NEAR EAST UNIVERSITY

INSTITUTE OF GRADUATE STUDIES

DEPARTMENT OF MICROBIOLGY AND MEDICAL MICROBIOLGY

THE PREVALENCE OF HEPATITIS D IN INDIVIDUALS WHO WERE FOUND TO BE HBsAg POSITIVE IN A UNIVERSITY HOSPITAL IN THE TURKISH REPUBLIC OF NORTHERN CYPRUS

PhD. THESIS

Msc LUMA HUSNI AHMED ALZUBI

Nicosia

February, 2025

LUMA HUSNI ALZUBI

THE PREVALENCE OF HEPATITIS D IN INDIVIDUALS WHO WERE FOUND TO BE HBsAg POSITIVE IN UNIVERSITY HOSPITAL IN THE TURKISH REPUBLIC OF NORTHERN CYPRUS

PhD THESIS

2025

NEAR EAST UNIVERSITY

INSTITUTE OF GRADUATE STUDIES

DEPARTMENT OF MEDICAL MICROBIOLOGY AND CLINICAL MICROBIOLOGY

THE PREVALENCE OF HEPATITIS D IN INDIVIDUALS WHO WERE FOUND TO BE HBsAg POSITIVE IN A UNIVERSITY HOSPITAL IN THE TURKISH REPUBLIC OF NORTHERN CYPRUS

PhD. THESIS

Msc LUMA HUSNI AHMED ALZUBI

Supervisor

Assist. Prof. Eşref ÇELİK

Nicosia

February, 2025

Approval

We certify that we have read the thesis submitted by **"The Prevalence of Hepatitis D in Individuals Who Were Found To Be HBsAg Positive in A University Hospital in The Turkish Republic of Northern Cyprus"** and that in our combined opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Doctor of Philosophy of Microbiology and Medical Microbiology.

Examining Committee	Name-Surname	Signature
Head of the Committee:	**PROF. DR AYSEGUL TAYLAN OZKAN**	.....
Committee Member:	**...PROF. DR. KAYA SÜER**.....	.....
Committee Member:	**. DOÇ. DR. EMRAH GÜLER**.....	.....
Committee Member:	**...YRD . DOÇ .DR HULUA ARIK**...	.....
Supervisor:	**... YRD . DOÇ .DR EŞREF ÇELIK**.....	.....

Approved by the Head of the Department

16/06/2025

.....

Prof. Dr.EMRAH RUH

Head of Department

Approved by the Institute of Graduate Studies

.../.../2025

Prof. Dr. Kemal Hüsnü Can Başer

Head of the Institute

Declaration

I hereby declare that all information, documents, analysis and results in this thesis have been collected and presented according to the academic rules and ethical guidelines of Institute of Graduate Studies, Near East University. I also declare that as required by these rules and conduct, I have fully cited and referenced information and data that are not original to this study.

Msc LUMA HUSNI AHMED ALZUBI

27/2/2025

Acknowledgments

First of all, I would like to extend my appreciation to my lovely family; my father, and my mother for their financial and moral support throughout this process.
Secondly, I am very grateful to my supervisor**YRD . DOÇ .DR EŞREF ÇELIK**
who has devotedly explained every stage of my thesis project and shared her valuable information with me. Also, I would like to offer my unlimited thanks and great gratitude for her endless support, understanding spirit, constant encouragement, and helpful approach throughout my master's program. It would be very difficult for me to complete my thesis without her precious help and support.
I would also like to extend my appreciation to all lecturers at the Department of Medical Microbiology and Clinical Microbiology Near East University.

Msc LUMA HUSNI AHMED ALZUBI

Abstract

The Prevalence of Hepatitis D in Individuals Who Were Found To Be HBsAg Positive in A University Hospital in The Turkish Republic of Northern Cyprus

Msc Luma Husni Alzubi

Supervisor: YRD . DOÇ .DR EŞREF ÇELIK

PhD, Department of Microbiolgy and Medical Microbiolgy

Febrauary, 2025

Objective: Although HDV infections are present all over the world, the prevalence varies from country to country and even from region to region. It was aimed to determine the prevalence of hepatitis D in individuals who were found to be HBsAg positive (+) in Turkish Republic of Northern Cyprus (TRNC).

Material and Method: 422 HBsAg(+) and outpatients were included in this cross-sectional study, which included HBsAg (+) patients obtained from the information system of the TRNC, Near East University Hospital between January 01, 2018 and September 31, 2022. The prevalence of HDV in HBsAg (+) patients was evaluated. For this purpose, the anti-HDV and HDV-Ag positivity of the patients known to be positive for HBsAg were examined by ELISA in the serum. HDV-RNA determination was analyzed by RT-PCR method from the samples of patients with positive anti-HDV and HDV–Ag.

Results: The ratio of both genders to each other was determined as male/female 2.64. The mean age of HBsAg (+) patients was 33.51 ± 7.2 years. We determined that the highest HBsAg positivity ratio was from Nigerian patients (n=176, 41.7%). HDV-Ab was positive in only 3 (0.71%). of the 422 patients included in the current study. HDV-Ag and HDV-RNA positivity were not detected in any of the 422 individuals.

Conclusion: Anti-HBc IgM results of three individuals with positive HDV-Ab were negative, suggesting that HDV might have emerged as a superinfection in these individuals. The positive anti-HBc total results of three people with HDV-Ab positivity show that HDV is considered as superinfection in these individuals, that is, there is no acute infection. One of the countries with no data on HDV prevalence is TRNC. National data from countries with no data on HDV prevalence may significantly affect HDV prevalence globally.

Keywords: Hepatitis D, prevalence, North Cyprus, HBs-Ag, Anti-HDV

Özet

Kuzey Kıbrıs Türk Cumhuriyeti'nde Bir Üniversite Hastanesinde HBsAg Pozitif Saptanan Bireylerde Hepatit D Sıklığı

Msc Luma Husni Alzubi

Supervisor: YRD . DOÇ .DR EŞREF ÇELIK

PhD, Department of Microbiology and Medical Microbiology

February,2025

Amaç: HDV enfeksiyonları tüm dünyada bulunmasına rağmen prevalansı ülkeden ülkeye ve hatta bölgeden bölgeye değişmektedir. Kuzey Kıbrıs Türk Cumhuriyeti'nde (KKTC) HBsAg pozitif (+) hastalarda hepatit D prevalansının belirlenmesi amaçlandı.

Gereç ve Yöntem: 01 Ocak 2018 – 31 Eylül 2022 tarihleri arasında KKTC Yakın Doğu Üniversitesi Hastanesi bilgi sisteminden alınan HBsAg (+) hastaların dahil edildiği bu kesitsel çalışmaya ayakta tedavi gören ve 422 HBsAg (+) hasta dahil edildi. HBsAg (+) hastalarda HDV prevalansı değerlendirildi. Bu amaçla, HBsAg pozitif olduğu bilinen hastaların anti-HDV ve HDV-Ag pozitiflikleri serumda ELISA yöntemi ile incelendi. HDV-RNA tayini, anti-HDV ve HDV-Ag pozitif olan hasta örneklerinden RT-PCR yöntemi ile analiz edildi.

Bulgular: Her iki cinsiyetin birbirine oranı erkek/kadın 2,64 olarak belirlendi. HBsAg (+) hastaların yaş ortalaması 33,51 ± 7,2 idi. En yüksek HBsAg pozitiflik oranının Nijeryalı hastalarda (n=176, %41,7) olduğunu belirledik. HDV-Ab sadece 3'ünde (%0,71) pozitif saptandı. Mevcut çalışmaya dahil edilen 422 hastanın hiçbirinde HDV-Ag ve HDV-RNA pozitifliği saptanmadı.

Sonuç: HDV-Ab pozitif olan üç kişinin anti-HBc IgM sonuçlarının negatif olması HDV'nin bu kişilerde bir süperenfeksiyon olarak ortaya çıkmış olabileceğini göstermektedir. HDV-Ab pozitif olan üç kişinin anti-HBc total sonuçlarının pozitif çıkması, bu kişilerde HDV'nin süperenfeksiyon olarak kabul edildiğini, yani akut enfeksiyon olmadığını göstermektedir. HDV prevalansına ilişkin veri bulunmayan ülkelerden biri de KKTC'dir. HDV prevalansı hakkında verisi olmayan ülkelerden alınan ulusal veriler, küresel olarak HDV prevalansını önemli ölçüde etkileyebilir.

Anahtar Kelimeler: Hepatit D, prevelans, Kuzey Kıbrıs, HBs-Ag, Anti-HDV

Table of Contents

Approval ..... **i**
Declaration ..... **ii**
Acknowledgments ..... **iii**
Abstract ..... **iv**
Table of Contents ..... **v**
List of Tables ..... **vii**
List of Figures ..... **ix**
List of Abbreviations ..... **x**

CHAPTER I

Introduction **1**
Statement of Problem 1
Purpose of The Study 2
Research Questions/Hypothesis 2
Research of Study 2
Limitations 2

CHAPTER II

Literature Review **3**
Human Liver 3
Anatomy and Physiology 3
Cellular Structure 5
Related Testing and Imaging Methods 7
Pathophysiology of Liver Diseases 9
Viral Hepatitis Types 10
Overview of Hepatitis Delta 12
History of Classification of HDV 12
Virology 13
Outcomes 16
Epidemiology and Geographic Distribution of HDV 21
Paths of Transmission 27
Viral Dominances among Hepatitis 27
Symptoms and Incubations 28
Diagnosis 28

Prevention and Treatment……30
Key Factors……..31

CHAPTER III

Methodology 32
Rearch Design 32
Patients Groups and Ethics 32
HDV Prevalance 32
Evaluation of Anti-HDV Positivity, with ELISA 33
Evaluation of HDV-Ag Positivity, with ELISA 35
Evaluation of HDV-RNA, with PCR 36
Anti HBc IgM, with ELISA 40
Anti HBc Total, with ELISA 41
ALT *and AST Level* *42*
Statistical Analysis 43

CHAPTER IV

Results 44
Demographic Results 44
Anti-HDV-Ab 49
HDV-Ag 49
HDV-RNA 50
Anti-HBc-IgM 50
Anti-HBc Total 50
ALT and AST Level 51

CHAPTER V

Discussion 53

CHAPTER VI

Conclusion and Recommendations 59
Conclusion 59
Recommendations 59

REFERENCES 61

APPENDICES 70
Appendix A: Ethical Approval Document 71
Appendix B: Similarity Report 72
Appendix C:CV 73

List of Tables

	Page
Table 1. Assessment of Liver Function in Cases of Chronic Viral Hepatitis	8
Table 2. Characteristics of A-E Hepatitis	11
Table 3. Clinical Characteristics of Individuals with HDV Co-Infection and Super-Infection	17
Table 4. Primers and Probes Used in HDV PCR Protocols	38
Table 5. HDV RT-PCR Stages	39
Table 6. Interpretation of the HDV-Ab ELISA Kit Used	47
Table 7. Interpretation of the HDV-Ab ELISA Kit Used	49
Table 8. Interpretation of the HDV-Ag ELISA Kit Used	50
Table 9. The Characteristics of The Three Anti-HDV-Ab (+) Patients	51
Table 10. ALT and AST Distributions According to Anti-HDV-Ab Test Results	52

List of Figures

	Page
Figure 1. Anatomy and Hepatic Blood Flow of Liver	3
Figure 2. Blood Supply to The Liver and Portion of Liver Lobules	4
Figure 3. Summary of Essential Functions of Liver	5
Figure 4. Schematic Representation of The Cell Types Found in Liver	6
Figure 5. Sinusoid Diagram	7
Figure 6. Viral Life Cycle	15
Figure 7. Diagram of Virion and Genome for HDV	16
Figure 8. Markers in Super-Infected Patients. A) Simultaneous co-infection results in clearance of both viruses (B) HDV super-infection of an HBV carrier (C) HDV super-infection of a chronic HBV carrier	18
Figure 9. Serologic Course of (A) Acute HDV Infection (Healing) and (B) Chronic HDV Infection	20
Figure 10. Three Different Natural History of Super-Infection. A) Acute phase (replication of HDV and suppression of HBV) ALT level is high. B) Chronic phase (HDV reactivated low HBV level) ALT level moderate. C) Late phase (development of cirrhosis and hepatocellular carcinoma)	21
Figure 11. HDV genotype distribution worldwide	23
Figure 12. Geographical Schematic Representation of Globally Distribution of Dominant HDV Genotype	24
Figure 13. Prevalence of HDV Positivity Among Immigrant Individuals in Europe in 2012	25
Figure 14. Working Mechanism of ELISA Test Methods	33

Figure 15. ELISA Kit Used in the Quantitative Determination of Anti-HDV 34

Figure 16. ELISA Kit for HDV – Ag 35

Figure 17. PCR Kit for HDV - RNA 37

Figure 18. RT-PCR in NEU-H 37

Figure 19. Experimental Design 40

Figure 20. Abbott Architect C16000 Device 42

Figure 21. The Gender Distribution Ratio of a Total of 422 HBsAg (+) Patients Admitted to NEU-H between 2018-2022 44

Figure 22. Age Distribution of a Total of 422 HBsAg (+) Patients Admitted to NEU-H between 2018-2022 45

Figure 23. Distribution of 422 HBsAg (+) Patients Admitted to NEU-H between 2018-2022 by Nationality 46

Figure 24. HBsAg (+) distribution ratio in NEU-H (2018-2022), in a total of 422 cases 48

Abbreviations

%:	Percentage
<:	Lesser symbol
>:	Greater symbol
±:	Plus-minus sign
°C:	Degrees Celsius
µM:	Micromolar
µL:	Microlitre
Alb:	Albumin
ALP:	Alkaline Phosphatase
ALT:	Alanine aminotransferase
Anti-HCV:	Hepatitis C virus antibody
AST:	Aspartate aminotransferase
BD:	Bile duct
Blb:	Bilirubin
c:	Chronic

DNA: Deoxyribonucleic acid

ELISA: Enzyme-linked immunosorbent assay

GGT: Gamma glutamic transferase

Gt: Genotypes

HA: Hepatic artery

HAV: Hepatitis A virus

LSEC: Liver sinusoidal endothelial cells

KC: Kupffer cells

NC: Natural killers

qHSC: Quiescent hepatic stellate cells

HBsAg: Hepatitis B surface antigen

HCC: Hepatocellular carcinoma

HCV: Hepatitis C virus

HD-Ag: Hepatitis delta antigen

HDV: Hepatitis D virus

HEV: Hepatitis E virus

HSPG: Heparan sulphate proteoglycans

IgG: Immunoglobulin G

IgM*:* Immunoglobulin *M*

L-HDAg: Large hepatitis delta antigen

mRNA: Messenger ribonucleic acid

N: North

PCR: Polymerase chain reaction

PV: Portal vein

PT: Prothrombin time

RNA: Ribonucleic acid

RNP: Ribonucleoprotein

SD: Standard deviation

S-HDAg: Small hepatitis delta antigen

Z: Zone

CHAPTER I
Introduction

In this section, the problem, purpose, importance, hypotheses and definition terms of the research are given.

Statement of the Problem

In short, hepatitis, known as liver inflammation, can develop due to many reasons such as alcohol use, drugs, poisoning, bacteria, and parasites, but the most important cause of hepatitis is viruses. Sero-epidemiological studies conducted in the 1980s reported that the prevalence of HDV in patients with HBV was 5%, and this corresponds to an estimated 20 million people worldwide (Lempp et al., 2016; Sureau & Negro, 2016). The prevalence of HDV in these years is in Southern Europe, the Middle East, East Africa and Asia; It was reported to be relatively higher than Northern Europe, South Africa and N-America (Taylor et al., 2013). HDV infections are found all over the world, but the prevalence varies by region. In Africa, the Middle East, and Italy (south part), anti-HDV antibodies are found in 20-40% of HBsAg carriers. In the United States, HDV-infection is uncommon, except in drug addicts and haemophiliacs, where prevalence ratios range from 1 to 10%. Gay men and healthcare workers are at high risk of contracting HBV but, for unknown reasons, are at low risk of HDV-infection. Furthermore, HDV infection is uncommon in Southeast Asia and China, where there is a large HBsAg carrier population. Haemodialysis patients, sexual contacts with infected people, and infants born to infected mothers (rare) are also at high risk of contracting HDV. Until now, HDV has infected over 10 million people worldwide.

Many other studies were conducted in the same period, and the results of these studies generally showed differences and inequalities in prevalence ratios at the regional level. While some studies reported that HDV prevalence could be neglected, some studies reported the presence of hyperendemic pockets of infection around regions where the prevalence could be neglected (Rizzetto et al., 1991). In this process, clinical research results according to the medical classification method revealed that hepatitis D is the main reason of cirrhosis and fulminant hepatitis worldwide. In USA, the ratio of anti-HDV in drug addicts using intravenous injectors with c-HBV was 50%, and anti-HDV ratio in 500 HBsAg carriers was 8%.

The results of the research also include serological findings showing that 30% of individuals infected with HBV and HDV are also exposed to HCV (Cross et al., 2008; Heidrich et al., 2009). In this triple-infection, HDV is the predominant-virus because it suppresses not only HBV replication but also HCV replication (Mathurin et al., 2000).

All the above-mentioned information shows us that the global presence of HDV has not decreased and is probably still underestimated when considered.

Purpose of the Study

The purpose of this study was to determine prevalence of hepatitis D in Northern Cyprus.

Research Questions / Hypotheses

Due to Hepatitis B's uncommon/low prevalence in Northern Cyprus, HDV prevalence is expected to be low.

Significance of the Study

This is the first study on the prevalence of hepatitis D in Northern Cyprus.

Limitations

The limitation of our study is that hepatitis D genotype determination was not performed.

CHAPTER II

General Information

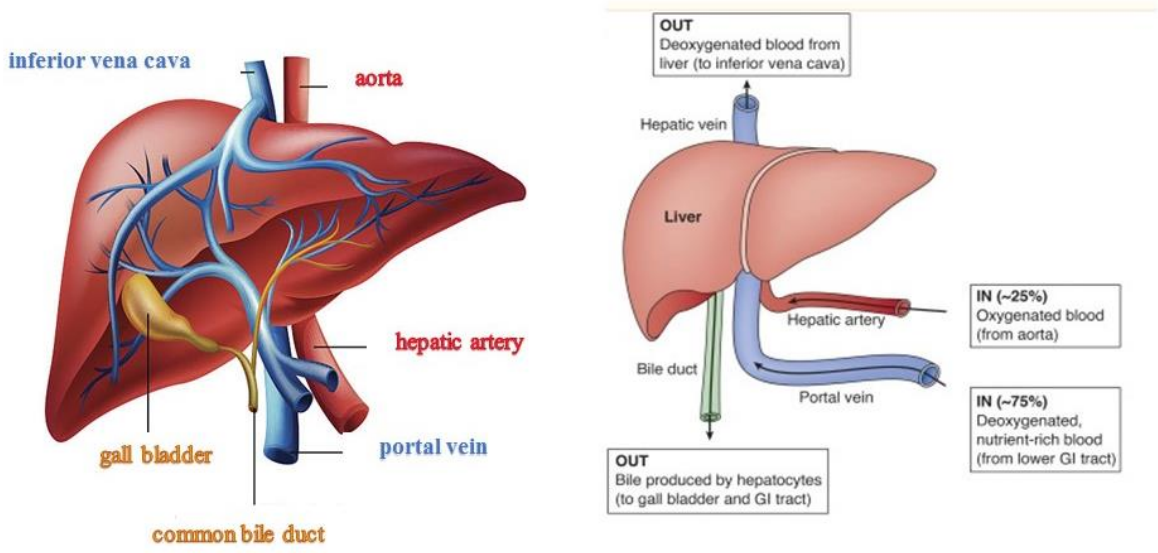
Human Liver

Anatomy and Physiology

The biggest secretory tissue in the human body, the liver is situated in the abdominal cavity (upper side) and has a dense vascular network. It comprises around 2% (≅ 1.2-1.7 kg) of an adult's body weight. This organ is also the largest gland in our body (Kalra et al., 2022) (Figure 1.).

Figure 1.

*Anatomy and Hepatic Blood Flow of Liver (*Schulze et al., 2019)

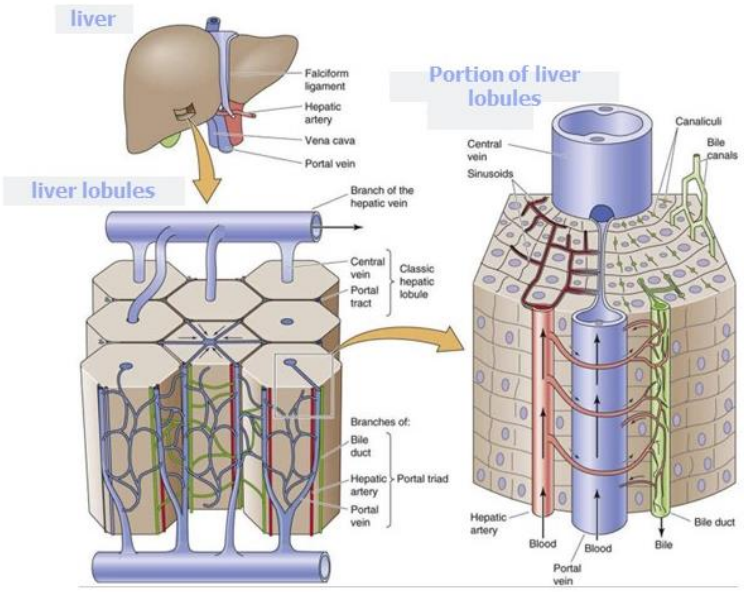


While the liver acts as an exocrine gland while secreting bile into the bile ducts (BD), it acts as an endocrine gland while secreting many chemicals and proteins into the blood. As well as functions as a gland, the liver is an organ that takes part in digestion. Another feature of the liver is that it is the only organ with dual blood flow. As in every organ, there is an artery that enters the liver, and the special name of this artery is the hepatic artery (HA). The “portal vein (PV)” is name given to the vein that emerges from liver and serves as the primary conduit for blood from stomach, large and small intestine, spleen and pancreas to liver. After undergoing processing in the liver, the blood flows through the hepatic vein and joins the systemic circulation through the inferior vena cava (Rehfeld et al., 2017) (Figure 2.).

Figure 2

Blood Supply to The Liver and Portion of Liver Lobules

(https://doctorlib.info/physiology/medical/253.html)



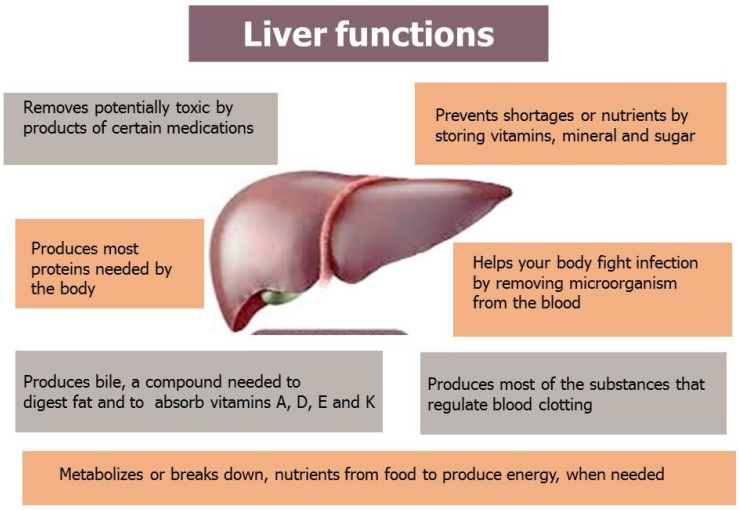
The liver works like a biochemistry factory with numerous functions. Among the functions of the organ, it is possible to consider (Fig 2.3):

- Protein synthesis
- Albumin (Alb) synthesis
- Synthesis of coagulation factors
- Synthesize fat, stores fat, and metabolizes fats (including fatty acids and cholesterol).
- Stores carbohydrates (glycogen), the source of fasting glucose.
- Produces bile and bile salts. Bile flows into the intestine via the biliary tract. Bile and bile salts provide fat absorption and thus the absorption of fat-soluble vitamins.
- It eliminates harmful substances released in the body in two ways. it either metabolizes (breaks down) or secretes it into bile.
- Detoxification of harmful biochemical products. The liver either metabolizes (breaks down) toxins or excretes them into bile (alcohol, drugs, and many poisons).
- It is essential for the excretion of ferrous pigments.

- Kupffer cells, or liver macrophages, are part of the mononuclear phagocytic system. These cells perform phagocytosis and are involved in the hepatic and systemic response to pathogens.

Figure 3.

Summary of Essential Functions of Liver

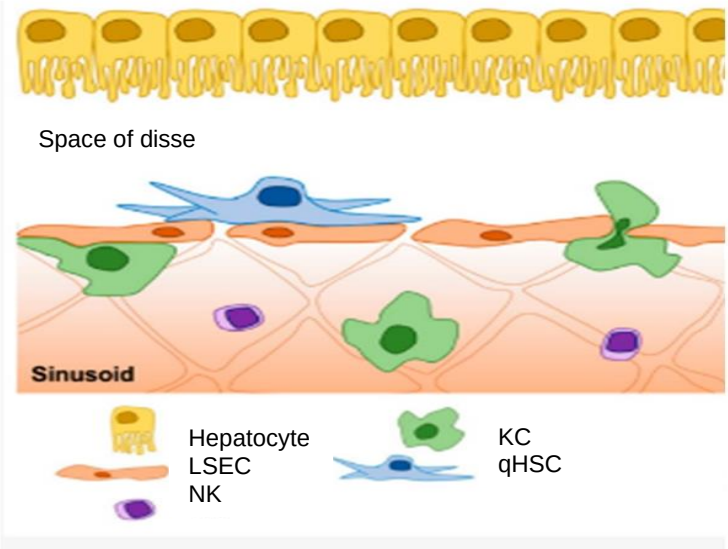


Cellular Structure

The liver's structural organization, which is made up of parenchymal and vascular elements, is tailored to specific functions as a strategically important protector located between the intestinal tract and the rest of the organism (Elias, 1949). The liver's strategic localization ensures the processing of nutrients (via food and water) entering the body. This functional tissue is made up of at least seven different types of cells, including hepatocytes, cholangiocytes, lymphocytes, sinusoidal endothelial, Kupffer, stellate, and pit cells (Sanz-García et al., 2021, Miao, Z., et.al.2022).) (Figure 4). Its structural unit is the polyhedral hepatic lobule. Nearly 2 mm long and 0.7 mm wide, the hepatic lobule has hepatic tracts and central venules (Fawcett, 1955). The liver's functional unit is a lobule, which is hexagonal in shape and has a triad of portals (PV, HA, BD) at each corner. The lobule consists of hepatocytes.

Figure 4.

Schematic Representation of The Cell Types Which Plays A Critical Role in Maintaining The Liver's Physiological Functions Found in A Normal Liver (Sanz-García et al., 2021).



*LSEC: sinusoidal endothelial cells (for liver), KC: Kupffer cells,NC: natural killer cells, qHSC: quiescent hepatic stellate cells

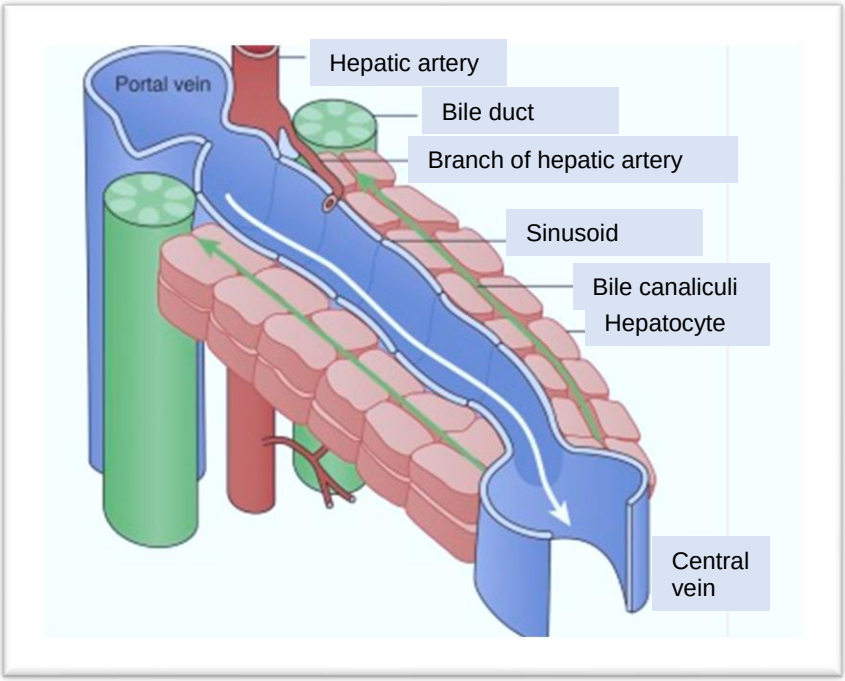
Large polygonal cells, hepatocytes, are responsible for many of the synthetic and metabolic functions that take place in the liver. These cells, which constitute the majority of liver cells, constitute approximately 80% of the mass/volume ratio of the liver. Hepatocytes have physiologically different apical and basolateral membranes. Therefore, hepatocytes are functionally divided into three regions:

- Zone-I (Z-1) is the best perfused and first regenerated zone. Since it is considered as the peri-portal location of hepatocytes, it is the closest region to oxygenated blood and nutrients. This region has an important role in oxidative metabolism (e.g., bile formation).
- Z-II is the pericentral area, located among areas I and III.
- Z-III has the least perfusion because it is farthest away from the portal triad. A major role in the following processes: detoxification, glycogen synthesis, drug biotransformation, glycolysis, and glutamine formation (https://www.ncbi.nlm.nih.gov/books/NBK535438/).

Bile and blood flow are diametrically opposed. The liver's bile exits through ducts (formed by the apical membranes of adjacent hepatocytes), while the dual blood supply enters to perfuse the liver (Schulze et al., 2019, Miao, Z., et.al.2022). Thus, it reaches the HV located in the centre of the lobule through the sinusoidal lumens of the lobule (Fig 2.5). The space between the basolateral membrane surrounding hepatocytes and the sinusoidal lumen is called the space of Disse. This cavity contains an extracellular matrix that helps provide the scaffold for the lobule. The matrix is composed of various collagens, proteoglycans and other proteins. The area of Disse also contains Kupffer cells (macrophages), which are tasked with filtering out unnecessary or pathological substances from the circulation, and Ito cells (star cells), which both act as fat stores and help the liver regenerate (Saxena et al., 1999; Si-Tayeb et al., 2010, Rizzetto, M. 2022).

Figure 5.

Sinusoid Diagram (Schulze et al., 2019)



Related Testing and Imaging Methods

Clinicians request liver function tests to help them evaluate a patient's liver. The components of this panel are helpful both portrait of the processes occurring in the liver and in assessing the extent of any damage to the liver. Elevations in

circulating levels of enzymes such as AST, ALT, alkaline phosphatase, and GGT are indicative of hepatocyte damage, while alterations in bilirubin (Blb) concentrations serve as an additional marker of potential liver injury (Hoekstra et al., 2013, Miao, Z., et.al.2022).Among these enzymes, specific than AST, which is found in a variety of tissues. Alkaline phosphatase (ALP), like AST, can be found in bone as well as the biliary tree, indicating that it is not as unique for the liver as ALT, but when combined with other components of the panel, it does provide evidence of hepatocellular (HC) damage. Elevated ALP, for example, indicates biliary tract lining damage (Table 1).

Table 1.

Assessment of Liver Function

(https://www.semanticscholar.org/paper/Liver-function-tests-in-chronic-viral-hepatitis-Haklar/1646a4b60f58908f33a4210fe15df537f5b807b1).

Test	**Usage**
ALP	diagnosing cholestatic disorders
AST	sensitive evaluation for HBD (AST > ALT in alcoholic diseases)
ALT	sensitive and more specific test for HBD
PT	impaired synthesis functions in acute cases, indicative of the severity of cholestasis
Alb	indicator of chronicity and severity
Blb (direct and indirect)	diagnosis cholestasis and space-occupying lesions
Total Blb	diagnosis jaundice, modest correlation with severity

* PT: prothrombin time, HBD: hepatobiliary disease

In order to evaluate the functions of the liver, it is also necessary to evaluate its ability to synthesize proteins. Alb, one of the body's main proteins, is made in the liver. Its obligation is to keep the fluid in the vein in place. In liver diseases, Alb production is impaired and its amount in the blood decreases. As a result, the fluid in

the vein escapes and this causes swelling/edema in the abdomen. The change in the level of Alb, an important protein produced by the liver, not only provides information about how the liver works, but also varies depending on the patient's nutritional status and nephrotic symptoms. The half-life of 15-20 days generally prevents the use of Alb alone in the determination of acute liver dysfunctions. Therefore, when assessing liver function, Alb level and coagulation factors are evaluated together.

Ultrasound is also widely used in the evaluation of the liver because it is non-invasive and inexpensive. This imaging method can reveal the liver's border pattern, the location of cystic localization, and various pathologies. In the diagnosis and characterization of liver lesions, computed tomography or magnetic resonance imaging techniques are used (Scheidler et al., 1995; Brehmer et al., 2018).

Pathophysiology of Diseased Liver

The etiology of liver diseases has a wide spectrum. The wide variety of functions that the organ undertakes and the different types of cells in its structure are important factors that cause this. Type B and C hepatitis, alcoholic liver disease, and liver cirrhosis are among the most common liver diseases (Tsutsumi et al., 2017, Miao, Z., et.al.2022).

Although jaundice has a wide variety of causes, it is usually indicative of altered Blb metabolism (Nishikawa & Osaki, 2015). It is evaluated by fractional Blb obtained from the measurement of indirect and direct Blb. When expired red blood cells are broken down, the hemoglobin in them is converted to Blb and removed from the liver via bile. Blb, which cannot be eliminated from the body during liver diseases, accumulates in the blood and causes jaundice.

Cirrhosis occurs as a result of sustained liver damage, inflammation, fibrosis, and necrosis. Causes of cirrhosis often include alcoholism, chronic (c-) hepatitis B and C. Since cirrhosis is represented as end-stage-liver disease, the function of liver is greatly compromised. Symptoms of portal hypertension, hyperestrinism, and hypoalbuminemia occur due to the reduced ability of the liver to produce protein and remove toxic substances. Decreased coagulation factor synthesis results in coagulopathy.

Various viruses can cause liver damage. Hepatitis viruses A (HAV) and E (HEV) cause acute hepatitis. These types of hepatitis occur in people who travel a

lot, and in individuals who consume unclear water or seafood. Symptoms of these self-limiting diseases include vomiting and jaundice (Thuener et al., 2017, Brunetto, M. et.al 2023, Miao, Z., et.al.2022). Hepatitis B, C, and D are viruses (HBV, HCV and HDV) that can cause acute hepatitis that results in c-hepatitis. Hepatitis D relies on Hepatitis B to replicate. In people with hepatitis B, it can occur as a co- or super-infection, resulting in more severe symptoms. HBV and HCV can be spread through injection equipment or intravenous drug use, while Hepatitis B can also be spread from person to person through sexual contact (Ramachandran et al., 2019). The best treatment for HAV, HBV, and HCV are actually vaccination. *Immunoglobulin-G* (IgG) is an indicator of vaccination or previous exposure, while *Immunoglobulin*-M (IgM) is an indicator of acute infection.

Viral Hepatitis Types

Hepatitis can be briefly called inflammation of the liver. Individuals may develop hepatitis due to many reasons: alcohol use, drugs, poisoning, bacteria, parasites, but viruses represent the most important cause of hepatitis. Viral hepatitis is hepatitis caused by viruses. There are numerous viruses that cause liver inflammation, but the following five are the most common: HAV, HBV, HCV, HDV and HEV (Table 2).

Table 2.

Characteristics of A-E Hepatitis

Disease	Pathogen	Symptons	Incubation period	Transmission	Diagnostic test
Hepatitis A	HAV, picornaviridae	Fever, headech, malaise, jaundice	2-6 w	Ingestion	IgM andibodies
Hepatitis B	HBV, hepadnaviridae	Several liver damage, chronic disease occurs	3-26 w	Parenteral, sexual contact	IgM andibodies
Hepatitis C	HCV, flaviviridae	Same as HBV, more chronic	2-33 w	parenteral	PCR/viral RNA
Hepatitis D	HDV, deltaviridae	Severe liver damage, high mortality	6-26 w	Parenteral whenco-infected with HBV	IgM andibodies
Hepatitis E	HEV, caliciviridae	Pregnant women may be high risk and show high mortality chronic disease	2-6 w	Ingestion	IgM andibodies, PCR/viral RNA

- Hepatitis A: A disease caused by the hepatitis A virus, also known as infectious hepatitis and infectious jaundice. HAV does not become chronic, individuals infected with HAV recover in an average of 6-10 weeks. Since it is spread through the faeces and urine of the patient, it causes epidemics in environments where the sewage system is bad. Since HAV is a vaccine against it, it is a disease that can be prevented by vaccination.
- Hepatitis B: Hepatitis B virus (HBV), also referred to as serum hepatitis, is the causative agent of hepatitis B, which can develop into a chronic condition in 10-15% of infected individuals. This disease is transmitted through exposure to infected blood and bodily fluids, including mother-to-child transmission during childbirth, unprotected sexual contact, and the use of unsterilized instruments during medical procedures such as dental work, dialysis, and surgery. Vaccination against HBV is available, making hepatitis B a vaccine-preventable disease.
- Hepatitis C: This disease, also known as Non-A, Non-B hepatitis, is caused by the hepatitis C virus (HCV). 70-80% of cases become chronic. It is transmitted by blood and body secretions. It is transmitted through unprotected sexual contact, manicure, pedicure, tattoo, dental, dialysis, surgery, or blood transfusion. We have no vaccine against the HCV.
- Hepatitis D: Delta hepatitis is caused by the HDV. It was discovered (in 1977, Rizzetto, M. 2022) by the presence of a novel delta antigen by immunofluorescence staining in hepatocytes of HBV patients. This virus can only infect hepatitis B patients. If the patient does not have hepatitis B, it cannot be transmitted. It worsens hepatitis B and accelerates the progression to cirrhosis. We have no vaccine available for this type.
- Hepatitis E: HEV, which is also known as orally transmitted non-A, non-B hepatitis, primarily spreads by the fecal-oral route. This disease is more prevalent in areas with inadequate sanitation infrastructure. Unlike some other forms of hepatitis, such as HBV and HCV, HEV typically presents as an acute infection and does not progress to a chronic state. Although no vaccine is currently available for hepatitis E, preventative measures such as improved sanitation and hygiene can help mitigate its spread. Pregnant

women are particularly susceptible to severe complications from hepatitis E, which may rarely progress to a chronic form. (Miao, Z., et.al.2022).

Overview of HDV

A liver inflammation brought on by the delta-type virus HDV requires HBV for replication. The most severe type of C-viral hepatitis is this one. Because the presence of co-infection further accelerates death due to liver damage. The one and only method of avoiding HDV are to get an HBV vaccine.Rizzetto, M. 2022).

History and Classification of HDV

The last quarter of the 20th century has been the year when important discoveries took place in hepatology. With the discovery of hepatitis B surface antigen (HBsAg), the mysterious door of viral hepatitis was opened. In the same years, the characterization of the HBV virion and nucleocapsid was followed by the discovery of the HAV. HDV, on the other hand, was provided by the identification of the delta antigen-antibody system in HBsAg carriers (Rizzetto et al., 1977, Stoll, F., et al 2022, Rizzetto, M.2022). The findings of an Italian study found that while the delta antigen is distinct from other known antigenic properties of HBV, it is related to HBV infection since HBsAg is also detected in the blood of all patients with the novel antigen. Due to the topic's popularity, a study with chimps in the United States disclosed that delta is not an HBV antigen, and instead HDV, a new and distinct human RNA (ribonucleic acid) virus (Rizzetto, 2015, Brunetto, M. et.al 2023). HDV is the only virus in the *deltaviridae* family. The rarest human infectious agent is HDV, which possesses a circular RNA genome of 170 bases (Rizzetto, 1983, Rizzetto, M. 2022).). The 8 identified genotypes are common in the following regions: Genotype (Gt) 1: worldwide, but especially in Europe, the Middle East, North (N) America and N-Africa (Le Gal et al., 2017; Stockdale et al., 2020). Gt 2-8, is more localized. Gt 2 and 4: in Asia. Gt 3: in America (especially the Latin). Gt 5,6,7 and 8: in Africa (Taylor et al., 2013; Stockdale et al., 2020).
HDV infection is transmitted by parental exposure, just like HBV, and the most effective transmission route is HBsAg-positivity [HBsAg (+)]. The HBsAg is found in the envelope of HDV particles. HDV is thought to be a satellite virus of HBV. HDV, on the other hand, does not similar homologies with HBV and can replicate

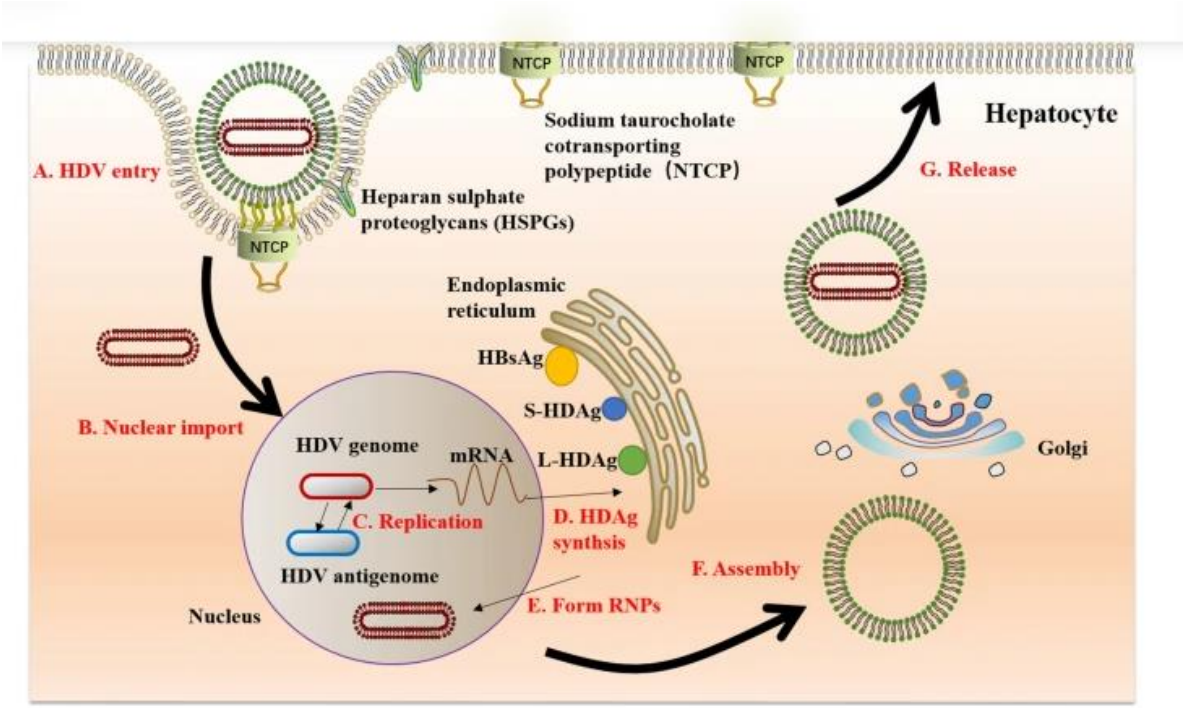
independently of HBV. Transmission to HBsAg (+) animals has been reported, including results from studies in HDV-positive animal serum using very low titrations (1/10211). Factors such as vertical transmission from mother to child, and homosexual random intercourse, which are among the important risk factors in HBV transmission, seem to be risk factors that are not considered in HDV-infection (Rizzetto, 2015). In comparison to HBV mono-infection, HDV-infection, which is recognized as the most severe form of viral hepatitis in humans, aggravates route of HBV infection and causes early decompensation of liver function (Rizzetto & Alavian, 2013). In contrast, research from several nations has linked HDV with benign clinical problems like normal liver function. This also suggests that it might be linked to various HDV-infection subtypes (Rizzetto & Ciancio, 2012, Rizzetto, M. (2022).).

Virology

In terms of replication time and structure, HDV, the sole member of the genus Deltaviridae, resembles viroids and virusoids. (Rizzetto, 2015, Stoll, F., et al (2022). In order to maintain the stability of the HDV life cycle, which is schematically depicted in Figure 6, post-translocation alterations are essential.

Figure 6.

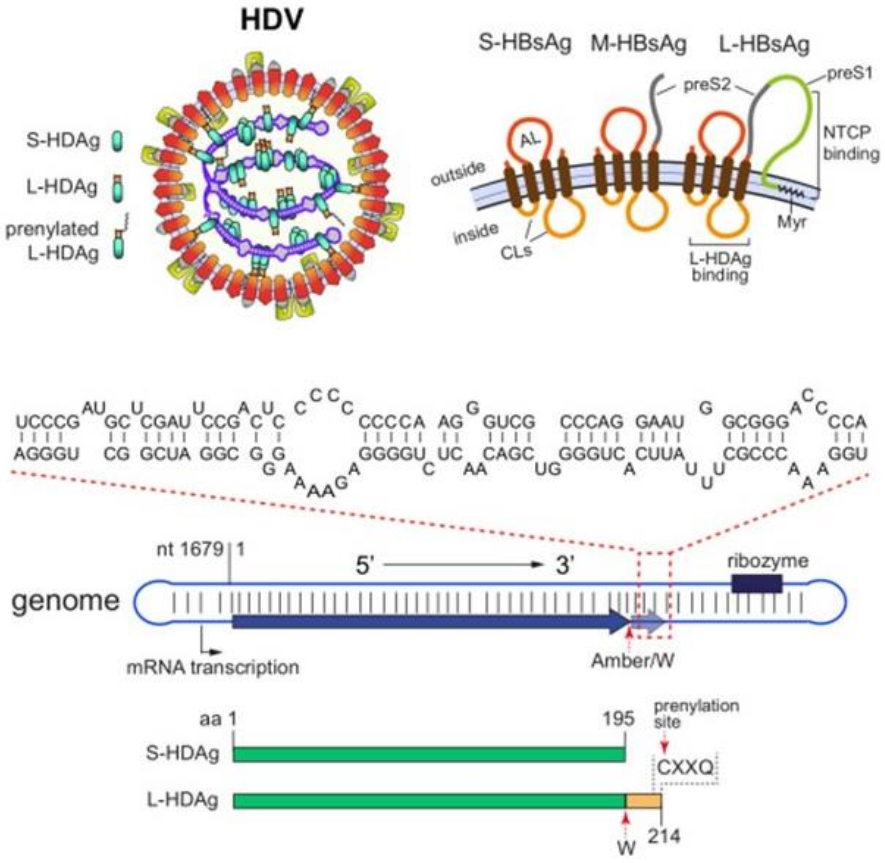
Viral Life Cycle (Chen et al., 2021)



Inside the HDV virion is the RNP complex consisting of two isoforms of HD-Ag, S- and L-HD-Ag, and outside is an HBV-derived envelope. This envelope contains small (S-), medium (M-), and large (L-) HBsAg proteins. HDV genome is single-stranded and circular RNA virus. However, it has a rod-like structure with base pairings and branches that are folded over each other (Urban et al., 2021). When HDV is encased by HBsAg, the same entrance method as HBV is used and it multiplies in hepatocyte cells. The virus binds to heparan sulphate proteoglycans (HSPG) found on the hepatocyte surface, and the pre-S1 domain of L-HBsAg binds to the HBV receptor (Yan et al., 2014 , Stoll, F., et al (2022). . After the hepatocytes are infected with HDV, the hepatocytes produce polymers, and then the ribozyme activity of the virus allows the virus to self-lyse and finally circularise. Viral mRNA virus migrates to the cytoplasm to synthesize L- and S-HD-Ag. Protein products combine with viral genomic RNA to form RNP (Urban et al., 2021) (Figure 7).

Figure 7.

Diagram of Virion and Genome for HDV



Researchers working towards elucidating the unusual and complex replication of HDV also suggested from their data that viruses other than HBV, such as flavivirus and hepacivirus, may package the HDV-RNP (Yan et al., 2014; Perez-Vargas et al, 2019 , Rizzetto, M. 2022).

Outcomes

The outcome of the disease is frequently determined by whether HDV is regarded as a co-infection or a super-infection. There are two acute HDV infection scenarios: individuals infected with HBV and HDV at the same period / synchronously, or individuals who are HBsAg transmitters who are subsequently infected with HDV. There are differences in the course of the disease between these two acute HDV phases: In the latter case, the disease enters a more severe and chronic course. In co-infection, both HBV and HDV occur simultaneously. HDV and HBV co-infections are often acute and self-limited-infections. The biphasic increase in serum aminotransferase is one of the indicators that can help differentiate between individuals with coinfection and patients with acute HBV. Less than 5% of

HBV/HDV co-infected patients have c-HDV infection. Table 3 shows the clinical characteristics of people who have HDV co- and super-infection

Table 3.

Clinical Characteristics of Individuals with HDV Co-Infection and Super-Infection

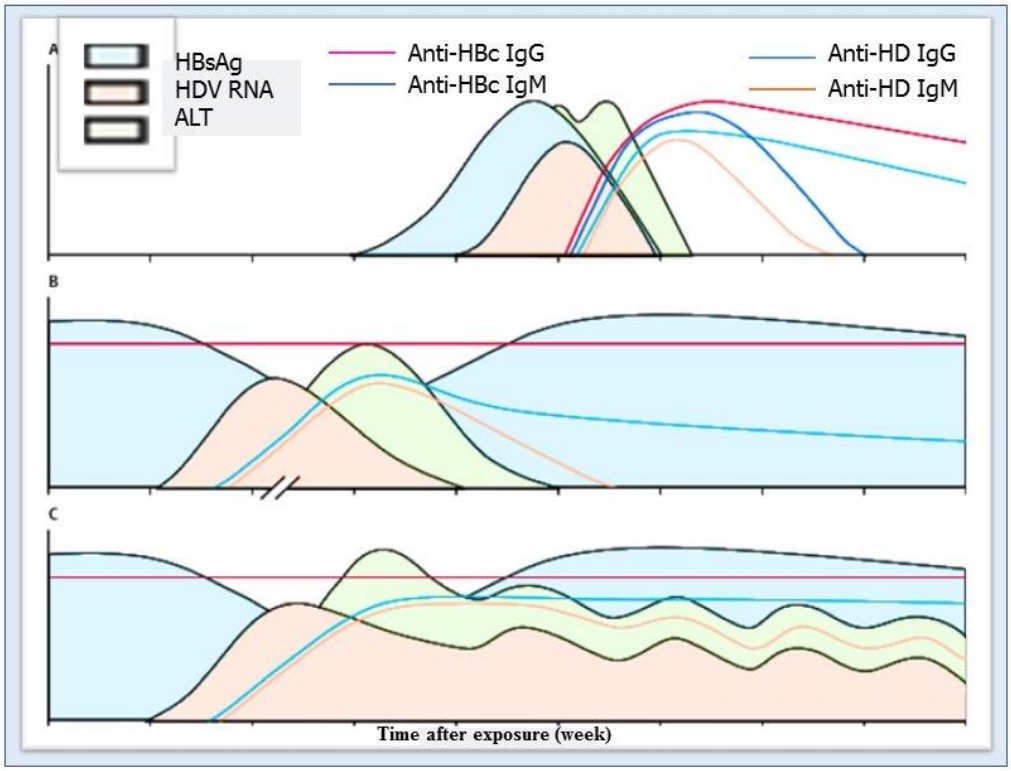
	Coinfection	Superinfection
HBV infection	Acute	Chronic
HDV infection	Acute	Acute
Serum markers		
HBsAg	Positive and transient	Positive and persistent
IgM anti-HBc	Positive	Negative
Anti-HBs	Positive in recovery phase	Negative
Anti-HDV	Late acute phase, low titer	Rapidly increasing, high titer
IgM anti-HDV	Positive, transient	Rapidly increasing, high titer
HDV RNA	Positive, early and transient	Positive, early and persistent
ALT level	Biphasic elevation	Monophasic elevation
Chronicity	<5%	70–90%
Outcomes	Recovery with seroclearance	Usually persistent infection

Super-infection: This happens when c-HBV carriers become infected with HDV. In 80% of cases, this results in severe acute hepatitis and c- HDV infection. The viral fulminant form, the most severe form of acute illness, occurs 10 times more commonly in HDV infections as compared to other types. It is characterized by personality changes, sleep problems, confusion, poor concentration, and occasionally hepatic encephalopathy, expressed by abnormal behaviour and coma. Fulminant hepatitis has an 80% mortality ratio. In approximately 60-70% of patients, c-hepatitis D infection progresses to liver cirrhosis. Cirrhosis can develop as soon as 2 years after infection or as late as 5-10 years later. HC carcinoma occurs at the same ratio in chronically infected HDV patients as in normal HBV patients. Overall, HDV infections have a mortality ratio of 2% to 20%, which is ten times higher than HBV. The manifestation of HDV sickness is fairly broad; acute co-infection may generate more severe reactions than mono-infection HBV. These responses also may include

acute liver failure. The situation is slightly different in individuals with c-HBV, HDV super-infection usually results in c-HDV in these patients, while the natural course of the disease continues with the course of HBV in some patients (Hughes et al., 2011). As a result of a study, it was reported that HBsAg was cleared in 10% of patients with anti-HDV antibodies after 4 years of follow-up (Niro et al., 2001, Brunetto, M. et.al 2023). Figure 8 depicts the evolution of serological markers in superinfected patients. The progression of serological and virological markers in patients with super-infection can be observed in various scenarios. In simultaneous co-infection, both viruses are cleared in almost all patients. However, as shown by a break in the x-axis in the case of HDV super-infection of an HBV carrier, spontaneous clearance of HDV-RNA may take years to occur and, in some cases, may result in the loss of HBsAg. In contrast, a chronic illness brought on by HDV-super-infection of an HBV carrier is more typical.

Figure 8.

Markers in Super-Infected Patients. A) Simultaneous co-infection results in clearance of both viruses (B) HDV super-infection of an HBV carrier (C) HDV super-infection of a chronic HBV carrier

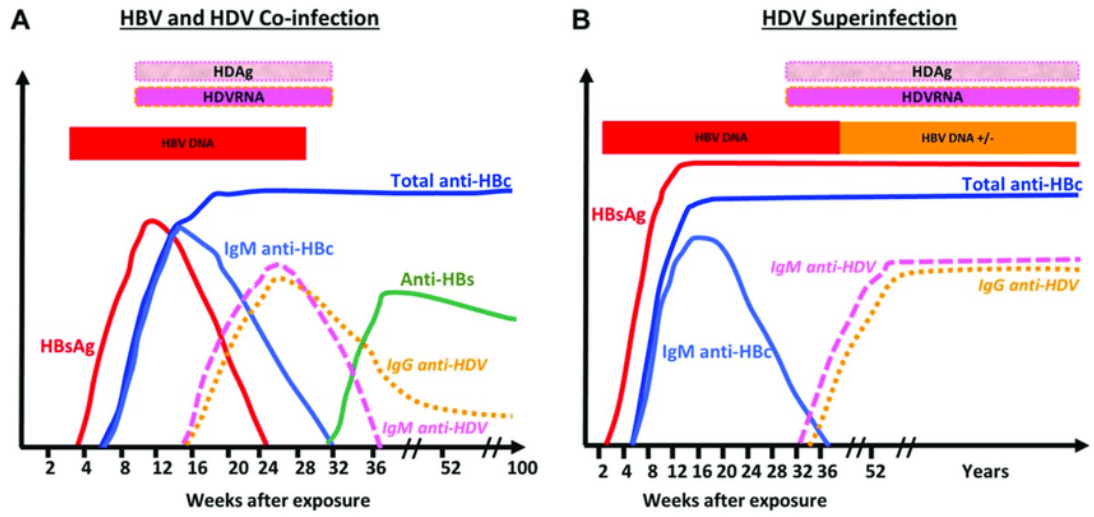


An undetected HBsAg carrier may experience acute hepatitis from super-infection. However, it's frequently misinterpreted as acute or c-HBV-related liver illness that's getting worse. Evaluations indicate that patients with HDV super-infection often have advanced severe hepatitis. These patients may progress to cirrhosis or die more rapidly than mono-infected HBV patients. Although the ratio of progression to cirrhosis is high, studies also report that there is no increase in the ratio of HC carcinoma due to suppression of HBV replication by HDV (Cross et al., 2008). Initially, HDV was thought to persist after transplantation as an isolated or latent infection; whereas, later research results indicated that the 5-year survival ratio after liver transplantation for HDV was more than 80% (Samuel et al., 1995; Lerut et al., 1999).

The first research results in which different genotypes of HDV were started to be evaluated were that the Gt affected the course of the disease. However, because recent research findings interpret the impact of Gt on the course of the disease differently, it is still challenging to evaluate the association between Gt and the disease's natural history. For example, patients with Gt 1 in Taiwan have a lower remission ratio than Gt 2 and Gt 4 mild liver disease is generally known in patients (Wu et al., 2006). In Japan, more cirrhosis progression has been reported in Gt 4 (Watanabe et al., 2003). In South America, information has been given regarding outbreaks of Gt 3 acute liver failure and severe hepatitis resulting in death (Niro et al., 1997).

Figure 9.

Serologic Course of (A) Acute HDV Infection (Healing) and (B) Chronic HDV Infection

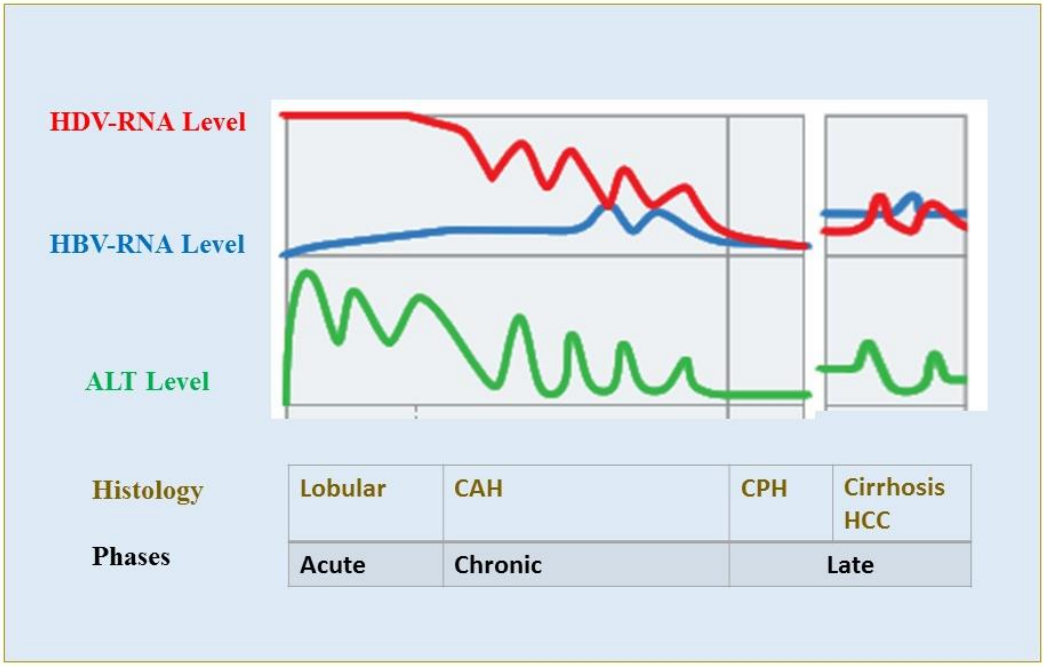


In summary, HDV-super-infection can be divided into three stages: The patient may experience severe fulminant hepatitis during the acute phase, which can swiftly progress to cirrhosis. Almost 90% of individuals who survive the acute phase pass into the chronic phase. The last name is last phase. As the virus becomes chronic, the risk of patients developing HC carcinoma also accelerates (Figure 10) (Chen, 2011).

Figure 10.

Three Different Natural History of Super-Infection. A) Acute phase (replication of HDV and suppression of HBV) ALT level is high. B) Chronic phase (HDV reactivated low HBV level) ALT level moderate. C) Late phase (cirrhosis and hepatocellular carcinoma development)

*CAH: chronic active hepatitis, CPH: chronic persistent hepatitis, CHC: hepatocellular carcinoma



Epidemiology and Geographic Distribution of HDV

Sero-epidemiological studies conducted in the 1980s reported that the prevalence of HDV in patients with HBV was 5%, and this corresponds to an estimated 20 million people worldwide (Lempp et al., 2016; Sureau & Negro, 2016). The prevalence of HDV in these years is in Southern Europe, the Middle East, East Africa and Asia; It was reported to be relatively higher than Northern Europe, South Africa and N-America (Taylor et al., 2013, Brunetto, M. et.al 2023).

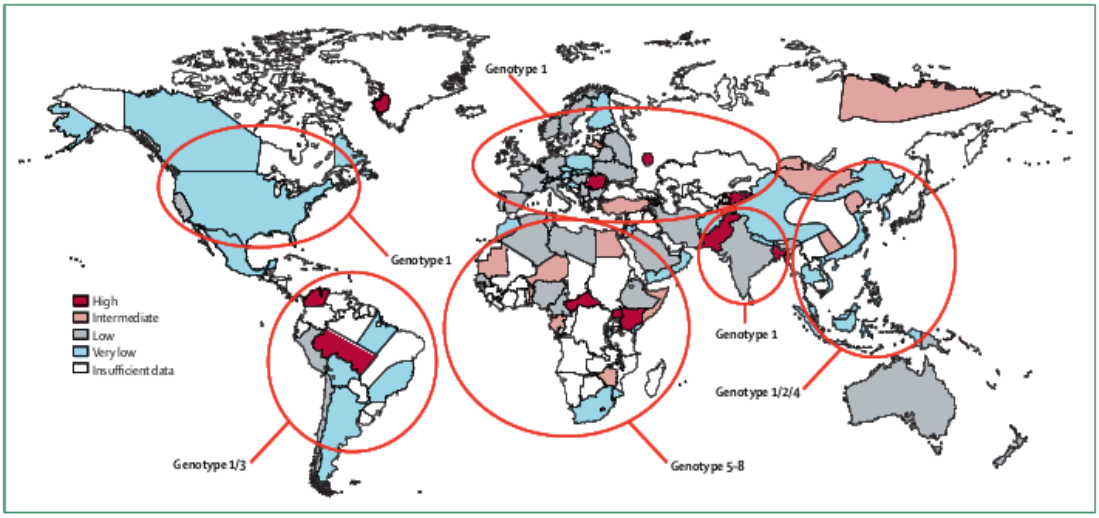
HDV infections are found all over the world, but the prevalence varies by region. Twenty to forty percent of HBsAg carriers in Africa, the Middle East, and Southern Italy have anti-HDV antibodies. Except for heroin addicts and hemophiliacs, where prevalence ratios range from 1 to 10%, HDV infection is uncommon in USA. Gay men and healthcare workers are at high risk of contracting HBV but, for unknown reasons, are at low risk of HDV infection. Furthermore, HDV infection is uncommon in Southeast Asia and China, where there is a large HBsAg carrier population. Haemodialysis patients, sexual contacts with infected people, and infants born to infected mothers (rare) are also at high risk of contracting HDV. Until now, HDV has infected over 10 million people worldwide.

Early research in the last quarter of the 20th century showed HDV infection to be endemic worldwide. Another important finding of the study was that there were large differences and contrasts in HDV prevalence. It was determined that HDV was

usually transmitted as super-infection in India, Africa and South America. Most of the children or adolescents chronically infected with HBV contracted HDV in adulthood, and it was reported that many of them died from periodic fulminant hepatitis D epidemics (Hadler et al., 1991). These infections seen in the Amazon basin were Gt 3 of HDV. Despite the implementation of vaccination, it was still a significant health problem in Amazon, while the prevalence of anti-HDV was found to be 41.9% in HBsAg carriers in Purusya (Braga et al., 2012). Likewise, outbreaks of fulminant and severe hepatitis caused by high HBV endemicity were still being recorded in Russia, Mongolia, and Greenland (Flodgren et al., 2000; Tsatsralt-Od et al., 2006; Børresen et al., 2010). Two subtypes of Gt 1 have been identified, 1A (predominant in Asia, common in the Mediterranean) and 1B (predominant in the Americas, common in the Mediterranean) (Figure 11).

Figure 11.

HDV Genotype Distribution Worldwide (Hughes et al., 2011)

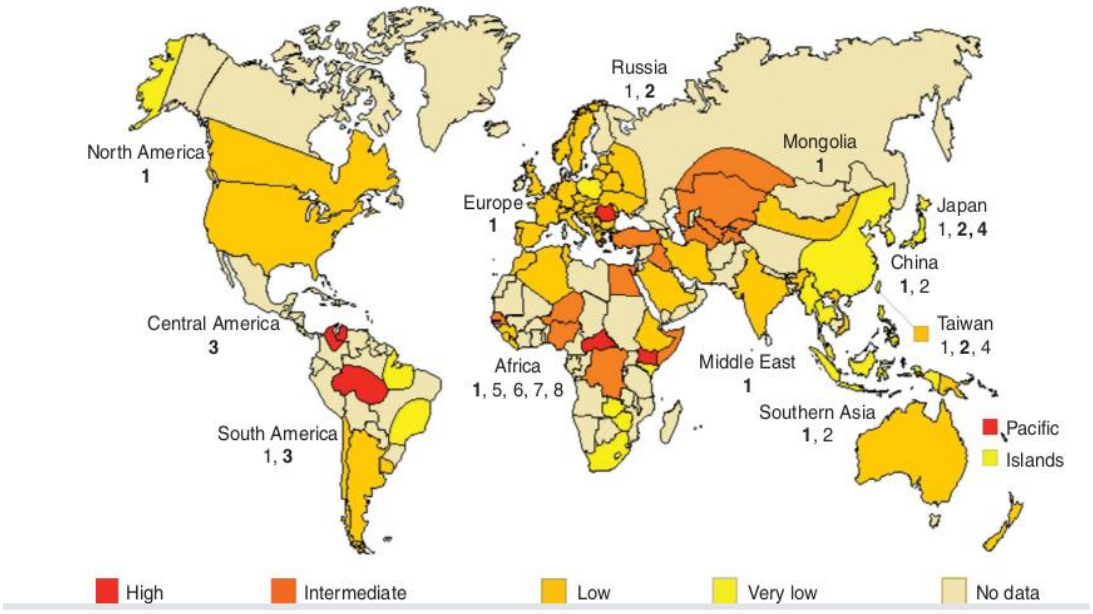


Notably, HDV prevalence was low in areas with low HBV prevalence in the 1980s, such as in areas with high HBV prevalence, such as Japan. In a study conducted in Japan in 2000, the prevalence of HDV was reported as 8.5%. The study, conducted in the Mediterranean Basin and Taiwan, revealed that HDV infection originates from people using injection drugs and sharing contaminated equipment. It has been observed that c-HDV case originating from its reservoir

affects the general population as a super-infection with close contact (Sagnelli et al., 1992). In Italy, men have been infected with HDV more than women. In Taiwan, the ratio of anti-HDV in prostitutes was 55%, and the ratio of anti-HDV in people who use drugs by injection was 91% (Rizzetto & Ciancio, 2012). Figure 12 displays the principal regions of HDV dispersion in the world.

Figure 12.

Geographical Schematic Representation of Globally Distribution of Dominant HDV Genotype (Negro, 2014)



Many other studies were conducted in the same period, and the results of these studies generally showed differences and inequalities in prevalence ratios at the regional level. While some studies reported that HDV prevalence could be neglected, some studies reported the presence of hyperendemic pockets of infection around regions where the prevalence could be neglected (Rizzetto et al., 1991, Brunetto, M. et.al 2023). Hepatitis D is the main risk factor of cirrhosis and fulminant hepatitis worldwide, clinical research findings using the medical categorization approach have shown.

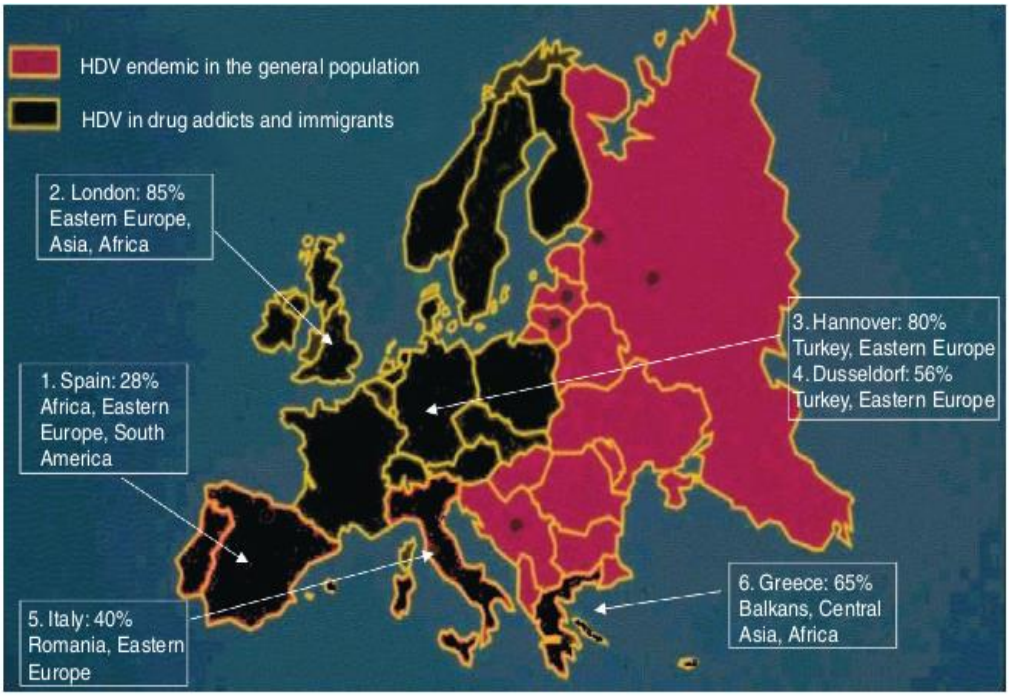
In the results of studies conducted in Italy in different years, the ratios of anti-HDV were determined as follows: 24.6% (in 1983) in carriers with liver disease;

23% (in 1987); 14% (in 1992) and 8.3% (in 1997) (Rizzetto & Ciancio, 2012). In Spain, it was reported that it decreased from 15% (1975–1985) to 7.9% (1986–1992). The HDV super-infection ratio in Taiwan decreased from 23.7% in 1983 to 4.2% in 1996. According to reports, from 1980 to 2005, Turkey's prevalence of anti-HDV in chronic HBsAg liver disease dropped from 31% to 11%. In Europe, the situation was different. It was determined that there was no decrease in HDV prevalence over the years. In the results of the study conducted in Italy in 2007, it was reported that there was no decrease in HDV prevalence (8.1%). According to the results of the study published in 2014, it was reported that the prevalence of anti-HDV in Italy was 8.4% and HDV was found in 7.4% of Italians and 11.5% of immigrants (Brancaccio et al. 2014). In a study conducted in England, it was determined that 8.5% of 1000 HBsAg carriers were positive for anti-HDV. In the results of these studies, it has been reported that this virus originates from immigrants as well as the prevalence of anti-HDV. Reports of HDV have also been reported from Northern European countries, but it has also been stated that HDV is limited to risk groups in countries such as Switzerland and the Czech Republic (Genné D & Rossi, 2011). Depending on the HDV prevalence seen in risk groups, there was an increase in liver-related diseases and mortality ratios in these populations (Soriano et al. 2011; Ionescu & MihaĬescu, 2011). In a study conducted in patients with c-hepatitis B in Turkey (between 2002 and 2004), anti-HDV was determined at a ratio of approximately 28% (Bahcecioglu et al. 2011). The prevalence among HDV (+) immigrant individuals in Europe in 2012 is given in Figure 13.

Figure 13.

Prevalence of HDV Positivity Among Immigrant Individuals in Europe in 2012

(Rizzetto & Alavian, 2013)



Since the beginning of the 2000s, taking preventive measures such as the initiation of vaccination against HBV and routinizing hygiene rules have also reduced the prevalence of HDV in many regions. However, since the beginning of the 2000s, an increase in HDV prevalence has been observed in some countries through immigrants coming to Europe from endemic regions (Rizzetto & Alavian, 2013). For example, while 1% anti-HDV positivity was detected in France until 2005, this ratio increased to 6.5 times in 2010 (Servant-Delmas et al., 2014). A similar situation was valid in Germany, and the prevalence of HDV increased from 7% to 14% (Wedemeyer et al., 2007, Adepoju, V. A., Udah, D. C., & Adnani, Q. E. S. (2024).

In USA, the ratio of anti-HDV in drug addicts using intravenous injectors with c-HBV was 50%, and the ratio of anti-HDV in 500 HBsAg carriers was 8%. In the results of the study, it was determined that HDV-positive individuals had cirrhosis at a higher ratio than individuals with mono-infection with HBV (almost 80% of these individuals were immigrants) (Gish et al., 2013). In Somalia, Egypt, and Saudi Arabia, patients with c-HBsAg hepatitis had HDV prevalence ratios of 47.4%, 24.4%, and 8.2%, respectively. In the Middle East and nearby areas, HDV is still endemic (Amini et al., 2013). HDV is endemic in Pakistan, Iran, and India. Although the frequency of HDV is low in the majority of HBsAg in Malaysia and Thailand people, the ratios among drug addicts are as follows: 20-34% and 21.8% (Theamboonlers et al. 2002). The prevalence of anti-HDV in China was found to be

variable between 13-15% (Ciancio & Rizzetto, 2002). 2006 In China, the anti-HDV ratio among injecting drug users was determined as 2% (Li et al., 2006).

In a study in collaboration with WHO, it was stated that HDV affects approximately 5% of individuals with chronic infection with HBV (2020). In addition, as a result of this report, it was reported that this co-infection is responsible for 1 in 5 cases of liver disease or liver cancer. As a result of the study, the points with a high prevalence of HDV occurrence were identified as Mongolia, Moldova, and countries in western and central Africa. Today, HDV infection continues to occur worldwide. Systematic examination results report that its prevalence is almost 15% among HBsAg (+) individuals, and its global prevalence is approximately 1% (Chen et al., 2019; Stockdale et al., 2020). The highest HDV prevalence among HBsAg (+) individuals is reported to be in Mongolia. The regions with the highest prevalence ratio (approximately 10%) are Moldova, West and Central African countries (Stockdale et al., 2020). When age and gender, which are demographic characteristics, are taken into consideration, it is reported that the elderly are more at risk than the young and men are more at risk than women (Stroffolini et al., 2017; Chen et al., 2019).

All the above-mentioned information shows us that the global presence of HDV has not decreased and is probably still underestimated when considered.

Paths of Transmission

HDV is transmitted parenterally, just like HBV. Exposure to HDV-infected blood or body fluids or through rupture of the skin (through injection, tattooing, etc.) causes HDV transmission. Therefore, the risk of HDV is higher in individuals who use narcotics, especially by injection. Studies also indicate that HDV is sexually transmitted. It is reported that intra-familial transmission is also common in regions with a high prevalence. Perinatal transmission of HDV is extremely rare, due to the attention paid to sterilization of medicinal products used in blood transfusion or haemodialysis procedures in developed countries. Although mother-to-child transmission is possible, this condition is extremely rare. HBV vaccination is not only preventive against HDV but also against HDV-co-infection. C-HBV carriers have a higher risk of HDV infection than healthy individuals. However, individuals who are not immune to HBV, that is, natural disease or unvaccinated individuals, are also at risk for HDV-infection due to the risk of being infected with HBV.

Individuals with HIV, HCV-infection are potentially at higher risk of contracting HBV-related HDV-co-infection.

Viral Dominances among Hepatitises

Co-infection or super-infection with HDV suppresses HBV replication in patients due to the activations of S-HDV and L-HDV proteins. These proteins induce interferon, which by lowering mRNA efflux prevents HBV replication. Most patients with HDV co-infection have reduced HBV DNA (deoxyribonucleic acid) and are HBeAg negative (70–90%) (Sagnelli et al., 2000; Heidrich et al., 2009; Zachou et al., 2010). Only when HDV infection clears, either spontaneously or after treatment with interferon-α, is HBV replication reactivated (Castelnau et al., 2006 , Adepoju, V. A., Udah, D. C., & Adnani, Q. E. S. (2024).

The results of the research also include serological findings showing that 30% of individuals infected with HBV and HDV are also exposed to HCV (Cross et al., 2008; Heidrich et al., 2009). In this triple infection, HDV is the predominant virus because it suppresses not only HBV replication but also HCV replication (Mathurin et al., 2000). HCV RNA was positive in 19% of patients with anti-HDV antibody positive, anti-HCV antibody positive and HBsAg (+) (Mathurin et al., 2000; Cross et al., 2008; Heidrich et al., 2009). Although HBV and HCV co-infection requires long-term follow-up, the majority of HCV RNA-positive (negative) patients are likely to have cleared HCV infection (Raimondo et al., 2006).

Symptoms and Incubation

When compared to hepatitis A, B, and C, HDV has a more serious medical course. After an incubation span of 3 to 7 weeks, it appears with nonspecific clinical signs such as exhaustion, lethargy, feeling nauseated, and eating loss. After these non-specific symptoms, which last for 3-7 days, viral replication decreases during this time. It can also occur after the symptoms of jaundice. In this case, while nausea usually continues in addition to fatigue from the symptoms, colour changes may occur in the patient's urine (dark) and stool (clay colour) due to anomalies in the Blb level. Acute co-infection (simultaneous HBV and HDV) presents symptoms ranging from mild to severe, indistinguishable from other acute types. In the case of super-infection, it accelerates the progression of the disease of the patient who already has

chronic HBV. The progression to cirrhosis is almost 10 years shorter in super-infected individuals than in mono-infected individuals.

Diagnosis

Type D hepatitis should be considered in people who have recently been infected with HBV or who test positive for HBsAg. Serological tests are used to confirm the diagnosis of type D hepatitis. HDV antibody is a biomarker of HDV infection (anti-HDV). Total anti-HDV antibody value can be measured with kits used in RIA or ELISA tests. Increased amounts of anti-HDV IgG and IgM are utilized to diagnose HDV infection, which again is confirmed by the detection of HDV-RNA in serum. For active HDV infection, immunoglobulin M (IgM) anti-HDV is the most important diagnostic marker predicting the progression of infection or transition to c-HDV infection. However, since IgM anti-HDV titer is found to be high in patients with active c-HDV infection, this marker is not diagnostic in individuals with acute HDV infection, just like in hepatitis A or B. The distinction between co-infected and super-infected individuals can be achieved using IgM anti-HBc. In this case, the presence of both IgM anti-HBc and IgM anti-HDV suggests co-infection, while super-infection is considered only in individuals with high IgM anti-HDV. In individuals with low HDV antigen levels, the amount of antigen can be determined by Western blot analysis. In the c-HDV phase, reverse transcriptase-polymerase chain reaction (RT-PCR) can be utilized to detect low HDV viremia 10-100 copies/ml. HDV-RNA levels are associated with liver damage and elevated ALT levels. Liver biopsy is the clearest method of assessing the severity of the disease and the appearance of HDV-Ag in the nuclei of hepatocytes is the gold standard of diagnosis. Markers of HDV infection disappear within months after recovery, including IgM and IgG antibodies. In c-hepatitis D infection, HDV-RNA, HDV-Ag, IgM anti-HD and IgG anti-HD antibodies remain (Chen et al., 2011; Hughes et al., 2011).

Diagnostic markers and processes in HDV infection can be summarized as follows (Hughes et al., 2011):

- Anti-HDV IgG antibody: It remains positive in all individuals previously exposed to HDV and persists long after viral clearance.

• Anti-HDV IgM antibody: It is positive during the acute phase of infection and negative in past infection, but may persist in a significant percentage of chronic HDV infection patients. While it is sometimes used as a potential marker for HDV replication, it is not completely sensitive or specific.

• HDV-RNA qualitative: It is positive in all chronic HDV patients, but negative in either spontaneous or treatment-induced viral clearance.

• HDV-RNA quantitative: It is a reliable method for predicting or monitoring therapeutic efficacy.

• HBsAg qualitative: It must be positive for HDV infectivity.

• HBsAg quantitative: It is positively correlated with HDV-RNA. Falling titre could indicate HBsAg loss and thus HDV clearance, which could be used to estimate or monitor treatment response.

• HBeAg: It is negative in about 85% of patients.

• HBV-DNA quantitative: Due to HDV suppression, the level is usually negative or low. However, it may be elevated in patients with detectable HBeAg. It can reactivate after natural or treatment-induced HDV clearance.

• ALT: Although it is typically elevated, it does not strongly correlate with the degree of histological liver damage.

Prevention and Treatment

HDV infection prevention is based on HBV infection prevention because HDV did require the HBV-Ag to cause infection. There is a high-yielding HBV vaccination but no HDV vaccine. To prevent, HDV-HBV co-infection, one can use the HBV vaccine or post-exposure prophylaxis (Hepatitis B Immune Globulin). Educating c-HBV carriers about transmission and dangerous behaviors is the only way to prevent HBV-HDV superinfection. Blood and blood products, sexual contact, sharing needles, and mother-to-child transmission are among the ways that HDV can spread.

HDV infection has no particular treatment option, and also immunosuppressive therapy has no clinical benefit. There is no scientific proof that antiviral medications such as ribavirin are also potent. High doses of α-interferon for infected patients have remission of disease, but most patients still have positive HDV-RNA, with or without improvement in disease conditions. The most difficult and complex aspect of HDV treatment is that the ideal treatment should be effective not only against HDV virus, but also against HBV virus that HDV uses as host. Research into recombinant therapy has demonstrated its effectiveness in treating HDV by reducing serum aminotransferase levels. However, treatment response tends to diminish after treatment discontinuation. Reports on interferon therapy indicate that high doses of interferon can lead to HBsAg loss (Farci et al., 2004). While some research results advocated the prolongation of the applied interferon treatment, some research results showed that prolonging the treatment period did not provide any additional benefit (Yurdaydin et al., 2007). Interferon-induced clearance of HDV-RNA has been linked to a decrease in HBsAg concentrations and, in some cases, HBsAg loss, with no reduction in HBsAg in treatment-resistant patients (Manesis et al., 2007). Interferon therapy appears to have an indirect effect, possibly through an effect on HBV or the immune function to infection. Orthotopic liver transplantation has been shown to be effective in the treatment of fulminant acute and advanced c-hepatitis D infections.

Key Facts

- HDV needs HBV for replication
- Affects approximately 5% of individuals with c-HBV
- HDV occurs in humans in two ways: i) co-infection or ii) super-infection.
- With the HBV vaccination program that started in the 1980s, the number of HDV infections decreased due to the decrease in the HBV risk of individuals.
- Co-infection is considered the most severe form of chronic viral hepatitis as it increases the risk of liver-related death.
- The most effective way to prevent HDV is to be vaccinated against HBV.

CHAPTER III
Material and Method

Research Design

We accessed primary records regarding the incidence of HBsAg (+) patients using the information in the Near East University Hospital (NEU-H) database. The patients included in the study consisted of outpatients, who came to the hospital for various complaints and routine examinations, and who did not have severe liver disease. This cross-sectional study, conducted in TRNC NEU-H between January 01, 2018 and September 31, 2022, included 422 HBsAg (+) and outpatients.

Patient Groups and Ethics

This study was carried out from serum samples diagnosed with Abbott Diagnostic Divison, HbsAg Qualitative Germany kits used in the diagnosis of HBsAg in the microbiology laboratory of our hospital. HBsAg positive sera were reserved for this study at -80 degrees Celsius. The study period spanned from January 2018 to December 2022, and HDV patients were identified using the B18.0 code from the International Classification of Diseases (ICD)-10 codes. A total of 422 HBsAg-positive outpatients were included in this cross-sectional study, which was conducted at NEU-H in TRNC between January 01, 2018 and September 31, 2022. The data of this patient group were accessed using the Microbiology laboratory patient information system and evaluated retrospectively. The following information was verified/used from the NEU-H information system used to determine the patient group to be included in the study: Demographic characteristics of HBV cases with confirmed HBsAg (+), such as age, gender, nationality and region of residence. Ethics committee approval was obtained from the NEU Ethics Committee with the date of 22.10.2020 /84

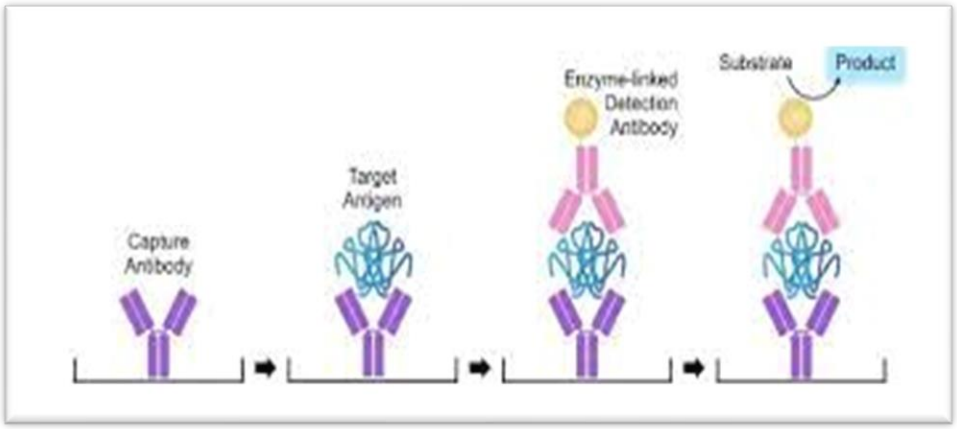
HDV Prevalence

HDV occurs as either co-infection or super-infection in HBsAg (+) patients. In both co- and super-infection cases, the standard determining parameter in clinical screening for diagnosing a patient as HDV- (+) is the positive detection of HDV antibody (anti-HDV) and/or HDV-Ag. Serum HDV- RNA measurement by RT - PCR is the method used to confirm the presence of HDV active infection. In this

study, the prevalence of HDV in HBsAg (+) patients was evaluated. For this purpose, the anti-HDV and HDV - Ag positivity of the patients known to be positive for HBsAg were examined by ELISA in the serum (Figure 14). HDV- RNA determination was analysed by RT- PCR method from the samples of patients with positive anti-HDV and HDV – Ag.

Figure 14.

Working Mechanism of ELISA Test Methods



Evaluation of Anti-HDV Positivity, with ELISA

Anti-HDV, which correlates with the clinical status of the HBsAg (+) individual, is a marker of HDV exposure. Anti-HDV positivity is not only a marker of HDV exposure in individuals with liver disease but also an indicator of HDV replication. Therefore, Anti-HDV positivity has almost diagnostic value for c-HDV as well. The serological presence of HDV was determined using the ELISA method in present study (Figure 15). Figure 15. *ELISA Kit Used in the Quantitative Determination of Anti-HDV*

The serum of HBsAg (+) patients were retrospectively tested for anti-HDV using the ELISA kit (Dia. Pro Diagnostic Bioprobes Srl, Sesto San Giovanni (MI), Italy) according to the manufacturer's instructions with 98.0% clinical specificity and sensitivity for detection of total anti-HDV antibodies, as declared by the manufacturer.

The test setup gives the critical optic density, which is a measure of positive or negative results for the serum examined. The test was repeated for samples with inconclusive results (grey zone).

Evaluation of HDV - Ag Positivity, with ELISA

Additional serum samples were taken from individuals who were found to be anti-HDV positive, and the presence of HDV- Ag was retrospectively tested using an ELISA kit (Dia. Pro Diagnostic Bioprobes Srl, Sesto San Giovanni (MI) – Italy; Figure 16). According to the manufacturer's written statement, the clinical sensitivity and specificity ratio of the kit used, were as follows: > 98% (for both parameters).

Figure 16.

ELISA Kit for HDV – Ag

The test setup gives the critical optic density, which is a measure of positive or negative results for the serum examined. The test was repeated for samples with inconclusive results (grey zone).

Evaluation of HDV- RNA, with PCR

Although the risk of HDV is low in a-symptomatic HBsAg (+) patents, often anti-HDV may represent the effect of a previous infection or an unrecognized/undetectable HDV infection. Because some of these patients may harbour HDV infection, it is reasonable to test all carriers for HDV-RNA even in the absence of severe or apparent liver disease.

Figure 17.

PCR Kit for HDV – RNA: Kit for the isolation of total nucleic acid (viral DNA and RNA) from mammalian serum and plasma

Figure 18.

RT-PCR in NEU-H

Kit (MagNa Pure LC Total Nucleic Acid Isolation Kit, Roche) designed for the clinical management of patients with chronic HDV infections with other laboratory markers of disease was used. With this method, the possibility of a permanent viral response can be evaluated as well as evaluating the viral response to the antiviral treatment administered by measuring the changes in serum HDV-RNA levels. The kit used can be used as a screening test for the detection of HDV-RNA in the blood as well as to confirm the presence of HDV infection.

After the patient's blood was transferred to 5 ml EDTA tubes, it was centrifuged at 800-1,600 g for 20 min to separate plasma/serum from blood samples, transferred to sterile tubes and stored at -80 °C. Using the MagNa Pure LC Total Nucleic Acid Isolation Kit (Roche) and the HP200 extraction methodology, total nucleic acids were extracted and suspended in 100 µl volumes. Afterward, 8 µl of the eluate was amplified in a 20 µl reaction that also contained 2 pmol of HDV probe, 14 pmol of HDV rev primer, 18 pmol of HDV fwd primer, and 5 µl of 4x Master Mix with UDG (FVMM, Thermo Fisher Scientific) (Table 4) (Beudeker et al., 2021).

Table 4

Primers and Probes Used in HDV PCR Protocols

Name	**5'-label-sequence-quencher-3'**
Forward primer	AGGAGGTGGAGATGCCATG
Probe	FAM- TCGCGTCCTTCTTTCCTCTTCGGGT-BHQ1
Reverse primer	GGGTTTCCACTCACAGGTT

RT-PCR program for LightCycler® 480 was started as given in Table 5.

Table 5.

HDV RT-PCR Stages

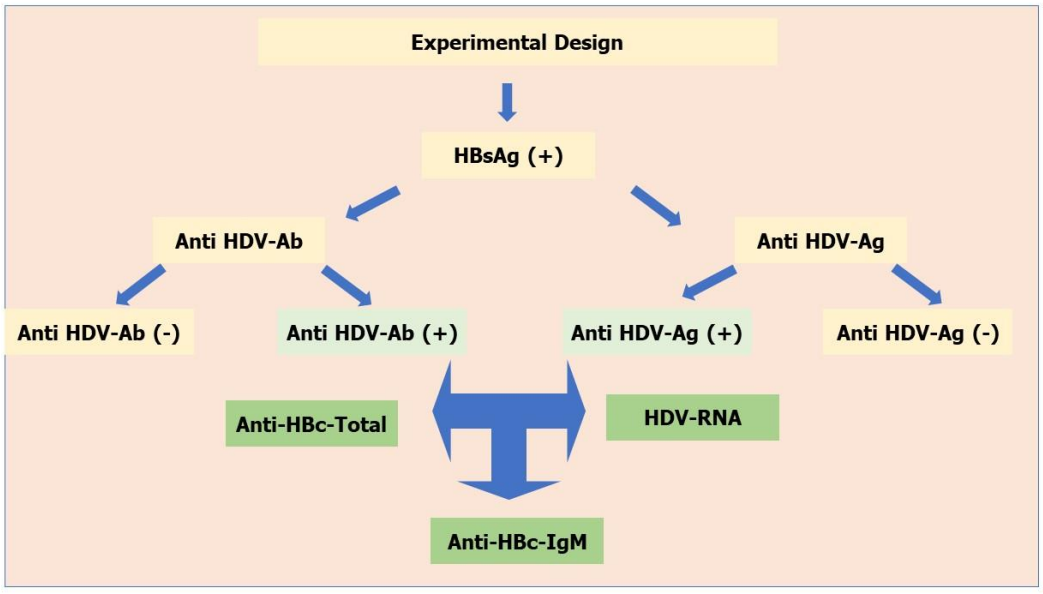
Profile	Cycle	Temperature (°C)	Time (s)
Reverse transcription	1	55	300
Taq activation	1	95	120
Denaturation	40	95	600
Annealing/Elongation		60	60
Cooling	1	40	30

A LightCycler 480 II (Roche) with the Fit points analysis module was used for amplification. Using a RealStar HDV RT-PCR Kit 1.0 (Altona), negative RT-PCR results from HBsAg (+) patients were verified in accordance with the manufacturer's instructions.

Our experimental study design was summarized in Figure 19.

Figure 19.

Experimental Design



Anti HBc IgM, with ELISA

The ELIS

A method was used for the qualitative determination of IgM antibodies to hepatitis B virus core antigen (anti-HBc IgM) in serum or plasma to aid in the detection of acute infection. Anti-HBc IgM ELISA kit (Abbott Diagnostic Division, Germany) was carried out in accordance with the manufacturer's instructions as follows:

- The samples were waited for 15-20 min to reach room temperature.
- Dilute Wash Buffer 1:20 with distilled water.
- Wells were marked with two wells as positive control, three wells as negative control, and one as blank.
- Diluted each sample 1:1000 with normal saline.
- 100 µl of sample was added to each well and then plate incubated for 30 min at 37 °C.
- After incubation, each well was washed 5 times with diluted washing buffer at the end.
- 100 µl of HRP conjugate reagent was added to each well except the blank and incubated at 37 ºC for 30 min.
- After each well was washed 5 times with diluted washing buffer, added 50 µl of Chromogen A and Chromogen B solution into each well (including the Blank) and incubated the plate at 37ºC for 15 min.
- After the incubation period, added 50 µl stop solution into each well and mixed gently.
- The intense yellow color was expected in the positive control and anti-HBc IgM (+) sample wells.
- The absorbance of the plate was read at 450 nm.
- Cut-off value (C.O) = nc (the means absorbance value of three negative controls) x 2.1
- S/C.0 < 1: Samples with an absorbance lower than the cut-off value were considered negative. That is, it shows that no IgM class antibodies against hepatitis B core antigen were detected with the antiHBc IgM ELISA kit.
- S/C.0 ≥ 1: Samples with an absorbance greater than the cut-off value were considered positive.
- S/C.0 = 0.9 - 1.1: Samples with an absorbance to the cut-off ratio between 0.9 -1.1 were borderline samples.

Anti-HBc Total with ELISA

Anti-HBc Total ELISA (Abbott Diagnostic Division, Germany AntiHBcTotal) is a method for the in vitro qualitative detection of total antibody to hepatitis B virus core antigen (Anti-HBc Total) in human serum or plasma. The ELISA method used to detect the total antibody against anti-HBc Total was performed in accordance with the manufacturer's instructions as follows:

- The samples were waited for 15-20 min to reach room temperature.
- Wells were marked with two wells as positive control, three wells as negative control, and one as blank
- Added 50 µl of each sample to the wells on the plate
- Added 50 µl of Anti-HBc· Peroxidase solution to each well (excepting blank well) and taped the plate, gently
- Plate incubated for 60 min at 37 °C
- After incubation, each well was washed 5 times with diluted washing buffer at the end.
- Added 100 µl of the mixture solution (mixed in equal volumes Chromogenic 3,3',5,5'-tetramethylbenzidine concentrate and Substrate buffer (Citrate acid buffer containing 0.03% H_2O_2)] to each well (including blank well)
- After 15 min incubation at room temperature, 100 µl of stop solution was added to each well and the absorbance of the samples was read at 450 nm.

The Cut-off Value was calculated according to the formula: Cutoff Value = 0.4 NCx (the mean of three negative controls) + 0.6 PCx (the mean of two positive controls)

ALT and AST levels

ALT and AST levels were measured using the Abbott Architect C16000 device (Figure 20) and kits suitable for this device (8L92-20 and 07D8121 respectively).

Figure 20.

Abbott Architect C16000 Device

Statistical Analysis

Data analysis were performed with the IBM SPSS (Ver. 20.0) program at a 95% confidence interval. In the study results, categorical variables were expressed as ratio/percentage and continuous variables were expressed as mean with standard deviation (mean ± SD).

CHAPTER IV

Results

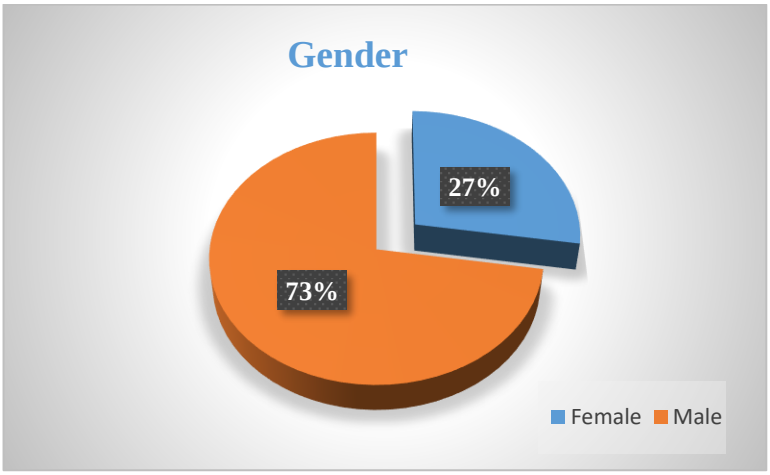
In this section, the findings reached in the light of the data collected for the study questions are mentioned.

Demographic Features

The gender distribution ratios of a total of 422 HBsAg (+) individuals among the patients admitted to NEU-H between 2018 and 2022 were as follows: 116 (27%) were female and 306 (73%) were male (Figure 21). The ratio of both genders to each other was determined as male/female 2.64.

Figure 21.

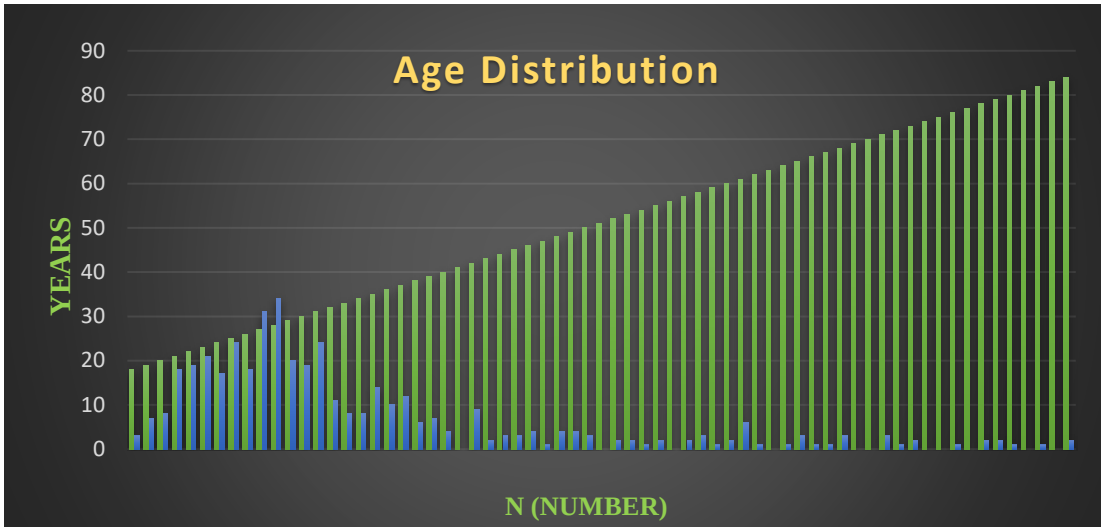
The Gender Distribution Ratio of a Total of 422 HBsAg (+) Patients Admitted to NEU-H between 2018-2022



The ages of a total of 422 HBsAg (+) patients admitted to NEU-H between 2018 and 2022 ranged from 18 to 84 years old. The mean age of HBsAg (+) patients was 33.51 ± 7.2 years. The mean age of female was 36.91 ± 5.1 and the mean age of male was 32.23 ± 8.2 (Figure 22).

Figure 22.

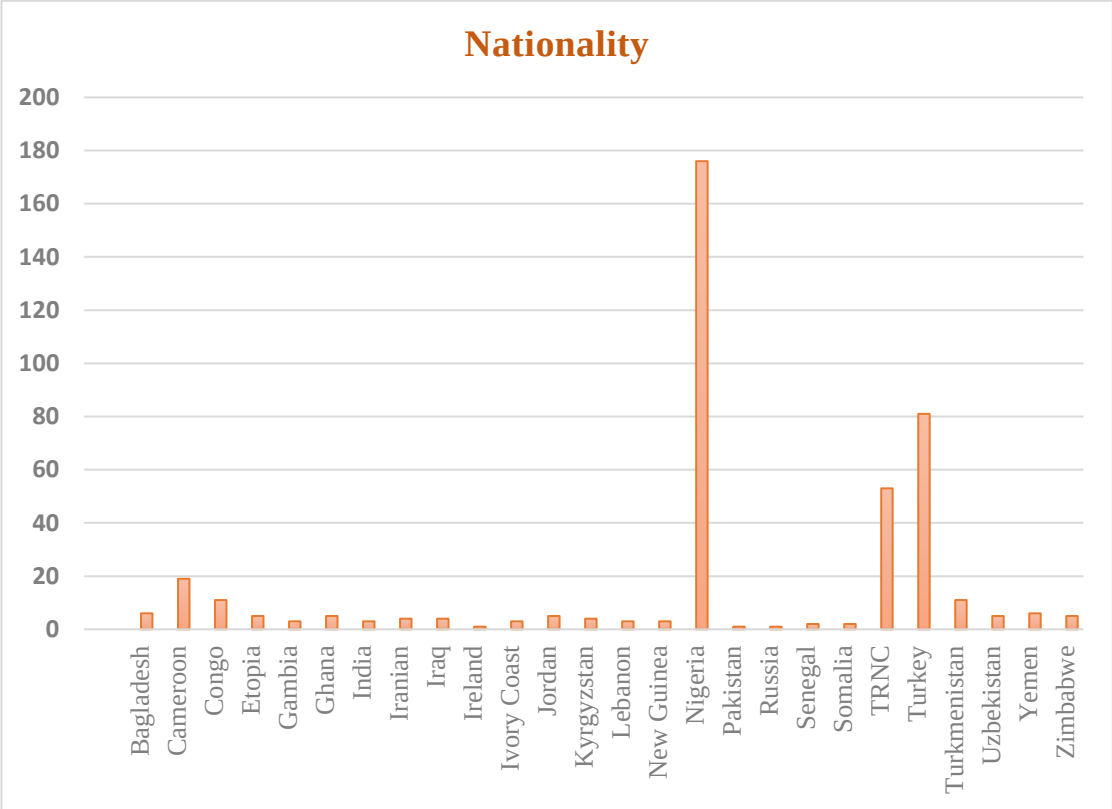
Age Distribution of a Total of 422 HBsAg (+) Patients Admitted to NEU-H between 2018-2022



When we analysed the distribution of 422 HBsAg (+) patients admitted to NEU Hospital between 2018 and 2022 by nationality, we determined that the highest HBsAg (+) ratio was from Nigerian patients (n=176, 41.7%). The distribution of other HBsAg (+) patients by country was determined as follows: 19.1% (n=81) from Turkey, 12.6% (n=53) from TRNC; 4.5% (n=19) from Cameron; 2.6% from Congo and Turkmenistan (n=11, for each country); 1.4% from Bangladesh and Yemen (n=6, for each country); 1.2% from Ethiopia, Ghana, Jordan, Zimbabwe, and Uzbekistan (n=5, for each country); 1.0% from Iranian, Iraq, and Kyrgyzstan (n=4, for each country); 0.7% from India, Gambia, Ivory Coast, Lebanon, and New Guinea (n=3, for each country); 0.5% from Senegal and Somali (n=2, for each country); 0.2 % from Ireland, Pakistan, and Russia (n=1, for each country) (Figure 23).

Figure 23.

Distribution of 422 HBsAg (+) Patients Admitted to NEU-H between 2018-2022 by Nationality



Demographic characteristics of HBsAg (+) patients were summarized in Table 6.

Table 6.

Demographic Characteristics of HBsAg (+) Patients

Features		**n**	**%**
Age groups	18-29	220	52.1
	30-49	153	36.3
	50 ≤	49	11.6
Gender	F	116	27.5

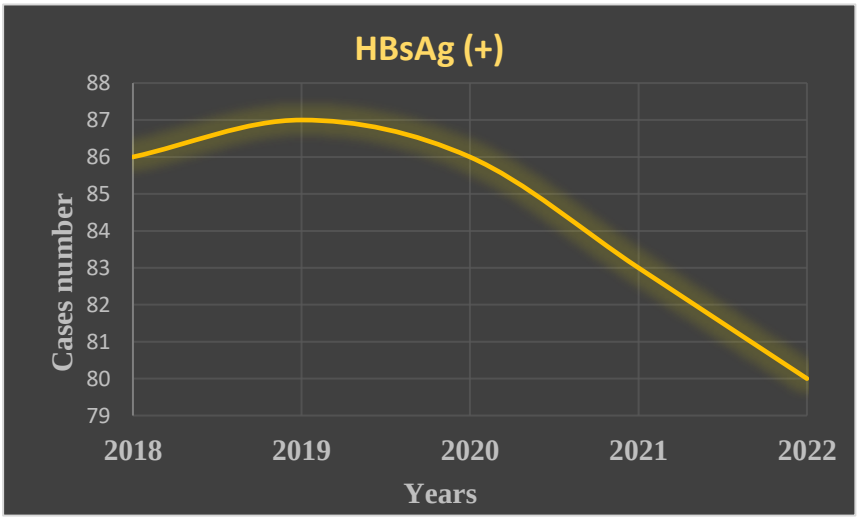
	M	306	75.5
Nationality	Turkey	81	19.2
	TRNC	53	12.6
	Nigeria	176	41.7
	Cameroon	19	4.5
	Congo	11	2.6
	Turkmenistan	11	2.6
	*Other	71	16.8
Total		**422**	**100**

* Countries with less than 10 HBsAg (+) patients. F: Female, M: Male, TRNC: Turkish Republic of North Cyprus

The distribution of patients with HBsAg (+) according to the years of admission to the NEU-H was given in Figure 12. It was determined that HBsAg (+) was detected in a total of 422 patients: 86 (20.4%) in 2018, 87 (20.6%) in 2019, 86 (20.4%) in 2020, 83 (19.6%) in 2021, and 80 (19.0%) in 2022.

Figure 24.

HBsAg (+) distribution ratio in NEU-H (2018-2022), in a total of 422 cases



Anti-HDV-Ab

The results were interpreted as the ratio between the cut-off value and the sample OD 450 nm or Co/S. The interpretations of the results were made according to Table 7 below.

Table 7.

Interpretation of the Anti-HDV-Ab ELISA Kit Used

Co/S	Interpretation
0.9	-
0.9-1.1	0
1.1	+

+: positive, -: negative, 0: Equivalent

No HDV-Ab (+) patients were detected according to the results that were evaluated with the cut-off/interpretation values given in Table 6. HDV-Ab was positive in only three of the 422 patients included in the current study. This means that the HDV-Ab (+) ratio in our sample was 0.71%.

HDV-Ag

The results were interpreted as the ratio between the cut-off value and the sample OD 450 nm or Co/S. The interpretations of the results were made according to the Table 8 below.

Table 8.

Interpretation of the HDV-Ag ELISA Kit Used

Co/S	Interpretation
0.9	-
0.9-1.1	0
1.1	+

+: positive, -: negative, 0: Equivalent

According to the results evaluated with the cut-off/interpretation values given in Table 7, three HDV-Ag (+) patients were identified. HDV Ag positivity was not detected in any of the 422 individuals.

HDV-RNA

HDV-RNA RT-PCR testing is requested from people who are HDV-Ab positive. Individuals with a positive HDV-RNA result are considered to have an active delta infection. In this study, HDV-RNA positivity was not detected by RT-PCR in any of the HBs Ag (+) patients.

Anti HBc-IgM

When anti-HBc IgM antibodies were evaluated by the ELISA method in the determination of acute HBV infection in three patients who were found to be HDV-Ab (+), IgM antibodies against hepatitis B virus core antigen were not detected in any of the three patients. Anti-HBc IgM results of three individuals with positive HDV-Ab were negative, suggesting that HDV might have emerged as a superinfection in these individuals.

Anti-HBc Total

Total antibodies of three HDV Ab (+) patients against hepatitis B virus core antigen evaluated by ELISA method were positive for all three patients. The positive

anti-HBc total results of three people with HDV-Ab positivity shows that HDV is considered as superinfection in these individuals, that is, there is no acute infection.

The characteristics of the three anti-HDV-Ab (+) patients, according to their demographics and test results, are given in Table 9.

Table 9.

The Characteristics of The Three Anti-HDV-Ab (+) Patients

Gender	**Age**	**Nationality**	**Anti-HDV Ab**	**Anti-HDV-Ag**	**HDV-RNA**	**Anti-HBc IgM**	**Anti-HBc Total**	
Male	25	Nigeria	+	-	-	-	+	Superinfection
Female	42	TRNC	+	-	-	-	+	Superinfection
Male	28	Nigeria	+	-	-	-	+	Superinfection

Two of the three HDV-Ab (+) patients were male and one was female. The ages of three HDV-Ab (+) patients were 25, 28, and 42 years old. Two of the three HDV-Ab (+) patients were Nigerian and the other was Turkish Cypriot.

ALT and AST levels

When the ALT and AST levels of the patients with positive HBsAg were evaluated, it was determined that the mean ALT level of the patients was 25.7 ± 0.2 (n=422) and the mean AST level was 22.8 ± 0.2 (n=422). The mean ALT level of the patients who were found to have negative anti-HDV-Ab (n=419) was 25.8 ± 0.1 and the mean AST levels were 22.7 ± 0.2. The mean ALT level of the patients who were found to have positive anti-HDV-Ab (n=3) was 25.2 ± 0.1 and the mean AST levels were 24.1 ± 0.2. According to the anti-HDV-Ab test results (positive or negative), there was no significant difference between the mean ALT and AST levels of the patients (p=n.s, Table 10).

Table 10.

ALT and AST Distributions According to Anti-HDV-Ab Test Results

		Anti-HDV-Ab (-) n=219	**Anti-HDV-Ab (+) n=3**	**P**
ALT (U/l)	mean ± SD	25.8 ± 0.1	25.2 ± 0.1	
	(min-max)	(25.7-26.0)	(25.1-25.3)	0.982
AST (U/l)	mean ± SD	22.7 ± 0.2	24.1 ± 0.2	
	(min-max)	(22.1-23.0)	(23.9-24.3)	0.977

CHAPTER V
Discussion

In this section, the findings are discussed within the framework of the studies in the literature.

Although there are reports published in different countries, especially in many European countries, in the literature, there are no published reports on HDV prevalence in TRNC. In this study, anti-HDV-Ab were detected in 3/422 of patients with HBsAg-positive TRNC. Although the sex, age, and nationality information of all patients were available in the study, the low HDV positivity ratio did not allow the analysis of a possible relationship between anti-HDV positivity and patient characteristics. In this study, anti-HDV-Ab was detected in only three patients. Anti-HDV-Ag could not be detected in the serum samples of all three patients. This result is quite consistent with the knowledge that HDV-Ag is often neutralized by anti-HDV-Ab and thus cannot be detected in immunocompetent individuals, as stated in previously reported reports (Alfaiate et al., 2015; Stroffolini, et al., 2016).

However, there is an inability to routinely check the anti-HDV test in individuals with HBsAg positivity. In order to determine the true prevalence of HDV, it is possible to determine the true prevalence values if the concept of dual reflex testing is applied by all clinicians. The double reflex test is applied by requesting Anti-HDV in individuals with positive HBsAg, and by looking for HDV-RNA in individuals with Anti-HDV positive (Palom, 2022).

Detection of anti-HDV in the individual is evidence of past or ongoing HDV infection [6]. HDV-RNA data indicate how many of the HBsAg (+) and anti-HDV (+) cases identified in this study have ongoing HDV infection (Kamili et al., 2017; Patel et al., 2019). Considering that the anti-HDV titters decreased over time during the healed co-infection process and HDV became chronic during the superinfection process, we can say that the HBsAg (+) and anti-HDV (+) cases we detected in our study probably reflect the ongoing HDV infection. Anti HDV positivity was found at the rate of 0.6% in the study conducted with serum samples of HBsAg positive cases in our hospital records, and HDV-RNA positivity was not found in any of them.

HDV infection continues to be a significant global health concern. While the distribution of the infection is subject to change with the diffusion of the HBV vaccine, certain geographic regions currently serve as reservoirs for the virus. Additionally, the actual burden of the infection seems to be underestimated, both in the general population and in at-risk populations (Niro et., 2021). The distribution of HDV infection varies significantly across geographic regions, with particularly high prevalence rates documented in Mongolia, the Republic of Moldova, and Western and Middle African nations (Stockdale et al., 2020). The prevalence of HDV in European countries such as the United Kingdom and France (not including Southern European countries) has started to increase in recent years in parallel with the immigration it has received (Jelen et al., 2016). In recent years, a downward trend has started in the prevalence of HDV in most European countries, especially in southern Europe, due to vaccination against HBV, mandatory tests applied to blood donors, improvement of hygiene conditions, and behavioural changes (Rizzetto & Ciancio, 2012). However, there has been a recent increase in the prevalence of HDV in Europe (excluding southern Europe) due to migration from areas where HDV is endemic and from areas where HBV vaccination is not widespread (Reinheimer et al., 2012; El Bouzidi et al., 2015; Cuenza-Gómez et al., 2016). We do not have information about the increase or decrease in the prevalence, since a study on the prevalence of Anti-HDV has not been done before in TRNC.

In the results of the research, it is estimated that the prevalence of anti-HDV in HBsAg (+) individuals is 4.5% worldwide (Stockdale et al., 2020). Considering the number of HBsAg (+) individuals worldwide, we can actually accept that this ratio corresponds to the range of 0.15-0.2 of the total population. When this ratio is considered according to the world population, we are talking about 12 million individuals with serological evidence of HDV. There are still limitations in the epidemiological data of anti-HDV worldwide. More data are needed from most countries in North America, Latin America, South Africa, and Asia before analyses can be made to determine accurate figures for the prevalence of anti-HDV. Anti-HDV prevalence estimation is highly heterogeneous, even among very close geographical regions. Stockdale et al., (2020) reported that they estimated that approximately 1 in 5 to 1 in 6 (respectively) cases of cirrhosis and HCC in individuals with HBV are due to HDV. In the study conducted by Miao et al., (2020)

they reported that they estimated 48-60 million cases of HDV infection among HBV-infected individuals worldwide. These ratios correspond to 0.8% of the general population and 13% of HBsAg-positive carriers (Miao et al., 2020).

When the articles examining the prevalence of HBsAg in the TRNC were examined, the prevalence of HBsAg in the country was found to be low endemicity (Süer et al., 2012, Güler et al., 2014, Arıkan et al., 2016, Güler et al., 2018). The incomplete determination of the prevalence of HDV globally also highlights the neglect of HDV screening in a way. The number of reported studies on HDV prevalence from low- and middle-low-income countries is quite limited. In fact, these countries make up almost half of the world's population. The HBV positivity rate in these countries is over 50% (Polaris Observatory Collaborators, 2018; Miao et al., 2020). Therefore, reports from these countries or studies evaluating the population of these countries are of great importance in determining global HDV prevalence.

Our results evaluate the effect of HDV infection in HBV (+) individuals in NEU-H in TRNC and, in a way, highlight the risk of HDV superinfection. Our study, in general, emphasizes the importance of determining the HDV burden in the TRNC as well as in the rest of the world. Due to the HDV burden, more efforts are needed to prevent or even eliminate rapid and serious/negative progression of liver diseases with screening, prevention and treatment.

The most critical parameter determining the epidemiology of HDV is individuals susceptible to HBsAg. Accordingly, HDV epidemiology has shown a downward curve in recent years due to the widespread use of vaccination against HBV. Since the 1990s, a significant improvement in HBV control has been observed in many countries, including low-income countries, with the introduction of vaccination programs against HBV. As a result of vaccination, both protection against HBV and regression in HDV epidemiology have gained It is possible to assume that the HDV prevalence is also controlled in places where the HBsAg prevalence is low, and accordingly, the population is more protected against infections. In summary, vaccination against HBV is the most effective method of controlling HDV infection. As a result of a study evaluating the effect of HBV vaccination on the worldwide prevalence of HBsAg and the risk of acquiring HDV, they reported that the prevalence of HBsAg and HDV may vary within the country,

and this situation may be important, especially in large countries (Polaris Observatory Collaborators, 2018). As a result of the study conducted in HBsAg (+) individuals in Turkey, anti-HDV was detected only in 2.8% of the Turkish population. Another striking emphasis in other studies from Turkey was the regional variation in HDV rates. For example, the anti-HDV ratio in patients with HBsAg-positive cirrhosis in Elazig and Van, eastern provinces of Turkey, was reported as 61.4% and 18.4% (Bahcecioglu et al., 2011; Dulger et al., 2016). Iran's situation was not much different from Turkey's. Anti-HDV ratios in patients with HBsAg-positive hepatitis in Iran also differed between regions: 65.5%-21.8% (Bakhshipour et al., 2013). HBV vaccination has become mandatory for children in the TRNC since 1999. The prevalence of hepatitis D is also relatively low, as demonstrated by their studies showing that the prevalence is low in the TRNC. The existence of more than 20 universities in the TRNC makes this country an island of education in a way. There are many students who come to universities to study at different levels, from undergraduate to doctorate. When the student population is evaluated, it is known that students of Turkish or African origin (Nigeria, Jordan, etc.) enter the island to study. There are individuals of many different nationalities who enter the island to work, as do the students who enter the island. Individuals entering the island both as students and to work are required by the Ministry of Interior to complete their immigration procedures. In order for individuals to obtain an education, residence or work permit on the island, they must first obtain a health report. In order to obtain these permits, HBsAg, Anti-HCV, Anti-HIV, Syphilis and tuberculosis tests must be done. According to this law, non-TRNC citizens with HIV positivity are deported from the island. Individuals diagnosed with hepatitis B and C, syphilis and tuberculosis in individuals who are not TRNC citizens can reside on the island, provided that the treatment costs are covered by the person himself.

HBsAg load was less than 1% in the America (central and Latin). In Africa and Asia, this rate is around 5%. HBV vaccination has been covered by the birth vaccine in only 11 countries in Africa, which in part may explain its high prevalence in low- and low-middle-income countries (Breakwell et al., 2017). A meta-analysis study determined that the combined HDV seroprevalence in central and western Africa was as follows: 25.6-33.7%, 7.3-9.5%. In the same study, it was stated that HDV seroprevalence was 0.05% of the general population in the eastern and

southern regions of Africa, but the data obtained from large settlements were scarce (Stockdale et al., 2020). In our study, the detection of Anti-HDV positivity among students who came to the TRNC for educational purposes and were found to be positive for HBsAg also emphasizes the importance of HBV vaccination.

It is a known fact that susceptibility to HDV infection varies between regions. The basis of these differences is mainly genetic and cultural differences. In our study, when HDV (+) of HBsAg (+) individuals was evaluated according to their nationality, we encountered a heterogeneous distribution. According to our findings, the highest HDV positivity was found in HBsAg positive individuals from Nigeria. These findings summarize the idea that Central Africa may be the main cradle of HDV diversification, particularly for HDV-1 (Le Gal et al., 2017) The fact that we could not make genotype determination in our research is seen as a deficiency of the study. According to recent reports from the Asian continent, anti-HDV ratio in the HBsAg (+) population have been reported as 50-60% for Mongolia, 82% for Uzbekistan, 2.1% for Afghanistan, 30-50 for Pakistan, and 42% for Kyrgyzstan (Mumtaz et al., 2005; Khan et al., 2008; Tsatsralt-Od, 2016; Chen X et al., 2017; Khodjaeva et al., 2019; Husseini, & Rostamzadeh, 2022;). In the results of studies with HBsAg (+) patients reported from India and Taiwan, the prevalence of HDV was reported as 5% and 6.5% (Huo et al., 1997; Acharya et al., 2006). In reports from China declared that 21 of 211 HBsAg (+) patients had HDV super-infection, 6.5% of 6.604 HBsAg (+) patients had IgM anti-HD, and 5% of these patients had genotype-2 HDV-RNA (Fu et al., 2016). In another report from China in 2019 reported that no HDV cases were detected in the HBsAg-positive population (Liu et al., 2019). Miao et al. underlined that there are regional differences in HDV burden in the results of their study, but they said China, India and Nigeria as the top three countries with the highest number of HDV-infected individuals (Miao et al., 2020).

According to our study results, we determined that age may be an effective factor among the risk factors affecting HDV exposure. Consistent with our study results, Groc et al. (2018) found a higher seroprevalence in individuals under 60 years of age as a result of their study. In contrast, Somi et al., (2009) reported that the risk of HDV increases significantly after the age of 40. In our study, although the number of cases was low, the age range was found to be 25 and 28, respectively, in Nigerian patients and 42 in TRNC patients.

Literature findings also reported a strong correlation between the prevalence of anti-HDV antibodies and specific population groups, including people who inject drugs (PWID), individuals receiving hemodialysis, commercial sex workers (CSWs), and men who have sex with men (MSM). Additionally, a significant association is known between anti-HDV prevalence and co-infection with HCV or HIV, which may be attributable to shared modes of transmission (Stockdale et al., 2020). It is well-established that the replicative activity of the HDV virus is a critical factor in the development of liver disease. Specifically, high levels of virus replication have been associated with the progression of cirrhosis and the onset of hepatic decompensation (Niro et., 2021). In our study, only one patient was found to be intravenous drug addict.

As emphasized in the results of studies on the prevalence of HDV infection in the literature, data on HDV prevalence are not available for many countries. One of the countries with no data on HDV prevalence is TRNC. National data from countries with no data on HDV prevalence may significantly affect HDV prevalence globally.

CHAPTER VI

Conclusion and Recommendations

In this section, the results reached in line with the aims and sub-objectives of the research and the suggestions developed based on these results are given..

Results

The ratio of both genders to each other was determined as male/female 2.64. The mean age of HBsAg (+) patients was 33.51 ± 7.2 years. We determined that the highest HBsAg (+) ratio was from Nigerian patients (n=176, 41.7%). HDV-Ab was positive in only 3 (0.71%). of the 422 patients included in the current study. HDV-Ag and HDV-RNA positivity were not detected in any of the 422 individuals. Research examining the prevalence of HBsAg in the TRNC emphasized that the prevalence of HBsAg in the country is low endemic. In parallel with the results of these studies, low HBsAg positivity can be explained as the reason for the low HDV prevalence.

Recommendations

Although the world has opened its eyes to HDV infection, HDV persists in countries where HBV remains endemic and with poor economies. HDV infection seems to be under control in high-income developed countries where HBV vaccine is administered. However, HDV infection remains a medical problem due to immigrants and drug addicts arriving in industrial areas from areas where HDV is endemic. Although vaccination against HBV has become widespread all over the world, unfortunately, some regions still have not reached a sufficient level in vaccination. Reports from around the world do not fully reflect the true burden of HDV infection. It is clear that virus replication is a very important parameter in HDV-induced or accelerated liver disorders. Therefore, new treatment strategies aim to interfere with the replication cycle of the virus. Widespread vaccination, optimal screening, comprehensive testing and timely treatment are among the main goals to eliminate or reduce the burden of hepatitis infections on the world.

Our results evaluate the effect of HDV infection in HBV (+) individuals in NEU-H in TRNC and, in a way, highlight the risk of HDV superinfection. Our study emphasizes the importance of determining the HDV burden in the TRNC, as in the rest of the world. Because of the HDV burden, more efforts are needed to prevent or even eliminate the rapid and severe/negative progression of liver diseases through screening, prevention and treatment.

References

Acharya, S. K., Madan, K., Dattagupta, S., & Panda, S. K. (2006). Viral hepatitis in India. *The National medical journal of India*, *19*(4), 203–217.

Amini, N., Alavian, S. M., Kabir, A., Aalaei-Andabili, S. H., Saiedi Hosseini, S. Y., & Rizzetto, M. (2013). Prevalence of hepatitis d in the eastern mediterranean region: systematic review and meta-analysis. *Hepatitis monthly*, *13*(1), e8210. https://doi.org/10.5812/hepatmon.8210

Arıkan, A., Şanlıdağ, T., Süer, K., Sayan, M., Akçalı, S., & Güle,r E. Molecular Epidemiology of Hepatitis B Virus in Northern Cyprus. (2016). *Mikrobiyoloji Bülteni*, 50(1):86-93.

Adepoju, V. A., Udah, D. C., & Adnani, Q. E. S. (2024). Prevalence, Risk Factors, and Clinical Profiles of Hepatitis D Virus in Nigeria: A Systematic Review, 2009–2024. *Viruses*, *16*(11), 1723.

Bahcecioglu, I. H., Aygun, C., Gozel, N., Poyrazoglu, O. K., Bulut, Y., & Yalniz, M. (2011). Prevalence of hepatitis delta virus (HDV) infection in chronic hepatitis B patients in eastern Turkey: still a serious problem to consider. *Journal of viral hepatitis*, *18*(7), 518–524. https://doi.org/10.1111/j.1365-2893.2010.01329.x

Bakhshipour, A., Mashhadi, M., Mohammadi, M., & Nezam, S. K. (2013). Seroprevalence and risk factors of hepatitis delta virus in chronic hepatitis B virus infection in Zahedan. *Acta medica Iranica*, *51*(4), 260–264.

Børresen, M. L., Olsen, O. R., Ladefoged, K., McMahon, B. J., Hjuler, T., Panum, I., Simonetti, J., Jones, C., Krarup, H., & Koch, A. (2010). Hepatitis D outbreak among children in a hepatitis B hyper-endemic settlement in Greenland. *Journal of viral hepatitis*, *17*(3), 162–170. https://doi.org/10.1111/j.1365-2893.2009.01159.x

Botelho-Souza, L. F., dos Santos, A.deO., Borzacov, L. M., Honda, E. R., Villalobos-Salcedo, J. M., & Vieira, D. S. (2014). Development of a reverse

transcription quantitative real-time PCR-based system for rapid detection and quantitation of hepatitis delta virus in the western Amazon region of Brazil. *Journal of virological methods, 197*, 19–24. https://doi.org/10.1016/j.jviromet.2013.11.016

Braga, W. S., Castilho, M.daC., Borges, F. G., Leão, J. R., Martinho, A. C., Rodrigues, I. S., Azevedo, E. P., Barros Júnior, G. M., & Paraná, R. (2012). Hepatitis D virus infection in the Western Brazilian Amazon - far from a vanishing disease. *Revista da Sociedade Brasileira de Medicina Tropical*, *45*(6), 691–695. https://doi.org/10.1590/s0037-86822012000600007

Brancaccio, G., Giuberti, T., Verucchi, G., Levantesi. M., Sacchini, D., Fattovich, G., Madonia, S., Fasano, M., Gavrila, C., Nardi, A., Gaeta, G., B., & Master-B Study Group. (2014). Epidemiological evolution of chronic hepatitis delta in Italy. An analysis of the master-B cohort. *Digestive and Liver Diseases, 46*, e12–e13.

Breakwell, L., Tevi-Benissan, C., Childs, L., Mihigo, R., & Tohme, R. (2017). The status of hepatitis B control in the African region. *The Pan African medical journal*, *27*(Suppl 3), 17. https://doi.org/10.11604/pamj.supp.2017.27.3.11981

Brehmer, K., Brismar, T. B., Morsbach, F., Svensson, A., Stål, P., Tzortzakakis, A., Voulgarakis, N., & Fischer, M. A. (2018). Triple Arterial Phase CT of the Liver with Radiation Dose Equivalent to That of Single Arterial Phase CT: Initial Experience. *Radiology*, *289*(1), 111–118. https://doi.org/10.1148/radiol.2018172875

Brunetto, M. R., Ricco, G., Negro, F., Wedemeyer, H., Yurdaydin, C., Asselah, T., ... & Buti, M. (2023). EASL Clinical Practice Guidelines on hepatitis delta virus. *Journal of hepatology*, *79*(2), 433-460.

Castelnau, C., Le Gal, F., Ripault, M. P., Gordien, E., Martinot-Peignoux, M., Boyer, N., Pham, B. N., Maylin, S., Bedossa, P., Dény, P., Marcellin, P., & Gault, E. (2006). Efficacy of peginterferon alpha-2b in chronic hepatitis delta:

relevance of quantitative RT-PCR for follow-up. *Hepatology (Baltimore, Md.)*, *44*(3), 728–735. https://doi.org/10.1002/hep.21325

Chen, Ding-Shinn (2011). *Tropical Infectious Diseases: Principles, Pathogens and Practice || Hepatitis B and Deltavirus Infections., 433–440.* doi:10.1016/B978-0-7020-3935-5.00066-5

Chen, L. Y., Pang, X. Y., Goyal, H., Yang, R. X., & Xu, H. G. (2021). Hepatitis D: challenges in the estimation of true prevalence and laboratory diagnosis. *Gut pathogens*, *13*(1), 66. https://doi.org/10.1186/s13099-021-00462-0

Chen, X., Oidovsambuu, O., Liu, P., Grosely, R., Elazar, M., Winn, V. D., Fram, B., Boa, Z., Dai, H., Dashtseren, B., Yagaanbuyant, D., Genden, Z., Dashdorj, N., Bungert, A.,

Chen, Y. S., Huang, W. H., Hong, S. Y., Tsay, Y. G., & Chen, P. J. (2008). ERK1/2-mediated phosphorylation of small hepatitis delta antigen at serine 177 enhances hepatitis delta virus antigenomic RNA replication. *Journal of virology*, *82*(19), 9345–9358. https://doi.org/10.1128/JVI.00656-08

Ciancio, A., & Rizzetto, M. (2002). Clinical patterns, epidemiology and disease burden of hepatitis D virus chronic liver disease (ed. Margolis H, Alter M, Liang T, Dienstag J), pp. 271– 275. International Medical Press, London.

Cross, T. J., Rizzi, P., Horner, M., Jolly, A., Hussain, M. J., Smith, H. M., Vergani, D., & Harrison, P. M. (2008). The increasing prevalence of hepatitis delta virus (HDV) infection in South London. *Journal of medical virology*, *80*(2), 277–282. https://doi.org/10.1002/jmv.21078

Cuenca-Gómez, J. A., Salas-Coronas, J., Soriano-Pérez, M. J., Vázquez-Villegas, J., Lozano-Serrano, A. B., & Cabezas-Fernández, M. T. (2016). Viral hepatitis and immigration: A challenge for the healthcare system. *Revista clinica espanola*, *216*(5), 248–252. https://doi.org/10.1016/j.rce.2016.02.005

Dashdorj, N., & Glenn, J. S. (2017). A novel quantitative microarray antibody capture assay identifies an extremely high hepatitis delta virus prevalence among hepatitis B virus-infected mongolians. *Hepatology (Baltimore, Md.)*, *66*(6), 1739–1749. https://doi.org/10.1002/hep.28957

Di Marco, V., Giacchino, R., Timitilli, A., Bortolotti, F., Crivellaro, C., Calzia, R., Iannuzzi, C., Prestileo, T., Vajro, P., Nebbia, G., Stringhi, C., Rosina, F., Biassoni, D., Callea, F., Rizzetto, M., & Craxi, A. (1996). Long-term interferon-alpha treatment of children with chronic hepatitis delta: a multicentre study. *Journal of viral hepatitis*, *3*(3), 123–128. https://doi.org/10.1111/j.1365-2893.1996.tb00002.x

Dulger, A., C., Suyak, B., Gonullu, H., Gonullu, E., Gultepe, B., Aydın, İ., Batur, A., Karadas, S., & Olmez, Ş. (2010). High prevalence of chronic hepatitis D virus infection in Eastern Turkey: Urbanization of the disease. Archives of Medical Science, 12(2):415-420. https://doi.org/10.5114/aoms.2015.52030

El Bouzidi, K., Elamin, W., Kranzer, K., Irish, D. N., Ferns, B., Kennedy, P., Rosenberg, W., Dusheiko, G., Sabin, C. A., Smith, B. C., & Nastouli, E. (2015). Hepatitis delta virus testing, epidemiology and management: a multicentre cross-sectional study of patients in London. *Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology*, *66*, 33–37. https://doi.org/10.1016/j.jcv.2015.02.011

Elias H. (1949). A re-examination of the structure of the mammalian liver; parenchymal architecture. *The American journal of anatomy*, *84*(2), 311–333. https://doi.org/10.1002/aja.1000840206

Farci, P., Roskams, T., Chessa, L., Peddis, G., Mazzoleni, A. P., Scioscia, R., Serra, G., Lai, M. E., Loy, M., Caruso, L., Desmet, V., Purcell, R. H., & Balestrieri, A. (2004). Long-term benefit of interferon alpha therapy of chronic hepatitis D: regression of advanced hepatic fibrosis. *Gastroenterology*, *126*(7), 1740–1749. https://doi.org/10.1053/j.gastro.2004.03.017

Fawcett, D.W., 1955. Observations on the cytology and electron microscopy of hepatic cells. *Journal of the National Cancer Institute*, *15*(5, Suppl.), 1475–1503.

Flodgren, E., Bengtsson, S., Knutsson, M., Strebkova, E. A., Kidd, A. H., Alexeyev, O. A., & Kidd-Ljunggren, K. (2000). Recent high incidence of fulminant hepatitis in Samara, Russia: molecular analysis of prevailing hepatitis B and

D virus strains. *Journal of clinical microbiology*, *38*(9), 3311–3316. https://doi.org/10.1128/JCM.38.9.3311-3316.2000

Fu, J., Guo, D., Gao, D., Huang, W., Li, Z., & Jia, B. (2016). Clinical analysis of patients suffering from chronic hepatitis B superinfected with other hepadnaviruses. *Journal of medical virology*, *88*(6), 1003–1009. https://doi.org/10.1002/jmv.24417 Khodjaeva, M., Ibadullaeva, N., Khikmatullaeva, A., Joldasova, E., Ismoilov, U., Colombo, M., Caviglia, G. P., Rizzetto, M., & Musabaev, E. (2019). The medical impact of hepatitis D virus infection in Uzbekistan. *Liver international : official journal of the International Association for the Study of the Liver*, *39*(11), 2077–2081. https://doi.org/10.1111/liv.14243

Genné, D., & Rossi, I. (2011). Hepatitis delta in Switzerland: a silent epidemic. *Swiss medical weekly*, *141*, w13176. https://doi.org/10.4414/smw.2011.13176

Gish, R. G., Yi, D. H., Kane, S., Clark, M., Mangahas, M., Baqai, S., Winters, M. A., Proudfoot, J., & Glenn, J. S. (2013). Coinfection with hepatitis B and D: epidemiology, prevalence and disease in patients in Northern California. *Journal of gastroenterology and hepatology*, *28*(9), 1521–1525. https://doi.org/10.1111/jgh.12217

Groc, S., Abbate, J. L., Le Gal, F., Gerber, A., Tuaillon, E., Albert, J. L., Nkoghé, D., Leroy, E. M., Roche, B., & Becquart, P. (2019). High prevalence and diversity of hepatitis B and hepatitis delta virus in Gabon. *Journal of viral hepatitis*, *26*(1), 170–182. https://doi.org/10.1111/jvh.12991

Güler, E., Güvenir, M., Arıkan, A., Uncu, M., Aykaç, A., & Süer, K. (2014). KKTC'deki HBV, HCV ve HIV seroprevalansının 3 yıllık değerlendirilmesi. *İnfeksiyon Dünyası Dergisi*, 141-182.

Güler, E., Süer, K., Arıkan, A., Güvenir, M., Şanlıdağ, T. Kuzey Kıbrıs'ta Hepatit B, Hepatit C ve İnsan İmmun Yetmezlik Virusü Seroprevalansı. (2018). *Bakırköy Tıp Dergisi*, 14(4):332-338.

Hadler, S. C., Alcala de Monzon, M., Bensabath, G., Martinez Duran, M., Schatz, G., & Fields, H. A. (1991). Epidemiology of hepatitis delta virus infection in less

developed countries. *Progress in clinical and biological research, 364*, 21–31.

Heidrich, B., Deterding, K., Tillmann, H. L., Raupach, R., Manns, M. P., & Wedemeyer, H. (2009). Virological and clinical characteristics of delta hepatitis in Central Europe. *Journal of viral hepatitis*, *16*(12), 883–894. https://doi.org/10.1111/j.1365-2893.2009.01144.x

Hoekstra, L. T., de Graaf, W., Nibourg, G. A., Heger, M., Bennink, R. J., Stieger, B., & van Gulik, T. M. (2013). Physiological and biochemical basis of clinical liver function tests: a review. *Annals of surgery*, *257*(1), 27–36. https://doi.org/10.1097/SLA.0b013e31825d5d47

Hong, S. Y., & Chen, P. J. (2010). Phosphorylation of serine 177 of the small hepatitis delta antigen regulates viral antigenomic RNA replication by interacting with the processive RNA polymerase II. *Journal of virology*, *84*(3), 1430–1438. https://doi.org/10.1128/JVI.02083-09

Hughes, S. A., Wedemeyer, H., & Harrison, P. M. (2011). Hepatitis delta virus. *Lancet (London, England)*, *378*(9785), 73–85. https://doi.org/10.1016/S0140-6736(10)61931-9

Huo, T. I., Wu, J. C., Lin, R. Y., Sheng, W. Y., Chang, F. Y., & Lee, S. D. (1997). Decreasing hepatitis D virus infection in Taiwan: an analysis of contributory factors. *Journal of gastroenterology and hepatology*, *12*(11), 747–751. https://doi.org/10.1111/j.1440-1746.1997.tb00364.x

Husseini, A. A., & Rostamzadeh, M. (2022). Phylogenetic analysis and prevalence of Delta hepatitis among HBsAg carriers in Afghanistan. *Molecular biology research communications*, *11*(4), 183–186. https://doi.org/10.22099/mbrc.2022.44692.1780

Ionescu, B., & Mihăescu, G. (2011). Hepatitis B, C and D coinfection in HIV-infected patients: prevalence and progress. *Roumanian archives of microbiology and immunology*, *70*(3), 129–133.

Jayan, G. C., & Casey, J. L. (2002). Inhibition of hepatitis delta virus RNA editing by short inhibitory RNA-mediated knockdown of ADAR1 but not ADAR2

expression. *Journal of virology*, *76*(23), 12399–12404. https://doi.org/10.1128/jvi.76.23.12399-12404.2002

Jelen, M. M., Hošnjak, L., Štunf, Š., Zagožen, A., Fujs Komloš, K., Markočič, P., Poljak, M., & Seme, K. (2016). Hepatitis D virus infection in Slovenian patients with chronic hepatitis B virus infection: a national prevalence study and literature review. *Acta dermatovenerologica Alpina, Pannonica, et Adriatica*, *25*(3), 49–53. https://doi.org/10.15570/actaapa.2016.14

Kalra, A., Yetiskul, E., Wehrle, C. J., & Tuma, F. (2022). Physiology, Liver. In *StatPearls*. StatPearls Publishing.

Kamili, S., Drobeniuc, J., Mixson-Hayden, T., & Kodani, M. (2017). Delta hepatitis: Toward improved diagnostics. *Hepatology (Baltimore, Md.)*, *66*(6), 1716–1718. https://doi.org/10.1002/hep.29564

Khan, A., Kurbanov, F., Tanaka, Y., Elkady, A., Sugiyama, M., Dustov, A., & Mizokami, M. (2008). Epidemiological and clinical evaluation of hepatitis B, hepatitis C, and delta hepatitis viruses in Tajikistan. *Journal of medical virology*, *80*(2), 268–276. https://doi.org/10.1002/jmv.21057

Le Gal, F., Brichler, S., Drugan, T., Alloui, C., Roulot, D., Pawlotsky, J. M., Dény, P., & Gordien, E. (2017). Genetic diversity and worldwide distribution of the deltavirus genus: A study of 2,152 clinical strains. *Hepatology (Baltimore, Md.)*, *66*(6), 1826–1841. https://doi.org/10.1002/hep.29574

Lempp, F. A., Ni, Y., & Urban, S. (2016). Hepatitis delta virus: insights into a peculiar pathogen and novel treatment options. *Nature reviews. Gastroenterology & hepatology*, *13*(10), 580–589. https://doi.org/10.1038/nrgastro.2016.126

Lerut, J. P., Donataccio, M., Ciccarelli, O., Roggen, F., Jamart, J., Laterre, P. F., Cornu, C., Mazza, D., Hanique, G., Rahier, J., Geubel, A. P., & Otte, J. B. (1999). Liver transplantation and HBsAg-positive postnecrotic cirrhosis: adequate immunoprophylaxis and delta virus co-infection as the significant determinants of long-term prognosis. *Journal of hepatology*, *30*(4), 706–714. https://doi.org/10.1016/s0168-8278(99)80203-7

Li, J., Wang, J., Tian, K., Wang, Y., Zhang, L., & Huang, H. (2006). Epidemiology of hepatitis B, C, D and G viruses and cytokine levels among intravenous drug users. *Journal of Huazhong University of Science and Technology. Medical sciences = Hua zhong ke ji da xue xue bao. Yi xue Ying De wen ban = Huazhong keji daxue xuebao. Yixue Yingdewen ban*, *26*(2), 221–224. https://doi.org/10.1007/BF02895821

Li, Y. J., Stallcup, M. R., & Lai, M. M. (2004). Hepatitis delta virus antigen is methylated at arginine residues, and methylation regulates subcellular localization and RNA replication. *Journal of virology*, *78*(23), 13325–13334. https://doi.org/10.1128/JVI.78.23.13325-13334.2004

Manesis, E. K., Schina, M., Le Gal, F., Agelopoulou, O., Papaioannou, C., Kalligeros, C., Arseniou, V., Manolakopoulos, S., Hadziyannis, E. S., Gault, E., Koskinas, J., Papatheodoridis, G., & Archimandritis, A. J. (2007). Quantitative analysis of hepatitis D virus RNA and hepatitis B surface antigen serum levels in chronic delta hepatitis improves treatment monitoring. *Antiviral therapy*, *12*(3), 381–388.

Mathurin, P., Thibault, V., Kadidja, K., Ganne-Carrié, N., Moussalli, J., El Younsi, M., Di Martino, V., Lunel, F., Charlotte, F., Vidaud, M., Opolon, P., & Poynard, T. (2000). Replication status and histological features of patients with triple (B, C, D) and dual (B, C) hepatic infections. *Journal of viral hepatitis*, *7*(1), 15–22. https://doi.org/10.1046/j.1365-2893.2000.00195.x

Miao, Z., Zhang, S., Ou, X., Li, S., Ma, Z., Wang, W., Peppelenbosch, M. P., Liu, J., & Pan, Q. (2020). Estimating the Global Prevalence, Disease Progression, and Clinical Outcome of Hepatitis Delta Virus Infection. *The Journal of infectious diseases*, *221*(10), 1677–1687. https://doi.org/10.1093/infdis/jiz633

Mumtaz, K., Hamid, S. S., Adil, S., Afaq, A., Islam, M., Abid, S., Shah, H. A., & Jafri, W. (2005). Epidemiology and clinical pattern of hepatitis delta virus infection in Pakistan. *Journal of gastroenterology and hepatology*, *20*(10), 1503–1507. https://doi.org/10.1111/j.1440-1746.2005.03857.x

Miao, Z., Xie, Z., Ren, L., & Pan, Q. (2022). Hepatitis D: advances and challenges. *Chinese Medical Journal*, *135*(07), 767-773.

Negro, F. (2014). Structure and molecular virology. In Viral hepatitis, 4th ed. (ed. Thomas HC, Lok ASF, Locarnini SA, Zuckerman AJ), pp. 395–402. Wiley, Blackwell.

Niro, G. A., Ferro, A., Cicerchia, F., Brascugli, I., & Durazzo, M. (2021). Hepatitis delta virus: From infection to new therapeutic strategies. *World journal of gastroenterology*, *27*(24), 3530–3542. https://doi.org/10.3748/wjg.v27.i24.3530

Niro, G. A., Gravinese, E., Martini, E., Garrubba, M., Facciorusso, D., Conoscitore, P., Di Giorgio, G., Rizzetto, M., & Andriulli, A. (2001). Clearance of hepatitis B surface antigen in chronic carriers of hepatitis delta antibodies. *Liver*, *21*(4), 254–259. https://doi.org/10.1034/j.1600-0676.2001.021004254.x

Niro, G. A., Smedile, A., Andriulli, A., Rizzetto, M., Gerin, J. L., & Casey, J. L. (1997). The predominance of hepatitis delta virus geno-type I among chronically infected Italian patients. *Hepatology (Baltimore, Md.)*, *25*(3), 728–734. https://doi.org/10.1002/hep.510250339

Nishikawa, H., & Osaki, Y. (2015). Liver Cirrhosis: Evaluation, Nutritional Status, and Prognosis. *Mediators of inflammation*, *2015*, 872152. https://doi.org/10.1155/2015/872152

Palom, A., Rando-Segura, A., Vico, J., Pacín, B., Vargas, E., Barreira-Díaz, A., Rodríguez-Frías, F., Riveiro-Barciela, M., Esteban, R., & Buti, M. (2022). Implementation of anti-HDV reflex testing among HBsAg-positive individuals increases testing for hepatitis D. *JHEP reports : innovation in hepatology*, *4*(10), 100547. https://doi.org/10.1016/j.jhepr.2022.100547

Patel, E. U., Thio, C. L., Boon, D., Thomas, D. L., & Tobian, A. A. R. (2019). Prevalence of Hepatitis B and Hepatitis D Virus Infections in the United States, 2011-2016. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, *69*(4), 709–712. https://doi.org/10.1093/cid/ciz001

Perez-Vargas, J., Amirache, F., Boson, B., Mialon, C., Freitas, N., Sureau, C., Fusil, F., & Cosset, F. L. (2019). Enveloped viruses distinct from HBV induce dissemination of hepatitis D virus in vivo. *Nature communications*, *10*(1), 2098. https://doi.org/10.1038/s41467-019-10117-z

Pouri, A. A., Ghojazadeh, M., Baiaz, B., Hamzavi, F. S., Pourasghari, B., & Somi, M. H. (2020). Prevalence of hepatitis D virus among HBsAg-positive individuals, 2015-2016: Azar cohort study. *Health promotion perspectives*, *10*(1), 38–42. https://doi.org/10.15171/hpp.2020.07

Raimondo, G., Brunetto, M. R., Pontisso, P., Smedile, A., Maina, A. M., Saitta, C., Squadrito, G., Tono, N., & Associazione Italiana Studio Fegato Cooperative Group (2006). Longitudinal evaluation reveals a complex spectrum of virological profiles in hepatitis B virus/hepatitis C virus-coinfected patients. *Hepatology (Baltimore, Md.)*, *43*(1), 100–107. https://doi.org/10.1002/hep.20944

Ramachandran, S., Groves, J. A., Xia, G. L., Saá, P., Notari, E. P., Drobeniuc, J., Poe, A., Khudyakov, N., Schillie, S. F., Murphy, T. V., Kamili, S., Teo, C. G., Dodd, R. Y., Khudyakov, Y. E., & Stramer, S. L. (2019). Recent and occult hepatitis B virus infections among blood donors in the United States. *Transfusion*, *59*(2), 601–611. https://doi.org/10.1111/trf.15057

Rehfeld, A., Nylander, M., & Karnov, K. (2017). *The Digestive System II: The Associated Organs. Compendium of Histology, 475–493.* doi:10.1007/978-3-319-41873-5_22

Reinheimer, C., Doerr, H. W., & Berger, A. (2012). Hepatitis delta: on soft paws across Germany. *Infection*, *40*(6), 621–625. https://doi.org/10.1007/s15010-012-0287-9

Rizzetto, M. (1983). The delta agent. *Hepatology (Baltimore, Md.)*, *3*(5), 729–737. https://doi.org/10.1002/hep.1840030518

Rizzetto, M. (2015). Hepatitis D Virus: Introduction and Epidemiology. *Cold Spring Harbor perspectives in medicine*, *5*(7), a021576. https://doi.org/10.1101/cshperspect.a021576

Rizzetto, M., & Alavian, S. M. (2013). Hepatitis delta: the rediscovery. *Clinics in liver disease*, *17*(3), 475–487. https://doi.org/10.1016/j.cld.2013.05.007

Rizzetto, M., & Ciancio, A. (2012). Epidemiology of hepatitis D. *Seminars in liver disease*, *32*(3), 211–219. https://doi.org/10.1055/s-0032-1323626

Rizzetto, M., Canese, M. G., Aricò, S., Crivelli, O., Trepo, C., Bonino, F., & Verme, G. (1977). Immunofluorescence detection of new antigen-antibody system (delta/anti-delta) associated to hepatitis B virus in liver and in serum of HBsAg carriers. *Gut*, *18*(12), 997–1003. https://doi.org/10.1136/gut.18.12.997

Rizzetto, M. (2022). Hepatitis D (delta). *New Microbiol*, *45*(3), 149-154.

Rizzetto, M., Ponzetto, A., & Forzani, I. (1991). Epidemiology of hepatitis delta virus: overview. *Progress in clinical and biological research*, *364*, 1–20.

Sagnelli, E., Coppola, N., Scolastico, C., Filippini, P., Santantonio, T., Stroffolini, T., & Piccinino, F. (2000). Virologic and clinical expressions of reciprocal inhibitory effect of hepatitis B, C, and delta viruses in patients with chronic hepatitis. *Hepatology (Baltimore, Md.)*, *32*(5), 1106–1110. https://doi.org/10.1053/jhep.2000.19288

Sagnelli, E., Stroffolini, T., Ascione, A., Bonino, F., Chiaramonte, M., Colombo, M., Craxi, A., Giusti, G., Manghisi, O. G., & Pastore, G. (1992). The epidemiology of hepatitis delta infection in Italy. Promoting Group. *Journal of hepatology*, *15*(1-2), 211–215. https://doi.org/10.1016/0168-8278(92)90038-q

Samuel, D., Zignego, A. L., Reynes, M., Feray, C., Arulnaden, J. L., David, M. F., Gigou, M., Bismuth, A., Mathieu, D., & Gentilini, P. (1995). Long-term clinical and virological outcome after liver transplantation for cirrhosis caused by chronic delta hepatitis. *Hepatology (Baltimore, Md.)*, *21*(2), 333–339.

Sanz-García, C., Fernández-Iglesias, A., Gracia-Sancho, J., Arráez-Aybar, L., A., Nevzorova, Y., A., & Cubero, F., J. (2021). The Space of Disse: The Liver

Hub in Health and Disease. *Livers*, 1(1):3-26. https://doi.org/10.3390/livers1010002

Saxena, R., Theise, N. D., & Crawford, J. M. (1999). Microanatomy of the human liver-exploring the hidden interfaces. *Hepatology (Baltimore, Md.)*, *30*(6), 1339–1346. https://doi.org/10.1002/hep.510300607

Scheidler, J., Fink, U., Steiner, W., & Steitz, H. O. (1995). Drei-Phasen-Spiral-CT--ein neues nichtinvasives Verfahren zur Differenzierung multifokaler Leberläsionen [3-phase spiral CT--a new noninvasive procedure for the differentiation of multifocal liver lesions]. *Aktuelle Radiologie*, *5*(1), 15–18.

Schulze, R. J., Schott, M. B., Casey, C. A., Tuma, P. L., & McNiven, M. A. (2019). The cell biology of the hepatocyte: A membrane trafficking machine. *The Journal of cell biology*, *218*(7), 2096–2112. https://doi.org/10.1083/jcb.201903090

Servant-Delmas, A., Le Gal, F., Gallian, P., Gordien, E., & Laperche, S. (2014). Increasing prevalence of HDV/HBV infection over 15 years in France. *Journal of clinical virology: the official publication of the Pan American Society for Clinical Virology*, *59*(2), 126–128. https://doi.org/10.1016/j.jcv.2013.11.016

Si-Tayeb, K., Lemaigre, F., P., & Duncan, S., A. (2010). Organogenesis and development of the liver. Developmental Cell, *16*, 18(2):175-89

Somi, M. H., Farhang, S., Miri, S. M., Pouri, A. A., Mjidi, G., & Alavian, S. M. (2009). The frequency of hepatitis D virus in patients with hepatitis B in Iran: an increasing rate?. *Tropical doctor*, *39*(3), 154–156. https://doi.org/10.1258/td.2009.080365

Soriano, V., Grint, D., d'Arminio Monforte, A., Horban, A., Leen, C., Poveda, E., Antunes, F., de Wit, S., Lundgren, J., Rockstroh, J., & Peters, L. (2011). Hepatitis delta in HIV-infected individuals in Europe. *AIDS (London, England)*, *25*(16), 1987–1992. https://doi.org/10.1097/QAD.0b013e32834babb3

Stockdale, A. J., Kreuels, B., Henrion, M. Y. R., Giorgi, E., Kyomuhangi, I., de Martel, C., Hutin, Y., & Geretti, A. M. (2020). The global prevalence of hepatitis D virus infection: Systematic review and meta-analysis. *Journal of hepatology*, *73*(3), 523–532. https://doi.org/10.1016/j.jhep.2020.04.008

Stroffolini, T., Sagnelli, E., Sagnelli, C., Russello, M., De Luca, M., Rosina, F., Cacopardo, B., Brancaccio, G., Furlan, C., Gaeta, G. B., Licata, A., Almasio, P. L., & behalf of EPACRON study group (2017). Hepatitis delta infection in Italian patients: towards the end of the story. *Infection*, *45*(3), 277–281. https://doi.org/10.1007/s15010-016-0956-1

Süer, H.K., Güvenir, M., Güler, E., & Diktaş, H. Kuzey Kıbrıs Türk Cumhuriyeti Yakın Doğu Üniversitesi Hastanesi'ne başvuran kan donörlerinde HBsAg, anti-HCV, anti-HIV ve siflis test sonuçlarının değerlendirilmesi. (2012). *Klimik Dergisi*, 25:99

Sureau, C., & Negro, F. (2016). The hepatitis delta virus: Replication and pathogenesis. *Journal of hepatology*, *64*(1 Suppl), S102–S116. https://doi.org/10.1016/j.jhep.2016.02.013

Stoll, F., Seidel-Glätzer, A., Burghaus, I., Göring, O., Sauter, M., Rose, P., ... & Blank, A. (2022). Metabolic effect of blocking sodium-taurocholate Co-transporting polypeptide in hypercholesterolemic humans with a twelve-week course of bulevirtide—an exploratory phase I clinical trial. *International Journal of Molecular Sciences*, *23*(24), 15924.

Taylor, J., Purcell, R., H., Farci, P. (2013). Hepatitis D (delta) virus. In: Knipe DM, Howley PM. Fields Virology. Philadelphia: Lippincott, Williams and Wilkins, 2222–2241

Theamboonlers, A., Hansurabhanon, T., Verachai, V., Chongsrisawat, V., & Poovorawan, Y. (2002). Hepatitis D virus infection in Thailand: HDV genotyping by RT-PCR, RFLP and direct sequencing. *Infection*, *30*(3), 140–144. https://doi.org/10.1007/s15010-002-2061-x

Thuener, J. (2017). Hepatitis A and B Infections. *Primary care*, *44*(4), 621–629. https://doi.org/10.1016/j.pop.2017.07.005

Tsatsralt-Od, B., Takahashi, M., Endo, K., Buyankhuu, O., Baatarkhuu, O., Nishizawa, T., & Okamoto, H. (2006). Infection with hepatitis A, B, C, and delta viruses among patients with acute hepatitis in Mongolia. *Journal of medical virology*, *78*(5), 542–550. https://doi.org/10.1002/jmv.20574

Tsutsumi, V., Nakamura, T., T., Ueno, T., Torimura, T., Aguirre-Garcı´a, J. (2017). Structure and Ultrastructure of the Normal and Diseased Liver, Liver Pathophysiology, 23-44. https://doi.org/10.1016/B978-0-12-804274-8.00002-3

Urban, S., Neumann-Haefelin, C., & Lampertico, P. (2021). Hepatitis D virus in 2021: virology, immunology and new treatment approaches for a difficult-to-treat disease. *Gut*, *70*(9), 1782–1794. https://doi.org/10.1136/gutjnl-2020-323888

Watanabe, H., Nagayama, K., Enomoto, N., Chinzei, R., Yamashiro, T., Izumi, N., Yatsuhashi, H., Nakano, T., Robertson, B. H., Nakasone, H., Sakugawa, H., & Watanabe, M. (2003). Chronic hepatitis delta virus infection with genotype IIb variant is correlated with progressive liver disease. *The Journal of general virology*, *84*(Pt 12), 3275–3289. https://doi.org/10.1099/vir.0.19499-0

Wedemeyer, H., Heidrich, B., & Manns, M. P. (2007). Hepatitis D virus infection--not a vanishing disease in Europe! *Hepatology (Baltimore, Md.)*, *45*(5), 1331–1333. https://doi.org/10.1002/hep.21590

Wu, J. C. (2006). Functional and clinical significance of hepatitis D virus genotype II infection. *Current topics in microbiology and immunology*, *307*, 173–186. https://doi.org/10.1007/3-540-29802-9_9

Yan, H., Peng, B., Liu, Y., Xu, G., He, W., Ren, B., Jing, Z., Sui, J., & Li, W. (2014). Viral entry of hepatitis B and D viruses and bile salts transportation share common molecular determinants on sodium taurocholate cotransporting polypeptide. *Journal of virology*, *88*(6), 3273–3284. https://doi.org/10.1128/JVI.03478-13

Yurdaydin, C., Bozkaya, H., Karaaslan, H., Onder, F. O., Erkan, O. E., Yalçin, K., Değertekin, H., Bozdayi, A. M., & Uzunalimoğlu, O. (2007). A pilot study of

2 years of interferon treatment in patients with chronic delta hepatitis. *Journal of viral hepatitis*, *14*(11), 812–816. https://doi.org/10.1111/j.1365-2893.2007.00875.x

Zachou, K., Yurdaydin, C., Drebber, U., Dalekos, G. N., Erhardt, A., Cakaloglu, Y., Degertekin, H., Gurel, S., Zeuzem, S., Bozkaya, H., Schlaphoff, V., Dienes, H. P., Bock, T. C., Manns, M. P., Wedemeyer, H., & HIDT-1 Study Group (2010). Quantitative HBsAg and HDV-RNA levels in chronic delta hepatitis. *Liver international: official journal of the International Association for the Study of the Liver*, *30*(3), 430–437. https://doi.org/10.1111/j.1478-3231.2009.02140.x

Appendix

App 1.

Etik Kurulu BaskanI

App 2.

Similarity reports

App 3.

CV

YAKIN DOĞU ÜNİVERSİTESİ
BİLİMSEL ARAŞTIRMALAR ETİK KURULU

ARAŞTIRMA PROJESİ DEĞERLENDİRME RAPORU

Toplantı Tarihi : 22.10.2020
Toplantı No : 2020/84
Proje No :1172

Yakın Doğu Üniversitesi Tıp Fakültesi öğretim üyelerinden Prof. Dr. Kaya Süer'in sorumlu araştırmacısı olduğu, YDU/2020/84-1172 proje numaralı ve **"Kuzey Kıbrıs'ta Bir Üniversite Hastanesi'nde HbsAg Pozitif Saptanan Hastalarda Hepatit Delta Virüs (HDV) Seroprevalansının İncelenmesi"** başlıklı proje önerisi kurulumuzca online toplantıda değerlendirilmiş olup, etik olarak uygun bulunmuştur.

Prof. Dr. Rüştü Onur
Yakın Doğu Üniversitesi
Bilimsel Araştırmalar Etik Kurulu Başkanı

5/13/25, 3:32 PM Turnitin Orijinallik Raporu

Turnitin Orijinallik Raporu

son Luma Son tarafından
Quick Submit (Quick Submit) den

13-May-2025 15:31 EEST' de işleme kondu
NUMARA: 2674787192
Kelime Sayısı: 11752

Benzerlik Endeksi	Kaynağa göre Benzerlik	
%15	Internet Sources:	%8
	Yayınlar:	%11
	Öğrenci Ödevleri:	%4

kaynaklar:

1 2% match (23-Şub-2016 tarihli internet)
http://ddoct.umfcluj.ro/component/eas-folderlistingpro/?data=[illegible]&format=raw&view=download

2 1% match (Emrah Güler, Luma Husni Ahmad Alzubi, Meryem Güvenir, Ulas Hurdoganoglu, Kaya Suer, Esref Celik. "Seroprevalence of Hepatitis D Virus in Northern Cyprus", Hepatitis Monthly, 2025)
Emrah Güler, Luma Husni Ahmad Alzubi, Meryem Güvenir, Ulas Hurdoganoglu, Kaya Suer, Esref Celik. "Seroprevalence of Hepatitis D Virus in Northern Cyprus", Hepatitis Monthly, 2025

3 1% match (19-Tem-2020 tarihli internet)
http://perspectivesinmedicine.cshlp.org/content/5/7/a021576.long

4 1% match ("Viral Hepatitis", Wiley, 2013)
"Viral Hepatitis", Wiley, 2013

5 1% match (Jiannis Vlachogiannakos, George V. Papatheodoridis. "New epidemiology of hepatitis delta", Liver International, 2020)
Jiannis Vlachogiannakos, George V. Papatheodoridis. "New epidemiology of hepatitis delta", Liver International, 2020

6 1% match (Ding-Shinn Chen, Pei-Jer Chen. "Hepatitis B and Deltavirus Infections", Elsevier BV, 2011)
Ding-Shinn Chen, Pei-Jer Chen. "Hepatitis B and Deltavirus Infections", Elsevier BV, 2011

7 1% match (Boris J.B. Beudeker, Jolanda J.C. Voermans, Corine.H. GeurtsvanKessel, Robert J. de Knegt et al. "Prevalence of hepatitis delta virus among chronic hepatitis B carriers in a large tertiary center in the Netherlands", Journal of Clinical Virology, 2021)
Boris J.B. Beudeker, Jolanda J.C. Voermans, Corine.H. GeurtsvanKessel, Robert J. de Knegt et al. "Prevalence of hepatitis delta virus among chronic hepatitis B carriers in a large tertiary center in the Netherlands", Journal of Clinical Virology, 2021

8 < 1% match (23-Kas-2021 tarihli internet)
https://repub.eur.nl/pub/135651/thesis-Miao-Eliminating-Hepatitis-D-and-E.pdf

9 < 1% match (27-Tem-2024 tarihli internet)
https://docs.neu.edu.tr/library/9328788174.pdf

10 < 1% match (27-Mar-2024 tarihli internet)
http://repository.sustech.edu/bitstream/handle/123456789/22885/Serodetection%20of%20Syphilis.....pdf?isAllowed=y&sequence=1

11 < 1% match (Almagul Jumabayeva, Alexander Nersesov, Maksut Kulzhanov, Margarita Nefedova et al. "Prevalence of Viral Hepatitis B, C, and D in Kazakhstan", The Scientific World Journal, 2022)
Almagul Jumabayeva, Alexander Nersesov, Maksut Kulzhanov, Margarita Nefedova et al. "Prevalence of Viral Hepatitis B, C, and D in Kazakhstan", The Scientific World Journal, 2022

12 < 1% match (17-Tem-2016 tarihli internet)
http://docplayer.es/342415-Anti-hbc-total-elisa-kapg4cbe3.html

13 < 1% match (18-Ara-2017 tarihli internet)
https://issuu.com/allo34/docs/fmo2/364

14 < 1% match (26-Tem-2024 tarihli internet)
https://1library.net/document/y909xxdy-hepatitis-b-anti-hbc-igm-catalog-wb.html

15 < 1% match (02-Nis-2012 tarihli internet)

https://www.turnitin.com/newssreport_printview.asp?[illegible]

LUMA HUSNI ALZUBI

Laboratory medical sciences

DATE OF BIRTH: 12 Jun 1996

GENDER: female

Country: JORDAN

CONTACT

IRBID –JORDAN

+962798460197

Lumaalzoubi96@yahoo.com

LANGUAGES

- English
- Arabic

COMPUTER SKILLS

- Microsoft program
- Email
- SPSS program
- Presentation program

EDUCATION

(2015 to 2019)
JORDAN UNIVERSITY OF SCIENCE AND TECHNOLOGY
Bachelor's **Laboratory medical sciences**
B. Project
CHIMERISM
Near East University /Medical Faculty/Cyprus (15-02-2019 until 21 6 -2021)
Master (M.SC.) Medical microbiology and Clinical microbiology.

(M.SC.) Project EVALUATION OF THE CORRELATION BETWEEN STOOL ANTIGEN TEST AND HISTOPATHOLOGY REPORT RESULTS OF HELICOBACTER PYLORI PRESENCE IN NEAR EAST UNIVERSITY HOSPITAL APPLICANTS

Near East University /Medical Faculty/KKTC, Northern Cyprus (11-11-2021 until 27-2-2025) (PhD program in medical microbiology and clinical microbiology

(PhD) Project THE PREVALENCE OF HEPATITIS D IN INDIVIDUALS WHO WERE FOUND TO BE HBSAG POSITIVE IN A UNIVERSITY HOSPITAL IN THE TURKISH REPUBLIC OF NORTHERN CYPRUS

WORK EXPERIENCE

Training for 6 months in a microbiology lab in Jordan from 1 Jan 2 24 to 1-6-2024)

SKILLS

- Have capacity to work under pressure and manage personal stress levels. And Creative, open-minded, flexible, and self-learner.
- Have a good problem-solving ability.
- Have good numerical and report writing skills.