cells multiplies rapidly and dramatically, initiating the erythrocytic schizogony stage. In this phase, the merozoites found in red blood cells change into a ring-shaped structure and start the hemoglobin breakdown process(Cowman et al., 2016). The ring stage then develops into trophozoites, which again turn into schizonts, and these schizonts break apart the red blood cell, releasing a large number of

merozoites(Daily, 2017).These merozoites can then infect other red blood cells, which is often when clinical signs appear(Thomas, 2014).The process through which the egress of the invasive stages from their host cells occurs is not thoroughly comprehended. Still, strong genetic evidence suggests that malarial cysteine proteases play a key role in making it easier for these invasive stages to leave their intracellular spaces, both in liver stage schizonts and blood stage schizonts(Development & Responsibility, 2007).

***Figure 2*.2 life cycle f plasmodium species**

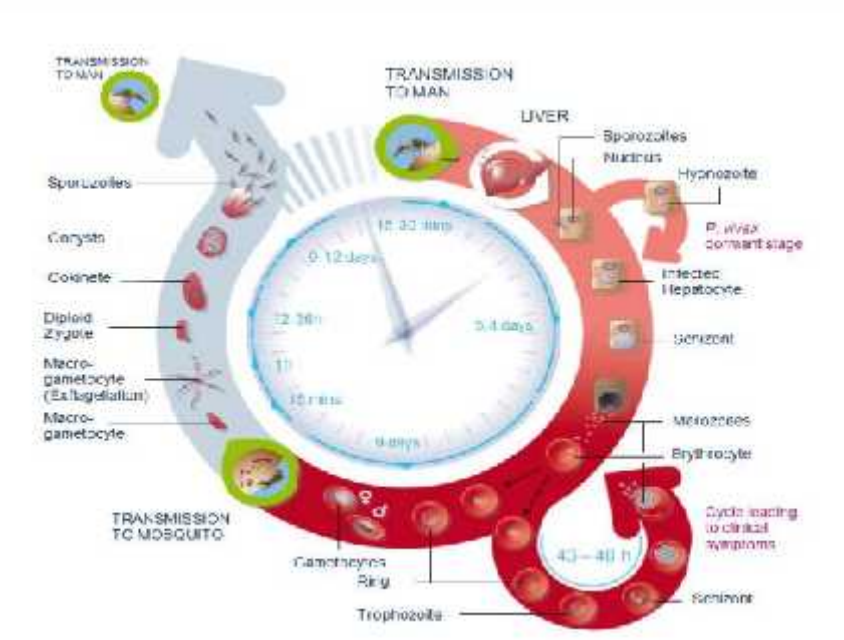


*Figure 2.2*illustrates the complex life cycle of Plasmodium species(Stephen et al., 2017).

Not all of the merozoites released from erythrocytes have the capability to infect other erythrocytes. Some of these merozoites undergo development into gametocytes, marking the initiation of the sexual stage after several rounds of asexual replication(Cowman et al., 2016).Researchers still don't know what causes macrogametocytes (female) and microgametocytes (male) to be made. During a blood meal, a female Anopheles mosquito eats mature gametocytes that are living in erythrocytes. These gametocytes are then transported to the mosquito's midgut, where they escape from the cells (Development & Responsibility, 2007).The process of microgametocyte Ex flagellation

produces eight haploid and mobile microgametes, which swiftly move to fertilize macrogametocytes, resulting in the formation of zygotes (Development & Responsibility, 2007).These zygotes change into ookinetes about a day after that. The ookinetes then move to an area outside of the midgut epithelium and the basal lamina on top, where they turn into oocysts. The oocysts break open after nine to twelve days, letting a lot of sporozoites into the mosquito's salivary gland epithelium. The mosquito's life cycle starts over when it feeds on the blood of a weak human host(Stephen et al., 2017).

2.2 Hemoglobin destruction

The parasite consumes the host's hemoglobin and gets its nourishment from the breakdown of many enzymes, including cysteine protease, in the digestive vacuole and This pathway offers a unique target for chemotherapy, which is exploited by a number of compounds, such as CQ and artemisinin, and for this reason, it is essential to give a summary in order to facilitate understanding of how these compounds function(Development & Responsibility, 2007).The malaria parasite consumes 60–80% of the available hemoglobin during the intra-erythrocytic stage by using an endo-lysosomal mechanism known as a cytostome. After being carried to the digestive vacuole, the hemoglobin is broken down to produce the parasite's own proteins(Cowman et al., 2016)**.**This happens in a semi-concerted manner, meaning that initially the native hemoglobin is broken down into haem and globin fragments by a family of proteases known as plasmepsins, and because heme is hazardous, it must be detoxicated by creating hemozoin through the process of biocrystallization(Stephen et al., 2017).Following that, cysteine proteases like falcipain-2 and -3 further break down the leftover globin fragments to produce peptide fragments with ten to fifteen amino acid subunits. The metalloprotease falcilysin then breaks these pieces up into oligomers made up of six to eight amino acid segments. These are then taken to the cytosol. Serine proteases and other aminopeptidases break down these oligomers further into individual free amino acids(Cowman et al., 2016).

2.3 Signs and Symptoms

The early signs of a Plasmodium infection are usually vague and mimic the symptoms of the flu, such as body aches, fever, chills, headaches, decreased appetite, nausea, anorexia, diarrhea, weight loss, splenomegaly, hepatomegaly, and vomiting. These symptoms can quickly worsen into serious consequences if left untreated, especially in the event of a P. falciparum infection. Cerebral malaria, hypoglycemia, metabolic acidosis, severe anemia, convulsions, mental disorientation, coma, and finally death are some of the potential effects(Tangpukdee et al., 2009).Many of these symptomatic manifestations are still not well understood. Even though less than 1% of instances of severe(Ladhani et al., 2007). Malaria results in fatalities; the disease still causes a significant number of deaths each year(Ladhani et al., 2007).

*Figure 2.3*symptoms of Malaria

Figure 2.3 depicts the common symptoms and the bodily areas affected by malaria(World & Report, 2019).

Acute renal failure (ARF) is a consequence that occurs in fewer than 5% of P. falciparum malaria patients who live in areas where malaria is common, and though it affects up to 30% of cases in malaria-endemic places, it is far more prevalent among travelers from non-endemic nations, and it has a fatality rate of up to 45%(World & Report, 2019).ARF frequently presents with symptoms including pain, nausea, and vomiting in addition to electrolyte abnormalities and increased urine protein output.

Intravascular hemolysis, intravascular coagulation, sepsis, cytoadherence of infected red blood cells, and dehydration are probably the main reasons. The precise mechanism behind malarial ARF is yet unknown(World & Report, 2019).The rate of hypoglycemia, on the other hand, varies by age group and area. For example, 30% of African children and 8% of South-East Asian adults have hypoglycemia. Problems with hypoglycemia have been linked to cytokines that stop gluconeogenesis from happening, lower glucose levels caused by hunger, and parasites using up glucose. Malaria with serious metabolic acidosis is one of the main symptoms. This is often thought to be the cause of death in both children and adults. Malarial acidosis has no known cause, but the main signs of it are high levels of lactate and ketoacids in the body and a bad metabolism of these acids. Acidosis is often linked to cerebral malaria and is the main cause of death from all the problems that come up after serious malaria(World & Report, 2019).Alteration in consciousness, coma, and the presence of asexual parasite forms in peripheral blood smears are symptoms that distinguish cerebral malaria (CM). African children experience the majority of CM cases, and although CM is the most extensively researched complication of severe malaria, it remains a condition that is not completely understood. CM carries a high mortality rate, even with prompt treatment, and often results in lasting brain damage, leading to long-term neurocognitive impairments in some survivors(Development & Responsibility, 2007).

2.4 Diagnosis

Due to the vague and general symptoms associated with Plasmodium infection, it is crucial to have precise and swift diagnostic methods to lower the resulting health issues and fatalities(T. W. Health & Foundation, 2010).While a clinical diagnosis of malaria based on physical examination can be indicative, it should always be validated through laboratory tests. Therefore, this confirmation is essential to guide malaria control efforts and to prevent the inappropriate treatment of individuals who are not infected, as this misuse of medications can lead to the development of drug resistance(T. W. Health & Foundation, 2010).A variety of methods, including antigen-based rapid diagnostic tests (RDTs) and microscopy, are frequently used to diagnose malaria. Because microscopic inspection of thick and thin blood smears is accurate and reliable in real-world circumstances, it is regarded as the gold standard for diagnosing malaria. Thin blood

smears are helpful in assessing the amount of parasitemia, whereas thick blood smears are utilized for the initial diagnosis (Lagerberg, 2008). Nevertheless, there are several drawbacks to microscopy, such as the need for specific tools and qualified individuals to carry out the examinations(Lagerberg, 2008).Rapid diagnostic tests, or RDTs, work by detecting antigens or enzymes unique to the malaria parasite; some of these tests are even capable of differentiating between various species of Plasmodium, and the RDTs are often more sensitive than classical microscopy. Because they don't require specialist equipment or experienced staff to operate, they have the advantages of speed and simplicity(Stephen et al., 2017).

2.5 Treatment

Since there isn't yet a vaccine that can effectively protect against malaria, chemotherapy is still the only realistic way to treat and stop malaria infections (Stephen et al., 2017).One of the following seven drug classes includes chemotherapy: aryl-amino alcohols (quinine, quinidine, mefloquine, and halofrantrine), artemisinins (artemisinin, artemether, and artesunate), hydroxynaphthoquinones (atovaquone), antimicrobials (doxycycline and clindamycin), 8-aminoquinolines (primaquine), 4-aminoquinolines (chloroquine, amodiaquine, and piperaquine), and antifolates (pyrimethamine, sulphadoxine, and proguanil) (Development & Responsibility, 2007).

2.5.1 Antifolates and hydroxynaphthoquinones

Since folate production is largely species-specific, it is a unique and important target for chemotherapy. An aromatic pteridine ring linked to para-aminobenzoic acid (PABA) and one or more glutamate residues make up folate, an essential vitamin, and it is an essential co-factor for many different activities, such as the synthesis and degradation of many amino acids and the production of purines and pyrimidines needed for DNA replication(Thomas, 2014).Antifolates are a class of antimalarial medications that impede certain enzymes involved in the synthesis and metabolism of folate (Scholar, 2007). Dihydropteroate synthase (DHPS) and dihydrofolate reductase (DHFR) are two examples of these enzymes, and the enzyme DHPS, which is not expressed in humans, produces dihydropteroate from pteridine pyrophosphate and para-aminobenzoic acid

(PABA). Tetrahydrofolate (THF) is produced in the meantime by DHFR from dihydrofolate (DHF). Antifolates were shown to be effective as early as the 1930s, and by the 1940s, companion medications and better pharmacokinetic profiles had been created. Because extremely potent quinoline derivatives were readily available, antifolates were not extensively employed at the time, despite their efficacy(Scholar, 2007).

2.5.2 Antimicrobials

Several medicines, like clindamycin and doxycycline, have been shown to work against plasma membranes. It is not recommended to use these medicines alone to treat malaria because they are not very good at killing malaria parasites and take a while to work(Lagerberg, 2008).The synthetic form of doxycycline is developed from the broad-spectrum antibiotic oxytetracycline, and tetracyclines are assumed to exert their antimicrobial actions via inhibiting protein synthesis because they are primarily bacteriostatic drugs. Similar antimicrobial action is exhibited by doxycycline against a variety of gram-positive and gram-negative species, including parasite Plasmodium(Thomas, 2014).It has been discovered that doxycycline is effective against P. falciparum's asexual erythrocytic forms but not against its gametocytes, and it's still unclear exactly how the medication works. The most frequent adverse effect is diarrhea(Development & Responsibility, 2007).As a member of the Lincomycin group, clindamycin is another bacteriostatic antibiotic that is safe to use on pediatric patients, and by blocking the ribosomal component 50S, it prevents bacteria from synthesizing proteins. For clindamycin, nausea, vomiting, and diarrhea are the most often reported adverse effects(Development & Responsibility, 2007).

2.5.3 8-Aminoquinolines

Although there are a number of synthetic 8-aminoquinolines available, only primaquine is now used, and the only antimalarial that is effective against the parasite in both its liver and sexual blood stages is primaquine(Scholar, 2007).It is noteworthy that the efficacy of this treatment against the latter stage is limited since it is only observed at

levels that are widely regarded as too hazardous for general usage. Primaquine has two functions: it is used to treat P. vivax's dormant hypnozoites and to prevent cancer. It's amazing that primaquine has been around for more than 60 years(Scholar, 2007).

2.5.4 Aryl-amino alcohols

The class of aryl-amino-alcohols includes a variety of substances, both synthetic and natural. Mefloquine, quinidine, halofantrine, and quinine. As early as 1630, quinine andquinidine, two naturally occurring alkaloids derived from the cinchona tree's bark, were among the earliest antimalarial medications used to treat malaria(Talapko et al., 2019).

2.5.5 4-Aminoquinolines

4-Aminoquinolines are members of a class of chemicals that share the quinoline framework, which is present in many naturally occurring and manufactured drugs that have pharmacological activity. This group includes piperaquine, amodiaquine, and chloroquine. Because of these drugs' exceptional clinical efficacy, little host damage, simplicity of administration, andSimple, economical manufacturing has become more popular. However, these substances are essentially useless for chemotherapy due to the extensive emergence of resistance, especially against chloroquine (ECDC, 2017).

2.5.6 Artemisinin and derivatives

It is made up of three isoprene units connected to cyclic organic esters with a peroxide bridge. Artemisinin (17), which is also called qinghaosu, is a sesquiterpene lactone. It is derived from the leaves of the sweet wormwood plant (Development & Responsibility, 2007). The medicinal herb extract, referred to as qinghao, has been used for approximately two millennia in the treatment of fevers. It was initially documented in the "52 prescriptions" found in the tomb of the Mawangdui Han Dynasty. The first recorded use of Qinghao for treating malaria dates back to the year 341 AD. The

antimalarial properties of qinghao were rediscovered in 1971(Development & Responsibility, 2007).

2.5.7 Chalcone compounds

The genome sequencing of Plasmodium has identified a number of unique targets that may be used in chemotherapy. Malarial cysteine proteases and parasite-induced permeation pathways are two of these targets. Red blood cells with an infection can activate pathways known as "parasite-induced permeation pathways," which increase the permeability of the cells to essential nutrients like carbohydrates, vitamins, and amino acids. Since these pathways are lacking in healthy cells, developing drugs targeting them would be appealingappealing(FMOH, 2017).

2.5.8 Hybrid drug theory

In order to construct a chemical entity with two or more structural domains, each with different biological roles and dual activities that are more medicinally or therapeutically effective than the individual components, hybrid molecules combine two medications into a single molecule(Griffith et al., 2007).The hybrid can interact with the target in essentially three different ways, and the way hybrid molecules behave depends on how they interact with two targets. These targets can be in close proximity to each other or be connected to one another and in a different case, the two targets are not part of the same organelle and operate separately. Finally, in the third case, the hybrid chemical uses two different pharmacophores to target the same biological entity at the same time—a feature that is sometimes compared to using a "double-edged sword (T. H. E. N. S. Health & Hackett, 1940).

2.6. Control and prevention

Key tactics against malaria infection include controlling and preventing both the parasite (Plasmodia) and its vector, Anopheles. Insecticide-treated nets (ITN), indoor residual spraying (IRS), immunization, adaptive immunity, and education are among the most significant control and prevention measures included in this section. Contrarily,

chemotherapy is covered in the section on chemoprophylaxis(Smith, 1928).Two of the most significant methods for controlling malaria vectors are ITNs and IRS. According to the World Health Organization (WHO), in 2011, only 11% of people at risk of malaria had protection from ITNs, and approximately 53% of individuals in malaria-endemic regions had access to an ITN. Unfortunately, there was a shortage of approximately 90 million nets in 2012. It's crucial to remember that an ITN usually has a five-year lifespan. (World & Report, 2019)**.**Health education strategies are crucial for empowering communities to actively contribute to malaria prevention initiatives. Effective awareness campaigns can educate those residing in malaria-prone regions about the disease's attributes, its mode of transmission, and the measures to be taken for its prevention. These approaches enhance the control and preventative measures implemented by campaigns such as the Roll Back Malaria (RBM) campaign. Moreover, providing comprehensive instruction on the proper utilization of ITNs can effectively reduce the global incidence of malaria.(World & Report, 2019).

2.7. Conclusion

Malaria is a complex disease that will pose a serious health risk for many years to come, even with the best of prognoses. Many epidemiological and ecological factors influence the effect of malaria on human well-being(Development & Responsibility, 2007).

CHAPTER THREE

MATERIALS AND METHODS

3.0 Study Design

The researcher will be extracting medically recorded data from Near East University Hospital for the last eight years as a retrospective study design, and after the data collection recorded from the hospital, the data samples will be analyzed using SPSS version 25 to analyze our studies. Whichwas conducted on 25 samples of malaria diagnosed in foreign patients. The data for this result was collected between 2016 and 2023. The age range of the samples utilized in this research was 19 to 42 years. The present study was carried out in the microbiology laboratory department of Near East University Hospital, with a specific concentration on outpatient visitors to our institution. The research sample consisted of twenty-five clinical specimens that were procured from patients across multiple nations, such as Turkey, Nigeria, Pakistan, the Congo, and Sudan.

3.1 Tools and equipment

The following equipment was utilized in this study: RDT cassettes, gloves, alcohol disinfection swabs, lancets, a register, microscopically slides, and a microscope.

3.2 Specimens Collection

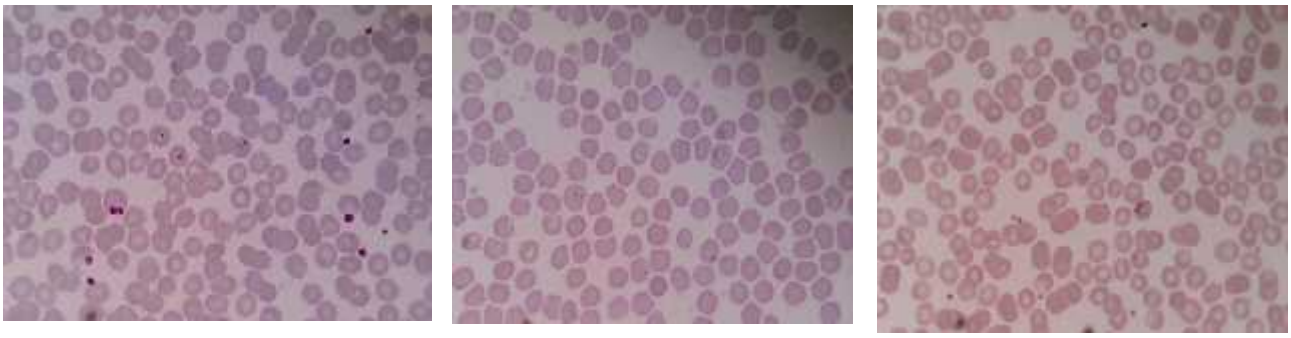
The research sample consisted of twenty-five clinical specimens that were procured from patients across multiple nations, such as Turkey, Nigeria, Pakistan, Congo, and Sudan from 2016 to 2023.

3.3 Specimen Processing

A blood collected from foreign patients thick and thin blood smears prepared and stained with Giemsa and investigated under microscope and initial identification of malarial parasites was conducted using conventional microbiological techniques. The blood samples obtained were collected from international patients through test tubes Giemsa staining, morphological categorization, and microscope identification came after the use of rapid diagnostic test (RDT) cassettes for analysis.

3.4 Morphology

Malarial parasites go through four different stages of development inside a human host: hepatic schizonts, intraerythrocytic trophozoites, schizonts, and gamonts. In mosquitoes, these parasites undergo three developmental stages, namely ooziness, oocysts, and sporozoites.The microbiology laboratory at Near East University Hospital has conducted numerous morphological identifications using microscopic examination.



A. Plasmodium falciparum. B. Plasmodium ovale. C. Plasmodium vivax.

Theabove picture results demonstrate three different microscopic investigations and reveals the unique features of three malaria parasites. The presence of various ring forms in individual red blood cells and its distinctive applique form help to identify Plasmodium falciparum. Plasmodium ovale is characterized by oval-shaped red blood cells and the presence of Schüffner's dots. Large amoeboid trophozoites, enlarged red blood cells, and Schüffner's stippling are all indicators of Plasmodium vivax. Every species displays distinct morphological indicators that suggest the presence of a malaria infection.

3.5 Giemsa staining procedure

Giemsa staining is an extensively employed technique in the field of cell identification and research, specifically in the detection of malaria-causing parasites like Plasmodium. The methodology commences with the preparation of a stain of thin blood on a microscope slide. Methanol is used to attach the smear after it has been allowed to air-

dry, preserving the cellular adhesion and structure on the slide. After the fixation procedure, the slide is stained with Giemsa stain, which is a diluted solution of methylene blue, eosin, and azure B. The slide is dyed to allow the dye to penetrate and subsequently attach to cellular components after a specific amount of time, often 30 to 45 minutes. Different cells and parasites found in the blood smear absorb the stain differently; the nuclei show a dark blue-purple staining pattern, but the cytoplasm shows softer colors. The slide is gently rinsed with water to remove any remaining color after staining, and then allowed to air dry. The slide is then ready for microscopic examination, where differences in color and morphology help identify and examine the parasites or cells that are present.

3.6 The steps for using the cassette

1. In the first step of the test, the patient's blood is mixed with a lysing agent in a well or test strip. Because of this, the red blood cells break, letting out more parasite protein.
2. A target antigen-specific dye-labeled antibody is on the nitrocellulose strip or in the plastic well of the strip. The test strip gets a small line of target-antigen-specific antibody added to it. There is also an antibody or antigen in the control line that is specific to the labeled antibody.
3. Blood and water that were already on the strip or in the well are mixed with a labeled antibody and pulled along the strip, going over the lines where the antibody is bound.
4. The test line will pick up and store a part of the labeled antibody-antigen complex when it recognizes an antigen. Extra antibody that has been labeled builds up on the control line. If you can see a control line, it means that the tagged antibody has gone all the way through the strip and passed the test line. This shows that some of the antibody that isn't bound is still connected to the dye and that some of the antibody's ability to catch things is still there.
5. When there are few parasites present (low antigen concentration), the number of dye particles that accumulate on the line will affect the test band strength. Higher parasite numbers may make the control band less intense because the test band picks up more tagged antibodies before it gets to the control.

3.7 Statistical Analysis

SPSS version 25 was used to analyze the study's results.

CHAPTER FOUR

RESULTS

4.0 Findings

Table 4.1Demographic variables of Malarial patients

N=25	Frequency	Percent	
Years	2016.0	1	4.0
	2017.0	1	4.0
	2018.0	2	8.0
	2019.0	9	36.0
	2021.0	4	16.0
	2022.0	6	24.0
	2023.0	2	8.0
	Total	25	100.0
	Mean	24.160	
	Std. Deviation	6.4335	
	Median	22.000	
Age	Maximum	42.0	
	Minimum	17.0	
	Range	25.0	
Gender	Female	7	28.0
	Male	18	72.0
	Total	25	100.0
Nationality	Congo	1	4.0
	Nigeria	18	72.0
	Pakistan	2	8.0
	Sudan	2	8.0

	Turkey	2	8.0
	Total	25	100.0
	Total	25	100.0

The table 4.1 presents a summary of the age distribution among individuals diagnosed with malaria. People between the ages of 19 and 30, who made up 80% of the population overall, were the demographic group most affected by the cases. These age groups—those between 31 and 40 years old and those between 0 and 18 years old—made up 12% and 4% of the population, respectively. People between the ages of 41 and 50 had the least effect, with a rate of 4%. No cases were found in people 51 to 100 years old. While the age distribution of patients was Mean 24.160, Std. Deviation 6.4335, Median 22.000, Maximum 42.0, Minimum 17.0. While presents a concise overview of the gender distribution among individuals affected by malaria. The data reveals that of the 25 patients, 18 are male, accounting for 72% of the total, while 7 are female, making up 28%. The findings indicate a greater occurrence of malaria among the male participants in the study sample. The table is crucial for comprehending the demographic distribution of the disease's impact based on gender. While national distribution of patient's malaria 1(4%) was Congo, 18(72%) were from Nigeria, 2(8%) were from Pakistan, 2(8%) were from Sudan, and 2 (8%) were from Turkey.

Table 4.2 Distribution of malarial patients

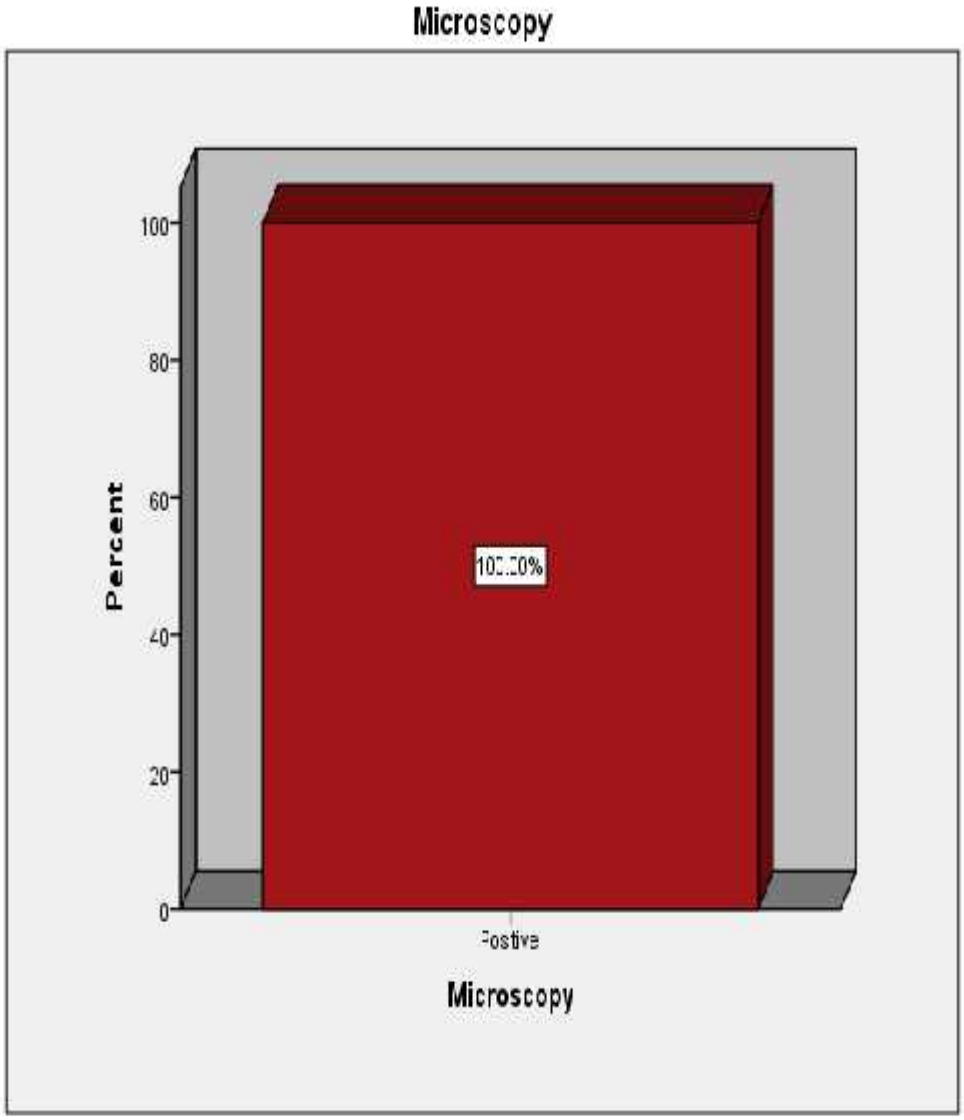
N=25	**Frequency**		**Percent**
Microscopy	Positive	25	100.0
	Pan	1	4.0
	Pf	19	76.0
Antigen test	Pf+Pan	2	8.0
	Pv	3	12.0
	Total	25	100.0
Plasmodium species	Plasmodium falciparum	21	84.0
	Plasmodium	1	4.0

ovale			
Plasmodium vivax	3		12.0
Total	25	100.0	

According to table 4.2 the Microscopy results of the all patients 25(100%) were malaria positive. the Antigen test the majority of the patients 19(76%) were pf positive, 3(12%) were Plasmodium vivax positive, while only 2(8%) were pf+pan positive. Furthermore, Plasmodium species

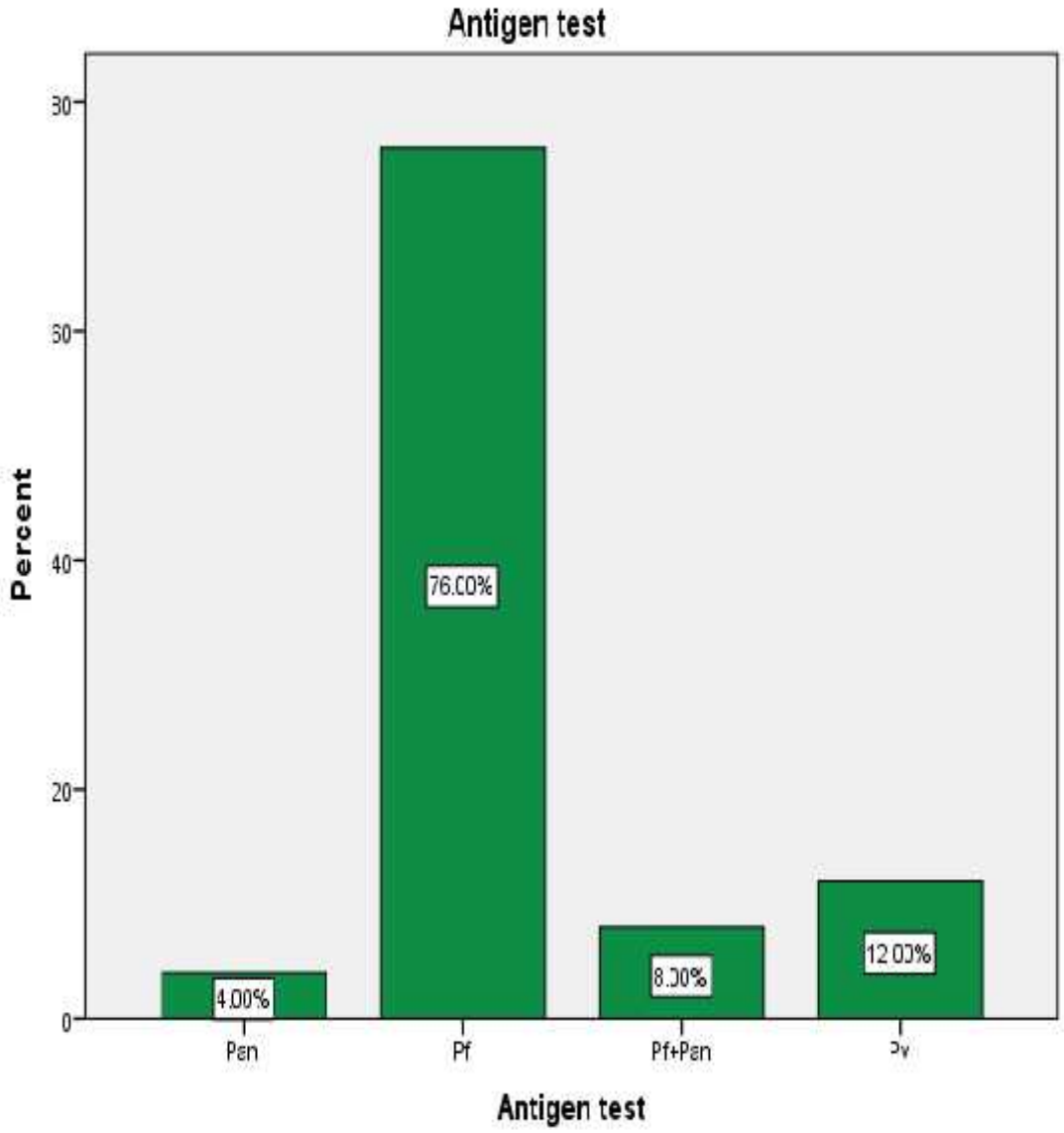
Test the majority of the patients 21(84%) were Plasmodium falciparum positive, 3(12%) were Plasmodium vivax positive while ony 1(4%) was Plasmodium ovale positive.

Figure 4.1 microscopical test of the patients



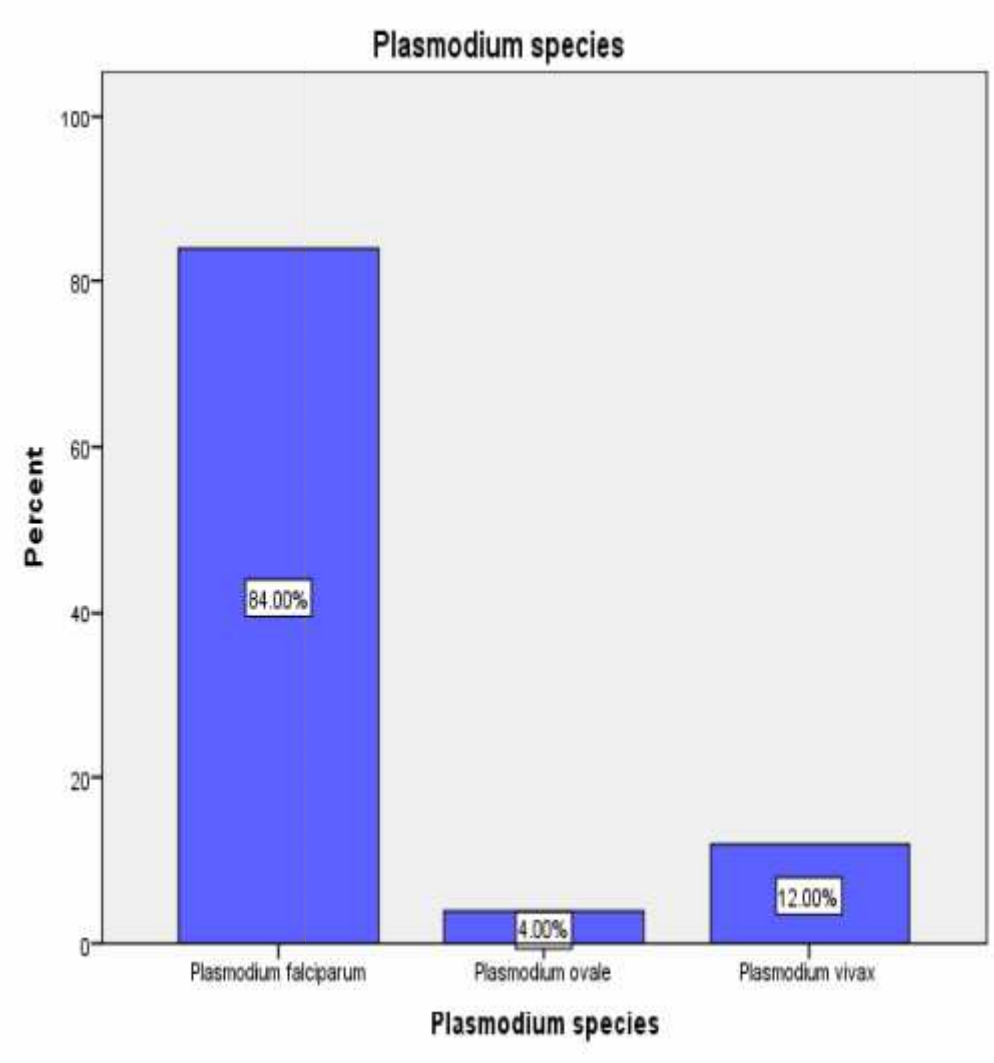
According to figure 4.1 the Microscopical test results shows that all the patients Malaria positive.

Figure 4.2Antigenic test of the patients



According to figure 4.2 the antigen test results, majority of the patients 19(76%) were Pf positive, 3(12%) were Plasmodium vivax positive, 2(8%) were pf+pan positive while only1 (4%) was Pan positive.

Figure 4.3plasmodium species test



According to figure 4.3 shows that Plasmodium speciestest and the majority of the patients 21(84%) were Plasmodium falciparum positive, 3(12%) were Plasmodium vivax positive while only 1(4%) was Plasmodium Ovale positive.

Table 4. 3Clinical outcomes of malarial foreign patients

N=25	Frequency		Percent
Fever	Positive	25	100.0
	Negative	2	8.0
Chills	Positive	23	92.0
	Total	25	100.0
	Negative	4	16.0
Anorexia	Positive	21	84.0
	Total	25	100.0
Tiredness	Negative	4	16.0
	Positive	21	84.0
Headache	Total	25	100.0
	Negative	10	40.0
	Positive	15	60.0
	Total	25	100.0
Body aches	Negative	9	36.0
	Positive	16	64.0
	Total	25	100.0
Diarrhea	Negative	18	72.0
	Positive	7	28.0
	Total	25	100.0
Abdominal pain	Negative	17	68.0
	Positive	8	32.0
	Total	25	100.0
Weight loss	Negative	25	100.0
Splenomegaly	Negative	16	64.0
	Positive	9	36.0
	Total	25	100.0
Hepatomegaly	Negative	16	64.0
	Positive	9	36.0

Total	25	100.0

According to table 4.3 The most prevalent symptoms of the condition include fever which all patients were positive, 23(92%) of the patients were feeling chills while the remaining 2(8%) were not, 21(84) were feeling anorexia while the remaining 4(16%) were not, 21(84) were feeling tiredness while the remaining 4(16%) were not, 15(60%) were feeling Headache while the remaining 10(40%) were not, 16(64%) were feeling body aches while the remaining 9(36%) were not, 7(28%) were Diarrheal positive while 18(72%) were negative, 8(32%) were feeling abdominal pain while 17(68%) were not, moreover 9(36%) were seen Splenomegaly and 9(36%) were seen Hepatomegaly.

CHAPTER FIVE

CONCLUTIONS, RECOMMENDATIONS

5.1 Conclusions

The thesis's extensive data demonstrate that malaria is a serious global health issue. There's a big risk of malaria, especially in places that are warm or subtropical. Anopheles mosquitoes spread the parasite Plasmodium, which is primarily responsible for it. From 2016 to 2023, this project looks into how malaria affects, spreads, and is treated in people who are not from Northern Cyprus who go to the Near East University Hospital.According to the data, malaria is more common in men (72% of reported cases are male), and most of those cases (80%) happen to people aged 19 to 30. Several things, like travel habits and work exposure, may have led to the observed demographic trend. The study looked at different types of Plasmodium and found that Plasmodium falciparum, which is known for being very dangerous, is very common. There are also obvious spikes in some months, which suggests that transmission changes with the seasons.The study's clinical results show that malaria can show up in many ways, from mild signs like fever and chills to more serious conditions like acute renal failure and cerebral malaria. The numbers above show how important it is to find problems quickly and act to stop bad things from happening, like death. Test results from several countries show how geography and the environment can affect malaria. They also show that people with malaria can have a wide range of symptoms.The study reinforces how important it is to keep an eye on things all the time, use cutting-edge testing tools, and have effective malaria treatment plans. It also shows how important it is to learn more about malaria and take steps to stop it, especially in places where it is widespread. Because the study had some flaws, like a small sample size and a focus on a small area of the world, it shows that we need more all-around research to fully understand how malaria affects people around the world. Overall, this study adds a lot to what we know about how malaria spreads, its signs, and how to treat it. It shows how important it is for the whole world to keep working on malaria research, prevention, and control.

5.2 Recommendations

Between 2016 and 2023, a big study was done at the Near East University Hospital in Northern Cyprus. The study made a lot of suggestions for future research into malaria.Programs for public health that are specifically targeted: Based on the observed demographic trends, some public health initiatives may be more successfully implemented. Preventive measures and educational campaigns should target the most vulnerable people, such as young men and those who travel or work in areas where they are more likely to contract malaria.New Approaches to Treatment and Diagnosis: Plasmodium falciparum's prevalence and the range of malarial clinical manifestations necessitate improved diagnostic techniques. These should be taken in addition to effective treatment programs, especially in regions where malaria is endemic.Understanding of and Ability to Adjust to Seasons: Since the study discovered seasonal peaks in malaria transmission, there might be a need for heightened awareness and preparedness during these times. This would mean dedicating more personnel and medical supplies during the months when the rate of transmission is highest.Public Instruction and Awareness Programs: It is crucial to carry out public education programs to raise public awareness of the indications, symptoms, transmission, and prevention of malaria, especially in endemic areas. These commercials should be appropriate in terms of language and culture.Finance for Anti-Malaria Initiatives: It is imperative that malaria prevention initiatives continue to get funding. The aforementioned measures encompass financing programs aimed at controlling mosquito populations, conducting studies to develop vaccines, and providing preventive drugs to susceptible communities.Strategic planning and implementation: Governments and health organizations should develop and implement policies with the purpose of eradicating malaria. This includes funding for scientific research, improvements to the healthcare system's infrastructure, and aid for areas impacted by malaria. To summarize, the study offers valuable knowledge about the spread of malaria in Northern Cyprus and emphasizes the necessity of a comprehensive strategy to tackle this ongoing worldwide health issue. Implementing these recommendations can lead to substantial progress in reducing the worldwide and local prevalence of Malaria.

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Name	Name of the Institution where take place	Year
Microbiology Laboratory Practical	Adal medical university	2020

Training		
Phlebotomy	Allison online	2021
Infection and immunity	Open University	2018
Virtual conference on Immunology aspects of coronavirus: Epitope Prediction and *insilico* vaccine design organized by LLB-School	LLB-School, University of Cambridge, United Kingdom	2020

Computer Knowledge

Program	**Use proficiency**
SPSS	Good
Common Computer Programs and Skills	Excellent

languages

Languages	**Speaking**	**Writing**	**Reading**
Somali	Excellent	Excellent	Excellent
English	Excellent	Excellent	Excellent
Arabic	Good	Excellent	Excellent