FROM ORIGINS TO OUTCOMES: INVESTIGATING THE COMPLEXITY OF PORTAL HYPERTENSION IN ETIOLOGY, DIAGNOSIS, TREATMENT AND COMPLICATIONS

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UNIVERSITY OF RIJEKA
FACULTY OF MEDICINE

INTEGRATED UNDERGRADUATE AND GRADUATE UNIVERSITY STUDY OF MEDICINE IN ENGLISH LANGUAGE

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GRADUATION THESIS

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Thesis mentor: Assoc. Prof. Goran Poropat, MD, PhD

The graduation thesis was graded on 27.06.2024 in Rijeka, before the Committee composed of the following members:

1. Assoc. Prof. Ivana Mikolašević, MD, PhD (President of the Committee)
2. Assist. Prof. Vanja Licul, MD, PhD
3. Assist. Prof. Neven Franjić, MD, PhD

The graduation thesis contains 66 pages, 12 figures, 3 tables, 124 references.

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List of abbreviations and acronyms

ADMA – Amino acid asymmetric dimethylarginine

ALP – Alkaline Phosphatase

ALT – Alanine aminotransferase

APRI – AST to Platelet Ratio Index

AST – Aspartate aminotransferase

BCS – Budd-Chiari Syndrome

CBG – corticosteroid-binding globulin

CECT – Contrast Enhanced CT

CFF – Critical flicker frequency

CHF – Congenital Hepatic Fibrosis

CLD – Chronic liver disease

CT – Computer Tomography

CTP – Child-Turcotte Pugh

EBL – Endoscopic Band Ligation

ECM – Extracellular Matrix

ELF – Enhanced Liver Fibrosis

eNOS – endothelial nitric oxide Synthase

ET-1 – Endothelin 1

EVL – Endoscopic Variceal Ligation

FHVP – Free hepatic venous pressure

GGT – gamma-glutamyl transferase

HA – Hyaluronic Acid

HBV – Hepatitis B Virus

HCC – Hepatocellular Carcinoma

HCV – Hepatitis C Virus

HE – Hepatic Encephalopathy

HESA – Hepatic encephalopathy scoring algorithm

HPS – Hepato-pulmonary Syndrome

HRS – Hepatorenal Syndrome

HSC – Hepatic Stellate Cells

HVPG – Hepatic portal-venous gradient

INR – Internation normalized ratio

IPH – Idiopathic Portal Hypertension

JRSPH – Japanese Research Society for Portal Hypertension

kPA – Kilopascals

LPV – Left Portal Vein

LSEC – Liver sinusoidal endothelial cells

MELD – Model for end stage liver disease

MRA – Magnetic resonance angiography

NAFLD – Non-alcoholic Fatty Liver Disease

NO – Nitric Oxide

NSBB – Non-selective beta-blocker

PBC – Primary Biliary Cholangitis

PDGF – Platelet derived growth factor

PHE – Portal Hypertensive Enteropathy

PHES – psychometric hepatic encephalopathy score

PHG – Portal Hypertensive Gastropathy

PIIINP – Procollagen III N-terminal peptide

PMN – polymorphonuclear leukocyte

PPHT – Portopulmonary Hypertension

PSC – Primary Sclerosing Cholangitis

PT – Prothrombin Time

PVT – Portal Vein Thrombosis

RAAS – Renin-angiotensin-aldosterone system

RAPV – Right anterior branch

RC – Red Color Sign

RPPV – Right posterior branch

RPV – Right Portal Vein

SAAG – Serum-ascites albumin gradient

SBP – Spontaneous Bacterial Peritonitis

SEC – Sinusoidal endothelial cell

SHBG – sex hormone-binding globulin

SOS – Sinusoidal Obstruction Syndrome

T4 – Thyroxine

T4 – Triiodothyronine

TBG – Thyroid-binding globulin

TE – Transient Elastography

TIMP-1 – Tissue Inhibitor of Metalloproteinase 1

TIPS – Transjugular Intrahepatic Portosystemic Shunt

TNF-α – Tumor necrosis factor α

VEGF – Vascular Endothelial Growth Factor

VLDL – Very low density lipoprotein

VOD – Veno-occlusive Disease

WHVP – Wedged hepatic Venous Pressure

1. Introduction

1.1. Background Information

Within the intricate vascular dynamics of the human body lies a condition of great clinical importance: portal hypertension. As a result of various hepatic pathologies, this phenomenon manifests itself as an increase in pressure in the portal vein system, followed by a cascade of complicated pathophysiological changes. From its subtle beginnings to its profound clinical implications, portal hypertension is a prime example of the intersection of pathophysiology and clinical medicine. This review will highlight the various facets of this condition, explore the underlying mechanisms, describe the clinical manifestations, and discuss the therapeutic options aimed at mitigating its impact on patient health and well-being.

1.2. History

Even though Claudius Galen (130-201 AD) born in Pergamon (today's north-western Turkey), was one of the first to describe the liver and its blood supply, it took over a century before portal hypertension and its consequences were first described. Galen theorized that the heart was the origin of all arteries, and the liver the destination of all veins, which somewhat still holds true today. A millennium later in the 1500s in Italy, Leonardo da Vinci (1450-1519) described the pathological changes of a high-pressure gradient in the liver vessels in his textbook "de humanis corpore". He described the anatomy as follows: section "... the artery and the vein which go from the spleen to the liver become so large, to block the blood coming from the mesenteric vein; the latter vein dilates and becomes tortuous like a snake, that the liver dries and become like frozen bran, in colour and consistency…". Leonardo wrongly postulated that the changes in the liver were caused by the changes in the vessels prior to the liver and not vice versa (1,2). With the fall of the ecclesiastical ban on performing autopsies, human medicine made great leaps forward over the next few centuries. In the 1800s, there was a breakthrough in portal hypertension, when not only the term "liver cirrhosis" was coined by Renè Laennec, who also invented the stethoscope, but also when the portal and collateral vein network was described in more detail.

In 1902 a lecturer at the Paris Hospital l'Hotel-Dieu, Augustin Gilbert and his colleague Carnot published a seminal work in which they described the symptomatic picture of cirrhosis and coined the term "portal hypertension." They postulated that cirrhosis could be leading to elevated pressure in the vessels leading towards the liver, followed by dilation of the physiological anastomoses between the portal and systemic venous circulation, already mentioning the vena oesophageales. The principal measurement of a difference in pressure was

made in 1937 when Thompson performed measurements in the portal vein and in the immediate IVC with an open abdominal approach. Subsequently, Lebon et al. diagnosed portal hypertension in Algeria in 1953 by percutaneous measurement by puncturing a large portal vein branch near the hepatic hilum and comparing it with the pressure in the splenic vein (3).

When portal hypertension and the associated complications became common knowledge in the medical world at the beginnings of the 20th century, the first forms of therapy were proposed. In order to combat the recurring esophageal bleeding, the idea was to reduce the either the inflow or outflow into or out of the portal vein circulatory system. This feat was first accomplished by Vidal in 1903, when he created the first portocaval shunt, after which the patient survived for four months. Further forms of therapy were developed in the second half of the 20th century, which we will discuss later. It is clear that portal hypertension has been a relevant topic for centuries and will continue to be the subject of much research in the future.

1.3. Definition of Portal Hypertension

Portal hypertension has been defined as follows:

"Portal hypertension is increased pressure within the portal venous system. It is determined by the increased portal pressure gradient (the difference in pressures between the portal venous pressure and the pressure within the inferior vena cava or the hepatic vein. This pressure gradient is normally less than or equal to 5 mmHg. A pressure gradient of 6 mmHg or more between the portal and hepatic veins (or inferior vena cava) suggests the presence of portal hypertension in most cases. When the pressure gradient is greater than 10 mmHg, portal hypertension becomes clinically significant." (4).

The pressure gradient is determined peri-interventionally and is defined as the hepatic venous pressure gradient (HPVG). Portal hypertension only describes the gradient itself and not the associated sequelae. Often, portal hypertension is not diagnosed until clinical manifestations occur and may be otherwise asymptomatic. This nuance is particularly important when defining the scope of this work.

1.4. Epidemiological Data about Portal Hypertension

Portal hypertension has a significant incidence and prevalence in different population groups and diseases. Close to 25% of patients with non-alcoholic fatty liver disease present with portal hypertension (5), whereas non-cirrhotic portal hypertension occurs in about 15,000 cases per 100,000 people with portal hypertension, from which only 14% are in an idiopathic form.

Cirrhosis, the leading cause of portal hypertension, has a prevalence of 270 cases per 100,000 in the United States, with an age-adjusted mortality rate of 18.1 deaths per 100,000. The

incidence of portal hypertension increases in women in their early 40s and in men in their early 30s, with idiopathic forms typically affecting 43- to 56-year-olds and noncirrhotic forms affecting 25- to 35-year-olds. Non-Hispanic blacks and Mexican Americans are more likely to be affected by cirrhosis. Men are more likely to develop idiopathic portal hypertension, while non-cirrhotic portal hypertension is more like to appear in women. Socioeconomic factors influence the prevalence of portal hypertension, with higher rates observed in low socioeconomic groups (5–11).

1.5. Significance of this topic

Portal hypertension is a complex disease with a multifaceted pathophysiology and clinical implications. Conducting in-depth research and analyses in this thesis contributes to expand the existing medical knowledge on this topic. It allows for a deeper understanding of the underlying mechanisms, risk factors, diagnostic modalities, treatment options, and outcomes. Portal hypertension is an important health problem worldwide, particularly due to its association with chronic liver diseases such as cirrhosis, viral hepatitis, and non-alcoholic fatty liver disease. It encompasses various disciplines, including hepatology, gastroenterology, cardiology, radiology, and surgery. The formulation of a comprehensive review on this topic encourages interdisciplinary collaboration and exchange of ideas and supports a holistic approach to understanding and managing portal hypertension, by utilizing different perspectives and expertise.

1.6. Objectives

The primary objective of this study is to provide a comprehensive assessment of the current understanding of portal hypertension, including its etiology, pathophysiology, clinical manifestations, diagnostic modalities, and therapeutic options. Through a review of the existing literature and clinical evidence, we aim to explore the mechanisms underlying portal hypertension and its associated complications. This work aims to provide an up-to-date elaboration of the existing literature to bring it up to current standards of practice. In addition, this thesis statement aims to critically assess the efficiency and reliability of available diagnostic and therapeutic modalities in the management to provide insights for optimizing clinical practice and directing future research efforts.

2. Anatomy and Physiology of the Portal System

Table 1: Liver Segmentation; Definitions of the terms of liver segmentation according to Couinaud's classification. (12)

Term	Definition
Lobes	The right and left lobes are separated by the umbilical scissura
Livers	The right and left livers are separated by the plane of the middle hepatic vein or the plane of the gallbladder
Sectors	Parts of a hemi-liver vertically separated by the plane of the right, middle and left hepatic veins
Segments	Independent functional units receiving an artery, a portal vein, and drained by a hepatic vein, horizontally separated by the plane passing by the portal vein bifurcation

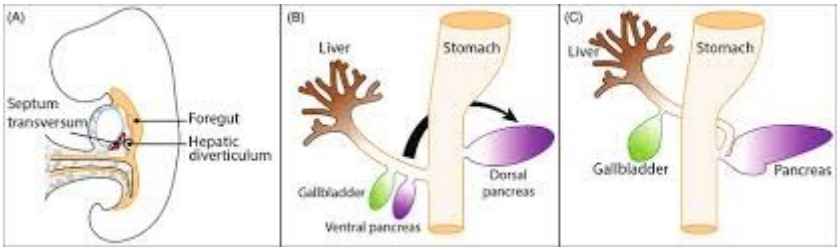

Figure 1:Embryological Development of the Liver (13)

2.1. Embryology

The embryological development of the veinous system, later turning into the portal circulation, starts in the fourth week of gestation and continues until the twelfth week. The cell accumulation, which builds up the hepatic diverticulum stems from endodermal cells, which developed from the foregut. It is fixed by the falciform ligament through which the umbilical vein runs. The principal portal network initially comprises the right and left vitelline veins, which play an integral part in the fetal circulation. As development progresses, selective involution occurs, particularly in the cranial portion of the left vitelline vein and its anastomoses, which are crucial for the formation of the proper divergence into the main portal stem and its left branch. Two anastomoses contribute to the formation of these veins and have major impact on the correct alignment and integration of the portal vein system into the liver architecture. As the liver develops from the hepatic primordium around the fourth week, the developing portal vein system begins to integrate into the liver's architecture, which is essential for its future vascularization and the metabolic functions of the liver. They become canalized and divide repeatedly within the mesoderm of the transverse septum to give rise to the intrahepatic biliary tree that forms the proximal branches and the hepatocyte cords that form, the terminal branches. Disruptions in these developmental processes can lead to congenital

anomalies such as atresia, duplication or malformation of the portal vein system, with significant clinical implications for liver function and overall health(14).

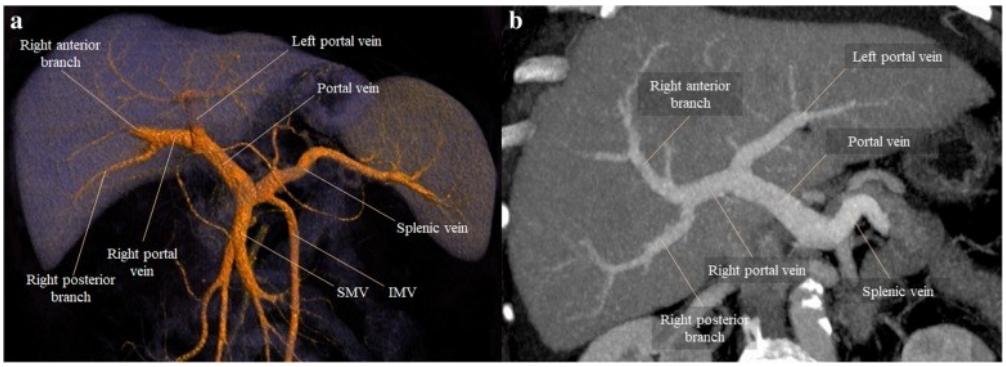

Figure 2: Normal portal vein branching patterns as visualized by contrast-enhanced CT imaging (14)

2.2. Anatomy of the Portal Vein System

The portal vein, which is about eight centimeters in length in adults, can be found under the right ribcage, in the right hypochondriac region and originates posterior to the pancreatic neck. Normally, this vein arises from the convergence of the superior mesenteric, draining the upper abdomen, and the splenic veins, known as the splenic-mesenteric confluence. There are a few cases, in which the inferior mesenteric vein immediately unites with the portal vein and even more rarely the portal vein is abnormally formed by the confluence of the cystic and gastric veins.

The liver is mainly supplied with blood from two origins: 70% by veinous blood supplied by the portal circulation and 30% oxygenated blood stemming from the hepatic arteries. The hepatic portal vein drains blood from the gastric region, intestine, pancreas and spleen via the *porta hepatis* directly to the liver, which also serves as the entrance for the arterial blood supply and the outlet of the ducts transporting the bile.

As it enters the liver, the main portal vein partitions into one two major branches, which in turn are subdivided into smaller subbranches and ultimately venules. These small vessels run parallel to the hepatic arterioles between the hepatic lobules and, in combination with one bile duct, make up part of the portal triad. The blood from these vessels will flow into the hepatic sinusoids, allowing for the untypical event where venous and arterial blood is directly mixed.

After the hepatocytes have processed the blood, it is being drained towards the central vein, which is placed in the middle of every singular hepatic lobule. These central veins then will confluence and eventually from the hepatic veins, which exit at the dorsal and superior side of the liver and drain into the IVC to distribute the processed blood to the rest of the body. This strategic anatomical layout not only supports liver function, but also plays a crucial role in systemic circulation (14–16).

2.3. Anatomical Variations

Anatomical variations in structures of veins occur in approximately 35% of people, including the following variants of portal vein morphology:

- Type I: bifurcation into Left Portal Vein (LPV) and Right Portal Vein (RPV)
- Type II: trifurcation of the main portal vein; emergence of the right posterior branch (RPPV) directly from the main portal vein.
- Type III: origination of the right anterior branch (RAPV) from the left portal vein.
- There are rare cases of duplication of the portal vein and variants in which the portal vein does not branch off.

Congenital anomalies in the portal veinous system may be possible, the most common being the absence of development of either of the main portal veinous branches. Such anomalies may be a cause for the formation of alternative pathways in the veinous system due to portal hypertension.

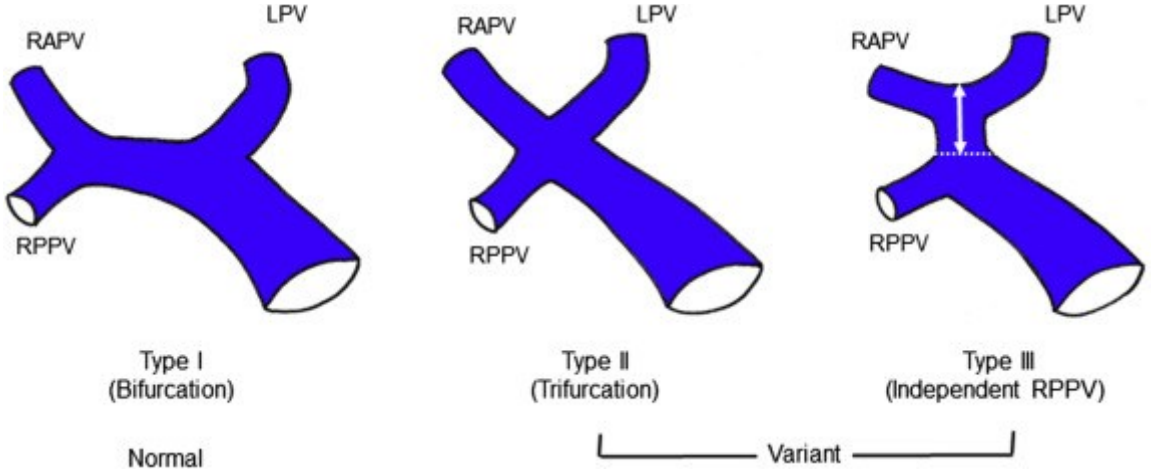

Figure 3: Anatomical Variations of the Portal Vein (17)

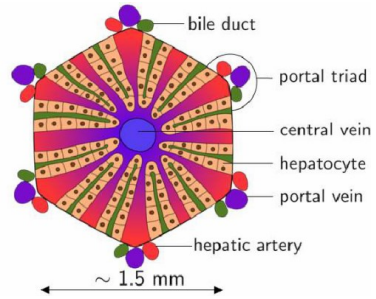

Figure 4: Structure of a Liver Lobule (18)

2.4. The "Workhorse" of the Liver

The liver's functional unit, the lobule, has a six sided shape with a centra portal triad - comprising of a portal vein, a hepatic artery, and a bile duct – in every corner. The structural

foundation of the lobule consists of hepatocytes, which are characterized by their physiologically distinct apical and basolateral membranes. These cells may be categorized into three zones according to their respective activity and blood perfusion.

- Zone I, commonly called the periportal region, contains hepatocytes that are well supplied with blood and are the first to regenerate. This zone is closest to oxygen and nutrient rich blood, being the main actor in processes like β-oxidation, gluconeogenesis, bile production, cholesterol synthesis, and the breakdown of protein components.
- Zone II, or the pericentral region, serves as a transitional area between zones I and III, and combines some of the functions of both zones.
- Zone III, which is furthest from the portal triad, is the least perfused. This zone is mainly responsible for detoxification, drug biotransformation, the formation of ketone bodies, glucose breakdown, formation of lipids, buildup of glycogen, and glutamine formation.

The bile stream is enhanced by the canaliculi, small channels made of the apical membranes of adjacent hepatocytes, forming so-called “chicken-wire pattern” which increases the surface area for the bile. This diverse and space-saving architecture enables an extremely efficient exchange of nutrients, toxins, particles, etc.

Notably, the canaliculi and the portal veins flow in contrary directions. While bile is secreted from the liver into the ducts, the combinatory blood supply made of the arteries and veins enhance the perfusion of the liver. Blood from the hepatocytes flows through sinusoidal lumens into the branch of the hepatic veins in the center of the hepatic lobule. Ultimately these branches converge and form the central veins within a lobule. These central veins will form the large vessels known as the hepatic veins and therefore represent the drainage for the entire liver. (19,20).

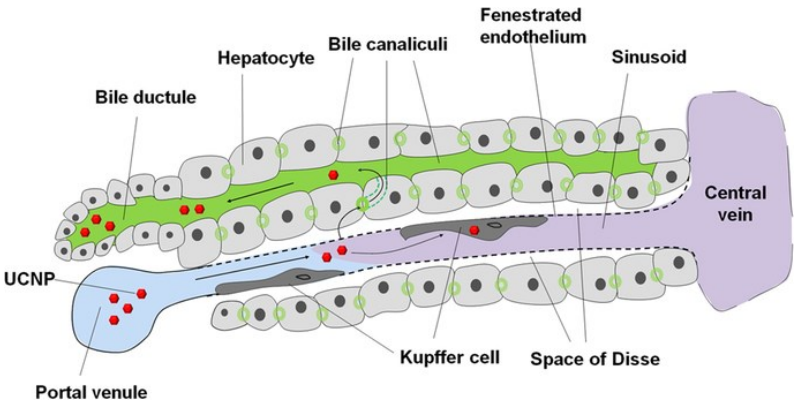

Figure 5: Schematic presentation of the kinetics in the liver tissue (21)

The space of Disse, which is a micro-anatomical region situated in the middle of the sinusoidal lumen and the basolateral hepatic membrane and is filled with microvillous structures that

originate from the hepatocytes. These microvilli facilitate communication with the capillaries and allow the hepatocytes direct access to the circulation. The space of Disse is filled with an extracellular matrix (ECM) containing various types of collagenous debris, proteoglycans, and other molecules, providing structural support to the hepatocytes and the lobule as a whole. This structural support is crucial, especially since hepatocytes do not have a typical basal layer.

In addition, the ECM harbors Kupffer cells, which are macrophages that help filter out harmful or unnecessary substances from the blood. Ito cells, also known as stellate cells, are also found in this space. These cells primarily store fat, including vitamin A, and can transform into myofibroblasts when needed, which help regenerate the liver (22).

2.5. Metabolic Functions of the Liver

In the liver, carbohydrate metabolism begins with the uptake of glucose, which is rapidly phosphorylated to glucose-6-phosphate. In the post-prandial phase, glucose is either converted into glycogen or converted into fatty acids and triglycerides, while during fasting, gluconeogenesis occurs using fatty acids or amino acids. The liver stores approximately 75-100 grams of glycogen and less than 5% of its mass in the form of triglycerides. Glycogen can be broken down through glycogenolysis to release glucose with the help of glucose-6-phosphatase (23).

For lipid metabolism, the liver absorbs free fatty acids and chylomicron remnants from the bloodstream via receptor-mediated endocytosis. It converts excess dietary glucose into free fatty acids, which are then converted into either triglycerides or ketones. Although triglycerides can be stored in the liver, this is generally undesirable due to the risk of pathological changes, so subcutaneous adipose tissue is a more suitable storage site. The liver exports triglycerides into the form of VLDLs (Very Low Density Lipoproteins), which serve both as a source of free fatty acids for other tissues and as a means of transportation for the storage of lipids in adipose tissue (24).

In protein metabolism, the liver acts as a hub for circulating amino acids and whole proteins or peptides, which are internalized by endocytosis into Kupffer cells and hepatocytes. Proteins are broken down into amino acids, which can then undergo various transformations such as deamination or transamination, whereby the amino acids are used as metabolic fuel or converted into other amino acids. Amino acids and proteins are not stored in the liver, and their deamination produces ammonia as a by-product. This plays an important role when considering the etiology and therapy of hepatic encephalopathy and portal hypertension (25).

Ammonia metabolism is of crucial importance, with a large proportion of it originating from the intestinal bacteria in the gut. Some of the ammonia is converted to glutamine in the tissues

and transported to the liver where it is metabolized and releases ammonia. This ammonia, together with the endogenously produced ammonia, is converted into urea by liver-specific enzymes of the urea cycle (26).

Finally, the liver plays a decisive role in lactate metabolism. Lactate, which is produced in the tissues through glycolysis, is converted back into glucose in the liver at the expense of 6 ATPs. Glucose is then exported from the liver and supports glycolysis in extrahepatic tissues in a process known as the Cori cycle (27).

2.6. Other Liver Functions

2.6.1. Bile Production

Bile is important not only for the digestion of lipids, but also as another mechanism for the elimination of waste and other products that are not excreted by the kidneys or metabolized elsewhere or in other circulatory systems. Bile mainly contains water, bile acids, salts, pigments, bilirubin, electrolytes, cholesterol and other compounds. It is secreted by the hepatocytes into the bile canaliculi and eventually ends up either in the gallbladder and/or is excreted into the duodenum via the sphincter of Oddi. It is important to note that bile, after being metabolized by the intestinal microbiota, can re-enter the portal circulation via the enterohepatic route.

2.6.2. Drug Metabolism

Another critical function that the public is most likely to be aware of is the metabolism and/or detoxification of drugs, toxins and other substances. This process takes place in the lysosomes and the biotransformation process is divided into phase I and phase II reactions. The main workhorse of phase I reactions is the cytochrome CYP450 subgroup of enzymes. The first phase reactions take place to make the metabolized compound more susceptible to phase II reactions, namely conjugation with other metabolites. These reactions are necessary to excrete and dispose of pathological and physiological substances.

2.6.3. Hormones and Coagulation

The involvement of the liver in thyroid hormone function is crucial because it is the main site for the activation of thyroxine (T4) into triiodothyronine (T3), which is the hormonally effective configuration of the thyroid hormone. This operation of deiodination involves the removal of one iodine molecule from T4, which is facilitated by hepatic enzymes such as the deiodinases. These enzymes also regulate the concentration of thyroid hormones.

In addition to its role in hormone metabolism, the liver is also involved in the production of almost all plasma proteins in our system. For example, albumin, the protein most frequently

synthesized by the liver, is crucial for maintaining oncotic pressure in the blood. In addition, the liver produces binding globulins such as thyroid-binding globulin (TBG), corticosteroid-binding globulin (CBG) and sex hormone-binding globulin (SHBG), which are essential for the transport and regulation of other hormones.

The coagulation is mainly affected and controlled by the liver as well, since it synthesizes almost all coagulation factors involved in both the intrinsic and extrinsic pathways, apart from factor VIII. These include vital proteins such as fibrinogen, prothrombin and factors V, VII, IX, X, XI and XII. The role of the liver in the production of protein C and protein S, which act as anticoagulants and balance clotting ability (19).

2.7. Pathophysiology of Portal Hypertension: A deep dive into cellular pathology

As already defined, portal hypertension is caused by an unusual resistance to flow in the portal venous system, which leads to increased pressure in the portal circulation. This condition results from increased intrahepatic vascular resistance caused by impaired sinusoidal circulation, which almost always results from chronic liver disease (CLD). There are several mechanisms and processes that are altered in CLDs at the cellular and molecular level. Most often, there is an interplay and combined downward spiral of different mechanisms that include extracellular matrix accumulation, fibrosis, inflammation and others that cause the deleterious effects on the liver and the pathologic changes in and around the liver (28)**.**

At the cellular level, liver sinusoidal endothelial cells (LSECs) and activated hepatic stellate cells play the major role in increasing intrahepatic resistance.

First, LSECs have so-called “fenestrae” that allow macromolecules to pass quickly. This ability is impaired by chronic damage, resulting in a loss of fenestration and so-called “capillarization". This effect leads to the development of a basement membrane that prevents the efficient passage of macromolecules. Another mechanism in LSECs is the ability to produce nitric oxide (NO), which enables the cells to adapt to fluctuations in flux. When cells lose their ability to produce it, they are less adaptable to a change in flow. Interestingly, autophagy of LSECs is a crucial process involved in the homeostasis of cells and the entire liver parenchyma. When their autophagy is impaired, the ability to repair and renew the cell population is reduced, leading to progressive pathologic turnover. One factor that cannot be influenced is age, which also leads to a decrease in fenestration, an increase in thickness and an increased susceptibility to chronic liver damage and diabetes (29).

Another unique cell type are the hepatic stellate cells (HSCs), which store vitamin A in their resting state. In CLDs, however, these cells are activated and further increase vascular

resistance. This occurs via the following mechanisms: stiffness, angiogenesis and contraction. Stiffness refers to the fibrotic changes and the actual mechanical stiffness of the liver and thus the passive, mechanically increased resistance. Most of the fibrotic material is synthesized by the HSCs and cross-links collagens. Hyperammonemia also leads to swelling of the HSCs, making them stiffer as well. In a maladaptive, synergistic manner, the HSCs follow the LSECs in their pathologic changes as the HSCs release vascular endothelial growth factor (VEGF). VEGF induces neoangiogenesis and reduces the adaptive capacity of LSECs, making them more susceptible to injury. Activated HSCs also contract, further increasing resistance.

Recent studies suggest that hepatic microvascular thrombosis may have also have significant in the progression of liver fibrosis but also of portal hypertension. This refutes the previous assumption that cirrhosis leads to an anticoagulated state due to reduced production of coagulation factors and thrombocytopenia (30).

Instead, cirrhosis may actually represent a procoagulant state. Thrombus formation in the microvasculature of the liver contributes to fibrosis and portal hypertension, a relationship first identified as “parenchymal extinction” in cirrhotic liver specimens (31).

In diseases such as congestive heart failure and Budd-Chiari syndrome, chronic liver congestion leads to congestive hepatopathy, another cause of portal hypertension. There is evidence that reducing hepatic thrombosis may alleviate fibrosis but may not adequately address all the underlying mechanisms of portal hypertension.

In addition to local changes, systemic factors such as increased portal blood influx from the splanchnic circulation and pathologic angiogenesis also contribute to the exacerbation of portal hypertension. Studies have shown that angiogenesis, particularly the formation of portosystemic collateral vessels, will further cause exacerbation of this disease. A therapeutic approach targeting pathologic angiogenesis has been explored, although it faces challenges due to the essential role of angiogenic factors in normal vascular function.

3. Etiology of Portal Hypertension

Table 2: The most common causes of portal hypertension (32)

Pre-Hepatic	PV/SV thrombosis Tumor compression of PV/SV Arteriovenous fistulas
Intra-Hepatic	
Pre-sinusoidal	Schistosomiasis Early PBC Chronic active hepatitis Congenital hepatic fibrosis Sarcoidosis Toxins Portosinusoidal vascular disorders
Sinusoidal	Cirrhosis Acute alcoholic hepatitis Cytotoxic drugs Vitamin A hepatotoxicity
Post-sinusoidal	Hepatic sinusoidal obstructive syndrome Alcoholic central hyaline sclerosis
Post-Hepatic	Right heart failure Pulmonary hypertension Budd-Chiari syndrome Hepatic sinusoidal obstructive syndrome

VOD, veno-occlusive disease; PV, portal vein; SV, splenic vein.

3.1. Differentiation of Etiology

Portal hypertension can be divided etiologically into prehepatic, intrahepatic and post-hepatic causes, each of which is associated with specific pathophysiological mechanisms.

Prehepatic causes refer to impairments that occur proximal (in this case, distal with respect to the regular alignment) to the liver and typically involve obstruction or thrombosis of the portal vein. Common conditions that contribute to prehepatic portal hypertension include portal vein thrombosis (PVT), which can result from hypercoagulable states, cirrhosis of the liver or as a complication of abdominal surgery. This category also includes congenital anomalies such as portal vein atresia, defined as the complete agenesis or underdevelopment of the portal vein and leads to increased vascular resistance and pressure in front of the liver.

Intrahepatic causes are diseases that affect the liver parenchyma and are the most common etiology for portal hypertension. Cirrhosis is the primary intrahepatic cause, in which progressive liver fibrosis leads to deformation of the cellular architecture and increased intrahepatic vascular resistance. Other causes include hepatic schistosomiasis, in which

Schistosoma eggs are deposited in the liver causing granulomatous reactions and fibrosis, and hepatic neoplasms that interfere with normal blood flow through the organ.

Post-hepatic causes are comprised of conditions that impede venous blood flow as it exits the liver. These are for one the rare Budd-Chiari syndrome, which is characterized by an impaired drainage of the liver at the level of the IVC or hepatic veins, leading to congestion and increased venous resistance within and before the liver. Congestive heart failure, particularly affecting the right heart, can also lead to hepatic venous congestion and subsequent portal hypertension by increasing back pressure into the hepatic circulation.

The distinction between these etiologic categories is critical for the targeted treatment of portal hypertension, as treatment strategies often depend on the underlying cause. Therapeutic approaches include anticoagulation for PVT, portal pressure-lowering agents such as beta-blockers or vasodilators for cirrhosis-related portal hypertension, and minimally invasive measures such as transjugular intrahepatic portosystemic shunt (TIPS) for cases with significant venous obstruction (32).

3.2. Portal Vein Thrombosis

Portal vein thrombosis (PVT) is the number one prehepatic cause of portal hypertension. It is often associated with liver cirrhosis but can also occur without liver disease due to factors such as malignancy, abdominal infection or pancreatitis. The term extrahepatic portal vein obstruction is used to describe chronic portal vein thrombosis leading to the formation of a portal vein cavernoma or collateral circulation surrounding the obstructed vessel. The main cause of PVT in individuals with cirrhosis is the liver disease itself, whereas in non-cirrhotic individuals it is often caused by inherited or acquired prothrombotic conditions such as myeloproliferative disorders, antiphospholipid syndrome or protein C and S deficiency. Other contributing factors include malignancies, pregnancy, chronic inflammation and the use of oral contraceptives. PVT does not usually cause symptoms, but if it leads to portal hypertension, it may manifest clinically as abdominal pain, fever and ascites. Diagnosis of PVT is made by liver function tests, which generally show normal results unless cirrhosis is present. Imaging techniques such as Doppler ultrasound, CT and MRI are crucial to substantiate the presence of thrombosis, followed by the assessment of its extent. Treatment focuses on anticoagulation to prevent the progression of thrombosis and manage complications. In addition to traditional therapies such as low-molecular-weight heparin, newer oral anticoagulants are increasingly being used.

3.3. Malignancies compressing the Portal Vein or Splenic Vein

Even though portal hypertension is rarely caused by malignant diseases, there are a few cases worth mentioning. Of course, the nearest anatomical structures are the most common causes of compression, such as the pancreas, stomach or bile duct cancer. Diagnosis, staging and treatment of the tumor itself are of paramount importance; when treating it, the secondary effects it has on the liver, for example, should not be overlooked. This study showed that gastrointestinal bleeding was not only caused by the tumor with structural invasion, but also by hemodynamic effects of portal hypertension (33).

3.4. Presinusoidal, Intrahepatic Causes for portal hypertension

Portal hypertension can be caused by various presinusoidal intrahepatic diseases. Schistosomiasis, less known in the Western world, is among the most typical etiologies worldwide, particularly in endemic regions such as Africa and South America, where parasitic worms lead to egg deposition in the liver, causing granulomatous reactions and subsequent fibrosis that obstructs the portal vein (34).

Similarly, autoimmune diseases such as primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) cause inflammation and fibrosis in the bile ducts, with PBC affecting small intrahepatic ducts and PSC affecting both intrahepatic and extrahepatic ducts, both representing an impairment to regular flow (35).

Sarcoidosis, although less common, can also cause portal hypertension due to the formation of non-caseating granulomas in the portal vein areas. In addition, congenital hepatic fibrosis, a rare genetic disorder, disrupts the development of the bile duct plates, leading to fibrosis and malformed bile ducts around the portal vein, which further increases resistance to blood flow and causes presinusoidal portal hypertension (36).

3.5. Intrahepatic sinusoidal Causes for Portal Hypertension

3.5.1. Cirrhosis

Cirrhosis is defined as follows, regardless of the underlying pathology:

> *"[…] the pathogenic consequence of a remarkably conserved response to injury within the liver, characterized by progressive fibrosis tissue deposition and eventual disruption of normal hepatic architecture. The hallmark of liver injury is activation of the hepatic stellate cell, which mediates the development of fibrous tissue and change in the composition of the extracellular matrix.* (37)

It represents the most common etiology for portal hypertension. This chronic liver damage is often caused by prolonged alcohol abuse, viral hepatitis or NAFLD. Other factors that

contribute to portal hypertension include acute alcoholic hepatitis, in which sudden, excessive alcohol consumption causes liver inflammation and swelling that further impedes blood flow. Chronic viral hepatitis, particularly hepatitis B and C infections, lead to progressive liver inflammation, necrosis and fibrosis, eventually culminating in the development of cirrhosis and portal hypertension in susceptible individuals. Hepatitis B virus (HBV) and hepatitis C virus (HCV) exert direct cytopathic effects on hepatocytes, triggering immune-mediated liver injury and promoting fibrous tissue production through the activation of HSCs as described above.
Of course, it is possible to further explain the etiology, pathogenesis and complications of liver cirrhosis, but this is beyond the scope of this paper (38).

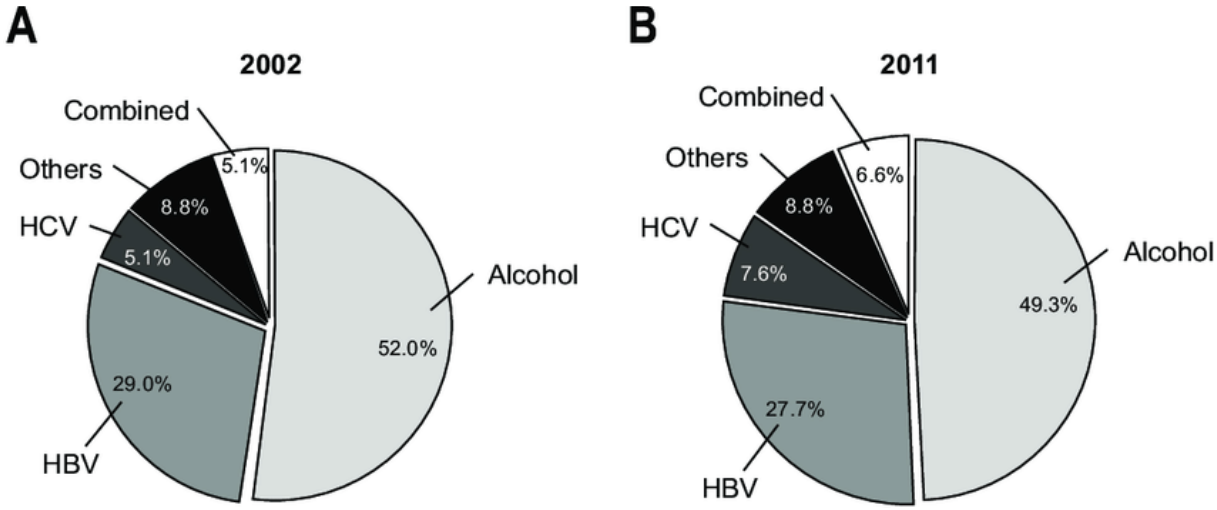

Figure 6: Causes for Portal Hypertension in 2002 and 2011 (39)

In addition, virus-induced oncogenesis of the liver and the advancement to hepatocellular carcinoma (HCC) further exacerbates the burden of portal hypertension in chronic viral hepatitis.
In addition, cytotoxic drugs, often chemotherapeutic agents such as platinum, “nitrogen mustard”, nitrosourea, alkyl sulfonates and triazines, can cause hepatotoxicity by damaging liver cells, contributing to the development and exacerbation of portal hypertension. The better-known active substances include cyclophosphamide and cisplatin (40).
Similarly, excessive intake of vitamin A can lead to direct hepatotoxicity and fibrosis. The mechanism of toxicity and subsequent cirrhosis is also caused by activation of the HSCs due to excess vitamin A, causing the HSCs to produce excess collagen and become hypertrophic. This toxicity is dose-dependent and reversible in its early stages. While acute toxicity may be mediated by a single dose or several doses in short succession, the symptoms are more likely to represent acute hepatitis. On the other hand, a state of hypervitaminosis lasting more than 3 months may lead to more specific symptoms, cellular changes and abnormal liver enzymes (41).

3.5.2. Non-Alcoholic Fatty Liver Disease (NAFLD)

Non-alcoholic fatty liver disease (NAFLD) has been shown to be another relatively common etiologic element in the development of portal hypertension, particularly in combination with metabolic syndrome and obesity. NAFLD represents a large variety disease advancement, on one hand only precipitating in simple steatosis, but may also escalate to non-alcoholic steatohepatitis (NASH) and even cirrhosis, rather than being limited to a single disease. An inherent resistance or insensitivity to insulin as seen in metabolic syndrome, dyslipidemia, oxidative stress and hyperglycemia are essential in the pathogenesis of NAFLD, leading to hepatocellular lipid accumulation, inflammation and fibrosis. Progressive fibrogenesis and the progression to cirrhosis in NAFLD patients can eventually result in the occurrence of portal hypertension and its associated sequelae (42).

3.6. Intrahepatic post sinusoidal Causes

3.6.1. Sinusoidal Obstruction Syndrome (SOS)

Which was described as “veno-occlusive disease (VOD)” in older literature, is another post-sinusoidal, intrahepatic, but rare cause of portal hypertension. It is a severe and in the worst case even a fatal pathology, usually triggered by drug or toxin exposure. Clinically, it shows a spectrum of symptoms similar to acute hepatitis, but with an unrepresentative change in serum enzymes. The pathogenesis of this disease is usually attributed to LSECs becoming necrotic and extruding into the sinusoids, leading to obstruction and congestion (43).

Alcoholic central hyaline sclerosis is an abnormal reaction to alcohol that causes an accumulation of fibrous tissue in the centrilobular (perivenular) zone, which also leads to increased resistance.

3.7. Post Hepatic Causes of Portal Hypertension

3.7.1. Cardiac Etiology

Logically, there are several cardiac abnormalities and pathologies that lead to portal hypertension. The most important mechanism is the increase in retrograde pressure from the lungs, the heart itself or at a point in the outflow from the liver to the heart. This leads to compression and obstruction of the sinusoids. Mechanisms include right ventricular dysfunction, low cardiac output, valvular heart disease, constrictive pericarditis and stenosis. Isolated left-sided heart failure may also lead to indirect liver damage, as the reduced cardiac output leads to impaired perfusion and tissue hypoxia. This manifests itself in the liver in the form of hepatocytic necrosis and an increase in liver serum markers (44).

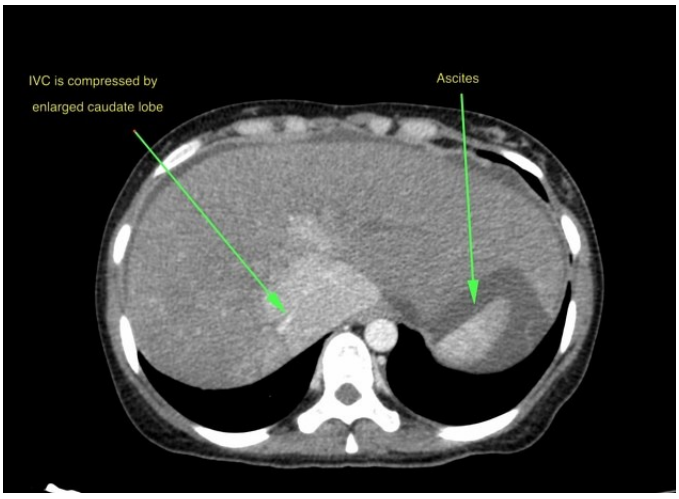

Figure 7: Budd-Chiari Syndrome in a native CT (45)

3.7.2. Budd-Chiari Syndrome

Budd-Chiari syndrome (BCS) is a seldom, yet serious condition defined by obstruction of venous outflow leading to hepatic congestion, ischemia and portal hypertension. It is an obstruction between the smallest hepatic venules and the transition zone between the IVC and the right atrium. With an incidence of around 1:1,000,000, it is also more likely to be encountered in younger women (46).

BCS can be caused by various causes, including thrombus formation within the hepatic veins or IVC directly, myeloproliferative disorders and compression of the hepatic veins by neighboring structures. Obstruction of hepatic venous flow disrupts normal liver perfusion, leading to hepatocellular damage, sinusoidal dilatation and the development of collaterals. The clinical presentation of BCS varies greatly in relation to the degree and location of venous obstruction, ranging from asymptomatic cases to acute liver failure. Common clinical manifestations include hepatomegaly, ascites and abdominal pain, often accompanied by the typical features of portal hypertension such as splenomegaly, variceal bleeding and hepatic encephalopathy. BCS can occur sporadically or as part of an underlying predisposition or prothrombotic condition. Known risk factors for BCS include myeloproliferative disorders such as polycythemia vera and essential thrombocythemia, inherited thrombophilia, pregnancy, use of oral contraceptives and certain autoimmune diseases (47).

3.8. Other Rare Causes

In addition to the causes already mentioned, portal hypertension may also be caused by rare diseases such as congenital liver fibrosis and idiopathic portal hypertension. Congenital hepatic fibrosis (CHF) is an autosomal recessive disease defined by fibrous deposits and dilatation of the intrahepatic bile ducts, leading to congestive hypertension within the portal circulation.

Idiopathic portal hypertension (IPH) is a diagnosis of exclusion necessarily demanding the diagnosis of portal hypertension, but with definite exclusion of cirrhosis, chronic liver disease or other identifiable causes.

3.9. Pathogenesis of Portal Hypertension

The pathogenesis focuses on hemodynamic changes characterized by abnormal resistance to flow in the portal circulation and the development of a hyperdynamic circulation. Chronic liver injury, as occurs in cirrhosis, underlies many of these changes and sets in motion a cascade of events that lead to increased portal pressure. At the same time, a compensatory response occurs, characterized by hyperdynamic circulation and arterial vasodilation. This hyperdynamic state leads to increased splanchnic blood flow, which exacerbates the condition in the circulation and further adds to the formation of collaterals and pathologic portosystemic shunting.

The major vascular components involved in pathogenesis are not only the intra- and extrahepatic circulation, the systemic or splenic circulation and the abnormal and diffuse circulation formed in collaterals. Of course, neoangiogenesis and collateral circulation change the situation and the hemodynamics, so that whenever new vascular formations occur, the risk of complications and the further course of action must be assessed.

As already mentioned, the microvasculature of the liver is altered in portal hypertension and forms the basis for the pathological downward spiral. LSECs and HSCs alter and influence each other via paracrine hormonal signaling using nitric oxide (NO) and endothelin-1 (ET-1). LSECs release these transmitters in response to stress or as needed. In the physiological state, these two hormones counteract and balance each other, resulting in appropriate relaxation and adaptation of HSCs. In cirrhosis, on the other hand, there is an overproduction and secretion of ET-1, which leads to the activation of the HSCs described above and thus to subsequent contraction and stiffening. NO contributes to the improvement of portal hemodynamics when it is properly secreted and metabolized. Normally, endothelial nitric oxide synthase (eNOS), produced in LSECs, contributes to HSC relaxation by synthesizing local NO that is distributed in a paracrine manner. Unfortunately, liver cirrhosis disrupts this adaptive mechanism on several levels, as not only the ability to produce NO but also the sensitivity of the HSC is reduced. Therefore, there is a synergistic pathological relationship between ET-1 and NO in cirrhosis (48).

Another pathological change is the so-called “sinusoidal vascular remodeling",” which is characterized by sinusoidal vasoconstriction and increased vascular resistance. This remodeling differs from the fibrosis and collagen deposition associated with HSCs. The motility and migration of HSCs are essential for their increased coverage of sinusoidal endothelial cells (SECs) (49).

In cirrhosis, bacterial translocation leads to increased production of tumor necrosis factor-α (TNF-α), which subsequently induces an increase in systemic NO production. The increased NO levels in both the systemic and splanchnic circulation contribute to decreased overall vascular resistance and a hyperdynamic circulatory state. This hyperdynamic circulation leads to sodium retention and ascites due to reduced effective circulatory volume, stimulation of the sympathetic nervous system, activation of the RAAS and increased release of ADH (50).

An extended duration of altered blood flow leads to compensatory, pathologic adaptation resulting in vascular remodeling. In portal hypertension, a sustained increased flow leads to dilatation of the vascular channels. This triggers endothelial signals that cause vascular remodeling, increasing width of the vessel and ability to react to this increased hemodynamics. This particular phenomenon was observed in blood vessels in the periphery, but also proven in experimental settings of portal hypertension, where it is thought to be caused by to the hyperactivity of eNOS. This must be considered as one of the breeding grounds for the formation of collaterals and varices, although the exact mechanism of regulation and unfolding is still not fully understood. In animal models, it has been shown that the development of a portosystemic shunt could be almost prevented by targeting vascular endothelial growth factor (VEGF) with antibodies (51).

When considering the above-mentioned changes, and particularly the hyperdynamic circulation, it is important to point out that several organs are affected that may not appear relevant at first glance. It must be made clear that the hyperdynamic state itself is not disruptive or harmful to the patient but is clinically and patho-etiologically relevant. Tachycardia, decreased systemic resistance in combination with increased cardiac output and hypotension are regularly documented in patients suffering end-stage liver disease and are almost exclusively due to the changes in splanchnic and systemic pressure (52,53).

Patients with cirrhosis have an increased baseline cardiac output, but regardless have an impaired contractile stress-related response. They display an impaired systolic and diastolic ventricular response, ventricular hypertrophy, ventricular dilatation and prolonged QT intervals. Although the burden of procedures like the terminal solution of a transplantation or placement of a TIPS is usually mild or asymptomatic, it can trigger overt heart failure.

In addition, cirrhotic cardiomyopathy in particular may be involved in the occurrence of hepatorenal syndrome, acute heart failure after TIPS and an increased cardiovascular morbidity and mortality following transplantation (54,55).

Liver cirrhosis often induces vasoconstriction within kidneys, which is accompanied by splanchnic vasodilation and hyperdynamic circulation and can cause hepatorenal syndrome.

This vasoconstriction results from effective hypovolemia and neurohumoral activation. Treatment strategies for hepatorenal syndrome usually target the cause itself and alter hormone and transmitter signaling (56).

Pulmonary vasodilation in cirrhosis can lead to ventilation-perfusion mismatch and arteriovenous shunts, resulting in hepatopulmonary syndrome and significant hypoxemia. In contrast, increased pulmonary vascular resistance due to endothelial dysfunction and vascular remodeling can lead to portopulmonary hypertension. In the brain, altered state of flow and the impaired vascular response caused by portal hypertension contribute to the development of hepatic encephalopathy, which we will discuss later in this paper (57).

If you look at all the mechanisms mentioned, it becomes clear that portal hypertension is not as simple as it first appears. There are numerous factors that are overlooked at first glance and do not appear to be as relevant to the pathogenesis, but in conclusion, portal hypertension is a multifaceted disease with many tributaries involved.

3.10. Pathogenesis of Ascites in Portal Hypertension

Ascites represents one of the cardinal and clinically relevant complications of portal hypertension and somewhat reflects on the degree of alteration of the physiological state. There are several mechanisms that play into the development of ascites, namely the hemodynamic change, change in oncotic pressure and sodium retention in the kidneys. Portal hypertension and the associated decrease in flow plus the stasis of the blood, leads to an accumulation of substances acting directly on the vessel wall, leading to vasodilation, therefore altered permeability (58). Of course, this precipitates in the splanchnic vascular network, since there is a consequent hypoperfusion with a reactive stimulation of the so-called renin-angiotensin-aldosterone system (RAAS). The release of these hormones is supposed to counteract the impaired flow and is followed by fluid retention, leading to extravasation of fluid into the abdominal cavity (59). Adding to that, due to cirrhosis or other functional abnormalities in the liver, the protein production is also affected. The most important component for the hydrostatic pressure is Albumin, which balances out the oncotic pressure of intra- and extracellular fluid. If there is a relative or absolute hypoalbuminemia, this exacerbates the preexisting conditions of fluid extravasation. The pressure gradient and the relative probability of fluid exiting the vessel may be calculated with the Starling Law, which is otherwise used for calculating the heart’s physiological ability to adapt to different dynamic conditions (60).

4. Clinical Manifestations

4.1. Clinical Manifestations

Portal hypertension is clinically manifested by various signs and symptoms that reflect its systemic effects on the body. First and foremost, portal hypertension can be diagnosed clinically with a fair degree of certainty as there are several characteristic features that may indicate the underlying condition. It is usually a slow process leading to the condition and changes that will be discussed here, which is why a long medical history often precedes the diagnosis and complications. Unfortunately, as mentioned above, cirrhosis and therefore portal hypertension are often caused by chronic alcohol consumption, where patients often delay further diagnosis and treatment until there is medical urgency or even an emergency. These clinical symptoms and manifestations are discussed in the following section.

4.2. Variceal Formation

The formation of varices is a characteristic feature that is frequently observed in the form of esophageal varices and gastric varices and carries a considerable risk of bleeding and life-threatening hemorrhage. Varices are a form of shunt connecting the portal and systemic circulation. Varices in the esophagus are specifically dilated distal esophageal veins that are categorized and graded based on their size, presence of red signs and bleeding tendency, with higher grades being associated with increased risk.

They are very commonly diagnosed in cirrhotic patients: almost 30% of patients with cirrhosis will also present with varices at diagnosis. When looking at the mortality rate in combination with an advanced liver disease, the underlying risk becomes apparent. A model-for-end-stage liver disease (MELD) score of over 20 points predicts a mortality of over 20% from an acute episode of variceal bleeding (61). Additionally sever portal hypertension, namely a hepatic venous pressure gradient of over 20 mmHg, further worsen the prognosis following variceal ruptures, increasing the likelihood of rebleeding and mortality. Overall, bleeding leads to a mortality rate of up to 20% in the 6 weeks afterwards (62).

These figures show how important varices are for the diagnosis, treatment and prognosis of portal hypertension. Clinically, they may present with a history of hematemesis, melena, hematochezia, unexplained weight loss, abdominal discomfort, pruritus, and hepatic

encephalopathy. Other tell-tale signs may be seen on examination, but these are discussed in more detail in the diagnostic section.

4.3. Ascites

Ascites, the pathological accumulation of fluid in the abdomen, a regular sequelae of advanced liver disease and portal hypertension. It is the most frequently encountered complication of decompensated liver cirrhosis and occurs in up to 50% of patients. Over 80% of ascites cases in the western world are caused by cirrhosis, followed by heart failure at around 10% (63). Of course, other less likely causes must also be considered, namely tuberculosis, pancreatic diseases or tumors. As with the previously mentioned varices, the diagnosis and treatment of ascites heavily impact the outcome and prognosis of the patient. The presence of ascites also indicates whether the liver cirrhosis is considered as compensated or decompensated. Patients presenting with ascites caused by cirrhosis have a 3-year survival rate of around 50%. An even more serious prognosis is refractory ascites and the 1-year survival rate, which is also around 50% (64). These figures show the significance and severity of ascites in portal hypertension. In most cases, patients present with progressive abdominal discomfort and bloating. This is also manifested by weight gain that is unrelated to diet and physical activity and is often one of the cardinal symptoms reported by a patient. Differential diagnosis and evaluation of other clinical features are critical to identify and localize the underlying disease. Ascites can be punctured and examined with fluid analysis, which can be not only diagnostic but also therapeutic. The exact mechanism and the advantages and disadvantages will be discussed later (65).

4.4. Splenomegaly

Splenomegaly is a common clinical manifestation of portal hypertension due a chronic increase in backflow towards the spleen, resulting splenic congestion. The mechanisms underlying splenomegaly in portal hypertension are a combination of passive congestion, red pulp hyperplasia and extramedullary hematopoiesis. It has been known for decades that it could be a complication of portal hypertension but has not been recognized for its significance. Recent studies have shown that measurement of splenic stiffness is a clinically important parameter for assessment and treatment planning (66).

4.5. Hepatic Encephalopathy

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome identified by cognitive impairment, impaired consciousness and motor dysfunction, often occurring in patients with a heavily impaired liver function or liver perfusion. It is not necessarily a manifestation of portal hypertension itself but may sometimes develop even after successful treatment and reduction

of the portal pressure gradient. Therefore, it is of explicit importance to distinguish whether HE has occurred due to acute progression of the underlying liver failure or whether it has developed because of the therapeutic measures. HE may be classified into three subcategories: Type A is HE with causative acute liver breakdown, Type B refers to encephalopathy due to portosystemic shunts without an underlying cellular disease. Type C is a combination of both, with the addition of the CLD element as it requires cirrhosis and portosystemic shunts. The pathogenesis of HE involves the accumulation of neurotoxic substances such as ammonia and alterations in neurotransmitter metabolism in the central nervous system. In addition, there are several factors that trigger HE and further exacerbate the condition. These include, for example, hypokalemia, hyponatremia, hypovolemia, increased systemic stress (especially infections, e.g. hepatitis, bacterial peritonitis), increased nitrogen load, renal failure, constipation and medications such as sedatives, tranquilizers or narcotics. Clinical assessment involves grading the severity of HE based on standardized scales such as the West-Haven criteria, which stratify patients according to the degree of change in mental status and neurological symptoms (67).

4.6. Coagulopathy and Bleeding Tendency

Coagulopathy and bleeding tendency are frequent complications of advanced liver disease and portal hypertension, which are due to multifactorial disorders of the coagulation cascade. In liver cirrhosis, impaired synthesis of coagulation factors, thrombocytopenia and altered platelet function contribute to a delicate balance between bleeding and thrombosis. While there is a systemic tendency to bleed, there is a higher likelihood of thrombus formation in the splanchnic and prehepatic circulation due to thrombocytopenia and the reduced number of metabolites involved in the coagulation cascade. This occurs due to the stasis and the altered blood flow, which favors the formation of clots and the precipitation of blood products (68).

5. Diagnostic Evaluation

5.1. History and Physical Examination

It has been established that portal hypertension is more of a clinical diagnosis, but it still needs to be definitively confirmed by measuring the hepatic portal venous gradient (HVPG). Even though this measurement is the only way to make the definite diagnosis, there are other non-invasive methods to assess portal hypertension. First and foremost, the patient's medical history is crucial in most cases and is often a reliable pillar for planning further therapy and diagnostics. Questions that may be relevant for diagnostic purposes relate to the underlying disease and conditions that the patient may already have.

It is important to keep the previously mentioned causes in mind as they can help in taking the correct history. There are prehepatic, intrahepatic and posthepatic causes which are helpful in further narrowing down the following procedure. Posthepatic causes such as right-sided heart failure may involve a whole host of other pathologies that should be treated simultaneously, as treating the cause may simultaneously alleviate the hypertensive symptoms. Cirrhosis of the liver as an intrahepatic cause may have a history of alcohol consumption and other metabolic disorders, which can be assessed by anamnesis (69).

5.2. Physical Examination Findings

It is paramount to address that patients with portal hypertension may present with a wide spectrum of symptoms and signs that are often related to the underlying disease. The most common findings have already been mentioned in the "Clinical Manifestations" section. However, it is important to mention other signs that are relatively common in patients, even if these manifestations are not directly related to portal hypertension.

Jaundice, although a seldomly encountered symptom of portal hypertension, is the yellow discoloration of the skin, sclerae and mucous membranes due to hyperbilirubinemia, typically exceeding 2-3 mg/dL or 0,34-0,51 mmol/l respectively. It indicates impaired hepatocellular function or obstruction of bile flow, leading to an accumulation of bilirubin in the blood. This can give us a clue, but should always be investigated further to determine the exact cause of jaundice (70).

Spider angiomas are telangiectasias characterized by a central arteriole surrounded by radiating capillaries. These lesions, which often occur on the face, neck and upper trunk, are associated with increased circulating estrogen levels due to liver dysfunction and decreased hepatic clearance. The exact pathogenesis is not known in detail, but is frequently observed in chronic alcoholics and liver cirrhosis (71).

Ascites, presents as the pathological extravasation of fluid more than 25 ml, as described in the section above. It is a common complication of portal hypertension, although it may be associated with other conditions. Increased abdominal pressure leads to early satiety, dyspnea, and malaise, while a more severe clinical presentation with high temperature, reflex abdominal distension, and an altered mental status may be caused by spontaneous bacterial peritonitis. Other manifestations in combination with ascites may help in the diagnosis, as weight loss may indicate malignant disease, while peripheral edema and orthopnea may indicate right heart failure. An invasive but very effective method of analysis is paracentesis of the abdominal fluid. The subsequent analysis of the fluid is crucial for further diagnosis. First of all, an erythrocyte count, the number of polymorphonuclear neutrophils and a bacterial culture should be carried

out. In addition, the proteins and albumin of the ascites fluid are measured in order to compare these values with the values in the blood. There is a gradient that can be calculated, the serum-ascites albumin gradient (SAAG). This gradient predicts portal hypertension with an accuracy of 97% and is therefore an extremely effective method for diagnosing portal hypertension. If the gradient is less than 1.1 g/dL, this may indicate other causes such as pancreatitis, tuberculosis, nephrotic syndrome or others. A non-invasive, inexpensive and highly specific test is an ultrasound, which shows free abdominal fluid in typical locations. These can be the Koller pouch, the Morrison pouch or the Douglas space in women. Of course, the fluid can also be seen on an X-ray or CT scan, but ultrasound is the method of choice (65).

5.3. Endoscopy

Upper endoscopy is the gold standard for the diagnosis and immediate treatment of the sequelae of portal hypertension, most commonly being varices. It is not only a diagnostic, but also a prophylactic and therapeutic tool. It may be used to assess asymptomatic changes in the upper GI-tract, like small gastric or esophageal varices, which will already be indicative of an underlying pathology, that is otherwise not known before.

Pathological changes due the hyperdynamic state and increased resistance in the portal circulation may precipitate in vascular changes in the stomach lining, manifesting as a mosaic-like pattern, not necessarily showing red spots upon endoscopic examination. This is diagnosed in an endoscopy and is called portal hypertensive gastropathy (PHG). It is often asymptomatic but may lead to long-term gastrointestinal blood loss, precipitating in iron-deficiency anemia, or acute bleeding episodes. This pathological adaptation may also be seen in the small intestine and shows as erythema, edema, and vascular lesions observed in the intestinal mucosa. The symptoms are similar to those of PHG but, if the diagnostic hallmarks are visible in the small intestine it is categorized as portal hypertensive enteropathy (PHE). Due to the depth at which the lesions may occur, a capsule endoscopy may also be indicated (72).

Prophylactic methods of upper endoscopy are often combined with prophylactic non-selective beta blockers, delaying the first episode of variceal bleeding. The method of choice is the so-called endoscopic band ligation (EBL), which is also being used in acute bleeding episodes. During the procedure, the patient is sedated or anesthetized to ensure compliance and minimize movement. The flexible endoscope is inserted through the mouth into the esophagus, allowing the physician to visualize the varices all along the esophagus into the stomach. Band ligation may happen immediately, like in emergency settings or after reconsideration according to location, risks and comorbidities. Post-procedure, the patient is monitored for any immediate complications, such as bleeding or adverse reactions to the sedation, and is typically discharged

the same day or kept for few days for monitoring. Even though there are alternative forms of treatment like tissue adhesive injection, EBL is the safer, more effective and connected to less complications like delayed rebleeding (73).

This very elegant technique, that utilizes the variability of an endoscope and works by enclosing the lesion with a round rubber (or similar materials) band, which is placed around the base of the tissue to compress the basal vasculature leading to hemostasis and subsequently local thrombus formation. There may be episodes of self-limited bleeding during or after the procedure due to rupturing of the varices. In the further therapy follow-up endoscopies are often scheduled to monitor for recurrence and ensure effective management of the varices (74).

5.4. Endoscopic Variceal Classification and Localization

Varices may form in various places throughout the abdomen, in the esophagus, in the paraumbilical area, at the upper end of the anal canal, retroperitoneally and in the bare area. A clinical symptom that may be very revealing and is also visible on inspection is the so-called "caput medusae", which translates to "head of Medusa". This describes the phenomenon of varices in the periumbilical area, which may extend over the entire abdominal cavity. The development of these various varices depends on the underlying pathology and the accompanying other diseases. These may include vascular anomalies, thrombus formation, congenital variations and malformations.

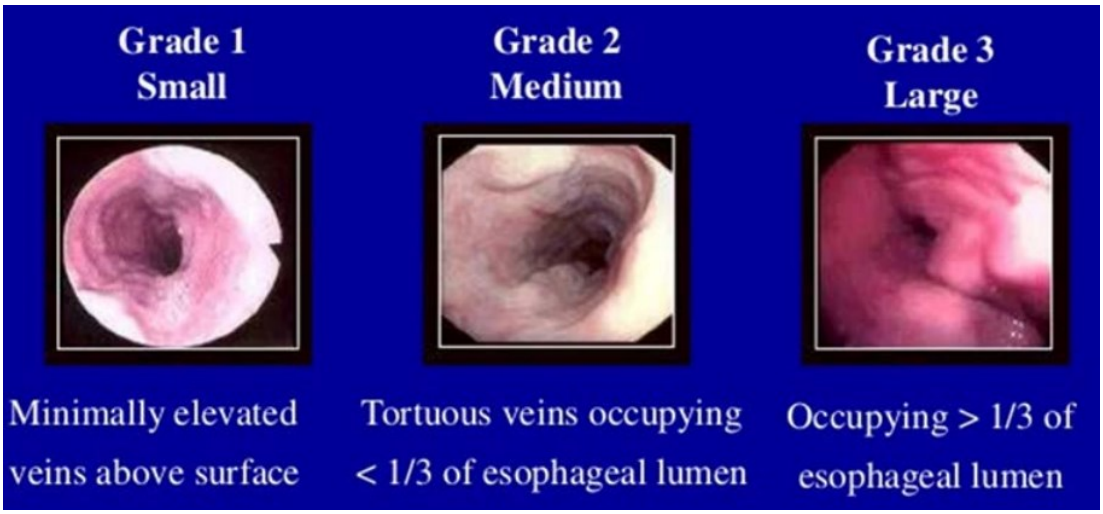

Figure 8: AASLD practice guidelines: prevention and management of gastroesophageal varices. (74)

Endoscopically varices may be visualized and have several ways of classifying them. There are various forms that may differ according to localization, morphologic appearance, risk of rupture, anatomy and other criteria. Gastric varices may be categorized according to Sarin, Hashizome or Arakawa. Gastric varices occur less frequently than esophageal varices but can also be further subcategorized according to their location and relation to esophageal varices,

which may help in the decision for treatment and risk stratification. Sarin categorized gastroesophageal varices are according to their extension into the stomach, and if they appear in presence of esophageal varices. Gastroesophageal varix (GOV) type 1 refers to esophageal varices that extend along the lesser curvature, while GOV type 2 involves esophageal varices extending along the greater curvature. Isolated gastric varix (IGV) type 1 represents variceal formations positioned in the fundus without esophageal involvement. In contrast, IGV type 2 are relatively rare and comprise of varices found in other parts of the stomach or the duodenum (75).

Esophageal varices are classified clinically according to their morphological features, size, location and grade of occlusion of the lumen. They are assessed by visualization with an upper gastrointestinal endoscopy. Even though there are several approaches to classification (76), the most in depth and descriptive form is according to the Japanese Research Society for Portal Hypertension (JRSPH) by size, shape, base color, “red color sign” (RC), location and the presence of esophagitis (75).

The shape can be divided into 3 types: F1s are morphologically linear varices that persist when insufflated. F2s are somewhat larger tortuous varices that occupy require less than thirty percent of the esophageal lumen and F3s are wide-reaching vessels that occupy more thirty percent of the lumen. Their color can also be designated, as there are varices whose general surface structure tends to glow white and some that look less bluish.

Red color signs are specific morphological signs that are scattered across the varices. Some of these are red wale markings, cherry red spots, hematocystic spots, and diffuse redness. When evaluating esophageal varices, it is relatively easy to categorize them according to their location in relation to the surrounding structures. The trachea and its branches can be used for this purpose. Locus superior refers to varices above/above bifurcation of the trachea, locus medialis are those directly next to/”above” the tracheal bifurcation and locus inferior describes these vessels near the stomach and the distal esophagus. A distinction is also made according to whether esophagitis is present or not.

5.5. Colonoscopy

Even though most manifestations of portal hypertension present in the upper gastrointestinal tract and are visualized by upper endoscopy, some pathological alterations are also visible in an endoscopy of the lower gastrointestinal tract. During a colonoscopy, portal hypertension can manifest through several characteristic findings in the colonic mucosa. These include mucosal edema, which presents as swelling and thickening of the mucosal lining due to fluid accumulation. Vascular ectasia is observed as dilated, tortuous blood vessels visible through the

mucosa, often referred to as portal hypertensive colopathy. Additionally, red spots and telangiectasis may be seen, indicative of petechiae. Rectal varices may appear similar to hemorrhoids but are instead caused by increased portal pressure, can also protrude into the lumen.

The appearance of colonoscopic lesions is highly correlated with an increased Child-Pugh and MELD score. Nevertheless, studies have shown that upper GI bleeds represent the main risk for potentially fatal complications and lower GI lesions are comparably insignificant (77).

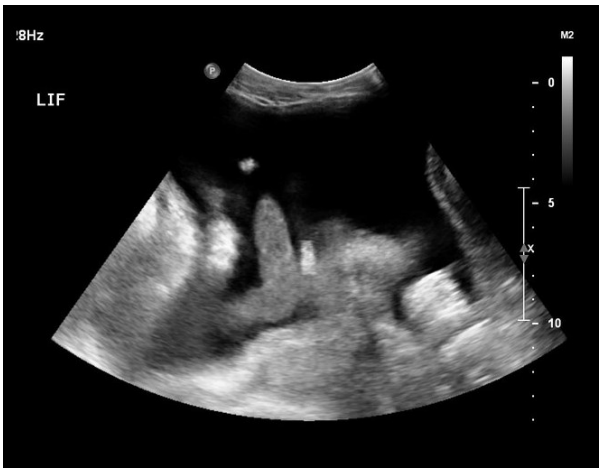

Figure 9: Cirrhosis in Portal Hypertension; a Case study, Radiopaedia (78)

5.6. Hepatosplenomegaly

Hepatomegaly, an abnormal enlargement of the liver, can be palpated during a physical examination and may indicate underlying liver disease or congestion due to portal hypertension. The liver may feel firm or irregular if cirrhosis is present. This is also visible on an ultrasound scan and may also show up on other X-ray examinations. The typical image of a bulge and loss of the sharp edge of the liver are typical signs of cirrhosis and hepatomegaly. Splenomegaly, on the other hand, is the enlargement of the spleen, which is often due to increased pressure in the splenic vein that opens into the portal vein. This increased pressure causes the spleen to enlarge and retain blood cells, leading to thrombocytopenia. Physiologically, the spleen has a pole-to-pole diameter of up to 120 mm, whereas in splenomegaly this diameter increases and can even reach 200 mm or more. This can also be easily visualized with ultrasound, CT, MRI or even a conventional X-ray.

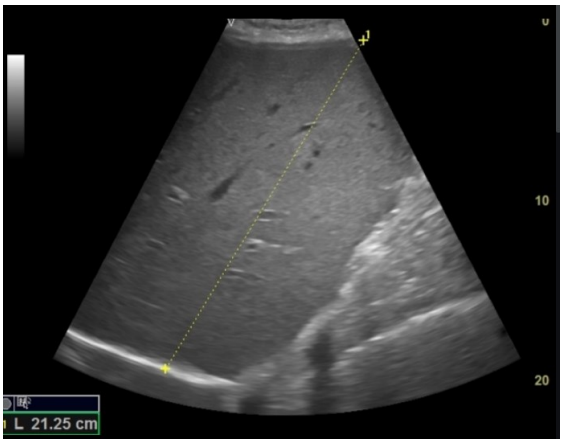

Figure 10: Hepatomegaly (79)

5.7. Caput Medusae

Caput medusae are dilated veins that radiate from the navel and resemble the head of Medusa. They result from the development of collateral veins that bypass the high-pressure portal system and direct blood into the systemic circulation. They are visible on inspection and can be differentiated from other conditions. It is a relatively unique sign that is a clear indication of portal hypertension. It is often accompanied by ascites, splenomegaly, varices in the esophagus and possibly in the stomach. They are often not as extreme as shown in figure 11, but the severity can reach even these proportions (80).

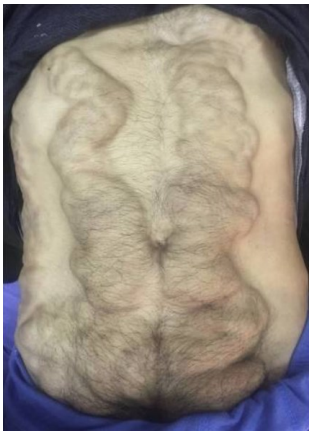

Figure 11: Caput Medusa (80)

5.8. Encephalopathy

Hepatic encephalopathy (HE), as mentioned above, is an impairment of brain function due to severe liver disease. Ammonia may be the main culprit in causing the symptoms, but there are no defined thresholds that will or will not exclude HE. Another proposed mechanism was the clearance of microbes and endotoxins via the mediated immune cells in the liver parenchyma, so toxins and infections have a pathologic synergistic effect in the development of HE (81).

Of course, hepatic encephalopathy is an unusual disease in terms of the variety of differential diagnoses that must be considered when a patient presents with similar symptoms. Some other pathologies that should be considered are hypoglycemia, hyponatremia, hypoxia, uremia, ketoacidosis, withdrawal, intoxications, metabolic alterations, stroke, and several others. A hallmark or tell-tale sign for the suspicion of hepatic encephalopathy is the so-called asterixis, which describes a tremoring or flickering of the hands, when they are hyperextended dorsally.

The most accurate and sensitive method of diagnosing hepatic encephalopathy is with the help of specific questionnaires, which already help in distinguishing between the previously mentioned differential diagnoses. There are a few options at hand, but the most accurate identification is with the help of psychometric hepatic encephalopathy score (PHES). Other scoring systems that may help in diagnostics are the widely known mini mental status tests, which help in patient memory assessment, the hepatic encephalopathy scoring algorithm (HESA), which unites clinical indicators from psychomotoric examinations and other assessments, giving the most accurate description of HE. HESA is an objective and reliable approach, but in reality, rarely used due to the time intensity and complexity of required parameters (82).

If the diagnosis of HE has been established there are monitoring questionnaires to reduce interobserver variability. Clinical Hepatic Encephalopathy Staging Scale (CHESS) denotes the severity of HE on a scale of 0 to 9, 9 being the highest severity (83).

Other clinically used questionnaires or assessments, that are typically used for other cognitive impairments like the Modified-orientation log, which originally was used for central nervous system impairment in traumatic brain injury patients or the Glasgow Coma Scale may also be used, sometimes even demonstrating a higher prognostic and predictive values than the widely used West Haven Criteria (84).

Flicker glasses are a non-invasive tool for the evaluation of hepatic encephalopathy in CLD patients, particularly portal hypertensive patients. Those goggles measure the critical flicker frequency (CFF), i.e. the Hertz at which a flickering beam is perceived as uniform by the human eye. Patients with HE typically have a lower CFF. This indicates cognitive impairment and correlates with the severity of HE. The flicker goggles provide a quantitative and objective method to detect minimal or misdiagnosed forms that may not be apparent during routine clinical examinations. Regular assessment of CFF allows the indication and adjustment of treatment to be relatively inexpensive.

HE can also be categorized only clinically using the so-called West-Haven classification, which classifies HE according to the degree of central nervous system impairment. (67)Table

Table 3: West Haven Criteria (85)

Grade	Level of consciousness	Personality and intellect	Neurologic signs	Electroence-phalogram (EEG)
0	Normal	Normal	None	None
Sub-clinical	Normal	Normal	Abnormal only on psychometric testing	None
1	Day/night sleep reversal, restlessness	Forgetfulness mild confusion, agitation, irratibility	Tremor, apraxia, incoordination, impaired handwriting	Triphasic waves (5 Hz)
2	Lethargy, slowed response	Disorientation to time, loss of inhibition, inappropriate behavior	Asterixis, dysarthria, ataxia, hypoactive reflexes	Triphasic waves (5 Hz)
3	Somnolence, confusion	Disorientation to place, aggressive behavior	Asterixis, muscular rigidity, Babinski signs, hyperactive reflexes	Triphasic waves (5 Hz)
4	Coma	None	Decerebration	Delta/slow wave activity

5.9. Muscle Wasting

Muscle wasting or sarcopenia is the loss of muscle tissue and strength. It often occurs in chronic liver disease and is due to malnutrition, altered metabolism and reduced protein synthesis by the liver. Loss of muscle mass is another feature for assessing the severity of cirrhosis, as it represents a more advanced stage. It can be observed as reduced muscle mass in the arms, legs and around the shoulders. This can be observed clinically but can also be visualized radiographically using a CT scan. In a recent study, the L3 skeletal muscle index was used to evaluate the prognosis and progression in patients with chronic liver disease (86).

5.10. Laboratory Investigations

Evidently, the liver is involved in various metabolic, hormonal, synthesis, coagulation and many other functions. Therefore, laboratory analysis of serum can give us great insights into the underlying condition and progression of the disease. There are typical liver markers used in daily practice that are also informative in the diagnosis of portal hypertension, cirrhosis and other liver diseases. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are key enzymes that are predominantly found in the liver. They may be present or altered in muscle disease, but their importance is focused on liver function. Elevated levels of these enzymes indicate injury or damage to liver cells, as they are disperse into the bloodstream when hepatocytes get destroyed. Not just the elevation, but also the relative ratio of AST to ALT may provide additional insights. For example, an AST/ALT ratio of more than 2:1 is often an indication of alcoholic liver disease.

Alkaline phosphatase (ALP) is another important liver enzyme, but also occurs in the bile or osseous structures. Increased serum ALP can indicate cholestasis, which is a blockage or impairment of bile flow that often occurs in diseases such as cirrhosis and bile duct obstruction. Gamma-glutamyl transferase (GGT) is useful in conjunction with ALP levels to differentiate liver-related causes from bone-related causes of elevated ALP, as GGT levels typically increase

in liver disease and bile duct problems. In a clinical setting, GGT levels are more relevant and ALP is not as routinely tested.

Bilirubin, a by-product of hemoglobin breakdown, is another important marker. Elevated serum bilirubin levels indicate impaired hepatic clearance or increased hemolysis and are often a sign of advanced liver disease and impaired liver function. The serum albumin level is critical in assessing the synthetic function of the liver, as the liver produces albumin. Decreased albumin may point towards CLD and/or cirrhosis and reflect decreased protein synthesis or increased loss. The prothrombin time (PT) and international normalized ratio (INR), although not enzymes, are important judge the liver's function to produce clotting factors. A prolonged PT/INR indicates impaired liver function, which is common in advanced liver disease and indicates reduced synthesis of clotting factors. Together, these enzymes and markers provide a detailed and comprehensive picture of liver health, the severity of liver tissue damage and the functional capacity of the liver in portal hypertension (87).

There are some other, more specific laboratory markers that have been briefly described in the sections on pathogenesis and etiology. Additionally, there are tests and scores, ranging from simple to complex, to identify the degree of disease and fibrosis.

The AST to Platelet Ratio Index (APRI) score is a mathematical equation used to evaluate liver fibrosis, especially in cases with chronic hepatitis C. It is calculated using this formula:

$$\text{APRI score} = \left(\frac{\text{AST level}}{\text{Upper limit of normal AST}}\right) \times 100 \div \text{Platelet count } (10^9/\text{L})$$

An APRI score of less than 0.5 suggests no or minimal fibrosis, whereas values between 0.5 and 1.5 suggests significant fibrosis and a score greater than 1.5 indicates a high likelihood of significant fibrosis or cirrhosis. It is important to note that while the APRI score can be useful, it is not definitive. The FIB-4 score is another non-invasive tool used to for a similar purpose, particularly in CLD with Hepatitis C and NAFLD. It combines readily available laboratory values into a formula to help predict the severity of the damage. The formula for calculating the FIB-4 score is:

$$\text{FIB-4 score} = \frac{\text{Age} \times \text{AST}}{\text{Platelet count} \times \sqrt{\text{ALT}}}$$

The Enhanced Liver Fibrosis (ELF) score combines three serum biomarkers associated with fibrosis into a single score: Hyaluronic Acid (HA), Procollagen III N-terminal peptide (PIIINP), and Tissue Inhibitor of Metalloproteinase-1 (TIMP-1). HA is a glycosaminoglycan that increases in the blood with liver fibrosis, PIIINP is a peptide released during the synthesis of type III collagen and is elevated in liver fibrosis, and TIMP-1 is a protein that inhibits enzymes

responsible for the breakdown of the extracellular matrix, with elevated levels indicating liver fibrosis. The ELF score is estimated using an equation that incorporates these three biomarkers, resulting in a numerical value that correlates with the extent of liver fibrosis. An ELF score less than 7.7 indicates no or mild fibrosis, a score between 7.7 and 9.8 indicates moderate fibrosis, and a score greater than 9.8 indicates severe fibrosis or cirrhosis. These non-invasive test provides an alternative to liver biopsy (88).

If we understand the mechanism of portal hypertension and cirrhosis, we can better understand why some serum markers may be helpful in the analysis. Markers for fibrosis, although not so commonly used, can indicate portal hypertension as they represent the pathological change in the liver. These are e.g. laminin and hyaluronic acid and can be directly linked to liver fibrosis. The FibroTest® is typically used to assess advanced fibrosis and is a panel of laboratory markers that predicts the condition of the liver. The reliability of FibroTest® has been demonstrated with a subsequent invasive HVPG measurement (89,90).

Other markers that may not be as specific, but still point us in the right direction, are serum markers of angiogenesis. These are vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). The former stimulates vessel formation and, in the case of portal hypertension, promotes the development of alternative vascular pathways, namely varices, while the latter adapts the stability of the vessels by influencing the endothelial wall (91).

It has been proven that blocking these two factors has led to a significant reduction in portal pressure and better regulation of mesenteric flow. Although this was only carried out on animal models, it nevertheless gives us an indication of the pathogenesis in humans (92).

Some alternative markers that can also be used in combination to assess the different aspects of the disease can be either markers of endothelial dysfunction, such as the amino acid asymmetric dimethylarginine (ADMA), which is associated with liver dysfunction and organ failure (93).

Circulating endothelial cells also indicate vascular injury and are almost always very low in healthy people. In a 2010 study, Abdelmoneim, *et al.* demonstrated the connection between increased circulating endothelial cells and portal hypertension (94).

5.11. Imaging Studies (Ultrasound, CT, MRI)

Radiologic imaging is indispensable in the diagnostics, staging and evaluation of portal hypertension and all associated diseases. They are non-invasive diagnostic methods and are frequently used due to their cost, time and effectiveness advantages. They do not require specific laboratory tests, which can sometimes only be performed in specialized facilities and are therefore not available for primary or secondary healthcare (95).

Portal hypertension can be recognized by several characteristic features on imaging examinations such as CT and MRI. Both modalities can reveal splenomegaly. Ascites in the abdominal cavity is another identifying feature. In addition, the presence of collateral vessels or varices, particularly in the esophagus, stomach and rectum, can be detected.

Portosystemic collaterals, including paraumbilical veins (caput medusae) and vessels at the gastroesophageal junction, may also be observed. The liver itself may show signs of hepatomegaly or atrophy, with a nodular surface due to cirrhosis (“buckling"). The portal vein often appears dilated and there may be signs of portal vein thrombosis. Compensatory enlargement of the hepatic artery can be noted, reflecting increased arterial blood flow due to decreased portal blood flow. In addition, periportal edema can be seen around the portal vein, indicating inflammation and increased pressure.

MRI, like CT, provides detailed images of these anatomical changes, but also offers advantages such as a higher resolution in the depiction of soft tissue and the potential to use different sequences to highlight different tissue features. MRI is especially useful in identifying subtle changes in liver tissue, distinguishing between different soft tissue types and assessing vascular structures without the need for iodinated contrast agents (96).

5.12. Transient Elastography

Because portal hypertension and liver disease, regardless of etiology, are such a widespread medical burden worldwide, a rapid, inexpensive and easy-to-perform diagnostic tool is needed. Over the last decade, a novel and surprisingly useful method has been developed that has been proven in numerous studies. This method is known as transient elastography (TE), which uses sonography to determine liver stiffness. The stiffness represents the degree of fibrosis in the liver and is therefore a real-time reflection of the progression and severity of the disease. This method has been shown to be effective as it has a direct and reliable correlation between TE results and the presence of increased HVPG. In a prospective study conducted in India, patients were assessed for liver stiffness using the FibroScan® device and then HVPG was measured invasively using a transfemoral or transjugular catheter. The study displayed a statistically significant correlation of Spearman’s rho 0.361, $P < 0.001$ between these two measurements (97), proving the reliability of this novel method of measurement.

It works by a mechanical impulse that generates an elastic shear wave that moves through the liver tissue. The speed of this shear wave correlates with the stiffness of the tissue, with faster propagation indicating more fibrotic tissue. During the procedure, a probe is placed intercostally that emits vibrations and ultrasound waves. Several measurements are taken, and the average value is calculated and expressed in kilopascals (kPa). The results usually range from less than

6 kPa (normal) to more than 12 kPa (indicating severe fibrosis or cirrhosis). TE is quick, painless and repeatable, making it ideal for the ongoing monitoring of liver diseases such as chronic hepatitis, non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease. Despite its advantages, such as the fact that it is non-invasive and suitable for application in the field, it has its limitations, including lower accuracy in obese patients and those with ascites. Compared to liver biopsy, which is invasive and carries risks, TE offers a safer and simpler alternative for initial assessment and disease monitoring, although it should be used alongside other clinical investigations for a comprehensive assessment of the liver (98).

A novel, non-invasive form of portal hypertension assessment has been developed, using the stiffness of the spleen as a parameter. Even though TE has been primarily used to examine the liver stiffness, new studies have proven a significant correlation between spleen stiffness and portal hypertension. Ultrasonographically the same 100 Hz module is used as in liver stiffness measurement, but there have been positive predictive values of over 90%. In a study from 2023 Odriozola et. Al. have proven, that utilizing the spleen stiffness measurement (SSM) in combination with the Baveno VII non-invasive, clinically proven risk stratification tool in predicting high-risk varices for cirrhotic patients, increase the accuracy, while optimizing negative and positive predictive values. SSM is another prime example on how volatile and expandable the topic of portal hypertension still is (99).

5.13. Assessment of Portal Vein Thrombosis

PVT may present as the underlying causes of portal hypertension or chronic liver disease or even a consequence of altered dynamic flow in the portal circulation. It can be acute or even life-threatening, so it is important to assess PVT radiologically. Doppler ultrasound is usually the first choice as it reveals a hyperechoic thrombus and a lack of blood flow in the portal vein. Contrast-enhanced CT (CECT) provides a detailed view of the abdominal organs and vasculature and shows filling defects within the contrast-enhanced portal vein, venous dilatation proximal to the thrombus and the presence of collateral vessels such as varices. MRI, particularly magnetic resonance angiography (MRA), offers high-resolution imaging without ionizing radiation, which can be used to detect signal gaps within flow-sensitive sequences and assess altered blood flow patterns. In chronic PVT, MRI can show features such as cavernous transformation. Although less common due to the availability of non-invasive alternatives, direct portal venography remains the gold standard for direct visualization of thrombus and collateral circulation. These imaging techniques are essential to confirm the presence of PVT, determine its extent, monitor response to treatment and plan surgical or interventional procedures (100,101)

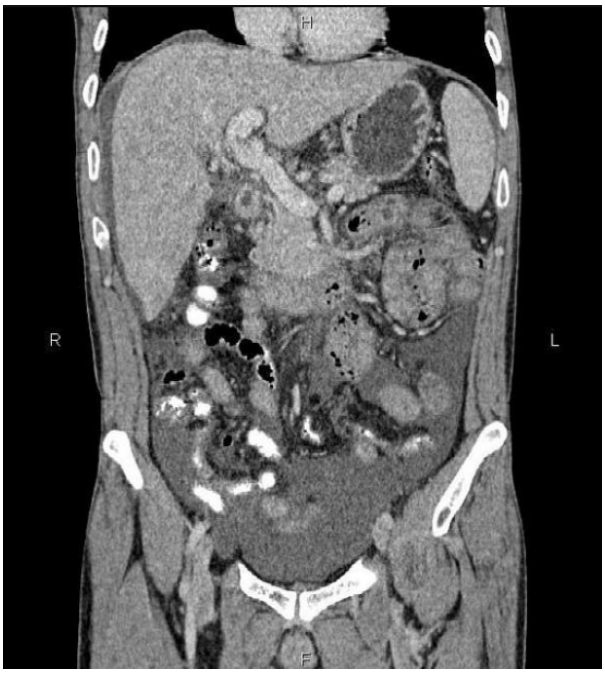

Figure 12: CT Abdomen: Portal Thrombosis in a cirrhotic patient (102)

5.14. Hepatic Venous Pressure Gradient (HVPG)

The HVPG is the essential measurement in the evaluation of portal hypertension and is the only definitive tool that describes the pressure values to clarify this diagnosis. The HVPG measures the pressure difference between the portal vein and the hepatic veins.

The procedure for measuring the HVPG involves several steps. First, the patient is usually sedated or given a local anesthetic and is performed in an interventional radiology suite. A catheter is placed in either the jugular or femoral vein and pushed up to the hepatic vessels, which is controlled fluoroscopically. The so-called wedged hepatic venous pressure (WHVP) is then determined by balloon dilatation in the portal vein, which accurately reflects the pressure upstream of the portal vein. The free hepatic venous pressure (FHVP) is determined after deflation of the balloon and measurement of the difference. The HVPG is therefore calculated by subtracting the FHVP from the WHVP. Physiologically, this gradient is between 1 and 5 mmHg. This gradient is a vital prognostic factor to assess the effectiveness of interventions such as beta blockers or endoscopic variceal ligation, TIPS and others, but is also a prognostic tool as a persistent HVPG of 16 mmHg or more despite therapy is connected to a worse prognosis and increased mortality. It can also help to differentiate between cirrhotic and non-cirrhotic causes such as PVT or schistosomiasis.

Although the invasive HVPG measurement is the gold standard, it inherits several risks and few disadvantages related to catheter insertion and radiologic monitoring.

This form of measurement may not be available everywhere as the procedure requires specialized equipment and expertise, limiting its availability to specialized centers. Although rare, complications such as bleeding, infection or vascular injury can occur.

Regardless, the HPVG is an indispensable tool for assessing the severity of liver disease, supporting treatment decisions and predicting clinical outcome. The HVPG guides and reinforces the management of patients with chronic liver disease and portal hypertension as it can be repeated regularly and always provides an accurate representation of the pressure in and over the portal circulation (103).

6. Complications of Portal Hypertension

As already mentioned, portal hypertension itself does not cause any damage and does not even cause symptoms in most patients. The clinical manifestations result from pathological adaptations and changes at the microscopic and macroscopic level. Nevertheless, portal hypertension can lead to a number of serious complications affecting various body systems. Thrombocytopenia often occurs due to congestive hepatopathy, while the formation of collateral shunting and variceal rupture are common. Bleeding from gastroesophageal, anorectal, retroperitoneal, stomal and other varices represents a significant risk. Chronic blood loss due to portal hypertensive gastropathy, enteropathy or coagulopathy may also be the reason for significant bleeding and/or sideropenic anemia. Ascites, the accumulation of fluid in the abdomen, and spontaneous bacterial peritonitis, an infection of this fluid, are common problems. Patients may also develop hepatic hydrothorax, in which fluid accumulates in the pleural cavity, and hepatorenal syndrome, a severe renal dysfunction. Hepatic encephalopathy, which is caused by the accumulation of toxins, hepatopulmonary syndrome and portopulmonary hypertension are other serious conditions. Cirrhotic cardiomyopathy, which is an inadequate response of the heart to stress, can also occur (4).

6.1. Variceal Rupture and Complications

About 90% of people with cirrhosis develop esophageal varices within a decade. Esophageal variceal hemorrhage is a potentially fatal complication with a mortality rate between 25% and 50%, so preventive measures are essential before the first hemorrhage occurs (104). A cohort study from 2016 revealed, that ff variceal bleeding occurs, there is an over 60% chance that it will recur within 5 years and a 5 year mortality of over 50% (105). Predictors of variceal bleeding include cherry red spots, size, infection, PVT and a high WHVPG. Circumstances that influence the likelihood of bleeding include postprandial increase in portal blood flow, elevated intra-abdominal pressure, toxic stress and physical activity (106).

Severe bleeding can even endanger the airway and require emergency intubation. The airway may also be obstructed due to include loss of consciousness due to circulatory collapse or encephalopathy. Complications of variceal bleeding arise from the bleeding itself or from the measures taken to control it, including hypovolemic shock, encephalopathy, aspiration and SBP. Admission to the intensive care unit is often required for hypotension, due to the maintenance of the airway, encephalopathy and aspiration is required (107).

6.2. Ascites and Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis (SBP) is a alarming and potentially fatal comorbidity in patients with advanced and CLD, particularly in patients with cirrhosis. It is an infection of ascites not requiring an identified pathogen in the abdomen. SBP develops when bacteria migrate from the intestine into the ascitic fluid. The most common pathogens causing SBP are Gram-negative bacteria like E. coli or Kl. pneumoniae and Gram-positive bacteria such as Streptococci. The impaired immune functions such as impaired hepatic reticuloendothelial function and. Reduced complement concentrations in the ascitic fluid contribute to susceptibility. Patients typically present with non-conclusive symptoms like fever, abdominal discomfort and tenderness. Patients may also develop hepatic encephalopathy, either in a mild or very severe form. As these symptoms are non-specific, an in-depth anamnesis and physical examination are crucial for plan further steps. The gold standard for the identification of SBP is a diagnostic paracentesis to localize the exact focus of infection. A polymorphonuclear leukocyte (PMN) count of $\geq$250 cells/mm^3 is indicative for SBP. Ascitic fluid cultures can reveal the causative organisms, although they are often inconclusive in practice. The cause of the ascites itself may need to be identified to exclude other differential diagnoses.

Immediate administration of antibiotic therapy is crucial for patients diagnosed with SBP. Empirical treatment usually begins with broad-spectrum antibiotic agents, for example ceftriaxone. Depending on the culture result and the patient's response, the treatment may need to be adjusted. Preventive measures significantly increase the prognosis for high-risk patients. The most important measure is antibiotic prophylaxis and, of course, treatment of the underlying cause of ascites. The mortality rate for the first episode of SBP is between 20% and 40%, while recurrent episodes can dramatically increase this rate.

Spontaneous ascitic bacterial peritonitis is a critical escalation of disease in cirrhotic patients that requires vigilant clinical attention. Accurate diagnosis, appropriate treatment, regular follow-up and prevention protocols are key to the management of SBP (108).

6.3. Hepatic Encephalopathy as a Complication of Portal Hypertension

As mentioned in the section on diagnosis and clinical manifestations, patients with portal hypertension and/or underlying CLD can present with hepatic encephalopathy (HE). If HE was initially scored with West Haven criteria of 0 or 1, the disease course may worsen with therapy or disease progression. If HE is rated 2 or 3 in the 90 days following a procedure, it is considered a complication of therapy and thus represents a new problem requiring treatment (109).

6.4. Portal Vein Thrombosis (PVT)

PVT is a serious condition that is either a the prehepatic cause for portal hypertension but can also be a complication of a pre-existing pathology. The altered state of coagulation, clotting and flow within the portal vein system and surrounding collateral vessels favours the development of PVT. This works in both directions: On the one hand, it aggravates the underlying disease, but on the other hand, it can also exacerbate existing complications. It can be an acute and life-threatening complication of portal hypertension and may even require urgent surgical intervention and strict anticoagulation (110).

6.5. Hepatorenal Syndrome

Hepatorenal syndrome (HRS) has traditionally been viewed as a functional impairment of the kidney due to intrarenal vasoconstriction in end-stage liver disease, acute liver failure, or alcoholic hepatitis. Recent evidence challenges this view, highlighting the roles of hemodynamic and inflammatory changes. The revised classification now identifies type 1 HRS as HRS with acute kidney Injury (AKI) and type 2 HRS as non-AKI-HRS (NAKI) and HRS with chronic kidney disease (CKD). HRS pathophysiology involves not just renal hypoperfusion from macrocirculatory dysfunction but also significant contributions from pro-inflammatory cytokines. These are often post infectious and are also potentiated by cholestasis due to the disbalancing effects of accumulating bile salts.

6.6. Hepato-Pulmonary Syndrome (HPS) and Portopulmonary Hypertension (PPHT)

HPS can be defined as an oxygenation disorder seen in patients with portal hypertension. It is diagnosed in combination with cirrhosis, venous obstruction, acute or chronic hepatitis. The main symptom is unspecific dyspnoea, which makes the diagnosis clinically challenging and demonstrates the importance of a proper medical workup of the history and comorbidities (111). PPH is a form of pulmonary arterial hypertension appearing together with portal hypertension, often associated, but explicitly does not require an underlying chronic liver disease. It is characterized by elevated pulmonary artery pressure due to increased resistance in the

pulmonary vasculature, but necessarily with the absence of any other etiology that may possibly cause pulmonary artery or venous hypertension. These may be a chronic thromboembolism, chronic lung diseases like COPD or even chronic heart disease. Clinically, PPHT presents with symptoms such as dyspnoea, fatigue, chest pain, and in advanced cases, syncope. These symptoms may be mistaken for a disease of cardiac origin, which is why high vigilance, and the consideration of portal hypertension should not be overlooked in a clinical setting. The pulmonary arterial pressure is obtained through right heart catheterization to differentiate PPHT from other causes of pulmonary hypertension. Liver transplantation may be considered in select patients, as it can potentially reverse PPH, but careful preoperative assessment and management are crucial due to the high perioperative risk. Early diagnosis and targeted therapy with vasodilators are essential to improve outcomes and treat portopulmonary hypertension (112) (11).

7. Management of Portal Hypertension

The primary approach to treating portal hypertension involves addressing the underlying causes of liver disease that contribute to increased portal pressure. This typically means managing chronic liver conditions such as cirrhosis due to viral hepatitis, alcohol use disorder, NAFLD, or other hepatic conditions like schistosomiasis. In our Western/European World the most common intervention in the sense of lifestyle modification is the encouragement to refrain from alcohol consumption. Other effective treatment may include antiviral therapies, weight loss and metabolic control for NAFLD, antibiotics, and potentially liver transplantation as the ultima ratio. By targeting the root causes, liver fibrosis may not be reverted, but stagnated at least and improve the symptoms (114).

7.1. Non-Selective Beta-Blockers

Pharmacological treatment with non-selective beta-blockers (NSBBs) is one of the mainstays of therapy due to their attractive properties. Some examples from this group are propranolol, nadolol or carvedilol, which is the drug of choice in Germany. Carvedilol is administered at a loading dose of 6.25 mg *per os* once at nighttime, which may be escalated to 12.5 mg daily in case of no significant side effects. and in view of its therapeutic effect. NSBBs work by reducing cardiac output and inducing splanchnic vasoconstriction, which lowers portal blood flow and pressure. These drugs are particularly effective in preventing first-time variceal bleeding (primary prophylaxis) but also in patients, which already experienced a variceal rupture (secondary prophylaxis). NSBBs are preferred due to their non-invasive nature, ease of

administration and proven efficacy, but also due to their prophylactic properties, but also in the treatment of existing complications and symptoms. (115)

7.2. Terlipressin

Terlipressin is a synthetic analogue of vasopressin and acts primarily as a vasoconstrictor, i.e. it constricts the blood vessels and thus increases blood pressure. This vasoconstrictor effect reduces blood flow in the splanchnic circulation, which is beneficial in portal hypertension and in the prevention and control of variceal bleeding.

In HRS 1 terlipressin is used to regain functionality in the kidneys. It does this by vasoconstriction in the splanchnic circulation, redistributing flow to the kidneys and improving their perfusion. It is usually administered intravenously and can be dosed acutely, in an acute variceal rupture for instance. In this case, a bolus and then only a few high doses can be administered. In the case of HRS, it can even be administered in smaller doses over several days. With respect to the patient and clinical response and the occurrence of adverse effects, it may be necessary to adjust the dosage or discontinue therapy (116).

7.3. Portosystemic Shunts for Refractory Disease

In the implantation of a transjugular intrahepatic portosystemic shunt (TIPSS), a stent is placed between one hepatic branch and a portal branch to ensure the outflow of blood towards the system and thus reduce portal pressure. It is performed by experienced interventional radiologists in specialist centers that specialize in minimally invasive procedures. TIPSS implantation can provide immediate improvement and is often considered the ideal form of treatment. This procedure aims to reduce the risk of complications and other clinical manifestations. It is indicated for persistent, recurrent or treatment-resistant upper GI bleeding due to portal hypertension, such as esophageal varices, as well as other complications of that do not respond to medical therapy, such as ascites, hepatic hydrothorax, Budd-Chiari syndrome and chronic complete portal vein thrombosis (117).

Contraindications include refractory overt hepatic encephalopathy (high West Haven classification of 3), severe circulatory disease such as heart failure and severe pulmonary hypertension (mean pulmonary artery pressure > 45 mm Hg), severe untreated valvular heart disease such as tricuspid regurgitation, persistent infection or sepsis, and severe uncorrectable coagulopathy or anatomic barriers, which are relative contraindications. The success rate has been over 80% for over 15 years and has risen steadily since then (118).

The procedure involves accessing the internal jugular vein, inserting a catheter into the hepatic vein and placing an expandable stent between the hepatic and portal veins. Complications can

include procedure-related problems, but they are extremely rare in experienced centres. TIPSS is considered a safe, effective and elegant method of treating portal hypertension. Periinterventional radiologists have the option of ligating or embolizing existing varices to treat pathological shunts immediately. This reduces the risk of further complications and ensures adequate flow through the liver (119).

7.4. Management of Complications of Portal Hypertension

The management of complications arising from portal hypertension is multifaceted and crucial to improving patient outcomes. For ascites, treatment usually includes dietary sodium restriction, diuretics such as spironolactone and furosemide, and in severe cases, large volume paracentesis. Refractory ascites is the most important indication for TIPS implantation and can often only be treated with this shunt. Hepatic encephalopathy is treated by reducing ammonia production with lactulose and antibiotics such as rifaximin.

Rifaximin is a broad-spectrum antibiotic that aims to reduce the ammonia-producing bacterial population in the gastrointestinal tract. This reduces the overall load of ammonia in the body and therefore also the amount that has to be broken down in the destroyed and/or damaged liver. Esophageal varices, which pose a significant risk of bleeding, are treated with endoscopic procedures such as band ligation or sclerotherapy in addition to pharmacological treatment with NSBBs. In addition, regular surveillance endoscopies are performed to monitor and treat varices before they bleed. Each of these interventions aims to control symptoms, prevent complications and improve the overall prognosis for patients with portal hypertension.

Management of HRS as a complication includes vasoconstrictive drugs like terlipressin, often combined with albumin to counteract splanchnic vasodilation and improve renal perfusion. Recurrent HRS is common, sometimes requiring long-term therapy, therefore further worsening the life quality of CLD patients. Factors such as high baseline serum creatinine, inflammation, and cholestasis can affect treatment response. Ultimately this may only be treated with supportive measures for the liver, transplantation of partial or total liver components and, most radically, combinatory transplantation of the liver and the kidney. (120) (121).

7.5. Treatment of Bleeding Varices

As already mentioned, bleeding varices frequent and acute complications of portal hypertension. They represent a severe stage of the disease and drastically increase the risk of death. Therefore, rapid response and treatment of these varices is of utmost importance. There are several ways to intervene in an acute scenario. The most common procedures are endoscopic variceal ligation (EVL), sclerotherapy, cyanoacrylate injections and others. EVL is an

inexpensive, quick and relatively simple form of intervention, but it also has its limitations. Larger lesions and perforations are not feasible for EVL and require other or additional forms of intervention. An example is the so-called “early TIPS” or emergency TIPS, where early TIPS is defined as the implantation of a shunt within 72 hours of EVL with the use of ligatures (122).

7.6. Liver Transplantation

Liver transplantation remains the final measure for the management of portal hypertension and its underlying causes. The decision for liver transplantation must be made taking into account the advancement, other diseases and the overall prognosis. Conservative symptomatic treatment as described above is only one measure until transplantation. Systems such as the MELD score help to assess the need for transplantation and structure the waiting list. In addition, modern techniques like living donor liver transplantation and split liver transplantation have expanded the donor pool and improved access for more patients. Explaining the aspects of liver transplantation in detail is far beyond the scope of this paper, but the therapeutic option must be mentioned (123).

8. Prognosis and Outcomes

Overall, it may be said that the diagnosis of portal hypertension and a concomitant liver disease does not pose a good prognosis. The mortality rate has been examined in a large retrospective observational study from 2023 analysing close to 60.000 patients, which had shown that regardless of the severity grade, the mortality rate was at 18%. The subdivision into “least severe”, “moderate severity” and “most severe” of patients was based on the diagnosis of cirrhosis and the occurrence of prior variceal bleeding or not. Alcohol was identified as the primary cause for cirrhosis and also represented a higher risk of a worse composite outcome than other aetiologies i.e. viral or autoimmune hepatitis. Alcoholic patients were also younger on average and were more likely to be classified into the “most severe” category.

It was observed that being the “most severe” class would also increase the likelihood for the development of complications like variceal haemorrhages and hepatic encephalopathy.

Despite modern interventions, patients with cirrhosis and portal hypertension face high morbidity and mortality. There is a need for improved management strategies and new therapies, especially to reduce the risk of variceal hemorrhage and worsening ascites(124).

9. Discussion

Portal hypertension presents significant challenges in clinical management due to its high morbidity and mortality rates. Despite advances in therapeutic interventions such as beta-blockers, variceal banding, and transjugular intrahepatic portosystemic shunts (TIPSS), patients continue to face substantial risks of variceal hemorrhage, hepatic encephalopathy, and complications of ascites.

The persistent high mortality rates among patients with portal hypertension indicate that existing treatments are not sufficiently effective. This underscores the need for improved therapeutic strategies and highlights the limitations of current medical management.

Variation in etiology related outcome suggests that the underlying cause of portal hypertension significantly influences disease progression and response to treatment. Thus, tailored therapeutic approaches that consider the specific etiology of portal hypertension are essential.

There is an urgent need for the development of novel therapies that target the fundamental mechanisms. Additionally, identifying reliable prognostic and not just diagnostic markers for portal hypertension could enhance the ability to predict patient outcomes and tailor treatments more effectively.

Designing representative clinical trials for portal hypertension is challenging due to the disease's heterogeneity and the range of complications and etiologies involved. Future research should focus on establishing a framework to have a more comprehensive understanding of the data.

10. Conclusion

Portal hypertension encompasses far more than one would expect when considering the simple definition of an increased hepatic venous gradient. The underlying mechanisms and diseases interact in ways that physicians are only now beginning to understand. The molecular and cellular changes are still subject to further analysis and may provide us with a deeper understanding of pathology and treatment in the future. With the rapid changes in the development and evolution of medicine in recent and coming years, we can expect to see innovations in treatment, diagnosis and prevention that will change the way we manage patients with portal hypertension for the better.

11. Summary

Portal hypertension is defined as an increased pressure within the portal circulation and is defined as such by determining the pressure difference between the systemic and portal circulation. Under physiological conditions, this gradient is less than 5 mmHg, but higher values lead to worsening of the underlying disease and other complications. The most common causes are cirrhosis, NAFLD, schistosomiasis, intoxication and others, although these vary according to age and geographical location. Understanding the pathogenesis is key to treatment, as there are several therapeutic options to prevent and treat portal hypertension. The therapies of choice are the introduction of non-selective beta-blockers, endoscopic variceal ligation and implantation of a transjugular intrahepatic portosystemic shunt. They are aimed at the most serious complications such as variceal bleeding, ascites or hepatic encephalopathy. Portal hypertension is a diagnosis that requires a high level of medical expertise in treatment and will be the subject of medical research in the near future.

12. Literature Cited

1. Balducci G, Sterpetti AV, Ventura M. A short history of portal hypertension and of its management. J Gastroenterol Hepatol. 2016;31(3):541–5.

2. Gulik T, Rosmalen J, Gulik M, Rosmalen B. The Liver in the middle ages, according to Galen. [cited 2024 May 27]; Available from: https://www.degruyter.com/document/doi/10.1515/9789048557417-007/html?lang=de

3. Bergstrand I, Ekman CA. Percutaneous lieno-portal venography. Acta Radiol. 1957 Apr 1;47(4):269–80.

4. Oliver TI, Sharma B, John S. Portal Hypertension. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 May 27]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK507718/

5. Mendes FD SA. Prevalence and indicators of portal hypertension in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2012;10(9):1028-33.e2.

6. Dhiman R, Chawla Y, Vasishta RK, Kakkar N, Dilawari JB, Trehan MS, et al. Non-cirrhotic portal fibrosis (idiopathic portal hypertension): experience with 151 patients and a review of the literature. J Gastroenterol Hepatol. 2002;17(1):6–16.

7. Iber F. Obliterative portal venopathy of the liver and “idiopathic portal hypertension.” Ann Intern Med. 1969;71(3):660–1.

8. Mahamid J, Miselevich I, Attias D, Laor R, Zuckerman E, Shaoul R. Nodular regenerative hyperplasia associated with idiopathic thrombocytopenic purpura in a

young girl: a case report and review of the literature. J Pediatr Gastroenterol Nutr. 2005;41(2):251–5.

9. Scaglione S, Kliethermes S, Cao G, Shoham D, Durazo R, Luke A, et al. The Epidemiology of Cirrhosis in the United States: A Population-based Study. J Clin Gastroenterol. 2015;49(8):690–6.

10. Sarin S, Kapoor D. Non-cirrhotic portal fibrosis: current concepts and management. J Gastroenterol Hepatol. 2002;17(5):526–34.

11. Vakili C, Farahvash MJ, Bynum TE. “Endemic” idiopathic portal hypertension: report on 32 patients with non-cirrhotic portal fibrosis. World J Surg. 1992;16(1):118–24, discussion 124-5.

12. Germain T, Favelier S, Cercueil JP, Denys A, Krausé D, Guiu B. Liver segmentation: Practical tips. Diagn Interv Imaging. 2014 Nov 1;95(11):1003–16.

13. Housset C, Chrétien Y, Debray D, Chignard N. Functions of the Gallbladder. In: Comprehensive Physiology. 2016. p. 1549–77.

14. Carneiro C, Brito J, Bilreiro C, Barros M, Bahia C, Santiago I, et al. All about portal vein: a pictorial display to anatomy, variants and physiopathology. Insights Imaging. 2019 Mar 21;10:38.

15. Lautt WW. Hepatic Circulation: Physiology and Pathophysiology [Internet]. San Rafael (CA): Morgan & Claypool Life Sciences; 2009 [cited 2024 May 27]. (Colloquium Series on Integrated Systems Physiology: From Molecule to Function to Disease). Available from: http://www.ncbi.nlm.nih.gov/books/NBK53073/

16. Okudaira M. Anatomy of the Portal Vein System and Hepatic Vasculature. In: Okuda K, Benhamou JP, editors. Portal Hypertension: Clinical and Physiological Aspects [Internet]. Tokyo: Springer Japan; 1991 [cited 2024 May 27]. p. 3–12. Available from: https://doi.org/10.1007/978-4-431-68361-2_1

17. Watanabe N, Ebata T, Yokoyama Y, Igami T, Sugawara G, Mizuno T, et al. Anatomic features of independent right posterior portal vein variants: Implications for left hepatic trisectionectomy. Surgery. 2017 Feb 1;161(2):347–54.

18. Ricken T, Werner D, Holzhütter H, König M, Dahmen U, Dirsch O. Modeling function–perfusion behavior in liver lobules including tissue, blood, glucose, lactate and glycogen by use of a coupled two-scale PDE–ODE approach. Biomech Model Mechanobiol. 2014 Sep 19;

19. Kalra A, Yetiskul E, Wehrle CJ, Tuma F. Physiology, Liver. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 May 27]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK535438/

20. Saxena R, Theise ND, Crawford JM. Microanatomy of the human liver-exploring the hidden interfaces. Hepatol Baltim Md. 1999 Dec;30(6):1339–46.

21. Seo H, Nam S, Im HJ, Park JY, Lee J, Yoo B, et al. Rapid Hepatobiliary Excretion of Micelle-Encapsulated/Radiolabeled Upconverting Nanoparticles as an Integrated Form. Sci Rep. 2015 Oct 23;5:15685.

22. Si-Tayeb K, Lemaigre FP, Duncan SA. Organogenesis and development of the liver. Dev Cell. 2010 Feb 16;18(2):175–89.

23. Adeva-Andany MM, Pérez-Felpete N, Fernández-Fernández C, Donapetry-García C, Pazos-García C. Liver glucose metabolism in humans. Biosci Rep. 2016 Dec 1;36(6):e00416.

24. Huang J, Borensztajn J, Reddy JK. Hepatic Lipid Metabolism. In: Monga SPS, editor. Molecular Pathology of Liver Diseases [Internet]. Boston, MA: Springer US; 2011 [cited 2024 May 27]. p. 133–46. Available from: https://doi.org/10.1007/978-1-4419-7107-4_10

25. Mortimore GE, Pösö AR, Lardeux BR. Mechanism and regulation of protein degradation in liver. Diabetes Metab Rev. 1989 Feb 1;5(1):49–70.

26. Adeva MM, Souto G, Blanco N, Donapetry C. Ammonium metabolism in humans. Metabolism. 2012 Nov 1;61(11):1495–511.

27. Rabinowitz JD, Enerbäck S. Lactate: the ugly duckling of energy metabolism. Nat Metab. 2020 Jul;2(7):566–71.

28. Iwakiri Y, Trebicka J. Portal hypertension in cirrhosis: Pathophysiological mechanisms and therapy. JHEP Rep. 2021 Jun 4;3(4):100316.

29. Age-related changes in the liver sinusoidal endothelium: a mechanism for dyslipidemia - PubMed [Internet]. [cited 2024 May 27]. Available from: https://pubmed.ncbi.nlm.nih.gov/17804522/

30. McConnell M, Iwakiri Y. Biology of portal hypertension. Hepatol Int. 2018 Feb;12(Suppl 1):11–23.

31. Wanless IR, Wong F, Blendis LM, Greig P, Heathcote EJ, Levy G. Hepatic and portal vein thrombosis in cirrhosis: possible role in development of parenchymal extinction and portal hypertension. Hepatol Baltim Md. 1995 May;21(5):1238–47.

32. Sakiani S, Heller T, Koh C. Current and investigational drugs in early clinical development for portal hypertension. Front Med. 2022 Oct 10;9.

33. Liu GP, Hu XK, Zhang ZL, Xu R, Sun CJ, Xin YN, et al. Portal hypertension caused by pancreatic cancer: Multidetector computed tomography diagnosis and multivariate analysis of variceal hemorrhage. J Cancer Res Ther. 2020;16(7):1672.

34. Sherlock S. Classification and functional aspects of portal hypertension. Am J Surg. 1974 Feb;127(2):121–8.

35. Warnes TW, Roberts SA, Smith A, Cope VM, Vales P, Haboubi NY, et al. Portal hypertension in primary biliary cholangitis: prevalence, natural history and histological correlates. Eur J Gastroenterol Hepatol. 2021 Dec 1;33(12):1595–602.

36. Tan CB, Rashid S, Rajan D, Gebre W, Mustacchia P. Hepatic Sarcoidosis Presenting as Portal Hypertension and Liver Cirrhosis: Case Report and Review of the Literature. Case Rep Gastroenterol. 2012 Apr 18;6(1):183–9.

37. Shackel NA, Patel K, McHutchison J. Chapter 78 - Cirrhosis. In: Ginsburg GS, Willard HF, editors. Genomic and Personalized Medicine (Second Edition) [Internet]. Academic Press; 2013 [cited 2024 May 27]. p. 935–54. Available from: https://www.sciencedirect.com/science/article/pii/B9780123822277000781

38. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatol Baltim Md. 2018 Apr;67(4):1560–99.

39. Kim HY, Kim CW, Choi JY, Lee CD, Lee SH, Kim MY, et al. Complications Requiring Hospital Admission and Causes of In-Hospital Death over Time in Alcoholic and Nonalcoholic Cirrhosis Patients. Gut Liver. 2016 Jan;10(1):95–100.

40. Sharma A, Houshyar R, Bhosale P, Choi JI, Gulati R, Lall C. Chemotherapy induced liver abnormalities: an imaging perspective. Clin Mol Hepatol. 2014 Sep 25;20(3):317–26.

41. Vitamin A. In: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012 [cited 2024 May 27]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK548165/

42. Nababan SHH, Lesmana CRA. Portal Hypertension in Nonalcoholic Fatty Liver Disease: From Pathogenesis to Clinical Practice. J Clin Transl Hepatol. 2022 Oct 28;10(5):979–85.

43. Sinusoidal Obstruction Syndrome (Veno-occlusive Disease). In: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012 [cited 2024 May 27]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK548032/

44. Rodriguez Ziccardi M, Pendela VS, Singhal M. Cardiac Cirrhosis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 May 27]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK431053/

45. Abbasi B. Radiopaedia. [cited 2024 May 27]. Acute Budd-Chiari syndrome | Radiology Case | Radiopaedia.org. Available from: https://radiopaedia.org/cases/acute-budd-chiari-syndrome

46. Bahr MJ, Caselitz M. Budd-Chiari-Syndrom. In: Manns MP, Schneidewind S, editors. Praxis der Hepatologie [Internet]. Berlin, Heidelberg: Springer; 2016 [cited 2024 May 27]. p. 25–9. Available from: https://doi.org/10.1007/978-3-642-41620-0_4

47. Darwish Murad S, Plessier A, Hernandez-Guerra M, Fabris F, Eapen CE, Bahr MJ, et al. Etiology, management, and outcome of the Budd-Chiari syndrome. Ann Intern Med. 2009 Aug 4;151(3):167–75.

48. Kim MY, Baik SK, Lee SS. Hemodynamic alterations in cirrhosis and portal hypertension. Korean J Hepatol. 2010 Dec;16(4):347–52.

49. Friedman SL, Rockey DC, McGuire RF, Maher JJ, Boyles JK, Yamasaki G. Isolated hepatic lipocytes and Kupffer cells from normal human liver: morphological and functional characteristics in primary culture. Hepatol Baltim Md. 1992 Feb;15(2):234–43.

50. Lee FY, Colombato LA, Albillos A, Groszmann RJ. Administration of N omega-nitro-L-arginine ameliorates portal-systemic shunting in portal-hypertensive rats. Gastroenterology. 1993 Nov;105(5):1464–70.

51. Fernandez M, Mejias M, Angermayr B, Garcia-Pagan JC, Rodés J, Bosch J. Inhibition of VEGF receptor-2 decreases the development of hyperdynamic splanchnic circulation and portal-systemic collateral vessels in portal hypertensive rats. J Hepatol. 2005 Jul;43(1):98–103.

52. Kim MY, Baik SK. [Pathophysiology of portal hypertension, what's new?]. Korean J Gastroenterol Taehan Sohwagi Hakhoe Chi. 2010 Sep;56(3):129–34.

53. Kowalski HJ, Abelmann WH. The cardiac output at rest in Laennec's cirrhosis. J Clin Invest. 1953 Oct;32(10):1025–33.

54. Systemic, renal, and hepatic hemodynamic derangement in cirrhotic patients with spontaneous bacterial peritonitis - PubMed [Internet]. [cited 2024 May 27]. Available from: https://pubmed.ncbi.nlm.nih.gov/14578859/

55. Rayes N, Bechstein WO, Keck H, Blumhardt G, Lohmann R, Neuhaus P. [Cause of death after liver transplantation: an analysis of 41 cases in 382 patients]. Zentralbl Chir. 1995;120(6):435–8.

56. Schrier RW, Arroyo V, Bernardi M, Epstein M, Henriksen JH, Rodés J. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. Hepatol Baltim Md. 1988;8(5):1151–7.

57. Fallon MB. Portopulmonary hypertension: new clinical insights and more questions on pathogenesis. Hepatology. 2003;37:253–255 - Google Suche [Internet]. [cited 2024 May 27]. Available from: https://www.google.com/search?client=opera-gx&q=Fallon+MB.+Portopulmonary+hypertension%3A+new+clinical+insights+and+more+questions+on+pathogenesis.+Hepatology.+2003%3B37%3A253%E2%80%93255&sourceid=opera&ie=UTF-8&oe=UTF-8

58. Teirstein AS, Judson MA, Baughman RP, Rossman MD, Yeager H, Moller DR, et al. The spectrum of biopsy sites for the diagnosis of sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis Off J WASOG. 2005 Jun;22(2):139–46.

59. Henriksen: Ascites and Renal Dysfunction in Liver... - Google Scholar [Internet]. [cited 2024 Jun 11]. Available from: https://scholar.google.com/scholar_lookup?title=Ascites+and+renal+dysfunction+in+liver+disease&author=JH+Henriksen&author=S+M%C3%B8ller&publication_year=2005&

60. Llach J, Ginès P, Arroyo V, Rimola A, Titó L, Badalamenti S, et al. Prognostic value of arterial pressure, endogenous vasoactive systems, and renal function in cirrhotic patients admitted to the hospital for the treatment of ascites. Gastroenterology. 1988 Feb;94(2):482–7.

61. Reverter E, Tandon P, Augustin S, Turon F, Casu S, Bastiampillai R, et al. A MELD-based model to determine risk of mortality among patients with acute variceal bleeding. Gastroenterology. 2014 Feb;146(2):412-419.e3.

62. Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. Hepatol Baltim Md. 2017 Jan;65(1):310–35.

63. Kibrit J, Khan R, Jung BH, Koppe S. Clinical Assessment and Management of Portal Hypertension. Semin Interv Radiol. 2018 Aug;35(3):153–9.

64. Planas R, Montoliu S, Ballesté B, Rivera M, Miquel M, Masnou H, et al. Natural history of patients hospitalized for management of cirrhotic ascites. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc. 2006 Nov;4(11):1385–94.

65. Chiejina M, Kudaravalli P, Samant H. Ascites. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 May 27]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK470482/

66. Ärzteblatt DÄG Redaktion Deutsches. Deutsches Ärzteblatt. 2023 [cited 2024 May 27]. Pfortaderhochdruck: Reduzierte Elastizität der Milz lässt klinisch relevante portale Hypertonie erkennen. Available from: https://www.aerzteblatt.de/archiv/234990/Pfortaderhochdruck-Reduzierte-Elastizitaet-der-Milz-laesst-klinisch-relevante-portale-Hypertonie-erkennen

67. Bleibel W, Al-Osaimi AMS. Hepatic Encephalopathy. Saudi J Gastroenterol Off J Saudi Gastroenterol Assoc. 2012;18(5):301–9.

68. Amitrano L, Guardascione MA, Ames PRJ. Coagulation abnormalities in cirrhotic patients with portal vein thrombosis. Clin Lab. 2007;53(9–12):583–9.

69. AASLD Practice Guidance on risk stratification and management of portal hypertension and varices in cirrhosis - PubMed [Internet]. [cited 2024 May 27]. Available from: https://pubmed.ncbi.nlm.nih.gov/37870298/

70. Cardoso R, Casela A, Lopes S, Agostinho C, Souto P, Camacho E, et al. Portal Hypertensive Biliopathy: An Infrequent Cause of Biliary Obstruction. GE Port J Gastroenterol. 2015 Mar 18;22(2):65–9.

71. Paller AS, Mancini AJ. 12 - Vascular Disorders of Infancy and Childhood. In: Paller AS, Mancini AJ, editors. Hurwitz Clinical Pediatric Dermatology (Fifth Edition) [Internet]. London: Elsevier; 2016 [cited 2024 May 27]. p. 279-316.e6. Available from: https://www.sciencedirect.com/science/article/pii/B9780323244756000121

72. Wong F. Portal Hypertensive Gastropathy. Gastroenterol Hepatol. 2007 Jun;3(6):428–73.

73. Deng Y, Jiang Y, Jiang T, Chen L, Mou HJ, Tuo BG, et al. Evaluation of the efficacy and safety of endoscopic band ligation in the treatment of bleeding from mild to moderate gastric varices type 1. World J Gastroenterol. 2024 Feb 7;30(5):440–9.

74. ASGE Guideline: the role of endoscopy in the management of variceal hemorrhage, updated July 2005 - PubMed [Internet]. [cited 2024 May 27]. Available from: https://pubmed.ncbi.nlm.nih.gov/16246673/

75. The general rules for recording endoscopic findings on esophageal varices. Jpn J Surg. 1980 Mar;10(1):84–7.

76. Esophageal Varices - DynaMed [Internet]. [cited 2024 May 27]. Available from: https://www.dynamed.com/condition/esophageal-varices#GUID-AADCCD5C-C263-462B-8CE9-52CD60FD5FE2

77. Mathur V, Kaur G, Prajapat RK, Parmar S, Poonam null. Colonoscopic findings in Patients of Portal Hypertension Due to Different Etiologies and their Correlation. J Assoc Physicians India. 2021 Sep;69(9):11–2.

78. Muzio BD. Radiopaedia. [cited 2024 May 27]. Cirrhosis and portal hypertension | Radiology Case | Radiopaedia.org. Available from: https://radiopaedia.org/cases/cirrhosis-and-portal-hypertension-1

79. Elfeky M. Radiopaedia. [cited 2024 May 27]. Tuberculosis - multisystem involvement | Radiology Case | Radiopaedia.org. Available from: https://radiopaedia.org/cases/tuberculosis-multisystem-involvement

80. Mohammed AA. Caput medusae sign; a unique finding during abdominal examination in patients with portal hypertension; case report. Ann Med Surg. 2020 Apr 24;54:54–6.

81. Shawcross DL, Sharifi Y, Canavan JB, Yeoman AD, Abeles RD, Taylor NJ, et al. Infection and systemic inflammation, not ammonia, are associated with Grade 3/4 hepatic encephalopathy, but not mortality in cirrhosis. J Hepatol. 2011 Apr;54(4):640–9.

82. Performance of the hepatic encephalopathy scoring algorithm in a clinical trial of patients with cirrhosis and severe hepatic encephalopathy - PubMed [Internet]. [cited 2024 May 27]. Available from: https://pubmed.ncbi.nlm.nih.gov/19455117/

83. Development of a clinical hepatic encephalopathy staging scale - PubMed [Internet]. [cited 2024 May 27]. Available from: https://pubmed.ncbi.nlm.nih.gov/17767470/

84. Salam M, Matherly S, Farooq IS, Stravitz RT, Sterling RK, Sanyal AJ, et al. Modified-orientation log to assess hepatic encephalopathy. Aliment Pharmacol Ther. 2012 Apr;35(8):913–20.

85. Anand A, Singh P. Neurological Recovery After Recovery From Acute Liver Failure: Is it Complete? J Clin Exp Hepatol. 2018 Jun 1;9.

86. Maruyama H, Kobayashi K, Kiyono S, Ogasawara S, Suzuki E, Ooka Y, et al. Compensating effect of minor portal hypertension on the muscle mass loss-related poor prognosis in cirrhosis. Int J Med Sci. 2017 Jul 19;14(9):804–10.

87. Lala V, Zubair M, Minter DA. Liver Function Tests. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 May 27]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK482489/

88. Loomba R, Adams LA. Advances in non-invasive assessment of hepatic fibrosis. Gut. 2020 Jul;69(7):1343–52.

89. Thabut D, Imbert-Bismut F, Cazals-Hatem D, Messous D, Muntenau M, Valla DC, et al. Relationship between the Fibrotest and portal hypertension in patients with liver disease. Aliment Pharmacol Ther. 2007 Aug 1;26(3):359–68.

90. Nagula S, Jain D, Groszmann RJ, Garcia-Tsao G. Histological-hemodynamic correlation in cirrhosis-a histological classification of the severity of cirrhosis. J Hepatol. 2006 Jan;44(1):111–7.

91. Increased angiogenesis and permeability in the mesenteric microvasculature of rats with cirrhosis and portal hypertension: an in vivo study - PubMed [Internet]. [cited 2024 May 27]. Available from: https://pubmed.ncbi.nlm.nih.gov/16911473/

92. Reversal of portal hypertension and hyperdynamic splanchnic circulation by combined vascular endothelial growth factor and platelet-derived growth factor blockade in rats - PubMed [Internet]. [cited 2024 May 27]. Available from: https://pubmed.ncbi.nlm.nih.gov/17654489/

93. Nijveldt RJ, Teerlink T, Van Der Hoven B, Siroen MPC, Kuik DJ, Rauwerda JA, et al. Asymmetrical dimethylarginine (ADMA) in critically ill patients: high plasma ADMA concentration is an independent risk factor of ICU mortality. Clin Nutr Edinb Scotl. 2003 Feb;22(1):23–30.

94. Abdelmoneim SS, Talwalkar J, Sethi S, Kamath P, Fathalla MMF, Kipp BR, et al. A prospective pilot study of circulating endothelial cells as a potential new biomarker in portal hypertension. Liver Int Off J Int Assoc Study Liver. 2010 Feb;30(2):191–7.

95. Walz JM, Boehringer D, Deissler HL, Faerber L, Goepfert JC, Heiduschka P, et al. Pre-Analytical Parameters Affecting Vascular Endothelial Growth Factor Measurement in Plasma: Identifying Confounders. PLoS ONE. 2016 Jan 5;11(1):e0145375.

96. Wan S, Wei Y, Zhang X, Yang C, Hu F, Song B. Computed Tomography-Based Texture Features for the Risk Stratification of Portal Hypertension and Prediction of Survival in Patients With Cirrhosis: A Preliminary Study. Front Med. 2022 Apr 1;9:863596.

97. Kumar A, Khan NM, Anikhindi SA, Sharma P, Bansal N, Singla V, et al. Correlation of transient elastography with hepatic venous pressure gradient in patients with cirrhotic portal hypertension: A study of 326 patients from India. World J Gastroenterol. 2017 Jan 28;23(4):687–96.

98. Afdhal NH. Fibroscan (Transient Elastography) for the Measurement of Liver Fibrosis. Gastroenterol Hepatol. 2012 Sep;8(9):605–7.

99. High accuracy of spleen stiffness measurement in diagnosing clinically significant portal hypertension in metabolic-associated fatty liver disease - PubMed [Internet]. [cited 2024 May 27]. Available from: https://pubmed.ncbi.nlm.nih.gov/36912787/

100. Harmanci O, Bayraktar Y. Portal hypertension due to portal venous thrombosis: Etiology, clinical outcomes. World J Gastroenterol WJG. 2007 May 14;13(18):2535–40.

101. Gaillard F. Radiopaedia. [cited 2024 May 27]. Portal vein thrombosis | Radiology Reference Article | Radiopaedia.org. Available from: https://radiopaedia.org/articles/portal-vein-thrombosis

102. Niknejad MT. Radiopaedia. [cited 2024 May 27]. Portal vein thrombosis in cirrhotic patient | Radiology Case | Radiopaedia.org. Available from: https://radiopaedia.org/cases/portal-vein-thrombosis-in-cirrhotic-patient

103. Kumar A, Sharma P, Sarin SK. Hepatic venous pressure gradient measurement: time to learn! Indian J Gastroenterol Off J Indian Soc Gastroenterol. 2008;27(2):74–80.

104. García-Pagán JC, Reverter E, Abraldes JG, Bosch J. Acute variceal bleeding. Semin Respir Crit Care Med. 2012 Feb;33(1):46–54.

105. Cho H, Nagata N, Shimbo T, Sakurai T, Sekine K, Okubo H, et al. Recurrence and prognosis of patients emergently hospitalized for acute esophageal variceal bleeding: A long-term cohort study. Hepatol Res Off J Jpn Soc Hepatol. 2016 Dec;46(13):1338–46.

106. Guinazu C, Fernández Muñoz A, Maldonado MD, De La Cruz JA, Herrera D, Arruarana VS, et al. Assessing the Predictive Factors for Bleeding in Esophageal Variceal Disease: A Systematic Review. Cureus. 15(11):e48954.

107. McKay R, Webster NR. Variceal bleeding. Contin Educ Anaesth Crit Care Pain. 2007 Dec 1;7(6):191–4.

108. Ameer MA, Foris LA, Mandiga P, Haseeb M. Spontaneous Bacterial Peritonitis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 May 27]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK448208/

109. Butterworth RF. Complications of cirrhosis III. Hepatic encephalopathy. J Hepatol. 2000;32(1 Suppl):171–80.

110. Faccia M, Ainora ME, Ponziani FR, Riccardi L, Garcovich M, Gasbarrini A, et al. Portal vein thrombosis in cirrhosis: Why a well-known complication is still matter of debate. World J Gastroenterol. 2019 Aug 21;25(31):4437–51.

111. Machicao VI, Balakrishnan M, Fallon MB. Pulmonary complications in chronic liver disease. Hepatol Baltim Md. 2014 Apr;59(4):1627–37.

112. Saleemi S. Portopulmonary hypertension. Ann Thorac Med. 2010 Jan;5(1):5–9.

113. Angeli P, Bernardi M, Villanueva C, Francoz C, Mookerjee RP, Trebicka J, et al. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol. 2018 Aug;69(2):406–60.

114. Nakhleh RE. The pathological differential diagnosis of portal hypertension. Clin Liver Dis. 2017 Sep;10(3):57–62.

115. Rabiee A, Garcia-Tsao G, Tapper EB. Nonselective Beta-Blockers in Portal Hypertension: Why, When, and How? Clin Liver Dis. 2022 Mar;19(3):118.

116. Wong F, Pappas SC, Curry MP, Reddy KR, Rubin RA, Porayko MK, et al. Terlipressin plus Albumin for the Treatment of Type 1 Hepatorenal Syndrome. N Engl J Med. 2021 Mar 4;384(9):818–28.

117. Amesur NB, Novelli P. Transjugular Intrahepatic Portosystemic Shunt. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 May 27]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK513268/

118. Buttner L, Aigner A, Pick L, Brittinger J, Steib CJ, Boning G, et al. 25 years of experience with transjugular intrahepatic portosystemic shunt (TIPS): changes in patient selection and procedural aspects. Insights Imaging. 2022 Apr 13;13(1):73.

119. Boike JR, Thornburg BG, Asrani SK, Fallon MB, Fortune BE, Izzy MJ, et al. North American Practice-Based Recommendations for Transjugular Intrahepatic Portosystemic Shunts in Portal Hypertension. Clin Gastroenterol Hepatol. 2022 Aug;20(8):1636-1662 e36.

120. Arroyo V, Ginès P, Gerbes AL, Dudley FJ, Gentilini P, Laffi G, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. Hepatol Baltim Md. 1996 Jan;23(1):164–76.

121. Prowle JR, Bellomo R. Sepsis-associated acute kidney injury: macrohemodynamic and microhemodynamic alterations in the renal circulation. Semin Nephrol. 2015 Jan;35(1):64–74.

122. Lahbabi M, Mellouki I, Aqodad N, Elabkari M, Elyousfi M, Ibrahimi SA, et al. Esophageal variceal ligation in the secondary prevention of variceal bleeding: Result of long term follow-up. Pan Afr Med J. 2013 May 3;15:3.

123. Klupp J, Kohler S, Pascher A, Neuhaus P. Liver transplantation as ultimate tool to treat portal hypertension. Dig Dis Basel Switz. 2005;23(1):65–71.

124. Lee NHC, Kiddle SJ, Chandankhede S, Agrawal S, Bean DM, Hunt PR, et al. Evaluating clinical outcomes and prognosis in patients with cirrhosis and portal hypertension: a retrospective observational cohort study. BMJ Open Gastroenterol. 2023 Nov 29;10(1):e001234.

13. Curriculum Vitae

Thomas Maximilian Helmberger was born and raised in Munich, Germany, attending a primary state school and afterwards attending the bilingual secondary school Phorms Munich for 4 years. He graduated from Derksen high school in 2017 and worked afterwards in emergency services and as a private tutor for mathematics, physics and English. In 2018 he enrolled into the Medical Studies in English Language at the University of Rijeka, Croatia. Thomas M. Helmberger will return to the South of Germany and continue his education in internal and emergency medicine.