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SEROPREVALENCE OF HCV INFECTION AND POTENTIAL INFLUENCING FACTORS IN NORTHERN CYPRUS

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DEDICATION

To my Beloved Parents, Brothers and Sisters (Zainab, Amin, Abdallah, Abdurrahman, Ramla, Umhani) and Friends (Fatima, Qadra).

Specially To my dear parents Ali and Mariam, who always encourage me to higher ideas of life, took pains and sacrificed their comforts for my brilliant future. And because of their support, help, prayers, and love I got what I'm in.

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ABBREVIATIONS

HCV	Hepatitis C Virus
RNA	Ribonucleic Acid
HCC	Hepato-cellular Carcinoma (HCC)
U.S	United States
ORF	Open reading Frame
UTR	Un-translated Regions
NANB	Non- Hepatitis A and B
RVR	Rapid Virological Response
IFN	Interferon
WHO	World Health Organization
SPSS	Statistical Package of Social Sciences
ELISA	Enzyme-linked Immunosorbent Assay

ABSTRACT

In the United States, hepatitis C virus (HCV) infection is a primary cause of liver-related mortality, cirrhosis, and hepatocellular cancer. HCV was discovered more than three decades ago, and a blood test for HCV was developed a few years later. Infections were an issue before the screening began, mostly as a result of blood contamination. Transfusion-related exposure and inappropriate injection administration are the most prevalent ways to get HCV. Acute infections are undervalued and under-reported in monitoring systems, which do not account for the probability of acute illness as a cause of HCV infection. The purpose of this study is to look at HCV, its risk Patients at a Northern Cyprus hospital in the Near East were tested for seroprevalence and other variables. For this study, a total of 10698 people without any health conditions were considered. With the use of the ELISA quantitative method, these participants were tested for HCV antibodies. For seropositive patients, the rate of seroprevalence was calculated using age and gender classifications. 7084 (66.2 percent) males and 3614 (33.8 percent) females were among the 10698 people who were contacted for the research and had their serum tested for HCV antibodies. Seroprevalence was 0.8 percent overall. Northern Cyprus has a low frequency of HCV, according to the research. In addition, elderly people have been found to be more vulnerable to infection than younger people. According to the age, patients ranging between 0-20 were positive 17(0,6%),21-40 were positive 42(,8%),41-60 were positive 10(,7%),>60 were positive 20(1,8%). Individuals' vulnerability to HCV infections has been raised by factors and behaviors such as the use of risky injections, particularly by traditional practitioners. According to data from the Near East University Hospital from 2017, there is still a danger of contracting HCV from individuals who are unaware that they have the condition. A combination of a risk assessment tool and the usage of the internet should be investigated to increase screening efficiency.

Keywords: Seroprevalence, HCV infection, HCV genotypes, Hepatitis, Northern Cyprus.

ÖZET

Amerika Birleşik Devletleri'nde, hepatit C virüsü (HCV) enfeksiyonu, karaciğer ile ilişkili mortalite, siroz ve hepatoselüler kanserin birincil nedenidir. HCV otuz yıldan uzun bir süre önce keşfedildi ve birkaç yıl sonra HCV için bir kan testi geliştirildi. Enfeksiyonlar, tarama başlamadan önce, çoğunlukla kan kontaminasyonunun bir sonucu olarak bir sorundu. Transfüzyonla ilişkili maruziyet ve uygun olmayan enjeksiyon uygulaması, HCV'ye yakalanmanın en yaygın yollarıdır. Akut enfeksiyonlar, HCV enfeksiyonunun bir nedeni olarak akut hastalık olasılığını hesaba katmayan izleme sistemlerinde göz ardı edilmekte ve yeterince rapor edilmemektedir. Bu çalışmanın amacı HCV ve riskine bakmaktır Yakın Doğu'da bir Kuzey Kıbrıs hastanesindeki hastalar seroprevalans ve diğer değişkenler açısından test edildi. Bu çalışma için herhangi bir sağlık sorunu olmayan toplam 10698 kişi değerlendirildi. ELISA kantitatif yönteminin kullanılmasıyla bu katılımcılar HCV antikorları için test edildi. Seropozitif hastalar için yaş ve cinsiyet sınıflandırmaları kullanılarak seroprevalans oranı hesaplandı. Araştırma için temasa geçilen ve serumlarında HCV antikor testi yaptırılan 10698 kişiden 7084'ü (yüzde 66,2) erkek ve 3614'ü (yüzde 33,8) kadındı. Seroprevalans genel olarak yüzde 0.8 idi. Araştırmaya göre, Kuzey Kıbrıs düşük bir HCV sıklığına sahiptir. Ek olarak, yaşlıların enfeksiyona karşı genç insanlara göre daha savunmasız olduğu bulunmuştur. Bireylerin HCV enfeksiyonlarına karşı savunmasızlığı, özellikle geleneksel pratisyenler tarafından riskli enjeksiyonların kullanımı gibi faktörler ve davranışlar tarafından artırılmıştır. Yakın Doğu Üniversitesi Hastanesi'nin 2017 yılı verilerine göre, hastalığından habersiz kişilerden HCV'ye yakalanma tehlikesi hala var. Tarama verimliliğini artırmak için bir risk değerlendirme aracı ve internet kullanımının bir kombinasyonu araştırılmalıdır.

Anahtar Kelimeler: Seroprevalans, HCV enfeksiyonu, HCV genotipleri, Hepatit, Kuzey Kıbrıs.

CHAPTER ONE

1.0 INTRODUCTION

1.1. Overview

Hepatitis C virus (HCV) infection is a main cause of liver-related deaths, cirrhosis, and hepato-cellular carcinoma in the United States (Ly *et al*., 2016; Allison *et al.,* 2015). Screening of blood that is being supplied was not considered initially until 3 years after HCV was discovered. Up until then, infection as a result of the blood products had become the major concern (Lynch & Wu, 2016; Smith *et al*, 2012; CfDC, 1998). HCV infection can be contracted through exposure to blood percutaneously as a result of injections that are unsafe. HCV treatments were known for their side effects and these effects made the treatment to not be often used. Presently, the treatment options are becoming safer and tolerable and the curative therapies have become controlled, also making prevention a priority as well as the clinical management of HCV (Lynch & Wu, 2016). These advances are notable but it doesn't completely eradicate the morbidity and mortality rate which is associated with HCV.

Up to 20% of case related to acute hepatitis have been discovered to be of HCV, following this, up to 80% of the discovered acute infectious cases will develop to chronic infection. HCV cases globally take up to millions of individuals and the chronic hepatitis C patients are susceptible to concerns which are life threatening and are also vulnerable to liver disease like cirrhosis. Cirrhosis is developed in 20% of the cases and for up to 5%, the annual cases of hepato-cellular carcinoma (HCC) are prevalent in cirrhotic patients (Alberti *et al*., 1999; Hoofnagle, 2002; Chen & Morgan, 2006). A relation has been found with HCV and some hepatic manifestations such as diabetes mellitus type 2 and glomerulo-pathies (Carrozzo & Scally, 2014; Ozkok & Yildiz, 2014; Grimbert, 1996).

HCV causes severe chronic liver disease that can advance to cirrhosis and cancer and kills approximately 500,000 people worldwide each year. Although our insights into the molecular virology of HCV infection has advanced significantly, the precise molecular mechanisms underlying disease progression to fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) remain unknown. (Kishta et al., 2020).

Global burden of HCV infection has been estimated at 1.6 percent (range: 1.3–2.1 percent), which equates to 115 million (range: 92–149 million) individuals. However, not all of these individuals are presently infected with HCV; some have cured themselves of the virus either spontaneously or through treatment. Thus, the global viremic prevalence (that is, the proportion of individuals positive for HCV RNA) is lower, estimated at 1% (range: 0.8–1.14 percent) or 71 million (range: 62–79 million) individuals infected with HCV. (Manns et al., 2017). Prevalence rates are highest in developing poor countries in Africa and Asia, while developed, industrialized nations in Europe and North America have relatively low prevalence rates. Chronic infection rates are highest in Egypt, Pakistan, and China. Unfortunately, African countries, with the exception of Egypt, Morocco, and South Africa, lack reliable data. In these countries, the major route of transmission is believed to be unsafe injections using contaminated equipment, as in Egypt, where the HCV epidemic has been attributed primarily to the extended use of parenteral anti-schistosomal treatment (antimony potassium tartrate, tartar emetics) with nondisposable glass syringes for more than 30 years. Chronic HCV infection is the leading cause of cirrhosis and the leading reason for liver transplantation in Egypt. (Mohamed et al., 2015). Globally, people that are infected are an approximate of 27% for cirrhotic disease and 25% for HCC, these estimates are found in HCV already infected individuals (Perz *et al*., 2006). The patterns of HCV infection are in terms of region or location of the people as well as their temporal differences (Alter *et al.,* 2000). There are countries that have average number of prevalence of HCV and they include Spain and Australia among other countries but they differ when it concerns the age category prevalence. The middle age of 30-49 entails the greater prevalence of the infections in general while the ages lesser and more than that have lower prevalence United States of America (Alter *et al*., 1999; Armstrong *et al*., 2002). This pattern is similar to that observed in Australia as it was also discovered in the

country that the age range of HCV infection transmission is profound amongst young adults (Law *et al*., 2003). In countries such as United States and other countries with epidemiology that is perceived as likewise, more variations in the prevalence of HCV infection occurs amongst individuals that are already at risk of the infection (Alter, 2002; CfDC, 1998; Dore et al., 2003; Gérard *et al*., 2005; Payan *et al*., 2005). Increase in prevalence with the age category has been observed in Turkey and China as well (Domínguez *et al.,* 2001; Sun *et al*., 2001; Sun *et al*., 1999; Campello *et al*., 2002; Sagnelli *et al*., 2005). For the generation that is older, specifically the individuals within the age range of 50 years and above, the risk and prevalence of HCV infection is great and it has been like that for many years. The variations that occur for HCV prevalence are high when it is concerning geographical region of people in many countries with this pattern and regions with more endemic occurrences such as China and Italy that have a great population of the older persons have multiple prevalence of HCV in folds (Zhang *et al*., 2005; Di Stefano *et al*., 2002; Maio *et al*., 2000; Okayama *et al*., 2002).

High prevalence can be discovered in countries like Egypt and the prevalence keeps increase as people age but this doesn't mean that the HCV are only be seen within this age group, high rates of infection can also be seen among individuals of all ages (Perz *et al*., 2006; Abdel-Aziz *et al*., 2000). The risk to this infection started long before now and it is still continuous with difference in the region of the individuals (Perz *et al*., 2006; Medhat *et al*., 2002).

Acute infections are most times without symptoms or the symptoms show up later, this does not make diagnosing HCV easy to do, determining if a patient is infected by HCV is challenging. Over the years, the acute and chronic or resolved infection were not easily differentiated because some countries take the chronic infections more seriously and as well have ore data recorded on the chronic than the acute infections. This does not exclude the countries that have proper and effective surveillance systems, they also underestimate the rate at which HCV acute infection occurs (Hagan *et al*., 2002; Robotin *et al*., 2004; Spada *et al*., 2001). The rate at which this infection occurs in countries has been predicted with the help of mathematical models and they have defined the prevalence of this infection based on age

related factors. Chronic liver disease may occur when the infection has prevailed in an individual for years after the period, they became infected (Perz & Alter, 2006). The emergence and prevalence in U.S are one that can be said to be recent. The full magnitude of the presence of this infection which now has been linked to chronic liver disease has not been fully identified as people get infected increasingly and with life threatening symptoms (Armstrong *et al.,* 2000; Deuffic *et al*., 1999).

Looking into history of the HCV infection occurrence, countries like Italy had the emergence of the infection many years ago and it is believed that the magnitude of the HCV chronic disease case might have gotten to its highest level. However, the changes in disease transmission patterns that result in younger persons acquiring infection could result in future increases in chronic disease (D euffic *et al*., 1999). For decades now, Egypt has had risk which is still in play presently and the intensity of this highly prevalent infection will go on as time goes by (Deuffic-Burban *et al.,* 2006).

The overall prevalence of HCV infection in Cyprus is reported as 0.5% and the most dominant genotype in Cyprus was found to be genotype 1(S. Ashkani-Esfahani *et al.,2017*). Although Turkey was in the middle endemism, Northern Cyprus was of low endemism for the prevalence of the HCV. This was supported by *Altındiş* et al. who reported that anti-HCV prevalence was 0.46% (M. Altindis *et al.,2006*) and *Suer* et al. indicated that anti-HCV prevalence was 0% among blood donors (H.K. Süer *et al.,2012*). The prevalence of HCV in north Cyprus indicated that the highest prevalence was 0.9% (T. Şanlıdag *et al.,2016*).

HCV is a blood-borne virus that is not found in the majority of bodily fluids except those containing blood. Numerous risk factors contribute to the majority of HCV transmission globally, including unscreened blood transfusions, unsafe therapeutic injections, injection drug use, and reuse of contaminated medical equipment and other healthcare-related procedures. Developed countries have accumulated proof that injection drug use is the primary source of new HCV infections within their borders over the last few decades. In the majority of developing countries, unsafe medicinal injections and transfusions are likely to be the primary modes of transmission, particularly in countries where age-specific seroprevalence rates

indicate an ongoing risk of HCV infection. (AM, 2017). Due to the possibility of blood exposure in hemodialysis settings, patients on dialysis are at risk of contracting HCV from another patient. Unfortunately, HCV infections and transmissions persist in outpatient dialysis units. (Fabrizi F *et al.,2015*).

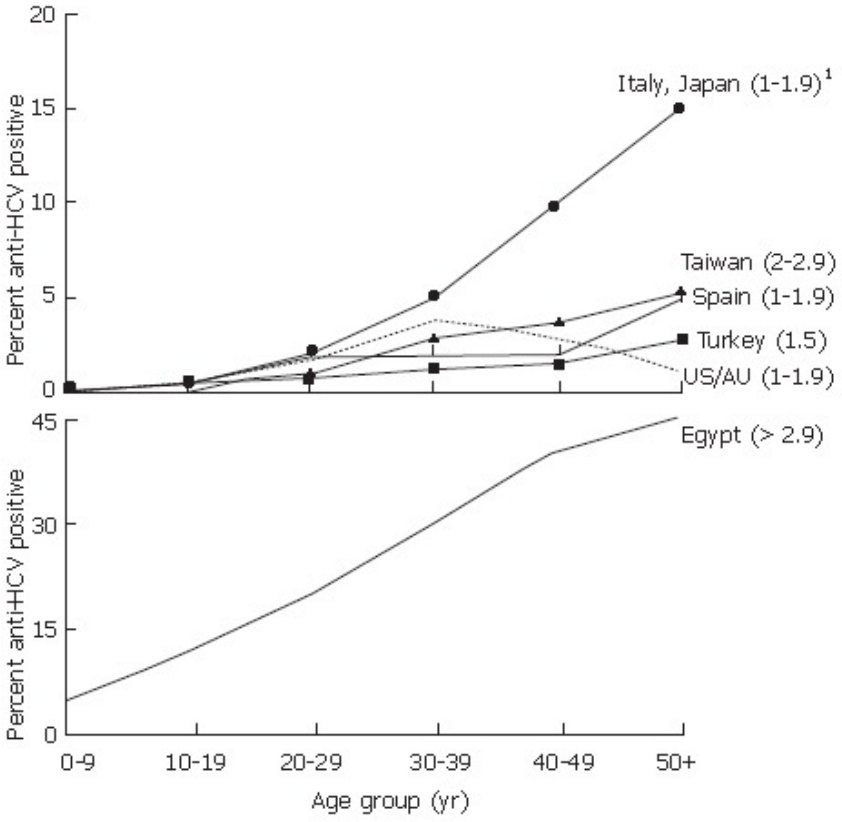

Figure 1: HCV epidemiology (*(Zein, N. N, 2000*)

1.2. HCV Morphology

HCV belongs to the family of Flaviviridae specifically referred to as Hepacivirus and comprises of a spherical shaped virus called RNA virus. The single positive-strand RNA genome has several thousands of nucleotides with large translational open reading frame (ORF). This gives room for encoding amino acids which are up to 3,000 and large polyprotein

in structures. These amino acids are bounded by highly conserved untranslated regions (UTR) (Choo *et al*., 1991) and their proteins that are of structure and those that are not of structures are produced as a result in different forms. There is the core protein which is responsible for structuring viral nucleocapsid with E1 and E2 as the glycoproteins.

There is the peptide which is short in membrane known as the P7 and is suspected to be making room for the release of the viral particles that are infectious while there are the six nonstructural proteins that take part in the processing of the poly-protein and the replication of the virus (Penin *et al*., 2004; Steinmann *et al*., 2007). In humans and chimpanzees, there is the outcome of acute and chronic hepatitis (high propensity). When these infections are not managed properly or treated, the chronic HCV has the ability to advance to cirrhosis and hepato-cellular carcinoma in some of the infected patients. There are genotypes and sub genotypes that belong to the HCV and these all have their differences in terms of the genes which responsible for encoding the envelope glycol-proteins. The envelope glycoprotein then contains “hypervariable” region (Levinson & Jawetz, 1996).

An attempt to understand what the life cycle of a virus can be uncertain as the growth was not done in a cell culture initially which makes it a bit difficult to predict what the lifecycle looks like. Fast forward to many years after, the virions of HCV have been created with cell structures and studied (Heller *et al*., 2005; Kato *et al*., 2007) with the aid of the electron microscopy (Yu *et al*., 2007). There are other viruses that belong to the same viral family as HCV and are capable of replicating in the cytoplasm while allowing for the translation of the RNA genome into large polyproteins. From this polyprotein, there are viral proteins which are formed and they are termed functional. To attain an effective anti-HCV therapy, it is essential to target the protease. The replication of HCV replication tallies with the HCV replication model in the liver which is enhanced by liver-specific micro-RNA. The liver-specific micro-RNA is also known as miR-122 and it functions to enhance the synthesis of Micro-RNAs which also enhance cellular mRNA synthesis in the cells in many tissues.

1.3.HCV Genome

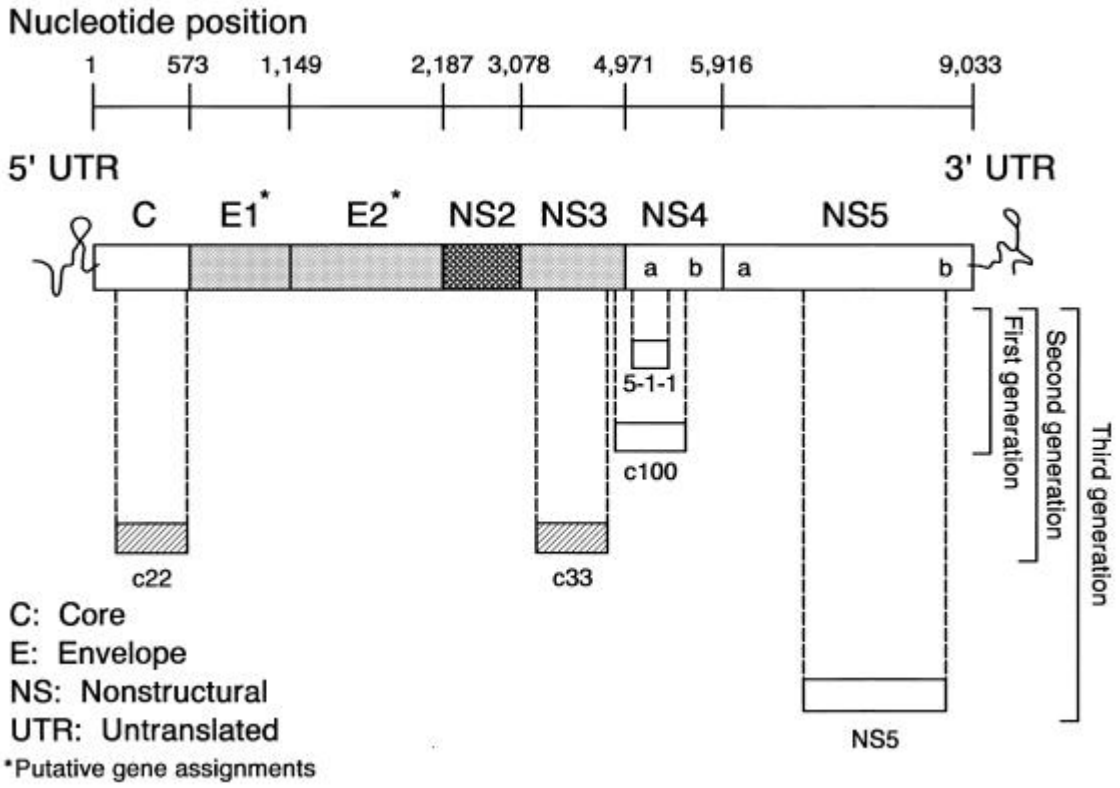

Figure 2: Genomic organization of HCV. ((Zein, N. N, 2000)

1.4. The Viral Replication Cycles

To understand the virology and life cycle of HCV, there have been investigations that have considered with the aid of hepatitis C virus culture systems as well as assays for replicating have been helpful. For therapeutics which is novel such as fusion, posttranslational processing, HCV replication, viral assembly, entry and attachment, there are some steps in

how the HCV is formed and when it is resolved and these are seen as targets that are relevant (93).

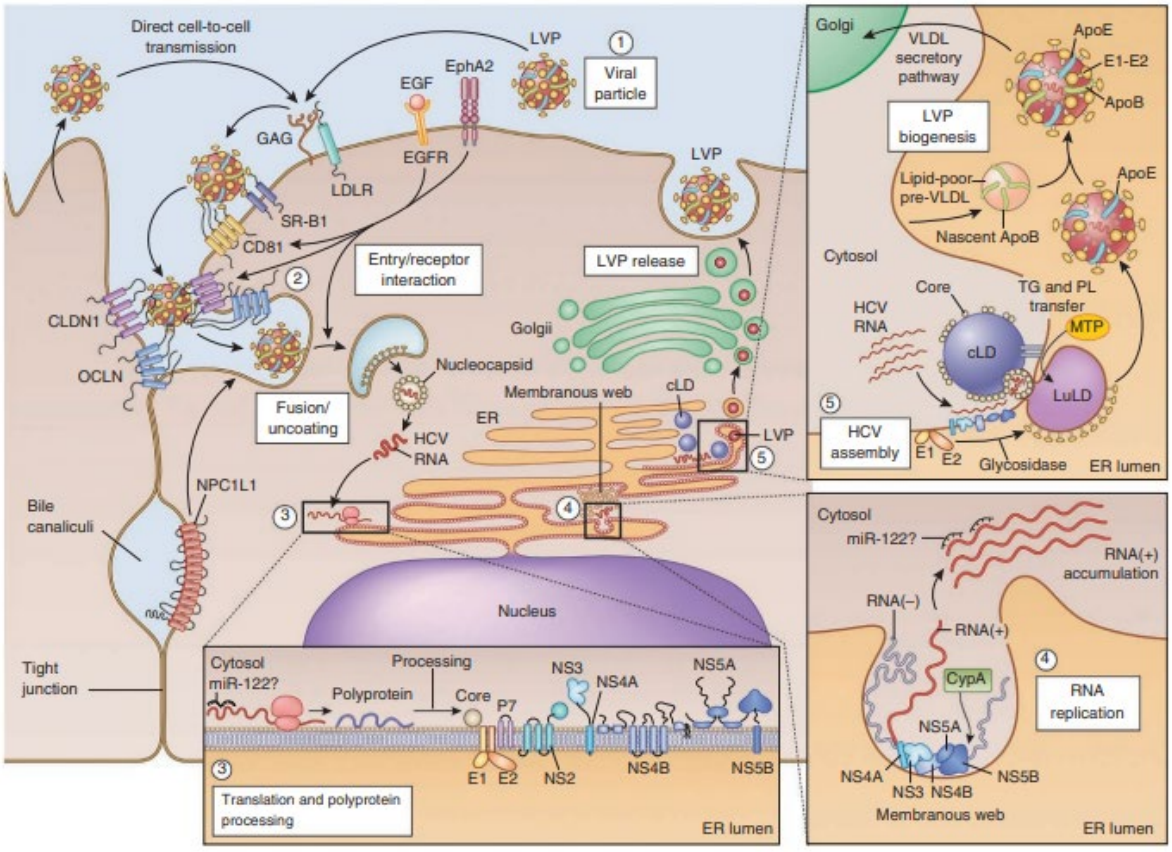

Figure 3: HCV life cycle and points of intervention (Scheel & Rice, 2013)

1.5.HCV Genotypes

HCV genotypes are of variants with genotype 1 being the one that is most prevalent and is characterized by the locations of the individuals with the least prevalent being genotype 4 (Gower *et al*., 2014; Messina *et al*., 2015). Genotype 1a is mostly found in countries such as USA and also found in Europe and 1b can be found in most countries in the world but is regarded as one with prevalence which is great in countries such as USA. For the Northern part of America and in Europe, the genotype 2 prevalent while for the prevalence of the HCV genotype 3 India is the country. 4 on the other hand, appears to be common in North Africa

and the Middle East and in the Middle East, the genotype 5 classification of HCV infection is reported.

These genotypes vary by their pathogenesis and their infectivity and this has an influence how the infection will advance to cirrhosis and then be diseased by hepatocellular carcinoma. The response to antiviral treatment is also a variant attributed to these different genotypes. It was discovered that HCV genotypes 1 and 4 are able to resist interferon-based therapies as compared to genotypes 2 and 3 that cannot (Chayama & Hayes, 2011; Chevaliez & Pawlotsky, 2007; El-Shamy & Hotta, 2014).

Consequently, HCV heterogeneity creates a challenge to the development of pan-genotypic anti-viral treatments. In addition, HCV heterogeneity obstructs the development of a successful vaccine to against all HCV genotypes. Of course, HCV heterogeneity could also affect viral diagnosis.

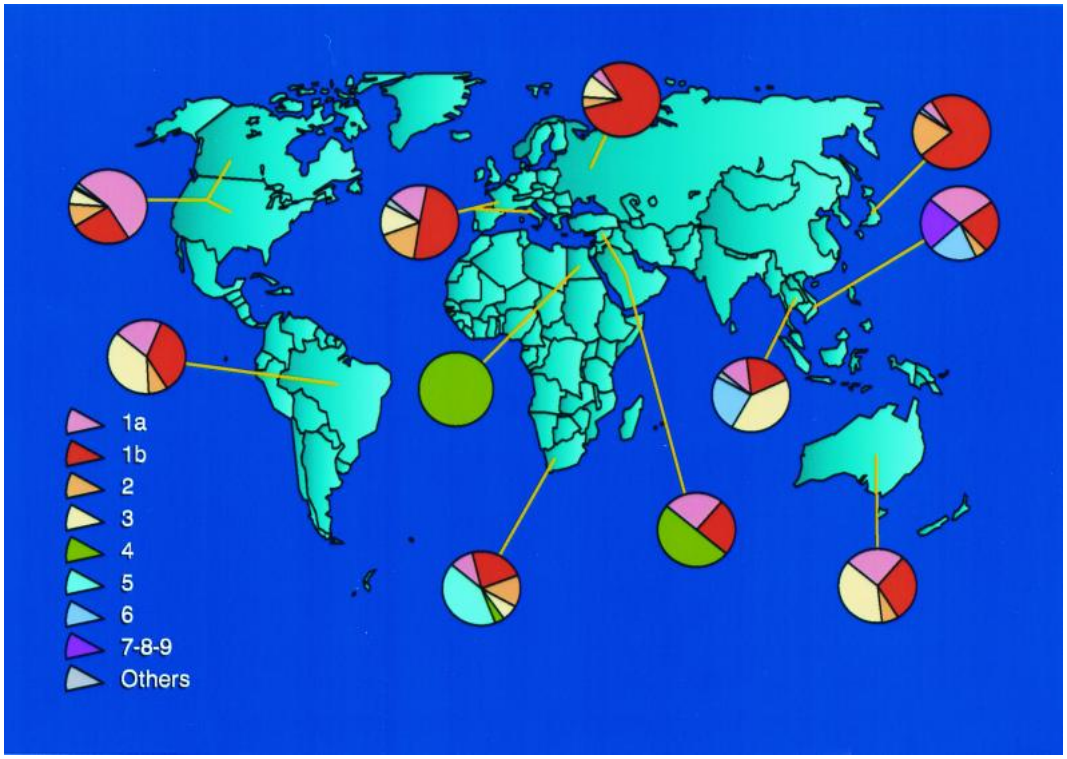

Figure 4: Geographic distribution of HCV genotypes (NN, 2000)

1.6.HCV Mutations

There are targets which are therapeutic for HCV infection and they include; NS3/4A protease, the NS5B polymerase, and the NS5A replication complex. The data set that was explored showed that the prevalence of variants that are resistant is low after analysis for mutation was done. The genotype that is detected often in patients infected with HCV is the genotype 1 HCV the NS3/4A mutations. These mutations are seen most especially in the HCV patients with genotype 1a (Costantino *et al*., 2015).

As a result of the presence of mechanisms of actions that vary for NS5B Inhibitors, there was no form of resistance on both sides of the inhibitors. A high genetic barrier was discovered to be possessed by Sofosbuvir. In this respect, few of the patients that failed the therapy manifested signs of resistant mutants after undergoing trials and clinical practical. Patients who failed the treatment showed a baseline C316N/H/F and these patients had 6HCV-genotype-1b patients. On the other hand, some of the patients were discovered to have HCV genotype 1a and they had a relapse. A great number of patients that undergone the newly emerging therapies such as IFN-free DAA were able to attain SVR. HCV genome on the other hand varies greatly with the production of multiple mutants that are resistant are brought forth during HCV replication.

1.7. Problem Statement

HCV can cause the liver to become inflamed and the majority of the patients are asymptomatic. It’s important to know the seroprevalence and the risk factors that can lead to HCV.

1.8. Justification of the Study

Studies related to seroprevalence and risk factors of HCV in patients have been done throughout the world however little information is available from Northern Cyprus. This investigation expected to evaluate data on the seroprevalence and risk factors of hepatitis C in patients in Northern Cyprus.

1.9. Objectives

The objective of this study is to investigate HCV; its risk factors and seroprevalence in patients at near east hospital in Northern Cyprus.

1.10. Significance of Study

Information from the hospital will help with distinguishing risk factors of hepatitis C in patients and the findings of this study will serve as guidance for the international communities operating in Cyprus. This study will also provide up to date information to future researchers about the prevalence of hepatitis C in North Cyprus patients.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1. History and Definition of Hepatitis C

Hepatitis as a virus initially became known as one that has two classes named the Hepatitis A type which is known as the infectious one while the other class is the Hepatitis B known as the serum. The absence of assays back then made the distinction of the two forms of hepatitis to only be carried out with incubation and studying the circumstances of exposure (Krugman *et al*., 1967). Researchers believed more in the occurrence of Hepatitis B, that decades ago when the studies on epidemiology and immunoglobulin prophylaxis research based on hepatitis occurring as a result of transfusion (Feinstone *et al*., 1975; Prince *et al*., 1974; Seeff *et al*., 1977). It was believed that this type of viral hepatitis had more probability of developing. These studies did not only stop there for Hepatitis A and B but became a foundation for potential discovery of hepatitis C many years after leading to the observation of the participants of the study with blood tests being carried as regularly as possible to detect biochemical abnormalities when they occur, especially the aminotransferases. Also, when the diagnosis of hepatitis was done, it was done based on these aminotransferases as serum level becomes elevated; the diagnosis was not based on jaundice onset or other symptoms which then gives an expansion on the disease spectrum. The blood samples that were under surveillance were as well stored in freezers to be used in future when carrying out research.

Acute hepatitis was discovered in the studies that have been carried out on transfusion and this occurred in the incubation period of hepatitis A and B and none of the symptoms were evident, not even jaundice was discovered as a symptom. Decades ago, the illness was referred to as hepatitis C briefly (Prince *et al*., 1974). The first Hepatitis B was also discovered within the same frame of time as the studies of transfusion was going on (Blumberg *et al*., 1965) hepatitis A's discovery was not very far off from the discovery of B virus (Feinstone *et al.*, 1973). Following these, there was now the development of assays which serological for the purpose of testing the samples that have been stored. This then led to the beginning of the anticipation that the hepatitis which occurs as a result of transfusion with hepatitis were discovered to be similar. For the purpose of detecting Hepatitis B, the samples were tested and they were non-reactive as well as when the samples were tested for Hepatitis A, giving rise to the acronym NANB meaning that it was negative reaction for both Hepatitis A and B hepatitis (Feinstone *et al*., 1975). A non-hepatic reaction was defined as an entity and with periodic inoculation of chimpanzees while making used of the sera that has been stored for future studies, there was a demonstration of how biochemical abnormalities develop in the animals showing an agent of transmission can be in form of NANB hepatitis (Alter *et al*., 1978; Tabor et al., 1978). Hepatitis C virus (HCV) was proven to be the causal agent after more than a decade later. HCV was identified with the conduction and development of serological tests (Choo *et al.,* 1989; Kuo *et al*., 1989). It was confirmed that NANB hepatitis and HCV were not different from each other as the sera that was stored was tested with the donors' and recipients' blood (Alter *et al*., 1989).

2.2. Pathophysiology

Hepatic cells do not get directly and instantly destroyed by chronic hepatitis C virus, the destruction of the hepatic cells stems an immune response that is capable of the induction of the total elimination of fibrosis and hepatic cell (Heydtmann *et al*., 2001). The CD4 and CD8T- cell responses of HCV are weaker in the chronic stage as compared to in the acute phase of the infection (Wedemeyer *et al*., 2002). This explains that the patents that have been discovered to have poor responses in the acute stage of the infection to have advanced phase of

the infection to chronic stage, they become chronic carriers of HCV while those who have good responses in acute stage can avoid being the chronic carriers of HCV.

2.3. Diagnostic Tests

For HCV infection, the diagnostic that can be carried out are classified into molecular tests which are for done for viral particles and serological assays for antibodies. The diagnosis for HCV is based on screening which is done on a large scale to detect the serum antibodies. These screening assays which are dependent on the detection of the antibodies which have also resulted to the decrease in the rate of infection with blood transfusion which could be as a result of contaminated blood. Also, as the seroconversion occur, the tests most times are positive in results.

Infections have the ability to resolve with time and for HCV, the antibodies decrease as the infected patients have their infections resolved as spontaneous as possible and at times, the rate of spontaneous infection resolved has been under estimated (Takaki *et al*., 2000). The detection of antibodies is done with the aid of sensitive enzyme immunoassays while the ones currently used are of the third generation and entail proteins that are not structural as well as the core protein, and carry out the detection of antibodies within a month to two months of infection. Patients with immunosuppressant can have negative results that are untrue those have HIV-1 infection are not excluded from having this negative result as well as the HCV-associated essential mixed cryoglobulinemia and renal failure. Antibodies against HCV can still be detected while the treatment is going on and after the treatment regardless of the response (Pawlotsky, 2002; Pawlotsky *et al*., 2000).

An introduction has been done concerning the assays with HCV RNA detection based for molecules with HCV RNA tests being reliant on the method and with the test being qualitative called PCR which coupled with a limit of detection which is lower and has less than a hundred copies of HCV RNA per mL of serum (50 IU/mL). In order to carry out the test for HCV RNA, the identification of the infection is possible and to carry out specific test on the infection (Pawlotsky, 2002; Pawlotsky, 2000). An assay which is qualitative for PCR is effective as the transaminase concentrations are also showing normalcy with the presence of other causes of liver diseases prior to the development of antibodies. For the measurement of

the core antigens of HCV, ELISA test was employed to making it feasible for qualitative and qualitative PCR (Pawlotsky, 2002; Pawlotsky, 2000). Occult infection with HCV has been considered for suspicions with the negative HCV PCR in the serum, and abnormal transaminases. On the other hand, positive HCV PCR in the liver and positive detectable HCVRNA in peripheral blood mononuclear cells or positive in-situ hybridization were also detected and these have been emphasized because the confirmation of these findings will result to the extension of HCV infection as well as risk of HCV infection (Castillo *et al.,* 2003).

2.4. Treatment

Hepatitis C does not have vaccine and the prevention measures are the most important efforts that one can make when it comes to the Virus. Prevention can be done by avoiding excess exposure to blood. Over the last decade, there has been obvious progress in a bid to manage chronic hepatitis C. This is in the aspect of improving the histology and eliminating any form of viral presence. Taking the history of this virus into consideration, there are treatments goals that have been suggested and they include: making sure that any form of extra hepatic onset is alleviated, helping to prevent contamination of health works and drug users and prevention of cirrhosis and its complications with actions such as avoidance of high alcohol intake (Corrao & Arico, 1998), taking care of disorders that present themselves such as disorders related to metabolism (Hickman *et al*., 2002) and being aware of what necessary steps should take to cure the patients of acute HCV with Peg interferon Alfa which influences the rate of people that have their acute HCV result to chronic HCV by reducing the rate. A treatment plan for HCV for the chronic HCV carriers comprises of the use of Peg interferon alfa-2a (Pegasys), ribavirin and protease inhibitor (Levinson & Jawetz, 1996). One of the difficulties in developing an HCV vaccine is evoking a strongly protective immune response capable of fixing the high level of genetic diversity of six major genotypes and over 86 subtypes. Additionally, rapid mutation of HCV results in the emergence of viral quasispecies capable of evading the immune response in infected individuals. Nevertheless, sudden viral clearance in 20% to 30% of acutely infected patients shows that multiple HCV infection is

preventable if an effective memory response is created following vaccination. (He et al., 2020).

Treatment of HCV is also done by the combination of pegylated interferon (peg-IFN) and ribavirin allowing for the removal of the virus to take place in the average number of the genotype of the HCV infected patients. However, some patients experience side effects that prolong their recovery or do not respond well to the therapy. There are also cases of relapse post therapy. It has been emphasized that the patients that would respond well to these therapies should be predicted and identifies so as to help manage health care costs. Genotypes and viral RNA measurements are of great consideration in order to enhance and optimize the treatment Of HCV infection. This is as a result of the fact that a relation with the sustained virological response can only be attained with low viral load and a non-genotype 1. Rapid virological response (RVR) defined by undetectable HCV RNA at one month of treatment is becoming more acknowledged as a powerful tool for predicting treatment response. There are several factors that helps to modulate response to the antiviral treatment, these factors include insulin resistance, ethnicity and obesity among other factors.

When there is cirrhosis or fibrosis in a severe stage on pretreatment liver biopsy, it is predicted that there is a poor response to treatment and characterization of the liver that has been done recently coupled with the investigations on liver, gene expression profiling serum proteome has resulted to provision of being able to make predictions regarding what will become of the patients that have been infected when they are undergoing treatment. It is important that more efforts be made to be able to determine how the HCV infected patients will react to therapy and to also enable the treatment to be given according to the responses.

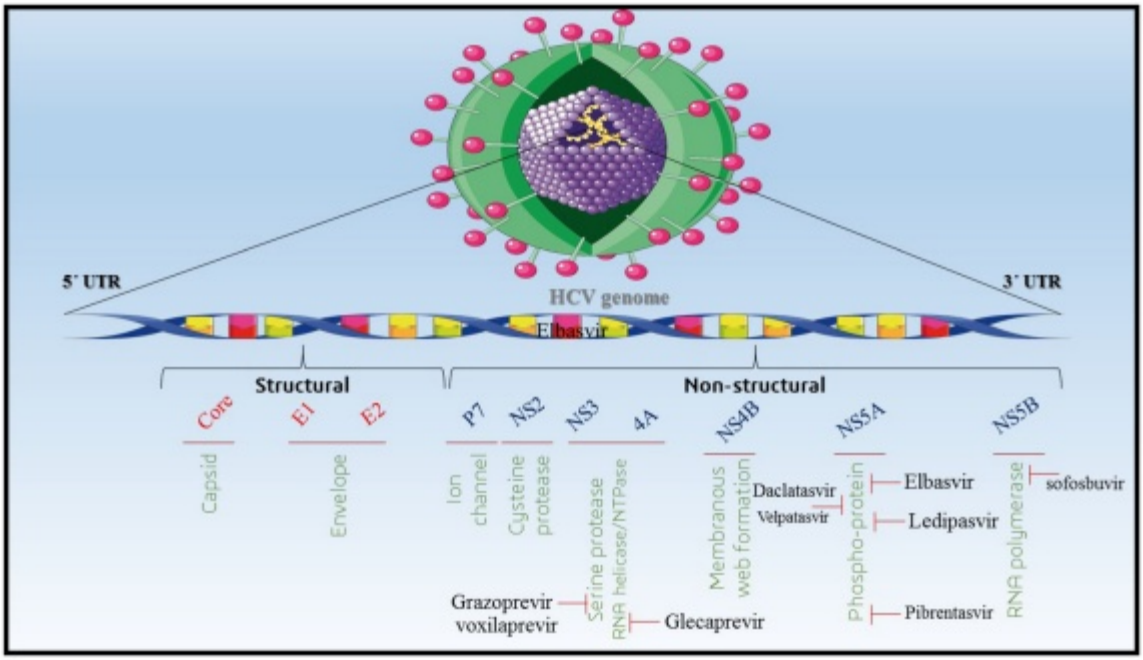

Figure 5: Antiviral drugs against hepatitis C virus (Keikha *et al.,* 2020)

Patients suffering from chronic hepatitis C in majority of the countries are given care which is fitting with the inclusion of ribavirin (PEG IFN/riba) and dual therapy with pegylated interferon (IFN) alpha. In order to attain sustained virological response (SVR), dual PEG IFN/riba therapy was employed for the infected patients with HCV genotype 1 as compared other forms of genotypes such 2 or 3 that have a better and higher rate of SVR.

There is no affordability for the PEG IFN/riba therapy which is of combination and it can also take longer than expected and hence allowing for the side effects to manifest and likewise making it difficult to tolerate these side effects. In order to tackle HCV genotype 1, there are inhibitors related to the protease which has been encoded with virus known NS3/4A in 2011 that were introduced to be a part of standard therapy for this purpose. The SVR rate had also undergone increase in rate up to 70% as a result of the combination of inhibitors that of the first generation considering the therapy called PEG IFN/riba. Some people with underlying conditions or recipients of transplants, this is as a result of the fact that there are to underlying IFN resistance as well as increased drug toxicity and emergence of protease

inhibitor resistance mutation. Efforts have been made to ensure that the populated with special underlying conditions that might result to the side effects kicking in, do not have prolonged treatment and their treatment options are enhanced.

Genotype	Treatment Options	Duration of Treatment	Strength of Evidence
Genotype 1a without/with compensated cirrhosis	Ledipasvir/sofosbuvir	12 weeks	I, A
	Velpatasvir/sofosbuvir	12 weeks	I, A
	Grazoprevir/elbasvir	12 weeks	I, A
	Paritaprevir/ritonavir/ombitasvir/dasabuvir ± ribavirin	12 weeks/24 weeks	I, A
	Ledipasvir/sofosbuvir for patients who are non-black, HIV uninfected, without cirrhosis, and whose HCV RNA < 6 million IU/mL	8 weeks	I, B
	Daclatasvir/sofosbuvir	12 weeks/24 weeks	I, B/IIa, B
	Simeprevir/sofosbuvir ± ribavirin	12 weeks/24 weeks	II, B
Genotype 1b without/with compensated cirrhosis	Ledipasvir/sofosbuvir	12 weeks	I, A
	Velpatasvir/sofosbuvir	12 weeks	I, A
	Grazoprevir/elbasvir	12 weeks	I, A
	Paritaprevir/ritonavir/ombitasvir/dasabuvir	12 weeks	I, A
	Ledipasvir/sofosbuvir for patients who are non-black, HIV uninfected, without cirrhosis, and whose HCV RNA < 6 million IU/mL	8 weeks	I, B
	Daclatasvir/sofosbuvir	12 weeks/24 weeks	I, B/IIa, B
	Simeprevir/sofosbuvir	12 weeks/24 weeks	II, B
Genotype 2 without/with compensated cirrhosis	Velpatasvir/sofosbuvir	12 weeks	I, A
	Sofosbuvir + weight-based RBV	12 weeks/16 weeks	I, A/IIb, C
	Daclatasvir/sofosbuvir	12 weeks/16–24 weeks	IIa, B
Genotype 3 without/with compensated cirrhosis	Velpatasvir/sofosbuvir	12 weeks	I, A
	Daclatasvir/sofosbuvir ± ribavirin	12 weeks/24 weeks	I, A/IIa, B
	Sofosbuvir + weight-based RBV + weekly peg-IFN	12 weeks	I, A
	Sofosbuvir + weight-based RBV	24 weeks	I, B
Genotype 4 without/with compensated cirrhosis	Ledipasvir/sofosbuvir	12 weeks	I, A/IIa, B
	Velpatasvir/sofosbuvir	12 weeks	I, A
	Grazoprevir/elbasvir	12 weeks	I, A/IIa, B
	Paritaprevir/ritonavir/ombitasvir + weight-based RBV	12 weeks	I, B
	Sofosbuvir + weight-based RBV	24 weeks	IIa, B
	Sofosbuvir + weight-based RBV + weekly peg-IFN	12 weeks	II, B
	Simeprevir/sofosbuvir	12 weeks	II, B
	Daclatasvir/sofosbuvir	12 weeks	II, B
Genotype 5 and 6 with and without cirrhosis	Velpatasvir/sofosbuvir	12 weeks	I, B
	Daclatasvir/sofosbuvir	12 weeks	I, B
	Ledipasvir/sofosbuvir	12 weeks	IIa, B
	Sofosbuvir + weight-based RBV + weekly peg-IFN	12 weeks	IIa, B

Figure 6: Highlighted recommendations by IDSA for treatment HCV genotypes (Keikha *et al*., 2020)

2.5. Prevalence and Risk Factors of Hepatitis C

The projections of HCV for modeling have been employed to determine the prevalence of HCV which is ranged from 1.0 to 2.3% (Kershenobich *et al*., 2011). Data was extracted from World Health Organization (WHO) and it was discovered that Brazil has a prevalence of hepatitis C infection from about 2.5% to 10% (Te *et al*., 2010). The system in Brazil also ensured that for cases of Hepatitis C regardless of the cases being acute or chronic, there is appropriate and mandatory notification. This was in play since 1996. This led to the stability of detection rates for anti-HCV which were of 10 cases out of 100,000 persons within 5 years. However, the bulk of the cases were recorded in the southeast region (Pereira *et al.,* 2013). Studies were conducted in Brazil with small population in consideration (Foccacia *et al*., 1998; Zarife *et al*., 2006; Ivantes & Silva, 2010) and it was revealed that the risk factors report was more obtained from the populations in areas that were restricted (Carneiro *et al*., 2001; Perone *et al*., 2008; Lopes *et al*., 2009; NishiokaSde *et al*., 2002; Freitas *et al*., 2008). On the other hand, the chronic HCV patients were found in laboratories that located in Brazilian macro-regions with predominance for genotype 1 then followed by genotypes 3, 2, 4 and 5 (Campiotto *et al*., 2005).

In Serbia, the population with the prevalence of anti-HCV positive has been mentioned to be on the average. By this fact, the country is stated to be an endemic country but under the mid-endemic countries in Europe. Other countries that are classified as mid-endemic include Poland and Ireland. The Great Britain and France on the other hand have been discovered to be of lower prevalence. Higher prevalence is evident in countries such as Spain, Italy and Portugal with up to 2% prevalence. In Europe, it was revealed that anti-HCV positive persons were in Russia and Ukraine (Kim & Chang, 2013).

2.6. Hepatitis C in North Cyprus and Turkey

North Cyprus is also known as the Turkish Republic of Northern Cyprus. The population in North Cyprus approximately 800.000 residents. North Cyprus is recognized by Turkey and is mostly affiliated to the country. There is also the Greek side of Cyprus known as South Cyprus. North Cyprus is known for the large population of students as the island

comprises of universities that accommodate university students. It is also known for its welcoming embrace towards tourists from all over the world (Demetriou *et al*., 2011).

There is much variation in the percentage of prevalence of HCV in Turkey and anti-HCV frequency was reported to be 0.05% in blood donors and 51.6% in patients undergoing hemo-dialysis. The ranges for blood donors do not generally exceed 1% (Sumer *et al*; 2000). A study in in Akdeniz University Hospital showed that most observed genotype of HCV was the type 1 which was very common. However, other forms of HCV genotypes were also discovered (Sağlik *et al*., 2014). A Western Turkey research for the determination of the genotypes of HCV also revealed that the genotype 1 is more rampant in the infected patients unlike the other forms of HCV genotypes (Altuglu *et al*., 2008). The prevalence and risk factors of the HCV infection in the TRNC will be reviewed in this study.

CHAPTER THREE

3.0 MATERIALS AND METHODS

3.1. Materials

The serum anti Hepatitis C virus (HCV) levels for HCV infection was performed by enzyme linked immunosorbent assay (ELISA) technique with Architect I 1000 SR (Abbott Diagnostics, Chicago USA) analyzer. Architect HCV test results were evaluated on sample/Cutoff(S/Co) and <1.0 values are nonreactive; >=1.0 values are reactive. Demographic characteristics including age, gender, origins, clinics, and serological results were documented and assessed retrospectively. The rate of HCV positivity was assessed among different age groups in the ranges of 0-18, 19-30, 31-40, 41-50 and over 50 and within different citizens living in Northern Cyprus.

3.2. Study Setting

The investigation was done in near east university hospital patients admitted between January to December 2017 and screened for HCV using ELISA.

3.3. Type of Study

The study design was retrospective cross-sectional study.

3.4. Sample Size

In order to select the sample size, the convenient sampling was considered with the patients being individuals that have been admitted at the Near East University Hospital and were tested for the Hepatitis C Virus (n=10698). The ELISA test was employed in order to identify the risk factors of HCV and the seroprevalence.

3.5. Process

I took all the patients that were done to the HCV test from January to December 2017 to understand how the disease is prevalent in North Cyprus.

3.6. Ethical Approval

The study protocol was approved by the institutional review board of Near east university hospital YDU/2020/86-1246 project number with the meeting date on 24.12.2020. The names of the respondents were covered and privacy of data maintained. The independent variables included in the data analysis were age, sex, and the attended clinics. There were one main outcome variables, namely, seroprevalence of HCV.

3.7. Study Data Analysis

The data obtained from this study were inputted and analyzed with the help of statistical software known as Statistical Package for the Social Sciences (SPSS) software version 20.0. The variables under categories were compared and computed with the aid of Fisher's exact test or Pearson Chi-square test. The p value was discovered to be <0.05 depicting statistical significance.

Data from the returned pretested survey was coded and gone into Statistical Package for Social Sciences (SPSS) version 16 software. Descriptive statistics were used to analyze the data [frequency and percentages; mean ± standard deviation (SD)].

CHAPTER FOUR

4.0 RESULTS

This chapter interprets the results carried out in the research work. Table 4.1 shows a total number of 10,698 patients which were included in this study of which 7084 were male making up 66.2% of the patients and 3614 were female making up 33.8% of patients. Furthermore table 4.2 shows the seroprevalence of HCV given that the HCV seropositive rate amongst patients is 0.8%. The distribution of HCV seropositivity within the ages of the patients is interpreted in table 4.3 showing a total number of 10,698 patients which were analyzed in this study with a mean Age: 32.8±16.60 (between 0-99 years). As a result of the analysis, it was determined that HCV seropositivity increased with age significantly (p=0.000). This indicates that old age is a risk factor for HCV infection. Table 4.4 interpretation of significant value shows that there was no statistically significant relationship between HCV seropositivity and gender (p=0.360). table 4.5 elaborated on the distribution and comparison HCV seropositivity within the age groups of the patients showing that when HCV seropositivity is compared with age groups, it is seen that HCV seropositivity is significantly higher in people over 60 years of age (p=0.002). The distribution of HCV seroprevalence in

hospital clinics was interpreted in table 4.6 showing that infectious disease clinic had the highest percentage of patients (54.3%) while neurology clinic had the least percentage of patients (0.1%).

Table 4.1. Gender distribution of patients

A Total of 10,698 patients have been included in this study of which 7084(66.2%) were male and 3614(33.8%) were female as indicated in Table 4.1

Gender			
		No of patients	Percentage (%)
	Male	7084	66,2
	Female	3614	33,8
	Total	10698	100,0

Table 4.2. Seroprevalence of HCV

HCV seropositive rate is 0.8% as shown in Table 4.2.

HCV seropositivity		No of patients	Percentage (%)
	Negative	10609	99,2
	Positive	89	0,8

	Total	10698	100,0

Table 4.3. Distribution of HCV Seropositivity Within Age

A Total of 10,698 patients were analyzed in this study with a mean Age: 32.8±16.60 (between 0-99 years) as shown in Table 4.3. As a result of the analysis, it was determined that HCV seropositivity increased with age significantly (p=0.000). This indicates that old age is a risk factor for HCV infection as shown in Table 4.3.

HCV seropositivity	Mean age	No of patients	Std. Deviation
Negative	32,80	10609	16,539
Positive	39,37	89	21,829
Total	32,86	10698	16,599

Table 4.4. Comparison of Gender and Seroprevalence of HCV in the Patients

No statistically significant relationship was found between HCV seropositivity and gender (p=0.360) as demonstrated in Table 4.4.

	Gender			
HCV seropositivity	Male	Female	Total number (%)	p-value
Negative	99,1%	99,3%	99,2%	0.360
Positive	0,9%	0,7%	0,8%	
Total	100,0%	100,0%	100,0%	

Table 4.5. Distribution of HCV Seropositivity with in Age Groups

When HCV seropositivity is compared with age groups, it is seen that HCV seropositivity is significantly higher in people over 60 years of age (p=0.002) as shown in Table 4.5.

	Age groups				
HCV seropositivity	0-20	21-40	41-60	>60	Total
Negative	99,4%	99,2%	99,3%	98,2%	99,2%
Positive	0,6%	0,8%	0,7%	1,8%	0,8%
Total	100,0%	100,0%	100,0%	100,0%	100,0%

Table 4.6. Distribution of HCV Seroprevalence in Hospital Clinics

Clinics		No of patients	Percentage (%)
	Emergency	49	0,5
	Chest Diseases and Allergy	12	0,1
	Eye Diseases	23	0,2
	Obstetrics	1007	9,4
	Blood Bank	1335	12,5
	Cardiology	980	9,2
	ENT	169	1,6
	Neurology	8	0,1
	Oncology	9	0,1
	Orthopedics and Traumatology	237	2,2
	Plastic Surgery	179	1,7
	Brain Surgery	109	1,0
	Urology	153	1,4

	Infectious Diseases	5813	54,3
	Pediatrics	13	0,1
	Internal Medicine	199	1,9
	Dermatology	57	0,5
	Dialysis	67	0,6
	Gastroenterology	31	0,3
	General Surgery	248	2,3
	Total	10698	100,0

CHAPTER FIVE

5.0 DISCUSSION

In our study 10698 subjects were recruited for the study and had serum tested for HCV antibody, 7084(66.2%) males and 3614(33.8%) females). The overall seroprevalence was 0.8%. Of the sera collected 89(0.8%) was discovered to be positive with the help of ELISA anti hepatitis C Virus test version 2. For a retest of the samples that were positive, the Deciscan HCV was considered with the prevalence being 0.8% (89/10698). Of the 10698 study participants, 7084 (66.2%) were males and 3614 (33.8%) were females. Tables 4.1 and 4.3 provide the demographic characteristics of the study's subjects in terms of age and gender. When the HCV was checked for by serological testing, 0.8 percent of the study participants were found to be seropositive. This was done for all of the attendees. Males had a greater prevalence of active HCV infection (66.2 percent, 7084/10698) than females (33.8 percent, 3614/10698). Anti-HCV antibodies were found in 0.6 percent of participants aged 0-20 years, 0.8 percent of patients aged 21-40 years, 0.7 percent of patients aged 41-60 years, and 1.8

percent of participants aged >60 years in our study. When HCV seropositivity is compared to age categories, it is shown that seropositivity in those over 60 years of age is considerably greater (p=0.002).

In a research by Ramarokoto *et al*., (2008), a survey was done to determine the overall seroprevalence of hepatitis C and the risk factors that are thought to be associated to hepatitis C. The overall seroprevalence was 0.97 percent. The frequency did not differ considerably by gender, although it did rise as people became older. The existence of HCV antibodies was revealed to be linked to a number of medical histories, including admission to the hospital, dental treatment, and past therapeutic injections. However, there was no link found between previous blood transfusions and the existence of HCV antibodies (Ramarokoto *et al*., 2008). Another research in Rwanda found that the frequency of HCV infection and the variables that placed persons at risk of infection were both quite high. The prevalence was found to be highest in older participants (19/67) and lowest in younger people (28.4%). (Umumararungu *et al.,* 2017). In Romania, the prevalence rate of HCV infection was examined in the adult population and found to be significantly different from other locations (Gheorghe *et al*., 2010).

Another research evaluating the incidence of hepatitis C infection in the general population in Yemen's central area found that age and degree of education were linked to HCV Ab positive. There was no link observed between the gender of the participants and their monthly income (Gacche & Al-Mohani, 2012). Iran was investigated to see how frequent HCV infection is, and it was shown that the prevalence was more depending on gender in the nation, with men having a greater HCV infection prevalence rate than women (Merat *et al*., 2010).

A review study reviewed the HCV prevalence found in several research studies, with an estimate of high prevalence and the categories at high risk. Anti-HCV prevalence in the general population has been estimated to be as high as 1.50 percent (Han *et al*., 2019).

Another research in the municipality of San Juan, Puerto Rico, evaluated the prevalence of HCV infection and investigated determinants of seropositivity and showed that the overall weighted prevalence of HCV infection was 6.3 percent (Pérez *et al*., 2005).

5.1. CONCLUSION

In conclusion, this study demonstrates a significant rise in HCV seropositivity instances in senior patients over time, highlighting the importance of ongoing monitoring in the medical management of older HCV patients. Because of the rising number of HCV infections throughout the world, more study into the disease's prevalence is needed.

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Yakın Doğu Üniversitesi Tıp Fakültesi öğretim üyelerinden Yrd. Doç. Dr. Ayşe Arıkan Sarıoğlu'nın sorumlu araştırmacısı olduğu, YDU/2020/86-1246 proje numaralı ve **"Seroprevalence of Hepatitis C Virus Infection of Northern CyprusandPotential Influencing Factors"** başlıklı proje önerisi kurulumuzca online toplantıda değerlendirilmiş olup, etik olarak uygun bulunmuştur.

Prof. Dr. Rüştü Onur

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